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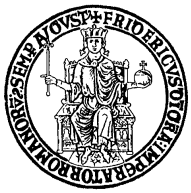

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"SAFETY AND ACCEPTABILITY OF INTRAUTERINE DEVICE IN WOMEN WITH EPILEPSY"

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1.1 EPILEPSY

1.1.1 Epidemiology and Definition

Epilepsy is the most common serious neurological disease, distributed worldwide and affecting all ages and races. The incidence is about 50 cases per 100,000 persons per year in developed societies and 100-190 per 100,000 in developing countries [1,2]. The prevalence is estimated at 5-10 cases per 1000 persons, excluding single seizures, febrile seizures and patients in remission.

The lifetime prevalence of a single seizure is 2 to 5% [3]. Estimates of the prevalence and incidence of epilepsy worldwide vary considerably, likely reflecting differences in measurement and reporting, along with clinical characteristics such as etiology and seizure type. A systematic review and meta-analysis of international studies published in 2017 [4], showed a point prevalence of active epilepsy of 6.38 per 1,000 persons, and an annual cumulative incidence of epilepsy of 67.77 per 100,000 persons. The prevalence of epilepsy did not differ by age group, sex, or study quality. The active annual period prevalence, lifetime prevalence, and incidence rate of epilepsy were higher in low to middle income countries. This is likely due to the increased risk of endemic conditions, such as malaria or neurocysticercosis, the higher incidence of road traffic injuries and birth-related injuries, variations in medical infrastructure and availability of preventative health programs and accessible care.

Epilepsy can have substantial physical, psychological and social impact on patients and carries serious risks of injury, impairment of brain function and death.

An epileptic seizure is a transient event caused by an occasional, sudden and excessive discharge of cerebral neurons [5]. Epilepsy is present when seizures are recurrent and not caused by transient metabolic or toxic disorders. A recurrent tendency to have seizures arises secondary to a variety of underlying brain disorders. A causative pathology can be identified in a proportion of cases, but in some patients no cause is found and only a descriptive diagnosis is possible [6]. Over the years, the

wide range of motor, sensory, autonomic, cognitive and psychic phenomena that are produced during epileptic seizures have been described and classified.

1.1.2 Seizure classification

There are many reasons why the classification of seizures and epilepsy is important, both for the individual patient and for the advancement of knowledge of epilepsy. It allows communication within and between the clinical and research settings. It is also important for the diagnosis, prognosis and choice of treatment for any given patient. Accurately identifying the type of seizures is the first step towards a correct diagnosis in a patient with epileptic seizures.

Classically, two major seizure types have been recognized: those arising from focal cortical disturbances – partial or focal seizures, and those characterized by synchronous discharge of both hemispheres - generalised seizures. Differentiation between focal and generalised seizures requires both clinical and electroencephalography (EEG) findings.

This formed the basis for the revised International Classification of Epileptic Seizures (ICES), introduced by the International League Against Epilepsy (ILAE) in 1981 [7,8]. This classification divides seizures into partial and generalised, with partial seizures subsequently divided further into ‘simple’ and ‘complex’, depending on whether consciousness is retained or lost. In most surveys, partial seizures appear to be the most common seizure type, with complex partial and secondarily generalized seizures comprising around 60% of prevalent cases, primary generalised tonic-clonic seizures about 30%, and generalised absence and myoclonus less than 5% [3]. These however may be biased, being largely based on populations of patients with relatively severe epilepsy, including large numbers with focal epilepsy. For less severe cases it is often more difficult to determine clinically and electroencephalographically whether it is of primary generalised or focal type.

1.1.3 Syndromic diagnosis of epilepsy

The description of the seizure types is insufficient to provide accurate guidance on treatment, severity of disease and prognosis. An advance in modern epileptology has been the recognition of epileptic syndromes, which are defined by the combination of seizure types, other clinical symptoms, physical signs on examination, imaging findings and laboratory findings. Each epilepsy syndrome has diverse underlying causes and prognoses and requires different short-term and long-term management.

The fact that epilepsy is not a single disease entity has already been recognized several decades ago. For example, the World Health Organization (WHO) Dictionary of Epilepsy [9] proposes the following definition of epilepsy: 'chronic brain disorder of various aetiologies characterised by recurrent seizures due to excessive discharge of cerebral neurones (epileptic seizures), associated with a variety of clinical and laboratory manifestations. Single or occasional epileptic seizures (such as febrile convulsions and the seizures of puerperal eclampsia) as well as those occurring during an acute illness should not be classified as epilepsy.'

The Commission on Classification and Terminology of the ILAE describes epilepsy as requiring '…. two or more seizures.' There still is diagnostic inaccuracy of the term 'epilepsy', which needs to be completed with the definition of seizure types, epilepsy syndromic diagnosis and underlying aetiology. The identification of an epilepsy syndrome requires specific clinical information, including age of onset, seizure manifestations, precipitating factors, associated central nervous system (CNS) symptoms and signs, severity, and course. Findings from other investigations such as EEG and brain imaging are also needed.

The 1989 ILAE Classification of the epilepsies and epileptic syndromes (1989) attempted to provide such a syndromic classification and recognizes the heterogeneity of epilepsy. It specified over 40 distinct types of syndromes, classified both according to seizure type and aetiology. However, this is problematic, due to overlap between syndromes, inadequate definitions of syndromes and the complexity of the classification.

A Task Force for the classification and terminology concluded that the classification would need to be reviewed periodically based upon emerging new information. This has subsequently been reviewed, given problems identified through use and progress in the understanding of the basis of the epilepsies. The ILAE Task Force also proposed that the terms partial and localisation-related be replaced with 'focal' [10]. In 2017 The International League Against Epilepsy (ILAE) presents a revised operational (pratical) classification of seizure types based on the 1981 Classification, extended in 2010 [4,11]. (TABLE 1). The purpose of such a revision is to recognize that some seizure types can have either a focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types, and to adopt more transparent names.

Changes include the following: (1) "partial" becomes "focal"; (2) awareness is used as a classifier of focal seizures; (3) the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are eliminated; (4) new focal seizure types include automatisms, behavior arrest, hyperkinetic, autonomic, cognitive, and emotional; (5) atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset; (6) focal to bilateral tonic–clonic seizure replaces secondarily generalized seizure; (7) new generalized seizure types are absence with eyelid myoclonia, myoclonic absence, myoclonic–atonic, myoclonic–tonic–clonic; and (8) seizures of unknown onset may have features that can still be classified. The new classification does not represent a fundamental change but allows greater flexibility and transparency in naming seizure types.

