Pregnancy and epilepsy

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Abstract

Objective. *The main goal of this review is to provide some answers about the best therapy of pregnant women with epilepsy and/or women with epilepsy taking oral contraception.* ***Methods.*** *We have collected information's concerning the problems that may arise before and after a pregnancy, involving the best therapeutically options for a pregnant woman.* ***Results.*** *Women with epilepsy have frequent menstrual disorders, reproductive endocrinological disturbances, ovulatory dysfunction and infertility, presenting a risk of contraceptive failure associated with some antiepileptic. Antiepileptic drugs have some side effects on pregnancy by increasing the rate of abortion, preterm labor and vaginal bleeding, especially in polytherapy. Pregnancy can affect the pharmacokinetics of antiepileptic drugs at any level from absorption, distribution, metabolism, and therefore we have showed a list of the most used antiepileptic and how they can affect a future pregnancy from conceiving until delivery and after.* ***Conclusions.*** *Epilepsy represents a sensible field in relationship with pregnancy that involves contraception, heredity and teratology, especially if we consider that the risk of a convulsive seizure to mother and child is frequently over weighted by a continued therapy.*

Keywords: *epilepsy, contraception, pregnancy, teratology*

Introduction

Epilepsies are the most common neurological diseases of women who have a pregnancy in which the approximate incidence is 1%[(1)]. Pregnancy is a state characterized by rapid pharmacokinetics than any period of life. Therefore, a good management of the patients with epilepsy should take into consideration some basic issues like: the interaction between some antiepileptic and oral contraception that can cause an unwanted pregnancy, the possible teratogenicity effects of some antiepileptic on the baby and the identification of antiepileptic drugs which can control seizures better during the evolution of a pregnancy. The British National Formulary also emphasizes the benefit of continuing the therapy in pregnancy, stating that the 'risk of harm to the mother and fetus from a convulsive seizure outweighs that of continued therapy'[(2)]. The most important therapeutic problems that involve epileptic women having a pregnancy or epileptic women taking oral contraception are still under debate.

We have analysed the most recent research articles related on the topic and we have corroborated the informations aimed at preventing side-effects on pregnant epileptic women.

Contraception

Women with epilepsy have frequent menstrual disorders, reproductive endocrinological disturbances, ovulatory dysfunction and infertility. In addition, when using antiepileptic drugs, a higher risk of bleeding and contraceptive failure has been associated in these women. There is still an increased risk for contraceptive failure with the use of P450 3A4 enzyme-inducing antiepileptic drugs (AEDs) such as phenobarbital, carbamazepine, phenytoin, felbamate, topiramate and oxcarbazepine, as these substances increase the metabolism of ethinylestradiol and progestogens[(3)]. The solution in this case is to use no inducing AEDs or when using AEDs to be associated with the use of oral hormonal contraceptive pills which contain equal or more than 50 micro of estrogen, or intrauterine devices[(4)].

Levonorgestrel implants are contraindicated in women receiving these AEDs because of contraceptive failure. It is recommended that medroxyprogesterone injections should be given every 10 rather than 12 weeks to women who are receiving AEDs. As far as we know, there are no interactions among the combined oral contraceptive pill, progesterone-only pill, medroxyprogesterone injections or levonorgestrel implants and the AEDs valproic acid (sodium valproate), vigabatrin, lamotrigine, gabapentin, tiagabine, levetiracetam, zonisamide, and ethosuximide[(3)].

Outcome of pregnancy

Antiepileptic drugs could have many effects on pregnancy by increasing the rate of abortion, preterm labor and vaginal bleeding, especially in polytherapy. Current studies have reported that the rate of some complications such as hyperemesis gravidarum, pregnancy induced hypertension, preeclampsia, cesarean delivery, placental abruption, and perinatal mortality are more higher in these women.

The first minute Apgar score was significantly lower in these neonates which may be due to background problems during pregnancy or some problems in their cardiac, respiratory, and neurological systems. Reduced Apgar scores occurred more frequently in the valproic acid andphenitoin groups at 1 minute. Small gestational age was frequent for valproic acid and carbamazepine[(5)]. It also further strengthens a hemorrhagic phenomenon which can occur in the infants of epileptic mothers and it seems to be the result of a deficiency of vitamin K-dependent clotting factors. Different probable mechanisms have been reported for AED-induced teratogenicity and the most important of them include folic acid antagonism, fetal tissue binding and toxic effects of metabolic products[(6)].

