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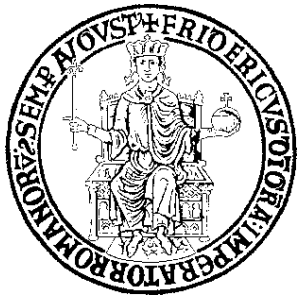

Doctorate in Neuroscience

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Cognitive disorder, quality of life and sexual function in women with gynecological cancer

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ACADEMIC YEAR 2018/2019

To my family

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INDEX

1) Female Sexual dysfunction and quality of life

In recent years, female sexuality has begun to be considered an important component of women's health, also recognized as a basic human right, as stated by the (WHO) (2002).

Many women experience problems with sexual function at some point, and some have difficulties throughout their lives. Female sexual dysfunction (FSD) can occur at any stage of life. It can occur only in certain or in all sexual situations.

Sexual response involves a complex interplay of physiology, emotions, experiences, beliefs, lifestyle and relationships. Disruption of any component can affect sexual desire, arousal or satisfaction, and treatment often involves more than one approach.

There are limited data on the incidence and prevalence of female sexual dysfunction. The available data differ considerably because of variations in the definitions of sexual dysfunction, different diagnostic categories used, composition of sample populations, and methods of data collection.

Incidence of FSD has been estimated to range from 25.8% to 91.0% depending on the source. A 2006 review by Hayes and colleagues reported a prevalence of desire difficulties in 64% of women, arousal difficulties in 31%, orgasm difficulties in 35%, and sexual pain in 26%. A study by Burri and Spector (2001) from the United Kingdom found that 5.8% of the population sampled reported current symptoms that met the criteria for an FSD diagnosis and 15.5% reported lifelong FSD.

Multiple factors must be taken into consideration when attempting to identify a causative agent for sexual dysfunction.

Medical and surgical conditions with the potential to cause sexual dysfunction can range from anatomic processes to lower urinary tract problems; endocrine disorders; malignancies; inflammatory diseases, such as fibromyalgia and rheumatoid arthritis; and neurologic conditions, such as multiple sclerosis, among others. In addition, there are a lot of secondary

(acquired) problems that can lead to sexual dysfunction, such as childbirth, hormonal changes, menopause, breastfeeding, trauma, and so on.

Psychological factors, such as depression and anxiety, are also possible causes, as are associated treatments/medications, such as antidepressants, antipsychotics, and hormonally mediated methods of birth control. Lifestyle factors, such as dangerous diet, weight, lack of exercise, smoking, and alcohol or other substance abuse, can further contribute, as can psychosocial factors of age, education, income, and ethnicity. Other miscellaneous factors include previous history of sexual abuse, sexual orientation, type of sexual practices, negative attitudes toward sex, and negative body image (Khajehei M, 2015).

There are a variety of therapeutic approaches that can aid in the management of desire and arousal disorders. Clinicians should try to discover any identifiable/treatable cause of sexual dysfunction in women amenable to intervention before making a primary diagnosis of sexual dysfunction.

Different approaches will be helpful for different populations. Current treatment modalities for disorders related to sexual desire or arousal can be broken down into two broad categories: hormonal and nonhormonal treatment. Hormonal treatment includes: systemic or vaginal estrogen replacement, androgen supplementation, Tibolone, a selective estrogen receptor modulator (SERM) or Ospemifene (SERM). Nonhormonal treatment includes: Flibanserin, nutritional supplements or psychotherapy.

Weighing the risks and benefits of specific treatments, such as hormonal versus nonhormonal treatment, is of preeminent importance (Clayton, 2019).

a) Lifespan changes in sexual function and quality of life

Across the life span, women experience changes in environment, partners, roles, lifestyle, and biological and reproductive statuses, all of which can impact upon sexual functioning. In women, the fluctuations in levels of sex steroids that occur with aging as well as in context of discreet reproductive events (i.e., the menstrual cycle, pregnancy, peripartum, and the peri-menopause) can influence both sexual functioning and mood. Most women tolerate such hormonal transitions during these reproductive events without serious adverse effects.

i) Reproductive years: effect of hormonal treatment on sexual function and quality of life

During the peak reproductive years, hormonal patterns become established and regular ovulatory and menstrual cycles occur. These physiological events appear to be influenced by sexual activity; e.g., sexual activity that occurs more frequently than once per week is associated with regular menstrual cycles and reduced anovulatory cycles (Halpern CT, 1997). In addition, psychological stresses such as fear of or desire for pregnancy and infertility concerns can negatively affect sexual experiences.

Women seeking to avoid pregnancy frequently use oral contraceptives, which may increase SHBG and lower free testosterone levels, inadvertently affecting sexual desire. Little difference in the effects of different formulations of hormonal contraceptives (e.g., oral, transvaginal, and injectable) on sexual functioning has been found. However, triphasic oral contraceptives have been found to be associated with more sexual thoughts, fantasies, and sexual interest than monophasic oral contraceptives (McCoy NL, 1996).

Though, available data support a favorable impact of contraceptive use on the psychosocial well-being of women, contrasting data are reported on QoL.

In our study (Di Carlo C, 2014 a), we demonstrate that the E2V/DNG pill is associated with a significant improvement of Global health and Vitality perception and with an improvement in female sexual function with no difference between age groups.

Nexplanon®, a single-rod etonogestrel (ENG)—containing contraceptive implant (or Implanon NXT® in other countries; MSD, Milan, Italy)—provides an alternative way of delivering progestogens. We studied the bleeding profile of this progestogen demonstrating that the ENG sub-dermal implant is a well-tolerated contraceptive method, with a high proportion of women experiencing a favorable bleeding profile (Di Carlo C, 2015 b).

Moreover, our data (Di Carlo C, 2014 c) show that the etonogestrel (ENG)-releasing implant significantly improved general Quality of Life (QoL) of women, after an early phase in

which it reduced some index related to the emotional sphere, as vitality, mental health, social functioning and emotional role functioning. Also, the implant does not have a negative impact on female sexual function, but have some positive effects.

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ETONORGESTREL IMPLANT

Bleeding profile in users of an etonogestrel sub-dermal implant: effects of anthropometric variables. An observational uncontrolled preliminary study in Italian population

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Abstract

Purpose: The purpose of this study is to evaluate the menstrual profile in users of the etonogestrel (ENG)-releasing implant (Nexplanon®) and the possible correlation with anthropometric variables.

Methods: Ninety-two healthy women, desiring long-term contraception with the ENG implant were enrolled in a prospective observational study. Anthropometric variables were measured at baseline and after 3, 6, 9, and 12 months. Patients recorded daily the occurrence of any bleeding or spotting. The bleeding/spotting pattern was evaluated over consecutive 90-day intervals (''Reference Periods'' – RPs). Patients who showed a favourable bleeding profile (amenorrhoea, infrequent, or normal bleeding) for 50% or more of the RPs were assigned to group A, while patients with a favourable bleeding profile for less than 50% of the RPs were assigned to group B.

Results: Sixty-eight women (79%) were assigned to group A; 18 (21%) to group B. Group B had a lower baseline body mass index (BMI) than group A (24.84 ± 4.95 kg/m^2 versus 20.75 ± 4.41 kg/m^2; $p < 0.005$).

Conclusions: The ENG sub-dermal implant is a well-tolerated contraceptive method, with a high proportion of women experiencing a favourable bleeding profile. The lower basal BMI in Group B in comparison with Group A may account for the higher percentage of irregular bleeding.

Keywords

Body mass index, etonogestrel, Implanon, menstrual bleeding patterns, Nexplanon, progestin-only contraception

History

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Introduction

Nexplanon®/Implanon® NXT is a subdermal implant that releases etonogestrel (ENG), providing contraceptive protection for up to 3 years [1]. An ENG subdermal implant (Implanon®) was first marketed in Europe in 1998 and it has been available since several years in many countries worldwide.

In comparison with Implanon®, Nexplanon®/Implanon® NXT has a preloaded applicator, which is designed to reduce insertion errors and the implant contains barium sulphate, which makes it visible by imaging techniques [2].

This contraceptive is suitable for contraception in most women, even in those with a history of venous thromboembolism or congenital and acquired cardiovascular disease [3,4]. Most women find ENG contraceptive implants acceptable, with first year continuation rates of approximately 80% in published studies [5]. However, these rates vary greatly depending on geographical area, with 90% continuation rate at 2 years in developing countries compared with 55% in developed ones [5,6].

In 2009, an analysis of 11 international clinical trials showed that only 5% of patients suffered from relevant side effects. The most commonly occurring were headache (15%), weight increase (12%), acne (12%), breast pain (10%), emotional liability (6%), and abdominal pain (5%) [7]. Bleeding irregularities are reported to be the second most common reason of discontinuation [8]. Almost one-third of European women who stopped using the method indicated that bleeding problems were the cause [5]. Among the subjects who suspended therapy as a result of bleeding irregularities, about 64% did so in the first year of treatment. Our previous data show that in a healthy Italian population, choosing this implant, there was no persistent negative effect on emotiveness and on sexual function but significant positive effects on general quality of life [9].

The aim of this study was to evaluate the menstrual bleeding profile of an healthy Italian female population using the ENG-releasing implant for contraception and to verify whether there is any correlation between different anthropometric and biological variables and the menstrual bleeding profile.

Methods

This prospective observational study was carried out in the Contraception Clinics of the Department of Obstetrics and Gynaecology, University Federico II, Naples, and Department

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of Medicine and Pharmacology, University of Salerno, Italy, from November 2011 to November 2012.

Inclusion criteria were desire for long-term contraception, good health, and regular menstrual cycles. The exclusion criteria included the following: previous hormonal contraception in the last month; abnormal menstrual bleeding prior to the use of the contraceptive method; endocrine dysfunctions and concomitant treatment with other hormones; uterine lesions; bleeding disorders; liver or renal disease; use of anti-coagulant therapy and contraindications to contraceptive steroids.

Ninety-nine women met the inclusion and exclusion criteria and were included in the study, after having signed an informed consent. Before enrolment, each patient underwent a pelvic examination a trans-vaginal ultrasound performed on one of the first 5 d of the menstrual cycle. Nexplanon was inserted between days 1 and 5 of the menstrual cycle.

Weight, height, and BMI were recorded for each patient at baseline and at each follow-up visit. An increase or reduction of 1000 g in body weight was considered a significant change. In case of implant removal, the time and the reason for discontinuation were recorded. Patients were asked to record every day on a diary the occurrence of any bleeding or spotting. The following definitions for bleeding patterns were used [10–12]:

- *bleeding-day* – any day with vaginal discharge containing blood that required more than one sanitary pad or tampon per day;
- *spotting-day* – any day with vaginal discharge containing blood that required at most one sanitary pad or tampon per day;
- *bleeding-free day* – a day during which neither bleeding nor spotting was reported;
- *bleeding–spotting episode* – one or more consecutive days during which bleeding or spotting was entered in the diary, bounded by bleeding-free days.

Data related to bleeding patterns were summarized in a suitable format in which medically relevant bleeding variables were identified and evaluated over consecutive 90-d periods. We referred to these as ''reference periods'' (RPs) that correspond to intervals between follow-up visits. The latter took place three (RP1 = 0–89 d), six (RP2 = 90–179 d), nine (RP3 = 180–269 d), and 12 months after insertion of the implant (RP4 = 270–360 d).

The RPs analysis included all subjects who had at least two RPs (6 months of follow-up) that could be evaluated. A RP was considered invalid and excluded from analysis if bleeding information was missing for three or more consecutive days or if non-permitted concomitant medications were used. If missing data were spread across two RPs, then both RPs were excluded. If diary data were missing for at most two consecutive days, the missing values were converted in the same bleeding–spotting (B–S) response reported on the day immediately preceding the missing values. If the data were missing on the first 1 or 2 d of treatment, then the day immediately following the missing data was used.

The characterisation of clinically important types of bleeding patterns was based on the original World Health Organization (WHO)-recommended definition [10–12]:

- *amenorrhoea*: no bleeding or spotting days throughout the 90-d reference period;
- *infrequent bleeding*: less than three bleeding–spotting episodes in a 90-d reference period, excluding amenorrhoea;
- *normal frequency*: 3–5 bleeding–spotting episodes in a 90-d reference period;
- *frequent bleeding*: more than five bleeding–spotting episodes in a 90-d reference period;
- *prolonged bleeding*: any bleeding-spotting episode (uninterrupted) lasting more than 14 d in the 90-d reference period.

In this study, amenorrhoea, infrequent bleeding, and normal bleeding were considered as characterising a 'favourable bleeding profile'; frequent bleeding and prolonged bleeding were considered to be features of an ''unfavourable bleeding profile''. Indeed, according to the WHO definition, from 3–5 bleeding/spotting episodes in a 90-d RP are considered to be a normal frequency of 'menses' or bleeding episodes [11], and women presenting with this profile (infrequent and normal bleeding) or with amenorrhoea have been reported to have a better compliance to the implant [13].

Patients were stratified into two groups according to the bleeding profile. Those who had a favourable bleeding profile (amenorrhoea, infrequent or normal bleeding) for 50% or more of the RPs were assigned to group A, while participants with a favourable bleeding profile in less than half of the RPs were assigned to group B.

For statistical analysis, we resorted to the SPSS 20.0 software package (SPSS Inc. Chicago, IL). Data distribution was evaluated by means of Shapiro Wilks' test and descriptive statistics were reported accordingly. The Chi-squared (χ^2)-test and Student's *t*-test were used to compare categorical and continuous data between groups, respectively. The level of significance for all tests was set at $p < 0.05$.

Results

Two women changed their mind and refused the insertion of the implant after enrolment. Four participants kept the implant for less than 6 months and were excluded from the analysis. Thus, 86 women completed at least 6 months of follow-up and were included in the analysis. Six patients decided to remove the implant after nine months of follow-up: one for weight gain, one for pregnancy desire, and four for bleeding irregularities. Two patients had their implant removed after 12 months for bleeding irregularities.

When stratifying the patients according to the proportion of RPs with favourable profile, it appeared that 68 women (79%) showed a favourable menstrual profile (group A), while the remaining 18 (21%) had an unfavourable menstrual profile (group B).

Baseline demographic characteristics and clinical data of the total population and of the two groups are reported in Table 2. A statistically significant difference was found in baseline BMI between the two groups ($p < 0.005$). Patients of group B had a lower baseline BMI than patients of group A (Table 1).

During treatment, no significant change in body weight was observed and no significant difference in body weigh increase was evident between the two groups (Table 1). The gynaecological history and implant placement circumstances of the total study population and of the two groups are shown in Table 2.

Women of Group B reported a longer duration of menstrual bleeding before the study; on the contrary, no significant difference was found between groups regarding bleeding frequency and age at menarche (Table 2). Last contraceptive methods and implant placement were not different between the two groups (Table 2).

The bleeding profile over the four RPs is reported in Table 3. During RP1, the bleeding profile most frequently observed was amenorrhoea (70% of patients), while in RP2 and in RP4, the most frequent patterns were infrequent bleeding (37% and 36% of participants, respectively); 35% of the patients reported normal bleeding during RP3.

Discussion

Four out of five (79%) participants developed a favourable menstrual profile during the first 12 months of use of Nexplanon®.

Table 1. Bleeding profile of total population during 12 months of treatment.

Bleeding profile	RP1 ($N=86$)	RP2 ($N=86$)	RP3 ($N=80$)	RP4 ($N=78$)
Amenorrhea	60 (69.8)	22 (25.6)	22 (27.5)	22 (28.2)
Infrequent bleeding	8 (9.3)	32 (37.2)	16 (20.0)	28 (35.9)
Normal bleeding	2 (2.3)	12 (14.0)	28 (35.0)	18 (23.1)
Frequent bleeding	14 (16.3)	14 (16.3)	8 (10.0)	8 (10.3)
Prolonged bleeding	2 (2.3)	6 (7.0)	6 (7.5)	2 (2.6)

Values are given as *n* (%). RP, reference period. Bleeding patterns were defined per 90-d periods from the implant placement to 12 months.

Table 2. Demographic and clinical characteristics of the total population and the two groups.

	Total group ($N=86$)	Group A ($N=68$)	Group B ($N=18$)	*p* Value Group A versus group B
Mean age (years ± SD)	31.8 ± 7.26	32.3 ± 7.4	30.1 ± 6.6	0.27
Marital status				0.19
Never married	16 (18.6%)	14 (20.6%)	2 (11.1%)	
Not married but living with partner	15 (17.4%)	14 (20.6%)	1 (5.6%)	
Married	48 (55.8%)	34 (50.0%)	14 (77.8%)	
Divorced, separate or widowed	7 (8.1%)	6 (8.8%)	1 (5.6%)	
Mean BMI (weigh/high^2 ± SD)	23.9 ± 5.1	24.84 ± 4.95	20.75 ± 4.41	0.002
Weight increase during follow up				0.7
No	56 (65.1%)	44 (64.7%)	12 (66.7)	
Yes	30 (34.9%)	24 (35.3%)	6 (33.3)	
Mean baseline Endometrium thickness at TV-USG (mm ± SD)	3.80 ± 1.72	3.88 ± 1.75	3.51 ± 1.60	0.42

Patients were stratified according RPs with favourable bleeding pattern (amenorrhea, infrequent bleeding, and normal bleeding) into group A (≥50% of RPs) and group B (<50% of RPs). The Chi-squared test and Student's *t*-test were used to compare categorical and continuous data between groups, respectively. The level of significance for all tests was set at $p<0.05$.

Table 3. Gynecological anamnesis and implant placement time of the total population and of the two groups.

	Total group ($N=86$)	Group A ($N=68$)	Group B ($N=18$)	*p* Value
Mean age at menarche (years ± SD)	12.4 ± 1.6	12.6 ± 1.8	12.1 ± 1.1	0.28
Cumulative no. of previous pregnancy*				
≤1	13 (13.1)	12 (17.6)	1 (5.6)	0.002
2–3	42 (48.8)	38 (55.9)	4 (22.2)	
≥4	31 (36.0)	18 (26.5)	13 (72.2)	
Usual duration of bleeding (days)	4.7(±1.5)	4.85 (±1.5)	4.0 (1.0)	0.011
Usual frequency of bleeding*				
Oligomenorrhea	6 (7.0)	4 (5.9)	2 (11.1)	0.12
Normal	64 (74.4)	54 (79.4)	10 (55.6)	
Polimenorrhea	16 (18.6)	10 (14.7)	6 (33.3)	
Last contraceptive methods*				
None	24 (27.9)	22 (32.4)	2 (11.1)	0.20
Hormonal	16 (18.6)	10 (14.7)	6 (33.3)	
IUD	14 (16.3)	10 (14.7)	4 (22.2)	
Foam, condoms, diaphram, spermicide	30 (34.9)	24 (35.3)	6 (33.3)	
Others	2 (2.3)	2 (2.9)	0 (0.0)	
Post-partum placement*				
No	86 (100)	68 (100)	18 (100)	–
Yes	0	0	0	
Post-IVG placement*				
No	66 (76.7)	56 (82.4)	10 (55.6)	0.017
Yes	20 (23.3)	12 (17.6)	8 (44.4)	
During lactation placement*				
No	82 (95.3)	64 (94.1)	18 (100)	0.29
Yes	4 (4.7)	4 (5.9)	0 (5.0)	

Patients were stratified according RPs with favourable bleeding pattern (amenorrhea, infrequent bleeding, and normal bleeding) into group A (≥50% of RPs) and group B (<50% of RPs). The Chi-squared test and Student's *t*-test were used to compare categorical and continuous data between groups, respectively. The level of significance for all tests was set at $p<0.05$.

*Data are shown as number (percentage).

An unfavourable bleeding profile was associated with a lower BMI. The number of bleeding days increased after the first RP.

This is the first study, to our knowledge, that evaluates menstrual bleeding profile in Italian women relying on the ENG implant. The main limitations are the self-reporting of the bleeding days by the participants and the lack of measurement of oestrogen- and ENG levels at baseline and during follow-up. A multivariate analysis might have confirmed the effect of BMI on bleeding profile, but the small size of our study sample did not allow us to perform this analysis.

Our data are in line with those brought to light by earlier investigations which showed a similar overall incidence (23–25%) of unfavourable bleeding profile [6,7–14]. In our study, six patients (7%) decided to have the implant removed before the end of the first year because of menstrual irregularities. Casey et al. [14] and Blumenthal et al. [8] report a removal rate for bleeding irregularities of 15% and 11%, respectively. Implanon® users report abnormal bleeding patterns less frequently in comparison with users of other progestin-only contraceptives [15]. This may be due to the fact that they show the highest rate of follicular growth, and have the thickest endometrium, showing signs of weak proliferative activity [15].

We also observed that the menstrual bleeding profile changes during the first year of treatment with the implant; indeed, during RP1, the most frequent bleeding profile is amenorrhoea, while during the other RPs there is an increase in the percentage of patients experiencing bleeding/spotting (Table 3). This phenomenon may reflect the progressive decrease in ENG serum level during the first 12 months of use [16]. The high serum level of ENG during the first months after implant insertion may induce endometrial atrophy and, consequently, amenorrhoea. The sustained and continuous action of the progestin on the endometrium induces of a progressive instability of the tissue, with a tendency for small surface blood vessels to break down and bleed unpredictably [17–19]. This was not observed during the last RP (RP4) as the majority of the participants reported having experienced infrequent bleeding at that time. It should be noted that, at this point, six women with unfavourable bleeding profile during the previous RPs had already decided to have their implants removed.

Data in the literature about correlation between BMI and bleeding patterns are conflicting, with some studies reporting a negative statistical significant correlation between bleeding/spotting days and BMI [6] and other studies reporting that BMI did not predict bleeding or removal for bleeding risk [14]. In this study, we observed a baseline BMI significantly lower in patients with an unfavourable bleeding profile. According to these data, Casey et al. [20] demonstrated that obese women were 2.6 times less likely to have implant removal for bleeding as compared with normal weight women after adjusting for age and parity. It could be hypothesised that the effect of higher endogenous oestrogen levels in women with higher BMI stabilizes the endometrium.

In conclusion, the implantable ENG-releasing implant induces a favourable menstrual bleeding pattern in most users. A lower BMI is associated more commonly with frequent- or prolonged bleeding. Further randomised controlled studies should explore preventive and therapeutic options to control bleeding irregularities.

Declaration of interest

Costantino Di Carlo has been a consultant for Merck Sharp and Dohme on several occasions. The other authors report no conflict of interest. The authors alone are responsible for the content and the writing of the paper.

References

1. Mäkäräinen L, van Beek A, Tuomivaara L, et al. Ovarian function during the use of a single contraceptive implant: implanon compared with Norplant. Fertil Steril 1998;69:714–21.
2. Varma R, Mascarenhas L. Endometrial effects of etonogestrel (Implanon) contraceptive implant. Curr Opin Obstet Gynecol 2001; 13:335–41.
3. Faculty of Sexual and Reproductive Healthcare. UK Medical eligibility criteria for contraceptive use. UK, 2009;47–67.
4. Graesslin O, Korver T. The contraceptive efficacy of Implanon®: a review of clinical trials and marketing experience. Eur J Contracept Reprod Health Care 2008;13:4–12.
5. Power J, French R, Cowan F. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods of preventing pregnancy. Cochrane Database Syst Rev 2007;18:CD001326. doi:10/1002/14651858. CD001326. pub2.
6. Mansour D, Korver T, Marintcheva-Petrova M, et al. The effects of Implanon® on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008;13:13–28.
7. Darney P, Patel A, Rosen K, et al. Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. Fertil Steril 2009;91:1646–53.
8. Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M. Tolerability and clinical safety of Implanon®. Eur J Contracept Reprod Health Care 2008;13:29–36.
9. Di Carlo C, Sansone A, De Rosa N, et al. Impact of an implantable steroid contraceptive (etonogestrel-releasing implant) on quality of life and sexual function: a preliminary study. 2013 Gynecol Endocrinol 2014;30:53–6.
10. Belsey EM, Farley TM. The analysis of menstrual bleeding patterns: a review. Contraception 1988;38:129–56.
11. Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Program of Research, Development and Research Training in Human Reproduction. Contraception 1986;34: 253–60.
12. Fraser IS. Bleeding arising from the use of exogenous steroids. Baillieres Best Pract Res Clin Obstet Gynaecol 1999;13:203–22.
13. Croxatto HB, Urbancsek J, Massai R, et al. A multicentre efficacy and safety study of the single contraceptive implant Implanon®. Implanon Study Group. Hum Reprod 1999;14:976–81.
14. Casey PM, Long ME, Marnach ML, Bury JE. Bleeding related to etonogestrel subdermal implant in a US population. Contraception 2011;83:426–30.
15. Laban M, Abd Alhamid M, Ibrahim EA, et al. Endometrial histopathology, ovarian changes and bleeding patterns among users of long-acting progestin-only contraceptives in Egypt. Eur J Contracept Reprod Health Care 2012;17:451–7.
16. Huber J, Wenzl R. Pharmacokinetics of implanon. An integrated analysis. Contraception 1998;58:85S–90.
17. Hickey M, Higham JM, Fraser IS. Causes and management of endometrial breakthrough bleeding. Reprod Med Rev 2001;9: 153–71.
18. Livingstone M, Fraser IS. Mechanisms of abnormal uterine bleeding. Hum Reprod Update 2002;8:60–7.
19. Hickey M, d'Arcangues C. Mechanisms underlying menstrual bleeding disturbances with progestogens. Ernst Schering Res Found Workshop 2005;52:191–217.
20. Casey PM, Long ME, Marnach ML, et al. Association of body mass index with removal of etonogestrel subdermal implant. Contraception 2013;87:370–4.

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ORIGINAL ARTICLE

Effects of estradiol valerate and dienogest on quality of life and sexual function according to age.

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Abstract

This is an observational study on 102 women aged 25–45 years to evaluate if the E2V/DNG pill has any impact on quality of life (QoL) and sexual function (FSF). Thirty-nine women were younger than 35 years (group A), and 63 women were 35 years old or older (group B). At baseline and after 6 months, patients received the Italian validated version of the Short Form-36 questionnaire and the Italian validated version of the Female Sexual Function Index questionnaire. Group A showed an overall higher perception in all QoL scores at baseline and after 6-months ($p < 0.05$). E_2V/DNG treatment did not exert any significant effect on QoL perception in group A apart from an increase in the GH domain (general health). In group B we observed a significant improvement both in GH and in VT (vitality) scores. We found a significant reduction in ''lubrication'' after 6 months both in group A and B ($p < 0.01$) and a significant improvement in ''satisfaction'' and ''pain'' scores in group A and in ''desire'', ''satisfaction'' and ''total'' score in group B ($p < 0.01$). The E2V/DNG pill is associated with a significant improvement of GH and VT and with an improvement in FSF with no difference between age groups.

Keywords

Contraception, dienogest, lifestyle, natural-oestrogen, sexuality

History

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Introduction

The compliance to hormonal contraception and its continuation rate are largely affected by patients'satisfaction with the different methods, which, is in turn, influenced by their subjective experience and by the impact on their quality of life (QoL) as well as sexual function (FSF).

QoL and FSF have become important health indicator [1,2]. However, data on the effects of hormonal contraception on QoL and FSF are limited, with most reports focusing on contraceptive safety and efficacy, weight gain, bleeding irregularities, nausea, and effects on mood.

In 2009, a new oral contraceptive has been introduced in Italy. In this combined oral contraceptive (COC), estradiol valerate (E2V) is combined with dienogest (DNG) in a quadriphasic dose regimen (E2V/DNG), using an estrogen step-down and progestogen step-up approach. Specifically, the 28-tablet pack contains 2 tablets containing 3 mg of E2V, 5 tablets containing 2 mg of E2V and 2 mg of DNG, 17 tablets containing 2 mg of E2V and 3 mg of DNG, 2 tablets containing 1 mg of E2V, and 2 inert tablets. The association of E2V with a highly potent progestogen in this dynamic dosing strategy provides a good cycle control [3].

Moreover, the use of E2V/DNG for six months induces a significant reduction of heavy menstrual bleeding, with an average 65% reduction in mean blood loss [4]. Therefore, this contraceptive is generally considered as particularly suitable for perimenopausal women suffering from abnormal uterine bleeding.

However the metabolic neutrality of E2V compared to ethinylestradiol (EE) could recommend this COC as a good choice for women of all ages needing contraception.

Aim of this observational study was to evaluate if the E2V/DNG pill has any impact on the QOL and sexual activity of healthy women aged 25–45 years.

Methods

From January 2011 to September 2013 154 subjects, who had been prescribed E2V/DNG (Klaira®, Bayer S.p.A., Italy) for contraception in the Clinic of our Institution, were evaluated for inclusion in this observational prospective study.

Obviously, none of the patients presented any contraindication to the use of combined oral contraceptives. Before prescription, as is routine in our Department, medical and gynecological history was taken and all subjects underwent gynecological examination, Pap smear, blood pressure measurement and calculation of BMI.

Inclusion criteria were: age between 25 and 45 years; active sexual life (≥4 intercourses in the last month); good understanding of the Italian language, committed relationship since at least one year.

Exclusion criteria were: evidence of adnexal pathologies, suspicion of organic sexual disorders identified during pre enrollment examination; cardiovascular, hepatic or renal impairment;

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abortion in the previous 4 months; presence of irregular menstrual bleeding; known or suspected malignant or premalignant disease; contraceptive (included intrauterine device) use in the previous 4 weeks.

Enrollment was stopped when 120 women had been included in the study, after having signed an informed consent. The protocol of the study was approved by our Institutional Review Board and the study was conducted according to the guidelines of the Declaration of Helsinki (1975).

All eligible patients started treatment with E_2V/DNG as a 28 days continuous, four-phases dose regimen.

Before starting treatment and after 6 months, patients were interviewed by two medical doctors, who evaluated effects of treatment on QOL using the Italian validated version of the Short Form-36 (SF-36) questionnaire [5] and on sexual activity using the Italian validated version of the Female Sexual Function Index questionnaire (FSFI) [6–8].

The SF-36 questionnaire contains 36 questions grouped into eight categories: physical functioning, physical role functioning, bodily pain, general health, vitality, mental health, social functioning, and emotional role functioning [5].

The FSFI questionnaire contains 19 questions grouped into six domains: (i) sexual desire; (ii) sexual excitement; (iii) the need for lubrication; (iv) attainment of orgasm; (v) general sexual satisfaction; and (vi) experience of pain during sex. All questions are formatted using a multiple-choice system. A score of 0–5 is assigned to each response, and a final sexual satisfaction value is derived mathematically, with the ultimate sexual function score ranging from 2 to 36. A lower score indicates poorer sexual function. A score of 26.55 or less indicates a risk of sexual dysfunction [7,8].

Moreover, at the six months follow up visit, patients were interviewed about Global Satisfaction for the use of this COC trough a VAS score [scale: 0–10] and onset of any adverse events. In the same occasion, changes in quality of life perception in relation with COC use were evaluated through specific questions with Likert-scale assessment (scale: 1 – no agreement; 5 – complete agreement) as follow: ''*Do you think your QoL has been improved by COC therapy''* and *''Did you experience an improvement in dysmenorrhea which can be attributed to COC therapy?''*.

Data analyses were performed using the SPSS 15.0 software package (SPSS Inc. Chicago, IL).

Data were evaluated for distribution by Shapiro Wilks' test and descriptive statistics reported accordingly.

Patients were stratified according to age into two groups: group A, including patients aged between 25–35 years, and group B, including patients aged 36–45 years.

Differences in proportions between the two groups were analyzed with χ^2-test; while Friedman's two-way analysis on ranks test with *post ho*c test by Conover [9] was used to compare questionnaires scores at baseline and at follow-up visits for each groups. The level of significance for all tests was set at $p < 0.05$.

Results

One-hundred twenty new users of E_2V/DNG were recruited for the study. Four women refused to start treatment after enrollment and baseline evaluation, having changed their mind, and seven were excluded from the study because of treatment discontinuation before 6 months. Seven patients do not fill the final follow-up questionnaire. Thus, questionnaires were examined in 102 patients. 39 women were younger than 35 years, and were included in group A, 63 women were 35 years old or older and represent group B.

Table 1. Baseline demographic characteristics of the patients.

	Group A ($n = 39$)	Group B ($n = 63$)	p Value
Age (years)	29.0 ± 3.1	41.3 ± 2.9	0.00
Parity (n)	0 [0–2]	2 [1–4]	0.00
BMI (Kg/m^2)	21.7 ± 1.6	22.3 ± 1.5	NS (0.74)
Smokers (>5 cigarettes/days)			
yes	18 (46.2)	34 (54.0)	NS (0.44)
no	21 (53.8)	29 (46.0)	
Comorbidity			NS (0.31)
Present	3 (7.7)	9 (14.3)	
Absent	36 (92.3)	54 (85.7)	

Date are given as mean ± SD, median [range] or number (percentage) as appropriate.

Baseline demographic characteristics of the patients are reported in Table 1. Twelve subjects (3 in group A and 9 in group B) showed the presence of comorbidity at enrollment, with no difference between the groups. These comorbidities did not contraindicate contraceptive use. Particularly, in group A one patient was affected by thalassemia minor, one by allergic asthma and one by hypothyroidism; while in group B, 4 patients were affected by hypothyroidism, 2 by spinal disc herniation, 1 by strabismus and 1 by vitiligo.

Obviously, the number of previous pregnancies was significantly higher in group B (older patients) in comparison with group A (Table 1).

The SF-36 scores at the beginning of treatment and after 6 months are reported in Table 2 both for group A and B. Group A showed an overall higher perception in all QoL scores than Group B both at baseline and after 6-month therapy ($p < 0.05$, Table 2).

E_2V/DNG treatment did not exert any significant effect on quality of life perception in group A apart from an increase in the GH domain (general health). In group B we observed a significant improvement both in GH and in VT (vitality) scores.

The FSFI scores before treatment and after 6 months are presented in Table 3. A significant reduction in ''lubrication'' was shown after 6 months therapy both in group A and B ($p < 0.01$, Table 3); on the other hand a significant improvement in ''satisfaction'' and ''pain'' scores was shown in group A and in ''desire'', ''satisfaction'' and ''total'' score in group B ($p < 0.01$, Table 3).

Group A showed a significant higher basal level in ''desire'', ''lubrication'', ''orgasm'', ''pain'' and ''total'' scores than group B ($p < 0.01$, Table 4) and a significant higher levels in all FSFI scores except for ''arousal'' at six months than group B ($p < 0.01$ and $p < 0.05$, Table 4).

''Global satisfaction'' of group A and B at the follow-up visit was high and significantly higher in group A than B (Table 4). Few patients reported adverse events; in particular: 2 patients of group A and 2 of group B reported headaches; 2 patients of group A and 3 of group B showed breast tenderness and 1 patients of group B reported nausea (Table 4).

According to the scores of the Likert scale, both younger (group A) and older (group B) patients reported an improvement in QoL and in dysmenorrhea which was attributed to treatment with E_2V/DNG (Table 4).

Discussion

Available data support a favorable impact of contraceptive use on the psychosocial well-being of women [10–12].

Indeed, a cross-sectional analysis found that sexually active women of reproductive age who use any form of contraception

Table 2. The Quality of Life domains (SF-36 scores) before start treatment and after 6 months, in group A and B.

	Group A ($n = 39$)		Group B ($n = 63$)	
SF-36 Score	Baseline	6 months	Baseline	6 months
PF	100 [95–100][a]	100 [75–100][a]	90 [75–100]	90 [75–100]
PRF	100 [75–100][a]	100 [75–100][a]	100 [50–100]	100 [50–100]
BP	100 [72–100][a]	100 [80–100][a]	64 [52–80]	74 [52–90]
GH	86 [45–100][a]	92 [45–100][a,c]	45 [25–75]	47 [25–100][d]
VT	75 [25–90][a]	75 [25–90][a]	40 [35–60]	45 [35–74][c]
SF	87 [25–100][a]	87[25–100][a]	75 [50–75]	75 [47–87]
ERF	66 [33–100][b]	66[33–100][a]	66 [33–100]	66 [33–100]
MH	76 [24–100][a]	80[24–100][a]	64 [60–80]	72 [60–80]

PF: physical functioning, PRF: physical role functioning, BP: bodily pain, GH: general health, VT: vitality, MH: mental health, SF: social functioning, ERF: emotional role functioning. Data are reported as median [CI, 95%]. [a]$p < 0.001$ versus Group B; [b]$p < 0.05$ versus Group B; [c]$p < 0.01$ versus baseline; [d]$p < 0.05$ versus baseline.

Table 3. The Female Sexual Function domain (FSFI scores) before start treatment and after 6 months, in group A and B.

	Group A		Group B	
FSFI score	Baseline	6 months	Baseline	6 months
Desire	4.8 [2.4–6.0][a]	4.8 [3.6–6.0][b]	4.8 [2.4–6.0]	6.0 [3.6–6.0][c]
Arousal	5.7 [1.2–6.0]	5.4 [2.7–6.0]	5.1 [1.2–5.7]	5.1 [2.7–6.0]
Lubrication	5.7 [3.9–6.0][a]	3.9 [2.4–5.7][b,c]	3.6 [2.1–5.7]	3.0 [2.7–5.7][c]
Orgasm	6.0 [4.4–6.0][a]	5.7 [4.4–6.0][b]	4.8 [2.4–6.0]	4.8 [4.4–6.0]
Satisfaction	4.8 [4.0–6.0]	5.6 [3.6–6.0][d]	4.8 [2.4–6.0]	5.2 [3.6–6.0][c]
Pain	4.8 [3.6–6.0][a]	5.6 [3.6–6.0][b,c]	3.6 [2.4–6.0]	3.6 [2.4–6.0]
Total	30.4 [23.8–34.7][a]	31.0 [21.5–34.7][b]	27.1 [12.9–34.7]	27.7 [21.5–34.7][c]

Data are reported as median [range].
[a]$p < 0.01$ versus group B; [b]$p < 0.01$ versus group B; [c]$p < 0.01$ versus baseline; [d]$p < 0.05$ versus group B.

Table 4. Global satisfaction and adverse events after 6 months therapy.

	Group A ($n = 39$)	Group B ($n = 63$)	p Value
Global satisfaction	8 [4–10]	7 [5–10]	0.02
Adverse effects			NS (0.90)
Present	4 (10.3)	6 (9.5)	
Absent	35 (89.7)	57 (90.5)	
Improvement in quality of life attributed to COC [1–5]	4 [1–5]	4 [1–5]	NS (0.07)
Improvement in Dysmenorrhea attributed to COC [1–5]	4 [1–5]	4 [1–5]	NS (0.48)

Data are reported as median [range].

have greater odds of reporting average or better mental QOL than those who use no contraception [13]. Similarly, in a recent study, Caruso et al. found an improvement in sexual behavior and in QoL of women on oral contraceptive continued-regimen [14]. The same authors reported an improvement in QoL and sexual function after 6 months of treatment with E2V/DNG contraceptive according to our data [15]. In a previous study, we investigated the effect of contraceptive etonogestrel implant on QOL and sexual function, finding no persistent negative effect on emotiveness and on sexual function and a significantly improvement of general QOL [16].

On the contrary, Li et al. found a decrease in social relationship QOL score in OC users [17]. In the present study we could not find any negative impact of the treatment on QoL, with a significant improvement in both groups in GH score and a significant improvement of VT score in older patients. These data could be probably explained with the reduction of bleeding, anemia and dysmenorrhea, due to the treatment.

The decrease in lubrication observed in both groups is a common phenomenon in women taking contraceptives.

Nevertheless we found a significant improvement in ''satisfaction'' and ''pain'' scores in group A and in ''desire'', ''satisfaction'' and ''total'' score in group B. The improvement in satisfaction was probably due to the contraceptive effect ensuring a more relaxed sexual life and to the reduction of pain.

Hypothetically, the lower impact of E2V on SHBG levels, determining higher concentrations of free testosterone in comparison to COC containing ethynilestradiol, may prevent the loss of sexual desire often observed in women taking oral contraceptives. Indeed, we did not observe any significant variation in ''desire'' in group A and found a surprising improvement of ''desire'' in group B.

Finally, patients of both groups attributed to the treatment an improvement in QoL and in dysmenorrhea.

This is an observational study with a short follow up period. Taking in account this important limits, we may conclude that the

E2V/DNG association is well tolerated in patients aged 25-45, and is associated with a significant improvement of GH and VT and with an improvement in sexual life with no difference between age groups.

Therefore this association, also for the great metabolic neutrality of E2V could be a good choice for all women requiring contraception independently of their age.

Declaration of interest

The authors report no declaration of interest.

References

1. Wood-Dauphinee S. Assessing quality of life in clinical research: from where have we come and where are we going? J Clin Epidemiol 1999;52:355–63.
2. Committee on Quality of Health Care in America Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington, D.C.: National Academy Press; 2001.
3. Düsterberg B, Nishino Y. Pharmacokinetic and pharmacological features of oestradiol valerate. Maturitas 1982;4:315–24.
4. Rafie S, Borgelt L, Koepf ER, et al. Novel oral contraceptive for heavy menstrual bleeding: estradiol valerate and dienogest. Int J Womens Health 2013;5:313–21.
5. Ware JE, Kosinski M, Gandek BG, et al. The factor structure of the SF-36 Health Survey in 10 countries: results from the International Quality of Life Assessment (IQOLA) project. J Clin Epidemiol 1998;51:1159–65.
6. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;26: 191–208.
7. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): Cross-validation and development of clinical cut off scores. J Sex Marital Ther 2005;31:1–20.
8. Nappi RE, Albani F, Vaccaro P, et al. Use of the Italian translation of the Female Sexual Function Index (FSFI) in routine gynecological practice. Gynecol Endocrinol 2008;24:214–19.
9. Conover WJ. Practical nonparametric statistics. Wiley series in probability and mathematical statistics. New York: Wiley; 1980.
10. Rosenfield JA, Zahorik PM, Saint W, Murphy G. Women's satisfaction with birth control. J Fam Pract 1993;36: 169–73.
11. Ott MA, Shew ML, Ofner S, et al. The influence of hormonal contraception on mood and sexual interest among adolescents. Arch Sex Behav 2008;37:605–13.
12. Matsumoto Y, Yamabe S, Ideta K, Kawabata M. Impact of use of combined oral contraceptive pill on the quality of life of Japanese women. J Obstet Gynaecol Res 2007;33:529–35.
13. Williams SL, Parisi SM, Hess R, Schwarz EB. Associations between recent contraceptive use and quality of life among women. Contraception 2012;85:282–7.
14. Caruso S, Malandrino C, Cicero C, et al. Quality of sexual life of women on oral contraceptive continued-regimen: pilot study. J Sex Med 2013;10:460–6.
15. Caruso S, Agnello C, Romano M, et al. Preliminary study on the effect of four-phasic estradiol valerate and dienogest (E2V/DNG) oral contraceptive on the quality of sexual life. J Sex Med 2011;8: 2841–50.
16. Di Carlo C, Sansone A, De Rosa N, et al. Impact of an implantable steroid contraceptive (etonogestrel-releasing implant) on quality of life and sexual function: a preliminary study. Gynecol Endocrinol 2014;30:53–6.
17. Li RHW, Lo SST, Teh DKG, et al. Impact of common contraceptive methods on quality of life and sexual function in Hong Kong Chinese women. Contraception 2004;70:474–82.

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CONTRACEPTIVE IMPLANT

Impact of an implantable steroid contraceptive (etonogestrel-releasing implant) on quality of life and sexual function: a preliminary study

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Abstract

The aim of the study was to determine the impact of etonogestrel (ENG)-implant used for contraceptive purpose on Quality of life (QoL) and on sexual function (FSF) of healthy Italian women. The Female Sexual Function Index (FSFI) questionnaire and the Short Form-36 (SF-36) validated questionnaire were administered at baseline, 3 and 6 months after insertion of Nexplanon. The implant seems to have a positive impact on QoL after the first three months of therapy. Users showed an improved general health status and physical role status. The implant did not show negative effects on libido and on sexual function. In the first three months of treatment, users experienced a temporary reduction of vitality, mental health, social functioning and emotional role functioning, which seem to disappear after six months of therapy.

Keywords

Contraception, etonogestrel-implant, quality of life, sexual function

History

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Introduction

The etonogestrel (ENG)-releasing implant Nexplanon® (or Implanon NXT® in other countries; MSD, Milan, Italy) is a subdermal, progestin-only contraceptive that provides effective contraceptive protection for up to 3 years [1,2].

The single implant contains 68 mg ENG, the active metabolite of desogestrel, a progestin widely used in hormonal contraceptives [1].

The decision to use hormonal contraception and the choice of its type made by women are largely affected by their satisfaction with the different methods, which, is in turn, influenced by their subjective experience and by the impact on their quality of life (QoL) as well as sexual function (FSF). Available data support an impact of contraceptive use on the psychosocial well-being of women [3,4]. Many studies on hormonal contraceptives systematically assessed how these methods affect sexual functioning or pleasure [5–9].

While many researchers have thoroughly documented the effects of hormonal contraceptive methods on ovulation [10], far fewer have demonstrated their effect on the peak in sexual interest that many women experience during ovulation or have explored how hormonal contraceptives enhance or hinder sexual enjoyment, thereby altering use patterns [11].

Moreover, there is also a paucity of data on the effects of hormonal contraception on QoL, with most reports focusing on contraceptive safety and efficacy, weight gain, bleeding irregularities, nausea and effects on mood.

Hormonal progestin-only contraceptives are known to be effective in decreasing pelvic pain caused by various disorders such as endometriosis, menorrhagia, dysmenorrhea and dyspareunia. Moreover, they are a highly effective form of contraception, which may help eliminate the fear of pregnancy, presumably providing a more relaxed and enjoyable sexual experience. All these effects may improve quality of life. On the other hand, these contraceptives are associated with weight gain and, seldomly, with acne, hair loss and hirsutism [12,13]; it is reasonable to consider that a deterioration of appearance would disappoint self-confidence and self-esteem, thereby having negative effect on QoL and sexual function. Mood changes, including nervousness and depression, are commonly mentioned side effects of implants [14]; however, the influence of progestin-contraceptive on mood and emotional state is not fully understood. The aim of this study was to evaluate the short-term influence of Nexplanon® on QoL and sexual function using validated questionnaires.

Methods

Between November 2011 and November 2012, a total of 52 subjects were referred to the Unit of Family Planning Center of our Institution for the first Nexplanon implant.

Inclusion criteria were: age between 18 and 45 years; body mass index (BMI) $> 20 \leq 22\,kg/m^2$; active sexual life ($\geq$4 vaginal intercourses in the last month); desire of long-term contraception with Nexplanon; good understanding of the Italian language.

