Epilepsy on high-risk pregnancy and perinatal outcomes

Epilepsia na gestação de alto risco e desfechos perinatais

Embarazo de alto riesgo y resultados perinatales

RESUMO

Objetivo: Análisar os resultados perinatais de gestantes com epilepsia como condição clínica pré-existente. Método: Trata-se de um estudo epidemiológico, observacional e retrospectivo, com abordagem quantitativa. A população foi constituída a partir da pesquisa de todos os prontuários, relatórios e cartão das gestantes atendidas e classificadas como alto risco com Condição Clínica Pré-Existente de Epilepsia e atendidas no ambulatório de alto risco referência da 15ª Regional de Saúde, localizado na cidade de Maringá/PR. Resultados: Observou-se que não houve nenhuma associação significativa entre epilepsia como condição clínica pré-existente e os resultados perinatais. Conclusão: Apesar de a gestação associada a epilepsia ser considerada de alto risco, o acompanhamento adequado em ambulatório especializado em pré-natal de alto risco e Unidade Básica de Saúde durante o pré-natal contribui significativamente para diminuir a taxa de complicações obstétricas, maternas e fetais.

DESCRITORES: Epilepsia;Cuidado pré-natal; Gravidez de alto risco.

ABSTRACT

Objective: To analyze the perinatal outcomes of pregnant women with epilepsy as a pre-existing clinical condition. Method: This is an epidemiological, observational and retrospective study with a quantitative approach. The population was constituted from the research of all medical records, reports and cards of pregnant women attended and classified as high risk with Pre-Existing Clinical Condition of Epilepsy and attended at the high risk reference clinic of the 15th Regional Health, located in the city of Maringá/PR. Results: It was observed that there was no significant association between epilepsy as a pre-existing clinical condition and perinatal outcomes. Conclusion: Although pregnancy associated with epilepsy is considered high risk, adequate follow-up in an outpatient clinic specializing in high-risk prenatal care and the Basic Health Unit during prenatal care significantly contributes to reducing the rate of obstetric, maternal and fetal.

DESCRIPTORS: Epilepsy; Prenatal care; High-risk pregnancy.

RESUMEN

Objetivo: Analizar los resultados perinatales de gestantes con epilepsia como condición clínica preexistente. Método: Se trata de un estudio epidemiológico, observacional y retrospectivo con enfoque cuantitativo. La población se constituyó a partir de la investigación de todas las historias clínicas, informes y cartillas de gestantes atendidas y clasificadas como de alto riesgo con Condición Clínica Preexistente de Epilepsia y atendidas en la clínica de referencia de alto riesgo de la XV Regional de Salud, ubicada en la ciudad. de Maringá / PR. Resultados: Se observó que no hubo asociación significativa entre la epilepsia como condición clínica preexistente y los resultados perinatales. Conclusión: Si bien el embarazo asociado a la epilepsia se considera de alto riesgo, el seguimiento adecuado en una consulta externa especializada en atención prenatal de alto riesgo y la Unidad Básica de Salud durante la atención prenatal contribuye significativamente a reducir la tasa de obstetricia, materna y fetal.

DESCRIPTORES: Epilepsia; Atenciónprenatal; Embarazo de alto riesgo.

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INTRODUÇÃO

Epilepsy is a chronic neurological condition characterized by seizures caused by abnormal and self-limited hypersynchronous electrical discharges, in a recurrent, unprovoked and unpredictable manner, affecting about 40 million people worldwide. [1] The prevalence is usually higher in the elderly, children and men, and most female patients are in the reproductive phase. [2] There are different presentations of epilepsy, which influence the course of treatment, prediction of new seizures, recognition of precipitating factors and prognosis. [3] The classification of epilepsy is divided into three levels and has a dynamic character. A priori, it is important to identify the type of epileptic seizure, based on the assumption that the responsible physician has already diagnosed epilepsy (it does not take into account the differentiation of epileptic and non-epileptic events); therefore, seizures can be of focal, generalized, or unknown onset. The second step involves knowing the type of epilepsy: focal (perceptive or dysperceptive, motor and non-motor seizures and even focal seizures that evolve to bilateral tonic-clonic), generalized (absence seizures, myoclonic, atonic, tonic and tonic-clonic), combined (Dravet and Lennox-Gastaut syndromes) or idiopathic. At the third level, the diagnosis of an epileptic syndrome is taken into account, that is, a set of factors such as electroencephalogram, imaging tests, crisis types, precipitating and triggering factors and fluctuation, as well as other clinical signs and symptoms such as intellectual and psychiatric dysfunction. [3]

