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Original article

Adverse drug reactions in high-risk pregnant women: A prospective study

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ABSTRACT

Background: Because pregnant women are often excluded from clinical trials, there is still very limited information about the risk and safety of prescription drugs during pregnancy.
Objective: We aimed to determine the prevalence of Adverse Drug Reactions (ADRs) in high-risk pregnant women after hospital admission. A prospective study was carried out in a teaching maternity hospital in Brazil during six months. Causality of ADRs was assessed through the Naranjo Algorithm and Korean Algorithm for ADR Causality Assessment. Severity of ADRs was assessed using Hartwig's Severity Assessment Scale.
Results: The prevalence of ADRs among the 294 inpatients studied was 8.8%. The mean age was 27.14 (±7.5) y.o. Patient's age was related to the presence of ADRs, while the manifestation of these events was not associated with any adverse pregnancy outcome. 75.9% of the ADRs reported in the study were of mild severity and 24.1% were of moderate severity. No ADR was caused by drug-drug interaction; however, a significant increase in blood pressure was observed in all patients using concurrent methyldopa and ferrous sulfate.
Conclusion: Overall, ADRs were not common events among high-risk pregnant women and no adverse pregnancy outcomes following these events were observed.

1. Introduction

Adverse Drug Reactions (ADR) – one of the most frequent complications during hospitalization, reaching up to 30% of inpatients – can be defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function (de Vries et al., 2008; Hakkarainen et al., 2012; Miguel et al., 2012). Consequences of ADRs include drug-related hospital admission, prolongation of hospital stay, increased risk of mortality and health problems that occur after hospitalization (Sultana et al., 2013; Pedrós et al., 2014; Nivya et al., 2015). ADRs previously reported in pregnancy include those associated with fetal disorders (e.g. malformations after use of thalidomide or antiepileptic drugs during pregnancy) and ADRs that affect the mother (e.g. gastrointestinal reactions after the use of antiretroviral drugs or iron preparations) (Dhanani et al., 2012; Wettach et al., 2013; Santini-Oliveira et al., 2014).

Because pregnant women are often excluded from clinical trials, which are the main premarketing methods used to detect and quantify ADRs, information about the safety of medications during pregnancy is limited, and epidemiological studies to assess the prevalence of these events in pregnant women are still needed, especially among patients at high risk for pregnancy complications (van Gelder et al., 2010; Sinclair et al., 2016). On the other hand, the use of prescription drugs is common during pregnancy, ranging from 23% to 96% of pregnant women worldwide (Mitchell et al.,

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2011; Daw et al., 2011; Matsui, 2012) and 90–95% in Brazil (Fonseca et al., 2002; Brum et al., 2011, Osorio-de-Castro et al., 2004). Furthermore, adverse drug reactions are more frequently observed among inpatients compared with outpatients and can be minimized if appropriate precautions - driven by increasing knowledge about the manifestations of these events - are taken by healthcare professionals (Hakkarainen et al., 2012; Alshammari, 2016). This study was designed to determine the prevalence of ADRs in hospitalized patients at high risk antepartum and their associated factors.

2. Materials and methods

A prospective study was carried out in a teaching maternity hospital in Aracaju, Brazil, from August 2012 to January 2015. All pregnant female patients admitted for labor with living fetus and diagnosed as having high-risk pregnancy during the study period were invited to participate in the study. High-risk pregnancy was defined as any pregnancy that threatens the health or life of the mother or her fetus due to a disorder or situation coincidental with or unique to pregnancy (Gray, 2006). Patients who left the ward before 24 h of admission were excluded. All patients were informed of the objective of the study and gave written consent before inclusion in the study, which was approved by the Ethics Committee of the Federal University of Sergipe, Brazil. Those under 18 years were required to have parental consent to participate in the study. The age of consent to sex in Brazil is 18 (16 with parental or guardian consent).

2.1. Data collection

Data were collected by six trained medical students using a pretested questionnaire that was applied to 30 patients who were not included in the final analysis. The medical records of all patients included in the study were reviewed in a daily basis until the end of the follow-up period, in order to update clinical information, focusing on ADR, potential predictive factors and related outcomes: age, previous pregnancies, previous abortions, previous deliveries, gestational age at birth, medication use during hospitalization, diagnosis, patients complaints during hospitalization and adverse clinical findings (e.g. vital signs and complementary diagnosis examinations).

