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Assessment of Drug Prescribing Pattern among Pregnant Women Attending Antenatal Care in Health Centers found in Arada Subcity, Addis Ababa, Ethiopia

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ABSTRACT:

Background: The physiological changes that occur in pregnancy challenge both health care providers and pregnant women managing disease states during pregnancy using medications given the fear of teratogenic effects and the potential for fetal harm. *Objectives:* To assess drug prescribing pattern among pregnant women attending antenatal care in health centers in Arada subcity, Addis Ababa. *Methods:* A retrospective cross sectional descriptive study was carried out on pregnant women who attended the antenatal clinics of health centers from June 2012 until March 2013, using the information gained from antenatal care follow-up cards by using data abstraction format. *Results:* The study was done by enrolling 314 pregnant women among whom 299 (95.2%) pregnant women used at least one drug during their pregnancy including iron/folic acid combination (excluding vaccination) and forty two different drugs were prescribed during all pregnancy stages. The most commonly used drugs were vitamin/mineral supplements, antibiotics, analgesics, and gastrointestinal drugs. A high proportion of drugs were prescribed from US FDA category A, followed by category B and C. A small percentage of drugs 2.44% and 5.09% were prescribed from drugs with positive evidence of risk (US FDA category D) during second and third trimesters, respectively. No drugs from proven fetal risk (US FDA category X) were prescribed. *Conclusion/recommendation:* A considerable proportion of pregnant women were exposed to drug, including those with Positive evidence of risk to the fetus, during pregnancy. Health care providers should weigh the therapeutic benefits of the drugs to the mother against its potential to the developing fetus before prescribing.

KEYWORDS*:* Pregnancy women, prescription, drug use, Arada subcity.

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INTRODUCTION:

Antenatal care (ANC) is organized medical service including examination and advising a pregnant woman with the objective that every wanted pregnancy culminates in the delivery of a healthy baby without impairing the health of the mother[1]. It is more beneficial in preventing adverse pregnancy outcomes when received early in the pregnancy and continued through delivery. Early detection of problems in pregnancy leads to more timely referrals for women in high-risk categories or with complications; this is particularly true in Ethiopia, where three-quarters of the population live in rural areas and where physical barriers pose a challenge to providing health care. Under normal circumstances, it is commonly recommended that women see a trained health provider at least four times during her pregnancy[2]. World health statistics reported that the proportion of women receiving ANC at least once during pregnancy was about 81% for the period 2005–2011, but for the recommended minimum of four visits or more the corresponding figure drops to around 55%.

Pregnancy complications are still a major health problem among women in developing countries. The maternal mortality ratio in developing countries is 240 per 100, 000 births versus 16 per 100, 000 in developed countries. There are large disparities between countries, with few countries having extremely high maternal mortality ratios of 1000 or more per 100, 000 live births. There are also large disparities within countries, between people with high and low income and between people living in rural and urban areas. Main causes for such unfavorable outcomes continue to be post-partum hemorrhage, puerperal sepsis, pre-eclampsia and eclampsia, obstructed labor, unsafe abortion and others which can be prevented by optimum ANC. Hence timely treatment of these conditions can reduce the prenatal morbidity and mortality[3].

In Ethiopia, an increasing trend of ANC services by pregnant women was recorded for 11 years between 2000 to 2011surveys. However, it is the lowest in the utilization of antenatal care services when compared with other sub-Saharan African countries[2].

In Ethiopia a current estimate of maternal mortality ratio (MMR) stands at 676 deaths per 100,000 live births. Furthermore, only 34% of women received ANC from a skilled provider and 8.7% from health extension worker, and 10% had a skilled provider at delivery, in part because more than 90% of women give birth at home[4] (EDHS,2011). As a result, an estimated 22,000 women and 100,000 newborns die from complications related to childbirth each year. Many of these deaths occur within 48 hours after birth and could be averted with access to basic health care[5].

According to the preliminary report of the 2011 Ethiopian demographic and health survey (EDHS) among women who were informed of signs of pregnancy complications at an ANC visit for their last live birth, almost half (48%) were informed of abdominal pain as a sign of pregnancy complications. More than one-third (36%) were informed of severe headache, one-fourth (25%) were informed of vaginal bleeding, and about one-fifth (22%) were informed of vaginal gush or fluid as signs of pregnancy complications. Fourteen percent of women were informed of fever, and 7% were informed of blurred vision as possible signs of pregnancy complications. Pregnant women requiring prescription drugs pose a challenge to physicians to avoid any risk to the mother and to the fetus[4].

The physiological changes that occur in pregnancy challenge clinicians managing disease states during pregnancy in the selection of medications best suited to treat their patients. Maternal drug use during pregnancy may pose a teratogenic risk to the fetus. However, the recommendation to avoid all drugs during early pregnancy is unrealistic and may be dangerous. Pregnancy should not deter clinicians from providing their patients with appropriate management of their medical conditions; hence, prescribing in pregnancy is an unusual risk benefit situation[6].

The rational use of the drugs during pregnancy requires a careful assessment as in addition to mother, the health and life of her unborn child. Information on the use of drugs during pregnancy is not available in most of the ante-natal clinics. Careful consideration of prescribing of drugs during pregnancy and patient counseling may reduce medication errors and patient safety[7].

Statement of the problem

Concern about the safety of drugs prescribed to pregnant women has been increasingly evident since the thalidomide crisis in the 1960's and the teratogenic effects of use of diethylstilbestrol in 1971, which led the US Food and Drug Administration (US FDA) to demonstrate safety and efficacy of any drug before it is marketed[8].

However, pregnant women are generally excluded from clinical trials for fear of potential hazardous effects to the developing fetus. Safety information regarding drug use in pregnancy is gathered through case reports, epidemiological studies and animal studies, all of which have limitations. Results related to effect of drug on pregnant animals cannot always be extrapolated in human population. Hence, for most drugs there is a serious lack of comprehensive and valid data concerning their teratogenic risks in human. Thus, administration of a drug to a pregnant woman represents a unique problem for the attending physician, not only in alleviating maternal suffering but also not to harm the fetus. The potential of short and long term toxicity following intra-uterine exposure to drugs emphasizes the need of having up-to date information on the types and frequencies of exposure of pregnant women to pharmacological agents[9].

