Potential teratogenicity risk and prescription drug use among pregnant women attending maternal and child health clinic of Kemisse General Hospital, Northeastern, Ethiopia

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Research article

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Abstract

Background Drug use during pregnancy requires special consideration because both fetus and the mother are affected. Drug teratogenicity is most likely to occur when drugs are taken during first trimester of pregnancy when fetal organs are formed. In addition, drugs at second and third trimester may affect the growth and functional development of the fetus or have toxic effect on fetal tissues. **Objective** The objective of this study was to assess potential teratogenecity risk and drug use pattern in Kemisse General Hospital. **Methods** An institution based cross sectional study was conducted by reviewing a one year medical records (from January 1, 2010 to December 31, 2011) of pregnant women attending maternal and child health clinic of the hospital. Systematic random sampling was employed to select a total of 263 pregnant women. Structured data abstraction format was used for collection of data and then data were coded, entered and analyzed by using Statistical Package for Social Sciences version 23. **Result** A total of 263 medical records of pregnant women were reviewed, of which 234 pregnant women were prescribed with a total of 430 prescription drugs. The average numbers of drugs per pregnant women was found to be 1.84. Most pregnant women 166 (63.2%) were in the third trimester and more than half of them (51.3%) were multigravida. The maximum number of drugs were prescribed in the second trimester 162 (37.67%) followed by third trimester 143(33.26%). Supplemental drugs were the most widely used medications 297 (69.07%) and followed by 82 (19.1%) drugs from category B; 54 (12.6%) drugs from category C; and the rest 7 (1.6%) drugs from category D. There was no any drug from category X. **Conclusion** Approximately one third of the pregnant women encountered with drugs from category B, C and D. However, there were no FDA category C and D drugs prescribed in first trimester. There was no drug utilized by pregnant women from FDA pregnancy risk category X.

Background

Drugs use in pregnancy should always question two important queries and maintain a fine balance of them; no harm should be posed to the baby due to the drug, and no harm must come to the mother or baby because of inadequate treatment (1). Medication use during pregnancy has been an issue of serious concern and needs monitoring since historical milestone of thalidomide disaster during the 1960s (2). The physiologic, pharmacokinetic and pharmacodynamic changes occur during pregnancy requires special therapeutic consideration in pregnant and lactating women. Not only the changes have occurred, but also these physiologic changes are not fixed throughout pregnancy but rather reflect a continuum of change as pregnancy progresses. Moreover, pregnant women have been often excluded from clinical trials and extrapolation of pharmacokinetics data from studies performed in non-pregnant adults or evidences generated from animal studies are not often suitable (3). Therefore, pregnancy management using medications has been challenging to both health care providers and pregnant women, given the fear of teratogenicity effects and the potential for fetal harms.

A large number of studies have reported that the utilization of a large number of drugs during pregnancy (4-8). Substantial number of drugs was also used from Food and Drug administration (FDA) pregnancy risk category D and X (9). Hence this study was carried out to evaluate the pattern of drug use and

potential teratogenicity risk to fetus in women attending Maternal and Child Health (MCH) clinic of Kemisse General Hospital (KGH) in eastern Amhara, Ethiopia.

Study area, design and period

The study was conducted at Kemisse General Hospital (KGH), located in Northeast Ethiopia, Oromia Special Zone, Amhara National Regional State, 331 km away from north of Addis Ababa. The hospital is the only general hospital in the zone and currently serving about 1.2 million catchment population from all population in the zone and nearby districts. An institution based cross sectional study was conducted from March 1 to April 20, 2019 by reviewing a one year medical records (from January 1, 2010 to December 31, 2011) of pregnant women attending maternal and child health (MCH) clinic of the hospital.

Study population

All medical records of pregnant women who attended MCH clinic of KGH from Jan 1, 2010 to Dec 30, 2011 were taken as a study population. Women came for Antenatal Care (ANC) and enrolled in routine ANC program from Jan 1, 2010 - Dec 31, 2011.

Sample size determination and sampling technique

By using single population proportion formula, the sample size was determined as follows:

$$n = \frac{Z^2 p(1-p)}{d^2} = \frac{(1.96)^2 \cdot (0.875) \cdot (1-0.875)}{(0.03)^2} = 467$$

, where n = desired sample size for population > 10,000, Z = confidence level at 95% (1.96), P = proportion of drug use during pregnancy, 87.5% (9), d = degree of accuracy desired (marginal error) is 0.03. Since the total number of pregnant women who attended MCH of KGH during the review period was 600 (< 10,000), correction formula was used to determine final sample size

$$n_f = \frac{n_i}{1 + \frac{n_i}{N}} = \frac{467}{1 + \frac{467}{600}} = \underline{263}$$

Where, n_f = final sample size, n_i = initial sample size, and N = study population. Systematic random sampling was employed to select the study units.