2.2. Identification of ADRs - causality and severity assessments

Adverse drug reactions were identified through the correlation between drug intake and the onset of the ADR. Two clinical pharmacists and an obstetrician physician determined causality assessment using the Naranjo Algorithm and Korean Algorithm for ADR Causality Assessment - version 2.0 (Naranjo et al., 1981; Son et al., 2011). Causality assessment of ADRs obtained with Naranjo criteria was categorized into *definitely* (scores from 9 to 13), *probable* (scores from 5 to 8), *possible* (1 to 4) and *doubtful* (less than 1). The Korean algorithm scores were categorized as follows: *certain* (score greater than 9), *probable/likely* (score from 6 to 8), possible (3–5), *unlikely* (1–2) and *contradictory* (score less than 0). To be considered an Adverse Drug Reaction, the event must be categorized as *probable,* at least in both scales. The identification of drug-drug interactions was based on the database DRUGDEX®, Micromedex base, considering only the interactions clinically manifested. Severity of the reactions was assessed using Hartwig's Severity Assessment Scale – which classifies ADRs into mild, moderate and severe (Hartwig et al., 1992).

2.3. Sample size and statistical analysis

Considering previous prevalence studies in which ADR in pregnant inpatients ranged from 0.3% to 12.1%, as well as absolute accuracy of 5% and confidence interval of 95%, a minimum sample of 162 individuals was determined (Lacroix et al., 2007; Hernández-Hernández et al., 2002). Data analysis was performed using SPSS software, release 12. Statistical analyzes involved descriptive analyzes, chi-square and Kruskal–Wallis test to test the relationship between ADR manifestation and other independent variables (age, diagnosis, previous pregnancies, previous abortions, gestational age at birth, drugs).

3. Results

We selected 308 patients, 14 of whom declined to participate in the study (refusal rate = 4.6%). The age of patients varied from 14 to 48 years, with a mean age of 27.14 (±7.5) years. 44.9% of patients were aged from 20 to 30 years old. All patients had previous pregnancies, 79.6% were admitted during the third trimester of pregnancy, and 31.3% had at least one previous spontaneous abortion. In 98.0% of cases, fetal heart rate on admission was >130 beats/min (Table 1).

3.1. Prescribed drugs

The average number of prescribed drugs per patient was 5.32 (SD 2.13). The most prescribed drugs were scopolamine (72.1%), metamizole (60.9%), betamethasone (56.5%), cefalotin (54.1%), fer-

Table 1
Sociodemographic and pregnancy characteristics.

Characteristic	Patients	
	N	%
Maternal age at delivery (years)		
<20	81	25.5
20–30	132	44.90
30–40	67	22.79
40+	14	4.76
Gestational age		
Non-informed	18	6.12
First trimester	1	0.34
Second trimester	41	13.95
Third trimester	234	79.59
Fetal heart rate (bpm)		
Non-informed	1	0.34
110–120	2	0.68
120–130	2	0.68
130–140	121	41.16
140–150	138	46.94
150–160	30	10.20
Number of previous pregnancies		
Non-informed	4	1.36
1–4	169	57.49
5–8	99	33.67
9–13	22	7.48
Previous labor		
Non-informed	4	1.36
1–4	240	81.63
5–8	45	15.30
9–12	5	1.71
Previous abortion		
Non-informed	4	1.36
None	202	68.70
1–3	87	29.59
4–6	1	0.35

CI = 95%.

Table 2
Adverse drug reactions and patients' characteristics.