Regardless of the limited information on the safety of drugs in pregnancy, drug use in pregnancy is common[10].

Supplementary drug treatment like iron, folic acid, calcium, vitamins are prescribed commonly to improve overall nutritional status of mother and fetus. In addition, drugs may also be prescribed for conditions not related to pregnancy such as upper respiratory infections, urinary tract infections and gastrointestinal infections to name some. Also pregnant women are prescribed drugs to treat pre-existing chronic conditions such as diabetes, hypertension or epilepsy or to treat pregnancy related disorders such as pregnancy induced hypertension and gestational diabetes. Therefore, judicious use of drugs, adequate knowledge, positive approach and awareness towards the drug use are mandatory prerequisites for good maternal and child health[11].

In the developing world, including Ethiopia, poor health seeking behavior of patients, delayed initiation of ANC, low level of educational status of mothers, lack of up to date information for health care providers, especially relatively for low level health institution workers like health centers, poor access to health facilities, and low level of training of health care providers at health center level could aggravate irrational use of drugs during pregnancy[12].

Although several large surveys were conducted in other country especially in the developed world, there were only a few such researches that describe the extent and type of drugs prescribed during pregnancy in Ethiopia.

Therefore, this study will be conducted to determine the type and extent of prescribed drugs among the pregnant women attending antenatal Out Patient Department (OPD) of health centers, which found in Arada subcity and describe the pregnancy risk level of medications prescribed during pregnancy according to the US-FDA pregnancy risk classification of drugs.

It is believed that, assessing the pattern of prescription and informing the concerned body for possible intervention of the correct drug utilization of pregnant women will have a paramount importance to improve service quality.

Literature review

Historical background

There was a general belief among clinicians and patients that developing embryos and fetuses were protected in uterus by a “placental barrier.” The placental barrier was believed to insulate the fetus from substances ingested by the mother in much the same way that the blood-brain barrier is believed to protect the brain from certain medications. The concept of a placental barrier has been abandoned. It is now understood that the placenta affects not whether a medication gets to the developing fetus, but rather the extent to and rate at which it does. Although medications that are lipid soluble, have a high pH, or have a low molecular weight cross the placenta more readily than others do, it should be assumed that any drug absorbed through oral ingestion will enter the fetal circulation[13].

Women may require medicines to treat pre-existing medical conditions, incidental illness or disorders which are associated with pregnancy. Early accidental medication exposure during pregnancy or intentional medication treatment of pregnant women is of concern because use of certain medicines in pregnancy can lead to congenital abnormalities in the fetus and other harmful effects. Concern about the safety of medicines prescribed to pregnant women has been increasingly evident since the thalidomide tragedy in the 1960s[14].

The first international conference on congenital malformations was held in July, 1960. Very little was mentioned about drug teratogenesis. Joseph Warkany (1961), in his review of environmental teratogenic factors, mentioned antimetabolites and then recent descriptions of a masculinizing effect of some gestates. Wiedemann (1961) first described a new syndrome of severely malformed babies and in December 1961 the two first publications pinpointing thalidomide as the cause of such malformations appeared. This made the world aware of the difficulties of medication use in women. Thalidomide was used in the treatment of different disorders such as anxiety, insomnia, gastritis and tension; it was furthermore promoted as a safe anti-emetic medication during pregnancy. The medicine was withdrawn from the market a few years after its introduction due to severe teratogenic effects including limb defects, ear malformations and/or hearing loss, ocular anomalies and other anomalies[15].

The occurrence of the defects made medical professionals realize that medicines have the potential to cross the placenta and harm the developing fetus. A major function of the placenta is to enable the transfer of oxygen and nutrients from the mother to the fetus, and to eliminate metabolic waste products from the fetus.

Tran placental transfer involves passive transfer, active transport, facilitated diffusion, phagocytosis and pinocytosis. Almost all medicines taken by a woman during pregnancy have the potential to enter the foetal circulation. Most medicines cross the placenta mainly by passive diffusion[16].

About 7% of all neonatal deaths worldwide are caused by congenital abnormalities. Although congenital anomalies' account for a smaller percentage of deaths of neonates and infants aged 1–59 months in middle-income and low-income countries than in the wealthiest countries, more than 95% of all child deaths due to congenital anomalies occur in these settings. Thus congenital anomalies affect all countries and represent a significant challenge to public health globally.

However, the background prevalence rate for congenital abnormalities in the developing countries is unknown. In many developing countries, birth defects registries are absent and the health care services, from antenatal through obstetric to postnatal and adolescent health care, are challenged with fundamental gaps in the understanding, prevention and treatment of congenital anomalies. Without comprehensive data on congenital anomalies in this region, it is difficult to evaluate possible teratogens and to institute comprehensive and effective prevention and care services[17].

Drug use during pregnancy

Despite the common belief that the use of medications should as much as possible be avoided in pregnancy, there are several conditions in which it is almost impossible to prevent medication use. There might be chronic conditions which are already present before pregnancy, such as epilepsy, psychiatric disorders and HIV/AIDS, which need continued treatment during pregnancy. There are also conditions which occur during pregnancy, such as nausea, diabetes mellitus and hypertension, which may also require treatment. Pregnant women may also develop acute illnesses which are short term and often self-limiting (e.g. infections) but which require treatment[8].

About 8% of pregnant women need permanent medication treatment due to various chronic diseases and pregnancy-induced complications. Therefore the benefit of medication therapy to the mother has to be weighed against the potential risk to the developing fetus. In addition, unnecessary use of medicines should be avoided and discouraged particularly if the medication is being used to treat symptoms that are non-life threatening or self-limited.

Most women use prescribed medicines during pregnancy according to studies from western countries. The prevalence of medication use during pregnancy ranges from 27% to 85%. These proportions increase to up to 99% when multivitamins and minerals are also taken into consideration[18, 19, and 20].

The study done in India by Gawde *et al*. (2013) on 760 showed that all eligible pregnant women were provided with prophylactic iron and folic acid therapy. The occurrence of contraindicated medicines was desirably low. No woman was prescribed Category X drug. Pregnant women with diseases like hypertension, epilepsy and diabetes were continued with the appropriate drugs considering the risk benefit ratio. Anemia was common among all pregnant women and therefore it raises the concern about high morbidity and mortality associated with pregnancy outcome.

