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Adverse drug reactions reported during pregnancy and associated congenital disorders

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ABSTRACT

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Introduction: The main aim of this review is to bring forth the information about adverse drug events that take place because of the consumption of various sorts of medications during pregnancy and also to create awareness regarding birth defects. Not only the recognition of the unfavorable results of the drugs is difficult, but avoiding some of the medications, even during pregnancy, becomes out of the question. The non-inclusion of pregnant females in clinical trials is another factor adding to this problem. It was only after the thalidomide incidence when pharmacovigilance in pregnancy drew focus. Till today, many drugs have been reported to have severe outcomes on the developing fetus which have also had a great impact on their lives.

Methods: Several literary works from various platforms like Google Scholar, PubMed, The Lancet, American Journal of Perinatology, and many others concerning the adverse drug reactions during pregnancy and related fetal disadvantages were thoroughly reviewed.

Results: This review can cater us with a brief idea of the unpleasant results of antidepressants, antibacterials, antihypertensives, NSAIDs, and antithyroid drugs taken during the phase of pregnant nine months. Vaccines, on the other hand, are comparatively safe to use on preggers and are reported with no adverse results. Corona virus was also reported to cause serious illness in pregnant females. However, there were no reports of its vertical transmission. Drug exposure during pregnancy is not completely risk-free and can result in cardiac and CNS malformations, neural tube defects, and many other serious disorders.

Discussion: Numerous unpleasant reactions of the drugs on pregnant females and newborns have been unveiled. Nevertheless, many more such studies are obligatory for bringing forth new knowledge of the unfavorable outcomes of various drugs.

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Introduction

Pregnancy, the process of bringing a new life into the world, is a very exceptional and complex mechanism. Therefore, the health, well-being, and safety of the mother and her newborn are of utmost importance. Notwithstanding these safety concerns, the pregnant ladies are intentionally or unintentionally subjected to several

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drugs, or if put in simpler words, medicines during pregnancy are more like a norm than an exception (Dathe & Schaefer, 2019). A French study reported that about 90% of preggers are being prescribed medications (Dathe & Schaefer, 2019). However, understanding of the risk-free utilization of these drugs is still unsettled and there exists a gap between their safe use and extended outcomes.

Since the most vulnerable population of pregnant women is largely excluded from the clinical trials being held (apart from the products designed for specific use in pregnancy), a crucial need for pharmacovigilance in pregnancy is highly demanded. The WHO outlines pharmacovigilance as "the science and activities related to the detection, assessment, understanding, and prevention of adverse drug effects or any other possible drug-related problems." Moreover, it is not practicable to attain all the data regarding a drug's safe use during pregnancy and their ADRs on the unborn during a clinical trial, and therefore post-marketing evaluation of data is necessary, which makes pharmacovigilance in pregnancy of great significance. As well, most pregnancies are unplanned and females of childbearing age groups continue to take some prescription or non-prescription medicines, even though the advantages and harms of most of these drugs are either unrevealed or are inadequately recognized.

On January 29, 1848, a young girl named Hannah Greener breathed her last when she acted as a recipient for chloroform anesthesia for the removal of her infected toenail (Fornasier *et al*., 2018). This marked the beginning of Pharmacovigilance (Fornasier *et al*., 2018). Later, in the 1950s and 1960s, the thalidomide tragedy led to the prevalence of pharmacovigilance in pregnancy. It was when thalidomide was prescribed to pregnant patients for its off-label intends, as it was identified to ameliorate "morning sickness" or nausea. Following the few years of success and widespread use, approximately 10,000 children were reported to be born with phocomelia (shortened, absent or flipper-like limbs) (Kim & Scialli, 2011). It was an Australian obstetrician, Dr. McBride who put forth this link between thalidomide and congenital malformations of the newborns. Numerous reports of severe birth defects finally resulted in a ban of thalidomide (in many countries) in 1961 (Kim & Scialli, 2011).

The primary goal of this review is to provide a quick overview of adverse drug responses to commonly prescribed medications during pregnancy.

ADR and side effects

According to the World Health Organization (WHO), an adverse drug reaction (ADR) can be defined as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function." An ADR can either be mild, moderate, or severe. ADRs are unexpected and the terms- adverse drug reaction and adverse drug effect are replaceable.

