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The use and non-use of medications during pregnancy: potential risk factors for the development of congenital malformations

O uso e o não uso de medicamentos na gravidez: potenciais fatores de risco para o desenvolvimento de malformações congênitas

El uso y no uso de medicamentos durante el embarazo: potenciales factores de riesgo para el desarrollo de malformaciones congénitas

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ABSTRACT

Objective: To know the behavior of women in the state of Roraima regarding the use of medications during pregnancy. **Methods:** Survey using an epidemiological form. **Results:** Of the total of 158 participants, 37.3% bear children with congenital malformations and 62.7% did not. The mean age (p=0.0380) together with low family income (p=0.0259) between the groups was statistically significant, with women aged between 13 and 25 years old (p=0.0006) are at greater risk of having children with congenital defects. Furthermore, the lack of maternal compliance to drug treatment (p=0.0260; OR: 2.727; CI: 1.156-6.434) was also associated with the development of these abnormalities. In addition, the use of analgesics (p=0.0577; OR: 3.725; CI: 1.070-12.975) and antibiotics (p=0.0588; OR: 2.259; CI: 1.009-5.057) before and during the gestational period, seems to favor the appearance of congenital malformations. **Conclusion:** Women in the age group of 13 to 25 years old, with income less than or equal to the minimum wage and who do not use medications prescribed during pregnancy, are associated to the development of children with congenital malformations. In addition, the use of analgesics and antibiotics before and during the gestational period seems to favor the appearance of these abnormalities.

Keywords: Pregnant Women, Drug Compliance, Teratogens, Congenital Abnormalities, Drug-Induced Abnormalities.

RESUMO

Objetivo: Conhecer o comportamento das mulheres do estado de Roraima em relação ao uso de medicamentos durante a gestação. **Métodos:** Inquérito por meio de ficha epidemiológica. **Resultados:** Do total de 158 participantes, 37,3% gestaram crianças com malformações congênitas e 62,7% não. A média de idade (p=0,0380) juntamente com a renda familiar baixa (p=0,0259) entre os grupos foi estatisticamente significante, sendo que as mulheres na faixa etária de 13 a 25 anos (p=0,0006) possuem maior risco de

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apresentarem filhos com defeitos congênitos. Além do mais, a ausência de adesão materna ao tratamento medicamentoso (p=0,0260; OR: 2,727; IC: 1,156-6,434) também se associou ao desenvolvimento dessas anormalidades. No mais, o uso de analgésicos (p=0,0577; OR: 3,725; IC: 1,070-12,975) e antibióticos (p=0,0588; OR: 2,259; IC: 1,009-5,057) antes e durante o período gestacional, parece favorecer o aparecimento das malformações congênitas. **Conclusão:** Mulheres na faixa-etária de 13 a 25 anos de idade, com renda inferior ou igual a um salário-mínimo e que não fazem o uso de medicamentos prescritos durante a gestação, se associam ao desenvolvimento de crianças com malformações congênitas. Além disso, a utilização de analgésicos e antibióticos antes e durante o período gestacional parece favorecer o aparecimento dessas anormalidades.

Palavras-chave: Gestantes, Adesão à Medicação, Teratógenos, Anormalidades Congênitas, Anormalidades Induzidas por Medicamentos.