Another study in north India reported that an average of 1.73, 2.89 and 2.49 drugs per pregnant women, were used during first, second and third trimester of pregnancy, respectively. A majority of the drugs used, were from category-A, followed by category-B and category-D. However, category C and X drugs constituted 2.90% and 5.71% of drugs used during the third trimester and first trimester, respectively[21].

A study done in Sweden by assessing the prescribed drug register and the medical birth register showed that 57.6% purchased at least one prescribed drug during pregnancy. The most dispensed drugs during pregnancy were B-lactam antibacterial and penicillin. Agreement between drugs recorded in antenatal medical records and dispensed drugs were highest for drugs used for chronic conditions. The agreement was particularly high for thyroid therapy (85.3%), anti-intestinal inflammatory drugs (80.3%), antiepileptic (69.2%), immunosuppressant's (67.4%), and insulin (63.8%)[22].

A study in France reported that 99% of a sample of 1000 women living in Haute-Garonne in South West France received a prescription for at least one medication during pregnancy with a mean of 13.6 medications per woman. The mean number of prescribed medicines per woman was 5.2 in the first trimester, 7.1 in the second trimester and 6.6 in the third trimester. While in Australia a survey

on patterns of medication use during pregnancy showed that women used an average of 0.7 to 0.8 prescribed and 2.3 to 2.6 non-prescribed medicines (a total of 3.1 to 3.3) during the three pregnancy trimesters, compared with 1.0 prescribed and 2.2 non prescribed medicines prior to pregnancy. Use of prescribed and non-prescribed medication was 96 to 97% across trimesters[23].

In the US, Refuerzo *et al*. (2005) conducted a study on the frequency of prescription, OTC, and herbal use. They found that 96.9% of the women had taken at least one medication while pregnant. After excluding prenatal vitamin and iron supplements, they found 62.8% used OTC medications[24].

A study in the UK by Headley *et al.* (2004) on the self-reported use of all types of medicinal products collected during pregnancy in a large cohort in southwest England, reported that 92.% of pregnant women had used at least one product at some stage. After exclusion of iron, folate, vitamins, supplements, herbal and homeopathic products and skin emollients, 83% had used conventional therapeutic medications.

A survey conducted in obstetrics out-patient department (OPD) at Manipal teaching hospital in western Nepal reported that problem oriented drug use was due to nausea/vomiting (4.7%), dyspepsia (3.1%), and per vaginal spotting/bleeding (3.4%), mainly. Most of the women got 2–3 drugs and commonly included nutritional supplementation and tetanus toxoid. The most commonly prescribed drugs were nutritional supplements like iron, folate, calcium, vitamins (72.8%), followed by tetanus toxoid (12.4%), gastrointestinal (5%), and antimicrobials (4.6%). During the course of pregnancy (approximately 9 months), the use of nutritional supplementation agents increased whereas the use of gastrointestinal and psychotropic medications decreased. Antiemetics were predominantly used in the first trimester and antacids in the second trimester of pregnancy[25].

A survey conducted in America showed that majority of pregnant women were prescribed a prescription drug (56%), and 4% of women were prescribed a category D or X drug. The most common classes of medications prescribed were antibiotics (62%), analgesics (18%), asthma medications (18%), and antiemetics (17%). Women with a chronic health condition, gestational diabetes, a prenatal hospitalization, a history of infertility, or symptoms of acid reflux were also more likely to use a prescription drug than women without these conditions. Nulliparous women and women who were married or living with a partner were less likely to use category D or X drugs during pregnancy than women without these characteristics[26].

Engeland *et al.* (2008) found that among more than 100,000 pregnant women in Norway in 2004–2006; approximately 57% received a prescription medication. Medicines taken by the women were varied. They included analgesics, vitamin/mineral supplements, antacids, antispasmodics, antiemetic, benzodiazepines and antibiotics.

The study done in Ethiopia by Mohammed *et al*. (2013) on 339 women showed that 187 (55.2%) had used at least one prescription only medications (POM) during pregnancy. Majority 191 (56.3%) of medications used were from category-C followed by category-B 165 (48.7%) and category-A (35.4%). 57 (16.8%) and 24 (7.1%) were from category D and X respectively. Statins and warfarin were medications from category-X. The most commonly used medications were antibiotics (42.5%) and analgesics (40.1%) [27].

Kebede *et al*. (2009) conducted a study to assess drug use among antenatal women in Addis Ababa. A total of 1268 women were included in the study; of which 71.3% of them were prescribed at least one drug during pregnancy. More than thirty four percent of the pregnant women had received iron with folic acid or vitamin only. The number of women for whom drugs were prescribed increased from 29.9% in the first trimester to 70.4% and 70.3% in the second and third trimesters, respectively. Anti-anemic preparations were the most frequently prescribed class of drugs 46.8% during all the trimesters followed by systemic antibacterial 15%, analgesics 6.3%, and antacids 4.3%. Nearly 4% of the pregnant women in this study were prescribed a category D or X medication, with 3.6% exposed to category D medications and approximately 0.2% exposed to category X medications[12].

To anticipate and avoid medication exposure in early pregnancy, when prescribing a medication to a young woman, clinicians should consider that she may already be or soon become pregnant[28].

The reviewed studies have shown medication use during pregnancy is prevalent and that some potentially harmful medicines are being prescribed to pregnant women.

Among the most frequently used medicines identified by the different studies were: analgesics, vitamins/mineral supplements, antacids, antispasmodics, antiemetic, and antibiotics. The studies have also shown that medication use prevalence during pregnancy varies.

Safety of drugs used during pregnancy

Although clinical trials address questions regarding drug safety for most segments of the population, pregnant women constitute one special group that is "orphaned" with respect to this issue. The lack of adequate pregnancy safety information for the vast majority of medications, combined with a need to make appropriate treatment decisions and to communicate risk information to a potentially vulnerable population, are some of the most challenging and critical women's health issues[27].

The evaluation of the benefit of drug administration during pregnancy often constitutes a challenge. The deleterious effects of a drug on the fetus depend on: (1) the chemical and physical nature of the drug. (2) The extent of fetal exposure based on its pharmacokinetics and primarily placental transfer and drug disposition in the fetus. This is because the pharmacokinetics of a pregnant woman is different from her non-pregnant counterpart in various ways. It represents a complex interrelationship between drug absorption, distribution and metabolism and (3) most importantly, on the developmental stage at the time of exposure.