Exclusion criteria were: evidence of adnexal pathologies; cardiovascular, hepatic or renal impairment; the same contraindications and special warnings or precautions for progestin-only contraceptive use; pregnancy, lactation or abortion in the previous 4 months; known or suspected malignant or premalignant disease; hypersensitivity to any component of the study drug; contraceptive (included intrauterine device) use in the previous 4 weeks.

Forty-six patients satisfied the inclusion criteria and were included in the study after having signed informed consent. For this observational study design a submission of Institutional

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Review Board was not sought, since this was an observational study on a contraceptive device requested by the patients.

Demographic data were collected from all participants. Before inclusion in the study, medical and gynecological history was taken and all subjects underwent a gynecological examination, Pap smear, evaluation of blood pressure, calculation of the BMI and complete hematochemical tests. Nexplanon was inserted between the first and the fifth day from the beginning of the last menstrual cycle. Before implant, and after 3 and 6 months, patients were interviewed by two female medical doctors, who evaluated effects of Nexplanon on QoL using the Italian validated version of the Short Form-36 (SF-36) questionnaire [15] and on sexual activity using the Italian validated version of the Female Sexual Function Index (FSFI) questionnaire [16,17]. The SF-36 questionnaire contains 36 questions grouped into eight categories: physical functioning, physical role functioning, bodily pain, general health, vitality, mental health, social functioning and emotional role functioning [15]. The FSFI questionnaire contains 19 questions grouped into six domains: (i) sexual desire; (ii) sexual excitement; (iii) the need for lubrication; (iv) attainment of orgasm; (v) general sexual satisfaction; and (vi) experience of pain during sex. All questions are formatted using a multiple-choice system. A score of 0–5 is assigned to each response, and a final sexual satisfaction value is derived mathematically, with the ultimate sexual function score ranging from 2 to 36. A lower score indicates poorer sexual function. A score of 26.55 or less indicates a risk of sexual dysfunction [16,17].

Data analyses were performed using the SPSS 15.0 software package (SPSS Inc. Chicago, IL). The level of significance for all tests was set at $p < 0.05$.

Data were evaluated for distribution by Shapiro–Wilks' test and descriptive statistics reported accordingly. Friedman's two-way analysis on ranks test with *post hoc* test by Conover [18] was used to compare questionnaires scores at baseline and at follow-up visits.

Results

Forty-six new implant-users were recruited for the study. Three women refused to insert the implant after enrollment and baseline evaluation, having changed their mind, and five were excluded from the study because during 6 months of treatment the relationship with their partner finished. Five patients maintained the implant for less than 3 months. Consequently, QoL score and SF were examined in 33 patients, those who filled the final follow-up questionnaire.

Baseline demographic characteristics of the patients are reported in Table 1. The SF-36 scores before implant insertion and after 3 and 6 months are presented in Table 2. The implant did not seem to have a significant impact on physical functioning and bodily pain. Physical role functioning and general health scores showed a significant improvement at 3-month follow-up in comparison with baseline; these scores had a further significant improvement at 6-month follow-up both in comparison with baseline and with 3-month follow-up. On the other hand, vitality, mental health, social functioning and emotional role functioning were reduced at 3-month follow-up in comparison to baseline. All these domains returned to the values similar to baseline by 6 months. Social functioning and mental health was significantly higher in comparison with both baseline and 3 months values (Table 2).

Table 3 shows the changes of FSFI scores at the 3rd and 6th months of treatment with respect to baseline values. A significant improvement in general sexual function score was observed at 3-month follow-up ($p < 0.01$). FSFI scores did not significantly improve at 6-month follow-up in comparison with 3-month follow-up. The early global positive effect indeed, was related to improvement at 3 months in arousal, orgasm, satisfaction and pain domains.

Adverse events arose during the first 3 months of treatment: 4 patients (12.1%) reported weight gain; 2 patients (6.0%) reported hot flashes; 6 (18.1%) had hypomenorrhea/amenorrhea, one (3.0%) had menstrual bleeding, and 3 (9.1%) reported menorrhagia, without discontinuation. All subjects reported relief of symptoms at the 6-month follow-up except for 2 (6.0%) patients, who reported further menorrhagia episodes.

Discussion

To our knowledge, this was the first study investigating the effects on a novel, progestin-only contraceptive implant (Nexplanon) on QoL and sexual function of healthy Italian women.

Table 1. Baseline demographic characteristics of the patients.

Age (years)	31.1 ± 7.2
BMI (kg/m^2)	23.3 ± 1.3
Duration of menses (d)	4.9 ± 2.1
Menstrual cycle length (d)	28.4 ± 2.2
Vaginal delivery (*n*)	0 [0–4]
Cesarean section (*n*)	0 [0–4]
Abortion (*n*)	0 [0–3]

Data are given as mean ± SD or median [range], as appropriate.

Table 2. The QoL domains (SF-36 scores) before implant insertion, after 3 and 6 months.

SF-36 Score	Baseline	3 months	6 months
PF	100 [88.78–99.10]	100 [84.13–96.48]	100 [86.73–96.30]
PRF	50 [52.99–74.29]	100 [75.62–91.65]*	100 [85.56–96.25]†,‡
BP	100 [83.88–95.76]	80 [79.62–87.78]	80 [82.49–91.44]
GH	72 [59.05–73.74]	76 [73.08–82.01]†	92 [87.13–93.84]†,¶
VT	70 [62.92–71.93]	45 [36.22–49.54]†	70 [61.12–72.82]
SF	62 [57.77–71.63]	50 [42.72–58.31]	75 [77.95–85.32]†,¶
ERF	100 [59.81–87.40]	33 [26.50–51.86]†	100 [51.21–81.94]¶
MH	64 [61.49–74.02]	52 [36.89–51.42]†	72 [69.40–76.78]*,¶

PF: physical functioning, PRF: physical role functioning, BP: bodily pain, GH: general health, VT: vitality, MH: mental health, SF: social functioning, ERF: emotional role functioning. Data are reported as median [CI, 95%].
*$p < 0.05$ versus baseline.
†$p < 0.01$ versus baseline.
‡$p < 0.05$ versus 3-month follow-up.
¶$p < 0.01$ versus 3-month follow-up.

Table 3. The Female Sexual Function domain (FSFI scores) before implant insertion, after 3 and 6 months.

FSFI score	Baseline	3 months	6 months
Desire	4.8 [4.3–5.0]	4.8 [3.6–6.0]	4.8 [4.5–5.1]
Arousal	5.7 [4.2–5.2]	5.7 [2.7–6.0]*	5.7 [4.8–5.5]
Lubrification	5.4 [4.5–5.2]	5.1 [3.0–5.7]	5.1 [4.3–5.0]
Orgasm	5.6 [4.2–5.0]	5.6 [4.4–6.0]*	5.6 [5.2–5.6]
Satisfaction	4.8 [4.2–5.0]	5.6 [3.6–6.0]†	5.6 [4.8–5.4]†
Pain	5.6 [4.3–5.3]	5.6 [3.6–6.0]†	5.6 [4.9–5.6]
Total	27.8 [25.1–29.5]	31.6 [21.5–34.7]†	31.6 [28.4–31.5]*

Data are reported as median [CI, 95%].
*$p < 0.05$ versus baseline.
†$p < 0.01$ versus baseline.

Our data show that the implant significantly improved general QoL of women, after an early phase in which it reduced some index related to the emotional sphere, as vitality, mental health, social functioning and emotional role functioning. Moreover, our data demonstrated that the implant does not have a negative impact on female sexual function, but have some positive effects.

Mood changes, including nervousness and depression, are commonly mentioned side effects of implants [13,19], although these effects accounted for low rates of removal [19]. QoL scores for each domain were not significantly changed or even significantly improved after 6 months, suggesting that subjects were generally satisfied with the implant; therefore, they continued treatment.

Progesterone seems to have an inhibitory effect on human sexuality: the pre-menstrual progesterone fall is associated with an increase of peri-menstrual desire [20]. Nelson et al. showed that women using injectable progestin as Depot Medroxyprgesterone Acetate (DMPA) reports loss or reduction of libido [21]. Comparable data have been reported by Gezginc on the ENG-implant [22]. On the other hand, and in accordance with our data, Ott et al. [23] and Fortenberry et al. [24] found that sexual interest did not change significantly in DMPA users.

Our data showed an increase in arousal, orgasm and satisfaction domains at 3-month follow-up. This positive effect was probably due to the contraceptive effect that may ensure a more relaxed sexual life, without risk of undesired pregnancies and with a high closeness to the male partner. A significant reduction of pain during sex intercourse at 6 months of follow-up was demonstrated. This effect has also been shown during treatment with combined oral contraceptive (COC) [8]. This data may reflect the positive effect of continued progesterone treatment on dysmenorrhea and dyspareunia [25]. Moreover, the same effect may be responsible of an improvement in physical role functioning and in general health. On the other hand, social functioning and emotional role functioning was significantly reduced in first 3 months of treatment. These indexes have been previously associated with disturbance of vaginal bleeding. Matshumoto et al. have demonstrated that in patients with irregular cycle, the QoL in social relationship was significant improved during treatment with COC [26]. The disturbance of vaginal bleeding patterns is a common adverse events associated with progestin-only contraception. Indeed, it seems to be one the most frequent reason for discontinuing progestin-implant [27–29]. However, acceptability of bleeding patterns is influenced by factors (personal, social or cultural) other than bleeding patterns themselves. A decrease in social relationship QoL score has yet been demonstrated in OC users [30]. The mechanism of the presumed negative effect of hormonal contraception on social relationship is still unclear. Our data, surprisingly, show a restoration of these indexes after 6 months of therapy. Recently, a cross-sectional analysis found that sexually active women of reproductive age who use any form of contraception have greater odds of reporting average or better mental QoL than those who use no contraception [31].

Different motivations for using contraception may result in differential impact on QoL. Our data show that in a healthy Italian population, choosing implant only for long-term contraception, there was no persistent negative effect on emotiveness and on sexual function but significant positive effects on general QoL. Counseling about the choice of contraceptive methods is known to help women make informed choices and to result in longer and more effective contraceptive use [32]. The effect on QoL and on sexual function induced by this new form of contraceptive suggests that the ENG-implant was the favorable choice in healthy women in presence of desire of long-term contraception.

Declaration of interest

All authors disclose no conflicts of interest.

References

1. Etonogestrel implant (Implanon) for contraception. Drug Ther Bull 2001;39:57–9.
2. Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M. Tolerability and clinical safety of Implanon. Eur J Contracept Reprod Health Care 2008;13:29–36.
3. Rosenfield JA, Zahorik PM, Saint W, Murphy G. Women's satisfaction with birth control. J Fam Pract 1993;36:169–73.
4. Oddens BJ. Women's satisfaction with birth control: a population survey of physical and psychological effects of oral contraceptives, intrauterine devices, condoms, natural family planning, and sterilization among 1466 women. Contraception 1999;59:277–86.
5. Schaffir J. Hormonal contraception and sexual desire: a critical review. J Sex Marital Ther 2006;32:305–14.
6. Sanders SA, Graham CA, Bass JL, Bancroft J. A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. Contraception 2001;64:51–8.
7. Davis AR, Castano PM. Oral contraceptives and libido in women. Annu Rev Sex Res 2004;15:297–320.
8. Caruso S, Agnello C, Romano M, et al. Preliminary study on the effect of four-phasic estradiol valerate and dienogest (E2V/DNG) oral contraceptive on the quality of sexual life. J Sex Med 2011;8:2841–50.
9. Guida M, Di Spiezio Sardo A, Bramante S, et al. Effects of two types of hormonal contraception-oral versus intravaginal-on the sexual life of women and their partners. Human Reprod 2005;20:1100–6.
10. Hatcher RA. Contraceptive technology. Vol. 18th rev. ed. New York: Ardent Media; 2004.
11. Anderson-Hunt M, Dennerstein LD, Hatton L, et al. Hormones and female sexuality: developing a method for research. In: Zeidenstein S, Moore K, eds. Learning about sexuality: a practical beginning. New York: The Population Council & The International Women's Health Coalition; 1996:260–77.
12. Brache V, Massai R, Mishell DR, et al. Ovarian function during use of Nestorone subdermal implants. Contraception 2000;61:199–204.
13. Sivin I. Clinical effects of Norplant subdermal implants for contraception. In: Mishell Jr DR, ed. Long-acting steroid contraception. New York: Raven Press; 1983:89–116.
14. Westhoff C, Truman C, Kalmuss D, et al. Depressive symptoms and Norplant contraceptive implants. Contraception 1998;57:241–5.
15. Ware JE, Kosinski M, Gandek BG, et al. The factor structure of the SF-36 Health Survey in 10 countries: results from the International Quality of Life Assessment (IQOLA) project. J Clin Epidemiol 1998;51:1159–65.
16. Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cut off scores. J Sex Marital Ther 2005;31:1–20.
17. Nappi RE, Albani F, Vaccaro P, et al. Use of the Italian translation of the Female Sexual Function Index (FSFI) in routine gynecological practice. Gynecol Endocrinol 2008;24:214–19.
18. Conover WJ. Practical nonparametric statistics. Wiley series in probability and mathematical statistics. New York: Wiley; 1980.
19. Brache V, Faundes A, Alvarez F, Cochon L. Non-menstrual adverse events during use of implantable contraceptives for women: data from clinical trials. Contraception 2002;65:63–74.
20. Graziottin A. Libido: the biologic scenario. Maturitas 2000;34:S9–16.
21. Nelson AL. Counseling issues and management of side effects for women using depot medroxyprogesterone acetate contraception. J Reprod Med 1996;41:391–400.
22. Gezginc K, Balci O, Karatayli R, Colakoglu MC. Contraceptive efficacy and side effects of Implanon. Eur J Contracept Reprod Health Care 2007;12:362–5.
23. Ott MA, Shew ML, Ofner S, et al. The influence of hormonal contraception on mood and sexual interest among adolescents. Arch Sex Behav 2008;37:605–13.
24. Fortenberry JD, Hensel DJ. The association of sexual interest and sexual behaviors among adolescent women: a daily diary perspective. Horm Behav 2011;59:739–44.

25. Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. Contraception 1998;58:99S–107S.
26. Matsumoto Y, Yamabe S, Ideta K, Kawabata M. Impact of use of combined oral contraceptive pill on the quality of life of Japanese women. J Obstet Gynaecol Res 2007;33:529–35.
27. Fan M, Sujuan G. Menstrual bleeding patterns in Chinese women using the Norplant subdermal implant. Hum Reprod 1996; 11:14–19.
28. Grubb GS, Moore D, Anderson NG. Pre-introductory clinical trials of Norplant implants: a comparison of seventeen countries' experience. Contraception 1995;52:287–96.
29. Peralta O, Diaz S, Croxatto H. Subdermal contraceptive implants. J Steroid Biochem Mol Biol 1995;53:223–6.
30. Li RHW, Lo SST, Teh DKG, et al. Impact of common contraceptive methods on quality of life and sexual function in Hong Kong Chinese women. Contraception 2004;70:474–82.
31. Williams SL, Parisi SM, Hess R, Schwarz EB. Associations between recent contraceptive use and quality of life among women. Contraception 2012;85:282–7.
32. Davie JE, Walling MR, Mansour DJ, et al. Impact of patient counseling on acceptance of the levonorgestrel implant contraceptive in the United Kingdom. Clin Ther 1996;18:150–9.

2) Female sexual pain disorders

Genito-pelvic pain/penetration disorder (GPPD) is a new diagnostic category in the DSM-5 that merges the previous diagnosis of vaginismus and dyspareunia into a single sexual pain disorder associated with vaginal penetration.

The estimated prevalence for dyspareunia ranges from 6.5% to 45.0% in older women to 14% to 35% in younger women. Estimates for prevalence of vaginismus are hard to find in the literature. Current available data indicate a prevalence of 7.8% for vulvar pain and 1.0% to 6.0% for vaginismus (Jacques JD, 2010). Exact prevalence estimates are difficult to obtain because of the high variability between studies secondary to discrepancies in classification systems, different definitions, and variable survey methods.

The clinician should look for a variety of possible anatomic and functional causes of GPPD which can be divided into irritative, anatomic, and infectious. Irritative causes include poor lubrication, atrophic vaginitis, vulvar dermatoses, and vulvodynia. Anatomic causes include endometriosis, fibroids, bladder or uterine prolapse, gynecologic malignancy, and scar tissue from previous surgical procedures or episiotomy.

a) Sexual function and Quality of life in endometriosis patients

Endometriosis is a global disease affecting 5–15% of women during their reproductive years. According to main international guidelines, endometriosis should be viewed as a chronic disease that requires a life-long individualized management plan with the aim of avoiding repeated surgical procedures. General principles that should guide medical management of endometriosis are not different from those applicable to other chronic inflammatory disorders (ASRM Practice Committee, 2014).

However, endometriosis is also a disease that affects young, sexually active women during different phases of their sexual life and during development of their sexual behavior. Consequently, sexual health is a major concern for endometriosis patients and should also be a primary concern in endometriosis care and research. It is absolutely necessary to bridge the artificial divide between reproductive and sexual health in endometriosis patients and their partners.

Pain during sexual intercourse is one of the main symptoms among endometriosis patients, and women with endometriosis are at an increased risk of experiencing sexual pain compared with the normal population. The WERF EndoCost study showed that 47% of endometriosis patients suffer from dyspareunia; dysmenorrhea was reported by 57% and chronic pelvic pain by 60% of the women (De Graaff et al., 2013).

It is supposed that the concurrent presence of deep dyspareunia and superficial dyspareunia provoked vesitibulodynia. The presence of these symptoms is also associated with a higher prevalence of depression symptoms (OR 1.07; CI 1.02–1.12) (Yong et al., 2015). Moreover, endometriosis lesions are associated with central and peripheral hyperalgesia caused likely by local neuroinflammation, neuroangiogenesis and dysregulation of sensory and autonomic fibers.

Symptomatic endometriosis negatively affects all domains of female sexual function. The cumulative prevalence of sexual dysfunction, in these patients, using the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale (FSDS), were 32% and 78%, respectively, with a significant correlation between stage of disease. Specifically, compared with the patients with no to mild pelvic pain, those with moderate-to- severe pelvic pain had a 3.4-fold (CI 1.3–8.8) higher risk of sexual dysfunction. Patients with endometriosis stage III or IV had a 4.4-fold (CI 1.3–15.5) higher risk than those with stage I or II (Jia et al., 2013).

Sexual pain in endometriosis patients induces a fear-avoidance reaction, leading to arousal/desire disorder and sexual distress in the majority of patients. Biopsychosocial variables of sexual pain play a critical role in the fear-avoidance model. Senses of incertitude, fear, expectations and guilt are often reported in qualitative studies. Similarly, personality traits, coping strategies (catastrophizing) and the occurrence of mood/anxiety disorders are crucial in the evolution from coital pain to sexual dysfunction and distress. The partner's perception of sexual pain and the sociocultural context in which sexual pain and fertility concerns are experienced may exacerbate sexual distress, lack of arousal/desire and avoidance. As result, decreased lubrification and loss of genital congestion (also worsened by pharmacological hypogonadism) heighten pelvic floor tone, risk of vaginismus and pain. Central sensitization caused by chronic pelvic pain leads to hyperalgesia and allodynia, worsening dyspareunia in a circular model. Hallmarks of endometriosis, such as delay of diagnosis and worsening and recurrence of pain, exacerbate dyspareunia and dysfunctional behavior, prolonging the distress (Pluchino N, 2016).

Currently, hormonal contraceptives, progestins, danazol, GnRH agonists and antagonists and aromatase inhibitors are used in clinical settings for the medical management of endometriosis-associated pain and for secondary prevention.

Although they reduce or counteract the effects of estrogens on endometriosis growth and inflammation, endogenous and exogenous sex steroids interact with nociceptive processes at multiple levels of the peripheral and central nervous system. Pharmacological hypogonadism and hormonal therapy affect brain areas involved in sexual response (desire, arousal, libido), in emotional and behavioral changes (mood, anxiety, fear) as well as in peripheral genital response to sexual stimuli (Martin VT, 2009).

All combined oral contraceptives (COC) and progestins are effective in relieving pelvic pain and deep dyspareunia in endometriosis patients in several studies. Progestins are increasingly and successfully employed as treatment for endometriosis and their use can be safely suggested in many women with contraindications to estrogens as well as in those who do not tolerate estrogens.

We investigated (Sansone A, 2017) the effects of Nexplanon®, a single-rod etonogestrel (ENG)—containing contraceptive implant (or Implanon NXT® in other countries; MSD, Milan, Italy)—contraceptive on QoL, sexual function, and pelvic pain in women affected by endometrioma-like ovarian cysts.

In our study, we confirm the favorable effects of ENG implants to counteract pelvic pain and improve QoL and sexual function in women with suspected endometriosis by ultrasound without surgical indication. Indeed, we found a significant reduction in VAS score of dysmenorrhea and dyspareunia, a significant improvement of several domains of QoL and of pain, desire, and satisfaction domains, and FSFI total score during the 12 months of therapy.

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Effects of etonogestrel implant on quality of life, sexual function, and pelvic pain in women suffering from endometriosis: results from a multicenter, prospective, observational study

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Abstract

Purpose Progestins are successfully employed as treatment for endometriosis. Our study evaluates the effects of the etonogestrel (ENG) implant on pelvic pain, quality of life, and sexual function in women requiring long-term reversible contraception and presenting ovarian cysts of probable endometriotic origin.

Methods We enrolled 25 women asking for contraception with the ENG implant and presenting a cyst with the ultrasound features of an endometrioma and pain symptoms. Patients were interviewed on pain symptoms (dysmenorrhea, dyspareunia, dyschezia, and dysuria) using a VAS score (0–10), on quality of life (QoL) using the Short Form-36 questionnaire, and on sexual activity using the Female Sexual Function Index (FSFI) questionnaire before inserting the implant (T0) and after 6 (T1) and 12 months (T2).

Results We found a significant decrease in dysmenorrhea and dyspareunia VAS scores comparing baseline scores to 6 and 12 months. After 12 months, the bodily pain, general health, vitality, social functioning, and mental health domains of the QoL score were significantly improved. The total FSFI score results increased in comparison with baseline both at 6 and 12 months. In particular, we highlighted a significant improvement in desire, satisfaction, and pain domains already at 6 months; the arousal domain improved only after 12 months. Finally, mean diameters of endometrioma-like cysts were not changed after 12 months of treatment.

Conclusions Etonogestrel implants seem to be able to reduce pelvic pain, improve sexual function, and quality of life in patients with ovarian cysts suspected of endometriotic origin.

Keywords Endometriosis · Etonogestrel implant · Pelvic pain · Quality of life · Contraception

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Introduction

Endometriosis is a chronic estrogen-dependent gynecological disease characterized by the presence of endometrial glands and stroma outside the uterus; it occurs in 6–10% of women in their reproductive age, and up to 50% of infertile women [1]. Although alternate interesting hypotheses have been suggested [2], the etiology of endometriosis still remains controversial: immune, hormonal, genetic, and epigenetic factors may be all involved, and several theories have been proposed to explain it [3, 4]. In this regard, accumulating evidence suggests that once the endometriotic foci are established, a breakdown in the peritoneal homeostasis occurs: on one hand, peripheral mononuclear cells secrete inflammatory cytokines in early phases as well as angiogenic and fibrogenic cytokines in

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the late stages of the disease [5, 6] and on the other hand, immune-mediated scavenging systems fail to attack and remove endometriotic cells which, consequently, escape from the immune surveillance, implant, and proliferate [7].

Chronic pelvic pain (CPP) represents one of the main important symptoms of endometriosis. Its management includes both surgical and medical treatments. On one hand, surgery can remove endometriotic lesions at the moment of the direct pelvic visualization; since it cannot affect the pathogenic mechanisms of endometriosis, it is unable to "cure" the disease; and this may account for the high incidence of postoperative recurrence of symptoms and lesions [8], supporting the hypothesis that endometriotic lesions may re-form even after radical excision. On the other hand, pharmacologic approach aims to suppress ovulation and menstruation through hormonal treatments. Nevertheless, hormonal treatments for endometriosis-associated pain have several limitations to be taken into account: first of all, these treatments should be administered in continuous regimen and for long period (or at least until pregnancy desire ensues). In addition, most of the available therapeutic options are burdened by considerable systemic side effects [e.g., decrease in bone mineral density (BMD), climacteric complaints, and weight gain], which affect compliance and preclude long-term use [9]. However, when side effects or poor tolerability requires the termination of the treatment, pain frequently recurs and lesions could reappear.

According to the available evidence and the guidelines of the European Society of Human Reproduction and Embryology (ESHRE) [10], there are no major differences in terms of efficacy between various hormonal regimens. In particular, a consensus exists on the indication of estro-progestins and progestins as the first-line medical treatment option [11–13] for the management of pelvic pain, even in case of suspected endometriosis [10].

Progestins are increasingly and successfully employed as treatment for endometriosis and their use can be safely suggested in many women with contraindications to estrogens [14] as well as in those who do not tolerate estrogens. Nexplanon®, a single-rod etonogestrel (ENG)—containing contraceptive implant (or Implanon NXT® in other countries; MSD, Milan, Italy)—provides an alternative way of delivering progestogens [15]. After subdermal application, contraceptive action is achieved mainly by inhibition of ovulation for at least 3 years. As a positive side effect, this long-term progestogen delivery system has been shown to improve dysmenorrhea [16]. Among the previous published studies on the effects of ENG subdermal implant in patients affected by endometriosis, Yisa et al. [17] described a favorable effect on pelvic pain in five patients; others reported comparable average decrease in pelvic pain after the treatment with ENG implant or alternatively with medroxyprogesterone acetate [18]. Nevertheless, these studies were limited in sample size and did not allow to draw firm conclusion about the topic.

Based on this scenario, the aim of our multicenter observational prospective study was to evaluate the effect of the ENG implant on pelvic pain, quality of life, and sexual function in women requiring long-term reversible contraception and presenting ovarian cysts with ultrasound characteristics of endometriomas.

Materials and methods

We screened a population of 256 women asking for long-term reversible contraception with ENG implant, from July 2016 to November 2016, at the Contraception Clinic of the Department of Obstetrics and Gynecology at the "Federico II" University (Naples, Italy) at the University of Salerno (Salerno, Italy) or at the University of Catanzaro (Catanzaro, Italy). Among the screened population, we included women affected by one single ovarian cyst (monolateral) with characteristic of endometrioma at transvaginal ultrasound (TVUS), with mean diameter >15 and ≤ 30 mm; presence of dysmenorrhea, dyspareunia, or CPP; ineligibility or patient refusal for surgery or other hormonal treatment; age between 18 and 45 years; body mass index (BMI) >20 and ≤ 25 kg/m^2; active sexual life (≥ 4 vaginal intercourses in the last month); and good understanding of the Italian language. We excluded patients with evidence of other adnexal pathologies or suspicion of deep pelvic endometriosis or endometrioma with mean diameter >30 mm at TVUS; cardiovascular, hepatic, or renal impairment; contraindications and special warnings or precautions for progestin-only contraceptive use; pregnancy, lactation, or abortion in the previous 4 months; known or suspected malignant or premalignant disease; known hypersensitivity to any component of the ENG implant; and contraceptive (included intrauterine device) use in the previous 4 weeks.

Considering that the size of endometrioma-like cysts was below the guideline-based indication for surgery (30 mm) [10, 19], the patients' desire to avoid surgery and undergo long-term reversible contraception, and the indication of hormonal treatments even for suspected cases of endometriosis-associated pelvic pain [10], we decided to use ENG implants as the best available therapeutic approach.

The study design is in accordance with the Helsinki Declaration, conforms the Committee on Publication Ethics (COPE) guidelines (http://publicationethics.org/), and was approved by the Institutional Review Boards (IRB) of the "Federico II" University (protocol no: 181/16). All the patients enrolled in this study were well informed regarding the procedures that they underwent and signed a consent form allowing data collection for research purposes. All the

design, analysis, interpretation of data, drafting, and revisions followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [20], available through the Enhancing the Quality and Transparency of Health Research (EQUATOR) network (http://www.equatornetwork.org/).

The ENG implant was inserted between the first and fifth days of the menstrual cycle. We record gynecological history and clinical data before at the study start (T0) and at 6 (T1) and 12 month (T2) follow-up. During these events, patients underwent gynecological/pelvic examination, evaluation of blood pressure, BMI calculation, and TVUS. In addition, investigators interviewed patients on pain symptoms (dysmenorrhea, dyspareunia, dyschezia, and dysuria) using a VAS score (0–10), on quality of life (QoL) using the Italian validated version of the Short Form-36 (SF-36) questionnaire [25], and on sexual activity using the Italian validated version of the Female Sexual Function Index questionnaire (FSFI) [22].

The SF-36 questionnaire contains 36 questions grouped into 8 categories: physical functioning, physical role functioning, bodily pain, general health, vitality, mental health, social functioning, and emotional role functioning. Women were instructed to place a mark on a 0–100 scale for each item that best corresponded to their feelings, from the lowest to highest scores of a given category of the QoL questionnaire. Thereafter, the sum of all items of each category was performed. Mean values were calculated on the basis of individual items within a given category. Consequently, eight scale scores were obtained, with higher scores indicating better functioning [21]. The FSFI questionnaire contains 19 questions grouped into six domains: (1) sexual desire; (2) sexual excitement; (3) need for lubrication; (4) orgasm achievement; (5) general sexual satisfaction; and (6) pain during sex. All questions are formatted using a multiple-choice system. A score of 0–5 is assigned to each response, and a final sexual satisfaction value is derived mathematically, with the ultimate sexual function score ranging from 2 to 36. A lower score indicates poorer sexual function. A score of 26.55 or less indicates a risk of sexual dysfunction [22].

Patients were asked to record every day on a diary the occurrence of any bleeding or spotting. According to World Health Organization (WHO)-recommended definition, the unfavorable pattern defines the "frequent bleeding" (more than five bleeding–spotting episodes in a 90-day reference period) and "prolonged bleeding" (any bleeding–spotting episode uninterrupted lasting more than 14 days in the 90-day reference period) [23].

Data analyses were performed using the SPSS 22.0 software package (SPSS Inc. Chicago, IL, USA). The level of significance for all tests was set at $p < 0.05$. Data were evaluated for distribution using Shapiro–Wilks' test and descriptive statistics were reported accordingly. Wilcoxon test was used to compare questionnaires scores and ANOVA followed by Scheffe's post hoc analysis was used to compare VAS scores and endometrioma size at baseline and at the 6th and 12th month follow-up.

Results

Among the screened population, 25 women met the inclusion/exclusion criteria, signed informed consent and were enrolled in the study. Two women were excluded from the study, because they requested implant removal before the 6th month due to irregular bleeding. Therefore, 16 women completed the study period (7 women were lost to follow-up). Mean age and BMI of the study group were 31.06 ± 6.32 years and 22.25 ± 3.73 kg/m^2, respectively. As shown in Table 1, we found a significant decrease in dysmenorrhea and dyspareunia VAS scores comparing baseline to 6 and 12 months; nevertheless, while dysmenorrhea score was significantly lower at 12 than at 6 months, we could find significant differences between 12- and 6-month follow-up for dyspareunia.

Regarding QoL score, after 6 months, we found a significant improvement only in the social functioning domain; conversely, after 12 months, the improvement was significant also for bodily pain, general health, vitality, social functioning, and mental health (Table 2).

As shown in Table 3, total FSFI score resulted significantly increased in comparison with baseline both at 6 and 12 months. In particular, we found a significant improvement in desire, satisfaction, and pain domains, while lubrication and orgasm did not change significantly. The arousal domain improved only after 12 months.

Finally, after 6 and 12 months, mean diameters of endometriomas were not significantly changed compared to the baseline TVUS scans [26.19 ± 2.64 mm (baseline) vs. 26.07 ± 0.88 mm (T1) vs. 26.05 ± 0.87 mm (T2)].

No relevant adverse effects were reported during the study period. Middle adverse events arose during the first 3 months of treatment: 2 patients (12.5%) reported weight

Table 1 VAS score before implant insertion (baseline) and after 6 and 12 months

	Baseline	6 months	12 months
Dysmenorrhea	6.07 ± 0.88	4.94 ± 1.21**	4.50 ± 1.03**,#
Dyspareunia	1.61 ± 2.02	1.03 ± 1.48*	1.04 ± 1.38*
Dyschezia	0.63 ± 1.46	0.58 ± 1.38	0.58 ± 1.38
Dysuria	0.0	0.0	0.0

Data are expressed as mean ± standard deviations

*$p < 0.05$ vs. baseline, **$p < 0.01$ vs. baseline, #$p < 0.05$ vs. 6 months

Table 2 SF-36 scores before implant insertion (baseline) and after 6 and 12 months

SF-36 score	Baseline	6 months	12 months
PF	100.00 (80.85–97.27)	97.50 (83.06–96.32)	97.00 (84.50–96.50)
PRF	100.00 (66.60–102.77)	100.00 (75.33–102.79)	100.00 (75.87–103.00)
BP	80.00 (66.72–92.03)	100.00 (71.35–98.02)	100.00*,# (75.56–98.19)
GH	58.50 (46.47–74.53)	56.00 (43.45–71.17)	57.50*,# (45.31–73.32)
VT	57.50 (47.71–66.67)	57.50 (49.02–67.86)	59.00*,# (50.51–69.24)
SF	93.50 (79.16–95.47)	93.50* (82.07–95.81)	94.50*,# (83.59–96.16)
ERF	100.00 (67.05–103.70)	100.00 (77.84–105.41)	100.00 (78.04–105.31)
MH	65.00 (52.69–71.06)	67.00 (55.46–74.04)	68.00*,# (57.10–76.03)

Data are expressed as median (CI, 95%)

PF physical functioning, *PRF* physical role functioning, BP bodily pain, *GH* general health, *VT* vitality, *SF* social functioning, *ERF* emotional role functioning, *MH* mental health

*$p < 0.05$ vs. baseline, #$p < 0.05$ vs. 6 months

Table 3 Female Sexual Function domain (FSFI scores) before implant insertion (baseline) and after 6 and 12 months

Domain	Baseline	6 months	12 months
Desire	3.90 (3.51–4.44)	4.50* (3.87–4.91)	4.60* (4.04–4.94)
Arousal	4.05 (3.58–4.48)	4.20 (3.65–4.60)	4.30*,# (3.81–4.82)
Lubrication	4.35 (3.87–4.72)	4.50 (3.89–4.81)	4.65 (3.91–4.80)
Orgasm	3.60 (3.41–4.67)	4.20 (3.49–4.71)	4.40 (3.63–4.92)
Satisfaction	3.80 (3.44–4.41)	4.20* (3.63–4.67)	4.40* (3.78–4.77)
Pain	4.00 (3.57 –4.48)	4.40* (3.82–4.87)	4.40* (3.92–4.73)
Total FSFI score	24.00 (21.58–26.89)	25.35* (22.57–28.36)	26.25* (23.39–28.68)

Data are expressed as median (CI, 95%)

*$p < 0.05$ vs. baseline, **$p < 0.05$ vs. 6 months

gain and 1 patient (6.2%) reported hot flashes, both were not due to discontinuation of treatment. Nevertheless, an unfavorable pattern of menstrual profile was reported by 18.8% ($n = 3/18$) of initially enrolled women and, as previously reported, two of them had the implant removed and were excluded from the statistical analysis.

Discussion

Endometriosis represents a clinical and surgical challenge, considering that therapeutic strategy should be modulated and tailored on patient's characteristics. According to recent treatment cornerstones [10, 19], surgical approach should be recommended for endometriomas larger than 30 mm; conversely, in case of endometriomas smaller than 30 mm, pharmacological treatments could be a feasible option.

Progestins have been used in the treatment of pelvic pain in patients affected by endometriosis for more than 50 years. They have been reported to reduce or eliminate pain in approximately 90% of the patients [24]. For example, norethisterone acetate (NETA) has been shown effective in reducing CPP in women with confirmed endometriosis by laparoscopy [25]. In addition, the efficacy and safety of depot medroxyprogesterone acetate 104 mg/0.65 mL were compared with leuprolide acetate in two phase 3, multicenter, randomized, evaluator-blinded, comparator-controlled clinical trials [26, 27], showing a significant reduction in endometriosis-associated symptoms and signs (dysmenorrhea, dyspareunia, pelvic pain, and pelvic tenderness) after 6 months of treatment. More recently, dienogest (DNG) has been found to be effective in controlling endometriosis-related pelvic pain in several randomized controlled trials [28, 29]. According to recent evidence [30], NETA and DNG have shown similar effects on pain relief, psychological status, sexual functioning, and health-related QoL. In recent years, the use of the levonorgestrel-releasing intrauterine device (IUD-LNG) in women with endometriosis has been shown to provide a significant reduction of dysmenorrhea, pelvic pain, and deep dyspareunia in patients with recto-vaginal endometriosis, comparable to the effect achieved by gonadotropin-releasing hormone (GnRH) analogues [31]. Ylänen et al. [32] first proposed the use of a subdermal progestin (nestorone) implant for the treatment of pain in patients suffering from endometriosis, demonstrating a significant reduction of VAS score 81% of enrolled population.

Nexplanon®, the ENG implant, is an effective progestin-only contraceptive [33]. Ovulation inhibition constitutes its main contraceptive effect [34] and is quickly achieved after insertion, lasting for at least 3 years [32]. The ENG released by the implant might affect the lesions both directly, through progesterone receptors in the endometriotic lesions, and indirectly, suppressing the hypothalamus–pituitary–ovarian axis and thus reducing the estrogenic stimulus to the lesions [35]. Indeed, the use of the ENG implant generally leads to an inactive or weakly proliferative eutopic endometrium [34]. Moreover, different authors reported that the endometrial thickness on ultrasound scans does not usually exceed 4–5 mm during the treatment [15, 36]. Despite follicle growth and estrogen synthesis regularly occur under ENG implant, estrogen levels are similar to those of the early proliferative phase and do not show the increase which usually precedes ovulation [34].

In this study, we investigated the effects of ENG implants on quality of life, sexual function, and pelvic pain in women affected by endometrioma-like ovarian cysts, to provide robust data and add a piece of evidence to the topic. In full agreement with the previous analyses [17, 18], we confirm the favorable effects of ENG implants to counteract pelvic pain and improve quality of life and sexual function in women with suspected endometriosis by ultrasound without surgical indication. Indeed, we found a significant reduction in VAS score of dysmenorrhea and dyspareunia, a significant improvement of several domains of QoL and of pain, desire, and satisfaction domains, and FSFI total score during the 12 months of therapy. As corollary result, we did not find any significant change in the mean diameter of endometrioma-like cysts after the treatment. Interestingly, we did not observe any severe adverse event during the study. The irregularities of the menstrual profile and the compliance in our cohort are comparable to those observed in the previous studies [23, 37].

Several limitations of our study should be taken into account for data interpretation: first of all, we enrolled a relatively small sample size, although comparable with the other previous published studies; second, our cohort consists of patients with endometrioma-like ovarian cysts without surgical indication (< 30 mm in major diameter) [10, 19]. According to the ESHRE guidelines [10], hormonal treatment is recommended for pelvic pain even in case of suspected endometriosis; nevertheless, in this study, we could not rely on histological confirmation of endometriosis, since patients did not fall within surgical indication; third, we should take into account that the type of ovarian cyst could be misdiagnosed, although TVUS has been shown to have high sensitivity and specificity for endometriomas [38]; fourth, it was not possible to blind patients and investigators to study outcomes; and fifth, the study design was based on a single arm (no controls with placebo or other drugs), comparing patients at different times of follow-up.

Based on this scenario, we take the opportunity to solicit future randomized controlled trials on large population, to verify our preliminary results.

Author contributions AS: manuscript writing. NR: data collection. PG: manuscript writing. MG: data collection. ASL: manuscript editing. CC: project supervision.

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Compliance with ethical standards

Conflict of interest The authors have no proprietary, financial, professional, or other personal interest of any nature in any product, service, or company.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Vercellini P, Viganò P, Somigliana E, Fedele L (2014) Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 10:261–275. https://doi.org/10.1038/nrendo.2013.255
2. Nisolle M, Donnez J (1997) Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril 68:585–596. https://doi.org/10.1016/S0015-0282(97)00191-X
3. Laganà AS, Vitale SG, Salmeri FM et al (2017) Unus pro omnibus, omnes pro uno: a novel, evidence-based, unifying theory for the pathogenesis of endometriosis. Med Hypotheses. https://doi.org/10.1016/j.mehy.2017.03.032
4. Maniglio P, Ricciardi E, Laganà AS et al (2016) Epigenetic modifications of primordial reproductive tract: a common etiologic pathway for Mayer–Rokitansky–Kuster–Hauser Syndrome and endometriosis? Med Hypotheses. https://doi.org/10.1016/j.mehy.2016.02.015
5. Rakhila H, Al-Akoum M, Bergeron ME et al (2016) Promotion of angiogenesis and proliferation cytokines patterns in peritoneal fluid from women with endometriosis. J Reprod Immunol 116:1–6. https://doi.org/10.1016/j.jri.2016.01.005
6. Vetvicka V, Laganà AS, Salmeri FM et al (2016) Regulation of apoptotic pathways during endometriosis: from the molecular basis to the future perspectives. Arch Gynecol Obstet. https://doi.org/10.1007/s00404-016-4195-6
7. Laganà AS, Triolo O, Salmeri FM et al (2016) Natural Killer T cell subsets in eutopic and ectopic endometrium: a fresh look to a busy corner. Arch Gynecol Obstet. https://doi.org/10.1007/s00404-015-4004-7
8. Koga K, Takamura M, Fujii T, Osuga Y (2015) Prevention of the recurrence of symptom and lesions after conservative surgery for endometriosis. Fertil Steril 104:793–801. https://doi.org/10.1016/j.fertnstert.2015.08.026

9. Crosignani PG, Olive D, Bergqvist A, Luciano A (2006) Advances in the management of endometriosis: an update for clinicians. Hum Reprod Update 12:179–189. https://doi.org/10.1093/humupd/dmi049
10. Dunselman GAJ, Vermeulen N, Becker C et al (2014) ESHRE guideline: management of women with endometriosis. Hum Reprod 29:400–412. https://doi.org/10.1093/humrep/det457
11. Olive DL, Pritts EA (2002) The treatment of endometriosis: a review of the evidence. Ann N Y Acad Sci 955:360–372
12. Vercellini P, Fedele L, Pietropaolo G et al (2003) Progestogens for endometriosis: forward to the past. Hum Reprod Update 9:387–396. https://doi.org/10.1093/humupd/dmg030
13. Vercellini P, Crosignani P, Somigliana E et al (2011) 'Waiting for Godot: a commonsense approach to the medical treatment of endometriosis. Hum Reprod 26:3–13. https://doi.org/10.1093/humrep/deq302
14. Berlanda N, Somigliana E, Viganò P, Vercellini P (2016) Safety of medical treatments for endometriosis. Expert Opin Drug Saf 15:21–30. https://doi.org/10.1517/14740338.2016.1121991
15. Mäkäräinen L, Van Beek A, Tuomivaara L et al (1998) Ovarian function during the use of a single contraceptive implant: implanon compared with Norplant. Fertil Steril 69:714–721. https://doi.org/10.1016/S0015-0282(98)00015-6
16. Blumenthal PD, Gemzell-Danielsson K, Marintcheva-Petrova M (2008) Tolerability and clinical safety of Implanon®. Eur J Contracept Reprod Heal Care 13:29–36. https://doi.org/10.1080/13625180801960012
17. Yisa SB, Okenwa AA, Husemeyer RP (2005) Treatment of pelvic endometriosis with etonogestrel subdermal implant (Implanon®). J Fam Plan Reprod Heal Care 31:67–70. https://doi.org/10.1783/0000000052972799
18. Walch K, Unfried G, Huber J et al (2009) Implanon® versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis—a pilot study. Contraception 79:29–34. https://doi.org/10.1016/j.contraception.2008.07.017
19. Royal College of Obstetricians and Gynaecologist (2006) Endometriosis, investigation and management. RCOG Green- top Guideline No. 24
20. von Elm E, Altman DG, Egger M et al (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61:344–349. https://doi.org/10.1016/j.jclinepi.2007.11.008
21. Ware JE Jr, Kosinski M, Gandek B et al (1998) The factor structure of the SF-36 Health Survey in 10 countries: results from the IQOLA Project. International Quality of Life Assessment. J Clin Epidemiol 51:1159–1165
22. Nappi RE, Albani F, Vaccaro P et al (2008) Use of the Italian translation of the Female Sexual Function Index (FSFI) in routine gynecological practice. Gynecol Endocrinol 24:214–219. https://doi.org/10.1080/09513590801925596
23. Di Carlo C, Guida M, De Rosa N et al (2015) Bleeding profile in users of an etonogestrel sub-dermal implant: effects of anthropometric variables. An observational uncontrolled preliminary study in Italian population. Gynecol Endocrinol 31:491–494. https://doi.org/10.3109/09513590.2015.1018163
24. Gezer A, Oral E (2015) Progestin therapy in endometriosis. Women's Heal 11:643–652. https://doi.org/10.2217/whe.15.42
25. Vercellini P, Pietropaolo G, De Giorgi O et al (2005) Treatment of symptomatic rectovaginal endometriosis with an estrogen-progestogen combination versus low-dose norethindrone acetate. Fertil Steril 84:1375–1387. https://doi.org/10.1016/j.fertnstert.2005.03.083
26. Schlaff WD, Carson SA, Luciano A et al (2006) Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain. Fertil Steril 85:314–325. https://doi.org/10.1016/j.fertnstert.2005.07.1315
27. Crosignani PG, Luciano A, Ray A, Bergqvist A (2006) Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. Hum Reprod 21:248–256. https://doi.org/10.1093/humrep/dei290
28. Strowitzki T, Faustmann T, Gerlinger C, Seitz C (2010) Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study. Eur J Obstet Gynecol Reprod Biol 151:193–198. https://doi.org/10.1016/j.ejogrb.2010.04.002
29. Harada T, Momoeda M, Taketani Y et al (2009) Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis-a randomized, double-blind, multicenter, controlled trial. Fertil Steril 91:675–681. https://doi.org/10.1016/j.fertnstert.2007.12.080
30. Vercellini P, Bracco B, Mosconi P et al (2016) Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril 105:734–743e3. https://doi.org/10.1016/j.fertnstert.2015.11.016
31. Bayoglu Tekin Y, Dilbaz B, Altinbas SK, Dilbaz S (2011) Postoperative medical treatment of chronic pelvic pain related to severe endometriosis: levonorgestrel-releasing intrauterine system versus gonadotropin-releasing hormone analogue. Fertil Steril 95:492–496. https://doi.org/10.1016/j.fertnstert.2010.08.042
32. Ylänen K, Laatikainen T, Lähteenmäki P, Moo-Young AJ (2003) Subdermal progestin implant (Nestorone®) in the treatment of endometriosis: clinical response to various doses. Acta Obstet Gynecol Scand 82:167–172. https://doi.org/10.1034/j.1600-0412.2003.00054.x
33. Wenzl R, Van Beek A, Schnabel P, Huber J (1998) Pharmacokinetics of etonogestrel released from the contraceptive implant Implanon®. Contraception 58:283–288. https://doi.org/10.1016/S0010-7824(98)00110-3
34. Meckstroth KR, Darney PD (2001) Implant contraception. Semin Reprod Med 19:339–354. https://doi.org/10.1055/s-2001-18642
35. Varma R, Mascarenhas L (2001) Endometrial effects of etonogestrel (Implanon) contraceptive implant. Curr Opin Obstet Gynecol 13:335–341. https://doi.org/10.1097/00001703-200106000-00015
36. Van Den Bosch T, Donders GGG, Riphagen I et al (2002) Ultrasonographic features of the endometrium and the ovaries in women on etonogestrel implant. Ultrasound Obstet Gynecol 20:377–380. https://doi.org/10.1046/j.1469-0705.2002.00816.x
37. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS (2008) The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Heal Care 13:13–28. https://doi.org/10.1080/13625180801959931
38. Bazot M, Daraï E, Biau DJ et al (2011) Learning curve of transvaginal ultrasound for the diagnosis of endometriomas assessed by the cumulative summation test (LC-CUSUM). Fertil Steril 95:301–303. https://doi.org/10.1016/j.fertnstert.2010.08.033

b) Sexual function and quality of life in gynecological cancer patients

According to WHO-International Agency for Research on Cancer, gynecologic and female cancers (including corpus uteri, cervix, ovary and breast) have shown in 2008 a world incidence rate of 72.5/100,000 women per year. Corpus uteri cancer is the first most common gynecologic cancer in developed countries (22.7/100,000 women), followed by ovarian (15.7/100,000 women) and cervical cancer (12.1/100,000 women). Breast cancer is the female cancer with highest incidence in developed countries (109.5/100,000 women) (Ferlay J., 2010).

