Analiza jemanja zdravil, ki se uporabljajo pri zdravljenju hipertenzivnih stanj v nosečnosti

Analysis of the intake of drugs used in hypertensive disorders during pregnancy

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Izvleček

Izhodišča: Povišan krvni tlak in z njim povezana bolezenska stanja zapletejo 6–10 % nosečnosti. Pri zdravljenju se uporabljajo različna zdravila, ki so lahko povezana z nastankom prirojenih razvojnih nepravilnosti. Namen naše raziskave je bil ovrednotiti jemanje zdravil, ki se uporabljajo pri zdravljenju hipertenzivnih stanj (HS) v nosečnosti in ugotoviti njihov vpliv na pojavnost prirojenih razvojnih nepravilnosti.

Metode: V retrospektivno raziskavo smo vključili vse nosečnice, ki so med letoma 2002 in 2006 rodile v Porodnišnici Ljubljana. Uporabili smo podatke iz Nacionalnega perinatalnega informacijskega sistema, hkrati pa pregledali tudi vse porodne zapisnike iz istega obdobja. Za vsako nosečnico smo pridobili podatke o družinskih in osebnih boleznih, o jemanju zdravil ter prirojenih nepravilnostih novorojenčka. Raziskovalno skupino so sestavljale nosečnice, ki so jemale vsaj eno od zdravil, ki se uporabljajo pri zdravljenju povišanega krvnega tlaka v nosečnosti, kontrolno skupino pa nosečnice brez tovrstnega zdravljenja.

Rezultati: V raziskovalni skupini je bilo 708 preiskovank s popolnimi podatki, v kontrolni pa ostalih 26.027 nosečnic. Nosečnice v raziskovalni skupini so imele značilno več dejavnikov tveganja za razvoj HS. V raziskovalni skupini je bilo več novorojenčkov s katero koli prirojeno nepravilnostjo (9,6 %, $p < 0{,}001$). Med posameznimi nepravilnostmi je bilo značilno več prirojenih nepravilnosti centralnega živčevja in obtočil ($p < 0{,}001$).

Zaključki: Novorojenčki nosečnic raziskovalne skupine so imeli več prirojenih razvojnih nepravilnosti. Mnenja o prevladujočem vplivu HS kot osnovne bolezni, njenega zdravljenja ali soodvisnosti obeh dejavnikov na razvoj prirojenih nepravilnosti so deljena. Da bi natančneje ugotovili, kolikšen vpliv imajo opazovana zdravila in kako velik dejavnik predstavljajo HS, pa bi bile potrebne podrobnejše in drugačne raziskave.

Abstract

Background: High blood pressure and associated medical conditions occur in 6–10 % of pregnancies. Different drugs used in hypertensive disorders during pregnancy might be associated with the occurrence of congenital malformations. The purpose of this study was to evaluate the intake of drugs used in the treatment of hypertensive disorders (HD) and establish a possible association between the use of these medications in pregnancy and the occurrence of congenital malformations.

Methods: The retrospective study included all women who delivered between 2002 and 2006 at the Department of Obstetrics and Gynaecology in Ljubljana. For each subject we collected family and personal medical information, data on drug exposure and on neonatal congenital malformations. We acquired data from the National Perinatal Information System and individual labour and delivery records. The research group was composed of women taking at least one of antihypertensive drugs during pregnancy, and the control group consisted of all women without the mentioned therapy.

Results: In the research group, 708 mothers with complete data on the drug intake were compared to 26,027 controls. Women taking the therapy were older, had more often diabetes mellitus, chronic renal diseases, congenital heart defects and more risk factors for HD than women in the control group. An increased number of congenital malformations in newborns was found in women on therapy (9.6 %; $p < 0.001$). Congenital malformations of the cardiovascular system and the central nervous system prevailed ($p < 0.001$).