Data collection processes and data quality control

The data abstraction format used contained information regarding to obstetric history (age, trimesters of pregnancy, gravidity, number of visits), clinical and drug related data (common maternal disorders, common classes of drugs in each trimesters, and prescribed medications) and FDA pregnancy risk

category. Pretest was done at Bati primary hospital located in the nearby town. Important corrections and data cleaning on daily basis were made.

Data processing and analysis

The data were coded, entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 23 (IBM statistics, Armonk, NY, USA). Data were presented in tables and figure.

Results

Obstetric history of pregnant women

A total of 263 pregnant women medical records were reviewed for this study. The average maternal age in the study was 26.5 years. The majority of women expected to have child are in 25 – 34 years of age. Most pregnant women 166 (63.2%) were in the third trimester and more than half of them (51.3%) were multigravida and started their ANC visits after the 24th week of their pregnancy (55.1%). Out of 263 pregnant women, 145 (55.1%) had four to six antenatal visits (Table 1).

Table 1. Obstetric history of pregnant women attending MCH clinic of KGH, northeast Ethiopia from January 1, 2010 to December 31, 2011.

Variables	Frequency	Percentage
Age (in years)		
15-24	90	34.2
25-34	162	61.6
35-50	11	4.2
Trimesters of pregnancy		
1 st trimester	38	14.5
2 nd trimester	59	22.4
3 rd trimester	166	63.1
Gravidity		
Primigravida	38	14.5
Secundum gravida	90	34.2
Multigravida	135	51.3
Number of MCH visits		
<3	103	39.2
4-6	145	55.1
>7	15	5.7

Common Maternal disorders Anemia and vitamin deficiency in pregnancy is the most common maternal

disorder 229 (87.07 %) followed by intestinal parasite 14 (5.32%), nausea and vomiting 12 (4.56 %), dyspepsia 11 (4.23 %), and urinary tract infections 8 (3.04%) (Table 2). Common classes of drugs and prescribed medications in each Trimester From a total of 263 pregnant women, 234 had taken at least one drug with 88.97% prevalence of drug utilization. A total of 430 drugs were prescribed for these pregnant women. Among these, supplemental drugs 297 (69.1%) were the most frequently prescribed drugs followed by anti-bacterial 35 (8.1%) and analgesics 24 (5.6%). The maximum number of drugs were prescribed in the second trimester 162 (37.67%) followed by third trimester 143 (33.26%) and first trimester 125(29.07%). From antibiotics, amoxicillin, ceftriaxone and amoxicillin/clavunilic acid were mostly prescribed whereas paracetamol and diclofenac were frequently prescribed analgesics (Table 3).

Table 2: Common maternal disorders of pregnant women attending MCH clinic of KGH, northeast Ethiopia from January 1, 2010 to December 31, 2011.

Maternal disorders	Frequency	Percentage
Anemia and vitamin deficiency	229	87.07
Vaginal bleeding	2	0.76
A F I	6	2.28
Pneumonia	1	0.38
Malaria	1	0.38
Cough and cold	4	1.52
Dyspepsia	1	1 4.23
Gastritis	1	0.38
UTI	8	3.04
Nausea and vomiting	12	4.56
Intestinal parasite	14	5.32
HIV/AIDS	4	1.52
Diabetes mellitus	3	1.14
Amebiasis and gardiasis	2	0.76
Others	7	2.66
Total	305	116%

Table 3: Medications used by pregnant women at different trimesters and their US FDA pregnancy risk category in KGH, northeast Ethiopia from January 1, 2010- December 31, 2011.

Class of drugs	Drug name	1 st trimester frequency	2 nd trimester frequency	3 rd trimester frequency	Total Frequency	FDA risk category
Antibiotics	Amoxicillin	5	3	2	10	B
	Ceftriaxone	2	5	2	9	B
	Cephalexin	1	2	2	5	B
	Amoxillin/ clavulanic	3	1	2	6	B
	Ampicillin	3	2	0	5	B
Supplements	Iron	20	80	78	178	A
	Folic Acid	67	32	20	119	A
Painalgesics	Paracetamol	9	5	3	17	B
	Diclofenac	0	0	5	5	D
	Ibuprofen	0	2	0	2	D
	Tramadol	0	1	0	1	C
	Plasil	11	2	1	14	B
GI drugs	Omeprazole	0	10	0	10	C
	Cimetidine	0	2	0	2	B
	Coartem	0	0	1	1	C
Other antimicrobials	Clotrimazole	3	1	4	8	B
	Mebendazole	0	2	12	14	C
	Metronidazole	0	4	4	8	C
M Drugs	Insulin	1	2	0	3	B
ART Drugs	AZT/3TC/NVP	0	1	2	3	B
IV fluids	N/S,R/L	0	5	5	10	C
	Total	125	162	143	430	