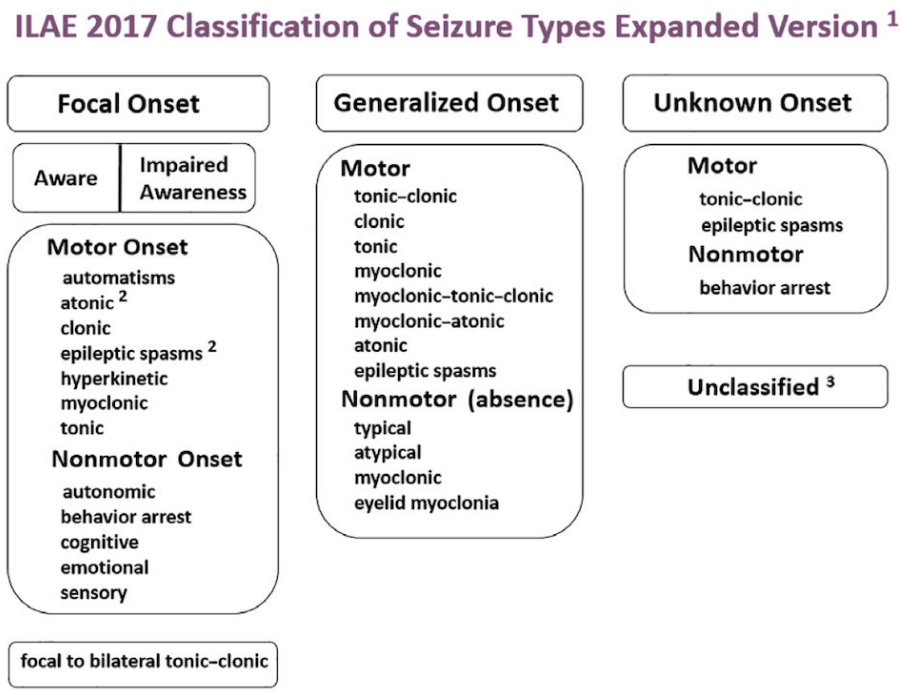

TABLE 1: The expanded ILAE 2017 operational classification of seizure types. The following clarifications should guide the choice of seizure type.
1Definitions, other seizure types and descriptors are listed in the accompanying paper and glossary of terms.
2Degree of awareness usually is not specified.
3Due to inadequate information or inability to place in other categories

1.1.4 Aetiology

In the 1989 ILAE classification, both focal and generalised epilepsies and syndromes are divided according to aetiology into idiopathic, symptomatic and cryptogenic varieties. Idiopathic epilepsies are not associated with structural brain lesions, neurological abnormalities other than seizures, or cognitive impairment. Conversely, in symptomatic epilepsy, seizures are the consequence of a focal brain abnormality.

Cryptogenic epilepsies are those in which a symptomatic aetiology is suspected but the aetiology is not known. The advances in neuroimaging over the past decade have allowed identification of an increasing number of underlying aetiologies and thus decreased the proportion of epilepsies and epilepsy syndromes considered to be cryptogenic. The 2001 Task Force proposed that the term cryptogenic be replaced by ‘probable symptomatic epilepsy syndrome’ to refer to syndromes

believed to be symptomatic, but in which no aetiology has been identified [10]. Epilepsy may develop for a number of reasons with brain trauma, CNS infections, cerebrovascular disease and brain tumours all increasing the incidence of epilepsy [12]. The aetiology varies considerably according to age. Onset of epilepsy during adult life is more commonly associated with an underlying neurological disorder than is the case with epilepsies developing in childhood. The aetiologies underlying focal epilepsy also vary according to geography, for example endemic infections such as neurocysticercosis are the commonest cause of epilepsy in parts of South America but are much less common in Europe [13]. Any condition causing cortical disruption may lead to seizures. The aetiology may be multifactorial, with patients with an inherited predisposition more prone to the development of acquired conditions. A prospective cohort population-based study of patients with newly-diagnosed epilepsy in the United Kingdom reported that the aetiology was cerebrovascular disease in 15%, cerebral tumour in 6%, alcohol-related in 6% and post-traumatic in 3% of patients [14]. Notably, seizures were classified as cryptogenic in 62% of cases.

Although the majority of epilepsies lack an overt genetic cause, underlying genetic contributions to aetiology have been estimated to be present in about 40% of patients with epilepsy [15]. and are particularly important in the idiopathic generalised epilepsies (IGE). There are over 200 Mendelian diseases which include epilepsy as part of the phenotype although these account for less than 1% of all epilepsies [15]. Many of these, such as tuberous sclerosis, are associated with structural lesions although several families exhibiting idiopathic epilepsy transmitted in a Mendelian manner have recently been found to have mutations in single genes. They are all dominantly inherited and all but one code for ion channels, underlying the importance of these signalling proteins in determining the excitability of neuronal circuits [16]. The theory of a genetically determined increased excitability of neuronal circuits provides an attractive explanation why otherwise normal individuals should develop unprovoked seizures without an identifiable locus of onset.

Although this pattern of Mendelian inheritance is rare, first degree relatives of patients with IGE have a roughly two- to threefold elevated risk of being affected [17]. Where these patterns of complex inheritance exist, the interaction of susceptibility genes and environmental factors is likely to be important. At present, a number of large families with many affected members are currently under investigation and it is likely that further genes will be identified, some of which will be responsible for monogenic epilepsy and others that turn out to be epilepsy susceptibility genes.

1.1.5 Diagnosis

Diagnosis of the epileptic nature of a seizure can be based on a precise systematic description of the episode by the patient and witnesses and might not need any specific investigation. The most important recent advance stems from the availability of smartphones, with which relatives can video-record the seizures. Unfortunately, many doctors lack knowledge of the semiology that allows differentiation between epileptic seizures and other disorders such as convulsive syncope and psychogenic non-epileptic attacks, resulting in much misdiagnosis [18,19]. In a study of patients previously treated for epilepsy in whom misdiagnosis was suggested after specialised neurological review, long-term monitoring with an implantable ECG recorder identified profound bradycardia or asystole in 21 % of patients[18]. Correct diagnosis of the underlying epilepsy syndrome can be complex because it needs application of multidimensional criteria and different investigations depending on the suspected disorder. [11]. Family and personal history, age of onset, seizure type, neurological and cognitive status, 12-lead ECG to rule out cardiac abnormalities, and an interictal EEG are mandatory. A brain MRI is generally needed, except for patients presenting with typical syndromes such as childhood or juvenile absence epilepsy, juvenile myoclonic epilepsy, or self-limited childhood epilepsy with centrotemporal spikes. Blood tests, lumbar puncture, and other investigations can be helpful when specific causes are suspected. Major diagnostic advances over the past decade include improved imaging technology and application of epilepsy targeted protocols for image acquisition and analysis (including three-dimensional fluid-attenuated inversion recovery and

voxel-based analyses of multiple contrasts), allowing detection of previously unrecognised subtle epileptogenic lesions; identification of new forms of autoimmune encephalitis, including those associated with anti-NMDA receptors [20], anti-$GABA_B$ receptors [21], and antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein (anti-Lgi-1), and contactin-associated protein-2 (anti-Caspr2) [22]; and application of genetic advances (including array comparative genomic hybridisation, candidate epilepsy gene panels, and whole-exome sequencing), leading to discovery of new gene mutations in rare epileptic disorders (either sporadic or familial) [23].