Conclusions: Newborns of mothers in the research group had more congenital malformations. Opinions whether the main cause for the development of congenital malformations is the underlying HD, its treatment or the mutual effect of both factors are divided. A more detailed study is required in order to accurately determine whether the risk factor is the therapy or the HD itself.

Introduction

Hypertensive disorders (HD) in pregnancy represent a spectrum of conditions complicating approximately 6–10 % of pregnancies, and are associated with increased maternal and fetal mortality and morbidity.[1] In order to reduce these risks, HD during pregnancy are usually carefully supervised and treated.[2] They are part of metabolic syndrome. Although medical treatment might be beneficial to the mother, it carries a potential risk to the fetus from both impaired uteroplacental perfusion and fetal exposure to the medication. Maternal drugs can have a direct toxic or teratogenic effect, defined as a defect or malformation in the development of the embryo or fetus.[3] The critical period for major congenital malformations is first-trimester exposure to teratogens, whereas exposure later in pregnancy is usually associated with minor congenital malformations. However, the information on the teratogenic effect of antihypertensive medication use during pregnancy is limited and contradictory.[4-9] Some authors state that maternal use of any antihypertensive drug during pregnancy is associated with an increased risk for any congenital malformation,[8] whereas some others have found an association only with a particular antihypertensive drug group.[9]

Therefore, the aim of this study was to determine the intake of drugs used in the treatment of HD during pregnancy, specific features of pregnant women taking such therapy, and to establish a possible association between the use of these medications in pregnancy and the occurrence of congenital malformations in newborns.

Methods

This retrospective study was based on the data obtained from the National Perinatal Information System of the Republic of Slovenia (NPISS) and from labour and delivery records. Pregnant women who delivered between 1 January 2002 and 31 December 2006 at the Department of Obstetrics and Gynaecology, University Medical Centre Ljubljana, were included. For each woman we collected family and personal medical information as well as the data on her diseases in pregnancy, use of drugs in pregnancy, and congenital malformations of her newborns.

Our research group consisted of women who were taking at least one drug used in

Table 1: Selected characteristics of women exposed to drugs used in hypertensive disorders during pregnancy (research group) and control group.

Characteristics	Research group	Control group
	Number (%)	Number (%)
Parity		
1*	204 (28.8)	9884 (38.0)
2	259 (36.6)	8668 (33.3)
3	134 (18.9)	4340 (16.7)
4	73 (10.3)	1883 (7.0)
≥ 5	38 (5.4)	1302 (5.0)
Family history		
Twins	52 (7.3)	1765 (6.8)
Congenital malformations	17 (2.4)	515 (2.0)
Hypertension *	278 (39.3)	4642 (17.8)
Diabetes mellitus *	148 (20.9)	4246 (16.3)
Personal history		
Congenital heart defect *	14 (2.0)	291 (1.1)
Chronic renal disease *	15 (2.1)	175 (0.7)
Diabetes mellitus type 1	5 (0.7)	103 (0.4)
Diabetes mellitus type 2 *	6 (0.8)	35 (0.1)
Thyroid diseases	20 (2.8)	598 (2.3)
Smoking	80 (11.3)	2575 (9.9)

** P< 0.05*

Table 2: Number of women (research group) taking drugs used in hypertensive disorders during different periods of pregnancy.

Drugs \ Time of exposure	$1^{st}+2^{nd}+3^{th}$ trimester	$2^{nd}+3^{th}$ trimester	3^{th} trimester	other combinations	Total
Methlydopa	9	31	155	0	195
β-blockers	10	2	5	7	24
Direct vasodilators	3	1	2	1	7
Ca-antagonists	0	0	1	0	1
ACE-inhibitors	0	0	1	4	5
ASA	11	342	12	4	369
Combination of drugs	41	48	9	9	107
Total	74	424	185	25	708

the treatment of HD during pregnancy. The observed medications were categorized into methyldopa, β-receptor antagonists (β-blockers), α-adrenergic antagonists, calcium channel antagonists (Ca-antagonists), direct vasodilatators, angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin receptor antagonists and acetylsalicylic acid 100 mg (ASA). The use of the drugs was analyzed according to their use in the first, second or third trimester of pregnancy. All women with incomplete data on drugs and their intake were excluded. The control group consisted of the women who took none of the drugs stated above. HD in pregnancy was classified according to the International Classification of Diseases (ICD-10).[10] All congenital malformations in newborns were classified according to ICD-10 codes Q00-Q99.

