Controversies in contraception for women with epilepsy

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Abstract

Contraception is an important choice that offers autonomy to women with regard to prevention of unintended pregnancies. There is wide variation in the contraceptive practices between continents, countries, and societies. The medical eligibility for contraception for sexually active women with epilepsy (WWE) is determined by the type of anti-epileptic drugs (AEDs) that they use. Enzyme inducing AEDs such as phenobarbitone, phenytoin, carbamazepine, and oxcarbazepine increase the metabolism of orally administered estrogen (and progesterone to a lesser extent). Estrogen can increase the metabolism of certain AEDs, such as lamotrigine, leading to cyclical variation in its blood level with resultant adverse effect profile or seizure dyscontrol. AEDs and sex hormones can increase the risk of osteoporosis and fracture in WWE. The potential interactions between AEDs and hormonal contraception need to be discussed with all women in reproductive age-group. The alternate options of oral contraception such as intrauterine copper device, intrauterine levonorgestrel release system, and supplementary protection with barriers need to be presented to them. World Health Organization has recommended to avoid combination contraceptive pills containing estrogen and progesteron in women who desire contraception and in breastfeeding mothers. Care providers need to consider the option of non-enzyme-inducing AEDs while initiating long-term treatment in adolescent and young WWE.

Key Words

Contraception, enzyme induction, epilepsy, pregnancy, women

Introduction

There are about 50 million people with epilepsy across the world. Men and women are affected almost in equal numbers in most continents. About half of the women with epilepsy are in the reproductive age-group of 15-49 years. Contraception offers considerable benefits to women. It enhances the autonomy of the women with regard to their health and personal life. It can promote their health by reducing the risk of adolescent pregnancy, recurrent pregnancies without adequate spacing, and risk of unintended pregnancies or unhealthy abortion practices. Studies have shown that contraceptive practices lead to reduced infant mortality. Barrier contraceptives offer the additional protection against human immunodeficiency virus (HIV) and sexually transmitted infections.

Most women with epilepsy (WWE) need to continue on anti-epileptic drugs (AEDs) in order to remain seizure-free during the 30-35 years of sexually active period. In the absence of effective contraceptive methods, there is increased risk of unplanned pregnancies and considerable emotional stress. The contraceptive needs of a client with epilepsy are often ignored and not discussed across with a clinician. Women may be embarrassed to discuss this in crowded practices and busy clinicians may overlook this important area. It is common experience that partners find unexpected and unplanned pregnancies pregnancy.

Controversies Regarding Contraception in WWE

There is much controversy regarding the choice of contraceptive method for WWE: Whether it should be hormonal contraception or other methods such as intrauterine devices, or barrier methods. Another important concern is the efficacy of hormonal contraception, when used along with AEDs. Other controversies are related to the potential risk of exacerbation of epilepsy or predisposition for osteoporosis when women use hormonal contraceptives. The objective of this review is to highlight the pharmacokinetic basis of the controversies regarding the contraceptive options of WWE and discuss the recommendations of the World Health Organization.
There is wide variation in the contraception practices across the world. The WHO statistics shows that globally around 54% of women in reproductive age-group adopt some method of contraception. This proportion is very low in African continent (24%) when compared to Asia (62%) or Latin America (67%). A recent study in the USA had shown that half of the pregnancies in WWE are unplanned. Although 70% had reported the use of some contraception methods only 53% were on reasonably effective methods of contraception. Further, 29% of them were using an enzyme-inducing anti-epileptic drug (EIAED) that may potentially decrease the efficacy of the oral contraceptives. Regrettably, there is little data available from India with regard to the contraceptive practices and experiences of WWE in India.

**Does Gender Influence the AED Metabolism in Human?**

Most of the AEDs are metabolized in the liver by oxidation followed by glucuronidation before they are eliminated through the kidneys. The limited data on the gender differences in the pharmacokinetics of AEDs indicate that gender does not influence the absorption, distribution, or elimination of AEDs in any clinically significant manner. Nevertheless, more recent data point towards sex-dependent differential gene expression of enzymes involved in the metabolism of AEDs.