	ADR		*p*
	Yes	No	
Mean age	28.6 ± 7.7, y.o.	25.7 ± 7.3, y.o.	0.026[a]
Diagnosis	*n* (%)	*n* (%)	0.104[b]
Preterm labor	16 (17.8)	74 (82.2)	
Premature rupture of the membranes	2 (3.3)	58 (96.7)	
Preeclampsia	9 (17.6)	42 (82.4)	
Urinary infection	6 (1.82)	27 (81.8)	
Gestational diabetes	4 (20.0)	16 (80.0)	
Other	0 (0)	27 (100)	
	Mean (SD)	Mean (SD)	
Previous pregnancy	3.08 (2.352)	2.69 (2.007)	0.470[a]
Previous childbirth	1.63 (1.909)	1.28 (1.673)	0.509[a]
Previous abortion	0.42 (0.722)	0.41 (0.765)	0.991[a]
Gestational age	29.05 (6.913)	27.91 (9.187)	0.964[a]

[a] Kruskal-Wallis.
[b] Pearson's Chi-square.

rous sulfate (44.2%), nifedipine (32.3%), methyldopa (25.2%), cefalexin (26.2%), hydralazine (23.1%) and paracetamol (20.1%). Magnesium sulfate - the drug of choice for prevention of seizures in the pre-eclamptic women, or prevention of recurrence of seizures in the eclamptic women (Duley et al., 2010) - was prescribed to 3 patients (0.1%).

3.2. Adverse drug reactions

Suspect events were assessed for causality in 211 of 294 patients (71.8%) and at least one adverse drug reaction reached 26 (8.8%) patients. Overall, 29 ADRs (1.1 per patient with ADR) were identified through the double screening method. With the exception of the patients' age, other characteristics such as diagnosis, number of previous pregnancies and previous abortions, gestational age at birth, prescribed drugs and number of drugs per patient ($p = 0.239$, Kruskal-Wallis Test) were not related to ADRs (Tables 2 and 3).

Manifestation of ADRs was not associated with any adverse pregnancy outcome, and it may be due to the low severity of ADRs: 22 (75.9%) of the ADRs reported in the study were of mild severity and 7 (24.1%) were of moderate severity, and none of them were significantly associated ($p > 0.05$) with any specific drug or class of drugs (Table 3), although moderate ADRs were caused mainly by betamethasone (4 cases of BP arising) and cefalotin (3 cases of tachycardia).

No ADR was caused by drug-drug interactions. However, we identified a recurrent clinically manifested drug-drug interaction in which one drug makes another less effective: an increase in systolic blood pressure was observed in all 14 patients using methyldopa and ferrous sulfate as well as an increase in both systolic and diastolic blood pressures in 7 patients. A decrease in blood pressure was observed in all patients after ferrous sulfate was discontinued.

4. Discussion

Although several studies have assessed the presence of adverse drug reactions among hospitalized patients, very few studies with hospitalized pregnant women have been performed and none of them included any high-risk pregnant women. A prospective study to estimate the incidence of ADRs related to the use of antiretroviral therapy in hospitalized pregnant women in southeast of Brazil observed that 20.2% of the patients without previous experiences with antiretroviral therapy presented an ADR (Miguel et al., 2012). In another prospective study, ADRs and allergy discrepancies were identified among 59 of 300 of women admitted to either the antenatal or the postnatal ward at an Australian tertiary-level maternity hospital (Cano and Rozenfeld, 2009). Among non-hospitalized pregnant women, a prospective pharmacovigilance survey of adverse drug reactions performed in southwest France found an incidence of ADRs of 0.3% (Lacroix et al., 2007). In our study, ADRs were identified in a prospective manner, using patient charts (medical and nursing records), laboratory data and drug prescriptions as sources of information combined with the causality assessment of each ADR; thus, although we assessed several suspect events, only a small but significant part of them were considered adverse drug reactions.

In our study, patient's aging was the only variable related to the manifestation of ADRs. In the literature, higher maternal age is associated with a range of adverse pregnancy outcomes and it usually implies in high-risk pregnancies, which leads to a higher number of prescribed medicines (Santini-Oliveira et al., 2014; Nash et al., 2015). However, we observed that the number of prescribed medicines did not influence the manifestation of ADRs. The presence of multimorbidities and related polypharmacy is associated with a higher risk for ADRs via age-related changes in pharmacokinetics and pharmacodynamics that influence drug elimination and response (Wacker et al., 2015; Kenny et al., 2013). Our findings

Table 3
Drugs used during hospitalization and clinical manifestation of adverse drug reactions.