1.1.6 Treatment:

Epilepsy is a varied disorder with many causes ranging from genetic causes through to acquired brain damage and insults. Disease outcomes are also heterogeneous. Most people have a relatively short-lasting susceptibility to seizures and enter remission shortly after starting treatment on small doses of anti-epileptic drugs (AEDs) [24-26]. However, 20–30% of people who develop epilepsy will have a chronic epilepsy that responds incompletely to AED therapy, who will require treatment with one or more drugs through their life. After the introduction of valproate in 1973, excluding benzodiazepines, there was a nineteen years gap before the introduction of vigabatrin, the first in a series of new antiepileptic drugs to be developed and licensed. Currently, AEDs approved by the US FDA are generally classified as one of two generations (TABLE 2).

The first-generation (standard) agents include carbamazepine, phenobarbital, phenytoin, primidone, ethosuximide and valproic acid. The second-generation (newer) agents include topiramate, felbamate, lamotrigine, tiagabine, gabapentin, levetiracetam, zonisamide and pregabalin. Many AEDs act by inhibition of voltage-gated sodium and calcium channels, or by potentiation of GABAergic inhibition [27,28]. Clinical experience suggests that the newer AEDs have a broader spectrum, as well as fewer adverse effects or drug interactions [27,28].

Antiepileptic drug	Year approved	Therapeutic efficacy
First generation (standard)		
Carbamazepine	1974	Broad spectrum
Clonazepam	1997	Broad spectrum, status epilepticus
Ethotoin	1957	Partial/generalized
Methsuximide	1982†	Absence seizures
Phenobarbital	1982†	Partial/generalized
Phenytoin	1982†	Partial/generalized
Primidone	1974	Partial/generalized
Valproic acid	1983	Broad spectrum
Second generation (newer)		
Acetazolamide	1990	Partial/generalized
Ethosuximide	2000	Absence seizures
Felbamate	1993	Broad spectrum, Lennox–Gastaut syndrome
Fosphenytoin	1996	Status epilepticus
Gabapentin	2000	Partial (add-on)
Lacosamide	2008	Partial (add-on)
Lamotrigine	1994	Broad spectrum
Levetiracetam	1999	Partial/generalized
Oxcarbazepine	2000	Partial/generalized
Pregabalin	2005	Partial (add-on)
Rufinamide	2008	Lennox–Gastaut syndrome
Tiagabine	1997	Partial (add-on)
Topiramate	1996	Broad spectrum
Vigabatrin	2009	Infantile spasms
Zonisamide	2000	Partial/generalized

† Approved before 1982.

TABLE 2: Overview of US FDA-approved antiepileptic drugs

Adequate comparison of AEDs is confounded greatly by the heterogeneity of epilepsy and by the different approaches to the use of AEDs (commonly as part of combined drug regimens).

The majority of RCTs available are industry studies, which aim to provide evidence to support registration. There are few comparative studies that compare drugs head-to-head over clinically relevant periods of time. The best evidence is for patients with localised-onset seizures for whom

treatment with a sodium channel drug (phenytoin, carbamazepine, oxcarbazepine or lamotrigine) would seem optimal, with newer drugs (oxcarbazepine or lamotrigine) being better tolerated.

The evidence for patients with generalized epilepsies and seizures is sparse. Valproate appears to have greatest efficacy in RCTs but is associated with significant weight gain and higher risks of fetal harm. With more AEDs becoming available there is a great need for clinically relevant head-to-head comparative RCTs hat can inform the choice of clinicians, patients and providers of care.

1.2 CONTRACEPTION

1.2.1 Introduction

Among the 1.9 billion Women of Reproductive Age group (15-49 years) worldwide in 2019, 1.1 billion have a need for family planning; of these, 842 million are using contraceptive methods, and 270 million have an unmet need for contraception [29,30]

Modern contraceptive prevalence among Married women of reproductive age (MWRA) increased worldwide between 2000 and 2019 by 2.1 percentage points from 55.0% (95% UI 53.7%–56.3%) to 57.1% (95% UI 54.6%–59.5%)1. Reasons for this slow increase include: limited choice of methods; limited access to services, particularly among young, poorer and unmarried people; fear or experience of side-effects; cultural or religious opposition; poor quality of available services; users' and providers' bias against some methods; and gender-based barriers to accessing services. The rate of unwonted pregnancies in the world still seems unacceptably high, at round 41 – 47 %, and millions of women still do not have access to effective, modern contraception. [31]

Modern contraception is any method that aim at preventing pregnancy by interfering with the normal process of ovulation, fertilization and/ or implantation. Effectiveness of methods is measured by the number of pregnancies per 100 women using the method per year (Pearl Index) (TABLE 3). Methods are classified by their effectiveness as commonly used into: Very effective (0–0.9

pregnancies per 100 women); Effective (1-9 pregnancies per 100 women); Moderately effective (10-19 pregnancies per 100 women); Less effective (20 or more pregnancies per 100 women)

There are two distinct categories of birth-control options for women: hormonal and non-hormonal methods. Non hormonal methods include intrauterine devices (IUDs), barrier methods, such as condoms, diaphragms and cervical caps, as well as the rhythm method.

A wide range of hormonal methods of contraception are available. These methods have different mechanisms of action and effectiveness in preventing unintended pregnancy.

The efficacy of agents such as oral contraceptives (OCs), also known as combined OC pills, and contraceptive patches, is highly dependent on correct use and individual lifestyles. Unlike barrier methods, hormonal contraceptives do not protect against HIV infection and other sexually transmitted diseases. The rhythm method or other methods that depend on hormonal changes are not reliable methods of birth control.