Data analyses were performed using SPSS Windows v15.0 (SPSS Inc., Chichago, Illinois). The χ^2 test for categorical and t-test for numerical variables was used to compare the two groups. The level of statistical significance was $p < 0.05$.

Results

During the five-year period, 764 pregnant women received at least one of the observed drugs during pregnancy; 56 (7.3 %) women were excluded because of incomplete data.

The research group consisted of 708 pregnant women and the control group of 26,027 women with no exposure to observed medications.

Compared with the control group, the mothers in the research group were older (30.7 ± 1.9 vs. 29.6 ± 4.8; $p < 0.001$), had more often a congenital heart defect, chronic renal disease, diabetes mellitus type 2 and had family history of hypertension and diabetes mellitus; they were more likely to be multiparus (Table 1).

In the research group, 445 (62.3 %) women had at least one hypertensive disorder in pregnancy. The most frequent diagnoses were: chronic hypertension (I10) (26.7 %), gestational hypertension without significant proteinuria (O13) (25.7 %), moderate pre-eclampsia (O14.0) (17.8 %), pre-existing hypertensive disorder with superimposed proteinuria (O11) (15.6 %) and severe pre-eclampsia (O14.1) (10.1 %).

Table 3: Congenital malformations identified among newborns according to fetal exposure to observed drugs during pregnancy.

Congenital malforamation	Research group	Control group
	Number (%)	Number (%)
Congenital malformations of the nervous system *	11 (1.6)	205 (0.8)
Congenital malformations of the eye, ear, face and neck	1 (0.1)	65 (0.2)
Congenital malformations of the circulatory system *	21 (3.0)	404 (1.5)
Congenital malformations of the respiratory system	0 (0)	37 (0.1)
Cleft lip and cleft palate	0 (0)	3(0.0)
Other congenital malformations of the digestive system	1 (0.1)	116 (0.4)
Congenital malformations of the genital organs	11 (1.6)	251 (0.9)
Congenital malformations of the urinary system	5 (0.7)	136 (0.5)
Congenital malformations and deformities of the musculoskeletal system	6 (0.8)	247 (0.9)
Other congenital malformations	12 (1.7)	348 (1.3)
Chromosomal abnormalities, not classified elsewhere	0 (0)	15 (0.1)
All malformations *	68 (9.6)	1708 (6.4)

**P< 0.05*

Table 2 summarizes the observed drugs among women in the research group and the time of exposure during pregnancy. The most frequently prescribed drugs were ASA (369/708; 52.1 %), methyldopa (195/708; 27.5 %) and drug combinations (107/708; 15.1 %). Approximately a half of the women used drugs during the second and third trimester (424/708; 59.9 %). ASA in the second and third trimester was the most frequently reported medication (342/708; 48.2 %), followed by methyldopa in the third trimester (155/708; 21.9 %).

Newborns exposed to the observed drugs during pregnancy had more congenital malformations than newborns in the control group (9.6 % vs. 6.4 %, $p < 0.001$) (Table 3). In these newborns significantly more congenital malformations of the nervous system and malformations of the circulatory system were diagnosed. The highest proportion of congenital malformations was observed among newborns of women who received direct vasodilatators, followed by methyldopa and drug combinations (Table 4).

Discussion

The aim of this study was to determine the intake of drugs used in the treatment of HD during pregnancy, and establish a possible association between the use of these medications in pregnancy and the occurrence of congenital malformations in newborns.