Drug	FDA pregnancy risk classification	Patients with clinically manifested ADR (26)		Patients without clinically manifested ADR (268)		Total	*P*[a]	OR	*C*
		N	%	*N*	%				
Cefalexin	B	5	19.2	72	26.9	77	0.441	0.65	0.28–1.49
Cefalotin	B	14	53.8	145	54.1	159	0.865	0.99	0.46–1.78
Betamethasone	C	15	57.7	151	56.3	166	0.865	1.05	0.57–1.97
Hydralazine	C	9	34.6	57	21.3	68	0.072	1.96	0.95–3.98
Methyldopa	C	8	30.8	66	24.2	74	0.311	1.36	1.25–4.99
Nifedipine	C	9	34.6	86	32.1	95	0.720	1.12	0.56–2.2
Paracetamol	C	5	19.2	54	20.1	59	0.906	0.94	0.42–2.93
Scopolamine	C	16	61.5	196	73.1	212	0.085	0.59	0.25–1.03
Metamizole	D	18	69.2	161	60.1	179	0.485	1.49	0.67–2.78
Ferrous sulfate[b]	–	13	50.0	117	43.7	130	0.734	1.29	0.58–2.23

Total sample: 294.
[a] Chi-square test; OR = odds ratio; CI = confidence interval.
[b] Ferrous sulfate has not been formally assigned to a pregnancy category by the FDA.

seem to indicate that the age-related changes play a more important role than polypharmacy in the manifestation of ADRs in high-risk pregnant women.

We did not observe any association between ADRs and adverse pregnant outcomes. We believe this may be due to the fact that no ADR reported in our study was of high severity and most of the drugs prescribed during hospitalization have been assigned to Food and Drug Administration (FDA) pregnancy categories B and C. Although the FDA updated the pregnancy risk letter categories in 2015 with new information to make them more meaningful to both patients and healthcare providers, this new approach did not guide prescribers in our study.

We also believe that the lack of adverse pregnant outcomes in our study may be due to the relatively short duration of treatment to which pregnant inpatients are exposed when compared to pregnant outpatients. However, Wacker et al. (2015), in a cohort study of prospectively observed pregnant women who spontaneously contacted a teratology information service in Berlin for drug risk consultation, did not find evidence for an increased risk of adverse pregnancy outcomes after average drug exposure during pregnancy, compared with non-exposed or insignificantly exposed pregnancies.

As for the clinically manifested drug interactions involving methyldopa, Orbach and colleagues (2013) state that the effects of hypertension have not been separated appropriately from the effects of the medications that are used in pregnant women. In our study, we were able to identify the adverse effect of medications through causality assessment and we also did not find any association between the use of antihypertensive drug and adverse effects. Nevertheless, the concurrent use of methyldopa and ferrous sulfate proved to be largely ineffective to control blood pressure in pregnant women. The absorption of methyldopa is significantly reduced when taken with a dose of ferrous sulfate, increasing both systolic and diastolic blood pressures in hypertensive patients (Campbell et al., 1988). In general, methyldopa is the first choice for antihypertensive therapy in pregnant women and its safety has been shown in several studies (Al Khaja et al., 2014). The present findings recommend caution in the concurrent use of these drugs, a potential problem which may be circumvented if scheduling adjustments are made.

Our study had limitations. The assessment of causality through the Naranjo Algorithm and Korean Algorithm for ADR Causality Assessment required that patients who remained at the service less than 24 consecutive hours were excluded from the final sample. This may have introduced some bias in the study once ADRs that have manifested and disappeared in a short period of time were not identified. In addition, ADR probability scales have inherent limitations, especially in the distinction between probability categories. Nevertheless, Naidu (2013) states that grades of causality (e.g., "possible," "probable," "definite") offer little practical advantage and recommend binary yes/no causality (i.e., related/not related) for study investigators or regulatory reporting requirements, an approach adopted in our study.

5. Conclusion

In conclusion, Adverse drug reactions were not highly prevalent among high-risk pregnant women admitted for labor in a teaching maternity hospital and no adverse pregnancy outcomes following these events were observed. Although this may be due to the safety profile of drugs commonly used in the management of at-risk pregnancies, larger studies are still needed to confirm these findings. Our results also suggest that the age-related changes play a more important role in pregnant women than polypharmacy in the manifestation of ADRs. Moreover, all patients using methyldopa and ferrous sulfate had an increase in blood pressure, and we recommend caution in the concurrent use of these drugs.

Conflict of interest

The authors report no conflict of interests.

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