When associated with pregnancy, epilepsy poses risks for both the mother (gestational hypertension and preeclampsia) and the fetus (mainly due to the teratogenic potential of most antiepileptic drugs). [2] Studies to date on the outcomes of epilepsy during pregnancy are conflicting, especially due to methodological flaws. There is huge variation between the number of participants, the location where the research was applied and particular and/or psychosocial factors (such as refractoriness to treatment or non-adherence to drugs due to adverse effects). However, there are significant rates of severe fetal malformations (structural abnormalities related to the midline and neural tube closure, sometimes incompatible with extrauterine life) and mild (less affecting quality of life). The most common complications include cardiac malformations, cleft palate and spina bifida. [2]

Focal seizures that do not progress to the bilateral tonic-clonic form do not usually directly impact the fetus, although there are some reports that, during focal seizures with loss of consciousness, this situation causes fetal stress and consequent deceleration of the heartbeat for a few minutes. [4] On the other hand, generalized tonic-clonic seizures (including those of focal onset) are associated with hypoxia and lactic acidosis, which can affect the fetus through the placenta and lead to asphyxia. They can also cause falls that result in uterine trauma, subsequently harming the fetus.

Most pregnancies are unplanned; thus, it is imperative to guide the epileptic patient about contraceptive methods from the first consultation, preferably before she starts her sexual life. This is because antiepileptics are metabolized by the same cytochrome that processes reproductive hormones. Thus, there is a pharmacokinetic interaction that leads both to the failure of the oral hormonal contraceptive and to the decrease in the effectiveness of the drug that should treat epilepsy. [2]

Furthermore, it is essential that the patient, upon discovering the pregnancy, does not suspend the use of antiepileptic drugs, as stable/under control epilepsy in the year before conception is an important predictor of the pattern of seizures during pregnancy. It is ne-

cessary for the patient to consult her responsible physician to decide whether to change the dose or change the class or medication. It is known that most antiepileptic drugs have some teratogenicity, and thus the effects on the fetus are dose-dependent; the least tolerated drug in this regard is valproate, 5 which has been gradually replaced by safer formulations (such as levetiracetam and brivaracetam). 6 Researchers still disagree about the improvement or worsening of the pattern of crises with monotherapy, polytherapy or no medication and the withdrawal, addition or substitution of the drug of choice, so the conduct must be personalized and discussed between doctor and patient. [3]

Treatment control must be optimized to achieve favorable clinical stability for the mother-infant binomial. [2] Video and electroencephalogram exams should preferably be performed in a hospital environment and by a qualified team. [1] Outpatient follow-up can also be done regarding the frequency and type of seizures. Moreover, pregnancy increases the clearance of some drugs and presents volume expansion and hormonal fluctuations, which directly affect the plasma concentration of antiepileptic drugs; the goal is that this concentration does not fall by more than 35% from the pre-conception value. [2] New therapies are being developed that have proven to be effective, such as transcranial magnetic stimulation, [7] however, there is still no proof of its effectiveness in a larger sample of patients. Finally, it is necessary to supplement the pregnant woman with folic acid, a B-complex vitamin related to the correct closing of the neural tube (which guarantees better future cognitive development). Epileptic patients should receive a dose about ten times that of the general population. [8]

Therefore, even though epilepsy is the most treated neurological condition during pregnancy, there is still a considerable gap in knowledge about this disease. Some countries, like Thailand, [9] did not even present data on this disease, while others (usually economically stable and first world) have more numerous studies and for a longer time. Even in Brazil, research is still scarce, especially in specific cases (such as refractoriness).[10] In view of the above, it is important to carry out more studies on this disease that affects so many women, especially of childbearing age.

> **Quando associada à gestação, a epilepsia apresenta riscos tanto para a mãe (hipertensão gestacional e pré-eclâmpsia) quanto para o feto (principalmente devido ao potencial teratogênico da maioria das drogas antiepilépticas)[2].**

Therefore, the aim of this study was to analyze the perinatal outcomes of pregnant women with epilepsy as a Pre-Existing Clinical Condition.

METHODS

This is an epidemiological, observational and retrospective study with a quantitative approach.

The population was constituted from the research of all medical records, reports and cards of pregnant women attended and classified as high risk with Pre-Existing Clinical Condition (CCPE) of Epilepsy and attended at the high-risk outpatient referral center of the 15th Regional Health, located in the city of Maringá/PR.

Data were abstracted from a database called High-Risk Pregnancy (GAR) from the thesis entitled "Factors associated with maternal, fetal and neonatal outcomes in high-risk pregnancies". The research has already been submitted to the Research Ethics Committee of the State University of Maringá, as recommended in the Health Research Standards of the National Health Council, resolution No. 466 of December [12], 2012 and approved according to opinion No. 2.287.476.

The independent variable was epilepsy as CCPE. The outcome variables were: prematurity, low birth weight, Apgar<7 at the 1st and 5th minutes, fetal death, neonatal death and cesarean delivery.