<table>
<thead>
<tr>
<th>Method</th>
<th>Contents</th>
<th>Effectiveness (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Hormonal contraception</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined oral contraceptive pills (COCP)</td>
<td>Contains progesterone and estrogen</td>
<td>92-99</td>
<td>Loses potency when used along with AIEAD</td>
</tr>
<tr>
<td>Progesterone only pill (POP)</td>
<td>Contains progesterone only</td>
<td>90-97</td>
<td>Less interaction with AIAEDs</td>
</tr>
<tr>
<td>Combined hormone skin patch</td>
<td>Contains progesterone and estrogen as in COCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined hormone vaginal ring</td>
<td>Contains progesterone and estrogen as in COCP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Implants</td>
<td>Progesterone only</td>
<td>&gt;99</td>
<td>Effective for 3-5 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No interaction with AEDs</td>
</tr>
<tr>
<td>Injections</td>
<td>Progesterone only injections</td>
<td>Medroxy progesterone</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>Combined injections</td>
<td>Contains progesterone and estrogen</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>Intruterine system</td>
<td>Contains levonorgestrel</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>Copper intrauterine device</td>
<td>Copper</td>
<td>&gt;99</td>
</tr>
<tr>
<td></td>
<td>Emergency contraception</td>
<td>Levonorgestrel</td>
<td>60-90</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Hypothalamus</th>
<th>Pituitary</th>
<th>Ovary</th>
<th>Uterus</th>
<th>Cervix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesteron</td>
<td>Disturbs the pulsatile secretion of GnRH</td>
<td>No LH surge</td>
<td>Anovulation</td>
<td>Decidualization (prevents implantation)</td>
<td>Cervical mucus changes (prevents penetration of sperm)</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Decreases FSH secretion</td>
<td>Interferes with follicle maturation anovulation</td>
<td>Prevents breakthrough bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sexually active women often resort to contraceptive methods to prevent unplanned pregnancies and hormonal methods are some of the preferred choices. In the USA, about 22% of WWE in the age-group 26-45 years have reported using oral contraceptives (OC) and half of them have not received information on possible interaction between AEDs and OC. Two-third of women who were prescribed EIAEDs were unaware of the potential interaction between AED and oral contraceptive pill (OCP) and the risk of unplanned pregnancy. Hormonal contraceptives are also used for other indications such as to postpone menstrual bleeding and for the treatment of a variety of gynecological disorders.

**Commonly Used Contraceptives**

A wide range of reliable methods of modern contraceptives are marketed, although there is some variation in their availability between countries [Table 1]. Hormonal contraception aims at prevention of pregnancies by several pathways [Table 2]. It may prevent follicule maturation and ovulation, or act on the uterus and cervix to prevent fertilization or implantation.

The most widely used oral contraceptives contain a combination of progesterone and estrogen and are known as combination oral contraceptive pill (COP). Depending upon the progestin used in the pill, combination oral contraceptive (COC) can be classified as first generation (norethynodrel, norethindrone acetate, or ethynodiol acetate), second generation (Levonorgestrel), third generation (desogestrel or gestodene), and fourth generation...
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From day 1 to 21 and in triphasic regime, the progestin dosage remains the same of placebo or iron therapy, when withdrawal bleeding occurs. Progestin (blue line) is present for day 1-21 followed by 7 days consecutive therapy are shown. In cyclic therapy, the progestin dosage varies according to the day of the cycle in order to mimic the physiological trends [Figure 1]. In biphasic pills, the dosage of progesterone is low for the first 10 days and higher for the next 11 days. In triphasic COP, the dosage of progesterone increases in three steps on 5th, 10th, and 14th day. The interaction between hormones and the AEDs are at different levels at different phases of menstrual cycle with multiphasic pills. This can lead to considerable variation in the blood levels of AEDs and possible risk of breakthrough seizures or adverse effects. These cycles have a hormone-free interval of 7 days or 4 days, during which time, the blood level of AEDs may increase significantly. The WHO has observed that there is no evidence that multiphasic COPs are safer or more effective than monophasic COPs. In most developing countries, low-dose monophasic COPs are widely available and acceptable. There is no justification at present to recommend multiphasic COPs in preference to monophasic COPs. From the view point of interaction between AEDs and hormones, it is better to select a continuous dosing oral pill than a multiphasic pill.

Combination hormone contraception is also available as skin patches that release a constant quantity of progesterone — Norelgestromin (150 ug/day) and ethinyl estradiol (20 ug/day) to the circulation. COC is also available as vaginal rings. Other topical methods of administration such as gels and sprays are being evaluated.