The OCs are among the most widely used agents, since these preparations are highly effective

when used properly. Designed to simulate the 28 days of the natural menstrual cycle, most OCs consist of an estrogenic and/or a progestogenic agent. A variety of OCs are available, with substantially different components, doses and side effects. The primary mechanism underlying OC action is inhibition of ovulation. Although they essentially act by suppression of gonadotropins by feedback actions of estrogenic and/or progestogenic components, other effects include changes in cervical mucus, and the endometrium. Two types of OC pills are widely available: combination pills and progestogen-only pills. The combined daily OC pill is composed of low-dose synthetic estrogen and progestogen. They are usually taken for 21 days with a 7-day gap (usually filled with either sugar or iron pills), during which withdrawal bleeding occurs. The two major synthetic estrogens used in OCs are ethinyl estradiol and mestranol. Mestranol is a prodrug and, hence, is inactive until it is converted to ethinyl estradiol in the body (mestranol is not available in the USA). The main synthetic

progestogens include norethindrone, levonorgestrel, norgestimate, norgestrel, desogestrel and drospirenone. Currently available combined OCs can be divided into three types: monophasic (only one dose of estrogen and progestogen during the 21 days), biphasic (varying doses of estrogen and progestogen) and triphasic (varying doses of estrogen and progestogen). In monophasic combinations, the progestogen and estrogen are present in fixed amounts and, hence, the blood levels rise and fall together. Biphasic and triphasic combinations are developed to mimic nearly physiological levels. In the biphasic regimen, the progestogen dose is increased during the last 11 days of the cycle, while the triphasic regimen consists of a progestogen/estrogen regimen that is changed three times during the cycle by altering the doses of either progestogen or estrogen or both. The progestogen-only pill – 'minipill' – contains progestogen without estrogen and is taken continuously. However, they are slightly less frequently used than combination OCs. Nonoral hormonal short acting contraceptive preparations include transdermal patches, that provides monophasic combination of estrogen and progestin delivered via a transdermal system (one patch per week for 3 weeks and then no patch for 1 week)., and vaginal rings, that is a once-amonth vaginal contraceptive that releases a continuous low dose of estrogen and progestin.

A revolution of global impact in the world of contraception is represented by long-acting reversible contraceptives (LARC), which have proven to be 20 times more effective than the more traditional short-acting reversible contraceptives (SARC) [32]. Long-acting hormonal contraceptives include injectable progestogens, subdermal implants and hormone-releasing IUDs.

METHOD	HOW IT WORKS	EFFECTIVENESS: pregnancies per 100 women per year with CORRECT use	EFFECTIVENESS: pregnancies per 100 women per year as COMMONLY used
Combined oral contraceptives (COCs) or "the pill"	Prevents the release of eggs from the ovaries (ovulation)	0.3	7
Progestogen-only pills (POPs) or "the minipill"	Thickens cervical mucous to block sperm and egg from meeting and prevents ovulation	0.3	7
Implants	Thickens cervical mucous to blocks sperm and egg from meeting and prevents ovulation	0.1	0.1
Progestogen only injectables	Thickens cervical mucous to block sperm and egg from meeting and prevents ovulation	0.2	4
Monthly injectables or combined injectable contraceptives (CIC)	Prevents the release of eggs from the ovaries (ovulation)	0.05	3
Combined contraceptive patch and combined contraceptive vaginal ring	Prevents the release of eggs from the ovaries (ovulation)	0.3 for both	7 for both
Intrauterine device (IUD): copper containing	Copper component damages sperm and prevents it from meeting the egg	0.6	0.8
Intrauterine device (IUD) levonorgestrel	Thickens cervical mucous to block sperm and egg from meeting	0.5	0.7
Male condoms **Female condoms**	Forms a barrier to prevent sperm and egg from meeting	2 5	13 21
Male sterilization (Vasectomy)	Keeps sperm out of ejaculated semen	0.1	0.15
Female sterilization (tubal ligation)	Eggs are blocked from meeting sperm	0.5	0.5
Standard Days Method or SDM	Prevents pregnancy by avoiding unprotected vaginal sex during most fertile days.	5	12
Sympto-thermal Method	Prevents pregnancy by avoiding unprotected vaginal sex during most fertile	<1	2
Emergency contraception pills (ulipristal acetate 30 mg or levonorgestrel 1.5 mg)	Prevents or delays the release of eggs from the ovaries. Pills taken to prevent pregnancy up to 5 days after unprotected sex	< 1 for ulipristal acetate 1 for progestin-only.	
Withdrawal (coitus interruptus)	Tries to keep sperm out of the woman's body	4	20

TABLE 3: Contraceptive methods, mode of action and effectiveness. **Reference*: Family Planning: A Global Handbook for Providers. 2018 World Health Organization and Johns Hopkins Bloomberg School of Public Health

1.2.2 Intrauterine contraception

Intrauterine contraception (IUC) belongs the LARC group and currently considered the most effective method for women regardless of age and number of births. To date is the most widely used reversible contraceptive method and is recommended by the major scientific gynecological societies in Italy and worldwide (RCOG 2016, ACOG 2017, NICE 2014, SIGO 2015, SOCG 2016) [33-35]. In Europe, the average use of IUC stands around 16-28 % but in Italy is still among the lowest ranked countries, despite the moderate increase recorded in recent years (5.8%) [36]. One possible reason lies in the lack of knowledge of the considerable differences between intrauterine device (IUD) and modern intrauterine systems (IUS). Many varieties of IUDs and IUSs are available today which allows the clinician and patient to choose a product which best fits the patient's medical and reproductive needs. Although the idea that placing something inside the uterus for contraception is not new, technologic advances have resulted in novel highly effective long-acting contraceptives that may provide more options and benefits.

Cupper Intra-uterine device

IUDs are plastic devices capable of bearing various metals, most often cupper (Cu-IUD), whose mechanism of action is based on the marked inflammatory reaction it causes as a foreign body at local level, which induces a cytotoxic action on sperm, oocytes and blastocysts. The mechanism of action for the copper IUD is primarily related to copper ions' effect on sperm motility and viability. Cervical mucus changes and polymorphonuclear lymphocyte recruitment to the uterus helps the efficacy of the device [37]. However, a recent study showed no increase in inflammatory cell populations of the cervix with copper IUD use [38]. The results of this study imply that the contraceptive mechanism of action for the copper IUD may be the effects of copper on the sperm or oocyte. Although copper IUDs typically do not change menstrual frequency, currently available products can increase menstrual flow and cramping-type abdominal pain; approximately 10 to 13% of users will have the IUD removed for bleeding in the first year of use [39]. Very few medical contraindications exist for IUD use, particularly for copper-containing IUDs. Contraindications applicable for all IUDs include uterine cavity anomalies, malignancy and pregnancy.

Most medical conditions create no restriction for copper IUD use. Use of hormonal IUDs has comparatively more restrictions; however, there are still fewer restrictions for the hormonal IUD than for combined hormonal contraceptives.

For example, all hormonal contraceptives are not recommended in women with breast cancer, while the copper IUD may be used. However, in women with thrombogenic mutations, hypertension, or deep venous thrombosis, the benefits of hormonal IUD use outweigh the risk of using such a

product. In some situations, a hormonal IUD can be used when combined hormonal contraceptives or a copper IUD is contraindicated or relatively contraindicated, such as abnormal uterine bleeding with high risk for unopposed estrogen[40].