The inclusion criteria will be: pregnant women classified with epilepsy as CCPE for care at the high-risk outpatient clinic who gave birth at the referral hospital. Pregnant women who gave birth outside the referral establishment to the risk outpatient clinic and who did not present epilepsy as a risk will be excluded from the study.

RESULTS

Of the 3,448 pregnant women seen at the high-risk outpatient clinic, 70 (2.03%) were at risk for epilepsy, of which the predominant characteristics were: age between 20 and 34 years (78.6%), brown skin (50.0%) ; live with a partner (55.7%); less than 8 years of schooling (54.3%); and unpaid work (61.4%), as shown in table 1.

Table 2 presents epilepsy as a Pre-

-Existing Clinical Condition and its statistical association with perinatal outcomes, however, it was observed that there was no significant association.

DISCUSSION

Epilepsy is a non-communicable chronic neurological disease characterized by alterations in synaptic transmission and in neuronal excitability. The worldwide prevalence is relatively low (0.5%) [11], but about 40% of women with epilepsy are of childbearing age. 9 In this study, the incidence of epilepsy among pregnant women was higher than expected according to the literature, possibly due to the sample size or the reference outpatient care in high-risk prenatal care.

The field of study regarding epilepsy in pregnancy is still precarious. Few studies have been carried out on maternal exposure to antiepileptic drugs, associating this fact with perinatal outcomes. Most studies are observational, in addition to having a small sample of patients and resulting in conflicting information. [12, 13]

Epilepsy is strongly associated in the literature with unfavorable perinatal outcomes with several complications, both fetal and maternal, from fetal growth restriction, low birth weight, prematurity and delays in cognitive and motor development to bleeding during and after delivery, fetal and infant mortality and increased risk of preeclampsia. [9, 12, 14] Children of epileptic mothers also suffer from major and minor congenital malformations, neonatal infections, asphyxia-related complications, neonatal hypoglycemia, breathing difficulties, and Apgar changes at the 5th minute. [11] Other situations found were an increase in the rate of perinatal infections, abrupt detachment and placental infarction. [11, 14] Some studies followed the children of epileptic women after birth, also pointing to cognitive sequelae with regard to motor, language and socio-personal

Table 1 – Sociodemographic profile of pregnant women stratified as high risk with and without epilepsy as a pre-existing clinical condition. Maringá, PR – Brazil, 2021.

Variables	Without epilepsy		With epilepsy		p
	n	%	n	%	
Age					**0,09**
10 to 19	270	97,5	7	2,5	
20 to 34	2353	97,7	55	2,3	
35 and up	755	99,0	8	1,0	
Color					**0,16**
White	1948	98,3	34	1,7	
Black	147	99,3	01	0,7	
Brown	1277	97,3	35	2,7	
Yellow	6	100,0	-	-	
Marital status					**0,42**
Lives with her partner	1942	98,0	39	2,0	
Doesn't live with her partner	1436	97,9	31	2,1	
Education					0,19
< 8 years	1636	97,7	38	2,3	
≥ 8 years	1742	98,2	32	1,8	
Paid work					**0,001**
Yes	1933	98,6	27	1,4	
No	1445	97,1	43	2,9	

Source: Research data, 2021.

Table 2 – Association between epilepsy and perinatal outcomes of high-risk pregnancy, Maringá, PR – Brazil, 2021.

Perinatal Results	Epilepsy (n=70)		
	n	%	p
Prematurity (<37 weeks)	20	28,6	0,52
Low birth weight (<2,500 g)	16	22,9	0,55
Apgar 1st min. (<7)	13	18,6	0,85
Apgar 5th min. (<7)	05	7,1	0,66
Fetal death	-	-	-
Infant death	-	-	-
Cesarean	51	72,9	0,99

Source: Research data, 2021.

skills. [13] The present research, in turn, showed opposite results, with low rates of maternal-fetal complications associated with epilepsy, possibly due to the follow-up at the high-risk outpatient clinic with specialized consultations and comprehensive care for pregnant women, minimizing risks and providing quality prenatal care.

As for the time of delivery, it is also known that in women with epilepsy there is a greater chance of complications, but this is not explained in isolation by epilepsy. Seizures during childbirth are rare (only 2% of pregnant women with epilepsy), and the pregnant woman should bring her own medicines from home and take them normally. [15]

In these patients, the need for labor induction and elective and emergency cesarean section are more common (data corroborated by this study, in which more than 70% of epileptic pregnant women had a cesarean delivery), [11] which in the vast majority of cases is due to uncontrolled seizures, poor progress in labor, fetal presentation, placental issues, premature rupture of ovular membranes, and failure of induction (ie, many of these factors not closely linked to epilepsy or antiepileptic drug use). [13] Several studies indicate that these results have a multifactorial influence, involving ethnic, geographic and socioeconomic issues, in addition to comorbidities and treatment characteristics (drug of choice, dose and association scheme). [9, 12]