Summary of FDA drug risk category

Out of 430 drugs prescribed for pregnant women, 297 (69.1%) drugs were from FDA drug risk category **A**; 82 (19.1%) drugs were from category B; 54 (12.6%) drugs were from category C; and the rest 7 (1.6%) drugs were from category D. There was no any drug from category X (Table 4).

The average number of drugs per pregnant women who had at least one drug was found to be 1.84. Prevalence of drug utilization among pregnant women in this study was 88.97%. On the other hand, percentage of encounters with antibiotics prescribed was 35(8.14%) whereas percentage of encounters with injections was 37(8.6%). Moreover, the percentage of drugs prescribed with generic name was 412 (95.8%) (Table 5).

Table 4: Frequency distribution of FDA drug category of the drug prescribed at different trimesters in KGH, northeast Ethiopia from January 1, 2010- December 31, 2011.

US FDA risk category	1 st trimester	2 nd trimester	3 rd trimester	Total
A	87	112	98	297 (69.1%)
B	38	26	18	82 (19.1%)
C	0	22	22	54 (10.2%)
D	0	2	5	7 (1.6%)
Total	125	162	143	430

Table 5: Frequency and percentage distribution of prescribing pattern indicators in each trimesters in KGH, northeast Ethiopia in reference to WHO standards.

Prescribing indicators	1 st trimester	2 nd trimester	3 rd trimester	Total	WHO standard
Percentage of drugs prescribed with generic name	114	159	139	412(95.8%)	100%
Percentage of encounters with antibiotics prescribed	14	13	8	35 (8.14%)	< 30 (20–26.8%)
Percentage of encounters with injections prescribed	11	15	11	37(8.6%)	(13.4–21.1%)
Average <u>No</u> of drugs per prescription = 1.84 (430 drugs / 234 encounters)					≤ 2 (1.6–1.8)

Discussion

Out of 234 pregnant women who attended MCH clinic of a hospital, the mean age of pregnant women was 26.5 ($\pm$ 6.2) years and the majority of them were between 25 to 34 years which represents the normal reproductive age groups. This finding is line with a report by Legesse B et al (7). More than half of pregnant women had four to six antenatal visits and most of them were in third trimester and started their ANC visits after the 24th week of their pregnancy. This finding is not in accordance with the reports by Fanta, et al (10) and Chanie et al (8). However, considerable numbers of pregnant women were in the first and second trimester where the critical periods of organogenesis and organ development occur and drug-induced teratogenicity is assumed to reach highest.

The prevalence of drug utilization in this study was found to be 88.97%, comparable with prevalence of 85.1 % in eastern Ethiopia, Harar (11), 87.5% in northern Ethiopia (9) and 88.4% in north west Ethiopia, Bahirdar (12). But this value is lower than a study in Nekemte (96%) (13).

Most common diseases recorded were anemia and vitamin deficiency, intestinal parasite, nausea and vomiting, dyspepsia, urinary tract infections and acute febrile illness. Hence, the majority of medications prescribed were drugs used against these problems such as iron salts and folic acid, antibiotics such as amoxicillin, ceftriaxone, metronidazole and amoxicillin/clavunilic acid, gastrointestinal drugs like metoclopramide, mebendazole and omeprazole. All of these drugs were either from FDA category A, B or C. The result of study was relatively higher than study reported in Nigeria (14). This may be because of

difference in maternal health problems such that intestinal parasite was among commonly presented maternal disorders in this study that increase percentage of drug utilization.

The average number of drugs per pregnant women in this study was 1.84 which indicated that it was a bit out of range of standard set by WHO (1.6-1.8) (15) as compared to the reports from studies conducted at Ayder referral hospital, Mekele and Hiwot Fana specialized university hospital, Harar (2.17, 1.21) respectively (3, 11).

Looking at the medications prescribed for pregnant women, supplemental drugs utilization accounted 69% of the total drugs, which is higher than a study conducted in eight rural districts of Ethiopia where only 35.4% of pregnant women used iron supplements (16) and lower than study conducted at Addis Ababa (17) and Harar city (11) which showed that more than 90% and 84.88% of the mothers were supplemented with at least one iron/folic acid supplement respectively. Much has to be done to create awareness, access and improve supplemental drugs utilization to almost every pregnant mother.