Intra-uterine System

Hormonal IUDs have been available since 1976 but did not have increased acceptability as a contraceptive option until the introduction of Mirena, a levonorgestrel 52 mg IUS in 2001.
IUSs have completely revolutioned the classic mechanism of action of IUDs, through the release of a synthetic progestin (Levonorgestrel LNG), with the aim of creating a local hormonal environment inappropriate for pregnancy. Endometrial decidualization and qualitative and quantitative changes in cervical mucus become the main actors in the contraceptive action of IUSs. Thickening of the cervical mucus prevents the passage of sperm through the cervical canal. The endometrium becomes relatively insensitive to circulating estradiol and there is a marked antiproliferative effect with consequent atrophy and decrease of menstrual flow. Therefore the local hormonal environment inhibits tubal ciliary motility and sperm function, preventing fertilization [41, 42]. All these multiple, complex mechanism of action account for the extraordinary effectiveness of IUSs that, to date, boast a Pearl index of around 0.2 [43], with a remarkable similarity between the effectiveness obtained with “perfect” use and with “typical” use.

At the moment three IUSs have been approved for contraceptive use:

- LNG-IUS 52 mg
- LNG-IUS 19.5 mg
- LNG-IUS 13.5 mg

All IUS products initially cause irregular light bleeding. Over time, the levonorgestrel 52 mg IUS products result in a continued decrease in bleeding with 19 to 20% achieving amenorrhea within 1 year 1. With the levonorgestrel 13.5 mg, bleeding becomes lighter with longer use with the number of days of bleeding or spotting decreases dramatically during the second month [42]. In general, there are more spotting-only days than bleeding-only days during levonorgestrel 13.5 mg IUS use. However, the bleeding patterns are more irregular than with the 52 mg products with lower rates of amenorrhea (6% at 1 year and 12% at 3 years) [43]. The three systems have very similar physical characteristics and the same mechanism of action but differ as regards the doses

of LNG released, which explains the different impact on the genital apparatus of the women wearing them. (TABLE 4)

Parameter	LNG IUS 19.5 mg (Kayleena®)	LNG IUS 13.5 mg (Jaydess®)	LNG IUS 52 mg (Mirena®)
Max duration of use, years	5	3	5
Total LNG content	19.5 mg	13.5 mg	52 mg
Average release rate of LNG *in vivo* after the first year	12 µg/24 h	8 µg/24 h	20 µg/24 h
Dimensions of the T structure	28×30 mm	28×30 mm	32×32 mm
Diameter of the insertion tube	3.80 mm	3.80 mm	4.4 mm
Echography differences: silver ring	Improved visibility in echography	Improved visibility in echography	Absent
Color of removal strings	Blue	Brown	Brown

TABLE 4: Comparison of IUSs: chemical-physical properties and characteristics.

1.3 CONTRACEPTION IN WOMEN WITH EPILEPSY

Women with epilepsy (WWE), like healthy women, use different kinds of contraceptive methods, ie, hormonal contraception (HC), intrauterine devices (IUDs), barrier methods, or combinations of them. HC includes combined oral contraceptives (COCs), progestin-only pills, intramuscular injections, subdermal implants, skin patches, hormone-releasing IUDs, and vaginal rings. However, most WWE also use antiepileptic drugs. Contraceptive management in women with epilepsy is critical owing to potential maternal and fetal risks [44,45]. Many of these drugs do interact with HC, which may lead to contraceptive failure or impaired seizure control [46]. Either of these complications may have serious social, psychological, professional, and economic consequences. Additionally, many AEDs possess teratogenic potential and/or may exert a negative impact on cognitive and psychomotor skills of children exposed to these AEDs in the womb [45, 47,48]. Given the above, it is deeply concerning that ~50% of all pregnancies among WWE occur unintended [49, 50]. This is about the same proportion as found in the general population [51,52]. Risk factors for unintended pregnancy include low socioeconomic status, low education, and ethnicity Also, only half

of all WWE using contraception do so with a highly effective method (HC, IUDs, or surgery). Moreover, many WWE use enzyme-inducing AEDs that may impair the efficacy of highly effective HC [50].

It might be speculated whether better education of WWE could reduce the proportion of unplanned pregnancies. However, several studies show that a large proportion of doctors, including neurologists and gynecologists, lack sufficient knowledge about reproductive health issues of WWE and how these may be affected by AEDs [53-55]. Hence, the current treatment guidelines may not be followed [56]. More recent surveys found a trend from prescribing older AEDs toward newer AEDs with a more favorable interaction and safety profile, which may indicate a growing awareness among doctors [57,58]. However, most WWE do not receive necessary information [59]. A 2015 survey found that 7% of women received contraceptive counseling [60]. Even when information is provided, many WWE do not recall the information they were given. Consequently, most WWE have only limited knowledge about interactions between HC and AEDs and potentially harmful effects of AEDs on the child [61,62].

1.3.1 What AEDs do to HC

Many of the "old" or "first-generation" AEDs (phenytoin, phenobarbital, primidone, carbamazepine) and several of the "new" or "second-generation" AEDs (oxcarbazepine, eslicarbazepine, topiramate, felbamate, rufinamide, perampanel) have more or less pronounced enzyme-inducing effects. They may induce either cytochrome P450 (CYP) enzymes, uridine-diphosphate-glucuronosyltransferase (UGT) enzymes, or both, thereby accelerating the metabolism of steroid hormones. Contraceptive failure provoked by enzyme-inducing AEDs is common and may affect both oral and nonoral HC [63-65]. The estrogen compound used in combined HC usually is ethinyl estradiol (EE), which has been used for decades. EE has a well-known pharmacokinetic and interaction profile. It is mainly metabolized by CYP 3A4, but conjugation by UGT also plays a role [66]. Besides EE, there is a plethora of older and newer progestins used for

HC [67,68]. Their metabolism and possible interactions with AEDs are much less studied. In general, their metabolism is inducible like that of EE. Thus, their contraceptive effect may fail when they are coadministered with carbamazepine or other enzyme-inducing AEDs. Examples for this include oral levonorgestrel, oral norethindrone, and the subdermal etonogestrel implant [63,64,69,70]. The interaction potential of depot medroxyprogesterone acetate (DMPA) intramuscular injection has not been specifically studied. However, if an AED has been found to induce the metabolism of one specific progestin, it appears reasonable to assume that other progestins may be affected as well.