RESUMEN

Objetivo: Conocer el comportamiento de las mujeres del estado de Roraima en relación al uso de medicamentos durante el embarazo. **Métodos:** Encuesta mediante ficha epidemiológica. **Resultados:** Del total de 158 participantes, 37,3% dieron a luz niños con malformaciones congénitas y 62,7% no. La edad media (p=0,0380) junto con la renta familiar baja (p=0,0259) entre los grupos fue estadísticamente significativa, siendo las mujeres de 13 a 25 años (p=0,0006) las que tenían mayor riesgo de tener hijos con anomalías congénitas. Además, la falta de adherencia materna al tratamiento farmacológico (p=0,0260; OR: 2,727; IC: 1,156-6,434) también se asoció al desarrollo de estas anomalías. Además, el uso de analgésicos (p=0,0577; OR: 3,725; IC: 1,070-12,975) y antibióticos (p=0,0588; OR: 2,259; IC: 1,009-5,057) antes y durante el período gestacional parece favorecer la aparición de malformaciones congénitas. **Conclusión:** Las mujeres de 13 a 25 años, con ingresos inferiores o iguales a un salario mínimo y que no utilizan medicamentos prescritos durante el embarazo, están asociadas al desarrollo de niños con malformaciones congénitas. Además, el uso de analgésicos y antibióticos antes y durante el período gestacional parece favorecer la aparición de estas anomalías.

Palabras clave: Mujeres Embarazadas, Adherencia a la Medicación, Teratógenos, Anomalías Congénitas, Anomalías Inducidas por Medicamentos.

INTRODUCTION

Malformations are defined as congenital anomalies characterized by changes in the development of an organ or system. Among the causal agents are genetic, multifactorial and environmental aspects, the latter including teratogens. It has an incidence of 3 to 4% of live births, being the fourth cause of neonatal mortality worldwide, with 295,000 deaths reported annually (VERMA RP, 2021).

Prenatal care is essential as a public health policy of the Brazilian Unified Health System (Sistema Único de Saúde, SUS), with remarkable results in reducing maternal and infant morbidity and mortality (VIELLAS EF, et al., 2014; TOMASI E, et al., 2017).

Multi-professional performance since the periconceptional period may be able to positively influence epigenetic expression and reduce the occurrence of chronic diseases or congenital malformations in the fetus (ATRASH HK, et al., 2006; NOGUEIRA-DE-ALMEIDA CA, et al., 2019; FLEMING TP, et al., 2021). Such accomplishments can be achieved through strategies and advice regarding measures to be adopted or avoided during pregnancy (JOHNSON K, et al., 2006).

Among the strategies adopted worldwide, vitamin and microelement supplementation, such as folic acid and ferrous sulfate, stands out (JOHNSON K, et al., 2006; MASHUDA F, et al., 2014; BRANNON PM e TAYLOR CL, 2017; MEANS RT, 2020).

It is well known that the use of folic acid in the periconceptional period and during the first trimester of pregnancy reduces defects related to neural tube closure, cardiac and urinary anomalies, cleft lip, or palate etc. (MASHUDA F, et al., 2014; WILSON RD, et al., 2015; MEDAWAR G, et al., 2019).

Thus, the non-use of these medications by pregnant women can lead to the development of children with congenital malformations (GREEN NS, 2002; NORDENG H, et al., 2010; MASHUDA F, et al., 2014; OBEID R, et al., 2019). In addition to vitamins and nutritional supplements, other drugs are frequently used by pregnant women, including analgesics and antimicrobials, which are routinely prescribed by obstetricians or acquired through the habit of self-medication (CARMO TA e NITRINI SMOO, 2004; CABRAL RD, et al., 2011; WANDERLEY HYC e ARTIGALÁS OAP, 2011; PRICE HR e COLLIER AC, 2017; SILVA LKP e MARQUES AEF, 2019).

These medications are usually considered safe, however, depending on the dosage, the period in which it is administered and the time of use, it may have a teratogenic action and thus contribute to the appearance of congenital abnormalities (CABRAL RD, et al., 2011; WANDERLEY HYC e ARTIGALÁS OAP, 2011; SNIJDER CA, et al., 2012; ANDERSEN JT, et al., 2013).

A teratogenic agent is defined as any substance that, being present during embryonic or fetal life, produces a defect in the constitution of some organ or set of organs (FONTOURA FC e CARDOSO MVLML, 2014). The teratogenic effect of drugs has been recognized since 1950, when around 10,000 children were born with congenital changes resulting from the use of thalidomide during pregnancy (VARGESSON N, 2015).