Advances within the field of gynecologic oncology have induced higher rates of long-term survival. Moreover, early diagnosis of these cancers has enormously contributed to successful surgical and/or medical treatment in young-adult women. For all these reasons insights into cancer surveillance and containment of treatment side effects are becoming of greatest relevance. Survivors of gynecologic cancer are a heterogeneous group of women, with the most common of them diagnosed with endometrial cancer. The treatments are also heterogeneous—radiation and chemotherapy are often administered, either before or after an extensive surgical procedure, and either alone or in combination. Although our ability to effectively treat gynecologic cancers has improved, the sequelae of treatment often results in profound issues that affect the patient's QoL, lifestyle behavior (LB) and employment experience (EE). QoL and LB are particularly impaired by gynecologic cancers, given their impact on the overall patient's sexuality, body image and childbearing potential, with their consequent induction of severe emotional distress, anxiety, and behavioral disruptions.

Several studies have compared QoL of gynecologic cancer patients with healthy controls and family caregivers (Awadalla AW, 2007; Özaras G, 2010).

Controversial data exist in literature about the gynecologic cancer impact on QoL (Hawighorst-Knapstein S, 2004). Younger-age has been reported to negatively affect QoL domains in cervical cancer patients and positively affect QoL domains in endometrial and ovarian cancer (Capelli G, 2002). Moreover, it has been related with more severe side effects of chemotherapy and poorer emotional well-being in ovarian patient. On the contrary, older-age has been negatively related to physical and cognitive scores in gynecological cancer patients and to all QoL domains, except for emotional well-being, in breast cancer survivors (Nordin AJ, 2000). However, a relevant role of age on QoL scores has been questioned (Greimel E, 2002). Many relevant factors may interfere with QoL: stage and site of cancer, treatment modality, time since cancer treatment and comorbidity may interfere differently with QoL domains in different stage of life.

The need of a healthy lifestyle has been reported among cancer survivors. Very limited data are present in literature about life-style behavior in gynecological cancer patients in different life stages (Demark-Wahnefried W, 2009). An elevated rate of current smokers among younger cervical cancer survivors has been reported (McTiernan A, 2010). Weight gain has been shown in endometrial, ovarian and breast cancer survivors (Lasser K, 2000); differences in different life stage were not studied. Job loss is a possible consequence of gynecological cancer diagnoses (Spelten ER, 2002). Results about association of employment status and age in cancer patients are mixed and not specific for gynecologic cancer patients, reporting no or negative association. However, women have shown twice the risk of un-employment of men (Carlsen K, 2008).

In recent years, a study has been carried out in our department aimed at assessing the QoL, work experience and lifestyle in patients suffering from gynecological tumors (Bifulco G., De Rosa N., 2012). Out of a total of 286 patients, it was found that age significantly affects these parameters. In younger women, aged between 18 and 45, more important interference from cancer with family life and social activities and a greater impact on perception of health

has been observed. Young women have been most affected by fatigue, constipation, gastrointestinal symptoms, lymphoedema, poor perception of body image and sexual function. Cancer diagnosis also had an important negative impact on the work of younger patients.

In conclusion, we demonstrate that Younger patients need psychosocial support, more than midlife adults, to avoid negative social and employment experience and to overcome body changes following cancer treatment. Emotional and functional well-being increase over the first year following treatment, even in the absence of corresponding increase in physical well-being, suggesting adaptation to residual physical limitation. Midlife adults seem to maintain an adaptive level of well-being after cancer diagnosis and treatment greater than younger patients.

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Quality of life, lifestyle behavior and employment experience: A comparison between young and midlife survivors of gynecology early stage cancers

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ABSTRACT

Goals. To evaluate differences and changes in quality of life (QoL), lifestyle behavior and employment experience of young in comparison to midlife adults in response to early stage gynecologic cancer diagnoses.

Methods. 263 patients, divided into two age groups (Group A: ≤45 and Group B: >45 years), were interviewed on their QoL, lifestyle behavior (dietary habits, tobacco and alcohol use, physical activity) and employment experience (employment status and working time) at diagnosis and within 4 years from the treatment. The QoL was evaluated by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and its specific modules for each cancer type (in particular endometrium, cervix, ovarian and breast).

Results. Global health status was significantly different between the two groups. In the younger age group a more relevant cancer interference on family life and social activities and a greater impact on perception of health status have been observed. Young women were more affected by fatigue, constipation, gastrointestinal symptoms, lymphedema, poor body image and impaired sexuality.
Cancer diagnosis had a major negative impact on employment of younger patients.
Conversely, younger patients had overall better health behavior. They reported a higher daily intake of fruits and vegetables, along with lower alcohol consumption, furthermore they were a little more physically active than midlife adults.

Conclusions. To enhance quality of life and to promote healthy lifestyle behavior of female cancer patients, particularly in younger age, it is essential to assure multidisciplinary approaches with specific medical intervention and psychosocial supports. Indeed, midlife adults seem to have a more rapid adaptive tendency to return towards levels of well-being, following cancer diagnosis and treatment, than younger patients.

Introduction

Cancer diagnosis and invasive surgical and medical (chemotherapy and/or radiotherapy) treatments deeply impacts quality of life (QoL), lifestyle behavior (LB) and employment experience (EE) of patients. QoL and LB are particularly impaired by gynecologic cancers, given their impact on the overall patient's sexuality, body image and childbearing potential, with their consequent induction of severe emotional distress, anxiety, and behavioral disruptions.

According to WHO-International Agency for Research on Cancer, gynecologic and female cancers (including corpus uteri, cervix, ovary and breast) have shown in 2008 a world incidence rate of 72.5/100,000 women per year. Corpus uteri cancer is the first most common gynecologic cancer in developed countries (22.7/100,000 women), followed by ovarian (15.7/100,000 women) and cervical cancer (12.1/100,000 women). Breast cancer is the female cancer with highest incidence in developed countries (109.5/100,000 women) [1].

Advances within the field of gynecologic oncology have induced higher rates of long-term survival. Moreover, early diagnosis of these cancers has enormously contributed to successful surgical and/or medical treatment in young-adult women. For all these reasons insights into cancer surveillance and containment of treatment side effects are becoming of greatest relevance. Evaluation of QoL, LB and EE in these patients will provide useful information on after-treatment outcomes and needs.

Several studies have compared QoL of gynecologic cancer patients with healthy controls and family caregivers [2,3].

Controversial data exist in literature about the gynecologic cancer impact on QoL [4,5]. Younger-age has been reported to negatively affect QoL domains in cervical cancer patients and positively affect QoL domains in endometrial and ovarian cancer [6]. Moreover, it has been

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related with more severe side effects of chemotherapy and poorer emotional well being in ovarian patient [7]. On the contrary, older-age has been negatively related to physical and cognitive scores in gynecological cancer patients [8,9] and to all QoL domains, except for emotional well being, in breast cancer survivors [10]. However, a relevant role of age on QoL scores has been questioned [11]. Many relevant factors may interfere with QoL: stage and site of cancer, treatment modality, time since cancer treatment and comorbidity may interfere differently with QoL domains in different stage of life.

The need of a healthy lifestyle has been reported among cancer survivors [12]. Very limited data are present in literature about lifestyle behavior in gynecological cancer patients in different life stages [13–15]. An elevated rate of current smokers among younger cervical cancer survivors has been reported [16]. Weight gain has been shown in endometrial, ovarian and breast cancer survivors [17]; differences in different life stage were not studied. Job loss is a possible consequence of gynecological cancer diagnoses [18]. Results about association of employment status and age in cancer patients are mixed and not specific for gynecologic cancer patients, reporting no or negative association [19]. However, women have shown twice the risk of unemployment of men [20].

The aim of this study was to evaluate age-related differences and changes in QoL, LB and EE of gynecologic cancer survivors in a specific homogenous Southern-Italy population. To clarify these issues may be relevant for establishing and providing more personalized follow up programs to cancer patients, taking in account the increase number of young-adult survivors patients, the prolonged lifetime after cancer treatment and the unhealthy habits of cancer population.

Material and methods

286 eligible patients, referred to the follow-up program at the Unit of Gynecology Oncology of University Federico II of Naples, were interviewed by two medical doctors from 2006 to 2010. All patients gave their written consent to be enrolled.

To be eligible for enrollment, patients had to meet all of the following criteria: age between 18 and 65 years; previous diagnosis of stage I–II gynecologic (in particular uterine, cervical or ovarian) or breast cancer; 1–4 year interval from cancer treatment; stable clinical conditions and good comprehension of the questions, verified by the interviewers.

Patients were divided into two age groups: Group A (young adults, between the ages of 18–45 years) and Group B (midlife adults, between the ages of 46–65 years).

Demographic data were collected from all participants. Education level (EL) was divided between high school or less and college or more. Employment status (ES) had three levels (employed, homemaker/unemployed and retired) and changes in employment status, after cancer treatment, were identified as increase/decrease in working hours, as well as start/stop working.

Self reported information was obtained on tobacco and alcohol use, dietary habits and physical activity.

Smoking behavior (SB) was measured and articulated in "current" (>100 lifetime cigarettes and current use), "former" (>100 lifetime cigarettes and not current use) and "never" (<100 lifetime cigarettes) smokers. Changes in SB after cancer treatment were also evaluated.

Alcohol use (AU) was measured and four categories were chosen "abstainer" (<12 lifetime drinks), "current light/moderate or heavy" consumers (1–2, 3–4 or>4 drinks in the last week, respectively). Changes in AU after cancer treatment were also evaluated.

Dietary habits (DH) were evaluated considering the difference between patients body mass index (BMI) at last visit and the BMI at diagnosis (Δ BMI), number of servings of fruits and vegetables (F&V) consumed per day or week and self-control of their body weight following a balanced diet. Changes in DH after cancer treatment were evaluated.

Physical activity (PhA) was measured considering its frequency per year. PhA was considered "adequate" when consistently performed during the year and "insufficient" when occasionally performed. Patients who reported no participation in any physical activities (such as running, gardening or walking) in the last months were considered "physical inactive".

Medical data (including diagnosis, stage of cancer, type of treatment, time since the end of treatment, BMI at diagnosis and at last visit and physical and/or psychiatric comorbidities) were extracted from medical records.

Given that patients enrolled in the study had a cancer diagnosis between 2006 and 2010, in order to make uniform cancer staging classification, all histological diagnoses performed before 2009 were converted according to the last revised FIGO staging of cervical and endometrial cancer [21].

The QoL was measured by The European Organization for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire C30 (QLQ-C30), a 30-items cancer specific questionnaire for assessing the general QoL of Cancer patients [22]. The EORTC-QLQ-C30 incorporates five functioning domains: physical (PF2), role (RF2), cognitive (CF), emotional (EF), and social (SF); three symptom scales: fatigue (FA), pain (PA), and nausea/vomiting (NV); several single items which assess additional symptoms commonly reported by cancer patients: dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), and diarrhea (DI); the perceived financial impact of the disease and treatment (FI), and finally an overall QoL scale (QL2). Validated modules specific to tumor site (endometrial EN-24, cervical CX-24, ovarian OV-28 and breast BR-23 modules) were administered in addition to the core questionnaire [23–27]. These modules include 23–28 cancer-specific items consisting of multi-item scales on symptom experiences after cancer treatment, body image and sexual and/or vaginal functioning, along with single-item scales evaluating lymphedema, menopausal/urological/gastrointestinal/breast symptoms, peripheral neuropathy, muscular pain, taste change, hair loss, sexual worry and future prospective.

The EORTC QLQ-C30 and single modules were scored using the algorithm provided by the EORTC [22]. All scores were transformed to a 0–100 scale according to the guidelines for the scale to which they belong. In the scales that measured function, high score indicates a good function. In symptom scales and single items measuring symptoms, higher score indicates more severe symptoms. EORTC-specific modules have been designed for patients with specific-site cancers, to evaluate symptoms related to surgical and medical therapy for each specific cancer.

A modified grouping among specific items of the 4 modules has been developed to compare them between age groups. Items of each module have been grouped according to their comparability and seventeen scales were obtained. Four scales whose items were available both in EN-24, CX-24, OV-28 and BR-23: Symptom Experience (SE) (grouping pain in back and pelvis — ENBP, symptom experience — CXSE, chemotherapy side effects — OV-CMSE, and systemic side effects — BRST); Body Image (BI); Sexual Activity (SXA) and Sexual Enjoyment (SXE). Three scales whose items were available for 3 cancer type modules: Sexual vaginal functioning (SXV) (grouping SXV of EN-24, CX-24 and OV-28); Peripheral neuropathy (PN) (grouping Tingling/numbness of EN-24 — ENTN and PN of CX-24 and OV-28) and Hair Loss (HL) (grouping HL of EN-24, OV-28 and BR-23). Seven scales whose items were available for 2 cancer type modules: Sexual interest (SXI) (grouping SXI of EN-24 and OV-28); Lymphedema (LY) (grouping LY of EN-24 and CX-24); Future Prospective (FU) (grouping attitude to disease/treatment of OV-28 — OVADT and FU of BR-23); Gastrointestinal symptoms (GI) (grouping GI of EN-24 and OV-28); Muscular pain (MP) (grouping MP of EN-24 and Arm Symptoms of BR-23 — BRAS); Taste Change (TC)

Table 1
Disease characteristics of the two study groups.

	Group A [a] N = 106	Group B [b] N = 157	p value
Time since diagnosis (months)	32.73 ± 11.86	34.11 ± 13.77	0.11
Cancer site			0.0001*
Uterus	30 (28.3)	96 (61.1)	
Ovary	30 (28.3)	20 (12.7)	
Cervix	20 (18.9)	20 (12.7)	
Breast	26 (24.5)	21 (13.4)	
Stage			0.08
I	92 (86.8)	122 (77.1)	
II	14 (13.2)	33 (22.3)	
Treatment modality [c]			0.09
S	79 (74.5)	108 (68.8)	
S + RT	7 (6.6)	19 (12.1)	
S + CT	5 (4.7)	10 (6.4)	
S + HT	6 (5.6)	4 (2.5)	
S + CT + RT	5 (4.7)	15 (9.5)	
S + CT + HT	4 (3.8)	1 (0.6)	
Physical comorbidity			0.15
Yes	22 (20.8)	46 (29.3)	
No	84 (79.2)	111 (70.7)	
Psychiatric comorbidity			0.70
Yes	2 (1.9)	5 (3.2)	
No	104 (98.1)	152 (96.8)	

Data are reported as number (percentage rate) or means ± standard deviation.
* Statistically significant.
[a] Group A: young adulthood, between 18 and 45 years.
[b] Group B: midlife adulthood, between 46 and 65 years.
[c] S: surgical treatment, RT: radiotherapy, CT: chemotherapy, HT: hormonal therapy.

(grouping TC of EN-24 and OV-28) and Menopausal Symptoms (M) (grouping Hormonal of CX-24 — CXH and M of OV-28). Three scales whose items were available only for individual cancer type modules: Sexual worry (SW) of CX-24; Urological symptoms (UR) of EN-24 and Breast Symptoms (BS) of BR-23.

Statistical analysis

Data analyses were performed using the SPSS 15.0 software package (SPSS Inc. Chicago, IL, USA). The level of significance for all tests was set at $p<0.05$. Data were evaluated for distribution by Shapiro Wilks' test. For data with a normal distribution, Student's *t* test for unpaired data was used to examine differences in demographics and disease characteristics, in health behavior and in QoL between the two study groups. For those parameters, which did not present a normal distribution, comparison of variables was performed using Mann–Whitney test. Categorical variables were compared with the χ^2- or Fisher's test.

We estimated the mean value of each scale by age class and tumor site using linear regression models with the QoL scales' value as the dependent variable and age class, tumor site, time since diagnosis (<24 and ≥24 months), tumors stage (I and ≥II) and presence of comorbidities as independent variables. In the case of BMI variations, we adjusted also for initial BMI. All the models with the marginal predicted values for the groups and 95% confidence intervals (95% CI) were estimated using STATA 11.0.

Results

Patients

Two hundred and sixty-tree women gave their written informed consent and were judged, by the interviewers, able to comprehend the questionnaire.

Patients of Group A (N = 106) and of Group B (N = 157) showed, respectively, a mean age of 42.8 ± 2.2 (mean ± SD) years and of 55.7 ± 3.5 years. The interview was conducted after 32.7 ± 11.9 and 34.11 ± 13.8 months from cancer treatment for group A and B, respectively (Table 1).

Disease characteristics of the two study groups are reported in Table 1. A significant imbalance in cancer site was present in Group B patients, because of high number of endometrial cancer. However these differences are compatible with the age distribution of gynecologic cancer, with high incidence of endometrial cancer among women aged >45 years [1].

Quality of life

Quality of life scores are reported in Table 2 as univariate and in Table 3 as multivariate analysis.

The global health status has shown a slight imbalance between the two age groups. With respect to functional scales, a significant difference between the two groups has been detected in role, emotional and social functioning. On the other hand, not significant differences in physical and in cognitive functioning have been observed. Regarding symptoms scales, no differences were detected in nausea/vomiting, pain, dyspnea, insomnia, appetite loss, diarrhea and financial difficulties. The perception of more severe symptoms in group A patient have been observed in terms of fatigue, constipation,

Table 2
Means and SD of the EORTC QLQ-C30 subscale and specific modules: differences between young and midlife adults.

	Group A[a] N = 106	Group B[b] N = 157	p value
Global health status/QoL (QL2)	70.68 ± 16.99	72.82 ± 23.15	0.05*
Functional scales			
Physical functioning(PF2)	84.72 ± 13.04	78.34 ± 21.70	0.20
Role functioning (RF2)	86.64 ± 19.03	79.41 ± 25.33	0.02*
Emotional functioning (EF)	64.47 ± 21.15	69.21 ± 25.97	0.03*
Cognitive functioning (CF)	80.35 ± 21.68	78.77 ± 25.22	0.87
Social functioning (SF)	84.28 ± 22.75	93.42 ± 15.76	0.0001*
Symptom scales			
Fatigue (FA)	31.55 ± 18.35	29.23 ± 25.04	0.03*
Nausea and vomiting (NV)	4.72 ± 10.48	5.31 ± 11.48	0.87
Pain (PA)	17.30 ± 20.95	22.72 ± 27.81	0.50
Dyspnea (DY)	17.30 ± 22.17	12.10 ± 18.16	0.07
Insomnia (SL)	28.30 ± 31.47	38.00 ± 30.54	0.10
Appetite loss (AP)	6.29 ± 16.66	7.43 ± 18.33	0.67
Constipation (CO)	31.45 ± 30.11	22.93 ± 29.92	0.01*
Diarrhea (DI)	4.71 ± 11.67	8.49 ± 18.84	0.20
Financial difficulties (FI)	14.15 ± 26.41	11.89 ± 24.75	0.36
Specific Modules [c]			
Functional scale			
Sexual interest (SXI)	67.05 ± 33.0	70.07 ± 33.7	0.78
Sexual activity (SXA)	65.41 ± 28.8	81.62 ± 21.0	0.0001*
Sexual Enjoyment (SXE)	68.06 ± 25.6	51.11 ± 24.1	0.0001*
Symptom scale			
Lymphedema (LY)	46.67 ± 32.7	33.33 ± 23.7	0.035*
Urological symptoms (UR)	23.61 ± 26.5	18.23 ± 16.0	0.87
Future Prospective (FU/ADT)	56.00 ± 18.0	59.62 ± 33.3	0.14
Gastrointestinal symptoms (GI)	27.31 ± 14.4	9.77 ± 13.1	0.001*
Body image (BI)	47.98 ± 39.2	33.39 ± 41.1	0.009*
Sexual vaginal functioning (SV/SXV)	53.89 ± 25.0	29.68 ± 30.9	0.001*
Sexual Worry (SW)	50.00 ± 51.3	41.67 ± 44.4	0.47
Symptom experience (SE/BP/CTSE/CMSE)	30.90 ± 26.9	22.94 ± 23.3	0.007*
Peripheral neuropathy (PN/TN)	25.00 ± 20.5	31.37 ± 24.6	0.10
Breast symptoms (BS)	16.35 ± 14.0	15.87 ± 17.1	0.42
Muscular pain (MP/AS)	47.62 ± 30.8	36.94 ± 27.3	0.11
Hair loss (HL)	8.84 ± 25.7	3.84 ± 10.0	0.59
Taste change (TC)	0.0 ± 0	2.874 ± 13.6	0.97
Menopausal symptoms (H/M)	35.19 ± 20.2	18.12 ± 26.7	0.0001*

Data are reported as means ± standard deviation (SD).
* Statistically significant.
[a] Group A: young adulthood, between 18 and 45 years.
[b] Group B: midlife adulthood, between 46 and 65 years.
[c] To compare specific items-scales between age-groups items of each module have been grouped according to their comparability.

lymphedema, gastrointestinal symptoms, sexual vaginal functioning, symptom experience and menopausal symptoms ($p<0.05$). Specific modules showed higher sexual activity ($p<0.0001$) in midlife adult than in young women, who have higher sexual enjoyment ($p<0.0001$) but a poorer body image (<0.01).

Differences in the QoL domains between the two age groups are mostly conserved also when a multivariate analysis was performed, except for global health status, as well as fatigue and menopausal symptoms within the symptoms scales. Conversely, the multivariate analysis identified further differences according to age in physical and cognitive functioning, as well as in nausea and vomiting, insomnia, peripheral neuropathy, muscular pain and urological symptoms.

Global health status, on the other hand, showed a significant difference according to site of cancer, when adjusted for age class, time since diagnosis (<24 and ≥ 24 months), tumors stage (I and $\geq$II) and presence of comorbidities. Indeed, breast cancer had a negative impact on global health status and on physical, role and cognitive levels compared to endometrial, cervical and ovarian cancers. On the contrary cervical cancer patients showed higher emotional and social functioning scores.

At multivariate analysis also site of disease appeared to be a relevant factor for symptoms scores. Breast cancer patients showed a higher perception of fatigue and hair loss, cervical and breast cancer patient showed a higher score of pain and dyspnea along with a poorer body image, but a lower symptom experience. Endometrial cancer patients had overall lower level in symptoms scale, particularly for nausea and vomiting, insomnia and peripheral neuropathy. Furthermore breast cancer negatively affected sexual activity and sexual enjoyment compared to other cancers (Table 3).

Health behavior

No significant differences have been detected in SB between the two groups. However, a significant difference in SB changes after cancer diagnosis and treatment was detected ($p<0.0001$). Particularly, although most participants of both groups did not change SB, older patients more frequently changed their smoking habits; in Group B, indeed, 10% and 6% of patients reported decreasing or stopping to smoke, respectively, while only 3% of patients declared an increase in number of cigarettes smoked. In Group A, instead, 5% of patients stopped to smoke while 5% started to smoke (Table 4).

For AU, younger-adults (Group A) less likely than older one (Group B) were current (light/moderate or heavy) drinkers. A higher rate of patients of group A reported to be abstainer (Group A: 71% vs Group B: 47%; $p<0.001$) (Table 4).

With respect of PhA, no significant differences were observed between the two groups. Only a small number of patients referred an adequate PhA with a not significant increase in Group A (Group A: 18.9% and Group B: 9.6%). Although in both groups cancer diagnosis and treatment did not significantly influence PhA, greater number of patients of group B referred to start PhA after cancer treatment (Group A: 0% vs Group B: 7%, $p<0.005$). Reduced PhA was reported in 14% of patients in Group A and 7% in Group B, while an increased activity was referred by 9.4% in Group A and 4.5% in Group B ($p<0.005$) (Table 5).

Δ BMI has shown a significant difference between groups (Group A: 1.04 ± 1.7 vs Group B: -0.26 ± 3.4; $p<0.0001$). F&V consumption was higher in Group B than in group A ($p<0.005$). In contrast, no significant differences have been shown between the frequency of patients who followed a balanced diet. After cancer diagnosis and treatment no significant change in F&V consumption was detected between groups. However, young-adult women have been more influenced than older one in positive diet changes after cancer diagnosis and treatment; 20% of women of group A, indeed, reported to start a balanced diet after cancer diagnosis and treatment while 17.2% of women of group B declared to stop to follow a balance diet ($p<0.0001$) (Table 5).

Employment experience

No significant difference in education level was present between the two groups, which instead showed a significant difference in ES. Among employed patients, more patients of group A had a full-time work than patients of group B ($p<0.001$). Disease impact on ES changes differ significantly between groups, a greater number of Group A patients stopped working or reduced working-time after cancer treatment ($p<0.0001$) (Table 5).

Discussion

The results of this study reveal that younger age, in gynecological and breast cancer survivors, has a negative impact on emotional and social QoL domains and is related to a worst symptoms perception. Between other relevant factors (including site and stage of cancer, time since diagnosis and comorbidities) only cancer site seems to significantly affect QoL domains. Indeed, cancer site shows an important impact on symptoms perception.

Younger patients show a healthier lifestyle, except for smoking habits but they experienced higher weight gain in contrast with older patients. On the contrary, age seems to not correlate with change in lifestyle behavior after cancer diagnosis. Employment experience was deeply affected by cancer diagnosis particularly in young patients.

The major role of surveillance is to detect cancer recurrence and to impact survival outcomes. On the other hand, follow up visits represent the best opportunity for patients' counseling on benefits and pitfalls of disease monitoring and for evaluating the psychosocial impact of diagnosis, treatment and surveillance programs [12]. In addition to recurrence and side effects of treatments, cancer survivors, in comparison to age- and race-matched general population, are at greater risk for developing physical and psychosocial decline, second malignancies, cardiovascular disease, diabetes and osteoporosis [12]. Post-treatment follow-up visits may represent a “teachable moment” in which patients should be instructed on the advantages of adoption and maintenance of healthy behaviors along with avoidance of unhealthy habits to reduce adverse health consequences and improve QoL [12,27,28].

QoL of gynecologic cancer patients is significantly lower than healthy controls [3]. Global QoL, emotional and role functioning remains low throughout the course of disease up to 1 year after treatment in female cancer patients [11].

In this study, global health status of midlife adult has shown a slightly significant increase compared to young patients. Site of cancer seems to be a relevant impact factor on global QoL. Capelli et al. reported poorer QoL scores for younger patients affected by cervical cancer, along with a negative age correlation with QoL in ovarian and endometrial cancer [6], conversely no significant role for age in QoL recovery neither for breast cancer nor gynecologic cancer was reported by Greimel et al. [11]. Our data, showed that global health status was lower in cervical and in breast cancer patients when compared to other gynecological malignancy.

Lai et al. showed that sexual activity deteriorates with age [5]; Hawighorst-Knapstein et al., instead, found that sexual problems were related to treatment modality without correlation with age [4]. No significant impact on QoL and sexual function has been reported for adjuvant vaginal radiotherapy [29]. In our study, young patients were found to have a worst sexual activity (SXA) than midlife adults; they suffered much more from poor body image (BI), perceived worse sexual vaginal functioning (SXV) and more severe menopausal (M) symptoms, probably in relationship with rapid

body changes following surgical menopause. Sexual activity and enjoyment was particularly low in breast cancer patient.

Lifestyle behaviors are greatly impacted by cancer diagnosis and treatment. Current literature reports that ~70% of cancer survivors are overweight or obese [27]. Cancer patients tend to gain weight after cancer diagnosis [10,30]. Additional weight gain after cancer treatment has been found to reduce QoL and exacerbate risk for functional decline, comorbidity and perhaps even cancer recurrence and cancer-related death [31–34]. Existing evidence shows that women tend to gain weight after breast cancer diagnosis and treatment [16]. A significant gain in weight amounting to 2–3 kg after diagnosis of breast cancer was found by Yaw et al. [35]. Few data are present in literature about weight gain in endometrial and ovarian cancer patients; no data exists regarding cervical cancer patients. Increased recurrence risk and decreased survival with weight gain have been shown in breast cancer patients [36–38], while the association between weight gain and endometrial or ovarian cancer prognoses has not yet been well established [16].

In our study, cancer diagnosis, independently by the cancer site and stage as well as time since diagnosis and comorbidities, had a worst impact on body weight in younger patients than in midlife-adults, in which body weight has resulted approximately stable. Despite this, or maybe due to that, younger patients choose to start a balanced diet after cancer diagnosis, unlike midlife adults who, more often, did not change or even stopped to control their own body weight following a balanced diet.

Young patients had overall better health behavior. They showed higher F&V and lower alcohol consumption, along with a modest higher physical activity than midlife adults. However, young patients, current smokers at diagnosis as midlife adults, did not change their smoking habit after cancer diagnosis and treatment, in contrast with midlife adults.

Cancer survivors are more likely to be current smokers than the healthy population [10,39]. A high prevalence of smokers has been found in gynecologic cancer patients [15,40] and smoking rate has been shown higher in younger age group [14,15] and justified with their higher mental health instability [17,39]. Our data, instead, has showed a similar smoking rate between the two groups, who had very modest presence of psychiatric comorbidity (Table 1).

Modest or not statistically significant difference in alcohol or F&V consumption has been observed between cancer and non-

Table 3
Means and 95% CI of QLQ-C30 subscale and specific modules: multivariate analysis.

	Age						Cancer site												
	Group A[a]			Group B[b]			Uterus			Ovary			Cervix			Breast			
	N = 106			N = 157			N = 126			N = 50			N = 40			N = 47			R-squared
	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI		
Global health status/QoL (QL2)	71.0	66.9	75.2	72.6	69.2	76.0	74.2	70.2	78.1	71.9	66.0	77.9	72.8	65.8	79.8	65.4	58.9	71.9	0.1
Functional scales																			
Physical functioning(PF2)	85.6	82.1	89.1	77.8	75.0	80.6	85.3	82.0	88.6	82.5	77.5	87.5	79.9	74.0	85.7	68.4	62.9	73.8	0.2
Role functioning (RF2)	88.5	84.0	93.0	78.2	74.5	81.8	87.7	83.4	91.9	81.2	74.7	87.6	81.9	74.3	89.4	69.7	62.7	76.7	0.1
Emotional functioning (EF)	63.3	58.6	68.1	70.0	66.2	73.8	66.7	62.2	71.2	63.8	57.1	70.6	76.5	68.5	84.5	64.8	57.4	72.1	0.1
Cognitive functioning (CF)	82.1	77.5	86.7	77.6	73.9	81.3	84.2	79.8	88.6	86.4	79.8	92.9	71.4	63.6	79.2	66.0	58.8	73.1	0.1
Social functioning (SF)	83.0	79.4	86.6	94.3	91.3	97.2	88.9	85.4	92.3	92.9	87.7	98.1	95.0	88.9	100.0	84.2	78.5	89.8	0.2
Symptom scales																			
Fatigue (FA)	31.2	26.9	35.4	29.5	26.1	32.9	26.0	22.0	30.0	29.7	23.6	35.7	33.3	26.2	40.5	39.2	32.6	45.8	0.2
Nausea and vomiting (NV)	3.9	1.8	6.0	5.9	4.2	7.6	2.1	0.1	4.2	6.1	3.1	9.2	9.4	5.9	13.0	8.1	4.8	11.4	0.1
Pain (PA)	18.2	13.5	22.9	22.1	18.3	25.9	18.6	14.1	23.0	14.2	7.5	20.9	25.4	17.5	33.3	28.4	21.1	35.7	0.2
Dyspnea (DY)	14.4	10.6	18.1	14.1	11.0	17.1	6.6	3.0	10.2	14.6	9.2	20.0	20.2	13.9	26.6	29.0	23.1	34.9	0.1
Insomnia (SL)	23.7	18.0	29.4	41.1	36.5	45.7	22.5	17.0	27.9	49.2	41.1	57.4	38.1	28.5	47.7	45.8	36.9	54.6	0.2
Appetite loss (AP)	6.9	3.6	10.1	7.0	4.4	9.7	6.2	3.1	9.3	3.6	0.0	8.2	17.1	11.5	22.6	4.1	0.0	9.2	0.2
Constipation (CO)	33.6	27.8	39.3	21.5	16.8	26.2	28.2	22.7	33.7	22.1	13.8	30.3	23.7	14.0	33.5	28.3	19.3	37.3	0.1
Diarrhea (DI)	5.7	2.6	8.9	7.8	5.3	10.4	9.1	6.0	12.1	4.3	0.0	8.9	0.0	0.0	5.0	10.4	5.4	15.3	0.1
Financial difficulties (FI)	14.4	9.5	19.2	11.7	7.8	15.7	10.2	5.5	14.8	20.6	13.6	27.6	18.5	10.3	26.7	6.7	0.0	14.3	0.1
Specific Modules [c]																			
Functional scale																			
Sexual interest (SXI)	79.0	73.7	84.3	82.1	78.4	85.8	82.4	78.8	85.9	77.8	72.0	83.6	–			–			0.3
Sexual activity (SXA)	71.5	66.8	76.2	66.6	62.8	70.4	82.3	77.9	86.8	76.2	69.4	82.9	76.4	68.5	84.4	16.9	9.5	24.2	0.5
Sexual Enjoyment (SXE)	72.3	67.2	77.5	45.7	39.7	51.6	69.1	63.7	74.5	48.3	40.2	56.4	61.2	50.4	72.0	47.5	36.3	58.7	0.2
Symptom scale																			
Lymphedema (LY)	54.7	47.6	61.9	29.7	25.1	34.2	40.5	36.0	45.0	–			28.6	19.5	37.6	–			0.3
Urological symptoms (UR)	24.4	18.0	30.8	18.0	14.4	21.5	19.5	16.4	22.6	–			–			–			0.2
Future Prospective (FU/ADT)	57.0	50.6	63.4	58.3	50.7	65.9	–			50.0	42.7	57.3	–			65.5	58.0	73.1	0.2
Gastrointestinal symptoms (GI)	28.4	24.9	31.8	9.2	6.8	11.7	16.1	13.8	18.4	14.9	11.1	18.7	–			–			0.3
Body image (BI)	42.7	37.8	47.6	37.0	33.0	40.9	18.0	13.3	22.6	16.4	9.4	23.4	79.4	71.2	87.6	86.5	78.9	94.1	0.7
Sexual vaginal functioning (SV/SXV)	46.8	42.0	51.6	35.9	31.4	40.3	24.3	20.2	28.4	65.4	59.4	71.5	65.8	56.1	75.5	–			0.6
Sexual Worry (SW)	54.4	7.4	101.5	37.2	−9.8	84.3	–			–			45.8	32.9	58.8	–			0.0
Symptom experience (SE/BP/CTSE/CMSE)	35.7	31.1	40.4	19.7	15.9	23.4	35.6	31.2	40.0	24.7	18.1	31.4	14.6	6.8	22.5	12.0	4.8	19.3	0.2
Peripheral neuropathy (PN/TN)	22.7	17.9	27.5	32.7	29.1	36.3	21.3	17.5	25.0	36.8	31.0	42.6	43.7	35.9	51.6	–			0.3
Breast symptoms (BS)	15.8	9.5	22.1	16.6	9.5	23.7	–			–			–			16.1	11.6	20.6	0.0
Muscular pain (MP/AS)	51.3	43.8	58.8	35.2	30.1	40.3	45.1	39.9	50.2	–			–			27.9	18.7	37.2	0.1
Hair loss (HL)	5.5	2.5	8.6	5.9	3.5	8.2	0.1	0.0	2.5	0.0	0.0	2.1	–			59.6	51.7	67.6	0.5
Taste change (TC)	0.9	0.0	3.8	2.4	0.4	4.4	2.6	0.6	4.5	0.2	0.0	3.4	–			–			0.1
Menopausal symptoms (H/M)	31.1	22.7	39.4	25.5	16.5	34.5	–			27.6	19.4	35.9	29.6	19.0	40.1	–			0.1

QoL multivariate analysis using age class, tumor site, time since diagnosis (<24 and ≥24 months), tumors stage (I and ≥II) and presence of comorbidities as independent variables.

[a] Group A: young adulthood, between 18 and 45 years.

[b] Group B: midlife adulthood, between 46 and 65 years.

[c] To compare specific items-scales between age-groups items of each module have been grouped according to their comparability.

Table 4
Health behavior characteristics of patients: differences between young and midlife adults.

	Group A [a]	Group B [b]	p value
	N = 106	N = 157	
Smoking behavior (SB)			0.95
Current smokers	36 (34.0)	56 (35.7)	
Former smokers	25 (23.6)	35 (22.3)	
Never smokers	45 (42.5)	66 (42.0)	
Changes in SB after cancer treatment			0.0001*
No	96 (90.6)	126 (80.3)	
Reduction	0 (0)	16 (10.2)	
Increase	0 (0)	5 (3.2)	
Stop	5 (4.7)	10 (6.4)	
Start	5 (4.7)	0 (0)	
Alcohol use (AU)			0.001*
Abstainer	76 (71.7)	75 (47.7)	
Former	0 (0)	0 (0)	
Current			
Light	15 (14.2)	41 (26.1)	
Moderate	10 (9.4)	11 (7.0)	
Heavy	5 (4.7)	30 (19.1)	
Changes in AU after cancer treatment			0.02*
No	91 (85.8)	142 (90.4)	
Reduction	5 (4.7)	0 (0)	
Increase	0 (0)	0 (0)	
Stop	10 (9.4)	15 (9.6)	
Start	0 (0)	0 (0)	
Physical activities (PhA)			0.06
Adequate	20 (18.9)	15 (9.6)	
Insufficient	45 (42.5)	66 (42.9)	
Physical inactive	41 (38.7)	76 (48.4)	
Changes in PhA after cancer treatment			0.004*
No	81 (76.4)	128 (81.5)	
Reduction	15 (14.1)	11 (7.0)	
Increase	10 (9.4)	7 (4.5)	
Stop	0 (0)	0 (0)	
Start	0 (0)	11 (7.0)	
Dietary habits (DH)			
Δ BMI (actual BMI − at diagnosis BMI) [c]	0.96 [0.42–1.50]	−0.20 [−0.64–0.23]	
F&V consumption in a day/week [d]			0.003*
Never	6 (5.7)	0 (0)	
1–2 in a week	5 (4.7)	5 (3.2)	
3–4 in a week	5 (4.7)	10 (6.4)	
1–2 in a day	30 (28.3)	71 (45.2)	
3–4 in a day	60 (56.6)	71 (45.2)	
Followed a balanced diet			0.32
Yes	50 (47.2)	62 (39.5)	
No	56 (52.8)	95 (60.5)	
Changes in DH after cancer treatment			
F&V consumption in a day/week[d]			0.07
No	91 (85.8)	132 (84.1)	
Reduction	0 (0)	0 (0)	
Increase	15 (14.2)	25 (15.9)	
Stop	0 (0)	0 (0)	
Start	0 (0)	0 (0)	
Followed a balanced diet			0.0001*
No	78 (73.6)	126 (80.3)	
Reduction	0 (0)	0 (0)	
Increase	0 (0)	0 (0)	
Stop	6 (5.7)	27 (17.2)	
Start	22 (20.8)	4 (2.5)	

Data are reported as number (percentage rate) or means ± standard deviation.
* Statistically significant.
[a] Group A: young adulthood, between 18 and 45 years.
[b] Group B: midlife adulthood, between 46 and 65 years.
[c] BMI: body mass index. Data reported as mean [CI 95%] and adjusted for age class, tumor site, time since diagnosis (<24 and ≥24 months), tumors stage (I and ≥II) and presence of comorbidities.
[d] F&V: fruit and vegetable.

cancer population [14,39]. Cancer survivors are less likely than non-cancer controls to be current drinkers and more likely to be former drinkers [15]. In our study, midlife adults were more often alcohol light/heavy consumers and less likely changed their habit after cancer diagnosis.

Table 5
Employment status and experience: differences between young and midlife adults.

	Group A [a]	Group B [b]	p value
	N = 106	N = 157	
Education levels			0.43
High school or less	72 (67.9)	99 (63.1)	
College or more	34 (32.1)	58 (36.9)	
Employment status (ES)			0.0001*
Homemaker/Unemployed	41 (38.7)	71 (45.2)	
Employed	50 (47.2)	35 (22.3)	
Retired	15 (14.1)	51 (32.5)	
Working time in employed patients			0.001*
Full-time	34 (68.0)	11 (31.4)	
Part-time	16 (32.0)	24 (68.6)	
Changes in ES after cancer treatment			0.0001*
No	56 (52.8)	132 (84.1)	
Reduction	30 (28.3)	15 (9.5)	
Increase	0 (0)	0 (0)	
Stop	15 (14.2)	10 (6.4)	
Start	5 (4.7)	0 (0)	

Data are reported as number (percentage rate).
* Statistically significant.
[a] Group A: young adulthood, between 18 and 45 years.
[b] Group B: midlife adulthood, between 46 and 65 years.

Contrasting data have been published on changes in F&V consumption after cancer diagnosis [13,41,42]. In our study no changes were observed after cancer diagnosis in both groups, accordingly with Gruenigen et al. [42] and in contrast with Patterson et al. [13], who found that 40.4% of cancer patients (breast, prostate and colorectal cancer) made dietary changes and that this happened less likely in older patients.

On the basis of the data reported above, it is not possible to state that age deeply impacts on adoption of a new lifestyle in response to a diagnosis of cancer, in particular for dietary habits and physical activities. A slightly significant difference was observed between young and midlife adults on changing smoking and alcohol habits: while young patients decided to stop or reduce alcohol consumption, midlife adults decided to stop or reduce cigarette smoking.

Cancer diagnosis and treatment influence employment experience. A recent meta-analysis has shown that cancer survivors are 1.4 times more likely to be unemployed than healthy controls [3]. An increased risk for unemployment was identified for survivors of breast and gynecologic cancer [43]; these patients were less likely to have returned to work than other cancer patients [44]. Job loss, due to illness or imposition, was a real risk after gynecologic cancer diagnosis [45]. On the contrary, women with breast cancer did not retire because of their disease earlier than women without cancer; moreover the decision to change jobs was not imposed but chosen [46]. Patients who returned to work were most likely young and out of active treatment [44]. However the age effects on return to work is highly heterogeneous [18,43,44].

Our data shows that midlife-adults are more often unemployed/homemaker or retired than young-adults and that employed midlife adults work part-time in a higher rate of cases. Such observation is in agreement with the literature reporting a negative association between increasing age and return to work [19,47,63]. In contrast, cancer diagnosis and treatment affects more employment experience of younger patients; in a higher rate of cases, in fact, they chose to retire or to reduce working time.

Physical limitation, cancer-related symptoms, stage, time since diagnosis and socioeconomic factors are main reasons for unemployment or retirement [18,44,48]. In this study, the two groups did not differ significantly in respect to time since diagnosis, stage, treatment modality, physical or psychiatric comorbidity and educational level. Moreover, the cancer disease did not affect financial status of both groups as self-reported by patients in EORTC QLQ-C30. Given that only patients with early-stage cancer have been evaluated, physical

limitation and cancer-related symptoms were infrequently reported. Patients of both groups have shown in EORTC-QLQ-C30 analysis, a good global and health status, a comparable and high physical functioning and very low level of symptom scales (nausea/vomiting, pain, dyspnea, appetite loss and diarrhea). Moreover, young patients showed a significantly higher role functioning level referring fewer or no limits in working, doing daily activities or pursuing own hobbies, than midlife-adults. Conversely, the younger age group has shown a deeper interference of cancer on family life and social activities along with a greater impact on health status; referring a lower level of social functioning, body image and emotional functioning in functional scale and a high level of fatigue in symptom scale, which may be responsible for the choice of changing employment status.

Midlife adult QoL was mainly related to disease characteristics while, for younger patients, employment status and educational level were more relevant factors [5]. To our knowledge, only Kobhayashi et al. has shown a negative correlation between employment status and symptoms scale of EORTC QLQ-C30 in cancer patients [49]. Fatigue has been reported to have negative effect on return to work; it can affect the employment by decreasing work hours, increasing absence and reducing productivity [18,50,51]. However, these studies are uncertain, because of limited statistical test and measurement methods employed, and in contrast with Razavi et al. [52], who have shown no significant association between fatigue and return to work.

Conclusion

To enhance quality of life and to promote healthy lifestyle behavior in female cancer patients it is essential to assure multidisciplinary approaches with appropriate medical intervention and psychosocial support according to age. Younger patients need psychosocial support, more than midlife adults, to avoid negative social and employment experience and to overcome body changes following cancer treatment. Emotional and functional well-being increase over the first year following treatment, even in the absence of corresponding increase in physical well-being, suggesting adaptation to residual physical limitation [53]. Midlife adults seem to maintain an adaptive level of well-being after cancer diagnosis and treatment greater than younger patients.