On the other hand, there are many different HC preparations available, and they may contain not only different hormones, but also different doses of EE and different doses of the same progestin. The conclusions drawn from one study investigating one HC preparation may not necessarily apply to another HC preparation with the same active substances but different doses. Hence, even if the available data suggest that an interaction is unlikely to occur in a specific HC–AED combination, the attending physician and the patient should take any irregular bleeding as a sign of possible contraceptive failure. As a consequence of the pharmacokinetic interaction between enzyme-inducing AEDs and HC, the "classic" recommendation has been to use high-dose HC, ie, a daily EE dose of at least 50 μg [71-73]. However, this advice is theoretically derived, has not been clinically proven, and has considerable conceptual weaknesses, one of them being that the ovulation-suppressing dose of EE is ~100 μg [74]. Given the ever decreasing dose of EE in COCs, it may also be hard to find a contraceptive pill with such a high estrogen content. Moreover, despite this decades-old recommendation, a recent study from the Netherlands reported that 43.5% of WWE taking enzyme-inducing AEDs used a low dose of EE [75].

More recent recommendations take into account the mechanism of action of modern HC and focus on a high progestin dose instead, since in modern HC preparations, ovulation inhibition is mediated via the progestin, not EE [74]. Modern HC contains EE mainly for the purpose of creating a hormonal balance with the progestin component. Indeed, modern oral HC preparations typically contain ~1.5–

2 times the ovulation-inhibiting progestin dose [74]. However, as enzyme induction affects not only EE but also progestins [76], even the contraceptive effect of a "high" progestin dose may be impaired by enzyme-inducing AEDs, and clinical evidence for the "high progestin" concept is lacking. Consequently, neither high-dose EE nor high-dose progestin guarantees safe contraception in WWE taking enzyme-inducing AEDs, and additional contraceptive measures, eg, barrier methods, should be considered. This applies to combined (EE plus progestin) as well as progestin-only HC (oral or depot-formulations).

Hormone-releasing IUDs release a progestin and act locally on the endometrium. In contrast to systemic HC (oral, patch, vaginal ring, or implants), their contraceptive effect may not – at least in theory – be impaired by hepatic enzyme induction. Preliminary data from one study indeed suggest that this method is not affected by AEDs, which would make them a suitable alternative to systemic HC [77]. However, this study has not been confirmed. There is also one case report on contraceptive failure with a progestin-releasing intracervical device, presumably due to simultaneous use of carbamazepine [78]. However, there are no further such reports. Nevertheless, caution is advisable until possible interactions of locally acting HC with enzyme-inducing AEDs have been studied more systematically.

The most obvious solution to this drug interaction problem would be to not use enzyme-inducing AEDs together with HC. With today's spectrum of available AEDs, chances for the neurologist to avoid enzyme- inducing AEDs in fertile WWE are good. Indeed, recent surveys indicate that more and more WWE are prescribed newer, non enzyme-inducing AEDs [58]. In many countries however, these new AEDs may either not be available or just be too expensive. One of the "old", nonenzyme-inducing AEDs is valproate. It is very effective in a large variety of epileptic seizures and syndromes, usually well-tolerated, inexpensive, and a first-line drug for the treatment of epilepsy. It is one of the most used AEDs worldwide, but it has considerable teratogenic potential and may negatively affect the cognitive outcome of children exposed in utero. This is a substantial risk, especially because half

of all pregnancies in WWE occur unplanned. Moreover, typical side effects of valproate include hair loss and weight gain. Valproate may also cause polycystic ovary syndrome and metabolic disturbances. It is therefore prescribed less frequently for WWE, and the European Medicines Agency has advised physicians to not prescribe valproate to fertile women unless other treatments are ineffective or not tolerated [79]. If valproate is prescribed to fertile women, highly effective contraception and adequate adherence should be ensured.

When enzyme-inducing AEDs cannot be avoided HC should be combined with barrier methods. Recently, it has also been recommended to use HC in an extended-cycle pattern when enzyme-inducing AEDs are used simultaneously [74]. Without the pill-free week, gonadotropin secretion and ovarian function will be continuously suppressed, which will enhance contraceptive efficacy compared to the usual pattern of use (3 weeks “on”, 1 week “off”). Whether this alone provides reliable contraception despite enzyme induction remains to be proven. Until then, HC should be regarded as non-safe when combined with enzyme-inducing AEDs, and additional contraceptive methods (barrier methods) be employed.

1.3.2 What HC do to AEDs

While it has been known for over 40 years that enzyme-inducing AEDs may impair the contraceptive effect of HC [80,81], the possibility of the opposite had practically been ignored until 2001, when it was demonstrated that COCs may reduce the serum levels of lamotrigine by 60% and lead to loss of seizure control [82]. Later studies confirmed these findings and showed that it is the estrogen component (EE) that is responsible for this interaction [83,84]. In fact, it has been known long before 2001 that EE may affect the metabolism of quite many other drugs. [85,86]. Interestingly, EE has a unique dual effect on drug-metabolizing enzymes: while the activity of several CYP enzymes may be reduced, the activity of some UGTs may be increased [85]. Thus, the clinical efficacy of AEDs that undergo elimination by glucuronidation may be reduced. Surprisingly, studies on the possible effects of EE on the metabolism of AEDs are still sparse.

So far, an effect of EE on the metabolism of AEDs has been demonstrated only for lamotrigine and, to a lesser degree, for valproate. In contrast to lamotrigine, the effect on valproate is only moderate and much less well documented (only two small studies) [87,88]. However, as with lamotrigine, there is large interindividual variation, and in some patients this interaction may gain clinical relevance, ie, lead to increased seizure activity [88]. Oxcarbazepine and its derivative eslicarbazepine, as well as retigabine/ezogabine, are also subject to glucuronidation, but a possible effect of EE on their metabolism has not been examined so far.

It must be emphasized that, according to the current knowledge, only EE affects the metabolism of AEDs. There is no convincing data suggesting any clinically relevant effect of progestins ("mini-pill", implants, depot injections, hormonal IUDs, emergency pill) on the metabolism of lamotrigine or any other AED. In one small study, a desogestrel-only pill caused a 20%–100% increase in lamotrigine concentrations, but only in seven out of ten women [89]. However, this study from the year 2004 still exists only in an abstract form and it has not been confirmed by others.

It should also be noted that EE is used not only in oral preparations (COCs) but also in skin patches and the vaginal ring. Accordingly, it has been found that the EE-releasing vaginal ring may reduce lamotrigine serum concentrations in a similar manner as COCs [83,90]. Although not specifically studied, such an effect should also be anticipated for the EE-releasing skin patch.

CHAPTER II

OBJECTIVES

The first objective of this study was to evaluate the safety of two different LNG-IUS and Cu-IUD in WWE, by measuring AEDs concentrations and neurological symptoms before and after initiating the intra-uterine contraception.

The secondary aim was to assess efficacy and acceptability of this long acting methods in WWE.

CHAPTER III

METHODS

We conducted a pilot prospective cohort study on WWE, desiring contraception, at the Department of Obstetric and Gynecology of University of Naples "Federico II", from January 2019 to January 2021.