However, although different drug-associated anomalies have been documented since then, many of the mechanisms responsible for the impairment in human development are still not known (MOORE KL, et al., 2016).

The importance of these issues for pregnant women, women of childbearing age and health professionals who provide prenatal care is unquestionable. Even so, the subject is poorly explored in Roraima, which aroused the interest of researchers in knowing the behavior of women in the state of Roraima on the medications use during pregnancy.

METHODS

Ethical aspects

The research project that underlies this study, was approved by the Research Ethics Committee of the *Universidade Federal de Roraima* (CAAE: 70051417.6.0000.5302 Opinion 2,366,062 dated 11/06/2017). Each participant signed an Informed Consent Form after receiving all information about the objectives and procedures to be conducted in the research.

Casuistry

From November 2017 to November 2019, a total of 158 consecutive women was selected, who were attended at the Ambulatory of the Women's Health Reference Center (*Centro de Referência da Saúde da Mulher*, CRSM) and at the *Hospital Materno Infantil Nossa Senhora de Nazareth* (HMINSN), Boa Vista, state of Roraima, Brazil, both provided by the public health system.

Two groups were formed, one of women who have children with a clinical diagnosis of congenital malformation (n=59) and another of women who have children without congenital malformation (n=99), with the group of women who did not have children with congenital malformation, were selected only at the CRSM, during care at this service due to other conditions, such as diabetes, arterial hypertension, obesity, myoma, thrombophilia, among other diseases that can affect pregnancy.

The exclusion criteria adopted were age younger than 12 years and older than 45 years of age, women who declared themselves Indigenous, patients with human immunodeficiency syndrome and participants who did not agree to sign the consent or assent form.

Epidemiological data

An epidemiological data sheet related to the development of congenital malformations and the use of medications was completed, including social, environmental, economic, and housing factors.

Diagnosis of congenital malformation

Confirmation of the clinical evaluation of patients who have children with congenital malformations was performed at the CRSM by an experienced professional in fetal medicine (CDML), using ultrasound and complementary exams, such as karyotype, when possible. Patients were referred to the fetal medicine ambulatory of the CRSM, after identification of malformations during the performance of obstetric or morphological ultrasounds, conducted both in other sectors of the CRSM and in the Basic Health Units from the state of Roraima. In the HMINSN, the selected women were with their children being treated at the follow-up ambulatory, which is composed of a multidisciplinary team that assists children who need specialized follow-up due to prematurity, among them, those with a clinical diagnosis of readily established congenital malformation.

Statistical analysis

The results were analyzed using Grahpad software, version 3.1. Fisher's exact test, Odds Ratio (OR) and Chi-square were used to compare the independence between the proportions. Mean age values were compared using the t-test. Differences were considered statistically significant when $p \leq 0.05$ and a confidence interval of 95%.

RESULTS AND DISCUSSION

One hundred and fifty-eight women treated at the CRSM and HMINSN ambulatory agreed to participate in this research. Of this total, 59 (37.3%; mean age 27.3; SD=8.1) participants were included in the “Case group” because they had children with a compatible diagnosis of congenital malformation, and 99 (62.7%, mean age 29.8; SD=6.7) participants were included in the “Control group” because they did not have children with this diagnosis (Table 1). It is important to emphasize that the control group was composed of participants diagnosed with a high-risk pregnancy, but without evidence of congenital malformation for the embryo or fetus.

Regarding the mean age between the groups, the analysis found a statistically significant difference (p=0.0380), as shown in Table 1. This result suggests that, in general, the case group was composed mainly of younger women, when compared to the control group.

The result found in Roraima is similar to what Karai A, et al. (2019) observed in Hungary, these researchers observed that children of teenage mothers are at greater risk of presenting congenital malformations, in addition to having lower birth weight and being more likely to be referred for specialized care in neonatal intensive care units. Furthermore, it is noted that in addition to congenital malformations, young mothers are more likely to have perinatal mortality and the risk of having premature children, and prematurity among young mothers is a factor that contributes to the increase in cases of neonatal death in this same group (KANG G, et al., 2015).