Another issue involved is breastfeeding, suspended by many mothers due to the fear of the baby ingesting antiepileptic drugs through milk, which is still uncertain in the medical field; therefore, due to a combination of factors (discontinued breastfeeding, lack of physical and cognitive stimulation, and socioeconomic factors), children of epileptic mothers often show lower growth and weight gain in postpartum follow-up visits. [12] It was also found that pregnant women better informed about their condition had lower rates of anxiety regarding breastfeeding and congenital malformations due to the use of antiepileptics. [14]

The consensus regarding the risk of unfavorable obstetric outcomes in pregnant women with epilepsy has changed over time. A priori, these were associated with the use of drugs with significant teratogenic potential, such as sodium valproate and topiramate (especially in polytherapy). [13, 16] Today, however, treatment regimens have been changing (regarding both the dose and the choice of drug, in addition to the association with prenatal folic acid supplementation above the recommended levels in usual risk prenatal care) [12], and it is already speculated that these perinatal effects are not only due to the medications used to control the disease, but also to the pathophysiological processes of epilepsy itself. [9, 11, 12, 17]

Focal seizures were associated with a drop in fetal heart rate, especially at the time of delivery, but the babies had a favorable development later on. Generalized crises, on the other hand, are more worrisome, since they can lead to trauma, fluid and electrolyte imbalance, blood pressure changes and a drop in oxygenation. Thus, the following have been reported in generalized crises: prenatal hypoxia and ischemia (with structural and functional changes in areas of the brain responsible for fear and anxiety), areas of placental infarction and intrauterine intracranial hemorrhage with fetal death. [15]

Thus, it is necessary to evaluate the pros and cons of discontinuing the medication before or during pregnancy, since seizures can be considered more harmful than newer and safer antiepileptic drugs (such as carbamazepine, lamotrigine and levetiracetam). [11]

Some authors have also observed that unfavorable perinatal outcomes, especially intrauterine growth restriction and low birth weight, are linked not only to the use of antiepileptic drugs, but also to genetic and environmental factors such as comorbidities such as arterial hypertension, autoimmune disorders, and valvular heart disease. Therefore, there is no prominent need to discontinue their use. [13]

Furthermore, epileptic patients who intend to become pregnant should undergo multidisciplinary follow-up and reassess their treatment regimen, that is, it is imperative that the pregnancy be planned. This is because, in addition to fetal and obstetric complications, women with active epilepsy are at greater risk of preeclampsia, maternal infection, induction of labor, abrupt placental abruption and emergency and elective cesarean section. [11]

Furthermore, pregnancy is accompanied by several physiological processes that can alter the pharmacokinetics of many drugs, such as the volume of distribution and elimination and the plasma concentration of antiepileptics; therefore, a dose adjustment is also necessary to control the symptoms of the disease during pregnancy. [11, 12]

In short, the key is to avoid the use of sodium valproate (highly associated with congenital malformations) and to use the lowest effective dose of the medication of choice. [13] It is also worth noting that most of these unfavorable events predominate in the Americas and Southeast Asia, revealing how the risk of pregnancy in women with epilepsy is linked to the availability of resources and education both for the patient and the multidisciplinary team. [18]

Although epilepsy has not always been perceived as a high-risk aggravating factor in pregnancy, the management of pregnant women with epilepsy is not exactly simple; in addition, the care of these patients is usually fragmented and lacking in resources. [12, 13] In this research, it was illustrated that, in an adequate setting of specialized follow-up in high-risk prenatal care, epilepsy does not present significant risks to maternal-fetal well-

-being, with rates of perinatal complications statistically insignificant.

The main challenges involved in the overall process are the limited monitoring of the patient, the lack of resources to monitor the drugs used and the level of patient information, evidenced by the number of unplanned pregnancies that are found among these patients. Fundamental for the success of pregnancy, therefore, is the information and education of the pregnant woman, whether about the characteristics of the disease or regarding the treatment and the implications and risks of both on the baby and the pregnancy. [12, 13, 19] It has been shown that patients with a good relationship with the doctor (especially the neurologist) showed greater emotional stability, which reiterates the importance of a good support system for pregnant women with epilepsy.*

CONCLUSION

This epidemiological study explored perinatal outcomes in pregnant women with epilepsy as a pre-existing medical condition. The results demonstrate that, although pregnancy associated with epilepsy is considered high risk, adequate follow-up in a specialized outpatient clinic and UBS during prenatal care significantly contributes to reducing the rate of obstetric, maternal and fetal complications. Some variables, such as prematurity, low birth weight, Apgar less than 7 at the 1st and 5th minutes and cesarean section, were incidents in pregnant women with epilepsy, but did not show a significant association with the disease. Our study demonstrates, therefore, that adequate prenatal management of epileptic pregnant women is extremely important, contributing to better perinatal outcomes and outcomes.

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