Another popular hormonal contraceptive is progesterone only pills (POP). Unlike COP, POP has no hormone-free phase. Long-acting medroxy progesterone depot injections are available for longer term contraception for up to 3 months.

These injections have the advantage of better compliance but some women may experience excessive withdrawal bleeding which can be bothersome. Its metabolism is dependent on hepatic circulation and virtually 100% of the molecule is eliminated in the first pass itself. Hence, the blood levels are unaffected by EIAEDs and no dose adjustment is required.

Ormeloxifene is a selective estrogen receptor modulator that is an agonist at bone (mineralization) antagonist at breast and uterus. Unlike estrogen, ormeloxifene selectively modulates the estrogen receptors in such a way that it has less metabolic and thrombogenic properties while it maintains it contraceptive properties. This molecule is available in India as a legal oral contraceptive under the brand name Saheli.

Progestrone implants were developed in late 60s. The original implants consisted of six silicone capsules, each containing 36 mg of levonorgestreal (progestin) which when implanted subdermally would be effective for 5 years. Norplant II (Jadelle) consists of two small silicone rods each containing 75 mg of levonorgestrel in a polymer matrix and is effective for 5 years.

**Intrauterine Systems and Devices**

Copper-containing devices have been very successfully utilized in India and many other countries. This device releases a tiny quantity of ionic copper in to the uterine cavity and prevents fertilization or implantation. The Intrauterine system is a T-shaped device embedded with levonorgestrel that gradually elutes out. These are highly effective methods of contraception. It requires medical assistance to insert these devices. However, they are effective for up to 5 years.

**Interaction Between OCP and AEDs**

There is a complex pharmacokinetic interaction between hormonal contraceptives and AEDs. As a result, the blood levels of active ingredients of contraceptives and AED can get altered. The AEDs and steroid hormones share a common drug transporter P-glycoprotein (PGP) for its transport from the intestinal lumen in to the portal circulation. These transporters move AED, hormones, and several other drugs across the intestinal mucosa or blood brain barrier. Polymorphism of the genes that transcribe for the PGP can alter the degree of drug transport and bioavailability. AEDs and hormones may competitively interfere with each other for their transport across the intestinal wall. Recent studies have shown that progesterone may induce the expression of PGP and augment its transport.[7]

Sex hormones (testosterone, progesterone, and estrogen) are derived from 27 carbon cholesterol molecule by cleaving the side chain. The molecule undergoes further trimming to produce 21 carbon pregnanes (progesterone) or 19 carbon Androstanes (testosterone) or 18 carbon Estranes (estradiol). All these molecules are metabolized and eliminated from the body by oxidation and glucuronidation. About 75% of the oxidative metabolism of progesterone is mediated through CYP 450 group of enzymes located in the liver microsomes.[8] There are about 57 human genes that code for the various CYP group of enzymes. CYP family of enzymes demonstrate considerable
degree of enzyme induction — A process in which one molecule enhances the expression of an enzyme. The Nobel Prize for Physiology and Medicine for the year 1965 was awarded to François Jacob and Jacques Monod who had for the first time demonstrated the property of enzyme induction.

There had been several major discoveries in the pharmacogenomics of CYP 450 induction in the recent past. Essentially, there are certain nuclear receptors under the super family NR1 that combine with the inducing molecule such as AED which in turn results in increased gene expression and resultant production of CYP 450 proteins. CYP 3A4, 2B6, and 1A1 are induced by activation of the transcription factors pregnane X receptor, constitutive androstane receptor, and aryl hydrocarbon receptors. There is considerable cross talk between these receptors and other intracellular receptors and signalling pathways that lead to cross induction between molecules. There are endogenous ligands for these receptors which modulate the activity of the P450 family of enzymes according to the physiological demands.[9][10] The enzyme induction property may differ from one population and ethnic group to another and the degree of induction can vary with different AEDs.

**Effect of AEDs on Sex Hormones**

AEDs can be broadly classified as enzyme inducers, enzyme inhibitors, or those which have minimal effect on enzyme synthesis [Table 3]. The impact of enzyme induction is more profound on blood level of estrogen than progesteron. As a result, when hormonal contraceptives are introduced to women who are already taking EIAEDs, the blood levels of the steroid hormones can remain sufficiently low as to lose its protective effect [Table 4]. Lamotrigine (LTG) is peculiar in not influencing the metabolism or blood level of estrogen. Nevertheless, it increases the metabolism of progesterone (which is metabolized by CYP2C19, CYP 3A4, and CYP2C9). As a result, LTG reduces blood level of estrogen by 10-19%. Hence, it can make the hormonal contraceptive pills rather ineffective.

