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Original Article

Fetal Exposure to Risky Drugs: Analysis of Antenatal Clinic Prescriptions in a Nigerian Tertiary Care Hospital

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Abstract

Objective: To assess fetal outcomes after in-utero exposure to unsafe drugs.

Methods: This was a retrospective cohort study using data from medical records of pregnant women who received antenatal care over a two-year period (2019/2020). Inclusion was based on identification of prescription of potentially risky medications during pregnancy. Medication records, as well as delivery data, were extracted for analysis. The Australian drug evaluation committee classification system of risky medications was used for analysis.

Results: Results showed that 44–65% of medicines prescribed in pregnancy carry significant risks to fetal wellbeing. Fetal outcomes showed high levels of low birth weight, still birth, and early neonatal death. The common medicines prescribed irrationally in pregnancy were, among others, antibiotics, ACEIs, NSAIDs, Biguanides, and opiates, all of which are associated with adverse fetal outcomes.

Conclusion: There is a high level of fetal exposure to risky medications and adverse delivery outcomes. There is a need to improve prescription through prescriber training and awareness raising on existing guidelines on good prescribing practice for pregnant women.

Keywords: Drug prescriptions, fetal drug exposure, fetal wellbeing, low birth weight, pregnancy

Introduction

Pregnancy is a time of rapid fetal development and administration of drugs during pregnancy can carry the risks that could interfere with the organogenesis, structural growth, and other physiological processes of the fetus, which is particularly high in the first trimester of pregnancy. This is possible because many drugs can circulate freely in the maternal body and easily reach fetal circulation in concentrations that can cause major disruptions to development. In addition to the risk of disruptions to the fetal growth and development, drugs also have the potential to produce other subtle effects during post-delivery functional development of infants. There is literature evidence linking fetal drug exposure and learning difficulties, mental health disorders, obesity, organ dysfunction, and also a high risk of chronic diseases later in adult life.[1]

Fetal drug exposure is widely reported in high income countries; however data from low income countries is limited.[2] Recent studies in sub-Saharan African countries reported risky fetal exposure to antibiotics, analgesics, and antimalarial drugs.[3] The exposure, which is largely from prescriptions, is also exacerbated by the widespread self-medication practice among pregnant women as well as the general population.[4] One study reported that up to 80% of pregnant women may have used at least one risky drug through medical prescription or as over-the-counter medication.[5]

Among the most commonly reported fetal drug exposures that have been associated with various adverse outcomes are exposures to Benzodiazepines[5], Quinolones[6,7], antifungals,[8] Opioids,[9] NSAIDS,[10] Amlodipine,[11] and ACEIs/

ARBs.[12] Fetal exposure to certain types of drugs significantly increases the risk of low birth weight infant,[13] attention deficit problems in childhood, congenital malformations, as well as increased risk of childhood asthma.[14] The decision to prescribe drug(s) rests with the healthcare provider who is expected to follow the same principles of rational and safe use of drugs during pregnancy. The safety and audit of prescription medicines in pregnancy have received little research interest in this part of the country; therefore, this study aimed to audit prescription medicines given to pregnant women and also identify potential risks to fetal wellbeing.

Methods

This study was performed at the obstetrics and gynecology department of the University of Maiduguri teaching hospital, Nigeria. This was a retrospective study using medical records of women who received full antenatal care during a two-year period (January 2019–December 2020) from the hospital. The sample size was determined using the Andrew Fishers method and sample of medical records of five hundred women were selected using the simple random sampling method. Eligibility criteria included pregnant women who had received at least six months of antenatal care and also delivered in the hospital. Those who had missed more than half of their regular antenatal visits or were on antiretroviral therapy were not included in the study.

The data extracted from the medical records were of the subjects were demographic data, gravida, morbidity, potentially risky drugs, neonatal weight, neonatal deaths, stillbirth, APGAR score (5 minutes), and other relevant data. Data were entered into the SPSS version 21 for descriptive statistics, and fetal drug risk assessment was performed using the Australian drug evaluation committee classification or known as ADEC. The ethical approval for this study was obtained from the health research ethics committee of the University of Maiduguri teaching hospital Borno State, Nigeria.

Results

Demographic data showed that most pregnant women had secondary to tertiary education level (89%) with an average of 1 – 3 pregnancies (88%) per woman. Most of them presented themselves for their first antenatal care at 9 to 16 weeks of pregnancy (74.6%; Table 1).

Anemia was found to be common among pregnant women as reflected in the average pack cell volume of 30.4%, which was well below the recommended value. The results also showed that a quarter of them experienced pre-eclampsia (25.8%), while 4.6% experienced post-partum hemorrhage. There was a high incidence rate of low birth weight (64.8%), while stillbirths and early neonatal deaths occurred in 4% and 5.8% of pregnancies, respectively (Table 2).