Conflict of interest statement
The authors do not have any conflict of interest, as specified in the forms attached.

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References

[1] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Internet. International Agency for Research on Cancer: Lyon, France; 2010. Available from: http://globocan.iarc.fr, accessed on day/month/year.
[2] Awadalla AW, Ohaeri JU, Gholoum A, Khalid AO, Hamad HM, Jacob A. Factors associated with quality of life of outpatients with breast cancer and gynecologic cancers and their family caregivers: a controlled study. BMC Cancer 2007;7:102.
[3] Özaras G, Özyurda F. Quality of life and influencing factors in patients with a gynaecologic cancer diagnosis at Gazi University, Turkey. Asian Pac J Cancer Prev 2010;11(5):1403–8.
[4] Hawighorst-Knapstein S, Fusshoeller C, Franz C, Trautmann K, Schmidt M, Pilch H, et al. The impact of treatment for genital cancer on quality of life and body image–results of a prospective longitudinal 10-year study. Gynecol Oncol 2004 Aug;94(2):398–403.
[5] Lai BP, Tang CS, Chung TK. Age-specific correlates of quality of life in Chinese women with cervical cancer. Support Care Cancer 2009;17(3):271–8.
[6] Capelli G, De Vincenzo RI, Addamo A, Bartolozzi F, Braggio N, Scambia G. Which dimensions of health-related quality of life are altered in patients attending the different gynecologic oncology health care settings? Cancer 2002;95(12):2500–7.
[7] Le T, Leis A, Pahwa P, Wright K, Ali K, Reeder B, et al. Quality of life evaluations in patients with ovarian cancer during chemotherapy treatment. Gynecol Oncol 2004;92:839–44.
[8] Nordin AJ, Dixon S, Chinn DJ, Moloney I, Naik R, De Barros Lopes A, et al. Attitudes to radical gynecological oncology surgery in the elderly: a pilot study. Int J Gynecol Cancer 2000;10:323.
[9] Zhao H, Kanda K, Liu SJ, Mao XY. Evaluation of quality of life in Chinese patients with gynaecological cancer: assessments by patients and nurses. Int J Nurs Pract 2003;9:40–8.
[10] Park BW, Lee S, Lee AR, Lee KH, Hwang SY. Quality of life differences between younger and older breast cancer patients. J Breast Cancer 2011;14(2):112–8.
[11] Greimel E, Thiel I, Peintinger F, Cegnar I, Pongratz E. Prospective assessment of quality of life of female cancer patients. Gynecol Oncol 2002;85(1):140–7.
[12] Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Cohen HJ. Promoting healthy lifestyles in older cancer survivors to improve health and preserve function. J Am Geriatr Soc 2009 Nov;57(Suppl 2):S262–4.
[13] Patterson RE, Neuhouser ML, Hedderson MM, Schwartz SM, Standish LJ, Bowen DJ. Changes in diet, physical activity, and supplement use among adults diagnosed with cancer. J Am Diet Assoc 2003;103(3):323–8.
[14] Eakin EG, Youlden DR, Baade PD, Lawler SP, Reeves MM, Heyworth JS, et al. Health behaviors of cancer survivors: data from an Australian population-based survey. Cancer Causes Control 2007 Oct;18(8):881–94.
[15] Bellizzi KM, Rowland JH, Jeffery DD, McNeel T. Health behaviors of cancer survivors: examining opportunities for cancer control intervention. J Clin Oncol 2005;23(34):8884–93.
[16] McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. J Clin Oncol 2010;28(26):4074–80.
[17] Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284(20):2606–10.
[18] Spelten ER, Sprangers MA, Verbeek JH. Factors reported to influence the return to work of cancer survivors: a literature review. Psychooncology 2002;11(2):124–31.
[19] Carlsen K, Dalton SO, Diderichsen F, Johansen C, Danish Cohort Study. Risk for unemployment of cancer survivors: a Danish cohort study. Eur J Cancer 2008;44(13):1866–74.
[20] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009;105(2):103–4.
[21] Greimel E, Nordin A, Lanceley A, Creutzberg CL, van de Poll-Franse LV, Radisic VB, et al, EORTC Quality of Life Group. Psychometric validation of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer Module (EORTC QLQ-EN24). Eur J Cancer 2011;47(2):183–90.
[22] Greimel E, Kuljanic Vlasic K, Waldenstrom AC, Duric VM, Jensen PT, Singer S, et al, European Organization for Research and Treatment of Cancer Quality-of-Life Group on behalf of the EORTC Quality of Life Group. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module — EORTC QLQ-CX24. Cancer 2006;107(8):1812–22.
[23] Greimel E, Bottomley A, Cull A, Waldenstrom AC, Arraras J, Chauvenet L, et al, EORTC Quality of Life Group and the Quality of Life Unit. On behalf of the EORTC Quality of Life Group and the Quality of Life Unit. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. Eur J Cancer 2003;39:1402–8.
[24] Cull A, Howat S, Greimel E, et al. Development of a European Organization for Research and Treatment of Cancer questionnaire module to assess the quality of life of ovarian cancer patients in clinical trials: a progress report. Eur J Cancer 2001;37(1):47–53.
[25] Sprangers MAG, Groenvold M, Arraras JI, Sprangers MA, Groenvold M, Arraras JI, et al. The European Organisation for Research and Treatment of Cancer: Breast Cancer Specific Quality of Life Questionnaire Module: First results from a three-country field study. J Clin Oncol 1996;14:2756–68.
[26] Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37(11):1331–4.
[27] Demark-Wahnefried W, Aziz NM, Rowland JH, Pinto BM. Riding the crest of the teachable moment: promoting long-term health after the diagnosis of cancer. J Clin Oncol 2005;23:5814–30.
[28] Pinto BM, Eakin E, Maruyama NC. Health behavior changes after a cancer diagnosis: what do we know and where do we go from here? Ann Behav Med 2000;22:38–52.
[29] Becker M, Malafy T, Bossart M, Henne K, Gitsch G, Denschlag D. Quality of life and sexual functioning in endometrial cancer survivors. Gynecol Oncol 2011;121(1):169–73.
[30] Sprague BL, Trentham-Dietz A, Nichols HB, Hampton JM, Newcomb PA. Change in lifestyle behaviors and medication use after a diagnosis of ductal carcinoma in situ. Breast Cancer Res Treat 2010;124(2):487–95.
[31] Jones L, Demark-Wahnefried W. Recommendations for health behavior and wellness following primary treatment for cancer. National Academies Press: Washington, DC; 2007.
[32] Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. CA Cancer J Clin 2006;56:323–53.
[33] Herman DR, Ganz PA, Petersen L, Greendale GA. Obesity and cardiovascular risk factors in younger breast cancer survivors: the Cancer and Menopause Study (CAMS). Breast Cancer Res Treat 2005;93:13–23.

[34] Chlebowski RT, Aiello E, McTiernan A. Weight loss in breast cancer patient management. J Clin Oncol 2002;20:1128–43.
[35] Yaw YH, Shariff ZM, Kandiah M, Mun CY, Yusof RM, Othman Z, et al. Weight changes and lifestyle behaviors in women after breast cancer diagnosis: a cross-sectional study. BMC Public Health 2011;11:309.
[36] Chlebowski RT, Weiner JM, Reynolds R, et al. Long-term survival following relapse after 5-FU but not CMF adjuvant breast cancer therapy. Breast Cancer Res Treat 1986;7:23–30.
[37] Camoriano JK, Loprinzi CL, Ingle JN, et al. Weight change in women treated with adjuvant therapy or observed following mastectomy for node-positive breast cancer. J Clin Oncol 1990;8:1327–34.
[38] Heasman KZ, Sutherland HJ, Campbell JA, et al. Dietary fat consumption and survival among women with breast cancer. J Natl Cancer Inst 1985;75:37–41.
[39] Linsky A, Nyambose J, Battaglia TA. Lifestyle behaviors in Massachusetts adult cancer survivors. J Cancer Surviv 2011;5(1):27–34.
[40] Coups EJ, Ostroff JS. A population-based estimate of the prevalence of behavioral risk factors among adult cancer survivors and noncancer controls. Prev Med 2005;40(6):702–11.
[41] Wayne SJ, Lopez ST, Butler LM, Baumgartner KB, Baumgartner RN, Ballard-Barbash R. Changes in dietary intake after diagnosis of breast cancer. J Am Diet Assoc 2004;104(10):1561–8.
[42] von Gruenigen VE, Frasure HE, Jenison EL, Hopkins MP, Gil KM. Longitudinal assessment of quality of life and lifestyle in newly diagnosed ovarian cancer patients: the roles of surgery and chemotherapy. Gynecol Oncol 2006;103(1):120–6.
[43] de Boer AG, Taskila T, Ojajärvi A, van Dijk FJ, Verbeek JH. Cancer survivors and unemployment: a meta-analysis and meta-regression. JAMA 2009;301(7):753–62.
[44] Ross L, Petersen MA, Johnsen AT, Lundstroem LH, Carlsen K, Groenvold M. Factors associated with Danish cancer patients' return to work. A report from the population-based study. “The Cancer Patient's World”. Cancer Epidemiol 2011, doi:10.1016/j.canep.2011.06.001.
[45] Frazier LM, Miller VA, Horbelt DV, Delmore JE, Miller BE, Averett EP. Employment and quality of survivorship among women with cancer: domains not captured by quality of life instruments. Cancer Control 2009;16(1):57–65.
[46] Maunsell E, Drolet M, Brisson J, Brisson C, Mâsse B, Deschênes L. Work situation after breast cancer: results from a population-based study. J Natl Cancer Inst 2004;96(24):1813–22.
[47] Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychosocial problems among survivors of Hodgkin's disease. J Clin Oncol 1986;4(5):805–14.
[48] Carlsen K, Oksbjerg Dalton S, Frederiksen K, Diderichsen F, Johansen C. Cancer and the risk for taking early retirement pension: a Danish cohort study. Scand J Public Health 2008;36(2):117–25.
[49] Kobayashi K, Morita S, Shimonagayoshi M, Kobayashi M, Fujiki Y, Uchida Y, et al. Effects of socioeconomic factors and cancer survivors' worries on their quality of life (QOL) in Japan. Psychooncology 2008;17(6):606–11.
[50] Mock V. Breast cancer and fatigue: issues for the workplace. AAOHN J 1998;46(9):425–31.
[51] Kennedy F, Haslam C, Munir F, Pryce J. Returning to work following cancer: a qualitative exploratory study into the experience of returning to work following cancer. Eur J Cancer Care (Engl) 2007;16(1):17–25.
[52] Razavi D, Delvaux N, Brédart A, Autier P, Bron D, Debusscher L, et al. Professional rehabilitation of lymphoma patients: a study of psychosocial factors associated with return to work. Support Care Cancer 1993;1(5):276–8.
[53] Pearman T. Quality of life and psychosocial adjustment in gynecologic cancer survivors. Health Qual Life Outcomes 2003;1:33.

c) Vulvo-vaginal atrophy or genitourinary syndrome

Vulvo-vaginal atrophy (AVV), also known as genitourinary syndrome, is a female pathological condition that affects about one in two post-menopausal women and whose main symptoms are vaginal dryness (estimated at 75%), dyspareunia (estimated 38%), burning and vaginal pain (estimated 15%).

It occurs on average between 40 and 50 years and consists of the progressive modification of the structure of the vaginal and vulvar tissue as a consequence of the lack of estrogen.

The mucous membrane of the cervix, the epithelium of the vagina and vulva become thin and can be affected by petechial phenomena and other signs of inflammation and/or be more susceptible to trauma. The epithelium of childbearing age is made up of 4 overlaid cell layers that are renewed continuously while, in climacteria, the vaginal epithelium is made up of fewer cell layers (basal and parabasal) and is almost devoid of glycogen and therefore lactic acid (transformation of glycogen by the Döderlein bacillus) with consequent alkalinization of the vaginal environment (pH values between 6.0–8.0). Thus, the defense power of the vaginal environment also decreases and infections become more frequent. The vaginal mucosa bleeds at the slightest traumatism and becomes more sensitive.

Vaginal wrinkles decrease and a loss in local blood flow is observed with the disappearance of the mucous folds that make up the anterior and posterior vaginal columns, whereby the vaginal mucosa is smooth, loss of elasticity of the tissues is observed with reduction of the depth of the fornixes and of the vaginal ostium.

Even the vulva, albeit later, undergoes post-menopausal phenomena with decreasing fat, skin changes and hair changes that become gray, bristly, rare.

AVV in Italy is a disorder still under diagnosed: in addition to the reticence of women in discussing it with their gynecologist, even on the part of the doctor there is no proactivity in

this sense and the problem is rarely addressed with patients. More than 50% of doctors do not even ask if the problem exists and, even if the woman speaks about it, the therapeutic response is satisfactory only in 14% of cases.

In addition to negatively affecting the QoL of post-menopausal women, AVV, as it induces the appearance of non-specific symptoms such as burning, itching, dysuria, atypical vaginal bleeding, also has very strong consequences on married life , both from a relational point of view and with respect to sexual intimacy. Over 60% of women with vulvo-vaginal atrophy avoid intimacy with their partner. The AVV predisposes to the development of bacterial vulvo-vaginitis and relapsing cystitis with further aggravation of vaginal symptoms and further worsening of QoL. Although in daily practice doctors make a diagnosis of vulvo-vaginal atrophy thanks to their clinical judgment and visual inspection, today there is a more objective measuring tool: the Vaginal Health Index (VHI) which, through the analysis of 5 parameters (vaginal elasticity, vaginal secretions, ph, epithelial mucosa, vaginal moisture) allows you to arrive at a final score that defines the presence and level of vulvo-vaginal atrophy.

Different types of treatment are currently available. The most common treatment to date is systemic replacement hormonal treatment or local vaginal estrogen therapy, to be preferred when systemic therapy is not necessary for other reasons. These treatments are accompanied by non-hormonal lubricants, or treatments based on hyaluronic acid (AI). Although over 40% of women experience symptom relief, this is often considered insufficient.

In 2013, the FDA approved the use of ospemifene for the treatment of moderate-severe dyspareunia associated with menopausal VVA (De Gregorio MW, 2014).

i) Vulvo-vaginal atrophy treatment in cancer patients

The attention paid to safe and effective medical therapies that can cure VVA especially in cancer patients is increasing. Although systemic or local estrogen therapy is the most effective in the treatment of these dysfunctions, it can be contraindicated, representing a potential risk in cancer patients, while non-hormonal moisturizing and lubricating vaginal therapies can be used without limitations but the effectiveness is modest and transitory (Pruti S, 2011; Edwards D 2016). Estrogens administered topically vaginally are generally more effective in resolving vaginal dryness, but data regarding the use of these drugs in women with hormone-sensitive gynecological cancer are scarce (Dew, 2003). The development of new alternative, effective and safe therapies in these patients is therefore of particular relevance.

The Ospemifene belongs to the SERM family (selective estrogenic receptor modulators), the same class of the tamoxifen (triphenylethylene).

Each SERM has a selective agonist/antagonist effect on the various sensitive estrogen tissues and therefore has a peculiar therapeutic effect (treatment of osteoporosis, prevention or treatment of breast cancer) but also different side effects (e.g. increased risk of endometrial cancer, flushing of heat, thromboembolic events) (Martinkovich S, 2014). An ideal SERM should act as an agonist at the bone level, at the level of the cardiovascular system and at the brain level, but have a neutral or antagonistic effect at the breast or endometrial level.

Ospemifene is a metabolite of toremifene and has a vaginal agonist effect, with an endometrial and mammary safety profile (Wurz GT, 2014; Palacios S, 2016).

Its efficacy in treatment of VVA in menopausal patients has been demonstrated. Ospemifene improved the clinical signs of VVA significantly in both hysterectomized women and in women with an intact uterus (Simon I, 2014; Goldstein SR, 2014). The vaginal specular examination showed improvement in vaginal dryness, in the presence of petechiae, pallor

and mucosal fragility for the majority of patients three months (Constantine G, 2014) and 6 months (Simon JA, 2014) after therapy with ospemifene .

In our department during 2016-2017 we assessed the efficacy and safety of Ospemifene in the treatment of moderate-severe VVA in patients with cervical cancer (De Rosa N, 2017).

CC survivors exhibit more important menopausal symptoms than the general population (Froeding LP, 2014). Although a gradual improvement in emotional disturbances and QoL has been reported during the first 2 years since the diagnosis of CC, menopausal symptoms worsen over time (Mantegna G, 2013). About 80% of CC survivors suffer from sexual dysfunction (Maher EJ, 2008), with decreased vaginal sensitivity, desire and sexual arousal due to vaginal dryness, blood loss and dyspareunia following the development of post-treatment vaginal atrophy (Donovan KA, 2007).

Cervical cancer (CC) ranks fourth in frequency in women, with around 528,000 new cases in 2012 (GLOBOCAN 2012). It is frequently diagnosed in young women, in 2013 45% of women diagnosed with CC were under the age of 45 (Statens Serum Institut, 2013).

Human papilloma virus (HPV) infection is a pathognomonic event for the development of cancer. Invasive cervical tumors are preceded by preneoplastic lesions, Cervical Intraepithelial Neoplasia (CIN), which can persist for a long time, evolve into an invasive lesion or on the contrary regress spontaneously.

The natural history of the infection and its progression to carcinoma is influenced by numerous exogenous and endogenous factors including the number of sexual partners, the early age of the first sexual intercourse, tobacco smoke, a state of immunosuppression and the presence of co-infections. Particularly, we demonstrate that an healthy vaginal microbiota may influence positively the risks of progression of the CIN lesion (Lavitola G. 2020) and that the assumption of natural compounds based on echinacea reduces the risk of recurrence in HPV genital pathology (De Rosa N, 2018).

Early diagnosis thanks to the use of pap-test, colposcopy (Bifulco G, De Rosa N, 2015) and endocervicoscopy (De Rosa N, 2020 b) allows the early identification of preneoplastic lesions so that in the industrialized countries a reduction in the incidence of this tumor has been observed.

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Clinical Study

Impact of Ospemifene on Quality of Life and Sexual Function in Young Survivors of Cervical Cancer: A Prospective Study

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Background. Cervical cancer (CC) treatments impact quality of life (QoL) and sexual function (SF) of survivors. Treatment options to reduce sexual dysfunction are limited. The aim of this study was to assess the effectiveness of ospemifene in CC survivors with clinical signs and symptoms of vulvovaginal atrophy (VVA) focusing on their QoL and SF. *Materials and Methods.* Fifty-two patients with previous diagnosis of stage I-IIa CC suffering from VVA and treated with ospemifene were enrolled into a single arm prospective study. Patient underwent 6 months of therapy. At baseline and after 6 months all subjects performed Vaginal Health Index (VHI). The SF and QoL were measured by The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) and the Cervical Cancer Module (CXC-24). *Results.* After treatment a significant improvement of each parameter of VHI has been demonstrated. Global health status and emotional and social functioning scores improved significantly. On the contrary, general symptoms scales did not show significant difference from baseline data. Sexual activity, sexual vaginal functioning, body image, and sexual enjoyment scores increased significantly. *Conclusion.* Ospemifene seems to be effective in decreasing the VVA symptoms in CC survivors.

1. Introduction

Gynecologic cancer diagnosis and related surgical or medical treatments deeply impact quality of life (QoL) and sexual function (SF) of patients. QoL and SF are particularly impaired by cervical cancer, which arises in young-adult patients and impacts on sexual beings, body images, and childbearing potential with the consequent induction of severe emotional distress, anxiety, and behavioral disruptions.

Cervical cancer (CC) is the fourth most common cancer in women and the seventh overall with an estimated 528,000 new cases in 2012 [1]. It is diagnosed among relatively young women; 45% of women diagnosed in 2013 were younger than 45 years [2].

CC survivors have more pronounced menopausal symptoms, body image problems, and sexual problems than the general population [3]. A gradual improvement of emotional distress and QoL issues during the first 2 years after diagnosis of CC has been reported with the exception of lymphedema and menopausal symptoms [4]. Around 80% of CC survivors suffer from sexual dysfunction [5], such as the decrease in vaginal sensitivity, reduction of sexual desire, orgasm, and excitation due to vaginal dryness, sore and blood loss, dyspareunia, and vaginal atrophy following treatment [6].

Treatment modalities to reduce menopausal symptoms and sexual dysfunction are extremely limited for gynecologic cancer survivors. The use of hormones (e.g., local or systemic estrogen) poses a potential risk in patients with cancer. Therefore, the preferred first-line therapy for vaginal dryness and dyspareunia is usually nonhormonal treatments, such as moisturizers and lubricants [7]. Unfortunately, they have only partial effects on sexual dysfunction symptoms [8].

However, therapeutic options have now been increased; after over 20 years in development, ospemifene was approved in early 2013 by the US Food and Drug Administration

(FDA) for the treatment of moderate-to-severe dyspareunia associated with vulvar and vaginal atrophy (VVA) due to menopause [9].

Ospemifene is an estrogen receptor agonist/antagonist, also known as a selective estrogen receptor modulator (SERM), from the same chemical class (triphenylethylenes) as tamoxifen and toremifene, both of which are used in the treatment of breast cancer. Ospemifene is, in fact, one of the major metabolites of toremifene. It has an agonist effect on the vaginal epithelium and it has an endometrial and breast safety profile, which makes it unique [10, 11].

Ospemifene improved VVA clinical signs substantially both in hysterectomized women [12] and in women with intact uterus [13]. Vaginal visual examination demonstrated actual improvements in vaginal dryness, redness, petechiae, pallor, and mucosal friability with the majority of patients having no or mild VVA clinical signs at week 52 [12, 13].

Ospemifene (60 mg) in the patient cohort referring dyspareunia increased the percentage of patients who experienced improvement (80% versus 64% with placebo; $p = 0.001$), substantial improvement (53% versus 39% with placebo; $p < 0.001$), or relief (63% versus 42.5% with placebo; $p < 0.001$) [14].

The aim of the current study was to assess the effectiveness of the ospemifene in cervical cancer survivors with clinical signs and symptoms of vulvovaginal atrophy (VVA) focusing on their quality of life and sexual function.

2. Material and Methods

From January 2016 until July 2016, 56 eligible patients, referred to the follow-up program at the Unit of Gynecology Oncology of University Federico II of Naples, were enrolled into a single arm prospective study. All patients gave their written consent to be enrolled.

To be eligible for enrolment, patients had to meet all of the following criteria:

(i) Age between 18 and 60 years.

(ii) Previous diagnosis of stage I-IIa cervical cancer.

(iii) Five-year interval from cancer treatment.

(iv) Stable clinical conditions.

(v) Active sexual life (≥4 vaginal intercourses in the last month).

(vi) Diagnosis of vulvovaginal atrophy (VVA).

(vii) Good comprehension of the administered written questionnaires.

Brachytherapy or radiotherapy were considered as exclusion criteria.

Medical data (including diagnosis, stage of cancer, type of treatment, time since the end of treatment, and physical and/or psychiatric comorbidities) were extracted from medical records.

All cancer diagnoses performed before 2009 were converted according to the last revised FIGO staging of cervical cancer [15].

Before enrolment, all subjects underwent a gynecological examination, Pap smear, evaluation of Vaginal Health Index (VHI), and complete hematochemical tests.

Patients were treated with 60 mg tablet of ospemifene that is taken by mouth once a day for six months. After 6 months patients repeat gynecological examination and evaluation of VHI.

The VHI includes scoring of vaginal moisture, fluid volume, elasticity, pH, and epithelial integrity on a scale of 1 (poorest) to 5 (best) according to the methods of Robert Wood Johnson Medical School [16]. Lower is the score, greater is the atrophy [17].

Before treatment and after 6 months patients were interviewed on QoL and on SF.

The QoL and SF were measured by The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30), a 30-item cancer specific questionnaire for assessing the general QoL of cancer patients [18]. The EORTC-QLQC-30 incorporates five functioning domains: physical (PF2), role (RF2), cognitive (CF), emotional (EF), and social (SF); three symptom scales: fatigue (FA), pain (PA), and nausea/vomiting (NV); several single items which assess additional symptoms commonly reported by cancer patients: dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), and diarrhoea (DI); the perceived financial impact of the disease and treatment (FI); and finally an overall QoL scale (QL2). Validated module specific to tumour site (cervix, CXC-24) was administered in addition to the core questionnaire [19]. This module includes 24 cancer specific items on symptom experiences after cancer treatment including bladder symptoms, vaginal discomfort, abdominal pain, lymphedema, menopausal symptoms, and peripheral neuropathy and on body image and sexual function evaluating sexual activity, sexual enjoyment, sexual and vaginal functioning, and sexual worry.

2.1. Statistical Analysis. Data analyses were performed using the SPSS 20.0 software package (SPSS Inc., Chicago, IL, USA). The levels of significance for all tests were set at $p < 0.01$. Data were evaluated for distribution by Shapiro Wilks' test. Since data did not represent a normal distribution, comparison of variables was performed by using Wilcoxon test.

3. Results

Fifty-two patients completed the follow-up and were included into statistical analysis.

Clinical data and disease characteristics of the study group were shown in Table 1.

VHI resulted, at baseline, to be poor with a median total score of 10.00. After treatment an improvement of each parameter has been demonstrated (Table 2). In particular, elasticity, fluid volume, epithelial integrity, moisture, and pH showed a significant increase at 6-month follow-up. The overall median total score at 6 months reached value of 16.00 (Table 2).

QoL partially changed at 6-month follow-up. In particular, global health status and emotional and social functioning

Table 1: Clinical data and disease characteristics of the study group.

Age (years)	45.56 ± 5.44
Stage	
I (a, b)	19 (36.5)
IIa	33 (63.5)
Time since diagnosis (months)	74.63 ± 11.32
Treatment modality	
RH + BSO + PLND	48 (92.3)
RH + BSO + PLND + PALNS	4 (7.7)
Physical comorbidity	
No	39 (75.0)
Yes	13 (25.0)

RH: radical hysterectomy; BSO: bilateral salpingooophorectomy; PLND: pelvic lymph node dissection; PALNS: para-aortic lymph node sampling. Data are shown as mean ± SD or as number (percentage).

scores improved significantly (Figure 1). On the contrary, symptoms scales did not show significant difference from baseline data (Table 3).

Functional scale of CXC24 questionnaire, related to sexual function, showed an overall significant improvement. Indeed, sexual activity and sexual vaginal functioning scores increased significantly; body image and sexual enjoyment showed a slight but significant improvement (Figure 2). Regarding symptoms scales, lymphoedema, neuropathy, and menopausal symptoms remained unchanged after treatment but we demonstrated a significant reduction in symptoms experience and sexual worry scores (Table 3).

Patients referred no adverse events during study protocol.

4. Discussion

On behalf of our experience, this is the first prospective study that evaluates the effect on VHI, QoL, and SF of ospemifene in cervical cancer survivors.

Our data show an overall significant positive effect of therapy on sexual function of patients affected by vulvovaginal atrophy after cervical cancer treatment. Also QoL partially increases according to the positive effect demonstrated on symptoms experience and on social and emotional functioning.

Sexual function of CC survivors is inferior when compared with general population. About 80% of sexual active CC survivors have sexual dysfunction with negative effect on couple relations and QoL [20–22]. The majority of them show primarily dyspareunia and reduction of sexual desire one-year after surgical treatment [23]. Surprisingly, Lee et al. report, on the contrary, that, compared with healthy women, sexuality was not impaired in cervical cancer survivors who showed no evidence of disease after primary treatment and engaging in sexual activity [24]. However, the study group in this report includes also patients who performed conization, simple hysterectomy, or no surgery and moreover, 79% of the patients have the preservation of ovaries in situ.

Our data show that, about 6 years after treatment, CC patients have important symptoms of VVA. The median total VHI score of our study group is 10.

VVA commonly affects postmenopausal women [22]. It is estimated that up to 40% of postmenopausal women experience symptoms of VVA [23]. These women have a marked impact on sexual functioning, everyday activities, and body image perception [22, 24].

The decline in levels of circulating estrogen associated with the natural aging process or with the oophorectomy, for cancer patients, causes a breakdown of the collagen and elastin fibers in the vagina. The result is an overall loss of vaginal elasticity; the vagina loses its rugae and becomes short and narrow. The epithelium becomes thin and pale. This phenomenon is more pronounced after cancer surgical treatment; indeed, a narrow vaginal opening and a short vaginal stump can worsen VVA symptoms. Moreover, psychological implications of a gynecological cancer diagnosis deeply impact on body image perception and on emotional and social relationship.

We previously report that young gynecological cancer survivors are less sexually active than midlife adults; they suffer much more from their body images, have worse sexual vaginal functioning, and show more severe menopausal symptoms, probably in relationship with rapid body changes following surgical menopause [25].

Our study group of relatively young CC patients (mean age 45 years) shows low baseline scores in global health status and in sexual function; the patients express high level of sexual worry and poor body image. The need of specific intervention in these patients is unquestioned.

The principles of treatment of VVA are the restoration of urogenital physiology and the alleviation of symptoms [26]. Since approval of ospemifene, the therapeutic options for VVA in cancer patients can include only nonhormonal local therapies such as lubricants and moisturizers. However, the 2 principles of treatment usually are not achieved. Lubricants offer a temporary relief of vaginal symptoms, without restoration of urogenital physiology [27, 28]. Moisturizers improve lubrication but have no effect on the overall vaginal maturation index/value (VMI) [29, 30].

Ospemifene is the new nonhormonal proposal for the management of the VVA [10, 11].

In the study group the VHI increases significantly, reaching median value of 16, indicating the positive effect of the ospemifene on vaginal health of CC survivors. This effect was in accordance with the findings of previous studies in general postmenopausal population [12, 31–33]. Indeed, vaginal visual examination demonstrated improvements in vaginal dryness, redness, petechiae, pallor, and mucosal friability at 3 months [31] and 6 months [31, 32] after ospemifene therapy. In women reporting vaginal dryness and dyspareunia, 60 mg of ospemifene reduced both symptoms' severity as compared to placebo [33].

There is no adverse event or tumour recurrence in this study.

Ospemifene appears to have antiestrogenic effects on breast in experimental models. Indeed, in vitro studies showed that ospemifene induced a moderate, dose-dependent growth inhibition of estrogen-dependent MCF-7 cells [34]. In a ductal carcinoma in situ mouse model,

Table 2: Vaginal Health Index of study group at baseline and after 6 months.

	Baseline	6-month follow-up	p value
Elasticity	2.00 [1.52–1.87]	3.00 [3.11–3.59]	<0.001
Fluid volume	2.00 [1.44–1.72]	3.00 [2.48–3.06]	<0.001
pH	2.00 [1.95–2.35]	3.00 [2.66–3.15]	<0.001
Epithelial integrity	2.00 [2.10–2.44]	4.00 [3.48–3.94]	<0.001
Moisture	2.00 [1.99–2.39]	3.00 [2.74–3.22]	<0.001
Total	10.00 [9.54–10.23]	16.00 [15.01–16.41]	<0.001

Data are shown as median [95%, CI].

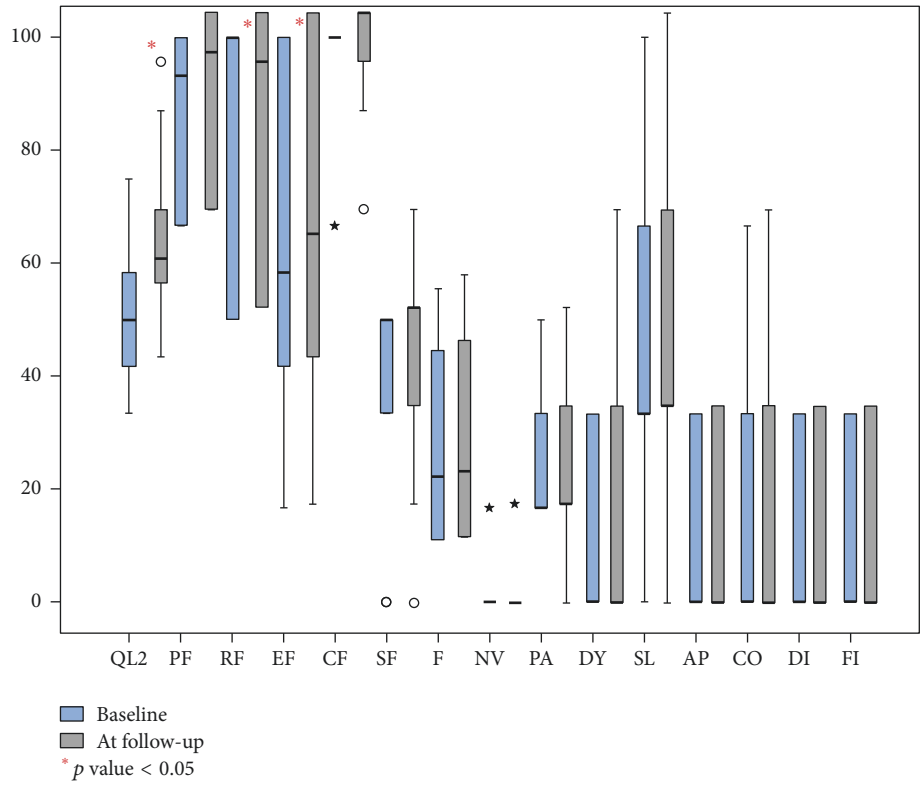

Figure 1: Median values of the EORTC QLQ-C30 subscale at baseline and at 6-month follow-up. QoL: global health status, PF: physical functioning, RF: role functioning, EF: emotional functioning, CF: cognitive functioning, SF: social functioning, F: fatigue, NV: nausea and vomiting, PA: pain, DY: dyspnoea, SL: insomnia, AP: appetite loss, CO: constipation; DI: diarrhoea, and FI: financial difficulties. ○ are extreme values; that is, they do not fall into internal fences. ★ are extreme abnormal values and represent cases/rows with values that exceed three times the height of the boxes.

cell proliferation was reduced significantly with use of ospemifene [35].

Effects of SERMs on cervical cancer cell are nowadays object of studies. Tamoxifen use exhibited only a marginal protection effect on cervical neoplasia. This finding might be explained by the fact that it acts as an ER agonist rather than antagonist in the uterus [36]. The long-term use of tamoxifen in breast cancer patients actually increases the risks of endometrial cancers [37]. On the contrary raloxifene, which has ER agonistic effect in bone, antagonistic effect in breast, and neutral effect in endometrium [38, 39], similarly to ospemifene, has shown a potential effect in curing both cancer and dysplasia in the cervix in transgenic mouse model [40].

The improvement of VHI in our study group was associated with the improvement in QoL and in SF of the patients. Sexual activity, sexual enjoyment, and sexual vaginal functioning improve significantly at follow-up visit. Sexual worry decreases significantly showing a better predisposition to sexuality.

Menopausal symptoms do not seem to change significantly (in the CXC-24 questionnaire MS correspond to hot flushes); on the contrary symptoms experience that includes vaginal and urinary symptoms shows a significant decrease. Obviously, perception of other cancer specific symptoms does not change significantly after treatment.

A limitation of the current study is the lack of a control group, as the objective was to evaluate changes before and

Table 3: Median values of the EORTC QLQ-C30 subscale and specific module CXC-24 at baseline and at 6-month follow-up.

	Baseline	6-month follow-up	p value
Global health status/QoL (QL2)	50.00 [50.14–55.31]	58.33 [58.88–65.47]	0.01
Functional scales			
Physical functioning (PF2)	93.33 [82.34–90.74]	93.33 [82.34–90.74]	1.0
Role functioning (RF2)	100.00 [71.67–84.74]	91.67 [72.54–85.15]	0.7
Emotional functioning (EF)	58.33 [59.96–96.78]	62.50 [62.75–78.28]	0.003
Cognitive functioning (CF)	100.00 [89.12–55.31]	100.00 [88.47–96.14]	0.16
Social functioning (SF)	50.00 [29.48–40.39]	50.00 [37.03–46.31]	<0.001
Symptom scales			
Fatigue (FA)	22.22 [24.73–35.09]	22.22 [24.22–34.33]	0.18
Nausea and vomiting (NV)	0.00 [0.43–3.42]	0.00 [0.43–3.42]	1.0
Pain (PA)	16.67 [24.47–31.94]	16.67 [24.02–31.75]	0.53
Dyspnoea (DY)	0.00 [5.93–14.58]	0.00 [5.55–14.58]	0.70
Insomnia (SL)	33.33 [42.74–58.54]	33.33 [42.74–58.54]	1.0
Appetite loss (AP)	0.00 [7.08–15.99]	0.00 [7.08–15.99]	1.0
Constipation (CO)	0.00 [12.51–25.94]	0.00 [11.21–24.69]	0.16
Diarrhoea (DI)	0.00 [5.37–13.86]	0.00 [6.50–15.29]	0.16
Financial difficulties (FI)	0.00 [5.93–14.58]	0.00 [4.81–13.13]	0.32
CXC-24			
Functional scale			
Body image (BI)	33.33 [20.25–31.04]	33.33 [23.14–33.27]	0.01
Sexual activity (SXA)	33.33 [12.63–21.99]	33.33 [24.72–36.82]	<0.001
Sexual enjoyment (SXE)	0.00 [8.26–17.38]	16.67 [14.52–27.78]	0.01
Sexual vaginal functioning (SXV)	41.67 [39.28–50.46]	66.67 [60.44–69.37]	<0.001
Symptom scale			
Symptom experience (SE)	9.09 [10.71–14.93]	9.09 [9.39–12.86]	0.001
Lymphoedema (LY)	33.33 [26.34–33.92]	33.33 [27.16–34.37]	0.56
Peripheral neuropathy (PN)	0.00 [5.79–16.00]	0.00 [4.43–13.51]	0.10
Menopausal symptoms (H)	66.67 [43.79–62.62]	66.67 [45.67–63.31]	0.92
Sexual worry (SW)	66.67 [68.96–79.75]	66.67 [46.73–63.52]	<0.001

Data are shown as median [95%, CI].

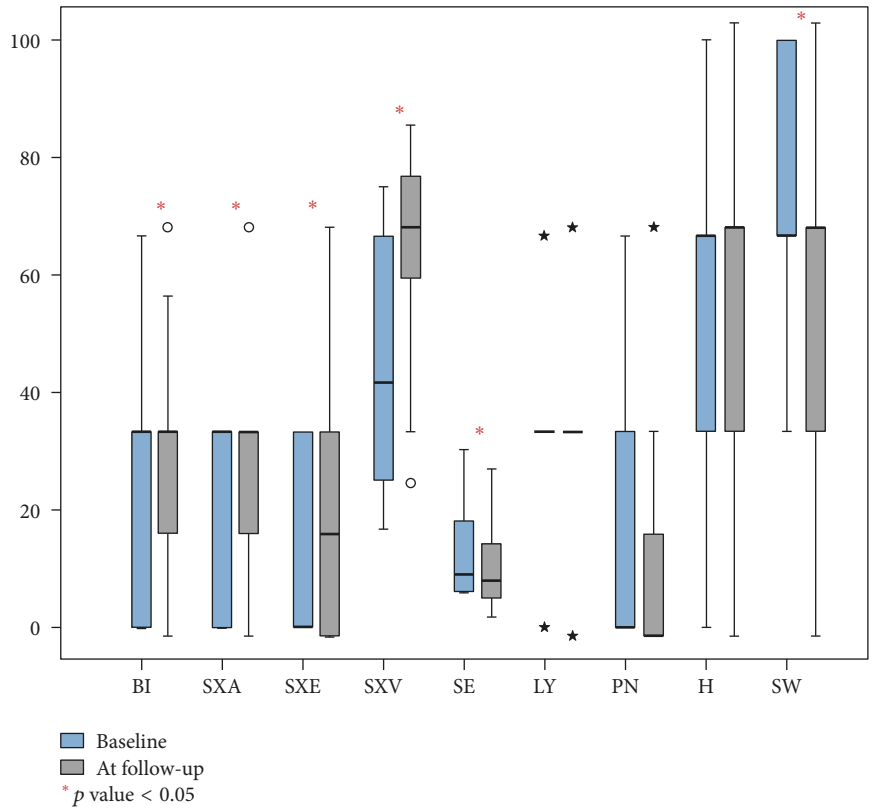

FIGURE 2: Median values specific cancer module CXC-24 at baseline and at 6-month follow-up. BI: body image, SXA: sexual activity, SXE: sexual enjoyment, SXV: sexual vaginal functioning, SE: symptom experience, LY: lymphoedema, PN: peripheral neuropathy, H: menopausal symptoms, and SW: sexual worry. ○ are extreme values; that is, they do not fall into internal fences. ★ are extreme abnormal values and represent cases/rows with values that exceed three times the height of the boxes.

after the ospemifene therapy in CC survivors with VVA as a whole and not to compare its efficacy with other treatment modalities. Thus, a hypothesis of placebo effect cannot be overruled. Moreover, the study does not take into account additional factors that may influence QoL and sexual function, such as marital and economical status of the patients.

Despite the above potential limitations, this study has a considerable strength. This is a prospective study, with a well-defined group of participants: young patients, with previous history of cervical cancer treated by surgery and/or chemotherapy and VVA symptoms.

We excluded patient treated by brachytherapy or radiotherapy to avoid inconclusive results, but for this reason the effect of ospemifene cannot be generalized to all CC survivors.

5. Conclusion

Ospemifene seems to be effective in decreasing the VVA symptoms in CC survivors improving VHI, sexual function, and QoL perception of the women. The occurrence of sexual dysfunction has to be recognized by clinicians, which should find the best option treatment for this kind of patient; the ospemifene nowadays is an effective and safety alternative option for the management of VVA in cervical cancer survivors.

Other prospective studies will establish the efficacy of this therapy on other gynecological cancer types and on patients who underwent brachytherapy or radiotherapy.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Nicoletta De Rosa and Giada Lavitola made the same contribution to the work.

References

[1] GLOBOCAN 2012 (IARC), Section of Cancer Surveillance (2017).

[2] Statens Serum Institut (2013) Cancer registeret. Talog analyse.

[3] L. P. Froeding, C. Ottosen, H. Rung-Hansen, D. Svane, B. J. Mosgaard, and P. T. Jensen, "Sexual functioning and vaginal changes after radical vaginal trachelectomy in early stage

cervical cancer patients: A longitudinal study," *Journal of Sexual Medicine*, vol. 11, no. 2, pp. 595–604, 2014.

[4] G. Mantegna, M. Petrillo, G. Fuoco et al., "Long-term prospective longitudinal evaluation of emotional distress and quality of life in cervical cancer patients who remained disease-free 2-years from diagnosis," *BMC Cancer*, vol. 13, article 127, 2013.

[5] E. J. Maher and A. Denton, "Survivorship, Late Effects and Cancer of the Cervix," *Clinical Oncology*, vol. 20, no. 6, pp. 479–487, 2008.

[6] K. A. Donovan, L. A. Taliaferro, E. M. Alvarez, P. B. Jacobsen, R. G. Roetzheim, and R. M. Wenham, "Sexual health in women treated for cervical cancer: Characteristics and correlates," *Gynecologic Oncology*, vol. 104, no. 2, pp. 428–434, 2007.

[7] S. Pruthi, J. A. Simon, and A. P. Early, "Current overview of the management of urogenital atrophy in women with breast cancer," *Breast Journal*, vol. 17, no. 4, pp. 403–408, 2011.

[8] D. Edwards and N. Panay, "Treating vulvovaginal atrophy/genitourinary syndrome of menopause: How important is vaginal lubricant and moisturizer composition?" *Climacteric*, vol. 19, no. 2, pp. 151–161, 2016.

[9] M. W. Degregorio, R. L. Zerbe, and G. T. Wurz, "Ospemifene: A first-in-class, non-hormonal selective estrogen receptor modulator approved for the treatment of dyspareunia associated with vulvar and vaginal atrophy," *Steroids*, vol. 90, pp. 82–93, 2014.

[10] G. T. Wurz, C.-J. Kao, and M. W. DeGregorio, "Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause," *Clinical Interventions in Aging*, vol. 9, pp. 1939–1950, 2014.

[11] S. Palacios and M. J. Cancelo, "Clinical update on the use of ospemifene in the treatment of severe symptomatic vulvar and vaginal atrophy," *International Journal of Women's Health*, vol. 8, pp. 617–626, 2016.

[12] J. Simon, D. Portman, and R. G. Mabey, "Long-term safety of ospemifene (52-week extension) in the treatment of vulvar and vaginal atrophy in hysterectomized postmenopausal women," *Maturitas*, vol. 77, no. 3, pp. 274–281, 2014.

[13] S. R. Goldstein, G. A. Bachmann, P. R. Koninckx, V. H. Lin, D. J. Portman, and O. Ylikorkala, "Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy," *Climacteric*, vol. 17, no. 2, pp. 173–182, 2014.

[14] D. J. Portman, G. A. Bachmann, and J. A. Simon, "Ospemifene, a novel selective estrogen receptor modulator for treating dyspareunia associated with postmenopausal vulvar and vaginal atrophy," *Menopause*, vol. 20, no. 6, pp. 623–630, 2013.

[15] S. Pecorelli, "Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium," *International Journal of Gynecology and Obstetrics*, vol. 105, no. 2, pp. 103-104, 2009.

[16] G. Bachmann, "Vulvo-vaginal complaints," in *Treatment of the postmenopausal woman*, R. Lobo, Ed., Raven, New York, NY, USA, 1994.

[17] M. A. Weber, J. Limpens, and J. P. W. R. Roovers, "Assessment of vaginal atrophy: a review," *International urogynecology journal*, vol. 26, no. 1, pp. 15–28, 2015.

[18] E. Greimel, I. Thiel, F. Peintinger, I. Cegnar, and E. Pongratz, "Prospective assessment of quality of life of female cancer patients," *Gynecologic Oncology*, vol. 85, no. 1, pp. 140–147, 2002.

[19] E. R. Greimel, K. K. Vlasic, A.-C. Waldenstrom et al., "The european organization for research and treatment of cancer (EORTC) qualtty-of-life questionnaire cervical cancer module: EORTC QLQ-CX24," *Cancer*, vol. 107, no. 8, pp. 1812–1822, 2006.

[20] I. D. White, "The Assessment and Management of Sexual Difficulties after Treatment of Cervical and Endometrial Malignancies," *Clinical Oncology*, vol. 20, no. 6, pp. 488–496, 2008.

[21] C. S. L. Corrêa, I. C. G. Leite, A. P. S. Andrade, A. de Souza Sérgio Ferreira, S. M. Carvalho, and M. R. Guerra, "Sexual function of women surviving cervical cancer," *Archives of Gynecology and Obstetrics*, vol. 293, no. 5, pp. 1053–1063, 2016.