Early age is considered to be associated with greater exposure to risk factors, related to the development of congenital malformations, such as teratogenic agents, due to the low level of maternal education, mainly due to early school leaving and inadequate prenatal care, which is characterized by a lower number of consultations and non-compliance with medical conduct, which includes the use of medications (HAN JY, et al., 2005; MALVASI A, et al., 2009; KANG G, et al., 2015).

When distributing the participants between the two groups and stratifying by age group (approximately every 10 years), statistically significant differences were observed between the frequencies of age groups from 13 to 25 years (p=0.0006) and 26 to 36 (p=0.0002). These results suggest that the risk of developing congenital malformation is higher in women aged 13 to 25 years (n=33; 56%) and lower in those aged 26 to

36 years (n=54; 54.4%), which supports the result found for the analysis of the average age in the two groups described above.

In addition, researchers at the Centers for Disease Control and Prevention, located in Atlanta, Georgia, observed a greater number of congenital anomalies among children of mothers in the age group (<20 and ≥40 years old) (GILL SK, et al., 2012), which corroborates the results of this study. Furthermore, advanced maternal age is often related to an increased incidence of fetal chromosomal abnormalities (ZHANG XH, et al., 2017).

Zhang XH, et al. (2017) observed that women over 35 years of age have a four to seven times higher risk of having children with chromosomal alterations compared to women aged between 25 and 29 years. Another statistically significant difference (p=0.0259) found in this study was in comparison between the groups, stratifying the participants according to family income (Table 1). The result suggests that the diagnosis of congenital malformation is more frequent among women included in the case group with income less than or equal to the minimum wage (n=25; 42.4%). On the other hand, the analysis suggests that this diagnosis is not frequent in the control group, with an equivalent stratification of 1.5 to 3.5 minimum wages (n=47; 47.5%).

In the state of Ceará, researchers also observed that mothers of children with congenital abnormalities earned less than 1.5 minimum wage during the time studied (FONTOURA FC e CARDOSO MVLML, 2014). In this same work, Fontoura FC e Cardoso MVLML (2014) reinforce that the greater number of years in school has a direct influence on increasing family income, which contributes to the reduction of cases of congenital malformations, however, this data was not observed in the present study. Furthermore, the researchers argue that the level of education directly reflects quality prenatal care, where a higher level of maternal education provides a better understanding of the need to monitor the pregnancy, so that there is adequate care for the mother and the embryo/fetus, including for those children who present developmental changes.

Researchers analyzed the prevalence of congenital abnormalities at birth in the city of Buenos Aires, Argentina, taking into account socioeconomic factors. Analysis of the results demonstrated that congenital malformations prevail among children born in public hospitals, geographically located in the southern region, compared to those born in private hospitals, located in the northern region.

Furthermore, they emphasize that low socioeconomic status is among the risk factors for the development of congenital malformations, due to young maternal age, inadequate nutrition and greater exposure to teratogens. Furthermore, they reinforce that the low socioeconomic factor is related to the lower detection of these developmental changes due to the lack of prenatal diagnosis and also postnatal detection (BRONBERG R, et al., 2020).

Even finding a significant result between family income, this study identified no statistical difference between the level of education in the case and control groups, even stratifying the participants in the number of years they attended school (1 to 9 years, 10 to 12 years and greater than 12 years), as shown in Table 1. The researchers believe that this lack of association is due to the fact that the sample size in this study is small, since it has already been documented that a higher level of maternal education reflects on an adequate prenatal care and better health care (MARIO DN, et al., 2019), which can reduce cases of birth defects.

The lack of zinc, folic acid and other vitamins in the maternal organism is related to the development of children with malformations, it is well known that a lack of folic acid even before conception is associated with changes in the formation of the neural tube (EMORDI VC e OSIFO DO, 2018).