The most frequent morbidities encountered were hypertension (53%), anemia (31.8%), and pre-eclampsia (25.8%). Other encountered diseases, albeit less frequently, were malaria, urinary tract infections, and also gestational hyperglycemia (Fig. 1).

Fetal exposure to potentially risky drugs was observed thoughout pregnancy with metronidazole (34.4%), Diclofenac (20.3%), and Captopril (21.1%) being most frequently

Table 1 Demographic Data

Variable	n (%)
Education	
Illiterate	2 (0.4)
Primary	53 (10.6)
Secondary	261 (52.2)
Tertiary	184 (36.8)
Occupation	
Civil service	139 (27.8)
Self-employed	169 (33.8)
Housewife	141 (28.2)
Student	51 (10.2)
Gravida	
1–3	440 (88)
4–6	51 (10.2)
>6	9 (1.8)
Average	2.4
Time of first antenatal visit (weeks)	
4–8	47 (9.4)
9–12	225 (45)
13–16	148 (29.6)
17–20	39 (7.8)
21–24	41 (8.2)
Mean (SD)	12.9 ± 4.4
Mean age (yrs.)	34.9 ± 7.4

Table 2 Maternal and Fetal Data

Variable	Result
Maternal data	
Packed cell volume	30.4±5.6
Bacteriuria	60.4%
Pre-eclampsia	25.8%
Post-natal hemorrhage	4.6%
Neonatal data	
Birth weight (kg)	2.6±0.7
APGAR score (5 minutes)	7.7±2.3
Still births	4%
Early neonatal death	5.8%

encountered. Other drugs of concern included Metformin, Levofloxacin, and Codeine, which were mostly prescribed during the third trimester of pregnancy (Fig. 2).

The prevalence of potentially risky drugs increased from 44.2% in the first trimester of pregnancy to 65.6% in the second trimester and then 60% in the third trimester. This represent an average of 56.6% of pregnancies had fetal exposure to risky drug (Fig. 3).

Based on the risk classification and risk description of drugs, it has been demonstrated that certain drugs, such as Captopril/Lisinopril (D), Diclofenac/Amlodipine and Metformin (C), Levofloxacin (B3), and Metronidazole (B2), pose various significant risks to the fetal organogenesis and development. In the case of Codeine-containing analgesics, despite the

Table 3 Prescription drugs and risk description

Drug	One	Two	Three	Classification	Risk description
Metronidazole	+	+	+	B2	Low birth weight, preterm delivery
Diclofenac	+	+	+	C	Premature closure of ductus arteriosus
Captopril/ Lisinopril	+	+		D	*Teratogenic*
Amlodipine	+	+	+	C	*Heart malformation, Hypospadia*
Diazepam					*Early motor deficit*
Metformin	+	+	+	C	*Low birth weight, high BMI, long term cardiometabolic disorders*
Hydralazine	+	+	+	C	*Low birth weight*
Gentamycin	+			B3	*Ototoxicity*
Levofloxacin	+	+	+	B3	*Arthropathy, preterm delivery*
Codeine	+	+	+	A	Neonatal respiratory depression

Notes: *+ = potentially risky, one, two and three = trimesters*

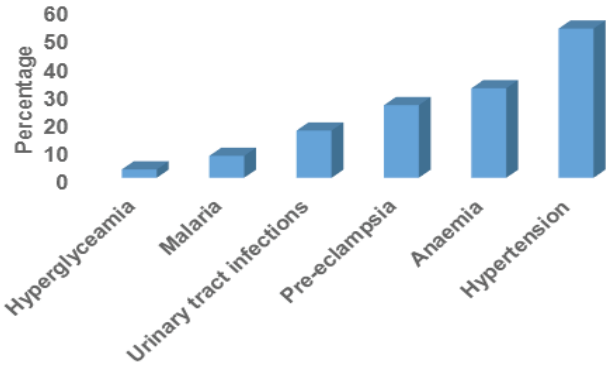

Fig. 1 Prevalence of Morbidities (n=500)