[22] J. Carter, R. Penson, R. Barakat, and L. Wenzel, "Contemporary quality of life issues affecting gynecologic cancer survivors," *Hematology/Oncology Clinics of North America*, vol. 26, no. 1, pp. 169–194, 2012.

[23] O. Lalos, L. Kjellberg, and A. Lalos, "Urinary, climacteric and sexual symptoms 1 year after treatment of cervical cancer without brachytherapy," *Journal of Psychosomatic Obstetrics and Gynecology*, vol. 30, no. 4, pp. 269–274, 2009.

[24] Y. Lee, M. C. Lim, S. I. Kim, J. Joo, D. O. Lee, and S.-Y. Park, "Comparison of quality of life and sexuality between cervical cancer survivors and healthy women," *Cancer Research and Treatment*, vol. 48, no. 4, pp. 1321–1329, 2016.

[25] G. Bifulco, N. De Rosa, M. L. Tornesello et al., "Quality of life, lifestyle behavior and employment experience: A comparison between young and midlife survivors of gynecology early stage cancers," *Gynecologic Oncology*, vol. 124, no. 3, pp. 444–451, 2012.

[26] K. B. Levine, R. E. Williams, and K. E. Hartmann, "Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women," *Menopause*, vol. 15, no. 4, pp. 661–666, 2008.

[27] R. E. Nappi and M. Kokot-Kierepa, "Women's voices in the menopause: Results from an international survey on vaginal atrophy," *Maturitas*, vol. 67, no. 3, pp. 233–238, 2010.

[28] N. Santoro and J. Komi, "Prevalence and impact of vaginal symptoms among postmenopausal women," *Journal of Sexual Medicine*, vol. 6, no. 8, pp. 2133–2142, 2009.

[29] D. W. Sturdee and N. Panay, "Recommendations for the management of postmenopausal vaginal atrophy," *Climacteric*, vol. 13, no. 6, pp. 509–522, 2010.

[30] I. van der Laak, L. de Bie, H. de Leeuw, P. de Wilde, and A. Hanselaar, "The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerized cytometry," *Journal of Clinical Pathology*, vol. 55, pp. 446–451, 2002.

[31] G. Constantine, S. Graham, W. D. Koltun, and S. A. Kingsberg, "Assessment of ospemifene or lubricants on clinical signs of VVA," *Journal of Sexual Medicine*, vol. 11, no. 4, pp. 1033–1041, 2014.

[32] J. A. Simon, V. H. Lin, C. Radovich, and G. A. Bachmann, "Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus," *Menopause*, vol. 20, no. 4, pp. 418–427, 2013.

[33] G. A. Bachmann and J. O. Komi, "Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: Results from a pivotal phase 3 study," *Menopause*, vol. 17, no. 3, pp. 480–486, 2010.

[34] T. L. Taras, G. T. Wurz, and M. W. DeGregorio, "In vitro and in vivo biologic effects of Ospemifene (FC-1271a) in breast cancer," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 77, no. 4-5, pp. 271–279, 2001.

[35] R. Namba, L. J. Young, J. E. Maglione et al., "Selective estrogen receptor modulators inhibit growth and progression of premalignant lesions in a mouse model of ductal carcinoma in situ," *Breast Cancer Research*, vol. 7, pp. 881–889, 2005.

[36] M. Friedrich, D. Mink, C. Villena-Heinsen, A. Woll-Hermann, and W. Schmidt, "Tamoxifen and proliferation of vaginal and cervical epithelium in postmenopausal women with breast cancer," *European Journal of Obstetrics Gynecology and Reproductive Biology*, vol. 80, no. 2, pp. 221–225, 1998.

[37] Y. Daniel, M. Inbar, A. Bar-Am, M. R. Peyser, and J. B. Lessing, "The effects of tamoxifen treatment on the endometrium," *Fertility and Sterility*, vol. 65, no. 6, pp. 1083–1089, 1996.

[38] V. C. Jordan, "Chemoprevention of breast cancer with selective oestrogen-receptor modulators," *Nature Reviews Cancer*, vol. 7, no. 1, pp. 46–53, 2007.

[39] J. S. Crabtree, B. J. Peano, X. Zhang, B. S. Komm, R. C. Winneker, and H. A. Harris, "Activity of three selective estrogen receptor modulators on hormone-dependent responses in the mouse uterus and mammary gland," *Molecular and Cellular Endocrinology*, vol. 287, no. 1-2, pp. 40–46, 2008.

[40] S.-H. Chung and P. F. Lambert, "Prevention and treatment of cervical cancer in mice using estrogen receptor antagonists," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 46, pp. 19467–19472, 2009.

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Clinical Study

Effects on Vaginal Microbiota Restoration and Cervical Epithelialization in Positive HPV Patients Undergoing Vaginal Treatment with Carboxy-Methyl-Beta-Glucan

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Objective. Evaluate the effects of carboxy-methyl-beta-glucan on cervical epithelialization and on the vaginal microbiota in patients with HPV infection or low-grade cervical preneoplastic lesion (CIN 1). *Materials and Methods*. Seven-hundred eighty-four women with positive HPV tests or diagnosed with CIN 1 were enrolled in a retrospective case-control study. All the recruited women performed, at baseline and after 6 months, Pap test, HPV test, evaluation of vaginal health according to the Amsel criteria, colposcopy, and punch biopsy. The study population was then divided into 2 groups in relation to the therapy performed during the follow-up period. Group A performed treatment with vaginal gel based on carboxy-methyl-beta-glucan (1 application/day for 20 days per month for 3 months). Group B was the control group. *Results*. The patients of group A had a significant improvement in the ectopia pattern and a greater number of cases with metaplasia in the maturation phase with a significant increase in Lugol uptake. In the experimental group, a significant improvement in the pH indices, a negative Swift test and a resolution of the leucorrhoea were observed. A negative result of the 37.1% Pap test and the 39.9% HPV test (vs. 15.2% and 16.5%, respectively) were demonstrated in the treatment group with respect to the control group. A negativization of the colposcopic pictures was observed with a reduction in the amount of CIN 1 found higher in the treatment group. *Conclusions*. Vaginal therapy based on carboxy-methyl-beta-glucan has been able to improve overall vaginal health; this effect seemed to positively impact the risk of persistence and progression of CIN.

1. Introduction

HPV (human papillomavirus) infection is transmitted mainly by sexual contact, and the cervix is the organ most sensitive to the oncogenic action of papillomavirus. The cervix is covered by two epithelia: the esocervical one and the paved type and the endocervical one and the cylindrical type. This transition zone represents, from a biological point of view, an area of instability because it allows easier access to the basal site of the target reserve cells of oncogenic agents such as HPV [1].

The HPV infection is very common especially in young women (highest incidence peak between 20 and 30 years). There is a percentage of women at risk who are positive for the infection but in whom the virus did not cause cervical precancerous lesions (CIN). When the virus integrates into the cells of the cervical epithelium, it determines a process of cellular transformation and gives rise to the CIN lesions [2, 3].

Recent data show a significant correlation between immune status and persistence of the virus. The vaginal microbiota plays an important role in modulating the immune system of the female genital tract [4]. *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii* appear to dominate the vagina of most healthy women. The composition of vaginal microbiota is

influenced by numerous factors: ethnicity, cyclical secretion of oestrogen and progesterone throughout the menstrual cycle, menstruation or menopausal state, the widespread use of synthetic hormones for contraceptive purposes, sexual intercourse, hygiene practices, and infection [5].

There is much evidence to correlate the persistence of HPV with the altered presence of vaginal lactobacilli and an altered microbiota. A balanced situation of the vaginal microbiota ensures a better response against HPV [6–9]. Even a well-epithelized cervix, with a healthy epithelium, with a mature and small extension of transformation zone area, offers an environment unfavorable to infection and persistency of the virus.

Current thinking suggests that the development of papillomavirus-associated disease requires the infection not just of an epithelial basal cell but more specifically an epithelial tissue stem cell at a pluristratified cutaneous or mucosal site. At the cervix, the transformation zone is maintained by a specialized type of cell known as the reserve cell. The cervical neoplasia develops primarily at the squamocolumnar junction because these cells fail to properly regulate viral gene expression, leading to a nonproductive or abortive infection rather than a productive infection. The idea that papillomaviruses generally reside in an epithelial stem cell following infection is compatible with our understanding of latency and reactivation from latency. During latency, the virus can be undetectable to the common diagnostic test [1, 10].

Maintaining adequate or improving the state of vaginal health and acting positively on the cervical epithelium and the vaginal microbiota could be a new strategy to prevent both the acquisition and persistence of HPV infection and the progression of CIN lesions.

1.1. Purpose of the Study. This study is aimed at evaluating the effects of local therapy with vaginal gel based on carboxy-methyl-beta-glucan on cervical epithelialization and the vaginal microbiota in patients with HPV infection or low-grade cervical preneoplastic lesion.

2. Materials and Methods

Seven-hundred eighty-four women with positive HPV tests or diagnosed with CIN 1, referred to the Colposcopy and Cervical Pathology Center of our Department, were enrolled in a retrospective case-control study.

All patients meeting the following enrollment criteria were selected:

(i) Age between 18 and 60 years

(ii) Caucasian origin

(iii) Positivity to HPV testing and/or positivity to CIN 1 at punch biopsy

(iv) Absence of contraindications to the proposed therapies

(v) Negative medical history for any type of pharmacological treatment that acts on the elements in the current or recent study (<3 months)

(vi) Negative medical history due to systemic pathology which can influence virus natural history, in particular immune disorders, and diabetes

The exclusion criteria were as follows:

(i) Age under 18 or over 60 years

(ii) Positivity to biopsy for CIN 2+ lesion

(iii) Suspected or diagnosed hypersensitivity/allergy to the components of the vaginal gel

(iv) A positive medical history for each type of treatment that acts on the current or recent study outcomes (<3 months)

(v) States of specific deficiency of the immune system

At the time of recruitment, each person was informed about the aims and methods of the study with the fulfillment of a written informed consent. The study was approved by the ethical committee of the Federico II University (*number protocol*: *260/18*).

The data of the patients in the study were extracted from the medical records of the patients who joined the center starting from January 2013.

For all the participants, the previous clinical history, age, specific risk factors, and previous cytology report according to the patient record were evaluated.

All the recruited women have undergone complete clinical examination and subsequent follow-up after 6 months; in particular, the women who performed gynecological and physical examination, Paptest and/or HPV test, and evaluation of vaginal health according to the Amsel criteria (presence of leucorrhoea, vaginal pH > 4.5, positivity of the Swift test, and presence of clue cells).

A targeted punch biopsy during colposcopy was obtained in case of the presence of ZTA (abnormal transformation zone).

The study population was then divided into 2 groups concerning the therapy performed during the follow-up period:

(i) Group A: 392 women with positive HPV test or CIN 1 diagnosis who performed the treatment with vaginal gel-based carboxy-methyl-beta-glucan (Colpofix®: 1 application/day for 20 days per month for 3 months);

(ii) Group B: 392 untreated women, as the control group

In Group A, the aspects of compliance, treatment security, and the onset of side effects or allergic sensitization were also evaluated.

2.1. Statistical Analysis. The number of the sample under examination was calculated starting from the assumption that, as reported in the literature [11], about 60% of low-grade cervical lesions regress spontaneously without any therapy over 12-24 months, and this value is also higher in case of positive HPV test only. Assuming a significant

Table 1: The demographic and anamnestic variables of the subjects under study.

	Groupp A ($N = 358$)	Group B ($N = 367$)	p value
Age (year)[§]	34.02 ± 6.5	34.2 ± 6.2	0.71
Parity (no.)[*]	1 (0-3)	1 (0-3)	0.52
Educational level[*]	2 (1-3)	2 (1-3)	0.64
Smoke[°]			
≤10 sig/die	190 (53.1)	187 (52.2)	0.81
>10 sig/die	168 (46.9)	171 (47.8)	
Alchohol habits[°]			
Weekly	301 (84.1)	318 (86.6)	0.33
Daily	57 (15.9)	49 (13.4)	
Sexual partners[°]			
≤4	94 (26.3)	112 (30.5)	0.20
>4	264 (73.7)	255 (69.5)	

[°]χ square, [§]t-test, [*]Mann–Whitney.

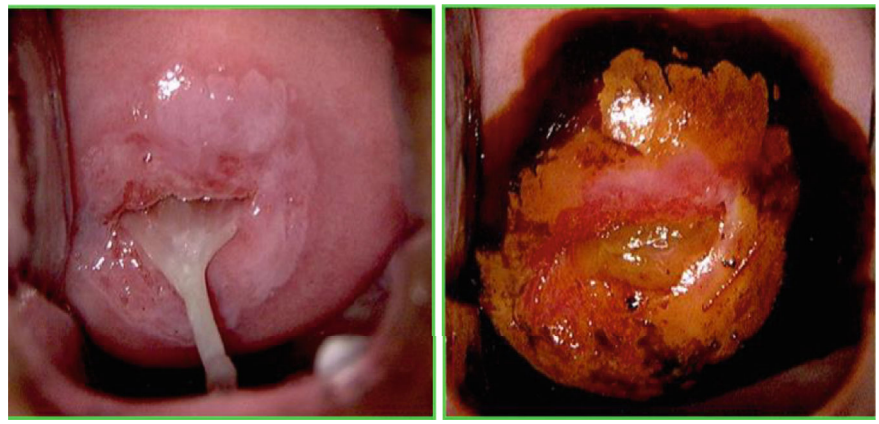

Figure 1: Abnormal transformation zone (ATZ)—CIN 1 before treatment with carboxy-methyl-beta-glucan.

increase of these regressions of at least 10% in the course of adjuvant therapy, setting the calculation with an alpha-error at 5% (CI. 95%) and a $1 - \beta = 80\%$ the sample size must be of at least 356 patients per group. Considering a 10% drop-out (for lack of data completeness), it was decided to increase this value to 392 patients.

SPSS software (version 20.0) was used for statistical analysis. The significance was set at a value of $p < 0.05$.

The demographic and clinical data of the two groups were compared with the Student t-test for data with parametric distribution (age, weight) and with the χ^2 test for ordinal variables (Pap test result, vaginal swab result, and colposcopic report). The differences in the number of CIN lesions and HPV test positivity between the two groups were evaluated with the χ^2 test. The measurement of the OR (odds ratio) was used to assess the risk of persistence of infection or lesions.

3. Results

At the end of the data analysis, 725 patients were found to meet the inclusion criteria and completed the follow-up as required by the protocol: 358 belonging to group A, 367 belonging to group B. The demographic and anamnestic variables of the subjects under study are reported in Table 1. The two groups were comparable to the aforementioned variables (p = NS).

As regards the vaginal and tissue health outcomes, it was observed that the patients who performed the therapy, concerning the control group, had a significant improvement in the ectopia pattern (Figures 1 and 2): a greater extension (> 20%) of metaplasia and a greater number of cases with metaplasia in the maturation phase with a significant increase in Lugol uptake (Table 2 and Figure 3(a)).

In the experimental group, a significant improvement in the pH indices, a negative Swift test, and a resolution of the leucorrhoea were observed (Table 2 and Figure 3(b)).

Table 3 shows the cytohistological, molecular, and colposcopic data of the patients in the study. A negative result of the 37.1% Pap test and the 39.9% HPV test (15.2% and 16.5%, respectively) were demonstrated in the treatment group to the control group. Consistent with these data, a negativization of the colposcopic pictures is observed with a reduction in the amount of CIN 1 found higher in the

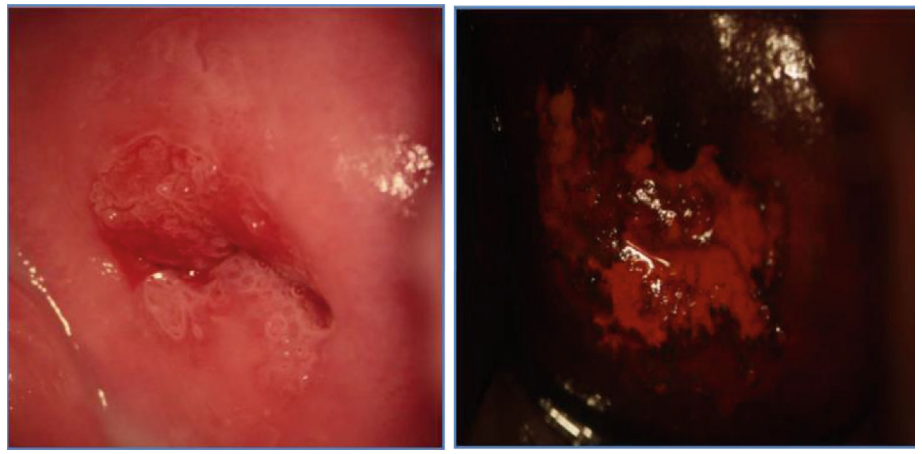

Figure 2: Normal transformation zone (NTZ) after treatment with carboxy-methyl-beta-glucan.

Table 2: Epithelialization and vaginal health indexes in the two study groups.

	Time 0 months		p value	Time 6 months		p value	Difference % group A	Difference % group B
	Group A ($N = 358$)	Group B ($N = 367$)		Group A ($N = 358$)	Group B ($N = 367$)			
Ectopia			0.10			0.006		
≤2/3	216 (60.3)	244 (66.5)		285 (79.6)	260 (70.8)			
>2/3	142 (39.7)	123 (39.7)		73 (20.4)	107 (29.2)		-48.6%	-13%
Metaplasia			0.11			<0.001		
≤20%	275 (76.8)	263 (71.7)		180 (50.3)	248 (67.6)			
>20%	83 (23.2)	104 (28.3)		178 (49.7)	119 (32.4)		114.5%	14.4%
Lugol test			0.97			<0.001		
Negative	52 (14.5)	53 (14.4)		164 (45.8)	95 (25.9)			
Positive	306 (85.5)	314 (85.6)		195 (54.2)	272 (74.1)		-36.3%	-13.4
pH			0.59			<0.001		
≤4.5	208 (58.1)	206 (56.1)		306 (85.5)	212 (57.8)			
>4.5	150 (41.9)	161 (43.9)		52 (14.5)	155 (42.2)		-65.3%	-3.7%
Swift test			0.41			<0.001		
Negative	188 (52.5)	204 (55.6)		313 (87.4)	212 (57.8)			
Positive	170 (47.5)	163 (44.4)		45 (12.6)	155 (42.2)		-73.5%	-4.9%
Leucorrhoea			0.10			<0.001		
Absent	57 (15.9)	76 (20.7)		260 (72.6)	117 (31.9)			
Present	301 (84.1)	291 (79.3)		98 (27.4)	250 (68.1)		-67.4%	-14.1%

treatment group. Overall a CIN 1 lesion regression is observed in the total population in 6 months of about 20% (from 63.2% to 48.0%).

No adverse effects were reported by patients in therapy (Figure 4).

The analysis of risk factors for the persistence of infection or lesions (Table 4) showed that, among the lifestyle risk factors, cigarette smoking (more than 10 sig/die) leads to an increase in the risk of persistence of the lesion about 2 times. The presence of ectopia, a vaginal pH greater than 4.5, and a positive Swift test entail a doubled risk of the persisting lesion, and the presence of leucorrhoea carries a risk of 3.5 times greater than the persistence of lesion. Performing the treatment in reverse halves this risk.

4. Discussion

Many factors have been reported regarding the risk of persistence of HPV infection and the progression of a CIN lesion. In recent years, many studies have shown that the stability and composition of the vaginal microbiome can influence viral clearance and probably also the progression of cervical preneoplastic lesions [1, 4–9].

Figure 3: (a) Epithelialization and vaginal health indexes in the two study groups. (b) Epithelialization and vaginal health indexes in the two study groups.

The treatment used is based on carboxy-methyl-beta-glucan, hydrophilic polymers capable of forming on the vaginal mucosa a mucoadhesive film that protects from external microbial agents and assists in maintaining and controlling the physiological conditions of the processing areas of the cervicovaginal mucosa by hydration. Carboxy-methyl-beta-glucan contributes to the maintenance and/or restoration of the vaginal microbiota through a prebiotic effect.

Our data have shown how in vivo carboxy-methyl-beta-glucan in polycarbophil vaginal therapy can improve cervical epithelialization. Indeed, an improvement in the ectopia pattern was observed with a reduction in severe ectropion (>2/3) in the therapy group compared to the control group, with a corresponding increase in the rate and extension of metaplasia and an improvement in the uptake of the Lugol test with a reduction in the proportion of patients with a noncaptive test.

The observed metaplasia and Lugol's test uptake were expressions of the repair process of ectopia with the conversion of a delicate tissue such as the cylindrical one into tissue more resistant to vaginal insults such as the multilayered squamous tissue.

This repair probably involves a reduction in the rates of tissue inflammation and predisposition to the development of infection. Indeed, the therapy has been shown to improve the vaginal health of patients who presented clinical signs of bacterial or fungal vulvovaginitis at the first visit. The therapy induced a resolution of the leucorrhoea, a normalization of the vaginal pH, and a negativization of the Swift test in a more significant percentage of cases compared to the group not in therapy.

Our data demonstrated a regression rate at 6 months from the histological diagnosis of CIN 1 significantly higher in the therapy group (23.7%; $n = 85/358$) than in the control group (6.8%; $n = 25/367$).

The literature reported a rate of spontaneous CIN 1 lesion remission of about 60% over a 12-24-month period [11]. Our data agree with the data of Scardamaglia et al.

Table 3: Cytological, molecular, colposcopic, and histological reports in the two study groups.

	Time 0 months		p value	Time 6 months		p value	Difference % group A	Difference % group B
	Group A ($N = 358$)	Group B ($N = 367$)		Group A ($N = 358$)	Group B ($N = 367$)			
Pap smear			0.75			<0.001		
Negative	67 (18.7)	72 (19.6)		175 (48.9)	117 (31.9)			
Positive	291 (81.3)	295 (80.4)		183 (51.1)	250 (68.1)		-37.1%	-15.2%
HPV test			0.55			<0.001		
Negative	2 (1.3)	4 (2.2)		61 (40.7)	33 (18.3)			
Positive	148 (98.7)	176 (97.8)		89 (59.3)	147 (81.7)		-39.9%	-16.5%
Colposcopy								
Negative	64 (17.9)	66 (18.0)	0.97	212 (59.2)	145 (39.5)	<0.001		
Positive	294 (82.1)	301 (82.0)		146 (40.8)	222 (60.5)		-50.3%	-26.2%
Biopsy								
Negative	131 (36.6)	136 (37.1)	0.89	216 (60.3)	161 (43.9)	<0.001		
Positive	227 (63.4)	231 (62.9)		142 (39.7)	206 (56.1)		-37.4%	-10.8%

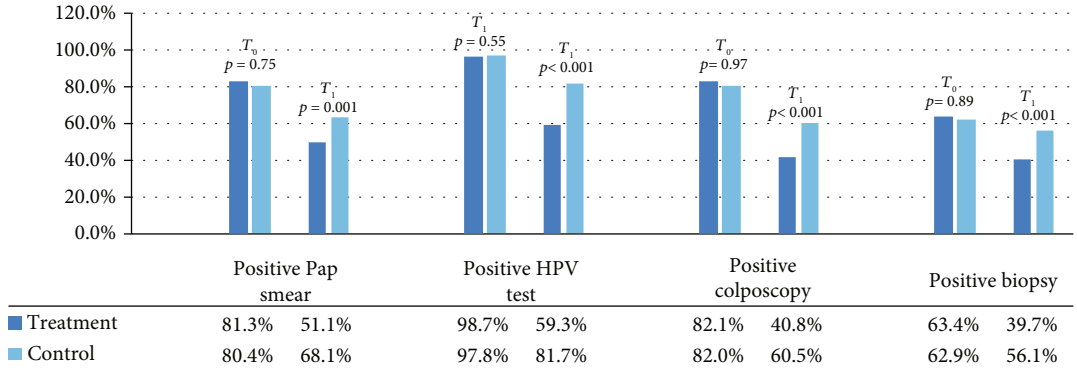

Figure 4: Cytological, molecular, colposcopic, and histological reports in the two study groups.

[12] and Stentella et al. [13] who demonstrated a significant regression of CIN 1 lesion in patients treated with carboxymethyl beta-glucan.

It is likely that the improvement observed in the study population was attributable to the therapy performed as the short follow-up interval (6 months). The effect probably depended on the ability of the medical device to promote greater stability of the vaginal environment.

The presence of bacterial vaginosis (VB) has been associated with a delay in HPV clearance in patients with CIN, suggesting that the presence of a poor lactobacilli microbiota (community state type-IV-CST IV) may play a role in this persistence. It was also shown that greater diversity of the vaginal microbiota (CST-IV) is associated with greater severity of CIN lesions [14].

The presence of lactobacilli-producing H_2O_2 seems protective in preventing the progression of dysplasia and ultimately the carcinogenic process. A greater prevalence of L. jensenii and L. coleohominis, both producers of H_2O_2, has been demonstrated in women with LSIL compared to HSIL. Furthermore, regardless of lactic acid concentrations, Lactobacilli spp. is capable of being cytotoxic when cultured in vitro against cervical cancer cells, but not in normal cells, highlighting an even more complex interaction between cervical cells, the microbiota, and the vaginal environment [6].

This study has shown that correcting the vaginal microbiota and favoring cervical epithelialization with a specific therapy favors CIN 1 lesion regression.

Our data confirmed that the presence of leucorrhoea, a positive Swift test, and a basic vaginal pH correlate with an at least doubled risk of persistence of CIN lesion at the cervical level.

Active and passive cigarette smoking is one of the major risk factors in the development of CIN in the presence of HPV infection [15]. Min et al. have recently shown that smokers have an increased risk of both CIN 1 (OR = 1.81; 95% CI, 1.26–2.60) and CIN 2/3 (OR = 1.77; 95% CI, 1.10-2.86) [16].

Alcohol consumption is known as a potential risk factor in acquiring HPV infection, although the data on the risk of persistence of lesions, the presence of cervical cancer, and alcohol consumption are few and controversial [17–19]. In our study, we showed an increased risk of persistent lesions in smokers but not in the presence of alcohol consumption.

Table 4: Relative risk of persistence of injury in relation to the variables under study.

	Case	Total	RR (IC 95%)
Smoke habits > 10 cig	216	384	2.04 (1.51-2.74)
Daily alcohol use	46	106	0.81 (0.53-1.21)
Partner > 4	255	519	1.17 (0.85-1.62)
Ectopia > 2/3	117	180	2.52 (1.78-3.58)
Metaplasia > 20%	145	297	1.06 (0.78-1.42)
Lugol test positive	305	466	9.52 (6.51-13.90)
pH > 4.5	126	207	2.07 (1.49-2.88)
Wift test positive	122	200	2.07 (1.48-2.89)
Presence of leucorrhoea	222	348	3.51 (2.58-4.76)
Treatment	142	358	0.51 (0.38-0.69)

The high number of patients, the execution of diagnostic tests (always performed by the same operators), and the short follow-up times (6 months) represented the strengths of this study.

The choice of enrolling only patients with reassessment time at 6 months from the first visit has allowed to minimize the variations of the vaginal environment induced by other environmental factors and to exclude that the observed improvement of colposcopic pictures and histological findings may be linked to the natural history of HPV infection. The choice of enrolling only Caucasian patients in the study erases the impact of ethnicity on the risk of CIN and cervical microbiota differences in other populations. Indeed, it has been demonstrated that the overall HPV prevalence rate of migrant women is four times higher than the overall prevalence observed among Italian women [20].

The limitations of the study were its retrospective nature and the lack of randomization with a placebo group.

In conclusion, vaginal therapy based on carboxy-methyl-beta-glucan turned out to improve overall vaginal health with a positive impact on the risk of persistence and progression of low-grade cervical lesions of the uterine cervix.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

This study was carried out in the context of colposcopic ambulatory of University of Naples Federico II. This article has been presented in 8th European Congress of EFC (European Federation For Colposcopy).

Conflicts of Interest

The authors declare that there is no conflict of interest.

Authors' Contributions

GL contributed in protocol development, data collection and management, and manuscript revisiting. LDC contributed in data collection and analysis and manuscript writing. NDR contributed in protocol development, data management and analysis, and manuscript writing. CN contributed in manuscript revisiting. GB contributed in manuscript editing and revisiting.

References

[1] N. Egawa, K. Egawa, H. Griffin, and J. Doorbar, "human papillomaviruses; epithelial tropisms, and the development of neoplasia," *Viruses*, vol. 7, no. 7, pp. 3863–3890, 2015.

[2] N. Munoz, "Human papillomavirus and cancer: the epidemiological evidence," *Journal of Clinical Virology*, vol. 19, no. 1-2, pp. 1–5, 2000.

[3] E. R. Myers, D. C. McCrory, K. Nanda, L. Bastian, and D. B. Matchar, "Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis," *American Journal of Epidemiology*, vol. 151, no. 12, pp. 1158–1171, 2000.

[4] A. Audirac-Chalifour, K. Torres-Poveda, M. Bahena-Román et al., "Cervical microbiome and cytokine profile at various stages of cervical cancer: a pilot study," *PLoS One*, vol. 11, no. 4, p. e0153274, 2016.

[5] A. Mitra, D. A. MacIntyre, J. R. Marchesi, Y. S. Lee, P. R. Bennett, and M. Kyrgiou, "The vaginal microbiota, human papillomavirus infection and cervical intraepithelial neoplasia: what do we know and where are we going next?," *Microbiome*, vol. 4, no. 1, p. 58, 2016, Review.

[6] E. Motevaseli, M. Shirzad, S. M. Akrami, A. S. Mousavi, A. Mirsalehian, and M. H. Modarressi, "Normal and tumour cervical cells respond differently to vaginal lactobacilli, independent of pH and lactate," *Journal of Medical Microbiology*, vol. 62, no. 7, pp. 1065–1072, 2013.

[7] E. Gillet, J. F. A. Meys, H. Verstraelen et al., "Bacterial vaginosis is associated with uterine cervical human papillomavirus infection: a meta-analysis," *BMC Infectious Diseases*, vol. 11, no. 1, 2011.

[8] J. E. Lee, S. Lee, H. Lee et al., "Association of the vaginal microbiota with human papillomavirus infection in a Korean twin cohort," *PLoS One*, vol. 8, no. 5, article e63514, 2013.

[9] W. Gao, J. Weng, Y. Gao, and X. Chen, "Comparison of the vaginal microbiota diversity of women with and without human papillomavirus infection: a cross-sectional study," *BMC Infectious Diseases*, vol. 13, no. 1, 2013.

[10] J. Doorbar and H. Griffin, "Refining our understanding of cervical neoplasia and its cellular origins," *Papillomavirus Research*, vol. 7, pp. 176–179, 2019.

[11] N. Bansal, J. D. Wright, C. J. Cohen, and T. J. Herzog, "Natural history of established low grade cervical intraepithelial (CIN 1) lesions," *Anticancer Research*, vol. 28, no. 3B, pp. 1763–1766, 2008.

[12] P. Scardamaglia, C. Carraro, P. Mancino, and P. Stentella, "Effectiveness of the treatment with beta-glucan in the HPV-CIN 1 lesions," *Minerva Ginecologica*, vol. 62, no. 5, pp. 389–393, 2010.

[13] P. Stentella, A. Biamonti, C. Carraro et al., "Efficacy of carboxymethyl beta-glucan in cervical intraepithelial neoplasia: a

retrospective, case-control study," *Minerva Ginecologica*, vol. 69, no. 5, pp. 425–430, 2017.

[14] A. Mitra, D. A. MacIntyre, Y. S. Lee et al., "Cervical intraepithelial neoplasia disease progression is associated with increased vaginal microbiome diversity," *Scientific Reports*, vol. 5, no. 1, 2015.

[15] H. T. Tsai, Y. M. Tsai, S. F. Yang et al., "Lifetime cigarette smoke and second-hand smoke and cervical intraepithelial neoplasm—a community-based case-control study," *Gynecologic Oncology*, vol. 105, no. 1, pp. 181–188, 2007.

[16] K. J. Min, J. K. Lee, K. A. So, and M. K. Kim, "Association between passive smoking and the risk of cervical intraepithelial neoplasia 1 in Korean women," *Journal of Epidemiology*, vol. 28, no. 1, pp. 48–53, 2018.

[17] A. Hjartaker, M. S. Meo, and E. Weiderpass, "Alcohol and gynecological cancers: an overview," *European Journal of Cancer Prevention*, vol. 19, no. 1, pp. 1–10, 2010.

[18] N. E. Allen, V. Beral, D. Casabonne et al., "Moderate alcohol intake and cancer incidence in women," *Journal of the National Cancer Institute*, vol. 101, no. 5, pp. 296–305, 2009.

[19] K. J. Min, J. K. Lee, S. Lee, and M. K. Kim, "Alcohol consumption and viral load are synergistically associated with CIN 1," *PLoS One*, vol. 8, no. 8, article e72142, 2013.

[20] M. L. Tornesello, R. Cassese, N. De Rosa et al., "High prevalence of human papillomavirus infection in eastern European and west African women immigrants in South Italy," *APMIS*, vol. 119, no. 10, pp. 701–709, 2011.

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Research Article

Effect of Immunomodulatory Supplements Based on Echinacea Angustifolia and Echinacea Purpurea on the Posttreatment Relapse Incidence of Genital Condylomatosis: A Prospective Randomized Study

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Introduction. HPV infection is a highly infectious disease; about 65% of partners of individuals with genital warts will develop genital condylomatosis. Only in 20-30% it regresses spontaneously and relapse rates range deeply (9-80%). Echinacea extracts possess antiviral and immunomodulator activities. The aim of this study was to evaluate the efficacy of the therapy, using a formulation based on HPVADL18® (on dry extracts of 200 mg Echinacea Purpurea (EP) roots plus E. Angustifolia (EA)), on the posttreatment relapse incidence of genital condylomatosis. *Materials and Methods.* It is a prospective single-arm study. Patients with a satisfactory and positive vulvoscopy, colposcopy, or peniscopy for genital condylomatosis were divided into two random groups and subjected to destructive therapy with Co2 Laser. Group A (N=64) immediately after the laser therapy started a 4-month treatment with oral HPVADL18®; Group B (N=61) did not undergo any additional therapy. Patients were subjected to a follow-up after 1, 6, and 12 months. Differences in relapse incidence between the two groups during follow-up controls were evaluated by $\chi 2$-test; the groups were stratified by age, gender, and condylomatosis extension degree. *Results and Discussion.* Gender, age, and condyloma lesions' extension degree showed no statistically significant differences between the two trial groups. The relapse incidence differs statistically between the two studied groups and progressively decreases during the 12 months after treatment in both groups. Statistically significant reduction of relapse rates has been shown in Group A in patients over 25 years old. This difference is significant for both men and women. The relapse incidence is superior in case of extended condylomatosis. *Conclusions.* In conclusion, the presence of a latent infection causes condylomatosis relapse; in order to reduce the relapse risk an induction of a protective immune response seems to be essential to allow rapid viral clearance from genital areas surrounding lesion and treatment zones. Echinacea promotes this process. EP and EA dry root extracts seem to be a valid adjuvant therapy in reducing relapse incidence of lesions in patients treated for genital condylomatosis.

1. Introduction

HPV infection is one of the most common sexually transmitted infections in the world. More than 50% of sexually active adults contract the infection during their life. In the two years after a sexual debut the sexual risk of infection varies from 40 to 80% depending on the studied population and the HPV type [1]. There is a similar incidence of genital condylomatosis in males and females (0-2% and 0-7%) [2–4]. In men, compared to women, infections with multiple genotypes and low-oncogenic risk genotypes are more frequent [5]. Only 20-30% of the genital condylomatosis regresses spontaneously. This is a highly infectious disease; about 65% of partners of individuals with genital warts will develop genital condylomatosis. The risk of infection and the risk of progression of HPV-associated lesions are related to several factors including number of sexual partners experienced

during the life and early age of the first intercourse; tobacco smoking; and eating habits [6–8].

It has long since known that the above-ground portion and the roots of Echinacea Angustifolia (EA) and of E. Purpurea (EP) possess anti-inflammatory and immunostimulatory properties. Numerous in vitro and in vivo studies have been recently conducted in an effort to validate some of the traditional uses of Echinacea extracts [9]. Early studies have shown that only a few Echinacea extracts possess significant antiviral activity. In particular, above-ground portions and roots of EP show a strong antiviral activity, as they have a virucidal effect against influenza virus, herpes simplex virus, and coronaviruses [10, 11]. The EP appeared much less effective against intracellular viruses [12, 13], which could be resistant to the EP inhibitory effect; on the contrary, viral particles located in the extracellular fluids appeared to be vulnerable. Therefore, EP can act during an initial contact with virus, that is, at the beginning of infection and also during the transmission of the virus from the infected cells.

Numerous viral and bacterial infections cause an increase of expression of proinflammatory cytokines, in particular, of IL-6 and IL-8, which are therefore considered as markers of an inflammatory state [14, 15]. Any compound or herbal extract that inhibits or inverts the increase of IL-6/8 can be considered a potential anti-inflammatory agent. All the portions of the roots, leaves, stems, and flowers of EP show this effect [16].

These studies make it evident that Echinacea not exactly acts as an "immunostimulant" or "immune system booster," but more likely has an immunomodulatory action, rather than a generalized immunostimulatory effect [17–20].

The aim of the present study was to evaluate the efficacy of the therapy, using a formulation based on 200 mg of HPVADL18® (equal to 4 mg polyphenols plus 0.6 mg of echinacosides), on the post-treatment relapse incidence of genital condylomatosis.

2. Materials and Methods

Between July 2014 and July 2017, all patients with a genital condylomatosis diagnosis received in the Colposcopy and Cervical-Vaginal Pathology Unit of University Federico II, Naples, were invited to participate in a prospective randomized trial.

Patients were properly informed and provided their written consent to participate in the trial and to undergo ambulatory diagnostic examinations; afterwards, colposcopy or peniscopy was conducted and, if appropriate, biopsy examinations. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The criteria for participation in the trial were as follows: satisfactory and positive colposcopy / peniscopy for genital condylomatosis (cervix, vagina, perianal vulva, or perineum for females and penis, scrotum, or anal region for males) and / or histological examination for koilocytosis or condylomatosis in case of positive cervical biopsy.

Patients with H-SIL cytological diagnosis, CIN 1-3 histologic diagnosis, or invasive cervical carcinoma, pregnant women, immunosuppressed patients, and individuals infected with Human Immunodeficiency Virus (HIV-positive) were not enrolled in the trial.

Colposcopy and peniscopy were conducted after an application of 3% acetic acid. Visible acetowhite lesions have been classified in accordance with the criteria of the International Federation of Cervical Pathology and Colposcopy [21].

In case of genital condylomatosis, to standardize extension of the lesions, genitals were divided into 10 genital areas for women, that is, cervix, left/right vaginal wall, left/right major labia, left/right minor labia, clitoris, pubis, perineum, and perianus and into 5 genitals arear for men, that is, pubis, scrotum, glans, preputial balanus grooves, and penis. Patients were classified into 3 lesion degrees, according to the number of genital areas affected by condylomas and the number of the condylomas:

(1) From 1 to 5 condylomas on 1-2 genital areas (mild and localized condylomatosis)

(2) > 5 condylomas on 2-3 genital areas (mild and diffuse condylomatosis)

(3) > 5 condylomas on > 3 genital areas (extended condylomatosis).

Patients with low grade (ZTAG1) or high grade (ZTAG2) cervical lesions were subjected to a targeted biopsy using a biopsy forceps (CFS CHIMO Schumacher Pliers) with 5-6 mm jaw in order to obtain 4-5 mm tissue specimens.

Two serial 4 micron sections of the formalin-fixed and paraffin-embedded sample were stained with hematoxylin and eosin. The specimens were examined by optical microscope and classified as normal, CIN 1, CIN 2, and CIN 3 carcinoma in situ or microinvasive carcinoma according to the criteria of the World Health Organization.

Patients with low grade (CIN 1) or high grade (CIN2-3) preneoplastic lesions were excluded from the trial and carried on all the therapeutic and diagnostic procedures as recommended by national and international guidelines.

Patients with genital condylomatosis, diagnosed through colposcopy, vulvoscopy, peniscopy, and/or biopsy examinations, were included in the study. All enrolled individuals were divided into two random groups and subjected to destructive therapy with Co2 Laser.

Group A immediately after the laser therapy started a 4-month treatment with oral immunomodulatory supplements based on HPVADL18®; Group B did not undergo any additional therapy (control group). The medical device administered to Group A was composed of 200 mg of HPVADL18® (equal to 4 mg polyphenols plus 0.6 mg of echinacosides), 40 mg vitamin C, 5 mg of zinc, and 0.5 mg of copper.

Patients were subjected to a follow-up colposcopy after 1, 6, and 12 months. In case the infection persisted and relapse condyloma lesions occurred, patients were again subjected to destructive therapy until the full lesion elimination.

Table 1: Clinical characteristics of the study groups.

	Group A *N = 64* *N (%)*	*Group B* *N = 61* *N(%)*	P value[1]
Age (years)			
≤ 25	9 (14.1)	7 (11.5)	NS
> 25	55 (85.9)	54 (88.5)	
Gender			
Females	48 (75.0)	41(68.9)	NS
Males	16(25.0)	19 (31.1)	
Grade[2]			
1	37 (57.8)	33 (54.1)	NS
2	22 (34.4)	22 (36.1)	
3	5 (7.8)	6 (9.8)	

[1]X_2 test.

[2]Patients were classified into 3 lesion degrees, according to the number of genital areas affected by condylomas and the number of the condylomas: (1) from 1 to 5 condylomas on 1-2 genital areas (mild and localized condylomatosis); (2) > 5 condylomas on 2-3 genital areas (mild and diffuse condylomatosis); and (3) > 5 condylomas on > 3 genital areas (extended condylomatosis).

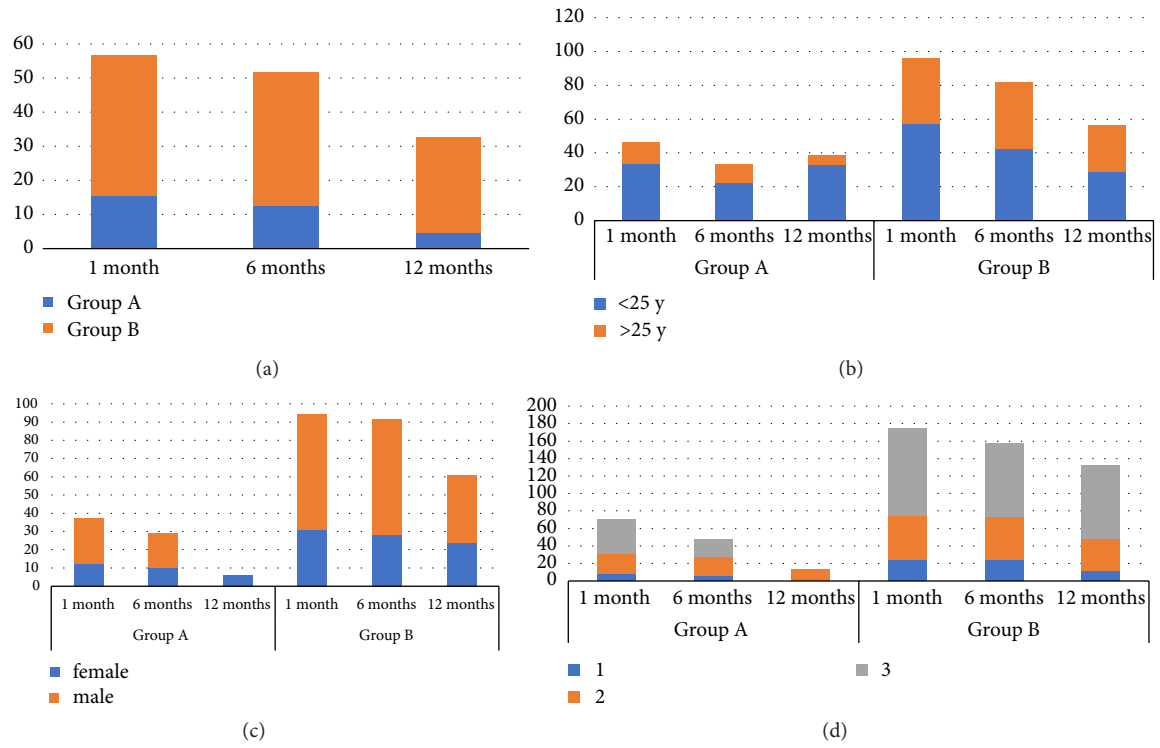

Figure 1: (a) Posttreatment relapses incidence in both study groups; (b) posttreatment relapses incidence stratified by age; (c) posttreatment relapses incidence stratified by sex; and (d) posttreatment relapses incidence stratified by lesion extension degree.

All colposcopy, peniscopy and biopsy examinations and therapies were performed by our team.

2.1. Statistical Analysis. Statistical analysis of the data was executed by SPSS software 20.0 (SPSS Inc., Chicago, IL, USA). Data with p-values <0.05 were considered statistically significant.

Demographic and clinical data of the two groups were compared by Student's t-test for the data with parametric distribution (age) and by $\chi 2$-test for ordinal variables (gender and condylomatosis extension degree). Differences in relapse incidence between two groups during follow-up controls were evaluated by $\chi 2$-test; the groups were stratified by age, gender, and condylomatosis extension degree.

Table 2: Posttreatment relapse incidence of genital condylomatosis stratified for age, gender, and grade.