Our inclusion criteria were:

- age 18–45 years
- regular menstrual cycles between 21 and 35 days in length
- seeking contraception
- confirmed diagnosis of epilepsy
- stable AED regimen (no change in dose or type 2 months before enrollment)
- well-controlled epilepsy (≤2 seizures per month, excluding focal seizures with no impairment of awareness).
- We included also nulliparous women.

Exclusion criteria are:

- short-acting hormonal contraceptive use in the month prior or medroxyprogesterone acetate in 6 months prior
- IUD controindications
- pregnancy in the last 2 months
- irregular menstrual cycles
- women with more pharmaco-resistant epilepsy in order to isolate effects of the progestin IUS on seizure frequency.

The study was conducted following the Declaration of Helsinki (1975) and Good Clinical Practice guidelines. Before enrolment, the purpose of the study was clearly explained, and all patients received detailed information about the study, to which they gave their consent. The information obtained were anonymized before analysis.

At the enrollment visit, baseline informations were obtained in order to record demographic characteristics, reproductive and contraceptive history, drugs and seizure history. All participants provided a description of seizure(s). Seizures were then categorized by the study neurologist and clarified with the treating neurologists. Each participant's neurologist also confirmed eligibility and AED type and dose. Each patient received a diary to record seizure type and occurrence and menstrual bleeding during the follow up. We inserted one of three different intrauterine devices: IUS (Levonorgestrel 52 mg or Levonorgestrel 19,5 mg) or Cu-IUD and evaluated AED concentrations at time 0. The device was placed in 5°-6° day of menstrual cycle.

All patients were divided in 3 groups: The first group received a Levonorgestrel 52 mg IUS (Mirena, Bayer, Whippany, NJ, U.S.A.); the second group received Levonorgestrel 19,5 mg IUS (Kyleena, Bayer, Whippany, NJ, U.S.A.); the third group received Cu-IUD.

All participants recorded bleeding and seizure type and occurrence in their daily diaries. Participants returned on day 21 (Time 1) of the first menstrual cycle and every 6 months. At each visit, we reviewed their diaries, medications and AED concentration.

Therefore, during these visits, participants self-administered a brief questionnaire created by the investigators to assess overall satisfaction with the IUS (very satisfied, somewhat satisfied, neutral, dissatisfied, or very dissatisfied), plans for continuation, and perceived impact of the IUD on epilepsy (better, no change, worse, or don't know). We ascertained adverse events with an open-ended question at each visit and by reviewing diaries. The effectiveness of these contraceptive methods (absence of unwanted pregnancy) was recorded.

Based on our clinical practice and prior study recruitment, we estimated that a study of 20 WWE seeking contraception would be feasible and adequate to provide preliminary data. We used descriptive statistics to characterize our sample.

CHAPTER IV

RESULTS

We screened 22 women and excluded 2: one for poor seizure control and one who changed AED type during the study. Table 5 summarizes baseline characteristic of the patients, including demographic and reproductive data, AED therapy and epilepsy syndrome.

VARIABLE	N= 20
AGE	35,9 (27-44)
BMI	24 (18-30)
PARITY:	
Nulliparous	3
Multiparous	9
Previous Caesarean section	8
SEIZURE TYPE:	
Focal	7
Genetic (idiopathic) generalized	8
Combined focal & generalized or unknown	5
EPILEPSY SYNDROME	
Genetic generalized epilepsy syndrome	8
Localization-related epilepsy syndrome	12
THERAPY	
Monotherapy	
-Lamotrigine	8
-Levetiracetam	2
Politherapy	
- Lamotrigine-Levetiracetam	5
- Lamotrigine-Oxcarbazepina	5

TABLE 5: BASELINE CHARATERISTICS OF PATIENTS

Nine used condoms prior to enrollment; all other patients are not using contraceptive methods. Half of women were treated with AED monotherapy, other half with polytherapy. Lamotrigine was the most commonly prescribed medication (n = 18). All participants completed the study, and none missed a visit. For the patients taking Lamotrigine, we evaluated AED serum concentration at all planned time points.

Our analysis included any seizures recorded by participants and showed that the most common pattern was to be seizure-free throughout the study including during the baseline month. Only two partecipants experienced seizure during the second and third month after Cu-IUD insertion, and one in the second month after 19 mg LNG-IUD.

Our preliminary data obtained to date, showed no relationship between IUD insertion, change in AED trough concentration (TABLE 6; FIGURE 1) and the occurrence or worsening of seizures. All partecipants endorsed no change in their epilepsy due to the IUD. By comparing, with paired sample t-test, baseline and T1, T2, T3 mean values of lamotrigine serum concentration of patients of three groups, no significant difference was observed.

No participants were dissatisfied. At 6 months, 50% of Group 1 said they were satisfied and only one partecipant reported an increasing weight. For the Group 2, all patients were very satisfied. Three women of third group reported heavy menstrual bleeding at 6 months control.

No pregnancies, IUD expulsions, or serious adverse events occurred.

Until now all women chose to continue IUD use.

	GROUP 1 52 mg IUS N: 8	GROUP 2 19.5 mg IUS N: 7	GROUP 3 Cu-IUD N:5
T 0	6 mcg/mL (± 2 SD)	6.25 mcg/mL (± 1.25 sd)	4.5 mcg/mL (± 0.57 sd)
T 1	5.8 mcg/mL (± 2.16 sd)	6 mcg/mL (± 0.81 sd)	4.5 mcg/mL (± 0.57 sd)
T2	5.6 mcg/mL (± 1.94 sd)	5.75 mcg/mL (± 0.95 sd)	4.5 mcg/mL (± 1 sd)
T3	5.8 mcg/mL (± 1.3 sd)	6.25 mcg/mL (± 0.5 sd)	4.25 mcg/mL (± 0.95 sd)

TABLE 6: MEAN OF LAMOTRIGINE SERUM CONCENTRATION AT THE SCHEDULED VISITS.