Congenital malformations are often observed in low- and middle-income countries (HOWSON CP, et al., 2008; WU VK, et al., 2013; SITKIN N, et al., 2015). Howson CP, et al. (2008) state that children who have severe congenital defects die prematurely in low-income countries and those who survive usually live with disabilities directly related or not to their condition.

In addition, families with low income or in extreme poverty have difficulty accessing health care, often due to failures in local public policies, related to the lack of initial recognition of the coverage areas where primary health care operates, to plan and evaluate health actions, which would thus meet the needs of families living in situation of extreme poverty in Brazil (FRANÇA VH, et al., 2016).

Table 1 - Results of statistical analyses between case and control groups regarding mean age, age group, years of schooling and family income.

Variables	Case group		Control group		Total (n=158)	IC 95%	P
	N	%	N	%	OR		
	59	37.3	99	62.7			
Age group							
13-25	33	56.0	27	27.3	3.385	1.718-6.669	0.0006*
26-36	14	23.7	54	54.5	0.2593	0.1264-0.5319	0.0002*
37-above	12	20.3	18	18.2	1.149	0.5089-2.594	0.8344
Mean age	27.3		29.8				
(SD)	8.1		6.7		-	-	0.0380*
Range	15 to 42		13 to 41		-	-	
Years of schooling							
Illiterate	0	0.0	0	0.0	-	-	
1-9	8	13.6	9	9.1	-	-	0.4229
10-12	31	52.5	47	47.5	-	-	
>12	20	33.9	43	43.4	-	-	
Family income (wages)							
≤ 1	25	42.4	22	22.2	-	-	0.0259*
1.5-3.5	22	37.3	47	47.5	-	-	
≥ 4	12	20.3	30	30.3	-	-	

Note: *** p≤0.05. **Source: Cardoso LS, et al., 2024.

Interesting results were also observed when comparing participants who reported not using medication between the case and control groups. As shown in **Table 2**, a statistically significant difference (p=0.0260) was found between the frequency of participants in the case group (n=15; 24.4%) when compared with the frequency of the control group (n=11; 11.1%). This result suggests that the lack of compliance to drug treatment prescribed by the doctor, such as the use of folic acid, during the periconceptional and gestational period, increases the risk of having children with a diagnosis of congenital malformation (GREEN NS, 2002; MASHUDA F, et al., 2014; OBEID R, et al., 2019).

It is well known in scientific circles that adequate folic acid supplementation before and during the gestational period is related to a reduction in the number of cases of congenital defects mainly related to the development of the nervous and cardiac systems (DEAN JH, et al., 2020; WANG D, et al., 2022). In the study by Dong J, et al. (2023), it was observed that starting folic acid supplementation approximately 1.5 months before the fertilization process and maintaining it for 4 months is the ideal option for preventing congenital malformations.

In addition, researchers believe that the non-use of drugs may be related to the young maternal age observed in this study, since younger women may be more likely to non-compliance with medical follow-up. Furthermore, there are reports of some women who failed to comply with the recommended medical treatment, as they feared about the safety on using drugs during pregnancy Nordeng H, et al. (2010), however, this point was not investigated in this study, therefore, further studies will be needed to determine whether this same event occurs among pregnant women in Roraima.

By stratifying the participants of each group in the several types of medication used before and during the gestational period (**Table 2**), this research found borderline results to identify statistically significant differences. It was evidenced that the frequency of analgesics (n=8; 13.5%) and antibiotics (n=16; 27.1%) use is higher in the case group than in the control group.

Table 2 - Results of statistical analyses between the case and control groups regarding compliance, lack of compliance and types of medication used by the participants of this research.