		Group A *N = 64* *N (%)*	*Group B* *N = 61* *N(%)*	P value[1]
	1-month follow-up			
Total group	Negative	54 (84.4)	36 (59.0)	*<.01*
	Positive	10 (15.6)	25 (41.0)	
Age (years)				
≤ 25	Negative	6 (66.7)	3 (42.9)	*NS*
	Positive	3 (33.3)	4 (57.1)	
> 25	Negative	48 (87.3)	33 (61.1)	*<.01*
	Positive	7 (12.7)	21 (38.9)	
Gender				
Females	Negative	42 (87.5)	29 (69.0)	*<.05*
	Positive	6 (12.5)	13 (31.0)	
Males	Negative	12 (75.0)	7 (36.8)	*<.05*
	Positive	4 (25.0)	12 (63.2)	
Grade[2]				
1	Negative	34 (91.9)	25 (75.8)	*NS*
	Positive	3 (8.1)	8 (24.2)	
2	Negative	17 (77.3)	11 (50.0)	*NS*
	Positive	5 (22.7)	11 (50.0)	
3	Negative	3 (60.0)	0 (0)	*<.05*
	Positive	2 (40.0)	6 (100)	
	6-month follow-up			
Total	Negative	56 (87.5)	37 (60.7)	*<.001*
	Positive	8 (12.5)	24 (39.3)	
Age (years)				
≤ 25	Negative	7 (77.8)	4 (57.1)	*NS*
	Positive	2 (22.2)	3 (42.9)	
> 25	Negative	49 (89.1)	33 (61.1)	*<.001*
	Positive	6 (10.9)	21 (38.9)	
Gender				
Females	Negative	43 (89.6)	30 (71.4)	*<.05*
	Positive	5 (10.4)	12 (28.6)	
Males	Negative	13 (81.2)	7 (36.8)	*<.05*
	Positive	3 (18.8)	12 (63.2)	
Grade[2]				
1	Negative	35 (94.6)	25 (75.8)	*<.05*
	Positive	2 (5.4)	8 (24.2)	
2	Negative	17 (77.3)	11 (50.0)	*NS*
	Positive	5 (22.7)	11 (50.0)	
3	Negative	4 (80.0)	1 (16.7)	*<.05*
	Positive	1 (20.0)	5 (83.3)	
	12-month follow-up			
Total	Negative	61 (95.3)	44 (72.1)	*<.0001*
	Positive	3 (4.7)	17 (27.9)	
Age (years)				
≤ 25	Negative	9 (100.0)	5 (71.4)	*NS*

Table 2: Continued.

		Group A N = 64 N (%)	*Group B N = 61 N(%)*	P value[1]
	Positive	0 (0)	2 (28.6)	
> 25	Negative	52 (94.5)	39 (72.2)	*<.005*
	Positive	3 (5.5)	15 (27.8)	
Gender				
Females	Negative	45 (93.8)	32 (76.2)	*<.05*
	Positive	3 (6.2)	10 (23.8)	*<.05*
Males	Negative	16 (100)	12 (63.2)	
	Positive	0 (0)	7 (36.8)	
Grade[2]				
1	Negative	37 (100)	29 (87.9)	*<.05*
	Positive	0 (0)	4 (12.1)	
2	Negative	19 (86.4)	14 (63.6)	*NS*
	Positive	3 (13.6)	8 (36.4)	
3	Negative	5 (100)	1 (16.7)	*<.05*
	Positive	0 (0)	5 (83.3)	

[1]X_2 test.

[2]Patients were classified into 3 lesion degrees, according to the number of genital areas affected by condylomas and the number of the condylomas: (1) from 1 to 5 condylomas on 1-2 genital areas (mild and localized condylomatosis); (2) > 5 condylomas on 2-3 genital areas (mild and diffuse condylomatosis); and (3) > 5 condylomas on > 3 genital areas (extended condylomatosis).

3. Results

One hundred and forty women appeared to be suitable for destructive therapy with Co2 Laser and were divided into Group A (n = 70) and Group B (n = 70) at random. Of these, 6 patients did not undergo a required operation and 9 patients did not undergo a programmed follow-up or interrupted the therapy before the 4-month period expired.

One hundred and twenty-five patients, 90 (72%) women and 35 (28%) men, completed the diagnostic-therapeutic procedure as scheduled by the protocol and were therefore included in the analysis. Of the studied population, 64 women (51.2%) underwent Echinacea therapy after the treatment (Group A) and 61 (48.8%) did not undergo any additional therapy (Group B, control group). The mean age of female patients in Group A is 33.0±8.4 years, in Group B 32.1±7.3 years (p = N.S.); the mean age of male patients in Group A is 31.4±7.2 years, in Group B 34.4±7.1 years (p = NS). Table 1 shows epidemiological data and condyloma lesions' extension degree for Groups A and B. There were no statistically significant differences in these data in the two trial groups. No severe side effects were recorded in Group A. Only 5 (7.8%) patients reported some digestive difficulties.

The relapse incidence differs statistically between the two studied groups (Table 2, Figure 1) and progressively decreases during the 12 months after treatment in both groups. Therapy does not seem to modify the relapse incidence in very young female patients under the age of 25. Instead, statistically significant reduction of relapse rates has been shown in patients over 25 years old. This difference is significant for both men and women. The relapse incidence is superior in case of extended condylomatosis (extension degree n.3) (Table 2, Figure 1).

4. Discussion and Conclusions

Clinical trials conducted on patients with genital condylomatosis show quite different relapse rates, depending on the studies and on the treatment and range from 9% to 80% [22–25]. Our data show a global relapse rate of about 30%.

Therapy with HPVADL18 is effective in reducing relapse incidence of lesions in patients treated for genital condylomatosis. Our data prove, indeed, that the relapse incidence of lesion is greater in the control group compared to the treatment group at the first, second, and third follow-up controls.

Spontaneous remission of genital condylomatosis is possible, but not frequent; the percentage of spontaneously recovered patients varies considerably and ranges from 0% to 50% [24, 25].

Most commonly used therapy is cryotherapy or diathermocoagulation (65% and 28%); drug therapy is much less frequent (6%). Approximately 50% of patients undergo a single treatment procedure; the number of patients that undergo more than one treatment procedures progressively decreases; 3% of patients undergo 5 or more treatments [26]. This pattern is similar for both sexes and is according to the anatomical site [26].

In compliance with these data, the difference in relapse incidence between the two trial groups is statistically significant even when these are stratified by gender and extension degree of the lesion.

On the other hand, age appears to be a determinant factor; in fact, in individuals under the age of 25, the therapy does not seem to influence significantly the relapse incidence of lesion. The small numbers of younger age groups, however, cannot induce us to generalize this data.

Based on these data, it follows that in very young individuals additional therapy with HPVADL18 could be superfluous. Moreover, individuals under the age of 25 show greater relapse incidence at the first follow-up.

The relapse incidence decreases progressively in both groups as the time passes and is related to the extension degree; in fact, the extension degree 3 of condylomatous lesions corresponds to a higher relapse incidence than degrees 1 and 2.

The presence of a latent infection causes lesion relapse; in order to reduce the relapse risk after the treatment of condyloma lesions, an induction of a protective immune response seems to be essential to allow rapid viral clearance from genital areas surrounding lesion and treatment zones. Introduction of an immunostimulatory substance such as Echinacea seems to promote this process.

The HPV-induced immune response is both humoral and cell mediated.

A humoral immune response to HPV capsid protein L1 is weak during natural infection.

The humoral immune response to the viral capsid can be detected averagely starting from 6 months after the infection, though 30-50% of patients with persistent infection will never present a seroconversion [27]. The seropositivity to the infectious genotype persists only in 50% of the cases, even when the initial lesion transformed to a cervical cancer [28]. When viral DNA has been eliminated, specific antibodies can be detected only in half of cases after 5 years [29].

HPV infection promotes a cellular immune response, especially in the active phase of the clearance of genital condylomatosis infection, when a cell infiltration of macrophages and T cells develops in correspondence to the lesion [30]. In the blood, an immune response of CD4+ T cells against E2, E6, and E7 proteins is associated with HPV 16 and HPV 18 infection and occurs in particular in early disease phases and in case of regressing lesions, less when a persistent disease takes place.

In individuals with a deficiency of cell-mediated immune response, HPV infection, genital condylomatosis, or precancerous lesions are destined to persist. Therefore, this type of response seems to be essential for the viral clearance.

The EP immunomodulatory effect has been widely demonstrated. EP extract was used for the preventive care and for the treatment of various viral infections [31].

In vitro studies have shown that EP acts directly on a number of cell types, including natural killer cells [32], polymorphonuclear leukocytes [33], and macrophages [34]. EP induces a proliferation of T cells. This has been conferred to the activation of macrophages that stimulates a production of IFN-γ and, consequently, a secondary activation of T lymphocytes [35]. IFN-γ is one of the fundamental mediators for the latency prevention [36]; it has been proven that this mechanism is responsible for reducing the latency incidence of herpes virus simplex infection and, consequently, reducing the relapse risk of HSV lesions [36]. It is possible that an analogous mechanism induces a cell-mediated response to HPV infection, which allows the reduction of the persistence of infection and, therefore, the lesion relapse.

This study has some limitations: this is a single institution study with a small number of participants and it lacks placebo controls. On the other hand, the strengths of this study are as follows: the rigorous inclusions criteria, the evaluation of patients at colposcope (so not only grossly visible genital warts were evaluated and treated but also small lesions), and the treatment modality with laser CO2 for all patients.

In conclusion, HPVADL18® seems to be a valid adjuvant therapy in reducing relapse incidence of lesions in patients treated for genital condylomatosis.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors state that there are no conflicts of interest.

References

[1] P. L. Reiter, W. F. Pendergraft, and N. T. Brewer, "Meta-analysis of human papillomavirus infection concordance," *Cancer Epidemiology Biomarkers & Prevention*, vol. 19, no. 11, pp. 2916–2931, 2010.

[2] Health Protection Agency, "Trends in genital warts and genital herpes diagnoses in the United Kingdom," *Health Protection Report*, vol. 1, no. 35, pp. 4–9, 2007.

[3] J. Monsonégo, J.-G. Breugelmans, S. Bouée, A. Lafuma, S. Bénard, and V. Rémy, "Anogenital warts incidence, medical management and costs in women consulting gynaecologists in France," *Gynecologie Obstetrique et Fertilite*, vol. 35, no. 2, pp. 107–113, 2007.

[4] X. Castellsagué, C. Cohet, L. M. Puig-Tintoré et al., "Epidemiology and cost of treatment of genital warts in Spain," *European Journal of Public Health*, vol. 19, no. 1, pp. 106–110, 2009.

[5] A. G. Nyitray, L. Menezes, B. Lu et al., "Genital human papillomavirus (HPV) concordance in heterosexual couples," *The Journal of Infectious Diseases*, vol. 206, no. 2, pp. 202–211, 2012.

[6] R. L. Winer, Q. Feng, J. P. Hughes, S. O'Reilly, N. B. Kiviat, and L. A. Koutsky, "Risk of female human papillomavirus acquisition associated with first male sex partner," *The Journal of Infectious Diseases*, vol. 197, no. 2, pp. 279–282, 2008.

[7] S. K. Kjaer, B. Chackerian, A. J. C. van den Brule et al., "High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse)," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 10, no. 2, pp. 101–106, 2001.

[8] P. C. Giraldo, J. Eleutério Jr., D. I. M. Cavalcante, A. K. S. Gonçalves, J. A. A. Romão, and R. M. N. Eleutério, "The role of high-risk HPV-DNA testing in the male sexual partners of women with HPV-induced lesions," *European Journal of Obstetrics & Gynecology and Reproductive Biology*, vol. 137, no. 1, pp. 88–91, 2008.

[9] M. Sharifi-Rad, D. Mnayer, M. F. Morais-Braga et al., "Echinacea plants as antioxidant and antibacterial agents: From traditional medicine to biotechnological applications," *Phytotherapy Research*, vol. 32, no. 9, pp. 1653–1663, 2018.

[10] J. Hudson, S. Vimalanathan, L. Kang, V. T. Amiguet, J. Livesey, and J. T. Arnason, "Characterization of antiviral activities in Echinacea root preparations," *Pharmaceutical Biology*, vol. 43, no. 9, pp. 790–796, 2005.

[11] S. Vimalanathan, L. Kang, V. T. Amiguet, J. Livesey, J. T. Arnason, and J. Hudson, "Echinacea purpurea aerial parts contain multiple antiviral compounds," *Pharmaceutical Biology*, vol. 43, no. 9, pp. 740–745, 2005.

[12] S. Pleschka, M. Stein, R. Schoop, and J. B. Hudson, "Antiviral properties and mode of action of standardized Echinacea purpurea extract against highly pathogenic avian Influenza virus (H5N1, H7N7) and swine-origin H1N1 (S-OIV)," *Virology Journal*, vol. 6, p. 197, 2009.

[13] M. Sharma, S. A. Anderson, R. Schoop, and J. B. Hudson, "Induction of multiple pro-inflammatory cytokines by respiratory viruses and reversal by standardized Echinacea, a potent antiviral herbal extract," *Antiviral Research*, vol. 83, no. 2, pp. 165–170, 2009.

[14] J. J. Burns, L. Zhao, E. W. Taylor, and K. Spelman, "The influence of traditional herbal formulas on cytokine activity," *Toxicology*, vol. 278, no. 1, pp. 140–159, 2010.

[15] J. B. Calixto, M. M. Campos, M. F. Otuki, and A. R. S. Santos, "Anti-inflammatory compounds of plant origin. Part II. Modulation of pro-inflammatory cytokines, chemokines and adhesion molecules," *Planta Medica*, vol. 70, no. 2, pp. 93–103, 2004.

[16] S. Vimalanathan, J. T. Arnason, and J. B. Hudson, "Anti-inflammatory activities of Echinacea extracts do not correlate with traditional marker components," *Pharmaceutical Biology*, vol. 47, no. 5, pp. 430–435, 2009.

[17] M. Altamirano-Dimas, M. Sharma, and J. B. Hudson, "Echinacea and anti-inflammatory cytokine responses: Results of a gene and protein array analysis," *Pharmaceutical Biology*, vol. 47, no. 6, pp. 500–508, 2009.

[18] A. Matthias, L. Banbury, L. M. Stevenson, K. M. Bone, D. N. Leach, and R. P. Lehmann, "Alkylamides from echinacea modulate induced immune responses in macrophages," *Immunological Investigations*, vol. 36, no. 2, pp. 117–130, 2007.

[19] P. Guiotto, K. Woelkart, I. Grabnar et al., "Pharmacokinetics and immunomodulatory effects of phytotherapeutic lozenges (bonbons) with Echinacea purpurea extract," *Phytomedicine*, vol. 15, no. 8, pp. 547–554, 2008.

[20] A. M. Sullivan, J. G. Laba, J. A. Moore, and T. D. G. Lee, "Echinacea-induced macrophage activation," *Immunopharmacology and Immunotoxicology*, vol. 30, no. 3, pp. 553–574, 2008.

[21] J. Bornstein, J. Bentley, P. Bösze et al., "2011 colposcopic terminology of the international federation for cervical pathology and colposcopy," *Obstetrics & Gynecology*, vol. 120, no. 1, pp. 166–172, 2012.

[22] L. A. Brodell, M. G. Mercurio, and R. T. Brodell, "The diagnosis and treatment of human papillomavirus-mediated genital lesions," *Cutis; Cutaneous Medicine for the Practitioner*, vol. 79, no. 4, pp. 5–10, 2007.

[23] N. Scheinfeld and D. S. Lehman, "An evidence-based review of medical and surgical treatments of genital warts," *Dermatology Online Journal*, vol. 12, no. 5, 2006.

[24] D. J. Wiley, J. Douglas, K. Beutner et al., "External genital warts: diagnosis, treatment, and prevention," *Clinical Infectious Diseases*, vol. 35, supplement 2, pp. S210–S224, 2002.

[25] C. M. Kodner and S. Nasraty, "Management of genital warts," *American Family Physician*, vol. 70, no. 12, pp. 2335–2346, 2004.

[26] M. M. Gianino, S. Delmonte, E. Lovato et al., "A retrospective analysis of the costs and management of genital warts in Italy," *BMC Infectious Diseases*, vol. 13, no. 1, p. 470, 2013.

[27] J. J. Carter, L. A. Koutsky, J. P. Hughes et al., "Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection," *The Journal of Infectious Diseases*, vol. 181, no. 6, pp. 1911–1919, 2000.

[28] J. J. Carter, M. M. Madeleine, K. Shera et al., "Human papillomavirus 16 and 18 L1 serology compared across anogenital cancer sites," *Cancer Research*, vol. 61, no. 5, pp. 1934–1940, 2001.

[29] S. S. Wang, M. Schiffman, R. Herrero et al., "Determinants of human papillomavirus 16 serological conversion and persistence in a population-based cohort of 10 000 women in Costa Rica," *British Journal of Cancer*, vol. 91, no. 7, pp. 1269–1274, 2004.

[30] S. A. Jenison, X.-P. Yu, J. M. Valentine, and D. A. Galloway, "Characterization of human antibody-reactive epitopes encoded by human papillomavirus types 16 and 18," *Journal of Virology*, vol. 65, no. 3, pp. 1208–1218, 1991.

[31] B. P. Barrett, R. L. Brown, K. Locken, R. Maberry, J. A. Bobula, and D. D'Alessio, "Treatment of the common cold with unrefined Echinacea: A randomized, double-blind, placebo-controlled trial," *Annals of Internal Medicine*, vol. 137, no. 12, pp. 939–946, 2002.

[32] N. L. Currier and S. C. Miller, "Echinacea purpurea and melatonin augment natural-killer cells in leukemic mice and prolong life span," *The Journal of Alternative and Complementary Medicine*, vol. 7, no. 3, pp. 241–251, 2001.

[33] D. R. Cundell, M. A. Matrone, P. Ratajczak, and J. D. Pierce Jr., "The effect of aerial parts of Echinacea on the circulating white cell levels and selected immune functions of the aging male Sprague-Dawley rat," *International Immunopharmacology*, vol. 3, no. 7, pp. 1041–1048, 2003.

[34] V. Goel, C. Chang, J. V. Slama et al., "Echinacea stimulates macrophage function in the lung and spleen of normal rats," *The Journal of Nutritional Biochemistry*, vol. 13, no. 8, pp. 487–492, 2002.

[35] L. Corey, "The current trend in genital herpes: progress in prevention," *Sexually Transmitted Diseases*, vol. 21, no. 2, pp. S38–S44, 1994.

[36] R. L. Sparks-Thissen, D. C. Braaten, and K. Hildner, "CD4 T cell control of acute and latent murine gamma herpes virus infection requires IFNγ," *Virology*, vol. 338, no. 2, pp. 201–208, 2005.

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INFECTIOUS AGENTS AND CANCER

RESEARCH ARTICLE Open Access

A prospective randomized study on limits of colposcopy and histology: the skill of colposcopist and colposcopy-guided biopsy in diagnosis of cervical intraepithelial lesions

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Abstract

Background: The main objective of our study was to evaluate the colposcopist ability to correctly identify the worst area of a cervical lesion where biopsy should be performed; the secondary objective was to investigate the influence of the colposcopist skill in grading cervical preneoplastic lesions.

Methods: 296 patients referred for colposcopy were enrolled in a prospective study. All patients were randomized in two groups: in the first group, "senior group", the colposcopy was performed by an experienced colposcopist; in the second group, "junior group", the colposcopy was performed by a less experienced colposcopist. A detailed colposcopic description, including a grading of the lesion, was completed for each case. During the colposcopic exam patients underwent two direct biopsies; each biopsy was labeled with letter A (suspicious area with most severe grade) or B (suspicious area with less severe grade) according to the judgment of the colposcopist. An experienced pathologist reanalyzed the histological slides, after routine diagnosis.

Results: The senior group identify the worst area of the cervical lesion in statistical significant higher rates than junior group. Specimen A resulted representative of the higher-grade lesion (A > B) in 73.7 % ($N = 28$) in senior group and in 48.4 % ($N = 15$) in junior group; while in 26.3 % ($N = 10$) the higher-grade lesion corresponded to specimen B (A < B) in senior group and in 51.6 % ($N = 16$) in junior group ($p < .05$).

Conclusion: The ability of a colposcopist in grading cervical lesion depends on his experience.

Keywords: Cervical intraepithelial lesions, Multiple biopsies, Colposcopic accuracy, Colposcopic grade

Background

Defining the presence, the extension and the severity of cervical intraepithelial neoplasia (CIN) is an important clinical issue in reducing cervical cancer risk and development. Colposcopy represents the second step of the diagnostic approach [1, 2]. One of the main roles of colposcopy is to guide the diagnostic biopsy. The result of the histological exam performed on the cervical biopsy is then considered as the best diagnosis in the preoperative approach to CIN.

Colposcopic accuracy varies according to the skill of the colposcopist, the age of the patients and the grade of the lesions. Mitchell and colleagues in a meta-analysis, reported that the sensitivity of colposcopy ranged from 64 to 99 % and the specificity from 30 to 93 % [3]. Indeed, colposcopic assessment more often overestimated the severity of the lesions.

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Mistakes in cervical histological findings on bioptic specimens, have also been documented, [4, 5] and histological CIN diagnoses are not entirely reproducible [6, 7]. Indeed, similarly to cytological interpretation, histological assessment of cervical dysplasia is complicated by inter-observer variability [8]. The strongest source of disagreement was the threshold between normal and CIN 1. Agreement was higher for CIN 3 than for CIN 2 [9]. Moreover, the proportion of false-positive diagnoses of CIN 2 or worse varied according to cytologic and HPV test results [10].

Many studies investigated the correlation between histological diagnosis from colposcopically directed punch biopsies and definitive diagnosis after conization or hysterectomy [11, 12]. Only few authors concluded that directed cervical biopsies provide a consistent estimate of the final grading of CIN lesions [13, 14], whereas most of the studies showed just a moderate correlation. A complete agreement between biopsy and cone specimen was reported in no more than 43- 51 % of cases [11, 12, 15–19]. About 14-24 % LEEP specimens were negative for dysplasia. Giannella L. et al. showed that a severe cervical lesion (CIN2) with a minor colposcopic impression may predict a lower grade lesion on cone specimen [20].

One of the potential explanations for negative LEEP findings following a biopsy diagnosis of HSIL includes misdiagnosis of the original biopsy [21].

The choice of cervical point where to perform the biopsy is crucial to obtain a proper diagnosis. Conventionally biopsy must be performed in the worst area of cervical lesion, and should be representative of the entire lesion.

The main aim of this study was to investigate the influence of the skill of the colposcopist in correctly grading cervical preneoplastic lesion. Moreover, we investigated how good are skilled and junior colposcopists in identifying the worst area of a cervical lesion where biopsy should be performed.

Methods

A prospective randomized study was carried out from January 2012 to October 2014, in the Unit of Cervico-Vaginal Pathology of the Department of Obstetrics and Gynecology of the University Hospital Federico II in Naples, Italy.

All women referred for colposcopic examination and undergoing cervical biopsy under colposcopic guidance were invited to participate in this study. Our Institutional Review Board approved the protocol of the study and the study was conducted according to the guidelines of the Declaration of Helsinki (1975).

After signing their informed consent, all patients with a positive cytology, were randomly assigned to two main groups (junior colposcopists and senior colposcopists) corresponding to three junior colposcopists (i.e. a post-graduate physician with one-year experience in a Unit of Cervicovaginal Pathology) and three senior colposcopists (i.e. a trained gynecologist with at least 5 years of practice in a second level Unit of Colposcopy and Cervicovaginal Pathology). A physician who was not involved in the examination used the computer-generated list to assign each patient to a colposcopist.

Colposcopy and guided cervical biopsies were performed in a single procedure.

Patients were eligible for enrolment according to both the following criteria:

- satisfactory colposcopy (squamo-columnar junction fully visible) with atypical transformation zone (aceto-white epithelium).
- aceto-white lesion extending for 2 or more quadrants (allowing the execution of a double biopsy).

A colposcopic suspect for invasive cervical cancer and pregnancy (which can alter colposcopic findings), were considered as exclusion criteria.

During colposcopic examinations, after application of 3 % acetic acid, all visible lesions were classified according to the 2011 Colposcopic Terminology of the International Federation for Cervical Pathology and Colposcopy [22].

The examiner performed, for each patient, two guided biopsies using cervical biopsy forceps with 5- to 6-mm jaws, yielding 3- to 4-mm biopsies. The two specimens were placed into two different vials of fixative.

An extensive description of the two cervical sites, where biopsies were performed, was recorded; in particular, the examiner specified:

1. the site of biopsies (dividing the cervix into 4 quadrants by 2 perpendicular lines drawn from 12 to 6 o'clock, and from 9 to 3 o'clock);
2. the grading (grade 1-minor or 2-major) and the colposcopic features (thin/dense aceto-white epithelium with fine/coarse punctuation or mosaic);
3. which biopsy was considered the most suspicious and representative of the whole cervical lesion (biopsy A) and which biopsy, performed on a less severe area of the lesion, was considered additional but not required to obtain histological diagnosis (biopsy B).

All cervical biopsies were firstly examined by the pathologist on duty at the Pathology Laboratory, who was unaware of the study. The specimens were composed of small or tiny fragments of cervical tissue. Two serial 4-μm sections of formalin-fixed, paraffin embedded

samples were stained with hematoxylin and eosin. The specimens were classified according to the World Health Organization criteria as normal, CIN 1, CIN 2, CIN 3/carcinoma in situ or micro-invasive carcinoma [23].

At the end of the study all the histologic sections were reviewed by an experienced gynecologic pathologist (LI). In uncertain cases immunohistochemical stains were performed with labeling index for Ki67 to evaluate the proliferative activity, and for p16 protein expression to determine the different degrees of CIN. 4-μm serial sections from representative blocks were cut, mounted on poly-L-lysine coated glass slides and used for the immunohistochemical staining for ki67 and p16 protein. Representative sections were incubated with the primary antibodies, overnight at 4 °C. Subsequently, the slides were incubated with biotinylated secondary antibodies, peroxidase-labelled streptavidin (DAKO LSAB kit HRP, Carpinteria, CA) and chromogenic substrate diaminobenzidine (DAB, Vector Laboratories, Burlingame, U.S.A.) for the development of the peroxidase activity. Slides were counterstained with hematoxylin, dehydrated and cover-slipped with a synthetic mounting medium (Entellan, Merck, Germany).

The experienced pathologist was blinded to the referral cytology and the colposcopic examination. The histology of the most severe lesion (specimen A or B) was recoded as the final diagnosis. Although some patients underwent cervical conization or loop electrosurgical excision procedure (LEEP) as treatment for cervical neoplasia, results of these procedures were not considered in determining the final diagnosis.

Statistical analysis

Statistical analysis was performed using SPSS software (version 20; SPSS, Inc. Chicago, IL, USA).

To compare demographic and clinical data between the two groups (senior group and junior group) Student's t-test and Mann–Whitney test were used.

The main endpoint was to test the hypothesis that expert colposcopists may perform with a higher degree of accuracy the guided cervical biopsy. If this were true, expert colposcopists would identify the worse biopsy in a higher percentage of cases in comparison to junior colposcopists.

Differences in proportions were tested with χ^2 test (sites of biopsies, histological diagnosis rates, gradation of colposcopist judgment attributed to biopsy sites) and with Wilcoxon's signed rank test (routine versus revision histological analysis). Statistical analysis for colposcopist evaluation attributed to biopsy sites was performed considering only patients with definitive diagnosis of CIN. A colposcopist evaluation reporting A = B was considered not informative and excluded from the statistical analysis. The level of significance for these tests was set at $p < 0.05$.

The significance of the association between colposcopic grading and biopsy histology was determined using χ^2 test, while the strength of the association was assessed using κ statistics. Prior to calculating the κ values the histological diagnosis were dichotomized into two classifications: Negative/Cervicites/Metaplasia/koilocytosis /Condylomatosis/CIN 1 and CIN 2/CIN 3. Standard definitions were used to interpret the κ statistics [24].

Results

A total of 296 gave their consent to participate in this study. At the time of colposcopy, 41 patients were excluded as they did not satisfy the inclusion criteria: 18 women had unsatisfactory or negative colposcopy, 19 women had limited extension of lesion involving 0–1 quadrant of the cervix and 4 women had a suspected invasive cervical cancer. Among the 255 enrolled patients in 4 cases one or both biopsy specimens were insufficient for a diagnosis. Therefore, 251 cases met all criteria for analysis according to the study protocol (Fig. 1).

The mean age of patients was 32.4 years (range 19–52; SD ± 8.5).

One hundred twenty seven cases were randomized into senior group (50.6 %), while 124 cases (49.4 %) into junior group. Demographic characteristics of the patients, indications for colposcopy, colposcopic grade and final histological diagnosis are shown in Table 1. No significant differences for age, parity, educational level, colposcopic indications, colposcopic grade and final histological diagnosis were found between the two groups (Table 1).

Data regarding histological diagnosis performed by the routine practice pathologist and by the experienced gynaecologic pathologist for specimen A and B are shown in Table 2. A significant statistical difference was found between routine and revised histological analysis only for specimen B ($p = .03$) (Table 2).

Considering only patients with definitive histological diagnosis of CIN (diagnosis performed by the expert pathologist) the senior group identify the worst area of the cervical lesion in statistical significant higher rates than junior group. Specimen A resulted representative of the higher-grade lesion (A > B) in 73.7 % ($N = 28$) in senior group and in 48.4 % ($N = 15$) in junior group; while in 26.3 % ($N = 10$) the higher-grade lesion corresponded to specimen B (A < B) in senior group and in 51.6 % ($N = 16$) in junior group (Table 3, $p < .05$). The difference was significant both in routine than in revised histological analysis (Table 3, $p < .05$).

A significant difference was also found in rate of colposcopist evaluations between groups when stratified by colposcopic findings of grade 1 and 2 (Table 4). Indeed, in presence of grade 1 lesions, junior colposcopist identified in A a less severe lesion than in B in a significant higher rate of cases than in senior group (A < B: 70.0 %

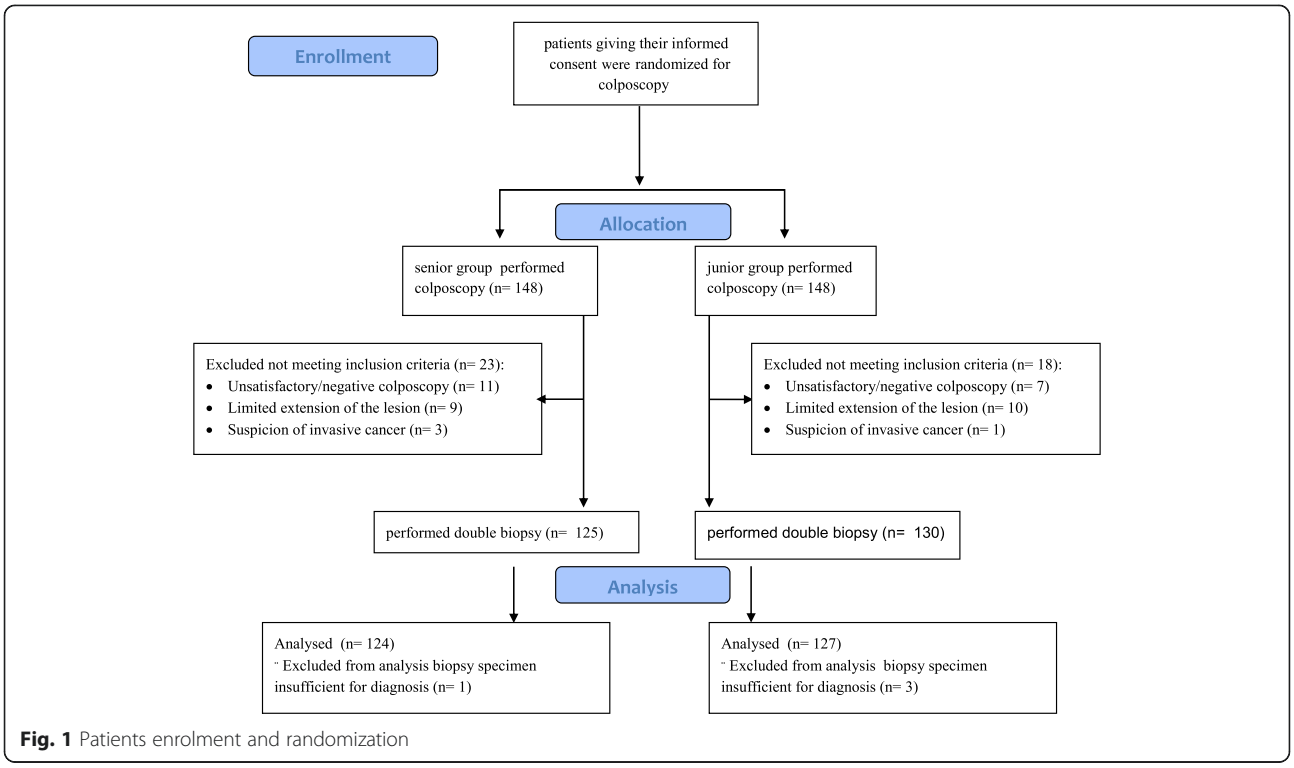

Fig. 1 Patients enrolment and randomization

Table 1 Patient demographic characteristics, colposcopic indication and findings, histological diagnosis for two groups

		junior group[a] (*N* = 124)	senior group[a] (*N* = 127)	*p Value*
Age (years ± S.D.)		32.2 ± 8.1	32.6 ± 8.9	.23
Parity (N ± S.D.)		0.62 ± 0.92	0.57 ± 0.85	.69
Educational level				.82
	Elementary education	3 (2.4)	2 (1.6)	
	Lower secondary education	50 (40.3)	51 (40.2)	
	Upper secondary education	58 (46.8)	60 (47.2)	
	Postsecondary education	13 (10.5)	14 (11.0)	
Colposcopic Indication[b]				.43
	ASC-US/ASC-H	35 (27.6)	32 (25.8)	
	AGC-NOS	4 (3.1)	5 (4.0)	
	L-SIL	57 (44.9)	66 (53.2)	
	H-SIL	31 (24.4)	21 (16.9)	
Colposcopic Grade[c]				.10
	TAG1	104 (83.9)	96 (75.6)	
	TAG2	20 (16.1)	31 (24.4)	
Final Histological Diagnosis				.91
	Negative/ Cervicites / Metaplasia	56 (45.2)	61 (48)	
	CIN1 / Koilocytosis / Condylomatosis	39 (31.5)	33 (26)	
	CIN 2/3	29 (23.4)	33 (26)	

[a]In senior group colposcopic examination and biopsies were performed by experienced colposcopists; in junior group post-graduate doctors with one-year experience in Unit of Cervicovaginal Pathology performed the diagnostic procedures
[b]Indications for colposcopy: Atypical squamous cells of undetermined significance (ASC-US); Atypical squamous cells – cannot exclude HSIL (ASC-H); Atypical Glandular Cells not otherwise specified (AGC-NOS); Low grade squamous intraepithelial lesion (LSIL); High grade squamous intraepithelial lesion (HSIL)
[c]TAG1: Atypical Transformation of Grade 1, TAG2: Atypical Transformation Grade 2

Table 2 Histological diagnosis of specimen A and B resulted from the routine analysis and from the revision analysis performed by an experienced gynecologic pathologist

Hystological Diagnosis	Specimen A N (%)			Specimen B N (%)		
	Routine Analysis	Revision Analysis[a]	*p Value*	Routine Analysis	Revision Analysis[a]	*p Value*
Negative	18 (7.2)	40 (15.9)	.34	35 (13.9)	51 (20.3)	.03
Cervicites / Metaplasia	116 (46.2)	96 (38.2)		95 (37.8)	102 (40.6)	
CIN1 / Koilocytosis / Condylomatosis	71 (28.3)	65 (25.9)		73 (29.1)	52 (20.7)	
CIN2	20 (8.0)	14 (5.6)		24 (9.6)	10 (4.0)	
CIN3	26 (10.4)	36 (14.3)		24 (9.6)	36 (14.3)	

[a]Revision analysis: analysis performed by experienced pathologist. In uncertain cases immunohistochemical stains were used, particularly, antibody against ki67 to evaluate the proliferative activity and p16 protein expression to determine the different degrees of CIN

vs. 36 %, $p = .01$). The difference was not significant in grade 2 lesions (Table 4).

The association between histological diagnosis and colposcopic grade was highly significant ($p < .001$) and the strength of the correlation, as assessed by the κ statistics, was fair for each specimen (A or B) and histological analysis (κ = 0.32; CI 95 %: .16-.47; and κ = 0.30; CI 95 %: .17-.44, for routine and revised analysis respectively) (Table 5). The highest κ value was observed in senior group (κ = .42; CI, 95 %: .25-.62) (Table 5). In junior group, the association between histological diagnosis and colposcopic grade was shown significant ($p < 0.05$) but the strength of this association was found slight (κ = .20; CI 95 %: −.01-.40) (Table 5).

Discussion and conclusion

This study prospectively investigates the ability of colposcopist in grading and performing diagnosis of a CIN lesion in uterine cervix.

Our data show a high significant correlation between colposcopic grading and histologic grading in single and in double biopsy both in routinely and in revision analysis as well.

This high correlation was lost when colposcopy was performed by less experienced examiner (junior Group). On the other hand, in senior group exact agreement was found in 85.1 % of grade 1 lesions and in 51.5 % of grade 2 lesions. Accordingly, the strength of this correlation, as assessed by κ statistics, is fair (κ = .42) in senior Group and slight in junior group (κ = .20). Baum ME el al. [25] and Benedet JL. et al. [26] have shown similar data in k statistic according to examiners experience. Overall the highest difficulty both in senior than junior group was the identification of grade 2 lesions.

In Benedet's report, the association between Pap smear cytology and colposcopic impression has been found higher significant than association between punch biopsy histology and colposcopy, indeed the strength of this correlation was moderate (κ = .56) [26]. However, also the correlation between cervical punch biopsy and LEEP biopsy was moderate (κ = .44) or even fair (κ = .31) [25–28].

The value of multiple or random cervical biopsies at the time of colposcopy for evaluation of an abnormal cytology has been discussed in the last decades. The number of specimens seems to influence the sensitivity of the diagnosis on cervical biopsies. The proportion of women with CIN 2 or worse increased when multiple random cervical biopsies in quadrants without lesions were performed [27]. Zuchna C. et al. [29] showed that two biopsies achieved a highly significant improvement in agreement between punch biopsy and cone specimen in comparison to one biopsy. On the contrary, in our

Table 3 Gradation of colposcopist judgment attributed to biopsy sites corresponding to specimen A and B before and after revision analysis in senior and junior group

Examiner group[a]	Colposcopist evaluation[b]	senior N (%)	junior N (%)	*p value*
Routine histological Analysis	A < B	10 (26.3)	16 (51.6)	.03
	A > B	28 (73.7)	15 (48.4)	
Revised histological Analysis[c]	A < B	12 (27.3)	19 (50.0)	.03
	A > B	32 (72.7)	19 (50.0)	

Statistical analysis was performed considering only patients with definitive diagnosis of CIN. A colposcopist evaluation reporting A = B was considered not informative and excluded from the statistical analysis

[a]In senior group colposcopic examination and biopsies were performed by experienced colposcopists; in junior group post-graduate doctors with one-year experience in Unit of Cervicovaginal Pathology performed the diagnostic procedures

[b]According to the judgment of the colposcopist biopsy A was considered the most suspicious and representative of the whole cervical lesion and biopsy B was considered additional but not required to obtain histological diagnosis

[c]Revision analysis: analysis performed by experienced pathologist. In uncertain cases immunohistochemical stains were used, particularly, antibody against ki67 to evaluate the proliferative activity and p16 protein expression to determine the different degrees of CIN

Table 4 Gradation of colposcopist judgment attributed to biopsy sites corresponding to specimen A and B stratified for colposcopic grading of the lesion in senior and junior group

Colposcopic Grading[c]	Colposcopist evluation[b]	Examiner Group[a]		*p value*
		senior group	junior group	
TAG1	A < B	9 (36.0)	21 (70.0)	.01
	A > B	16 (64.0)	9 (30.0)	
TAG2	A < B	5 (20.0)	0 (0.0)	.09
	A > B	20 (80.0)	12 (100.0)	

Statistical analysis was performed considering only patients with definitive diagnosis of CIN. A colposcopist evaluation reporting A = B was considered not informative and excluded from the statistical analysis.
[a]In senior group colposcopic examination and biopsies were performed by experienced colposcopists; in junior group post-graduate doctors with one-year experience in Unit of Cervicovaginal Pathology performed the diagnostic procedures.
[b]According to the judgment of the colposcopist biopsy A was considered the most suspicious and representative of the whole cervical lesion and biopsy B was considered additional but not required to obtain histological diagnosis.
[c]TAG1: Atypical Transformation of Grade 1, TAG2: Atypical Transformation Grade 2.

study, second biopsy did not increase the strength of correlation between colposcopic and histological grade neither in senior nor in junior group.

Colposcopic findings judged more representative of CIN lesion are presence of mosaics and punctuation both in colposcopic grade 1 and 2, while thin or dense aceto-white epitelium without vascular pattern are considered by colposcopist less representative of lesion grade. The ability of colposcopist in differentiating and grading two point of the same cervical lesion is limited.

In presence of a CIN lesion, the rate of colposcopic evaluations in biopsy sites (A and B) correct (A > B), was 62 %, on the contrary in 38 % of cases colposcopists do not identify the worst area of the cervical lesion (A < B).

Massad et al. [30] previously reported that colposcopic impression, colposcopic features as color, margin, vascularity and modification of Reid index do not discriminate between acetowhite lesion that arbor CIN2+ and those that not. However, the failure to detect CIN2+ lesion at colposcopy may reflects a measurable physical characteristic of the dysplastic epithelium. Yang B. et al. demonstrate that false negative colposcopic impression is sometimes secondary to the relative thinness of some CIN2-3 lesion [31].

The colposcopist experience influences significantly colposcopic accuracy in grading cervical lesion and in identify its worst area; indeed, junior colposcopist showed more difficulties in identify the worst area of the lesion, in about half of cases they fail in the classification of the lesion.

Colposcopic grade influence colposcopist judgment in less expert colposcopists; higher colposcopic lesion grade (grade 2) is associated with higher rate of correct evaluation in junior group (A > B). On the contrary junior colposcopist fail, significantly more than senior colposcopist, in identification of worst area was to perform biopsy in grade 1 lesion. Probably this is due to the larger extension of high-grade lesion and to the coexistence of low-grade area in high-grade lesion.

Overall, 42.2 % of histological reports have been modified after revision by experienced gynecologic pathologist:

Table 5 Association and strength of correlation between histological diagnosis and colposcopic grading in senior and junior group

		Histological Diagnosis[b]		*p value* [c] K Value; 95 % C.I.
Specimen	Colposcopic Grading[a]	Negative/CIN1 N (%)	CIN2/3 N (%)	
Routine analysis after single biopsy (A)				
total group	TAG1	176 (85.9)	24 (52.2)	*<.001* 0.32; .16-.47
	TAG2	29 (14.1)	22 (47.8)	
senior group	TAG1	87 (84.5)	9 (37.5)	*<.001* 0.42; .25-.62
	TAG2	16 (15.5)	15 (62.5)	
junior group	TAG1	89 (87.3)	15 (68.2)	*<.05* 0.20; −.01-.40
	TAG2	13 (12.7)	7 (31.8)	
Revision analysis after two biopsies (A and B)				
total group	TAG1	164 (86.8)	36 (58.1)	*<.001* 0.30; .17-.44
	TAG2	25 (13.2)	26 (41.9)	
senior group	TAG1	80 (85.1)	16 (48.5)	*<.001* 0.37; .15-.54
	TAG2	14 (14.9)	17 (51.5)	
junior group	TAG1	84 (88.4)	20 (69.0)	*<.05* 0.22; .03-.42
	TAG2	11 (11.6)	9 (31.0)	

[a]The histology of the most severe lesion obtained with specimen A or B was recoded as the final histological diagnosis
[b]TAG1: Atypical Transformation of Grade 1, TAG2: Atypical Transformation Grade 2
[c]The significance of the association between colposcopic grading and histological diagnosis was determined within group using χ^2 test, the strength of the association was assessed using κ statistics. To perform this analysis the histological diagnosis were dichotomized into two classifications: Negative/Cervicites/Metaplasia/koilocytosis/Condylomatosis/CIN 1 and CIN 2/CIN 3

20.8 % cases resulted in a reduction and 33 % showed an increase of lesion's grade, while in 46.2 % the adjustment did not influenced the grade of the lesion. This high rate of changed reports could be attributed to the use of immunochemistry for Ki-67 and p16INK4a antibodies that have been demonstrated in many studies valuable adjunctive aids in diagnosis of difficult cervical biopsy [32–34].

A significant statistical difference was found between routine analysis and revision analysis in specimen B. These data show that the second biopsy, performed in cervical area judged by colposcopist less representative of lesion grade and characterized at colposcopy by the absence of vascular pattern and by less marked signs of lesion makes more difficult in performing histological analysis.

In conclusion, our data suggest that a long time experience in a Colposcopic Unit is fundamental to ensure high accuracy of colposcopy, and that a one year colposcopy training program is not enough to achieve these skills. Also expert colposcopist when performs a guided biopsy may not identify the worst area of a CIN lesion, so neither colposcopic impression nor histology can be used alone to guide management.

The lack of a definitive diagnosis on excisional sample (LEEP or cold knife conizzation) cannot ensure the conclusion that perform a second biopsy have a minimal impact on colposcopy accuracy, further study are necessary to achieve this goal.

Competing interests
The authors do not have any conflict of interest.

Authors' contribution
BG and DRN have equally contributed to the elaboration of the manuscript. All the Authors' have given their contributions for the study: particularly, BG and DRN have contributed to conception and design of the study protocol and in the analysis and interpretation of the data, NC has supervised the proper conduct of the study and he has revised the article critically. BG, DCC, and PR are the senior colposcopists; BA, DRN, and LG are the junior colposcopists. IL is the experienced gynecologic pathologist and has contributed to draft and revise the study. NV gave substantial contribution in the acquisition of data. All authors read and approved the final manuscript.