Higher numbers of drugs were prescribed in second and third trimester of pregnancy which might increase the risk of fetal toxicity. The majority of drugs were from category A (69.1%). This finding was far higher than a study conducted at Adama referral hospital (18) and Fiche primary hospital, Ethiopia (10) and a study done in Sao Paulo (19) which indicated that 13.6%, 20.83% and 20.55% drugs were from category A respectively. However, this finding was in line with a study done in Swaziland that reported 64.9% drugs were under category A. Whereas the current study was lower than studies conducted in Hiwot Fana Specialized University Hospital (84.88%) (11), in different health facilities of Southern Tigray region (87.7%) (9) and India (91.13%) (20). The present study also showed that 19.1% of drugs were from category B, which was lower than a study conducted in Jimma (18) and Adama (21) where 60.2% and 62.4% were prescribed from category B.

Some group of drugs from category C (10.2%) and D (1.6%) were prescribed in this study. These values were lower than a study conducted at Addis Ababa where 21.43% and 16.96% drugs were from category C and D respectively (22). There were not drugs from category C and D prescribed during first trimester, but considerable number of drugs was prescribed during the second and third trimesters. According to present study, diclofenac and ibuprofen (those from category D) were used in third trimester for pregnant women to manage pain; however, this can cause early closure and constriction of ductus arteriosus with subsequent neonatal pulmonary hypertension and transient right-sided hypertrophic cardiomyopathy (23). Other drugs such as mebendazole, metronidazole, tramadol, and artemether/lumefantrine are only recommended for use during pregnancy when benefit outweighs risk.

Looking at the prescribing indicators, the present study showed that the percentage of drugs prescribed by the generic name was found to be 95.8%, which was comparable to a study done in Fiche Hospital (10) where 94.08% of the prescriptions were generic name drugs. Percentage of encounters with injections prescribed was 8.6%, less than a standard set by WHO (15). 8.14% of the total prescribed medications were antibiotics. Among these, amoxicillin, ceftriaxone and amoxicillin/ clavulanic acid were commonly prescribed which belongs to FDA category B drugs and are safe.

Conclusion

Most of the drugs utilized were supplemental in nature. There was no drug utilized by pregnant women from FDA pregnancy risk category X. Some drugs were utilized from FDA category D (Diclofenac and ibuprofen) for pain management, despite the fact that these drugs might have risk for pregnant women like ductus arteriosus with subsequent neonatal pulmonary hypertension and transient right-sided hypertrophic cardiomyopathy. FDA category A drugs were the most frequently prescribed drugs. However, approximately one third of the pregnant women encountered with drugs from category B, C and D which are thought to cause possible fetal harm. Hence, such inappropriate prescription of drugs should not be underestimated since it affects the life of both the mother and the fetus. Therefore, intensive assessment of pharmacotherapy given to pregnant women should be done with respect to the FDA risk category, the gestational period, and the risk-benefit balance of a drug before its prescription. Therefore, lack of awareness in respect to drug prescription and use should be improved with the proper implementation of information, education and communication.

LIMITATION OF THE STUDY

There was insufficient drug information on patients' medical records and some patient medical records didn't have diagnosis for the prescribed drugs at all. Some medical records were incomplete.

Retrospective nature of the study may not address the temporal relationship between the drug exposure and the pregnancy risk. Moreover, the retrospective study did not examine over-the-counter medications and herbal medicines that the pregnant women may self medicate but still might produce teratogenicity.

List Of Abbreviations

AFI	Acute Febrile Illness
AIDS	Acquired Immune deficiency syndrome
	Antenatal care
ANC	Anti Retroviral Therapy
ART	Kemisse General Hospital
KGH	Human immune virus
HIV	Maternal and child Health
MCH	National Institute of Child Health and Human Development
NICHD	Over the counter
	Principal Investigator
OTC	Standard deviation
PI	Sexual transmitted infection
SD	United state of food & drug administration
STI	World Health Organization
US-FDA	Upper Respiratory Tract Infection
	Urinary Tract Infection
WHO	
URTI	
UTI	

Declarations

Ethics approval and consent to participate

The research was approved by ethical review committee of College of Medicine and Health Sciences of Wollo University. Official support letter of permission was obtained and all necessary communications was made with KGH officials. Confidentiality and privacy of information get from the patient medical record was kept throughout the data collection and entire study period.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

Study concept and design was made by NN and BK. Data entry and first draft was done by NB. Analysis of the data, critical revision of the manuscript for important intellectual content and the final manuscript was done by BK. Both authors read and approved the final manuscript.

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