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Effects on the child

About 2.1% of children exposed to antiepileptic medications in utero have microcephaly. The intelligence score of children from mother with epilepsy is in the normal range but beneath the intelligence score of children from normal mothers.

Malformations occur 2-3 times higher in children of mothers with epilepsy. Major malformations include cleft lip, cleft jaw or cleft palate, spina bifida, malformations of the skeleton, malformations of the heart, hypospadias and gastro-intestinal atresia that need to be treated surgically. Minor anomalies represent slight deviations from the norm and can be considered harmless unless they are not in large number: hypertelorism, epicanthus, widened base of the nose, shortened nails and distal phalanges[7].

Heredity

A main problem of mothers who want a child is if the disease is hereditary. There are some forms that have a familial risk: epilepsy with focal seizures has a risk of 4%, childhood epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy have a risk of 10%, West syndrome and Lennox-Gastaut syndrome have a risk of 10%, and febrile convulsions are associated with 10% risk or more. Another comment is that children of women with epilepsy have a greater risk than descendent of male epileptic patients[7].

Treatment

Pregnancy can affect the pharmacokinetics of AEDs at any level from absorption, distribution, metabolism, to elimination. AED should not be stopped due to the risk of seizures during pregnancy that can be a danger for both mother and the fetus[8]. The most pronounced decline in serum concentrations is seen for AEDs that are eliminated by glucuronidation, in particular lamotrigine where the effect may be profound. Serum concentrations of AEDs that are cleared mainly through the kidneys, for example, levetiracetam, can also decline significantly. Some studies sustained that carbamazepine seem to be affected only marginally by pregnancy. Newer generation of AEDs such as pregabalin, lacosamide, retigabine, and eslicarbazepine acetate have not been well investigated yet in terms of pharmacokinetics during pregnancy. However, a study conducted in New York, has shown a possible link between lamotrigine, topiramate, gabapentin and congenital jaw or oral malformation[8].

The epilepsy of a pregnant patient must be treated exactly as a patient that is not pregnant. The drugs have to be administrated in mono-therapy in the lowest possible dosage to assure seizure free and no side effects.

If a patient plans a pregnancy and is not seizure free, the therapy must be optimized by increasing the dosage or simplifying the existing combination by eliminating the valproic acid or carbamazepine (if a case of spina bifida has been registered in the family).

Patients who are free from seizures and side effects are usually left to continue the medications, even if is polytherapy or valproic acid, the daily doses should be distributed in 3 or 4 administration a day.

An attempt to optimize the therapy should be made for those patients who are not seizure free. A prenatal diagnosis regarding neural tube defects will be considered by ultrasonography from 12th week and alpha-fetoprotein determinations. Oral clefts formations and heart defects can be detected using ultrasounds from 22nd to 24th week.

If a reduction of serum concentrations of drugs is followed by a seizure, it must lead to an increase of the dosage. If serum concentrations fall under therapeutic range, epileptic drugs must be increased even if the patients have no seizures. Moreover, a dose of 5 mg of folic acid should be taken during the first three months of pregnancy.

Diazepam intravenously it is known to be the drug of choice to stop seizures during labor and delivery. Phenytoin used during labour is controversial, because it inhibits the myometric contractions and prolongs labour.

Neonates should be administered 1 mg/kg of vitamin K, having in the view the deficiency of coagulation factors II, VII, IX, X which have been caused by the deficiency of vitamin K, on its turn, induced by the carbamazepine, phenobarbitone, phenytoin or pirimidone[9].

The combinations between valproic acid and carbamazepine and between carbamazepine and lamotrigine have proven to cause a large increase of carbamazepine epoxide. Epoxide is a product resulting from the metabolism of carbamazepine, phenytoin and phenobarbitone that can bind proteins and cause mutagenicity[4].

Levetiracetam

A study conducted on 671 pregnancies, confirms a low risk for major congenital malformations associated with levetiracetam monotheraphy. The risk is higher if levetiracetam is a part of a polytheraphy. Levetiracetam is a better therapeutically option than valproic acid[9].