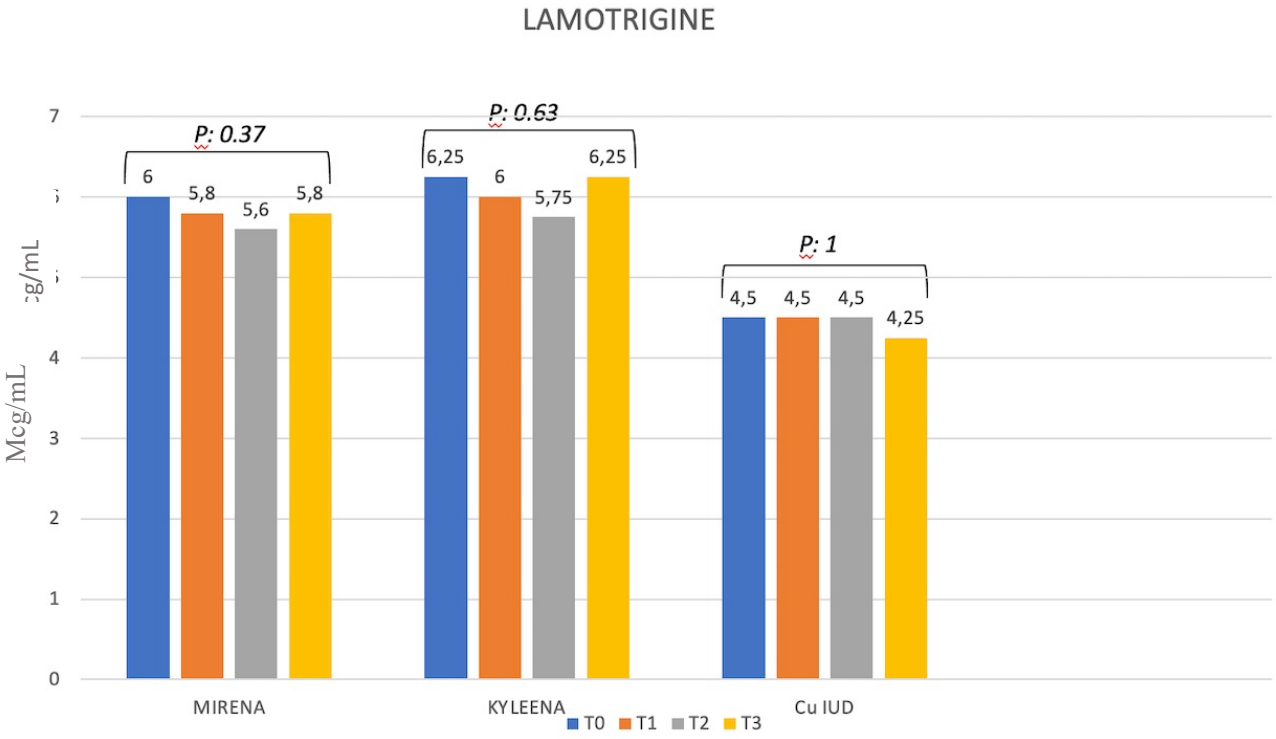

FIGURE 2: LAMOTRIGINE SERUM CONCENTRATION AT THE SCHEDULED VISITS:

T0: Before the insertion of IUD; T1: 21^{O} day of the first menstrual cycle; T2: 6 months later; T3: 12 months later

CHAPTER V

DISCUSSION

More than half of the WWE in the Epilepsy Birth Control Registry (EBCR) discontinued a contraceptive method. This rate is greater than the finding in the general population (52.1% [95% CI 48.14–54.26%] vs. 46%)[91]. Moreover, a greater percentage of the WWE who discontinued a method, discontinued more than one method in comparison to women in the general population (51.8%[47.56–56.04%] vs. 36.0%)[91]. This is particularly apparent for HC, for which reasons for discontinuation were unique to WWE; in fact HC, the one contraceptive category that is known to have interactions with some AEDs and has been associated with greater changes in seizure frequency than other categories [92], was discontinued significantly more often by WWE than by women in the general population (EBCR: 50.7% [47.8–53.7] vs. 32.1%), whereas IUD, which has been shown to have no interaction with AEDs [93,94] and has greater efficacy[95], was discontinued less (25.1% [18.9–31.7] vs. 36.4%).

Considering our preliminary data WWE who begin contraception with a IUS maintain stable seizure control. IUS, comparing to Cu-IUD, seem not to impact seizure control and do not result in adverse effects during 12 months after insertion.

According to data prospectively collected in diaries, all participants experienced no change after IUD insertion. Subjectively, no participant reported that the IUD worsened her epilepsy. Acceptability was high, and all participants continued using the progestin- containing IUD for contraception after the study.

Therefore, there is no difference between the three groups in AED concentration and seizure control. IUS is a safe, acceptable, long-acting and reversible alternative contraceptive for WWE. In fact OC efficacy is affected by enzyme-inducing AEDs that augment hepatic metabolism, while the progestin IUS prevents pregnancy primarily by thickening cervical mucus. This local mechanism of action is

unlikely to be influenced by changes in hepatic metabolism; one study found a high efficacy rate among progestin IUS users treated with coadministered enzyme-inducing antiepileptic drugs.

Clinicians caring for WWE face challenges when choosing contraception, and a recent U.S. nationwide analysis found lower uptake of effective contraception in WWE compared to women with other chronic medical conditions [96]. Bi-directional drugs interactions affect systemic hormonal methods such as COCs, the most commonly used method of contraception.

WWE and their children benefit from highly effective contraception and planned pregnancies. It is advisable to create gynecological-neurological teams, caring for WWE in reproductive age, and to take care about continuous education of patients regarding effective methods of family planning and about improvement of methods of informing patients about the teratogenicity of AEDs.

Our results, although preliminary, support that women with well-controlled epilepsy can use the progestin IUD without a clinically meaningful impact on seizures or AED concentrations.

Lamotrigine is commonly prescribed to reproductive-age WWE, and was the most prescribed AED in our study. For these WWE, contraceptive choice is complicated because the estrogenic components of OCs decrease lamotrigine concentrations substantially, by approximately 50%. Estrogen related changes can be obviated by using progestin only methods. Published cross sectional studies support minimal impact of progestin-only methods on lamotrigine concentrations. Reimers et al. [83] found comparable lamotrigine dose/concentration ratios in 16 WWE using progestin-only methods (three with an IUD), compared to 18 WWE not using a hormonal method. Among 12 WWE treated with lamotrigine and a progestin IUD, Ohman et al. demonstrated comparable lamotrigine dose/concentration ratios and lamotrigine metabolite (N-2-GLUC)/lamotrigine ratios compared to controls not using a hormonal method. In contrast to these cross-sectional studies, our prospective design allowed us to compare AED concentrations during 6 months of follow-up.

Our study has limitations. Each woman served as her own control; a comparison group of WWE unexposed to the IUD would be a more rigorous control group. However, results would be difficult to interpret unless matched on AED and baseline seizure control. Our study was exploratory

and limited by the small sample size. We did not assess daily AED compliance, which could account for observed variability in measured AED trough concentrations as well as seizure control. Moreover we evaluated only Lamotrigine serum concentration, so data on other AEDs changes are not known.

CHAPTER VI

CONCLUSIONS

Considering preliminary data, long-acting contraception with IUS is a safe method in WWE; our study in fact suggests that the effectiveness of this method is not affected by AEDs and do not affect AEDs serum concentration, which would make them a suitable and safe alternative to systemic hormonal contraception.

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