**Effect of Sex Hormones on Pharmacokinetics of AEDs**

Steroid hormones, particularly estrogen, can induce the enzymes and lower the blood level of the AEDs like phenobarbione, phenytoin, carbamazepine, and lamotrigine. As a result, a woman who is well-controlled on EIAEDs may experience breakthrough seizures, if she starts using COP. One does not experience this problem, when a WWE who is already using COP is initiated and titrated up on these AEDs.

**Specific issues related to lamotrigine and hormonal contraception**

When COP is used regularly, the blood level of lamotrigine would remain relatively low for most part of the cycle (day 2-20) due to its increased elimination. Ethinyl estradiol and other estrogens can induce the activity of UGT leading to increased glucuronidation and elimination of LTG and to a certain extent valproate. Blood levels of LTG were found to drop by 50% when exposed to estrogens as part of COP or post menopausal hormone replacement therapy.[11] As a result, several groups had empirically recommended to double the dose of LTG when COP is used concomitantly. However, the precise dose elevation need to be verified and cross checked with the patient’s experiences. The COP is used along with valproate, which is a strong enzyme inhibitor, the blood level of LTG does drop. The placebo/iron holiday window (day 21-28) in the COP regime may be associated with higher blood levels of LTG.[12] Some of these patients can experience adverse effects of higher dose of LTG during this phase of the therapy. Fluctuations in the blood levels of LTG can occur during the placebo phase with hormone combination vaginal rings and transdermal patches also. In a similar way, adverse effects related to high blood level of LTG can occur when women discontinue the use of COP. Patients who are on COP and EIAEDs need to be carefully monitored for cyclical aggravation of seizures during (day 5-20) or adverse effects (day 21-28). This is not a big problem with POPs.

**EIAEDs, oral contraception, and bone mineral metabolism**

Women in general have higher risk of low bone mineral density, osteopenia, and osteoporosis associated with increased risk of fracture. EIAEDs and valproate are known to accelerate this process. Hormone contraception can increase the bone demineralization and predispose to osteopenia. There is little data available on the magnitude of this problem and the specific risk factors.

**Choices for women who are already on EIAEDs**

Since EIAED is likely to reduce the blood levels of the hormones, the standard COPs, patches, rings, and post coital pills are likely to fail. The context and duration of contraception requirements, general physical condition, metabolic status,
level of independence, and personal preferences need to be taken in to consideration while choosing the contraceptive. The alternate options for oral contraception would be:
1. To use two tablets of standard pills (EE 30 mg) instead of one per day,
2. To switch to a higher estrogen (>50 ug EE) pill cycle.

However, regular use of pills that contain higher dose of estrogen has raised concerns of increased risk of thrombogenesis and breast cancer. In the classical COP regime, there is a 7 day hormone-free period when withdrawal bleeding occurs. In a patient who is on EIAED and at the risk of low hormone levels, this pill-free period can lead to unplanned pregnancy. Hence, an alternative could be to use regimes with short hormone-free intervals (4-5 days) or continuous dose medication for three months or so (tricycling). This technique is gaining wider acceptance.

There are wider choice in the parenteral options, such as:
1. Injection of medroxy progesterone,
2. Hormone eluting intrauterine devices or
3. Non-hormonal contraception such as intrauterine devices, and
4. Barrier methods. Often it would be helpful to combine more than one method to ensure adequate level of contraception.

There are situations, when women may prefer to continue hormonal contraception and switch to a non-EIAED. When a woman who is on COP and an EIAED is switched over to a non-EIAED, the higher dose COC need to be continued till the end of the cycle as the enzyme induction may persist for several days.

Emergency contraception is essentially administration of progesterone. Combination pills for emergency contraception have been withdrawn as more effective progesterone only pills have come out. Its metabolism of POP is increased by EIAEDs. Hence, they should be advised to take levonorgestrel 1.5 mg (Levonelle One Step) initially followed by a second dose (1.5 mg) 12 hours later. Another alternative is to resort to copper intrauterine device which needs to be inserted as soon as possible and not later than 5 days.