Topiramat

In a study on 207 pregnancies, topiramat was associated with 11 cases of oral clefts, 2 of hypospadias and 16 had major congenital malformation that raised some concerns. The risk reported for lamotrigine is very low overall but may be increased for oral clefts especially if it is administered in the first trimester, although a different approach suggests no increased risk.

Gabapentin

A premature infant was born with microcephaly, deformity of the face with cyclopia, missing nose and microstomia, hypoplasia of the suprarenal gland on gabapentin[8].

Vigabatrin

There have been described the following malformations in eight neonates linked to vigabatrin add-on therapy: missing diaphragm, spina bifida, microcephaly, hypospa-

dias, dysplasia of the hip, undescended testicles, clubfoot, cleft palate, and ventricle septum defect[8].

Phenytoin

Phenytoin is an enzyme inductor and it may lead to an increased failure rate of contraception, also implying vitamin K deficiency. The concentrations of phenytoin rise during the last trimester of pregnancy. Premature babies have a high concentration of serum phenytoin. The concentration in mothers' milk is 20% of the mothers' serum concentrations. Prenatal exposure can cause hypoplasia of distal phalanges of fingers[10].

Valproic acid

It is very clear that the teratogen risk for valproate is higher than for topiramate and all other AEDs reported, so far. The risk of valproate was high as 38.5% for doses greater than 1.100 mg per day in the Australian registry. Furthermore, valproate is associated with neural tube defects, which generally are more debilitating than cleft lip and palate associated with other AEDs and risk of spina bifida of 12.3%. Valproate stands out as the one AED that should be avoided during pregnancy, when alternatives are available.

Carbamazepine

Carbamazepine has been viewed by many as the AED of choice during pregnancy, because it has not been associated with cesarean section, preeclampsia, or premature delivery. A 2008 review concluded that carbamazepine monotherapy has one of the lowest risks of teratogenicity among antiepileptic treatments. Risk of all major congenital malformations was 3.3% with first-trimester carbamazepine mono-therapy exposure, while spina bifida was significantly associated with exposure to carbamazepine mono-therapy compared with no AED exposure. There was no significant association between exposure to carbamazepine mono-therapy and total anomalous pulmonary venous return, cleft lip with or without cleft palate, diaphragmatic hernia, or hypospadias. Carbamazepine exposure does not significantly decrease average fluency and originality and core language scores[11].

Lamotrigine

Prescribing of carbamazepine and sodium valproate have declined since 1994 despite having been the most commonly prescribed AEDs in pregnancy up to 2004.

Lamotrigine has been the most popular AED prescribed in pregnancy since 2004. Recent evidence suggests no greater risk of major cardiac malformations is associated with lamotrigine when compared to untreated pregnancies in women with epilepsy, but no formal guidance for the safety of lamotrigine has been realeased. However, one study does report an increased risk of isolated cleft palate/lip in lamotrigine exposed babies compared to the general population and the British National Formulary states that lamotrigine is associated with increased teratogenicity[12]. There was a trend toward a higher risk for recurrent malformations in pregnancies exposed to valproate and topiramate. Recurrent risks were also higher for pregnancies exposed to polytherapy regimens and for those whose dose of antiepileptic drug treatment has been increased after the first pregnancy[13].

The new epileptic drugs, lacosamide, eslicarbazepine acetate and retigabine (aka ezogabine), have become commercially available in Europe, but there is still a need of studies regarding the safety profile and effects on pregnancy.

Unfortunately, epilepsy and pregnancy represent a vulnerable topic for doctors to deal with it. Caught between teratogenity and risks of having new seizures, therapy for woman with a pregnancy demands the right balance that should generate at the end of a pregnancy a perfect ending: a seizure free mother with a healthy baby. In this moment, hope for the best therapy involves the new epileptic drugs, that still needs a lot of studies aiming to certify their safety profile.

From the old generation, carbamazepine will have its glory again, following several studies which have registered the lowest risks of teratogenicity among antiepileptic treatments. For the time being, it seems that lamotrigine and levetiracetam are the best options to use.

Future remarks

The present review present the major problems and therapeutically approaches concerning women with epilepsy, and it targets to facilitate the doctors' decisions when dealing with these problems, backing them in answering to the crucial question: 'What is the best choice?' ■

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