Variables	Case group (n=59)		Control group (n=99)		OR	IC 95%	p
	N	%	N	%			
Reported not using medication	15	25.4	11	11.1	2.727	1.156-6.434	0.0260*
Age group							
15-25	8	53.3	3	27.3	3.048	0.5733-16.200	0.2463
26-36	3	20.0	5	45.4	0.300	0.05291-1.701	0.2183
37-above	4	26.7	3	27.3	0.9697	0.1681-5.595	1.0000
Reported the habit of self-medication	25	42.4	41	41.4	1.040	0.5412-1.999	1.0000
Medications used before and during pregnancy					**OR**	**IC 95%**	**p**
Folic acid	15	25.4	20	20.2	1.347	0.6270-2.892	0.5528
Analgesic	8	13.5	4	4.0	3.725	1.070-12.975	0.0577
Antibiotic	16	27.1	14	14.1	2.259	1.009-5.057	0.0588
Antidepressant	1	1.7	4	4.0	0.4095	0.04465-3.755	0.6514
Antihypertensive	7	11.9	8	8.1	1.531	0.5251-4.466	0.5758
Anti-inflammatory	2	3.4	7	7.1	0.4612	0.09253-2.298	0.4855
Iron	17	28.8	31	31.3	0.8879	0.4384-1.798	0.8584
Vitamins	16	27.1	24	24.2	1.163	0.5573-2.426	0.7084

Note: *** p≤0.05. **Source: Cardoso LS, et al., 2024.

The use of medications other than vitamins or nutritional supplements during the gestational period is common (CARMO TA e NITRINI SMOO, 2004). Analgesics are often prescribed by doctors to treat symptoms such as pain and fever, even by obstetricians to pregnant women, with paracetamol being one of the most used drugs Wanderley HYC e Artigalás OAP (2011), which was also cited more frequently by women participating in this research.

Although in this study no significant results were observed when comparing the case and control groups in relation to the habit of self-medication, it is known that analgesics are easily accessible to any person, as they do not require a medical prescription for their commercialization (WANDERLEY HYC e ARTIGALÁS OAP, 2011).

Snijder CA, et al. (2012) concluded from their research that the use of mild analgesics, especially paracetamol, during the second trimester of pregnancy is associated with an increased risk of congenital cryptorchidism. The researchers observed that the number of women who use painkillers during pregnancy is high, and they use them mainly to combat headaches and muscle pain. Therefore, they emphasized the need for more studies on the topic, so that, if necessary, preventive measures can be adopted.

Antibiotics are also routinely used in obstetric practice. Even though not all classes have teratogenic effects Cabral RD, et al. (2011), it has already been observed that the use of trimethoprim even before conception is associated with the fact that women bear children with congenital malformations (ANDERSEN JT, et al., 2013). Kapapa M, et al. (2020) investigated the risk factors for congenital defects of the abdominal wall.

The researchers found that mothers of children with abdominal wall malformations use more medications, particularly paracetamol. Furthermore, they found an association between mothers who had children with gastroschisis and frequently used antibiotics significantly when compared to other groups. Therefore, they recommend that, to minimize the occurrence of gastroschisis, antibiotics be used sensibly. In other words, the results in border areas of the present study, both for the use of antibiotics and for the use of analgesics are relevant, but it is necessary to increase in casuistry to better elucidate the facts in Roraima.

CONCLUSION

In conclusion, the study demonstrates that women aged between 13 and 25 years old, with income less than or equal to the minimum wage and who do not use drugs prescribed during pregnancy, are associated to the development of children with congenital malformations in the state of Roraima. In addition, the use of analgesics and antibiotics before and during gestational period seems to favor the appearance of these abnormalities. This study began research related to changes in human development in Roraima. The state of Roraima is located in areas of the Brazilian and International Legal Amazon, in the Northern region of Brazil. It is expected that with the dissemination of these results, greater investments in research will be directed to this northern region of Brazil, in addition to reinforcing public health policies on the subject, in the form of health education for the general population, focusing on pregnant women and health professionals. Furthermore, it is believed that new investigations should be carried out, to better elucidate the data found, and also to open up research with women from other ethnicities, such as pregnant indigenous women in the State, since Roraima has the fifth largest indigenous population in the Brazil.

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