Tools for assessing reproductive risk of drugs

In order to guide health care providers in prescribing medicines to pregnant women several classification systems have been developed based on human evidence, and when unavailable, on animal data. The purpose of these classifications is to give information to health care professionals about possible or established risk or safety of using medicines during pregnancy. They also help to increase awareness among women and clinicians of adverse pregnancy outcomes associated with the use of certain medications. Thus, it should be possible to minimize the risks to the fetus by reference to these classification systems. Well-recognized classification systems are those from the United States, Australia and Sweden although the systems vary, general recommendations do apply for most medicines[29].

FDA pregnancy classification categories are explained in Table 1. Medicines in pregnancy categories C and D may have some potential risk to the fetus but that is considered to be outweighed by the potential benefits. The FDA considered that medicines in category X should not be prescribed to pregnant women because the risks outweigh the benefits.

A study conducted in Canada by Wen *et al* (2008) using a pharmacist database to estimate the frequency of exposure to prescription FDA category C, D, and X medicines in pregnant women showed that a total of 3604 (19.4%) of the women were found to have used FDA category C, D and X medications at least once during pregnancy. The pregnancy exposure rates were 15.8, 5.2 and 3.9%, respectively, for category C, D and X drugs, and were 11.2, 7.3 and 8.2%, respectively, in the first, second and third trimesters. The most common medicines were salbutamol, cotrimoxazole, ibuprofen, naproxen and oral contraceptives. Salbutamol and cotrimoxazole are category C medicines while ibuprofen and naproxen are category D medicines and oral contraceptives are category X medicines[30].

Table 1: FDA classification of drug safety during pregnancy

Category A: **Controlled studies show no risk.**	**Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.**
Category B: **No evidence of human risk in controlled studies.**	Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
Category C: **Risk cannot be ruled**	Either studies in animals have revealed adverse effects on the

out.	fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
Category D: **Positive evidence of risk.**	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g. if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
Category X: **contraindicated in pregnancy (proven fetal risk).**	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

Source: Up-to-date 19.2,2011

Autret-Leca *et al.* (2011) conducted a study in France primarily aimed at evaluating the incidence of exposure to teratogenic medicine during early pregnancy. A total of 1.1% women received at least one medication that was contraindicated during the first trimester, 9.5% received a medication that was not recommended, and 42.8% received a medication that was to be avoided.

A US retrospective study of prescriptions filled during pregnancy using data from eight health maintenance organizations, conducted between 1996 and 2000 found that 64% of pregnant women were dispensed a prescription medication during pregnancy and that 9.4% of pregnancies were exposed to medications with potential for foetal harm. In this study, it was found that 4.8% of pregnant women received a medication from category D and 4.6% received a medication from FDA category X within the 270 days prior to delivery. Overall, 3.4% of women were dispensed a category D medication and 1.1% were dispensed a category X medication after the initial prenatal care visit. The most frequently dispensed category D and X medicines included doxycycline, atenolol, secobarbital, lorazepam, clonazepam, alprazolam, propylthiouracil, temazepam, ergotamine, testosterone, flurazepam, triazolam, warfarin and simvastatin .

Similarly, another US study by Riley *et al*. (2005) reported that 4.0% of the women were prescribed category D or X medicines. The study was aimed at evaluating the extent of prescription drug use and the use of category D or X drugs during pregnancy and examining the maternal characteristics associated with use[28].

In study, which was cohort, undertaken by Bakker (2006) to compare the prescription of medicines in women over a period from 2 years before until 3 months after pregnancy, regarding the type of medicines used and the fetal risk in Netherlands, about 79.1% of the women received at least one prescription during pregnancy and 2.4% of medicines belonged to the FDA category D/X. The harmful medicines prescribed in the first trimester for pregnancy related symptoms were ovulation-stimulating medicines and for chronic conditions, antiepileptics. Doxycycline was responsible for the high percentage of harmful medicines for occasional use in the first trimester. The researchers in this study argue in favor for a cautious prescribing of medicines to healthy women in the fertile age, in which the prescription of harmful medicines should be avoided as much as possible[31].

Objectives of the study

General objective

The overall aim of the study was to assess drug prescribing pattern among pregnant women attending antenatal care in Health Centers in Arada sub city, Addis Ababa.

Specific objectives

- To determine the extent of drugs found during pregnancy.
- To identify the commonly prescribed drugs during pregnancy.

- To describe the pregnancy risk level of prescribed medications according to the US.FDA safety rating system.

METHODOLOGY

Description of the study area

The study was conducted in Addis Ababa, Arada subcity. Addis Ababa is a capital city of Ethiopia. It has latitude of 9°1'48''N and longitude of 38°44'24''E and an elevation of 1643meters above the sea level. Arada subcity is one of ten subcities of Addis Ababa. Covering 9.91 kilometer square and total population of 225,999 people. Moreover, 22,805 people live in one kilometer square. It has seven health centers, three of them are new ('Janmeda' Health Center, 'Afinchober' Health Center and 'Rasemmiru' Health Center).These new health centers started ANC services in 2013. The four old health centers are 'kebena' health center, 'Bata' health center, 'Samen' health center and "Arada" health centers. The Arada subcity has three general practitioner, 70 health officer, 192 nurses, 45 midwifes, 36 pharmacists, and 42 laboratory technicians workers. Since this study includes the data of 2012, the new three health centers, which started working in 2013, are excluded.

Study design

A retrospective cross sectional descriptive study was carried out on pregnant women who attended the antenatal clinics of health centers in Arada subcity from June 2012 to March 2013.

All pregnant women reside in Arada subcity and its surrounding and attended antenatal care service in health centers found Arada subcity from June 2012 until March 2013 were a source of population for the study. Pregnant women who were selected by systematic random sampling from source population were the study population for the study.

All pregnant women who take drugs during pregnancy, including prophylactic preparations such as iron preparations, folic acid and vitamins were included. Pregnant women, who were self-administered, were excluded from the study.