Our research group was composed of women who were taking at least one drug used in the treatment of HD during pregnancy. They were different in many ways from women in the control group (Table 1). Higher maternal age in the research group probably reflects the incidence of hypertension in the general population, where the prevalence of hypertension increases with age. There were more multiparous women in the research group. In 25–50 % of multiparous women, who had been suffering from gestational hypertension in the first pregnancy, the disease occurred in subsequent pregnancies; this share was even higher (76 %) if disease occurred in the first pregnancy before the 30th week of gestation.[11] A higher number of multiparous women in the research group may be due to complications and adverse outcomes of previous pre-

Table 4: Congenital malformation according to the observed drugs used during pregnancy.

Drugs \ Congenital malformations	Q 00–07	Q 10–18	Q 20–28	Q 30–34	Q 35–37	Q 38–45	Q 50–56	Q 60–64	Q 65–79	Q 80–89	Q 90–99	No. of malformations/ No. of women with therapy (%)
Methlydopa	3	1	8	0	0	0	7	2	4	9	0	34/195 (17.4)
β-blockers	0	0	0	0	0	0	0	0	0	0	0	0/24 (0)
Direct vasodilatators	0	0	2	0	0	0	0	0	1	0	0	3/7 (42.9)
Ca-antagonists	0	0	0	0	0	0	0	0	0	0	0	0/1 (0)
ACE-inhibitors	0	0	0	0	0	0	0	0	0	0	0	0/5 (0)
ASA	5	0	6	0	0	1	2	2	1	3	0	20/369 (5.4)
Drug combination	3	0	5	0	0	0	2	1	0	0	0	11/107 (10.3)
Total	11	1	21	0	0	1	11	5	6	12	0	68/708 (9.6)

Q00-07: *Congenital malformations of the nervous system;* Q10-18: *Congenital malformations of the eye, ear, face and neck;* Q20-28: *Congenital malformations of the circulatory system;* Q30-34: *Congenital malformations of the respiratory system;* Q35-37: *Cleft lip and cleft palate;* Q38-45: *Other congenital malformations of the digestive system;* Q50-56: *Congenital malformations of genital organs;* Q60-64: *Congenital malformations of the urinary system;* Q65-79: *Congenital malformations and deformations of the musculoskeletal system;* Q80-89: *Other congenital malformations;* Q90-99: *Chromosomal abnormalities, not classified elsewhere.*

gnancies, which are more frequent in pregnant women with high blood pressure.[12,13] Similarly to other studies, personal and family histories of women in our research group revealed more risk factors (diabetes mellitus, chronic renal diseases, congenital heart defect) for the development of arterial hypertension, which means that there was a basic profound disorder present.

In the group of observed drugs we categorized methyldopa, β-blockers, α-adrenergic antagonists, Ca-antagonists, direct vasodilatators, ACE-inhibitors and angiotensin receptor antagonists. Beside typical antihypertensive drugs that directly affect blood pressure reduction, ASA 100 mg was also included, as the use of low-dose ASA reduces the incidence of gestation hypertension in high-risk pregnancies[14] and the incidence of early-onset proteinuric pre-eclampsia and the related likelihood of preterm delivery.[14-15]

A particular congenital malformation is difficult to accurately attribute to a particular drug, if a pregnant woman is taking a number of different substances.[3] Therefore, we separately analyzed women taking one drug and those receiving two or more drugs (drug combination). Acetylsalicylic acid, methyldopa and drug combination were the most commonly reported drugs in our study. According to the recommendations, low-dose ASA is prescribed to a wide range of pregnant women with risk of developing gestational proteinuric hypertension and/or a history of complications due to hypertension in previous pregnancies.[15,16] Methyldopa is the preferred medication for the treatment of HD during pregnancy. It has been used for decades and has a well-defined safety profile.[1,17] Most women in our research group were taking one of the observed drugs in the second and third trimester, when the incidence of HD associated with pregnancy increases.[4] But the combination of several drugs was frequently prescribed during the entire course of pregnancy (Table 2). These were mostly pregnant women with chronic hypertension or women with gestational hypertension, where it was necessary to control blood pressure with polytherapy, or additional dose of ASA because of the risk factors.

