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 the risk of drug interference with organogenesis, structural growth and other physiological processes is particularly high in the first trimester of pregnancy. This is possible because many drugs freely can easily reach fetal circulation in concentrations that can cause major disruptions to development. In addition to risk of disruptions to 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 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 rather limited.[2] Recent studies in sub Saharan African countries reported risky fetal exposure to antibiotics, analgesics and antimalarial drugs.[3] The exposure largely from prescriptions is in addition to widespread practice of self-medication among pregnant women and 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 associated with adverse outcomes included Quinolones[6,7] antifungals,[8] Opioids,[9] NSAIDS,[10] Amlodipine,[11] Benzodiazepines[5] and ACEIs/ARBs.[12] Fetus exposed to some drugs significantly increase the risk of low birth weight,[13] attention

deficit problems in childhood, congenital malformations and higher risk of childhood asthma.[14] The decision to prescribe drug(s) rest 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, so this study aim to audit prescription medicines given to pregnant women and also identify potential risks to fetal wellbeing.

Methods

This study was carried in the obstetrics and gynecology department of the University of Maiduguri teaching hospital. This was a retrospective study using medical records of women who received full antenatal care during a two year period (January 2019–December 2020) in the hospital. The sample size was determined using Andrew Fishers method, however medical records of five hundred women were selected using 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 antiretroviral therapy were not included in the study.

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

Results

Demographic data showed that most pregnant women had secondary to tertiary education (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 observed to be common among pregnant women as reflected in an average pack cell volume of 30.4% which was well below recommended value. The results also showed

that a quarter of them had pre-eclampsia (25.8%) and 4.6% of them experienced post-partum hemorrhage. There was high incidence 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 frequently encountered morbidities included hypertension (53%), anaemia (31.8%) and pre-eclampsia (25.8%). Other less frequently encountered diseases included urinary tract infections, malaria and gestational hyperglycemia (Fig. 1).

Fetal exposure to potentially risky drugs occurred though out pregnancy with metronidazole (34.4%), Diclofenac (20.3%) and Captopril (21.1%) being most frequently encountered. Other drugs of concern included Metformin, Levofloxacin and Codeine largely prescribed during the third trimester of pregnancies (Fig. 2).

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%

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).

The names of drugs, their risk classification and risk description showed that Captopril /Lisinopril (D), Diclofenac/ Amlodipine and Metformin (C), Levofloxacin (B3) and Metronidazole (B2) pose significant risks to organogenesis and development. In the case of Codeine containing analgesics, while it may not pose direct teratogenic risk, it carry significant risk for post-delivery respiratory depression with the potential for early neonatal death (Table 3).

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*
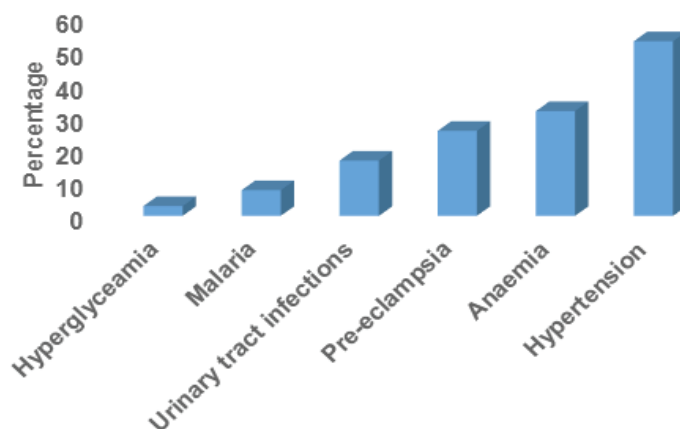

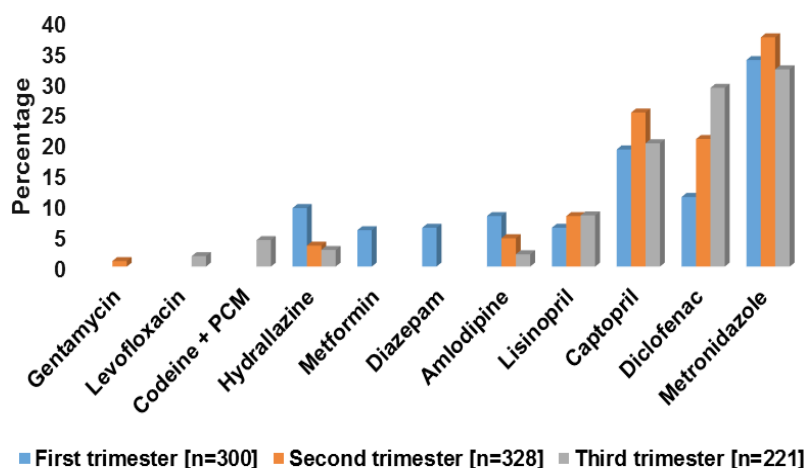**Fig. 1 Prevalence of Morbidities (n=500)**

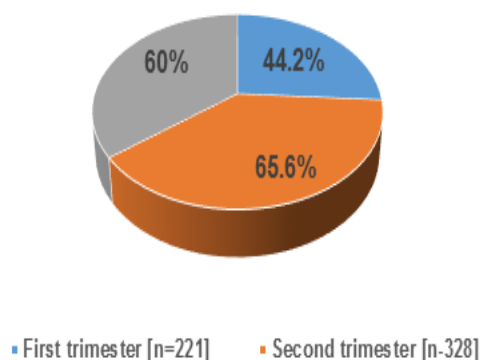**Fig. 2 Comparison of fetal Exposure To Risky Drugs (n=500)**

Fig. 3 Potentially Risky Prescription Drugs

Discussion

Fetal exposure to drugs cannot be totally 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 rest with the physicians and other healthcare professionals. The results study showed that almost two thirds of pregnant women were prescribed drugs that were potentially risky to fetal wellbeing. This result was comparable to a previous study,[15] although a similar study had reported much lower figure.[2] While there appeared to be more prescription drugs as pregnancy progressed, there was a lack of due diligence on fetal safety consideration on the part of prescribers. There were 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 switch to Insulin therapy once pregnancy has occurred.The risk of arthropathy associated with Quinolones, cranial nerve damage with aminoglycosides as well as low birth weight reported with metronidazole are well documented,[6] though there are contradictory conclusions as it relate fetal safety of metronidazole.

In addition to these known associations, antibiotics are 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 as well as 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 excluded ACEIs because of their risk of teratogenicity, so the use of Captopril/Lisinopril was irrational as safer alternatives like Methyldopa, Labetolol etc. are 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. However some studies have reported 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 abnormality,[12] however some studies have linked them to motor and communication deficits in childhood.[5, 25]

While it was difficult to track 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 acknowledge that some 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 medicines in pregnancy carry significant safety risk to fetal wellbeing in utero and 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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