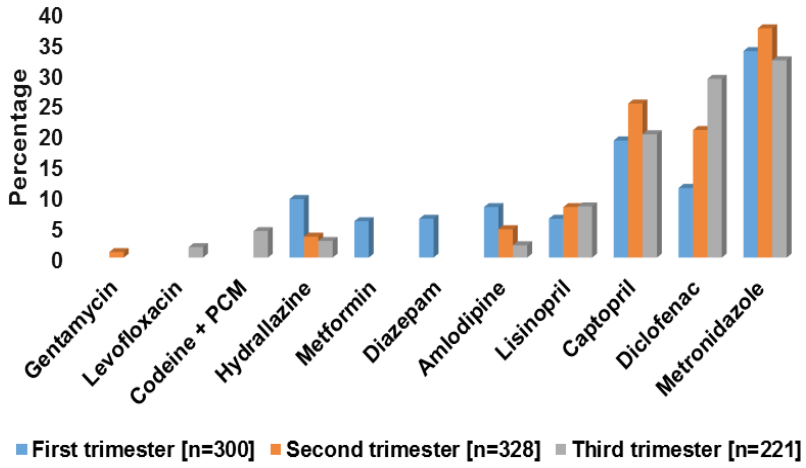

Fig. 2 Comparison of Fetal Exposure To Risky Drugs (n=500)

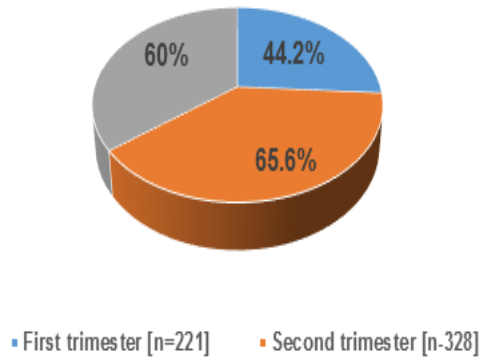

Fig. 3 Potentially Risky Prescription Drugs

fact that it may not pose a direct teratogenic risk, it carries significant risk for post-delivery respiratory depression with the potential for early neonatal death (Table 3).

Discussion

Fetal exposure to drugs cannot be completely avoided in pregnancy because of the need to manage maternal medical conditions. While general guidelines for drug safety in pregnancy are available, the decision for drug therapy rests with the physicians and other healthcare professionals provided care for these pregnant women. The results of this study showed that almost two thirds of pregnant women were prescribed drugs that are potentially risky to the fetal wellbeing. This result is comparable to a previous study,[15] although a similar study had reported much lower figure.[2] While there appeared to be more prescription drugs given as pregnancy progressed, there was a lack of due diligence on the fetal safety consideration on the part of prescribers. There are much safer alternatives to these risk drugs that are capable of producing comparable clinical outcomes. For instance, oral hypoglycemic drugs are contraindicated, with guidelines recommending a switch to the insulin therapy once pregnancy occurs. The risk of arthropathy associated with Quinolones, as well as cranial nerve damage with aminoglycosides and low birth weight with metronidazole has been reported and are well documented,[6] despite the existing contradictory conclusions on the fetal safety of metronidazole.

In addition to these known associations, antibiotics are well known to alter maternal and feto-placental microbiome,[16] which has been linked to childhood asthma.[17] They are also reported to cause altered fetal growth and childhood growth trajectory. [13,18] Some studies specifically reported increased risk of cerebral palsy and/or epilepsy with fetal exposure to macrolides.[14]

The recommendation for the treatment of hypertension in pregnancy has exluded the use of ACEIs because of their risk of teratogenicity; thus, the prescription of Captopril/Lisinopril is irrational when compared to the safer alternatives such as Methyldopa, Labetolol, and others that are also effective in achieving blood pressure control. In the case of Calcium

channel blockers, there is limited safety data, though, in recent years, Nifedipine has been considered safe in pregnancy. Nevertheless, some studies have reported the potential association between Calcium channel blockers and birth defects, such as heart malformation, hypospadias and low birth weight. [19,20]

The use of NSAIDs in pregnancy is not generally recommended because of their risk of premature closure of ductus arteriosus in the newborn and decreased neonatal renal function.[21,22] They have also been reported to carry the risk of low birth weight and development of asthma in infants.[5] Opioid use also carry a high risk of the occurrence of spina bifida among other congenital malformations.[9]

Metformin use in pregnancy exposes the fetus to the risk of higher body mass index in childhood and a significantly higher risk of cardiometabolic disorders later in adulthood. [23, 24] Benzodiazepines are not known to carry significant risk of congenital abnormalities; [12] however, some previous studies have linked them to childhood motor and communication deficits.[5, 25]

Although it is challenging to track the individual outcomes of fetal drug exposure, the high prevalence of low birth weight, still births, and early neonatal should be a matter of public health concern. It should also be acknowledged that a certain amount of the observed adverse fetal outcomes may be caused by other confounding variables acting alone or in conjunction with prescription drug exposure in utero. In conclusion, the prescription of contraindicated or unsafe drugs in pregnancy carries a significant safety risk to fetal wellbeing in utero and also to the post-delivery development. There should be improved awareness of safety guidelines and training of prescribers on safe use of drugs among pregnant women.

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