On the other hand, a side effect as defined by WHO is “any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine.” A side effect can be positive or negative. Most of the time one is familiar with these effects as they are usually expected.

Effect of drugs on pregnant women and developing fetus

Pregnancy is the most necessary phase in the lifespan of a female and so are some medications which are to be taken as a medical necessity. Some of these medicines are antidepressants, anticonvulsants, antiemetics, antihypertensives, antivirals, antithyroid drugs, anti-asthmatic drugs, and many others. However, these medicines can unknowingly be threatful to the unborn. Not all medications can be accused of crossing the placenta and causing direct harm to the baby (teratogenic effect), but there are a few which without crossing the placenta can still be harmful to the fetus by either changing the physiology of the mother (for example causing hypotension), or by narrowing the vessels of placenta resulting in a decrease of nutrient and gas exchange, or by even giving rise to severe uterine hypotonia that ultimately leads to anoxic injury. Also, 85.4 % of the drug admission was noticed during the first trimester of pregnancy, chiefly in the first six weeks of being pregnant when the women are usually unaware of them having conceived (Wettach *et al*., 2013).

Many adverse drug reactions (ADRs) have been reported for the frequently consumed drugs during pregnancy which includes fetal malformations (Wettach *et al*., 2013), neural tube defects (spina bifida, anencephaly) (Khan *et al*., 2020), chromosomal abnormalities (Wettach *et al*., 2013), growth retardation (Wettach *et al*., 2013), congenital heart disease, renal failure, fetal goiter, etc. Some antibacterials consumed during pregnancy can lead to ototoxicity (resulting in fetal deafness), Gray baby syndrome, musculoskeletal defects, hemolysis, jaundice of neonate, etc. Few oral antihyperglycemic medicines like tolbutamide and metformin can cause hypoglycemia in neonates along with some unspecified long-term effects on the fetus. Intake of aspirin at the time of conception can enhance the chances of miscarriage while high doses of aspirin during pregnancy (especially the third trimester) can be responsible for lung and hearts issues in the neonate and also some bleeding disorders for both mothers as well as the baby.

Some common drugs used during pregnancy and their ADRs

Antidepressants drugs

Anxiety and depression are the disorders enveloping the new generation, including the women of reproductive age.

The fetal safety concerns make their treatment clinically demanding and enigmatic. Depressive disorders are thought to affect 9-16 % of pregnant women, with some statistics claiming as high as 20 % and roughly 2-3 % of preggers consume anti-depressive drugs (Dubovicky *et al*., 2017). Both treated and untreated depression during the pregnant phase poses some risks (Dubovicky *et al*., 2017). Commonly used antidepressants during the pregnancy period include SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin-norepinephrine reuptake inhibitors) (Dubovicky *et al*., 2017; Anderson *et al*., 2020). Venlafaxine (an SNRI), under the brand name of Effexor®, is the first-line antidepressant used and is described to cause few heart defects, cleft-palate, anencephaly, gastroschisis etc (Anderson *et al*., 2020; Polen *et al*., 2013). Also, prenatal exposure to venlafaxine resulted in a decreased IQ of children (Dubovicky *et al*., 2017). An interconnection between paroxetine (an SSRI) treatment and risks of heart defects was also derived (Dubovicky *et al*., 2017; Einarson, 2010). With bupropion consumption in the first trimester, the possibility of the ventricular septal defect (VSD) was enhanced (Louik *et al*., 2014). Using antidepressants during the pregnancy period have a greater chance of preterm births, stillbirths, spontaneous abortions, respiratory distress, etc. and PPHN (primary pulmonary hypertension) of the newly born baby and neonatal withdrawal syndrome (Oyebode *et al*., 2012; Payne & Meltzer-Brody, 2009). Moreover, discontinuing antidepressants during pregnancy is also not recommended as it is associated with certain risks (Payne & Meltzer-Brody, 2009). Leaving depression untreated during pregnancy is another controversial thing as it can lead to postpartum depression or PPD which can arise some traumatic events like suicide and infanticide and also mother-baby relation disruptions (Dubovicky *et al*., 2017; Payne & Meltzer-Brody, 2009).