Sampling and sample size determination

All the old health centers were exclusively taken, since they have the 2012 data's, which were needed for this study. Cards were selected by using systematic random sampling. The sample size for the study was determined based on the prevalence of drug use during pregnancy. According to study done by Kebede et al. (2009), the prevalence of prescriptions drug use during pregnancy in Addis Ababa was 71.3%. By using single proportion formula taking the prevalence of drug use during pregnancy as71.3%.

$$N = \frac{(Z\alpha/2)^2 \times P(1-P)}{D^2}$$ Where;

N= desired sample size

$Z\alpha/2$=reflects the Standard score; we used 95 % confidence interval (CI) so the value of Z is 1.96.

P= proportion of prevalence (71.3% was taken from the previous studies)

D= margin of error between the sample and population, 5% marginal error is admitted.

$$N = \frac{(1.96)^2 \times 0.713(1-0.713)}{(0.05)^2} = \mathbf{314}$$

In Arada Health center the sample size was taken every 4^{th} by systematic random sampling from around 330 cards. In Samen Health Center every 3^{rd} from 250 cards and in Kebena Health Center and Bata Health Center the cards were selected every 2^{nd} by systematic random sampling

Variables

Independent variable: Age; Disease type; Number of ANC visit and Gestational age

Dependent variable: Type of drugs prescribed; Extent of drugs prescribed and Category of drugs

Methods of data collection

The data abstraction format was developed based on the antenatal care follow-up card used by the health institutions. The main focus of the data abstraction format was to gather data regarding maternal disorders, the type of drug prescribed, and the gestational age at which the drug was prescribed, the number of ANC visits the women had and the training level of the health care providers were recorded.

Data were collected by principal investigator and four students from School of Pharmacy, Addis Ababa University from April to May, 2013. The clinical records

(antenatal follow up card) of the pregnant women were reviewed and drugs prescribed for them during their pregnancy starting from the date of the initial encounter were recorded.

The data abstraction format was prepared carefully and a pretest was done in 'Janmeda' health center. Then the data abstraction format was edited accordingly.

Data processing and management

Data entry and cleaning was done using Epi-Info version 3.5.3 and analyzed using SPSS version 20 statistical software. Description of the study population was done by analyzing the distribution of the respondents by the variables in terms of frequencies and percentages. The frequency of drugs that were prescribed and the proportion of women to whom drugs were prescribed during each trimesters of the pregnancy were calculated.

The frequency of women prescribed drugs with a potential for fetal harm during pregnancy (at each trimester) was evaluated based on the U.S. FDA pregnancy risk classification system. FDA risk classification (A, B, C, D, or X) was assigned to individual drugs using Clinician's handbook of prescription drugs[32] and up-to-date 19.2 (2011)

Data entry, cleaning and analysis was done by the principal investigators with the help of the research advisor.

Ethical consideration

A written letter from School of pharmacy, department pharmaceutics and social pharmacy was presented to all medical directors of the health centers. Informed verbal consent was then obtained from each medical director of the health centers after giving verbal explanation on the nature of the study, its purpose, and the potential benefit involved. They were also told the information will be kept confidential and will be analyzed in aggregate.

RESULTS

Characteristics of pregnant women who attended ANC service

A total of 314 pregnant women's were enrolled in the study. Tables 2 and 3 give the characteristics of the study sample and maternal disorders and/or routine antenatal checkup (ANC) that lead to use of drugs during pregnancy. Majority 209 (66.6%) of the respondents were in the age group of 21-30 years with the mean age of 26.52 (SD=5.447; range = 17 to 49 years). Two hundred and thirty (73.25%) of the pregnant women had their first ANC visits between 13 and 24 weeks of their pregnancy; while 16 (5.1%) had their initial ANC visits before the 13th week and 68 (21.7%) started their ANC visits after the 24th week of their pregnancy. Two hundred twenty six (72.0%) of the respondents had four and above antenatal visits. Of total women, the number of women who had two and three antenatal visit were 25 (8.0%) and 55 (17.5%), respectively. Eight (2.5%) of women had one antenatal visit (table 2 and 3).

During first trimester, the maternal disorders most frequently recorded in the ANC follow up cards were nausea and vomiting (68.75%). During second trimester urinary tract symptoms (7.72%) and headache (7.72%) were the most frequently recorded disorders. upper respiratory tract infection (4.43%) and Backache (3.25%) were also the recorded maternal disorder during this trimester. During the third trimester backache (8.28%) and urinary tract symptoms were the first and second most frequently recorded maternal disorders, respectively. upper respiratory tract infection (5.41%) and constipation (2.86%) were also recorded. The proportion of cases of constipation increased over the trimesters; whereas a higher proportion of nausea and vomiting recorded in the first trimesters.

Table 2: Characteristics of pregnant women who attended ANC service in Health Centers found in Arada Subcity, Addis Ababa, 2013

Variables	**Number(n=314)**	Percentage (%)
Age		
17-20	49	15.6
21-30	209	66.6
31-40	51	16.5
41-50	5	1.6
Time of first visit		
At 1st trimesters	16	5.095
At 2nd trimesters	230	73.248
At 3rd trimesters	68	21.7
Number of total ANC visit		
1	8	2.5
2	25	8.0
3	55	17.5
4 and above	226	72

Table 3: Common maternal disorders according to gestational age in Health Centers found in Arada subcity, Addis Ababa, June 2013.

Maternal disorder	First trimester(n= 16)		Second trimester(n= 246)		Third trimester(n= 314)	
	N	%	n	%	n	%
Urinary tract symptoms	1	6.25	19	7.72	24	7.64
Backache	0	0	8	3.25	26	8.28
Headache	0	0	19	7.72	7	2.23
URTI	0	0	11	4.47	17	5.41
Nausea and vomiting	11	68.75	4	1.62	3	0.95
Dyspepsia	0	0	7	2.84	6	1.91
Abdominal cramp	0	0	7	2.84	6	1.91
Constipation	0	0	1	0.40	9	2.86
Genital infection	0	0	2	0.81	5	1.59
Diarrhea	1	6.25	2	0.81	0	0
Others*	0	0	3	1.23	9	2.86
Total	**13**	**81.25**	**83**	**33.74**	**112**	**35.66**

*Others includes=bleeding per vagina, toothache, tonsillitis, flank pain, joint pain, loss of appetite, nasal congestion, vaginal discharge, hemorrhoid, Skin disorder.