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References
1. Wright Jr TC, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D. 2006 consensus guidelines for the management of women with abnormal cervical screening tests. 2006 ASCCP-Sponsored Consensus Conference. J Low Genit Tract Dis. 2007;11(4):201–22.
2. Partridge EE, Abu-Rustum NR, Campos SM, Fahey PJ, Farmer M, Garcia RL, et al. Cervical cancer screening. National comprehensive cancer networks. J Natl Compr Canc Netw. 2010;8(12):1358–86.
3. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol. 1998;91:626–31.
4. Joste NE, Crum CP, Cibas ES. Cytologic/histologic correlation for quality control in cervicovaginal cytology; experience with 1.582 paired cases. Am J Clin Pathol. 1995;103:32–4.
5. Tritz DM, Weeks JA, Spires SE, Sattich M, Banks H, Cibull ML, et al. Etiologies for non-correlating cervical cytologies and biopsies. Am J Clin Pathol. 1995;103:594–7.
6. Malpica A, Matisic JP, Niekirk DV, Crum CP, Staerkel GA, Yamal JM, et al. Kappa statistics to measure interrater and intrarater agreement for 1790 cervical biopsy specimens among twelve pathologists: qualitative histopathologic analysis and methodology issues. Gynecol Oncol. 2005;99(3 suppl 1):S38–52.
7. Kalof AN, Cooper K. Our approach to squamous intraepithelial lesions of the uterine cervix. J Clin Pathol. 2007;60:449–55.
8. Stoler MH, Schiffman M, The Atypical Squamous Cells of Undetermined Significance–Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA. 2001;285:1500–5.
9. Dalla Palma P, Giorgi Rossi P, Collina G, NTCC Pathology Group, et al. The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. Am J Clin Pathol. 2009;132(1):125–32.
10. Dalla Palma P, Giorgi Rossi P, Collina G, NTCC Pathology Group. The risk of false-positive histology according to the reason for colposcopy referral in cervical cancer screening: a blind revision of all histologic lesions found in the NTCC trial. Am J Clin Pathol. 2008;129(1):75–80.
11. Skehan M, Soutter WP, Lim K, Krausz T, Pryse-Davies J. Reliability of colposcopy and directed punch biopsy. Br J Obstet Gynaecol. 1990;97:811–6.
12. Barker B, Garcia F, Lozevski J, Warner J, Hatch K. The correlation between colposcopically directed cervical biopsy and loop electrosurgical excision procedure pathology and the effect of time on that agreement. Gynecol Oncol. 2001;82:22–6.
13. Veridiano NP, Delke I, Tancer ML. Accuracy of colposcopically directed biopsy in patients with cervical neoplasia. Obstet Gynecol. 1981;58:185–7.
14. Cinel A, Oselladore M, Insacco E, Minucci D. The accuracy of colposcopically directed biopsy in the diagnosis of cervical intraepithelial neoplasia. Eur J Gynaecol Oncol. 1990;11:433–7.
15. Howe DT, Vincenti AC. Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? Br J Obstet Gynaecol. 1991;98:588–91.
16. Chappatte OA, Byrne DL, Raju KS, Nayagam M, Kenney A. Histological differences between colposcopic directed biopsy and loop excision of the transformation zone (LETZ): a cause for concern. Gynecol Oncol. 1991;43:46–50.
17. Buxton EJ, Luesley DM, Shafi MI, Rollason M. Colposcopically directed punch biopsy: a potentially misleading investigation. Br J Obstet Gynaecol. 1991;98:1273–6.
18. Bonardi R, Cecchini S, Grazzini G, Ciatto S. Loop electrosurgical excision procedure of the transformation zone and colposcopically directed punch biopsy in the diagnosis of cervical lesions. Obstet Gynecol. 1992;80:1020–2.
19. Massad LS, Halperin CJ, Bitterman P. Correlation between colposcopically directed biopsy and cervical loop excision. Gynecol Oncol. 1996;60:400–3.
20. Giannella L, Mfuta K, Gardini G, Rubino T, Fodero C, Prandi S. High-grade CIN on cervical biopsy and predictors of the subsequent cone histology results in women undergoing immediate conization. Eur J Obstet Gynecol Reprod Biol. 2015;186:68–74.
21. Witt BL, Factor RE, Jarboe EA, Layfield LJ. Negative loop electrosurgical cone biopsy finding following a biopsy diagnosis of high-grade squamous intraepithelial lesion: frequency and clinical significance. Arch Pathol Lab Med. 2012;136(10):1259–61.
22. Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. 2011 Colposcopic Terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012;120(1):166–72.
23. Wells M. Epithelial tumors. In: Tavassoli FA, Devilee P, editors. World Health Organization classification of tumors: pathology and genetics of tumors of the breast and female genital organs. Lyons, France: IARC Press; 2003. p. 269–70.
24. Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics. 1977;33:159–74.

25. Baum ME, Rader JS, Gibb RK, McAlister RP, Powell MA, Mutch DG, et al. Colposcopic accuracy of obstetrics and gynecology residents. Gynecol Oncol. 2006;103(3):966–70.
26. Benedet JL, Matisic JP, Bertrand MA. An analysis of 84244 patients from the British Columbia cytology-colposcopy program. Gynecol Oncol. 2004;92(1):127–34.
27. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, Qiao YL. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004;191(2):430–4.
28. Moss EL, Hadden P, Douce G, Jones PW, Arbyn M, Redman CW. Is the Colposcopically Directed Punch Biopsy a Reliable Diagnostic Test in Women With Minor Cytological Lesions? J Low Genit Tract Dis. 2012;16(4):421–6.
29. Zuchna C, Hager M, Tringler B, Georgoulopoulos A, Ciresa-Koenig A, Volgger B, et al. Diagnostic accuracy of guided cervical biopsies: a prospective multicenter study comparing the histopathology of simultaneous biopsy and cone specimen. Am J Obstet Gynecol. 2010;203(4):321e1–6.
30. Massad LS, Stewarts L, Jeronimo J, Schiffman M. National Institutes of Health/American Society for Colposcopy and Cervical Pathology Research Group. The accuracy of colposcopic grading for detection of high-grade cervical intraepithelial neoplasia. J Low Genit Tract Dis. 2009;13(3):137–44.
31. Yang B, Pretorius RG, Belinson JL, Zhang X, Burchette R, Qiao YL. False negative colposcopy is associated with thinner cervical intraepithelial neoplasia 2 and 3. Gynecol Oncol. 2008;110(1):32–6.
32. Klaes R, Benner A, Friedrich T, et al. p16INK4a immunohistochemistry improves interobserver agreement in the diagnosis of cervical intraepithelial neoplasia. Am J Surg Pathol. 2002;26:1389–99.
33. Zhang Q, Kuhn L, Denny LA, Ridder R, Herrington S, Jenkins D, et al. Impact of utilizing p16INK4A immunohistochemistry on estimated performance of three cervical cancer screening tests. Int J Cancer. 2007;120:351–6.
34. Galgano MT, Castle PE, Atkins KA, Brix WK, Nassau SR, Stoler MH. Using biomarkers as objective standards in the diagnosis of cervical biopsies. Am J Surg Pathol. 2010;34(8):1077–87.

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Diagnostic Accuracy of Endocervicoscopy in Identifying and Grading Cervical Intraepithelial Neoplasia Lesion

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Keywords
Endocervix · Cervical intraepithelial lesion · Endocervicoscopy · Colposcopy · Accuracy

Abstract
Introduction: Colposcopy represents the second step of the diagnostic approach of cervical intraepithelial lesions. Limits of colposcopy in studying cervix are essentially related to cervical anatomy. Nowadays, endocervical courettage is the standard technique to examine endocervix. Endocervicoscopy is a new imaging technique for the diagnostic work-up of endocervix in patients with cervical intraepithelial neoplasia (CIN). ***Objective:*** To evaluate endocervicoscopy accuracy to identify and grade cervical intraepithelial lesion in comparison to other procedures employed into the diagnostic workup of cervical pathology. ***Methods:*** A total of 634 women who performed colposcopy, endocervicoscopy and cytological or histological sampling were included in a retrospective study. The agreement between the endocervicoscopic and the colposcopic impressions, minor and major changes, and between these imaging techniques and histological diagnosis was assessed for the entire cohort. χ^2 test and *k* statistic were used in the statistical analysis. ***Results:*** The extension of the lesion resulted significantly greater at endocervicoscopy than at colposcopy. We showed a statistically significant association between colposcopy and endocervicoscopy findings. Overall, the correlation of minor or major findings between colposcopy and endocervicoscopy was statistically significant with a *p* value for all parameters <0.0001. Description of mosaic/punctuation, cuffed crypt (gland) openings and ridge sign showed a high *k* value (k = 0.68 [95% CI 0.64–0.73], k = 0.80 [95% CI 0.75–0.85], k = 0.78 [95% CI 0.64–0.90], respectively). The sensitivity (70.1%) and the specificity (77.0%) of endocervicoscopy for all CIN lesions were lower than colposcopy. ***Conclusion:*** Endocervicoscopy turned out to be a good method to identify and grade CIN lesions in a subset of patients where colposcopy was not satisfactory. It allowed us to overcome one of the limits of colposcopy in the evaluation of the squamo-columnar junction and to establish the real extension of the lesion into cervical cancer.

Introduction

Cervical intraepithelial neoplasia (CIN) is a precancerous lesion of the uterine cervix. In order to reduce cervical cancer risk and development, it is critical defining the presence, the extension and the severity of CIN. According to the European Guidelines for quality assurance in

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cervical cancer screening, the ASCCP and the National comprehensive cancer Network, Pap-smear and HPV tests are nowadays the screening tests for the identification of the patient at risk of CIN lesions [1–3]. Colposcopy represents the second step of the diagnostic approach [4].

Limits of colposcopy in studying cervix are essentially related to cervical anatomy. The conformation of the cervical canal and physiological modification of the transformation zone (TZ) may influence the adequacy of colposcopy delaying a complete evaluation of the squamo-columnar junction (SCJ) or/and the extension of the lesion into the cervical canal or hide the identification of an isolated endocervical lesion.

According to the National comprehensive cancer Network guidelines and the ASCCP guidelines positive high-grade cytology (ASC-H or high- grade squamous intraepithelial lesion) with an adequate colposcopy and no lesion observed or with an inadequate colposcopy or also low-grade cytology (ASCUS or low-grade squamous intraepithelial lesion) with an inadequate colposcopy are considered imperative reasons to perform endocervical examination [3, 5, 6].

Nowadays, endocervical courettage is the standard technique to examine endocervix. It is a blind technique, which consists in sampling endocervical mucosa with a curette. It has many limitations, in particular, it is invasive and painful, it has a high rate of false-negative findings (4–45%) and a low sensitivity (55–64%) [7, 8]. The small fragmented and poorly oriented specimens with deficient stroma influence pathologic interpretation: in 12% of cases, the sample results are inadequate or tissue retrieval is insufficient to obtain a diagnosis. In addition, the presence of ectocervical lesion might contaminate the EEC specimen (false-positive rate of endocervical involvement was 62.5%) resulting in more extensive treatment of a suspected endocervical lesion [7].

Endocervicoscopy is an alternative imaging technique for the diagnostic work-up of CIN. This technique combines conventional hysteroscopic instrumentation with the colposcopic classification system for the evaluation of the endocervical mucosa [9, 10]. Bifulco et al. [11] previously reported that endocervicoscopy plus biopsy have comparable sensibility, specificity and diagnostic accuracy of cervical curettage.

The aim of this study was to evaluate endocervicoscopy accuracy to identify and grade cervical intraepithelial lesion in comparison to other procedures employed in the diagnostic workup of cervical pathology.

Materials and Methods

This was a retrospective cohort study of women undergoing endocervicoscopy between January 2014 and December 2018 at Unit of Colposcopy and Cervico-vaginal Pathology of University Federico II, in Naples.

Women were included in the cohort if they were at least 18 years of age and satisfy one of the following criteria:

- A positive colposcopy with zone type 3 (ZT3);
- A negative colposcopy with ZT3 and positive cytology;
- A negative colposcopy with ZT1/2 and positive cytology for high-grade squamous intraepithelial lesion;
- A negative colposcopy with ZT1/2 and repeated positive cytology for low-grade squamous intraepithelial lesion;
- A positive cytology for abnormal glandular cell.

All data regarding patient's age, other diseases of gynecological interest, parity and previous gynaecologic surgery, cytology and histology were extracted from clinical records. During the study period, patients performed colposcopy with the standard technique. After the placement of a speculum, 5% acetic acid was applied to the cervix and TZ. The entire TZ was then examined and any areas of abnormality were noted. The colposcopic impression was recorded at this time and classified according to the 2011 Colposcopic Terminology of the International Federation for Cervical Pathology and Colposcopy [12]. The most suspicious area or areas were then biopsied under colposcopic guidance using cervical biopsy forceps with 5- to 6-mm jaws, yielding 3- to 4-mm biopsies. The specimen was fixed in formalin 10%.

All cervical biopsies were examined by the pathologist on duty at the Pathology Laboratory. The specimens were composed of small or tiny fragments of cervical tissue. Two serial 4-μm sections of formalin-fixed, paraffin-embedded samples were stained with hematoxylin and eosin. The specimens were classified according to the World Health Organization criteria as normal, CIN 1, CIN 2, CIN 3/carcinoma in situ or micro-invasive carcinoma or glandular atypia [13].

Endocervicoscopy was performed by the same equipment, the procedure was performed according to Bifulco et al. [11] using the traditional approach with the speculum [8]. In order to accurately measure the length of the lesion and its extension in the cervical canal, we used graduated Bettocchi/Di Spiezio Sardo intrauterine palpator 5 Fr (in millimetres/centimetres) [14].

Statistical Analysis

Statistical analysis was performed using SPSS software version 20 (SPSS, Inc., Chicago, IL, USA).

Clinical data were evaluated for distribution by Shapiro-Wilks' test, and descriptive statistic was reported accordingly.

The agreement between the endocervicoscopic and the colposcopic impressions and between these imaging techniques and histological diagnosis was assessed for the entire cohort.

The association between categorical variables (colposcopic/endocervicoscopic description of general principles, grade and figures, and histology results) was analysed using the χ^2 test. The difference in the extension of the lesion was assessed using student *t* test, according to data distribution. A p value of <0.05 was considered statistically significant. The *k*-values were used to evaluate the strength of the correlation between the endocervicoscopic and colposcopic impressions and the biopsy histologies. Standard defini-

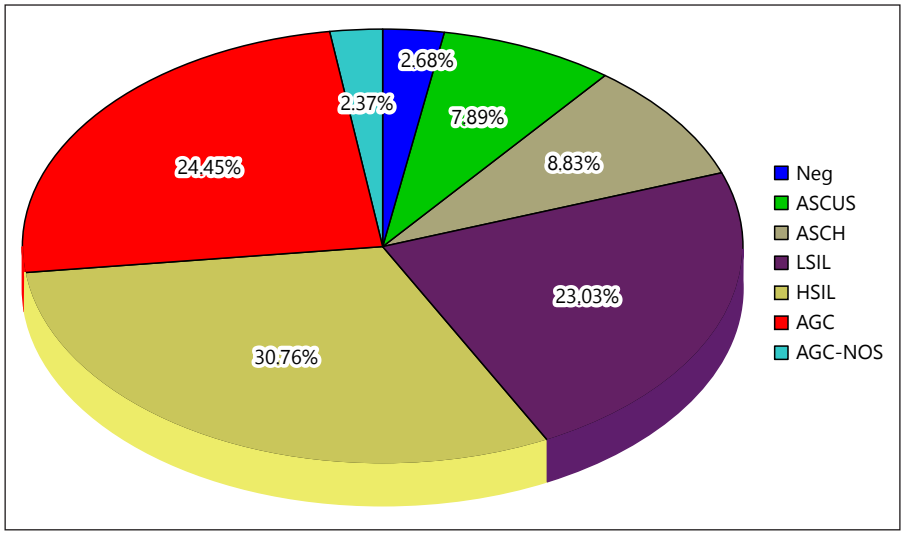

Fig. 1. Distribution of Pap smear results at enrolment of the study group. LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; AGC, abnormal glandular cell.

tions were used to interpret the k statistic [15]. If patients performed Loop Electrosurgical Excision Procedure (LEEP) or CONE Biopsy (Conization), we considered these as definitive diagnosis and included it in the statistical analysis.

Ethical Approval

The data presented are an amalgamation of hospital-registered clinical audits. All patients gave their written informed consent before performing the procedure. Ethical approval was not required because this was classified as a hospital audit of current clinical practice.

Results

Between 2014 and 2018, 710 endocervicoscopy were performed at our Department. Due to missing information about endocervicoscopy/colposcopy grading, or biopsy specimen, 76 women (10.7%) were excluded from the study. A total of 634 women were included in the final analysis. The mean age of the study group was 42.8 ± 11.5 years. The distribution of pap-smear results at enrolment was shown in Figure 1.

Correlation between colposcopic and endocervicoscopic general assessment and general principles was shown in Table 1.

The SCJ was defined as "visible" in 44.8% (n = 284) of colposcopy and in 96.5% (n = 612) of endocervicoscopy. The correlation was considered significant, but the k statistics was really poor (k = 0.039; Table 1). Mean distance, evaluated at endocervicoscopy, of SCJ or lesion from EUO into the endocervical canal was 3.14 ± 2.11 mm. In Figure 2, SCJ or lesion endocervical extension into the endocervical canal was categorised into 3 groups. Considering cases with "not visible SCJ" at colposcopy, 82% of cases showed localisation of this limit into the endocervical canal between 1.1 and 5.0 mm, only in 15.4% of cases this limit was >5.1 mm.

Regarding the description of lesion extension, data analysis showed a significant increase in lesion extension when it was studied during endocervicoscopy both when described in percentage than in quadrants distribution (Table 1).

Correlation between colposcopic and endocervicoscopic minor (grade 1) and major (grade 2) findings were shown in Table 2. Overall, the correlation between minor or major findings between colposcopy and endocervicoscopy was statistically significant with a p value for all parameters <0.0001. The strength of this correlation differed for each specific parameter. Indeed, according to the k statistics, the inner border showed the lowest k value (k = 0.29 [95% CI 0.19–0.37]). Followed by geographic or sharp border and description of acetowhite epithelium that showed a discrete k-value (k = 0.51 [95% CI 0.44–0.57]; k = 0.52 [95% CI 0.43–0.60]; k = 0.45 [95% CI 0.40–0.51], respectively).

Conversely, description of mosaic/punctuation, cuffed crypt (gland) openings and ridge sign showed an high k value (k = 0.68 [95% CI 0.64–0.73], k = 0.80 [95% CI 0.75–0.85], k = 0.78 [95% CI 0.64–0.90], respectively; Table 2).

In Figure 3a–c is shown sample type (cytology or histology) distribution in our study group that was considered the definitive diagnosis. Correlation between colposcopic and endocervicoscopic grade and definitive his-

Table 1. Correlation between colposcopic and endocervicoscopic general assessment and general principles (SCJ, TZ)

Colposcopy	Endocervicoscopy				*p* value	*k* value (95% CI)
SCJ	Visible	Not visible			0.003	0.039 (0.015–0.065)
Visible	281 (45.9)	3 (13.6)		284 (44.8)		
Not visible	331 (54.1)	19 (86.4)		350 (55.2)		
Total	612 (96.5)	22 (3.5)		634		
TZ	Type 1	Type 2	Type 3		<0.0001	0.35 (0.32–0.39)
Type 1	178 (98.9)	0 (0)	0 (0)	178 (28.1)		
Type 2	0 (0)	120 (27.6)	0 (0)	120 (18.9)		
Type 3	2 (1.1)	315 (72.4)	19 (100)	336 (53.0)		
Total	180	435	19			

	Colposcopy	Endocervicoscopy	
Size of the lesion			
Number of cervical quadrants	1.47±1.35	1.62±1.27	<0.0001
Percentage of cervix	16.66±15.40	17.89±15.00	<0.0001

SCJ, squamocolumnar junction; TZ, transformation zone.

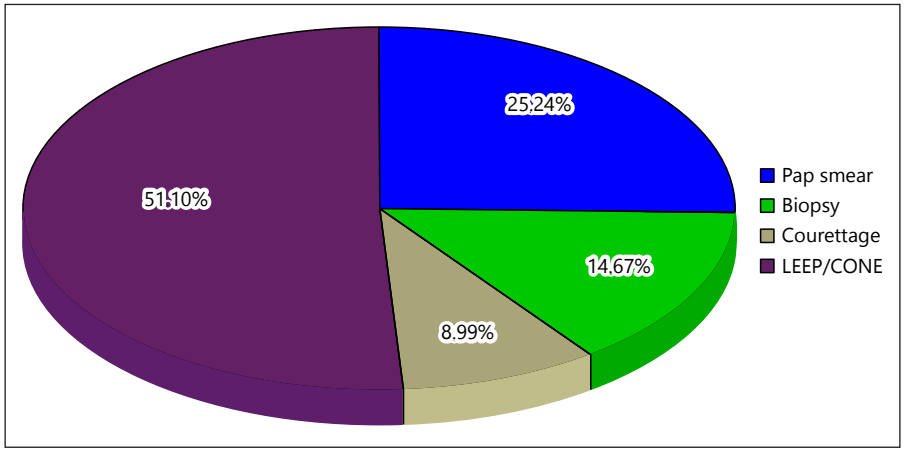

Fig. 2. Sample type distribution of the study group.

tology was statistically significant for both type of techniques (Table 3). However, the strength of this correlation was significantly lower for endocervicoscopy than for colposcopy (k = 0.39 [95% CI 0.34–0.44]) vs. k = 0.58 (95% CI 0.53–0.63), respectively (Table 3). Endocervicoscopy in a high percentage of cases underestimated lesion grade.

Discussion

Colposcopy is the gold standard for the diagnosis of intraepithelial cervical lesions. Endocervicoscopy is an imaging technique also employed for their diagnosis. In the present study, we showed a statistically significant association between colposcopy and endocervicoscopy findings. This study showed that endocervicoscopy can correctly identify the larger number of abnormal findings recognised at colposcopy. Description of mosaic/punctuation, cuffed crypt (gland) openings and ridge sign was correctly identified in a high percentage of cases, showing a high k value; on the other hand, some findings were missing, such as the intensity of acetowhite epithelium the inner border and geographic or sharp border (Fig. 4a–d). The closer contact between cervix and hysteroscope during the exam magnify vascularisation and crypt gland openings but saline solution lavage and direct light on the tissue reduce the opportunity in identifying acetowhite density and lesion border on the squamous tissue.

Table 2. Correlation between colposcopic and endocervicoscopic minor (grade 1) and major (grade 2) findings

	Endocervicoscopy				*p* value	*k* value (95% CI)
Colposcopy	Negative	Grade 1	Grade 2	Cancer	<0.0001	0.42 (0.37–0.48)
Negative	173 (59.0)	53 (34.0)	13 (7.5)	0 (0.0)		
Grade 1	53 (18.1)	73 (46.8)	20 (11.5)	0 (0.0)		
Grade 2	36 (12.3)	25 (16.0)	124 (71.3)	0 (0.0)		
Cancer	31 (10.6)	5 (3.2)	17 (9.8)	11 (100)		
Acetowhite epithelium	Absent	Thin	Dense	Total	<0.0001	0.45 (0.40–0.51)
Absent	197 (68.2)	41 (16.7)	3 (3.0)	241 (38.0)		
Thin	45 (15.6)	109 (44.5)	2 (2.0)	156 (24.6)		
Dense	47 (16.3)	95 (38.8)	95 (95.00)	237 (37.4)		
	289 (45.6)	245 (38.6)	100 (15.8)	634		
Mosaic/punctuation	Absent	Fine	Coarse	Total	<0.0001	0.68 (0.64–0.73)
Absent	207 (83.8)	35 (17.0)	12 (6.6)	254 (40.1)		
Fine	19 (7.7)	142 (68.9)	16 (8.8)	177 (27.9)		
Coarse	21 (8.5)	29 (14.1)	153 (84.5)	203 (32.0)		
	247 (39.1)	206 (32.5)	181 (28.4)	634		
Geographic border	No	Yes			<0.0001	0.52 (0.43–0.60)
No	513 (88.1)	3 (5.8)		516 (81.4)		
Yes	88 (11.9)	49 (94.2)		118 (18.6)		
	582 (91.8)	52 (8.2)		634		
Sharp border	No	Yes			<0.0001	0.51 (0.44–0.57)
No	414 (77.2)	2 (2.0)		416 (65.6)		
Yes	122 (22.8)	96 (98.0)		218 (34.4)		
	536 (84.5)	98 (15.5)		634		
Inner border	No	Yes			<0.0001	0.29 (0.19–0.37)
No	513 (84.1)	0 (0.0)		513 (80.9)		
Yes	97 (15.9)	24 (100.0)		121 (19.1)		
	610 (96.2)	24 (3.8)		634		
Cuffed crypt (gland) openings	No	Yes			<0.0001	0.80 (0.75–0.85)
No	432 (99.1)	48 (24.2)		480 (75.7)		
Yes	4 (0.9)	150 (75.8)		154 (24.3)		
	436 (68.8)	198 (31.2)		634		
Ridge sign	No	Yes			<0.0001	0.78 (0.64–0.90)
No	602 (98.2)	0 (0)		602 (95.0)		
Yes	11 (1.8)	21 (100)		32 (5.0)		
	613 (96.7)	21 (3.3)		634		

This result was related to the lower specificity and sensitivity of endocervicoscopy than colposcopy in identified CIN lesion.

In this study analysis, the sensitivity (true positive rate) of colposcopy as a diagnostic tool has been high for detecting all CIN lesion (91.4%) also for high-grade CIN or low-grade CIN was high (respectively, 87.8 and 89.6%). The specificity (true negative rate) was 90.2% for all lesions and was higher for high-grade CIN (97.6%) than for low-grade CIN (91.9%). However, the colposcopic accuracy varies according to the skill of the colposcopist, the age of the patients and the grade of the lesions, and a long-time experience in a colposcopic unit is fundamental to ensure high accuracy of colposcopy [16].

The sensitivity and the specificity of endocervicoscopy were lower than colposcopy; particularly, the sensitivity was for all CIN lesion 70.1% while specificity was 77.0%; the sensitivity for high-grade CIN or low-grade CIN was moderate (respectively, 63.2 and 61.0%). The specificity was higher for high-grade CIN (97.2%) than for low-grade CIN (78.7%).

Our data are in accordance with our previous study [11], in which endocervicoscopy plus biopsy had a high sensitivity (79%) and specificity (100%). Rahimi et al. [17] also demonstrated a high sensitivity of endocervicoscopy with biopsy (64%) for detecting high-grade CIN and moderate sensitivity (53%) for detecting low-grade CIN. According to us, they showed high sensitivity (81%) for low-grade CIN and, conversely, a low specificity (47%)

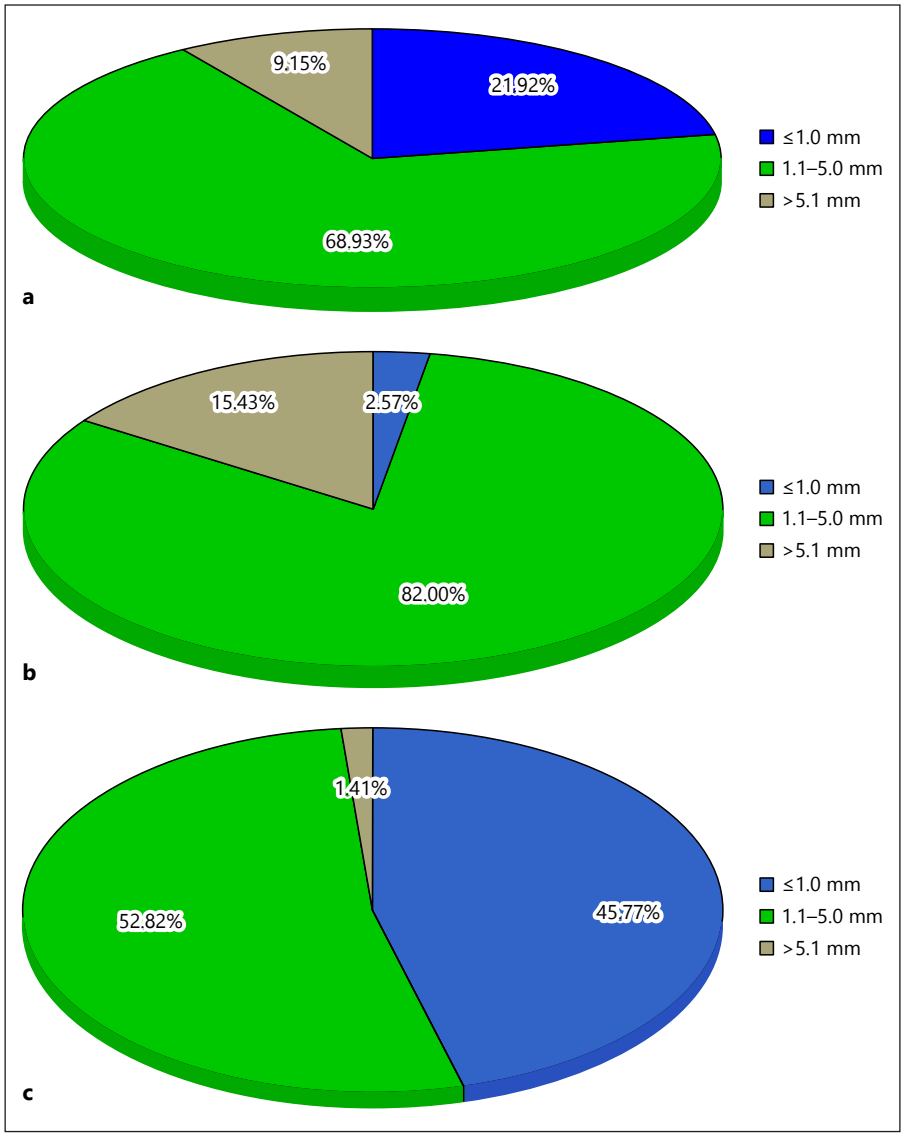

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Fig. 3. a SCJ or lesion endocervical limit from external uterine orifice established during endocervicoscopy; (**b**) SCJ or lesion endocervical limit from external uterine orifice in TZ type 3 at colposcopy; (**c**) SCJ or lesion endocervical limit from external uterine orifice in TZ type 2 at colposcopy. SCJ, squamo-columnar junction.

for high-grade CIN. These data suggest that endocervicoscopy is a reliable method to identify and grade CIN lesions. Probably adding this procedure in the work up of CIN lesion with colposcopy, cytology and histology may ensure the correct diagnosis and subsequently the best treatment option for the patient. Also combined imagine technique with specific biomarkers may ensure this goal [18].

We demonstrated that using endocervicoscopy we can establish the real extension of the lesion into cervical cancer.

In particular, endocervicoscopy allows overcoming one of the limits of colposcopy in the evaluation of the SCJ (Fig. 5a–d). The collected data have, in fact, highlighted that most of the cases with a not visible SCJ at colposcopy resulted in a visible SCJ at endocervicoscopy. Moreover, in the subgroup of patients with SCJ not visible, the SCJ was localised in a high percentage of the case (82.0%) into endocervical canal within 5 mm and in only 15.4% of cases the SCJ exceeded this limit (Fig. 3a–c). This observation has an important impact on CIN2+ treatment.

The early detection of cervical cancer improves survival and reduces the burden of cervical cancer treatments [19]. To perform adequate treatment of intraepithelial lesion may reduce the risk of relapses, re-intervention or progressive lesion. Invasive cervical cancer treatment even if personalised taking into account the performance status of the patient and employing new strategies such as sentinel lymph node biopsy [20] has still an important negative impact on the quality of life of pa-

Table 3. Correlation between colposcopic and endocervicoscopic grade and histology (CIN)

Colposcopy	Hystology				Total (n = 634)	p value	k value (95% CI)
	negative (n = 226)	CIN 1 (n = 82)	CIN 2–3 (n = 311)	Cervical carcinoma (n = 15)			
Negative	204 (90.3)	8 (9.8)	24 (7.7)	3 (20.0)	239 (37.7)	<0.0001	0.58 (0.53–0.63)
Grade 1	17 (7.5)	69 (84.1)	55 (17.7)	5 (33.3)	146 (23.0)		
Grade 2	5 (2.2)	5 (6.1)	173 (55.6)	2 (13.3)	185 (29.2)		
Carcinoma	0 (0)	0 (0)	59 (19.0)	5 (33.3)	64 (10.1)		
Endocervicoscopy						<0.0001	0.39 (0.34–0.44)
Negative	174 (77.0)	28 (34.1)	89 (28.6)	2 (13.3)	293 (46.2)		
Grade 1	47 (20.8)	44 (53.7)	63 (20.3)	2 (13.3)	156 (24.6)		
Grade 2	5 (2.2)	10 (12.2)	153 (49.2)	6 (40.0)	174 (27.4)		
Carcinoma	0 (0)	0 (0)	6 (1.9)	5 (33.3)	11 (1.7)		

CIN, cervical intraepithelial neoplasia.

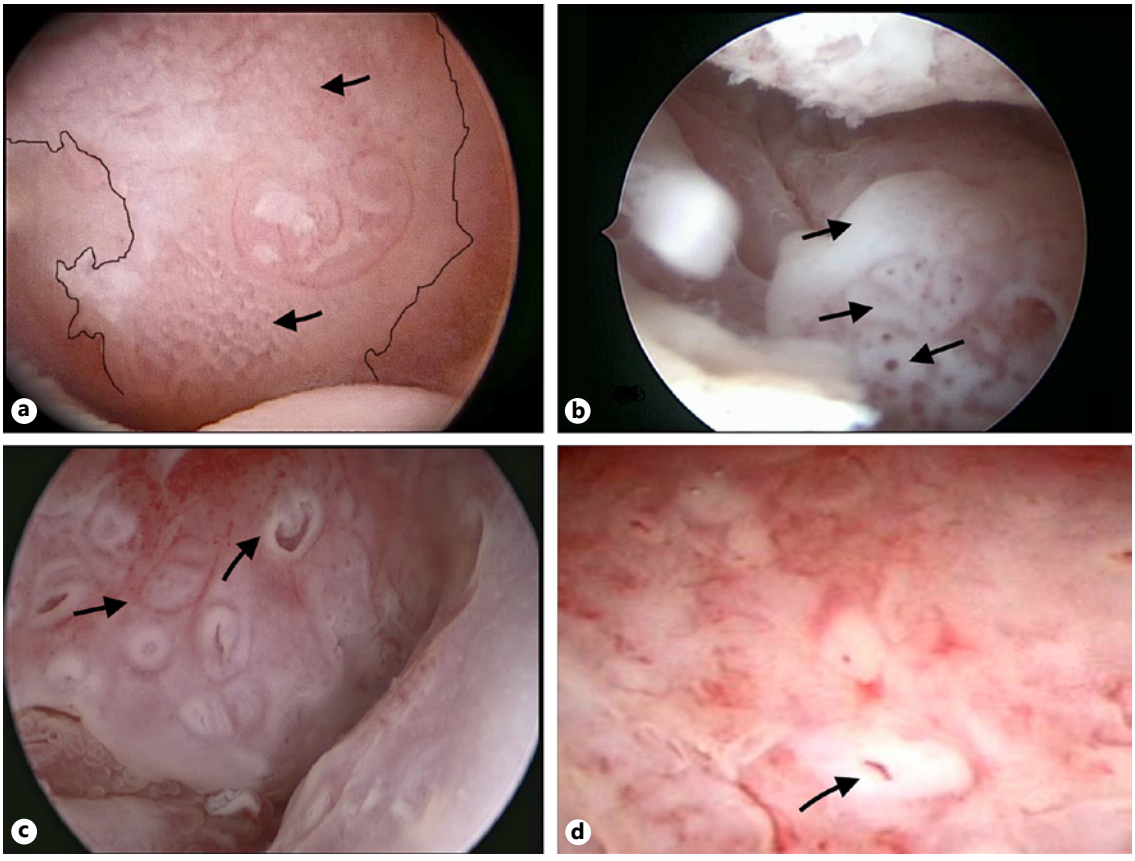

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Fig. 4. Minor and major changes at endocervicoscopy: (**a**) Thin acetowhite epithelium with fine punctuation; (**b**) dense acetowhite epithelium with coarse mosaic and punctuation and bridge sign exciding into cervical canal; (**c**) dense acetowhite epithelium with cuffed crypt (gland) openings and coarse mosaic; (**d**) cuffed crypt gland opening into endocervical canal in an atrophic endocervical epithelium. Details are signed with arrows. CM, coarse mosaic; CP, coarse punctuation; FP, fine punctuation; BS, bridge sign; CCO, cuffed crypt opening.

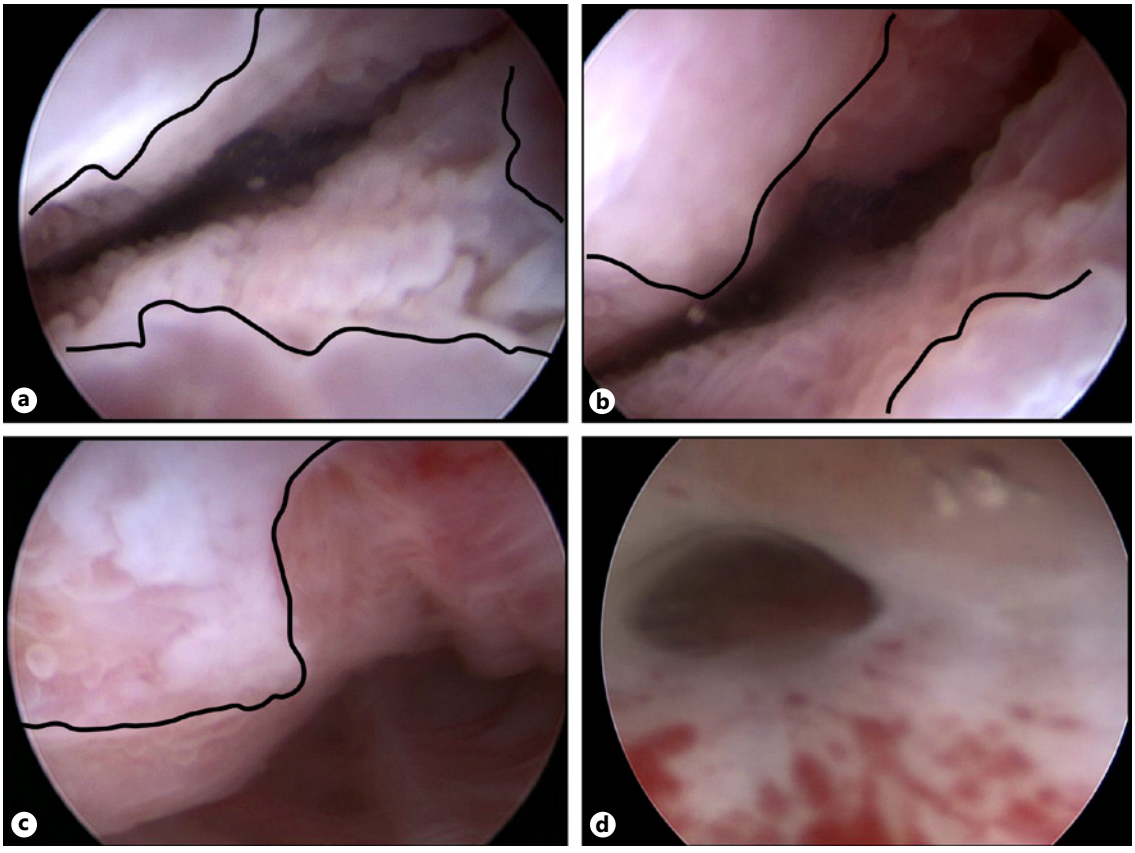

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Fig. 5. Endocervicoscopy squamocolumnar evaluation: (**a**) SCJ in a TZ type 1 at colposcopy; (**b**) SCJ in a TZ type 2 at colposcopy; (**c**) SCJ in a TZ type 3 at colposcopy; (**d**) inadequate endocervicoscopy. SCJ is signed in black.

tients [21, 22]. So the treatment of the CIN lesion should be minimally invasive but efficient.

Excision of TZ type 3 in many cases can be considered an overtreatment if the surgeon does not know the really endocervical extension of the CIN lesion and excise more tissue than necessary. To be extremely conservative in excisional treatment of CIN2+ has numerous advantages: first, it minimises the negative impact of the procedure in fertile women eager for offspring; then, it allows to have enough tissue without surgical damage to perform a correct follow-up after treatment and, in case of recurrence, to carry out a second conservative treatment [23, 24].

Bifulco et al. [11] previously demonstrated that endocervicoscopy guarantees the most appropriate depth of the surgical excision needed. Moreover, in patients where lesions were identified with endocervicoscopy, surgical excision margins of cone specimen were free from the disease. Status of the cone specimen margins is one of the main indicators of recurrence of CIN lesion [25].

Only in a small percentage of cases, the SCJ remains not visible at endocervicoscopy (3.5%, $n = 22$). These cases showed tight stenosis of the EUO during the exam; so that the analysis of the junctional area was impossible and inconclusive due to tissue damage at the orifice during the entry of the instrument into the endocervical canal. Stenosis of the EUO, abnormal bleeding, an excessive atrophic epithelium or presence of endocervical polyps represent the limits of the endocervicocopy in studying endocervical canal (Fig. 5a–d).

From our data emerged an important consideration regarding the TZ.

In colposcopic reports, TZ has been classified considering the localization, and accordingly the visibility, of SCJ in 3 types: ZT1: the SCJ is fully visible in eso-cervix; ZT2: SCJ is fully visible but is partially located into the cervical canal, ZT3: SCJ is totally or partially invisible. Of course, a more specific explanation with a topographical description is not possible at colposcopy. Endocervicoscopy allows to better define endocervical localization of SCJ, so

we proposed a new categorization for TZ when it was reported in endocervicoscopy, considering the distance of SCJ in millimetre from EUO to endocervical canal.

We particularly proposed to define as TZ type 1 when SCJ is esocervical and localisated until the EUO (distance = 1 mm); TZ type 2 when the SCJ is within 5.0 mm (>1.0 distance ≤5.0 mm); TZ type 3 when the SCJ is over 5.0 mm (distance >5.0 mm). This limit of 5 mm has been chosen according to our data since that using this cut-off there is a higher concordance between TZ definition in colposcopy and endocervicoscopy (98.59% for ZT2 and 97.43% for ZT3; Fig. 2).

Strengths and Limitations

The main strength of this study was the large population number and that both colposcopy and endocervicoscopy were performed by the same operators in a high specialised center. On the contrary, the limits were the retrospective design of the study and that the definitive anatomo-pathological diagnosis was obtained by different sampling methods.

Conclusion

In conclusion, although endocervicoscopy cannot replace colposcopy by presenting less power in grading the lesion and greater difficulty in performing a target-biopsy, it turned out to be an important tool, complementary to colposcopy, in the diagnostic and therapeutic pathway of CIN lesions.

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There are no acknowledgments to declare.

Statement of Ethics

Ethical approval was not required because this was classified as a hospital audit of current clinical practice. Nevertheless, all procedures involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Disclosure Statement

Drs. Nicoletta De Rosa, Giada Lavitola, Luigi Della Corte and Giuseppe Bifulco have no conflicts of interest or financial conflicts to disclose.

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Author Contributions

N.D.R.: protocol development, data management and analysis, manuscript writing. L.D.C.: data collection and analysis, manuscript revisiting. G.B.: manuscript editing and revisiting. G.L.: protocol development, data collection and management, manuscript revisiting.

References

1 Coleman D, Day N, Douglas G, Farmery E, Lynge E, Philip J, et al. European Guidelines for quality assurance in cervical cancer screening. Eur J Cancer. 1993;29A Suppl 4: S1–38.

2 Passamonti B, Gustinucci D, Giorgi Rossi P, Cesarini E, Bulletti S, Carlani A, et al. Cervical human papilloma virus (HPV) DNA primary screening test: results of a population-based screening programme in central Italy. J Med Screen. 2017 Sep;24(3):153–62.

3 Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al.; American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012 Apr; 137(4):516–42.

4 Khan MJ, Werner CL, Darragh TM, Guido RS, Mathews C, Moscicki AB, et al. ASCCP Colposcopy Standards: Role of Colposcopy, Benefits, Potential Harms, and Terminology for Colposcopic Practice. J Low Genit Tract Dis. 2017 Oct;21(4):223–9.

5 Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, et al.; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol. 2013 Apr;121(4):829–46.

6 Kyrgiou M, Tsoumpou I, Vrekoussis T, Martin-Hirsch P, Arbyn M, Prendiville W, et al. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: the Cochrane colposcopy & cervical cytopathology collaborative group (C5 group) approach. Cancer Treat Rev. 2006 Nov;32(7):516–23.

7 Andersen W, Frierson H, Barber S, Tabbarah S, Taylor P, Underwood P. Sensitivity and specificity of endocervical curettage and the endocervical brush for the evaluation of the endocervical canal. Am J Obstet Gynecol. 1988 Sep;159(3):702–7.

8 Klam S, Arseneau J, Mansour N, Franco E, Ferenczy A. Comparison of endocervical curettage and endocervical brushing. Obstet Gynecol. 2000 Jul;96(1):90–4.

9 Izzo S, Negrotti S, Stanco DI. Ardovino L'esame dell'endocervice: la colposcopia dell'endocollo, ovvero l'endocervicoscopia Patologia cervicovaginale: dal laboratorio alla clinica. Atti del XVII Congresso della SICPCV, Masson, Roma; 2002. pp. 119–30.

10 Börsch C, Lambrecht E. [Microcolpohysteroscopy]. Geburtshilfe Frauenheilkd. 1991 Mar;51(3):171–7.
11 Bifulco G, Piccoli R, Lavitola G, Di Spiezio Sardo A, Spinelli M, Cavallaro A, et al. Endocervicoscopy: a new technique for the diagnostic work-up of cervical intraepithelial neoplasia allowing a tailored excisional therapy in young fertile women. Fertil Steril. 2010 Dec; 94(7):2726–31.
12 Bornstein J, Bentley J, Bösze P, Girardi F, Haefner H, Menton M, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012 Jul;120(1):166–72.
13 Wells M. Epithelial tumors. In: Tavassoli FA, Devilee P, editors. World Health Organization classification of tumors: pathology and genetics of tumors of the breast and female genital organs. Lyons, France: IARC Press; 2003. pp. 269–70.
14 Nappi C, Di Spiezio Sardo A. State-Of-The-Art Hysteroscopic Approaches To Pathologies Of The Genital Tract. Endo Press® GmbH, 2015. Chapter 3, page 40.
15 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159–74.
16 Bifulco G, De Rosa N, Lavitola G, Piccoli R, Bertrando A, Natella V, et al. A prospective randomized study on limits of colposcopy and histology: the skill of colposcopist and colposcopy-guided biopsy in diagnosis of cervical intraepithelial lesions. Infect Agent Cancer. 2015 Nov;10(1):47.
17 Rahimi S, Marani C, Gardner F, Yeoh CC, Akaev I, Votano S. Endocervicoscopy and Biopsy to Detect Cervical Intraepithelial Squamous Neoplasia in Nonvisible Squamocolumnar Junction With Unsatisfactory Colposcopy: A Pilot Study. Technol Cancer Res Treat. 2018 Jan;17:1533034617753811.
18 Valenti G, Vitale SG, Tropea A, Biondi A, Laganà AS. Tumor markers of uterine cervical cancer: a new scenario to guide surgical practice? Updates Surg. 2017 Dec;69(4):441–9.
19 Vitale SG, Capriglione S, Zito G, Lopez S, Gulino FA, Di Guardo F, et al. Management of endometrial, ovarian and cervical cancer in the elderly: current approach to a challenging condition. Arch Gynecol Obstet. 2019 Feb; 299(2):299–315.
20 Rossetti D, Vitale SG, Tropea A, Biondi A, Laganà AS. New procedures for the identification of sentinel lymph node: shaping the horizon of future management in early stage uterine cervical cancer. Updates Surg. 2017 Sep;69(3):383–8.
21 Laganà AS, Garzon S, Raffaelli R, Ban Frangež H, Lukanovič D, Franchi M. Vaginal Stenosis After Cervical Cancer Treatments: Challenges for Reconstructive Surgery. J Invest Surg. 2019, Epub ahead of print.
22 De Rosa N, Lavitola G, Giampaolino P, Morra I, Nappi C, Bifulco G. Impact of Ospemifene on Quality of Life and Sexual Function in Young Survivors of Cervical Cancer: A Prospective Study. BioMed Res Int. 2017;2017: 7513610.
23 Frega A, Sesti F, De Sanctis L, Pacchiarotti A, Votano S, Biamonti A, et al. Pregnancy outcome after loop electrosurgical excision procedure for cervical intraepithelial neoplasia. Int J Gynaecol Obstet. 2013 Aug;122(2):145–9.
24 Sjøborg KD, Vistad I, Myhr SS, Svenningsen R, Herzog C, Kloster-Jensen A, et al. Pregnancy outcome after cervical cone excision: a case-control study. Acta Obstet Gynecol Scand. 2007;86(4):423–8.
25 Serati M, Siesto G, Carollo S, Formenti G, Riva C, Cromi A, et al. Risk factors for cervical intraepithelial neoplasia recurrence after conization: a 10-year study. Eur J Obstet Gynecol Reprod Biol. 2012 Nov;165(1):86–90.