**Choices for Women who are using Hormone Contraception and Require AED Therapy**

Use of oral hormonal contraceptives can induce the cytochrome P 450 family of enzymes and increase the metabolism of the AEDs with resultant break through seizures. This can occur even within a week and care should be taken while introducing such changes. It is important to discuss this issue with the patient. AEDs that are not metabolized through oxidation by CYP 450 group of enzymes are unlikely to interact with hormones and their potency is not affected. It would be preferable to initiate such an AED (levetiracetam, etc.) in such instances. At times, the use of contraceptives would be only for a short period when the dose of the AED may have to be maintained with the help of blood levels.

**Contraceptive use for other conditions and epilepsy**

Occasionally women are prescribed hormonal contraceptives to manage certain gynecological conditions such as polycystic ovarian disease. In such instances, the AEDs such as sodium valproate may have to be avoided as it is likely to contribute to the etiology of the polycystic ovarian disease (PCOD). It would be worth considering switching to another NIAED in such instances.

**Medical eligibility criteria for contraception**

WHO had taken the initiative to compile evidence-based guidelines on the use of contraceptives. This report was first published in 2000 and the fourth revision was published in 2010.[13] The goal of this document is to provide a set of recommendations that can be used for developing or revising national guidelines on who can use what contraceptive methods. It is expected that the clients are given adequate information in order for them to make informed voluntary choice of contraceptive method. The important pieces of information include relative effectiveness of the method, correct use of the method, how it works, common side effects, health risks and benefits of the methods, signs and symptoms that would necessitate a return to the clinic, information on return to fertility after discontinuation of the method, and information on the STI protection.

The working group had graded the medical conditions that may influence the choice of contraception in to four conditions [Table 5]. Accordingly, the working group had recommended that the risk associated with the use of COP in a woman who is on EIAED is unacceptable (condition 4). This necessitates alternate options of injectable hormonal contraception, intrauterine devices, or intrauterine systems. The risk outweighs the benefits when COP, patches, and vaginal rings are used along with lamotrigine or while breastfeeding [Table 6]. The Center for Disease Control,[14] Atlanta, USA and the Faculty of Sexual and Reproductive Healthcare, UK[15] have provided similar guidelines.

### Table 4: Effect of EIAED on efficacy of different hormonal contraceptives

<table>
<thead>
<tr>
<th>Contraceptive methods that may be influenced by EIAEDs</th>
<th>Contraceptive methods that may not be influenced by EIAEDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined oral contraceptive pill, Medroxyprogesterone acetate-depot, The combined contraceptive patch, Levonorgestrel releasing intrauterine devices, The combined contraceptive vaginal ring, Postcoital contraceptives Combined hormone monthly injections Progestogen-only pill (minipill), Progestogen implant,</td>
<td>Copper-containing intrauterine devices,</td>
</tr>
</tbody>
</table>

### Table 5: Conditions that influence the choice of contraception

<table>
<thead>
<tr>
<th>A condition which represents an unacceptable health risk if the contraceptive method is used</th>
</tr>
</thead>
<tbody>
<tr>
<td>A condition where the theoretical or proven risks usually outweigh the advantages of using the method</td>
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</tr>
<tr>
<td>A condition which represents an unacceptable health risk if the contraceptive method is used</td>
</tr>
</tbody>
</table>
Table 6: Medical Eligibility criteria and conditions for use of different contraceptive methods in women with epilepsy and antiepileptic drug usage

<table>
<thead>
<tr>
<th></th>
<th>COCpill/patch/ring</th>
<th>POP</th>
<th>Inj</th>
<th>Implant</th>
<th>IUD</th>
<th>cu IUCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EIAED*</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;6 wk (breast feeding)</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6wk-6 m (breast feeding)</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EIAED = Enzyme inducing anti epileptic drug. *Phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine

Conclusion

To summarize, it is preferable to use a non-EIAED in women in reproductive age considering her potential contraceptive needs. Alternatively, a woman who is on AED could consider intrauterine device.

It is important that neurologists who attend to women in reproductive age-group address their concerns regarding contraception. Patients themselves may not bring up their concerns. Most of the newer AEDs do not have much interaction with hormonal contraception. Women who are on EIAEDs need to be informed that they should consider using alternate methods of contraception and avoid oral pills as it may not have expected efficiency when used along with AEDs.

References

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