Prescribing pattern analysis of pregnant women

3.2.1. Extent and types of drugs prescribed during pregnancy

Including iron/folic acid combination a total of 299 (95.2%) pregnant women used at least one drug during their pregnancy (excluding vaccination) and forty two different drugs were prescribed during all pregnancy stages.

The study was done by enrolling 314 pregnant women among whom 16 (5.09%) of them were started visiting ANC during first trimester. all of them were 16 (100%) prescribed with Iron/folic acid combination, metoclopramide to 3 (18.75%), chlorpromazine and antibiotics to 2 (12.5%). one (6.25%) of them were prescribed with antiviral and acyclovir.

Excluding only iron/folic acid combination users, a total of 11 (58.75%) pregnant women received at least one drug during first trimester. The results are shown in table 5.

Among 314 pregnant women enrolled, 246 women were on ANC follow-up in second trimester. Out of these 223 (90.6%) were prescribed with iron/folic acid combination, Anti-infectives, especially systemic antibiotics were the second most widely prescribed class of drugs. Systemic antibiotics were given to (26%) of pregnant women. The most frequently used agents of this class were penicillins (53.125% of all systemic antibiotics), mainly amoxicillin 28 (8.9%). Analgesics, especially acetaminophen and diclofenac were prescribed to 16 (6.5%) and 12 (4.87) of the pregnant women. From gastrointestinal drugs antacids were prescribed to 7 (2.23%) of the pregnant women. During second trimester excluding only iron/folic acid combination users, a total of 137 (55.69%) pregnant women received at least one drug. the results are shown in table 5.

Table 4: Percentage of medication taken in all trimesters (including iron/folic acid combination) in Health Centers found in Arada subcity, Addis Ababa, June 2013.

Variables	**Number**	**Percentage (%)**
Medication given		
Yes	299	95.2
No	15	4.8

Table 5. Types of drugs used by pregnant women in all trimesters in Health Centers found in Arada subcity, Addis Ababa, June 2013.

Variables	**First trimester(n =16)**		**Second trimester(n =246)**		**Third trimester(n =314)**	
	N	%	n	%	n	%
Hematopoietic						
Iron/folic acid	16	100	223	90.6	142	45.2
Vitamin	0	0	3	1.2	7	2.2
Anti-infectives						
Antibiotics	2	12.5	64	26	68	21.65

Anthelmintic	0	0	6	2.44	6	1.9
Antiprotozoal	0	0	2	0.81	5	1.59
Antifungals	1	6.25	1	0.4	4	1.27
Anti-viral	1	6.25	0	0	0	0
CNS						
Antihistamines	1	6.25	6	2.44	7	2.2
Analgesics / anti-inflammatory						
Acetaminophen	0	0	16	6.5	7	2.2
Diclofenac	0	0	12	4.87	16	5.09
Ibuprofen	1	6.25	7	2.84	10	3.18
Indomethacin	0	0	0	0	3	0.95
Hydrocortisone	0	0	0	0	2	0.6
Pylocain cream	0	0	0	0	1	0.3
Gastrointestinal drugs						
Antacids	0	0	7	2.23	4	1.2
Metoclopramide	3	18.75	2	0.81	2	0.6
Chlorpromazine	2	12.5	2	0.8	2	0.6
Omeprazole	0	0	3	1.2	1	0.3
Bisacodyl	0	0	1	6.25	11	3.5
Hyoscine butyl Bromide	0	0	3	1.2	4	1.2
Respiratory system drugs						
Dextromethorphan	0	0	2	0.8	4	1.2

As shown in table 4 above, among 314 pregnant women, one hundred forty-two (45.2%) pregnant women prescribed with iron/folic acid combination during their third trimesters. Antibiotics were prescribed to 68 (21.65%) women, anthelmintic to 6 (1.9%), antiprotozoal to 5 (1.59%), antifungals to 4 (1.27%) women. Seven (2.2%) of them were prescribed with antihistamines. Among analgesics and anti-inflammatory drugs, the most frequently used agents of this class were diclofenac 16 (5.09%). Among gastrointestinal drugs antacids and bisacodyl were prescribed to 4 (1.2%) and 11 (3.5%) women, respectively. When iron/folic acid combination is excluded a total of 164 (52.23%) pregnant women were prescribed with at least one drug.

3.2.2. Drugs used during pregnancy with reference to us fda pregnancy risk classification system

Iron/folic acid combination, which is category A, was prescribed to all of 16 (100%) women who attended ANC. Eight (50%) of the pregnant women received a drug from category B; 3 (18%) women received from category C according to US FDA risk classification system. No drugs were prescribed during first trimester from category D and category X. The frequently prescribed category B drugs were amoxicillin, chlorpromazine, and metoclopramide; while the category C drugs prescribed were Grisofulvin, acyclovir, chlorpheneramine.

As shown in Table 6 below, among 246 pregnant women 225 (91.46%) were prescribed with drugs from Category A such as iron /folic acid combination and vitamin B. 91 (37%) women from category B drugs. The frequently prescribed drugs of this category were amoxicillin, acetaminophen, diclofenac, antacid (magnesium hydroxide), cloxacillin, erythromycin, and clotrimazole cream. 36 (14.63%) and 6 (2.44%) of women were prescribed with category C and Category D drugs, respectively.

Ciprofloxacillin, norfloxacillin, chloramphenicol, vitamin k, hyoscine butyl bromide, and omeprazole were the frequently prescribed drugs of category C during second trimester; while doxycycline was the only drug form category D. no drugs were prescribed from category X.