Antibiotics

Antibiotics have wide use in pregnancy in case of some bacterial infections like gonorrhea, UTI, chlamydia, bacterial vaginosis, etc. Frequently used antibiotics during pregnancy include erythromycin, penicillin, quinolones, and cephalosporins as these drugs are considered safe for use by a pregnant female and there are no reports of birth defects as such. There was also not so good proof of macrolide usage and related birth defects (Bahat Dinur *et al*., 2013; Andersson *et al*., 2021; Mallah *et al*., 2020). However, according to a Swedish report, macrolides elevated the possibility of cardiovascular malformations (Bahat Dinur *et al*., 2013). Higher chances of intussusception (Hviid & Svanström, 2009) and pyloric stenosis (Cooper *et al*., 2002) in early infancy were also linked to macrolide exposure. Sulfonamide or sulfa drugs exposure is associated with congenital malformations (Li *et al*., 2020), clubfoot, cleft lip/palate, and cardiovascular defects in the fetus (Hansen *et al*., 2016). Nitrofurantoin, the antibiotic used to treat urinary tract infections because of emerging resistance of UTI bacteria towards penicillin derivatives, was observed to cause hypoplastic left heart syndrome which is a very rare birth defect (Goldberg *et al*., 2015). During cyesis, kanamycin and streptomycin, the antituberculosis drugs, should preferably be kept away as they are responsible for the damage of the eighth cranial nerve (Holdiness, 1987). Inhibition of fetal bone growth and discoloration of the fetal tooth was also noticed with the use of tetracyclines (Muanda *et al*., 2017). Norfloxacin, a broad-spectrum fluoroquinolone, caused the fetal brain to experience diverticulum dilatation (proving its neurotoxic effect) in pregnant rats (Aboubakr *et al*., 2014). Similarly, its oral intake resulted in a lower number of fetuses, and administration during the organogenesis period was followed by a decrement in fetal weight as well as fetal length (Aboubakr *et al*., 2014).

Antihypertensive drugs

Amongst the common disorders hitting during pregnancy, high blood pressure or hypertension is the one. Hypertension in pregnancy carries a few risks such as reduced blood flow to the placenta and as a result to the fetus which can lead to decreased oxygen and nutrient supply to the baby. Blood pressure during pregnancy can be categorized as mild (SBP 140 to159 and DBP 90 to 109 mm Hg) or severe (greater than 160/110 mm Hg), according to most obstetric works of literature (Podymow & August 2008). Using ACE inhibitors, used for hypertension, produced congenital malformations, cardiovascular malformations (pulmonary stenosis, atrial and ventricular septal defects, etc.), and malformations of the central nervous system (CNS), including coloboma, microcephaly with a defect in the eye, spina bifida and renal dysplasia (Teratogenicity of first trimester ACE inhibitors, 2006). ACE inhibitors and angiotensin II receptor blockers were linked to the renal damage of fetuses (Moretti *et al*., 2012). Nevertheless, no teratogenic effects of diuretics have yet been reported after their use in pregnancy, incidences of preterm births and increased birth weight have been observed (Olesen *et al*., 2001). Diuretics can also decrease the maternal blood volume and cause disturbances in fetal electrolyte balance (Donovan, 2012). Exposure to beta-blockers in the first trimester for hypertension has been associated with organ-specific teratogenicity (cardiovascular and neural tube defects along with oral cleft), however, an enhancement in overall congenital malformations was not reported (Yakoob *et al*., 2013). Also, the use of calcium channel blockers (CCBs) in the third trimester was associated with a higher risk of jaundice, seizures or convulsions, and hematologic disorders in the neonates (Alabdulrazzaq & Koren, 2012).