3) Cognitive disorders and menopausal transition

Cognitive disorders are a common condition in women going through menopause. In a cross-sectional study of 16,065 women aged 40 to 55 from the Study of Women's Health Across the Nation (SWAN), 31% of premenopausal women experienced episodes of forgetfulness compared to 44% of women in early perimenopause 41% of late perimenopause women and 41% of postmenopausal women (Gold EB, 2000).

Although cognitive disorders increase with age, age alone does not justify these differences in menopausal forgetfulness rates. Other factors associated with cognitive disorders are: lower education level, financial difficulties and unemployment, surgical menopause, smoking (not current but past), ethnicity (non-white) and poor physical activity (Gold EB, 2000). In particular, although vaso-motor symptoms (VMS) are considered the cardinal symptom of menopause, memory decline is reported as the second most frequent symptom after joint disorders.

It is therefore appropriate to help women understand that cognitive disorders are common in menopause, this can help them normalize their experience and minimize worries.

Small decreases in some cognitive abilities begin as early as the third decade of life. But longitudinal studies reveal small changes in memory performance during the menopause transition, which are not explained by age or other factors investigated (Epperson CN, 2013; Greendale GA, 2009).

In a prospective study, the Penn Ovarian Aging Study, performed on 403 participants, verbal learning and mnemonic performance decreased from pre-menopause to peri- and post-menopause (Epperson CN, 2013). In SWAN, verbal memory also worsens during the menopause transition (Greendale GA, 2009). There is evidence of small, but significant, reductions in attention, processing speed and other cognitive abilities during the menopausal

transition. Therefore, the view that some middle-aged cognitive disorders are attributable to the menopausal transition is supported.

Some symptoms of menopause, depression, anxiety and sleep disturbances, are also related to the state of cognitive performance of middle age, but do not seem to explain the decline in memory. The values, in the scoring scales, of vasomotor symptoms are related to subjective cognitive disturbances but not to objective cognitive performances (Greendale GA, 2010; Woods NF 2007).

a) Hormone replacement therapy and cognitive disorders

Although some observational studies show a better cognitive level among women on hormone therapy during the transition of menopause, in randomized clinical trials, hormone therapy does not substantially affect cognitive function after spontaneous menopause (Henderson VW, 2014).

However, there are no in-depth studies in women with premature menopause, and there are no long-term studies on hormone therapy in women with moderate to severe VMS. In observational studies, hormone therapy used by younger women is associated with a reduced risk of Alzheimer's, but it is necessary to consider that hormone therapy subjects are often healthier than non-users; starting hormone therapy after 65 years of age increases the risk of two further cases of dementia per 1,000 people-years of use. Hormone therapy is not approved for the prevention or treatment of age-related cognitive decline or dementia.

4) Cancer-related cognitive impairment (CRCI)

It has long been observed that cancer survivors present cognitive dysfunctions at various stages of the disease course with negative consequences on QoL and functional independence. Nevertheless, until relatively recently, cancer-related cognitive impairment (CRCI) in patients with non-central nervous system neoplasms was largely unrecognized (Boykoff N, 2009).

The prevailing attitude was reinforced by the belief that chemotherapies were not able to cross the blood-brain barrier (Nelson WL, 2013) precluding the possibility of a direct neurotoxic effect of cancer therapies. However, since the 1990s, a growing number of scientific studies have verified the existence of CRCI, both on animal models and with neuroimaging evaluations, which allowed the discovery of specific physiopathological correlations (Wefel JS, 2015).

Research has largely focused on the neurotoxicity associated with chemotherapy, often referred to as "chemobrain" or "chemofog". However, CRCI has also been documented in the absence of chemotherapy, leading to hypothesized associations with cancer itself (Debess J, 2009), with surgical interventions (Wefel JS, 2004) and with other adjuvant therapies (Ernst T, 2002).

CRCI prevalence estimates vary widely, although current longitudinal studies suggest that about 40% of cancer patients present with CRCI before any treatment, up to 75% may have cognitive decline during treatment and up to 60% shows deterioration of cognition after completion of therapies (Ouimet LA, 2009, Janelsins MC, 2014).

CRCI characteristics differ between patients and with the course of the disease, although severity is typically mild to moderate and also depends on the patient's pre-morbid level of function. Generally, the severity of CRCI is generally milder than the cognitive impairment typical of common neurological populations, including those with neurodegenerative

diseases and stroke. Despite this, encephalopathies have been observed that involve dementia in the context of treatment with some cytostatic agents (Perry A, 2006). Furthermore, CRCI can persist for months or years after treatment (Ahles TA, 2010) and even minor impairments can have profound consequences on QoL, including work and social functioning.

To date, most CRCI research in patients with non-CNS cancer has involved women with breast cancer (Wefel JS, 2012; Janelsins MC, 2011; De Santis CE, 2013). Surveys have also been conducted in patients with testicular cancer (Wefel JS, 2014), lymphomas (Ahles TA, 2002), multiple myeloma (Jones D, 2013), colorectal cancer (Vardy JL, 2007), ovarian cancer (Correa DD, 2012) and prostate cancer (Chao HH, 2012). However, much of the literature concerning these populations is preliminary, with studies consisting mainly of small samples.

a) The aim of the study

The purpose of this study was to evaluate the perception of cognitive decrement in patients undergoing surgical and/or medical therapy for gynecological cancers.

b) Materials and methods

All women diagnosed from January 2017 to August 2019 with primary gynecological cancer and undergoing active medical treatment have been enrolled in a cross-sectional prospective study.

At the time of recruitment each person has been informed about the aims and methods of the study. The study was conducted according to the guidelines of the Declaration of Helsinki (1975). All patients signed informed consent before participation. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative was adopted to an accurate and complete report of this observational study (von Elm E, 2007). Considering that this analysis is purely observational, no study protocol was required by our Institutional Review Board.

To be eligible for enrollment, patients had to meet all of the following criteria: diagnosis of a gynecological malignant tumor (ovary, cervix, endometrium or vulva); tumor Stage FIGO (International Federation of Gynecology and Obstetrics) I-III; good comprehension of Italian language and the questions proposed, verified by the interviewers.

Patient with tumor stage FIGO IV and with diagnosis of central nervous system pathologies, potential psychiatric disorders or traumatic brain injury were excluded from the study.

Before starting treatment (surgical or/and medical treatment) and after 6 months, patients were interviewed, individually, by two medical doctors, to evaluate the effects of cancer treatment on perceived cognitive function on depression and on quality of life.

The cognitive functions were evaluated with the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog -version 3). The FACT-COG is the cancer patient's cognitive function assessment and includes four aspects: perceived cognitive impairments (PCI), impact on quality of life, comments from others (OTH), and perceived cognitive abilities (PCA) (Costa DSJ, 2018).

Depressive symptoms were assessed via the Beck Depression Inventory-II test which consists of 21 groups of items investigating patient condition in the last 2 weeks (Beck AT 1974). This scale has been utilized to assess depressive symptoms in gynecological cancer patients in prior studies (Manne SL, 2017; Gonzalez BD, 2017).

The QoL was measured by The European Organization for Research and Treatment of Cancer (EORTC) QoL Questionnaire C30 (QLQ-C30), a 30-items cancer-specific questionnaire for assessing the general QoL of Cancer patients. The EORTC-QLQC-30 incorporates five functioning domains: physical (PF2), role (RF2), cognitive (CF), emotional (EF), and social (SF); three symptom scales: fatigue (FA), pain (PA), and nausea/vomiting (NV); several single items which assess additional symptoms commonly reported by cancer patients: dyspnea (DY), insomnia (SL), appetite loss (AP), constipation (CO), and diarrhea (DI); the perceived financial impact of the disease and treatment (FI), and finally an overall QoL scale (QL2) (Greimel E, 2002).

Data regarding age, education level, marital status, lifestyle (smoke and alcohol habits), comorbidities (metabolic, endocrine or cardiac disfunction), menopausal state at diagnosis, cancer type, cancer stage, treatment modality were also recorded for each patient.

Statistical analysis

The FACT-Cog was scored using FACT-Cog Scoring Guidelines. PCI, QOL, OTH and PCA were reverse scored. Higher is the score, better is the condition.

The score obtained by the Beck Depression Inventory-II test can vary from 0 to 63. Higher scores indicated more severe depressive symptoms. A total score between 14 and 19 points corresponds to a mild depression; if it is between 20 and 28 points it is a moderate depression; a score of > 29 points indicates a serious depression (Hilsenroth MJ, 2004).

The EORTC QLQ-C30 was scored using the algorithm provided by the EORTC (Greimel E, 2002). All scores were transformed to a 0–100 scale according to the guidelines for the scale to which they belong. In the scales that measured function, a high score indicates a

good function. In symptom scales and single items measuring symptoms, a higher score indicates more severe symptoms.

SPSS software has been used for statistical analysis. The significance has been set with p-value <0.05.

The Shapiro Wilks test has been used to evaluate the data distribution. The differences between baseline and post-treatment results have been evaluated with Student's t-test for paired data or with the Mann-Whitney test according to the data distribution.

The results have been stratified by the menopausal state at diagnosis, type of tumor (endometrial, cervical, ovarian, vulvar) disease stage and type of treatment (chemotherapy or radiotherapy).

c) Results

Seventy-three patients completed the follow-up period and were included in the statistical analysis. The mean age at enrollment was 50 .2 ± 20.3 (S.D.) years. Table 1 summarizes patients' clinical and demographical data and disease characteristics of the study group. The large percentage of patients had a formal educational level, had a life partner and had a healthy lifestyle behavior.

Table 1. Patients demographics and clinical data of the studied population

Age (year) (mean ± s.d.)	50 .2 ± 20.3		
Menopause		**Cardiac or metabolic disease**	
Surgical	32 (43)	Present	
Spontaneous pre-surgery	41 (56.2)	absent	
Educational level		**Partner**	
High school or less	33 (45.2)	Present	61 (83.6)
Collage or more	40 (54.8)	absent	12 (16.4)
Smoke habit		**Alcohol consumption**	
Current smoker	12 (16.4)	Never	64 (87.7)
No smoker	61 (83.6)	weekly	3 (4.1)
		daily	6 (8.2)
Tumor site		**Tumor stage (FIGO)**	
Endometrium	40 (54.8)	I	26 (35.6)
Cervix	13 (17.8)	II	35 (47.9)
Ovary	16 (21.9)	III	12 (16.4)
Vulva	4 (5.5)		
Surgical treatment		**Recovery**	
Performed	69 (94.5)	Complete	69 (94.5)
Not performed	4 (5.5)	Uncomplete	4 (5.5)
Chemotherapy		**Radiotherapy**	
Performed	62 (84.9)	Performed	63 (86.3)
Not performed	11 (15.1)	Not performed	10 (13.7)

Data are presenting as: number (percentage).

A significant reduction in perceived cognitive impairments was demonstrated in all patients after treatment (CogPCI: 61.35±13.83 vs 55.05±16.56; $p < 0.05$). On the contrary, a significant improvement was shown in depression state (BDII: 21.14±11.23 vs 12.82±12.33, $p < 0.005$) (Table 2). In the six months after treatment, we missed demonstrating a significant reduction in QoL of patients (QL2: 65.53±16.97 vs 63.24±26.81; p = NS). A significant reduction was observed in Emotional and Role function domains.

Table 2. Effect of cancer treatment on perceived cognitive function on depression and QoL.

	At baseline	6 months after treatment	P value
Perceived Cognitive Impairments (CogPCI)	61.35±13.83	55.05±16.56	0.001
Impact of PCI on QoL (CogQOL)	8.19±4.48	7.5±4.62	NS
Comments from Others (CogOth)	13.16±3.81	12.39±4.47	NS
Perceived Cognitive Abilities (CogPCA)	13.83±5.78	14.67±5.88	NS
Beck depression Inventory II (BDI II)	21.14±11.23	12.82±12.33	0.005
Global health status/QoL (QL2)	65.53±16.97	63.24±26.81	NS
Functional scales			
Physical functioning(PF2)	74.06±21.73	72.32±24.98	NS
Role functioning (RF2)	83.79±24.69	72.37±31.22	0.03
Emotional functioning (EF)	50.68±25.53	39.15±27.41	0.01
Cognitive functioning (CF)	69.18±31.63	69.17±32.11	NS
Social functioning (SF)	74.66±28.20	79.90±29.91	NS
Symptom scales			
Fatigue (FA)	35.31±28.40	45.05±31.91	NS
Nausea and vomiting (NV)	9.82±23.71	18.49±26.14	0.03
Pain (PA)	43.61±23.10	39.04±35.81	NS
Dyspnea (DY)	32.88±24.53	30.14±30.51	NS
Insomnia (SL)	60.73±40.19	55.25±42.02	NS
Appetite loss (AP)	43.60±23.99	39.04±35.81	NS
Constipation (CO)	25.57±37.89	34.24±37.25	NS
Diarrhea (DI)	5.48±16.68	8.2±24.08	NS
Financial difficulties (FI)	17.81±27.82	20.09±27.63	NS

Data are presenting ad mean ± s.d.
P value was set < 0.05

When stratified for the menopausal state, at baseline we observed a significant reduction in perceived cognitive impairment in the patient who undergo surgical menopause (CogPCI: 61.83±13.6 vs 153.56±17.66; p-value <0.05), and a significant increase in depression state was observed both for surgical than for spontaneous menopause (Table 3A).

Table 3A. Effect of cancer treatment on perceived cognitive function on depression and QoL stratify for menopausal state.

	At baseline	6 months after treatment	P value
Spontaneous menopause (n = 32)			
CogPCI	60.75±14.29	56.96±15.09	NS
BDI II	24.00±10.96	14.84±14.44	0.001
RF2	82.29±25.72	62.50±30.23	0.01
EF	50.00±26.94	36.69±28.29	NS
Surgical menopause (n=41)			
CogPCI	61.83±13.61	53.56±17.66	0.03
BDI II	18.90±11.05	11.24±10.29	0.02
RF2	84.95±24.09	80.08±30.32	NS
EF	51.21±24.68	41.05±26.90	NS

Data are presenting as mean ± s.d; CogPCI: perceived cognitive impairments; BDI II: Back depression inventory II; RF2: role functioning, EF: emotional functioning.

When stratifying for tumor site we observed: a confirmed significant reduction in PCI and a significant improvement in BDII for ovarian and endometrial cancer (Table 3B).

Table 3B. Effect of cancer treatment on perceived cognitive function on depression and QoL stratify for cancer site.

	At baseline	6 months after treatment	P value
Ovarian Cancer (n = 16)			
CogPCI	64.12±14.33	53.87±11.74	0.01
BDI II	23.87±11.97	12.81±9.84	0.001
RF2	89.58±14.75	58.34±34.42	0.01
EF	55.20±30.71	32.29±28.36	0.03
Endometrial cancer (n = 40)			
CogPCI	64.47±10.69	55.02±17.78	0.008
BDI II	18.83±9.84	10.90±11.48	0.001
RF2	83.75±26.28	83.75±26.82	NS
EF	54.37±21.59	50.63±27.89	NS
Cervical Cancer (n=13)			
CogPCI	55.31±20.83	52.00±12.91	NS
BDI II	25.85±12.97	17.46±17.87	NS
RF2	74.36±30.89	64.10±31.07	NS
EF	33.97±28.56	32.05±30.96	NS
Vulvar Cancer (n= 4)			
CogPCI	54.50±4.04	49.50±25.98	NS
BDI II	17.00±2.31	17.00±12.70	NS
RF2	91.67±66.65	66.6738.49±	NS
EF	50.00±9.62	33.34±38.49	NS

Data are presenting as mean ± s.d; CogPCI: perceived cognitive impairments; BDI II: Back depression inventory II; RF2: role functioning, EF: emotional functioning.

Tumor stage I was associated only with a significant reduction in PCI; on the other hand, a significant improvement in BDII was observed in stage I and in stage II after treatment (Table 3C).

Table 3C. Effect of cancer treatment on perceived cognitive function on depression and QoL stratify for cancer stage.

	At baseline	6 months after treatment	P value
Stage I (n= 26)			
CogPCI	64.69±10.95	55.61±18.26	0.04
BDI II	17.15±9.99	13.11±15.09	0.05
RF2	87.17±27.61	74.36±32.40	0.05
EF	55.77±24.81	41.67±26.03	0.04
Stage II (n = 35)			
CogPCI	59.05±14.41	55.11±16.95	NS
BDI II	25.14±10.65	12.22±11.46	0.001
RF2	78.57±24.78	77.62±31.81	NS
EF	50.00±27.26	37.60±27.57	NS
Stage III (n = 13)			
CogPCI	60.83±17.15	55.83±12.14	NS
BDI II	18.13±12.22	13.91±8.21	NS
RF2	91.66±13.30	61.11±26.91	0.03
EF	41.67±20.41	38.20±31.68	NS

Data are presenting as mean ± s.d; CogPCI: perceived cognitive impairments; BDI II: Back depression inventory II; RF2: role functioning, EF: emotional functioning.

Patients who performed chemotherapy showed no significant difference in BDII score but a significant reduction in PCI (Table 3D).

Table 3D. Effect of cancer treatment on perceived cognitive function on depression and QoL stratify for chemotherapy treatment.

	At baseline	6 months after treatment	P value
Chemotherapy not performed (n=62)			
CogPCI	61.53±13.94	57.39±13.26	NS
BDI II	21.34±11.20	11.05±9.21	0.05
RF2	83.06±24.42	76.61±31.72	NS
EF	54.43±24.31	40.71±26.86	0.01
Chemotherapy performed (n=11)			
CogPCI	60.36±13.80	41.90±26.04	0.05
BDI II	20.00±11.91	22.81±21.15	NS
RF2	87.88±26.97	48.48±13.85	0.002
EF	29.54±22.47	30.30±30.10	NS

Data are presenting as mean ± s.d; CogPCI: perceived cognitive impairments; BDI II: Back depression inventory II; RF2: role functioning, EF: emotional functioning.

Patients who performed radiotherapy showed no significant difference in PCI and BDII while patients who not performed radiotherapy showed a significant difference in these variables (Table 3E).

Table 3E. Effect of cancer treatment on perceived cognitive function on depression and QoL stratify for radiotherapy treatment.

E	At baseline	6 months after treatment	P value
Radiotherapy not performed (n=63)			
CogPCI	62.95±13.66	56.47±15.52	0.001
BDI II	19.81±10.71	11.33±10.63	0.02
RF2	85.71±24.29	75.40±31.66	NS
EF	54.50±24.08	41.92±27.26	0.01
Radiotherapy performed (n=10)			
CogPCI	51.30±10.67	46.10±20.72	NS
BDI II	29.50±11.33	22.20±18.00	NS
RF2	71.67±24.90	53.33±21.94	NS
EF	26.67±21.80	21.66±22.29	NS

Data are presenting as mean ± s.d; CogPCI: perceived cognitive impairments; BDI II: Back depression inventory II; RF2: role functioning, EF: emotional functioning.

Regarding QOL domains, when stratifying for each variables, a significant reduction in RF was confirmed in ovarian cancer patient, in stage I and stage III patients and in patients undergone chemotherapy. A significant reduction in EF was observed in ovarian cancer, with a tumor at stage I, in patient not undergone chemotherapy or radiotherapy (Table 3).

d) Discussion and conclusions

According to our knowledge, this is the first prospective study who investigates cognitive impairment and depression state in gynecological cancer survivors at baseline and after treatment.

The results of this pilot study reveal that gynecological cancer survivors harm perceived cognitive impairment and a positive effect on depression state. No effect was shown on cognitive abilities, comments from others and effect of cognitive impairment on QoL.

Moreover, tumor site, stage and treatment modality seem to influence the variables analyzed. Particularly, ovarian cancer patients and endometrial cancer patients have had the greatest negative impact on perceived cognitive impairment, independently of the state of depression that increased after treatment. Cervical cancer and vulvar cancer patients did not show this negative effect.

Ovarian cancer patients had also a significant negative impact on role function and emotional function domain.

The tumor stage did not influence perceived cognitive impairment, since that a low stage of tumor is significantly associated with a cognitive impairment while a higher stage not.

The EORTC questionnaire domain on cognitive function is not significantly changed before and after treatment. This lack of evidence may reflect the not exhaustive evaluation of perceived cognitive impairment of this questionnaire.

The treatment of gynecological oncological diseases including surgery, radiotherapy, chemotherapy and / or medical therapies (aromatase inhibitors, tamoxifen) has a negative impact on a woman's QoL and on sexual function SF (Bifulco G, 2012; De Rosa N, 2017). Regarding the cognitive state in patients performed active treatment for gynecological cancer the literature data are scarce and concern mainly the ovarian tumor.

Surgical menopause was associated with faster cognitive decline in verbal memory, semantic memory, and processing speed following the surgery (Georgakis MK, 2019). Estrogens and progesterone have been reported to exert neuroprotective properties. Thus, it is plausible that early cessation of brain exposure to female sex hormones could be associated with short-term and long-term cognitive deficits. Recently, Gayatri Devi (2018) proposed the term of menopause-related cognitive impairment, to differentiate this condition from mild cognitive impairment, often synonymous with a dementia prodrome; it is characterized by a subjective change in cognition present in the context of persistent change in frequency and quality of menses for at least 12 months and not related to other factors.

In our study, patients who are yet in menopause before treatment had a not significant effect on perceived cognitive impairment, while patient who experiments menopause after treatment with prompt loss in ovarian function had a significant reduction in perceived cognitive impairment. A possible explanation of these data is that menopausal patients who performed subsequently demolition surgery for gynecological cancer have a minor impact of hormone loss on their body since this effect may have already occurred before and could be less evident during cancer treatment.

Moreover, in pre-menopause-patient who underwent surgery, we observed a better state of depression at baseline (mild depression), differently than the total population. This reflects, probably, the ongoing debate about whether the menopause transition and/or post-menopause is associated with an increased risk for depressive symptoms or disorder (Bromberger JT, 2018). Both groups, however, experiment with an increase in depression state after treatment.

Contrasting and poor data are reporting in the literature about the cognitive function after chemotherapy (Van Arsdale A, 2016; Hess LM, 2015). Our data confirmed that patients who performed chemotherapy showed a negative impact on perceived cognitive impairment and

reveal that they have no increase in depression state, which, at the end of therapy, results persistently a state of moderate depression.

Overall, patients with a diagnosis of gynecological cancer have at baseline, at the time of diagnosis, a moderate depression. Our findings are consistent with the literature reporting that between 20% and 30% of patients with gynecological cancer experience psychological distress at some point during their cancer journey (Zabora J, 2001).

However, we observed that only 6 months after therapy this condition seems to regress.

This singular effect may reflect the population studied: about 70% of patients had no other comorbidities and had a healthy lifestyle behavior (no alcohol consumption in 87.7% of patients and no smokers in 83.6%); additionally, 94.5% had a complete recovery after treatment and had a low tumor FIGO stage (I/II).

Our data are following other studies that reported that women are most vulnerable to anxiety and depression at diagnosis, with improvement over time (Stafford L, 2015). A current meta-analysis suggests that along the course for cancer treatment, depression is highest before the initiation of treatment (25.3%), dropping during treatment (23%) and decreasing again after the cessation of treatment (12.7%) (Watts S, 2015).

The previous study suggests that benefit finding, the process of deriving positive growth from adversity, may reduce depression by increasing acceptance of cancer and further underscores the importance of acceptance coping processes in gynecological cancer patients (Manne SL, 2018). In this subset of patients, moreover, QoL seems to be not significantly reduced in the interval studied. Neither the perceived cognitive impairment seems to impact the QoL.

This study has some limitations. First, it was an exploratory study and additional research is needed to confirm these observations. On the other hand, the generalization of our findings is limited by the sample characteristics, infact, the sample size is small for some subset of the tumor (i.e. vulvar tumor) and replication in larger samples is relevant.

One of the main strengths of this study is its prospective design and the short term from baseline and to after treatment evaluations that have the potential of excluding other relevant effects on cognitive state that can surge during the time.

In conclusion, our study suggests that CRCI is a true risk also in gynecological cancer survivors. The cognitive impairment does not seem to be dependent on depression or to a menopausal condition.

Assessing cognitive decline in cancer survivorship is essential for ensuring the optimum QoL and functioning. To evaluate only QoL could be not sufficient to weigh the patient's overall need. Self-reported cognitive dysfunction is a valid method for assessing this issue. Clinically depressed patients with cancer have lower treatment compliance, poorer treatment outcomes, lower QoL, experience increased periods of hospitalization and have poorer 5-year survival rates than their non-depressed counterparts (McDaniel JS, 1995). Consequently, the timely diagnosis and management of depression should be viewed as an important clinical focus.

5) References

- Adamczak M, Wiecek A. The adipose tissue as an endocrine organ. Semin Nephrol. 2013;33:2–13.
- American Society for Reproductive Medicine, Practise Committee. Treatment of pelvic pain associated with endometriosis: a committee opinion. Fertil Steril 2014; 101:927–935.
- Arnoldussen IA, Kiliaan AJ, Gustafson DR. Obesity and dementia: adipokines interact with the brain. Eur Neuropsychopharmacol. 2014;24:1982-1999.
- Awadalla AW, Ohaeri JU, Gholoum A, Khalid AO, Hamad HM, Jacob A. Factors associated with quality of life of outpatients with breast cancer and gynecologic cancers and their family caregivers: a controlled study. BMC Cancer 2007;7:102.
- Bachmann GA, Komi JO; Ospemifene Study Group. Ospemifene effectively treats vulvovaginal atrophy in postmenopausal women: results from a pivotal phase 3 study. Menopause. 2010;17(3):480-6.
- Beck AT and Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry, 1974;7(0): p. 151–69.
- Bifulco G, N. De Rosa, M. L. Tornesello et al. Quality of life, lifestyle behavior and employment experience: A comparison between young and midlife survivors of gynecology early stage cancers. Gynecologic Oncology 2012;124(3):444–451.
- Bonda DJ, Stone JG, Torres SL et al. Dysregulation of leptin signaling in Alzheimer disease: evidence for neuronal leptin resistance. J Neurochem. 2014;128:162–72.
- Bouret SG. Neurodevelopmental actions of leptin. Brain Res. 2010;1350:2–9.
- Bromberger JT, Epperson CN. Depression During and After the Perimenopause: Impact of Hormones, Genetics, and Environmental Determinants of Disease. Obstet Gynecol Clin North Am. 2018;45(4):663-678.
- Burri A, Spector T. Recent and lifelong sexual dysfunction in female UK popula- tion sample: prevalence and risk factors. J Sex Med 2001;8:2420–30.
- Capelli G, De Vincenzo RI, Addamo A, Bartolozzi F, Braggio N, Scambia G. Which dimensions of health-related quality of life are altered in patients attending the different gynecologic oncology health care settings? Cancer 2002;95(12):2500–7.
- Carlsen K, Dalton SO, Diderichsen F, Johansen C, Danish Cohort Study. Risk for unemployment of cancer survivors: a Danish cohort study. Eur J Cancer 2008;44(13):1866–74.

- Carter J, Penson R, Barakat R, et al. Contemporary quality of life issues affecting gynecologic cancer survivors. Hematol Oncol Clin North Am. 2012;26(1):169-94.
- Chung SH and Lambert PF. Prevention and treatment of cervical cancer in mice using estrogen receptor antagonists. Proc Natl Acad Sci U S A. 2009;17;106(46):19467-72.
- Clayton AH, Valladares Juarez EM. Female Sexual Dysfunction. Med Clin North Am. 2019;103(4):681-698.
- Constantine G, Graham S, Koltun W. D., and Kingsberg S.A. Assessment of ospemifene or lubricants on clinical signs of VVA. Journal of Sexual Medicine; 2014;(11)4:1033–1041.
- Correˆa CSL, Leite ICG, Andrade A.P.S., et al. Sexual function of women surviving cervical cancer. Archives of Gynecology and Obstetrics, 2016; 293 (5): 1053–1063.
- Costa DSJ, Loh V, Birney DP, et al. The Structure of the FACT-Cog v3 in Cancer Patients, Students, and Older Adults. J Pain Symptom Manage. 2018;55(4):1173-1178.
- Cowley MA, Smart JL, Rubinstein M, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature. 2001;411:480–4
- Crabtree JS, Peano BJ, Zhang X et al. Activity of three selective estrogen receptor modulators on hormone-dependent responses in the mouse uterus and mammary gland. Mol Cell Endocrinol. 2008;287(1-2):40-6.
- Daniel Y, Inbar M, Bar-Am A, Peyser MR, Lessing JB. The effects of tamoxifen treatment on the endometrium. Fertil Steril. 1996;65(6):1083-9.
- De Graaff AA, D'Hooghe TM, Dunselman GA, Dirksen CD, Hummelshoj L, Simoens S. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. Hum Reprod 2013;28:2677–2685.
- Lavitola G, Della Corte L,. De Rosa N, Nappi C., Bifulco G. Effects on vaginal microbiota restoration and cervical epithelialization in positive HPV patients undergoing vaginal treatment with carboxy-methyl-beta-glucan. Biomed Res. Int. vol. 2020 https://doi.org/10.1155/2020/5476389.
- De Rosa N, Giampaolino P, Lavitola G, Morra I, Formisano C, Nappi C, Bifulco G. Effect of Immunomodulatory Supplements Based on Echinacea Angustifolia and Echinacea Purpurea on the Posttreatment Relapse Incidence of Genital Condylomatosis: A Prospective Randomized Study. Biomed Res Int. 2019;2019:3548396. doi: 10.1155/2019/3548396. eCollection 2019.

- De Rosa N, Lavitola G, Della Corte L, Bifulco G. Diagnostic Accuracy of Endocervicoscopy in Identifying and Grading Cervical Intraepithelial Neoplasia Lesion. Gynecol Obstet Invest. 2020 Mar 17:1-10. doi: 10.1159/000506801.
- De Rosa N, Lavitola G, Giampaolino P et al. Impact of Ospemifene on Quality of Life and Sexual Function in Young Survivors of Cervical Cancer: A Prospective Study. Biomed Res Int. 2017;2017:7513610.
- Demark-Wahnefried W, Morey MC, Sloane R, Snyder DC, Cohen HJ. Promoting healthy lifestyles in older cancer survivors to improve health and preserve function. J Am Geriatr Soc 2009;57(Suppl 2):S262–4.
- Devi G. Menopause-Related Cognitive Impairment. Obstet Gynecol. 2018;132(6):1325-1327.
- Dew JE, Wren BG, Eden JA. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. Climacteric 2003;6:45–52
- Donovan KA, Taliaferro LA, Alvarez EM, et al. Sexual health in women treated for cervical cancer: characteristics and correlates. Gynecol 2007; Oncol 104(2):428–43.
- Edwards D and Panay N, Treating vulvovaginal atrophy/genitourinary syndrome of menopause: How important is vaginal lubricant and moisturizer composition? Climacteric. 2016; 19 (2): 151–161
- Enriori PJ, Evans AE, Sinnayah P, et al. Diet-induced obesity causes severe but reversible leptin resistance in arcuate melanocortin neurons. Cell Metab. 2007;5:181–94.
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Internet. International Agency for Research on Cancer: Lyon, France; 2010. Available from: http://globocan.iarc.fr, accessed on day/month/year.
- Francucci CM, Daniele P, Iori N, et al. Effects of raloxifene on body fat distribution and lipid profile in healthy post-menopausal women. J Endocrinol Invest 2005;28:623–631.
- Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395:763–70.
- Friedrich M1, Mink D, Villena-Heinsen C et al. Tamoxifen and proliferation of vaginal and cervical epithelium in postmenopausal women with breast cancer. Eur J Obstet Gynecol Reprod Biol. 1998;80(2):221-5.
- Froeding LP, Ottosen C, Rung-Hansen H, et al. Sexual functioning and vaginal changes after radical vaginal trachelectomy in early stage cervical cancer patients: a longitudinal study. J Sex Med 2014; 11(2):595–604.

- Genazzani A.R., Spinetti A., Gallo R., Bernardi F. Menopause and the central nervous system: intervention options. Maturitas, 1999; 3:103-110.
- Georgakis MK, Beskou-Kontou T, Theodoridis I, et al. Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis. Psychoneuroendocrinology. 2019; 19(10).
- GLOBOCAN 2012 (IARC), Section of Cancer Surveillance (2017).
- Goldstein SR, Bachmann G.A, Koninckx PR., et al. Ospemifene 12-month safety and efficacy in postmenopausal women with vulvar and vaginal atrophy. Climacteric, 2014:17(2): 173–182.
- Gonzalez BD, Manne SL2, Stapleton Jet al. Quality of life trajectories after diagnosis of gynecologic cancer: a theoretically based approach. Support Care Cancer, 2017 25(2): p. 589–598.
- Gorska E, Popko K, Stelmaszczyk-Emmel A, et al. Leptin receptors. Eur J Med Res. 2010;15 Suppl 2:50–4.
- Greimel E, Thiel I, Peintinger F, Cegnar I, Pongratz E. Prospective assessment of quality of life of female cancer patients. Gynecol Oncol 2002;85(1):140–7.
- Greimel E. R., Vlasic K. K.,. Waldenstrom A.C et al., European organization for research and treatment of cancer (EORTC) quality-of-life questionnaire cervical cancer module: EORTC QLQ-CX24. Cancer; 2006, 107(8): 1812–1822.
- Greimel E.R, Iel I., Peintinger F, et al. Prospective assessment of quality of life of female cancer patients Gynecologic Oncology; 2002, 85 (1): 140–147.
- Halpern CT, Udry JR, Suchindran C. Testosterone predicts initiation of coitus in adolescent females. Psychosom Med. 1997;59(2):161–71.
- Hawighorst-Knapstein S, Fusshoeller C, Franz C, et al. The impact of treatment for genital cancer on quality of life and body image– results of a prospective longitudinal 10-year study. Gynecol Oncol 2004;94(2):398–403.
- Hayes RD, Bennett CM, Fairley CK, et al. What can prevalence studies tell us about female sexual difficulty and dysfunction? J Sex Med 2006;3(4):589–95.
- Hess LM, Huang HQ, Hanlon AL, et al. Cognitive function during and six months following chemotherapy for front-line treatment of ovarian, primary peritoneal or fallopian tube cancer: an NRG oncology/gynecologic oncology group study. Gynecol Oncol. 2015; 139:541–545.
- Hilsenroth MJ, Segal DL. Comprehensive Handbook of Psychological Assessment. Wiley & Sons Inc 2004, Vol. 2, Ch. 5 p 51.

- Jacobsen DE, Samson MM, Emmelot-Vonkand MH, Verhaar HJJ. Raloxifene and body composition and muscle strength in post-menopausal women: a randomized, double-blind, placebo-controlled trial. Eur J Endocrinol 2010;162:371–376.
- Jacques JD, et al. Women's sexual pain disorders. J Sex Med 2010;7:616–31.
- Jia SZ, Leng JH, Sun PR, Lang JH. Prevalence and associated factors of female sexual dysfunction in women with endometriosis. Obstet Gynecol 2013;121:601–606.
- Jordan VC. Chemoprevention of breast cancer with selective oestrogen-receptor modulators. Nat Rev Cancer. 2007;7(1):46-53.
- Khajehei M, Doherty M, Tilley M. An update on sexual function and dysfunction in women. Arch Womens Ment Health 2015;18:423–33.
- Krychman ML, Pereira L, Carter J, Amsterdam A. Sexual oncology: sexual health issues in women with cancer. Oncology 2006;71:18–25
- Lalos O, Kjellberg L, and Lalos A. Urinary, climacteric and sexual symptoms 1 year a er treatment of cervical cancer without brachytherapy J. of Psych. Obstet and Gynecol. 2009; 30 (4):269–274.
- Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. JAMA. 2000;284(20):2606–10.
- Lee CC, Kasa-Vubu JZ, Supiano MA. Differential effects of raloxifene and estrogen on insulin sensitivity in postmenopausal women. J Am Geriatr Soc 2003;51:683–688. 594.
- Lee Y, Lim MC, Kim SI et al. Comparison of Quality of Life and Sexuality between Cervical Cancer Survivors and Healthy Women. Cancer Res Treat. 2016;48(4):1321-1329
- Lein ES, Hawrylycz MJ, Ao N et al. Genome-wide atlas of gene expression in the adult mouse brain. Nature. 2007;445:168–76.
- Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. Menopause. 2008 Jul-Aug;15(4 Pt 1):661-6.
- Maher EJ, Denton A. Survivorship, late effects and cancer of the cervix. Clin Oncol 2008; 20(6):479–487.
- Manne SL, Virtue SM, Ozga M et al. A comparison of two psychological interventions for newly-diagnosed gynecological cancer patients. Gynecol Oncol, 2017 144(2): p. 354–362.

- Manne SL, Kashy DA, Virtue S et al. Acceptance, social support, benefit-finding, and depression in women with gynecological cancer. Qual Life Res. 2018;27(11):2991-3002.
- Mantegna G, Petrillo M, Fuoco G, et al. Long-term prospective longitudinal evaluation of emotional distress and quality of life in cervical cancer patients who remained disease-free 2-years from diagnosis. BMC cancer 2013; 13(127).
- Martin VT. Ovarian hormones and pain response: a review of clinical and basic science studies. Gend Med 2009;6:168–192.
- Martinkovich S, Shah D, Planey SL, Arnott JA. Selective estrogen receptor modulators: tissue specificity and clinical utility. Clin Interv Aging. 2014;9:1437–1452.
- Matsunaga E, Nambu S, Oka M, Iriki A. Differential cadherin expression in the developing postnatal telencephalon of a New World monkey. J Comp Neurol. 2013;521:4027–60.
- McCoy NL, Matyas JR. Oral contraceptives and sexuality in uni- versity women. Arch Sexual Behav. 1996;25(1):73–90.
- McDaniel JS, Mussleman DL, Porter MR, et al. Depression in patients with cancer. Diagnosis, biology and treatment. Arch Gen Psychiatry 1995;52:88–99.
- McTiernan A, Irwin M, Vongruenigen V. Weight, physical activity, diet, and prognosis in breast and gynecologic cancers. J Clin Oncol 2010;28(26):4074–80.
- Mercer JG, Hoggard N, Williams LM, et al. Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions by in situ hybridization. FEBS Lett. 1996;387:113–6.
- Namba R, Young LJ, Maglione JE, et al. Selective estrogen receptor modulators inhibit growth and progression of premalignant lesions in a mouse model of ductal carcinoma in situ. Breast Cancer Res. 2005;7(6):R881-9.
- Nishimura M, Izumiya Y, Higuchi A, et al. Adiponectin prevents cerebral ischemic injury through endothelial nitric oxide synthase dependent mechanisms. Circulation. 2008;117:216–23.
- Nordin AJ, Dixon S, Chinn DJ, Moloney I, Naik R, De Barros Lopes A, et al. Attitudes to radical gynecological oncology surgery in the elderly: a pilot study. Int J Gynecol Cancer 2000;10:323.
- Özaras G, Özyurda F. Quality of life and influencing factors in patients with a gynaecologic cancer diagnosis at Gazi University, Turkey. Asian Pac J Cancer Prev 2010;11(5):1403–8.

- Paganini-Hill A. and Henderson V. Estrogen deficiency and risk of Alzheimer's Disease in women. American Journal of Epidemiology, 140: 256-261, 1994
- Palacios S and Cancelo M. J. Clinical update on the use of ospemifene in the treatment of severe symptomatic vulvar and vaginal atrophy. International Journal of Women's Health, 2016, 8: 617–626.
- Pluchino N, Wenger JM, Petignat P, Tal R, Bolmont M, Taylor HS, Bianchi-Demicheli F. Sexual function in endometriosis patients and their partners: effect of the disease and consequences of treatment. Hum Reprod Update. 2016 Nov;22(6):762-774.
- Pruthi S., Simon J. A., and Early A. P. Current overview of the management of urogenital atrophy in women with breast cancer. Breast Journal, 2011, 17 (4) : 403–408.
- Santoro N1, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. J Sex Med. 2009;6(8):2133-42.
- Scherer PE, Williams S, Fogliano M, et al. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem. 1995;270:26746–9.
- Sherwin B.B. Estrogen effects on cognition in menopausal women. Neurology, 48:S21-6, 1997
- Simon I, Portman D, and Mabey R. G., Long-term safety of ospemifene (52-week extension) in the treatment of vulvar and vaginal atrophy in hysterectomized postmenopausal women. Maturitas, 2014, 77 (3): 274–281.
- Simon JA, Lin V. H., C. Radovich, and G. A. Bachmann. Ospemifene Study Group. One-year long-term safety extension study of ospemifene for the treatment of vulvar and vaginal atrophy in postmenopausal women with a uterus. Menopause 2013; 20(4): 418–427.
- Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Stages of Reproductive Aging Workshop (STRAW). J Womens Health Gend Based Med. 2001 Nov; 10(9):843-8.
- Spelten ER, Sprangers MA, Verbeek JH. Factors reported to influence the return to work of cancer survivors: a literature review. Psychooncology 2002;11(2):124–31.
- Stafford L, Judd F, Gibson P, Komiti A, Mann GB, Quinn M. Anxiety and depression symptoms in the 2 years following diagnosis of breast or gynaecologic cancer: prevalence, course and determinants of outcome. Support Care Cancer. 2015 Aug;23(8):2215-24.
- Statens Serum Institut (2013) Cancer registeret. Talog analyse.

- Thundyil J, Pavlovski D, Sobey CG, Arumugam TV. Adiponectin receptor signalling in the brain. Br J Pharmacol. 2012;165:313–27.
- Tommaselli GA, Di Carlo C, Di Spiezio Sardo A, et al. Serum leptin levels and body composition in post-menopausal women treated with tibolone and raloxifene. Menopause 2006;13:660–668.
- Trayhurn P, Wood IS. Adipokines: inflammation and the pleiotropic role of white adipose tissue. Br J Nutr. 2004;92:347–55.
- Van Arsdale A, Rosenbaum D, Kaur G, et al. Prevalence and factors associated with cognitive deficit in women with gynecologic malignancies. Gynecol Oncol. 2016; 141:323–328.
- van der Laak JA, de Bie LM, de Leeuw H et al. The effect of Replens on vaginal cytology in the treatment of postmenopausal atrophy: cytomorphology versus computerized cytometry. J Clin Pathol. 2002 Jun;55(6):446-51.
- van Himbergen TM, Beiser AS, Ai M, et al. Biomarkers for insulin resistance and inflammation and the risk for allcause dementia and alzheimer disease: results from the Framingham Heart Study. Arch Neurol 2012;69:594–600.
- Venkatesh B, Hickman I, Nisbet J, Cohen J, Prins J. Changes in serum adiponectin concentrations in critical illness: a preliminary investigation. Crit Care. 2009;13:R105.
- von Elm E, Altman DG, Egger M, et al. JP (2007) STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 147(8):573-7
- Vong L, Ye C, Yang Z, Choi B, Chua Jr S, Lowell BB. Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. Neuron. 2011;71:142–54.
- Wan Z, Mah D, Simtchouk S, Klegeris A, Little JP. Globular adiponectin induces a proinflammatory response in human astrocytic cells. Biochem Biophys Res Commun. 2014;446:37–42.
- Waragai M, Ho G, Takamatsu Y, Sekiyama K, Sugama S, Takenouchi T, Masliah E, Hashimoto M1Importance of adiponectin activity in the pathogenesis of Alzheimer's disease. Ann Clin Transl Neurol. 2017;4(8):591-600.
- Watts S, Prescott P, Mason J, McLeod N, Lewith G. Depression and anxiety in ovarian cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open. 2015 30;5(11):e007618.

- Wennberg AM, Gustafson D, Hagen CE, et al. Serum adiponectin levels, neuroimaging, and cognition in the mayo clinic study of aging. J Alzheimers Dis 2016;53:573–581.
- Wilkinson M, Morash B, Ur E. The brain is a source of leptin. Front Horm Res.2000;26:106–25.
- World Health Organization. Sexual health: Working definitions. 2002. Available at: http://www.who.int/reproductive -health/gender/sexual_health.html (accessed November 8, 2013).
- Wurz GT, Kao CJ, and De Gregorio MW, "Safety and efficacy of ospemifene for the treatment of dyspareunia associated with vulvar and vaginal atrophy due to menopause," Clinical Interventions in Aging, 2014, 9:1939–1950.
- Xu Y, Kim ER, Zhao R, Myers Jr MG, Munzberg H, Tong Q. Glutamate release mediates leptin action on energy expenditure. Mol Metab. 2013;2:109–15.
- Yi CX, Meyer CW, Jastroch M. Leptin action in the brain: How (and when) it makes fat burn. Mol Metab. 2013;2:63–4.
- Yong PJ, Sadownik L, Brotto LA. Concurrent deep-superficial dyspareunia: prevalence, associations, and outcomes in a multidisciplinary vulvodynia program. J Sex Med 2015;12:219–227
- Zabora J, Brintzenhofeszoc K, Curbow B. The prevalence of psychological distress by cancer site. Psychooncology 2001;10:19–28.
- Zlokovic BV, Jovanovic S, Miao W, Samara S, Verma S, Farrell CL. Differential regulation of leptin transport by the choroid plexus and blood-brain barrier and high affinity transport systems for entry into hypothalamus and across the blood-cerebrospinal fluid barrier. Endocrinology. 2000;141:1434–41.