Among 314 pregnant women, 148 (14.13%) women were prescribed with category A drugs, iron/folic acid and vitamin B. 93 (29.61%) women from category B drugs, 58 (18.47%) women from category C and 6 (1.91%) of women from category D drugs. drugs from category X were not prescribed during third trimester. The most frequently prescribed category B drugs were antibiotics, especially amoxicillin. Bisacodyl, loratidine, metronidazole, and piperazine were also frequently prescribed drug of category B. from category C, frequently prescribed drugs were diclofenac, which is categorized as category C in third trimester only, dextromethorphan, xylometazoline, and chlorpheneramine/hydralazine combination. The category D prescribed drugs were doxycycline and ibuprofen. Ibuprofen is considered as category D in third trimester. 0ne (0.3%) of them was prescribed with drugs

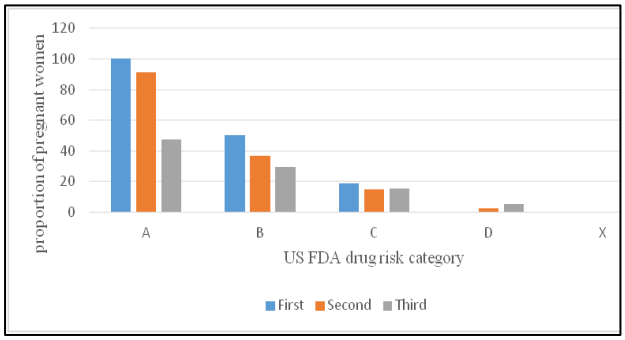
classified as having no evidence of safety during pregnancy in humans.

The proportion of women receiving drugs with Positive evidence of risk was higher in the third trimester compared to the first and second trimesters.

Table 6. Pregnant women exposed to drugs according to US-FDA risk category and gestational age (n=number of pregnant women) in Health Centers found in Arada subcity, Addis Ababa, June 2013.

US-FDA risk category	First trimester (n=16)		Second trimester(n=246)		Third trimester(n=314)	
	n	%	n	%	n	%
A	16	100	225	91.46	148	47.13
B	8	50	91	37	93	29.61
C	3	18.75	36	14.63	48	15.28
D	0	0	6	2.44	16	5.09
X	0	0	0	0	0	0

Figure1: proportion of pregnant women exposed to drugs according to US FDA risk category and gestational age



The extent and types of drugs prescribed with reference to us FDA pregnancy risk classification system.

As shown in table 7 and figure 2, 1 (12.5%), 4 (50%), and 3 (37.5%) different types of drugs were prescribed from category A, B, and C of the FDA risk classification system, respectively. Generally eight different types of drugs were prescribed during first trimester.

During second trimester 33 different types of drugs were prescribed, among these 2 (6.06%) were from category A; 16 (48.48%) from category B; 14 (42.42%) from category C; and 1 (3.03%) from category D of the FDA risk classification system.

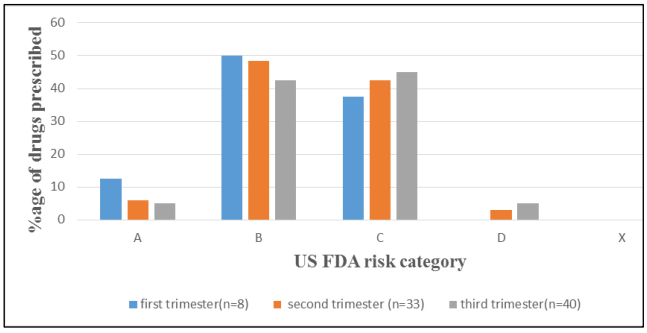
Forty different drugs were prescribed during third trimester. Among these 2 (5%) were from category A, 17 (42.5%) from category B, 18 (45%) from category C, and two (5%) drugs were from category D (doxycycline and ibuprofen) drugs. The numbers of types of drugs prescribed were high in third trimester as compared to the first and second trimesters.

Table 7: Data concerning fetal risk of drugs prescribed during pregnancy according to US-FDA risk category and gestational age (n= number of drugs) in Health centers found in Arada subcity, Addis Ababa, 2013.

US-FDA risk category	Number of drugs used in 1st trimester(n=8)		Number of drugs used in 2st trimester(n=33)		Number of drugs used in 3st trimester(n=40)	
	n	%	n	%	n	%
A	1	12.5	2	6.06	2	5
B	4	50	16	48.48	17	42.5
C	3	37.5	14	42.42	18	45
D	0	0	1*	3.03	2**	5
X	0	0	0	0	0	0

*doxycycline, **doxycycline and ibuprofen

Figure 2: percentage of drugs prescribed according to US FDA risk classification and gestational age



DISCUSSION

The aim of this study was to assess the patterns of drug prescribing by health care workers at health center levels during pregnancy. It was performed retrospectively on over 314 Arada subcity pregnant women who reside in

Arada subcity and attended the outpatient ANC clinics of the hospital from June 2012 until March 2013. Drug prescription was presented in terms of three trimesters of pregnancy; first trimester (weeks 0-12), second trimester (weeks 13-28) and third trimester (weeks 29-40).

The results of the present study show that including iron/folic acid combination a total of nearly 95% (314) pregnant women used at least one drug during their pregnancy (excluding vaccination).Our results are nearly comparable with the findings reported from the study done in France (99%), Australia (96 to 97%) and US (96.9%), but higher than those reported in a Sweden study (57.6%) and Ethiopian study (71.3%)[12,22,23, 24]. However, published studies on drugs used during pregnancy differ widely regarding variables such as variation in medications use between countries, size and demographic characteristics of the study population, the use of automated pharmacy records, patient interviews during pregnancy or after delivery, inconsistency of the methodologies (prescription collection, interview, chart review) and health care settings where these studies conducted and variations in prescribing practices between developed and developing countries. Moreover, the analysis of medications used in most studies has been done based on various risk classification systems. Hence, comparisons between studies from different countries and the subsequent interpretation of results of such studies are difficult.

In this study nearly 59% of pregnant women received at least one drug during first trimester, when iron/folic acid combination drug excluded, which was prescribed 100% during this trimester. Concerning iron/folic acid drug uses our results are comparable with the findings reported from the study done in India (100%) by Gawde et al. (2013), which showed that all eligible pregnant women were provided with prophylactic iron and folic acid therapy. This study also showed that a higher proportion of anti-emetics (metoclopramide (18.75% (16) chlorpromazine (12.5% (16) were prescribed in this trimester. This patterns in prescribing over the trimester was in agreement with the respective frequency of maternal disorder (nausea and vomiting) recorded over the trimester[1].