Non-steroidal anti-inflammatory drugs

These are the medicines used to relieve some of some usual complaints like flu, colds, headaches, and pain. Since most of these medications are available as over-the-counter (OTC) or non-prescription drugs, they are widely used by people everywhere including pregnant females. Commonly

used NSAIDs are ibuprofen, aspirin, naproxen, and a few others. Some studies reported adverse fetal outcomes with the first-trimester use of aspirin. These include cardiac and orofacial malformations (Nakhai-Pour & Bérard, 2008), overall congenital malformations (Nakhai-Pour & Bérard, 2008; Kozer *et al*., 2002), and also gastroschisis (Nakhai-Pour & Bérard, 2008; Kozer *et al*., 2002). Ibuprofen exposure in the first trimester resulted in reduced birth weight (by approx. 79 grams) (Nezvalová-Henriksen *et al*., 2016). An investigation revealed the higher possibilities of neonates with congenital malformations, especially cardiac septal defects, with the NSAID exposure in the early pregnancy (Ofori *et al*., 2006).

Thyroid drugs

For about more than 50 years, antithyroid drugs (ATDs) have been implied as a clinical approach towards treating hyperthyroidism. Treating hyperthyroidism of Grave's disease in pregnant women is significantly necessary to avoid any complications in the new mother and her baby (Andersen & Andersen, 2020; Andersen *et al*., 2014). Out of the available antithyroid drugs, while MMI (Methimazole) is recommended for non-pregnant persons, PTU (Propylthiouracil) is preferred in pregnancy (Andersen & Andersen, 2020; Kahaly *et al*., 2018). This is probably due to the few reported birth defects because of MMI (Andersen & Andersen, 2020). The associated birth defects with MMI (usage during the first trimester) are polydactyly, imperforate anus, malformations of the ear lobe, harelip, etc. (Li *et al*., 2015). Other defects due to MMI include psychomotor delay, scalp defects, omphalocele, esophageal atresia, choanal atresia, etc. (Kahaly *et al*., 2018; Li *et al*., 2015; Andersen *et al*., 2014). Moreover, the exposure to MMI and CMZ (Carbimazole, a prodrug of MMI) was also linked with increased risk of ventricular septal defect or VSD (Kahaly *et al*., 2018; Li *et al*., 2015). However, PTU exposure during pregnancy was not fully safe and was demonstrated to cause certain birth defects of the face & neck (fistula, sinus, cyst, preauricular sinus, or cyst) and also of the urinary system (congenital hydronephrosis, single cyst of kidney) (Andersen *et al*., 2014). But, PTU treatment during pregnancy had considerably reduced risks of birth defects as compared to MMI/CMZ (Andersen & Andersen, 2020; Li *et al*., 2015; Andersen *et al*., 2014).

Vaccines and ADR

Immunity acquired with vaccines is as effective in pregnant women as it is in non-pregnant ones. However, live attenuated vaccines are not used during pregnancy because of the risk of transplacental infections. Non-inclusion of pregnant women in the clinical trials, even of vaccines, have led to limited data on the safety and adverse effects of vaccines during pregnancy. But according to the available pieces of work, most of the vaccines are considered safe for use during pregnancy and have reported no such birth defects, especially the Tdap vaccine (Moro *et al*., 2017) and HPV vaccine (Scheller *et al*., 2017). The vaccine against the most known virus to cause morbidity and mortality in pregnant females, IIV (inactivated influenza vaccine) was reported with no high-quality evidence of severe birth outcomes (Giles *et al*., 2019; Kharbanda *et al*., 2017).

Corona and pregnancy

The world gets to grip with coronavirus disease 2019 or briefly, COVID-19, brought about by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and leaves the most vulnerable population of pregnant women in suspicion. Reports of the impact of COVID-19 on pregnancy or vice-versa are scarce (Moore & Suthar, 2020). Coronavirus is known to cause serious sickness in pregnant females as compared to non-pregnant ones and has also seen a growth in requirement for ventilation (Moore & Suthar, 2020, Alzamora *et al*., 2020), supplemental oxygen (Moore & Suthar, 2020), rate of ICU admissions (Moore & Suthar, 2020; Dashraath *et al*., 2020a), respiratory failure (Dashraath *et al*., 2020a, Alzamora, *et al*., 2020) as well as an increment in death rate (Moore & Suthar, 2020). Not only this but SARS-CoV-2 was reported to be responsible for high rates of cesarean delivery and pre-term births (Khalil *et al*., 2020, Alzamora *et al*., 2020). Increased rates of stillbirth were also observed during the pandemic but none were known to be because of SARS-CoV-2 directly (Khalil *et al*., 2020). But the possible reasons could be fear of catching an infection and as a result, unwillingness to visit a hospital as and when required, alterations in services of obstetricians due to lack of staff, absence or improper imaging scans, etc. (Khalil *et al*., 2020). No vertical transmission of COVID-19 has been reported as such (Dashraath *et al*., 2020b), especially in the third trimester (Chen *et al*., 2020).