We found that fetuses exposed to the observed drugs had significantly more congenital malformations; prevailing were congenital malformations of the nervous system and the circulatory system (Table 3). Despite a very small proportion of pregnant women with diabetes, congenital heart defect or higher average age in our research group (Table 1), these risk factors could not be excluded as

a cause of congenital malformations. Maternal use of antihypertensives in the first trimester is associated with increased risk for any congenital malformations.[8]

Some authors reported a higher incidence of congenital malformations of the circulatory system,[4,5,8] while others observed such an increase only in a certain group of antihypertensive drugs.[9] As greater risk of congenital malformations of the circulatory system is also described in newborns of women with both treated and untreated hypertension, the underlying hypertension might play an etiological role.[4]

We found a higher incidence of congenital malformations of the nervous system. To our knowlede, the association between ACE-inhibitors and congenital malformations of the nervous system was suggested in only one study,[9] based on three cases. Other authors did not relate individual cases of malformations of the nervous system to antihypertensive therapy.[8] Our results require further analysis. The association between high blood pressure itself, antihypertensive therapy and congenital malformations of the nervous system should be assessed separately.

The boundary between the teratogenic action of the maternal disease and the influence of drugs is not clear and is related to the heterogeneity and underlying mechanisms that lead to disease, and genetic characteristics of the mother and fetus. Therefore, diverse patterns of congenital malformations that occur in patients with the same disease or in patients taking the same drugs are being noted.

Methyldopa is a relatively safe drug.[1,17,18] We assume that a large percentage of malformations in our study may be due to an underlying disease (hypertension) or an associated disease of the mother (diabetes melitus), since most women received methyldopa only in the third trimester, which according to the literature is less risky for the development of major congenital malformations.

None of the β-blockers have been associated with teratogenicity.[1] Our results confirm the previous observations.

But seven women received direct vasodilators, of which three delivered a child with congenital malformations. The literature describes only one example that indicates a possible teratogenic effect of prazosin.[19] Due to the small number of subjects, our results could not be reliably attributed to the teratogenic effect of prazosin only, and might not exclude the impact of underlying disease or a random occurrence of congenital malformations in the fetus.

The impact of Ca-antagonists and ACE inhibitors on malformations is difficult to define, since we had only one case of intake for each medication; both children were born without malformations. Although studies do not indicate an increased prevalence of congenital malformations in offspring exposed to Ca-antagonists in utero,[6,20] their use in the first trimester of pregnancy should be dissuaded because of proven teratogenic effect in animals.[19] Taking ACE-inhibitors during the first trimester is associated with a higher incidence of cardiovascular malformations.[4,8,9]

ASA in low doses is a relatively safe drug.[15,18] The number of congenital malformations in women taking ASA does not exceed the incidence in the general population.

In the group of pregnant women taking a combination of several drugs, the incidence of congenital malformations was increased (9.6 %). However, in the case of multiple medication intake, an anomaly cannot be attributed to a single drug or to drugs at all. Using more drugs usually means that the disease itself has advanced.

Conclusion

In our study, the women taking the therapy were older, had more often diabetes mellitus, chronic renal diseases, congenital heart defects and more risk factors for HD than the women without antihypertensive therapy.

Their newborns had more congenital malformations. The results suggest that *in utero* exposure to medications used to treat HD might be associated with newborns' congenital malformation of the central ner-

vous system and the circulatory system. A further study is required in order to accurately determine whether the risk is due to the therapy, the underlying HD itself, or the interdependence of both factors.

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