During second trimester excluding only iron/folic acid combination drugs users, which was prescribed for around 91% women, nearly 56% of pregnant women received at least one drug. Nearly 52% pregnant women were prescribed with at least one drug during third trimester, excluding iron/folic acid drug, which was prescribed for nearly 45% of pregnant women. Among Analgesics and anti-inflammatory drugs, diclofenac were the most prescribed one, next to hematopoietic drug in third trimester. The third mostly prescribed drugs in this trimester were gastro intestinal drugs, especially bisacodyl. This pattern of prescribing is also in agreement with the respective frequency of maternal disorder (constipation) recorded the third trimester.

The most commonly prescribed class of drugs in this study was anti-anemic. Especially in first trimester almost all pregnant women who had started visiting ANC clinics were prescribed with anti-anemic drugs. The next group of drugs commonly prescribed during the antenatal period include the anti-infectives (mainly amoxicillin) followed by analgesics (especially paracetamol (6.5%) in second trimester and diclofenac (5.09%) in third trimester). Similar finding in drug use was also reported from a study done in Ethiopia by Kebede *et.al*. (2009) where it was found that next to vitamins and iron, the most frequently used medications were anti-infectives and analgesics.

Our study demonstrated that the number of women taking drugs decreased across the trimesters from first 68.75%, to 54.07% and 49.98% in the second and third trimesters of pregnancy, excluding iron/folic acid and vitamins. This result is not consistent with previous studies. This could possibly be due to the fact that the previous studies calculate the percentage of drug use in each trimester per total study population. Despite the fact that the proportions of their study participant in each trimester were not equal[12, 27]. But the numbers of types of drugs were prescribed increased across the trimesters and thus an increased trend of types of drugs across trimester was observed from first eight, to thirty three, and forty in second and third trimesters, respectively.

The US-FDA pregnancy risk classification system was used to evaluate the risk levels of drugs prescribed during pregnancy. Although this system of classification does not fully answer the question of whether it is appropriate to treat or not to treat an individual pregnant woman, it is a widely recognized classification and provides guidance on risk[29].

In the present study the majority of the drugs prescribed were from category A followed by category B, category C (drugs for which human safety during pregnancy has not been established) and category D (drugs with evidence of fetal risk) of the US FDA classification system.

The present study shows that some pregnant women were exposed to drugs that ought to be avoided during pregnancy. We had observed that 2.44% and 5.09% of drugs with positive evidence of risk (US FDA category D) were prescribed during second and third trimesters; respectively. There is positive evidence of risk to the fetus from these drugs. Doxycycline in both trimesters and ibuprofen only in third trimester were responsible for the high percentage of harmful medicines used in second and third trimesters. However, a similar finding was also reported from a study undertaken by Bakker (2006) in the Netherlands. No drugs with positive evidence of risk were prescribed during first trimester. In the present study we could not rule out the possibility that some women may have purchased these drugs from outside the clinics or the drugs they took may not have been documented by the health care providers in the medical chart. Therefore, on the overall, our estimates may be considered conservative[31].

None of the FDA Category X were prescribed across all trimesters in the present study. There are reports of potentially harmful medications use during pregnancy (category X drugs 0.2 to 4.6%) both from developed and developing countries. compared to our findings these studies reported a higher prevalence of category X medications use during pregnancy (Andrade et al, 2004; Kebede et al, 2009; Riley et al, 2005).This inconsistency in the results could be due to methodological differences, types of medications analyzed, differences in the health-care settings, and variation in awareness level of pregnant women as well as educational level of prescribers. But similar to our finding, a study done in India by Gawde et al. (2013) reported that no woman was prescribed Category X[1].

In third trimester, one (0.3%) of them was prescribed with drugs classified as having no evidence of safety during pregnancy in humans (pylocain cream).Medications without risk class could be due to the fact that some medications are either not approved by the FDA or they have not been given a category yet, this is because some medications that are marketed and approved in any other place outside the USA may not have an American approval or classification.

Since pregnant women and women of child bearing age are generally excluded from phase I to III of clinical trials, it is not easy to assess the risk potential of drug use during pregnancy on the developing foetus. Hence, a survey of this type, which identifies drugs, that are most commonly prescribed, highlights where further study into safety and efficacy may appropriately be pursued. Further, the analysis presented in our study show a well-considered and cautious drug-prescribing pattern during pregnancy by the health care providers (midwifes and nurses) in Arada subcity health centers. The study considered prescribed drugs only and is based on what health care providers at health center levels documents in an outpatient medical record and not on what is actually consumed by the patient. Additionally, we were not able to ascertain whether drugs that were prescribed before delivery and were supposed to be taken postnatally were used during pregnancy. It is possible that drug prescribed in the later part of pregnancy might be intended for use after delivery.

LIMITATIONS OF THE STUDY

This study provides neither information on drugs dispensed in inpatient settings nor over- the- counter medications (self-medication), it only limited to the prescribed drugs, which were documented on the ANC follow up cards. Using the existing data may under estimate the prevalence of drug use

The other limitation of the study is that it does not describe the practice of drug prescribing in other health institution like hospitals and health posts. It also limited to urban areas and it does not assess the practice of drug use in rural community, so generalization of the result is not possible.

CONCLUSION

A considerable proportion of antenatal care attendant pregnant women in Arada subcity were prescribed at list one drug during pregnancy.

Vitamin/mineral supplements, antibiotics, analgesics, and gastrointestinal drugs were the common medication taken by the pregnant women.

A high proportion of drugs were prescribed from US FDA category A followed by category B and C. Only few drugs

with positive evidence of risk (US FDA category D) were found being prescribed. In addition, none of the prescribed drug were found to have proven fetal risk (category X).

RECOMMENDATION

Unfortunately, there are no authoritative detailed guidelines for the prescribers to follow in prescribing medications for pregnant women. Hence, it is essential to have a set of guidelines on drug therapy during pregnancy in order for prescribers to select the least harmful drugs. This may include the continuing medical education of health care providers on the effects of medications on both the pregnant woman and the developing foetus. In addition, health care providers must be persuaded that not all symptoms should necessarily be treated with medications and that the therapeutic restraint may be the best interest of both mother and infant. Such guidelines may have the potential of reducing inappropriate prescribing of medications that are known to pose a risk to the mother or to the developing fetus.

Finally, this study provides no information on the possible teratogenic risks and side effects of drugs taken during pregnancy on the developing fetus. Hence, a prospective study is needed to assess the safety of exposure to drugs during pregnancy.

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