The immunity shift during pregnancy (cell-mediated to humoral immunity) exposes the mother to a higher risk to some pathogenic diseases. Vaccines have established a secured position in guarding against these communicable infections in the pregnant female, fetus as well as a newborn by providing passive immunity to the newly born baby, a reduction in the possibility of *in-utero* infections and fatal diseases, and also by deteriorating morbidity and mortality of the mother (Mackin & Walker, 2020). But instead of all these benefits known, the world still waits for a successful vaccine against COVID-19 for pregnant females (Mackin & Walker, 2020). Although being a high-priority group, pregnant women are excluded from the clinical trials and apart from some unintentional cases during the trials for COVID-19 vaccines, there has been no prior experience with preggers for mRNA vaccines (Rasmussen *et al*., 2021).

It is very well known that viral diseases and the usage of antivirals during the pregnancy period raise the possibility of neurodevelopmental congenital anomalies, like neural tube defects or NTDs of the newborn. These may include spina bifida (spinal cord malformations) and

hydrocephalus, anencephaly, etc. (malformations of the brain). In the same way, there may be some similar effects, as an outcome of COVID-19 infection or related drugs during pregnancy, which has yet been undiscovered (Khan *et al*., 2020). Although little is known, the chances of developing congenital birth defects are significantly increased if the mother contracts COVID-19 during her early pregnancy (Khan *et al*., 2020).

Remdesivir, a broad-spectrum antiviral nucleotide prodrug impedes the multiplication of SARS-CoV-2 in *in-vitro* studies and is considered safe to be used by pregnant females (Dashraath *et al*., 2020b). Many antiviral drugs like favipiravir, lamivudine, dolutegravir, etc. have proved efficacious against SARS-CoV-2 but either their results during pregnancy or on the fetus are unstudied or they are known for adverse birth results (Khan *et al*., 2020).

Discussion

There are previously reported studies that indicate adverse drug reaction during pregnancy showing congenital disorders like malformation, phocomelia caused by the use of thalidomide, and adverse drug reaction that affects mothers like gastrointestinal disorders caused by the use of iron formulation and antiretroviral preparations (Santini-Oliveira et al., 2014). As pregnant women are excluded from clinical trials, that is the main premarketing tool to identify and assess ADR. Therefore, the information related to the safety of medication during pregnancy is limited, and also there is w a requirement for epidemiological research to assess the prevalence of adverse events in pregnant women. This paper will help in enhancing the understanding of adverse drug reactions that may occur on consuming medications during pregnancy without having appropriate information about the outcomes. Also, this review will help arouse consciousness amongst researchers, drug manufacturers, pregnant and non-pregnant females worldwide regarding the unwanted results that may arise after taking some of the most frequently used drugs. Pharmacovigilance in pregnancy is, therefore, of utmost importance and must be talked about more often.

Conclusion

According to the published literature, it is quite elucidated that exposure to medications during pregnancy cannot entirely be safe. It may pose some risks both to the new mother as well as her newborn. Intake of antidepressants during pregnancy can cause heart defects, respiratory distress, primary pulmonary hypertension in the neonate, etc. Treatment with antibacterials can result in hypoplastic left heart syndrome and other congenital malformations, while treatment with high blood pressure medicines can cause cardiovascular and CNS malformations. NSAIDs consumption was associated with orofacial malformations along with cardiac defects. Reported ADRs of thyroid drugs were a psychomotor delay, polydactyly, scalp defects, imperforate anus, and a few birth defects of face and neck. Although coronavirus is known for inflation in rates of admissions in ICU, respiratory failure, C-section, and stillbirths, the adverse drug reactions of the antivirals consumed against it have yet been unrevealed. No vertical transmission of coronavirus has been reported yet. Therefore, it is being concluded from this paper that more studies are requisite for identifying adverse drug reactions and their associated fetal disorders during pregnancy.

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Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

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