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Review paper

Cardiac birth defects induced by maternal medications

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Abstract

Cardiovascular malformations form the largest group of congenital anomalies, typically quoted at 0.8% of all live births. Several medicinal drugs have been proven to cause cardiovascular malformations. We discuss here the risks of the major known medications, including lithium, valproic acid, ondansetron, methylphenidate, topiramate, and the newly recognised dydrogesterone. In contrast, we discuss the controversial and debated effects of selective serotonin reuptake inhibitors (SSR) and selective serotonin norepinephrine reuptake inhibitors (SNRI). Subsequently we describe the principles of counselling pregnant women and those planning pregnancy, who are exposed to these drugs.

Key words: lithium, ondansetron, cardiac malformations, maternal medications, dydrogesterone.

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Introduction

Congenital malformations occur in 3–5% of all pregnancies [1]. Cardiovascular malformations form the largest group of congenital anomalies, typically quoted at 0.8% of all live births [2]. While there have been suggestions that many drugs might cause cardiac malformations, only a small number of medications taken during organogenesis have been statistically proven to cause birth defects.

Over the last 35 years we have counselled numerous families and health professionals in different countries on the safety/risks of medications during pregnancy and lactation [3]. Recently we established a unique medical journal to allow clinicians, scientists, and other health professionals a forum to discuss these issues ("Motherisk International Journal") [4].

The objective of the present review is to update clinicians on emerging evidence of malformations associated with medications and to allow improved counselling and clinical management. Table 1 provides a summary of drugs taken by mothers, which have been documented to be associated with increased congenital cardiac malformations.

Lithium carbonate

Since the 1980s anecdotal and observational evidence of increased risk for Ebstein's anomaly (tricuspid insufficiency) has emerged [5]. Being a first-line medication for bipolar disorder, and because half of all pregnancies are unplanned, large numbers of women may expose their fetuses to teratogenic risks. Recently, large observational studies have shed new light on the size and determinants of such risks.

In a large American study, cardiac malformations occurred in 16 out of 663 infants exposed in utero to lithium (2.41%), as compared to 15,251 out of 1,322,955 non-exposed infants (1.15%), yielding an adjusted risk ratio of 1.65 (95% confidence interval [CI]: 1.02–2.68) [6]. This study had a sufficiently large sample size to calculate for the first time the dose-dependent relationship of the teratogenic effect of lithium: The risk ratio was 1.11 for a daily dose of up to 600 mg/day, 1.6 for

Table 1. Medications that have been associated with increased risk of congenital cardiac malformations

Medications	Risk of congenital cardiac malformations
Lithium	Cardiac malformations in general Specific focus on Ebstein anomaly and right ventricular outflow tract obstruction defects
Selective serotonin reuptake and serotonin-epinephrine reuptake inhibitors (SSRI, SNRI)	No apparent increased rates of VSD or ASD Debate whether there are more complex cardiac malformations
Valproic acid	Neural tube defects Genitourinary and musculoskeletal defects Limb defects Cognitive impairment Increased risk for autism Cardia defects (unspecified)
Ondansetron	Cardiac, mostly septum defects, mostly VSD Orofacial cleft
Topiramate	Conotruncal heart defects, ventricular septal defects, coarctation of the aorta and ductus arteriosus
Methylphenidate	Cardiac malformations in general
Dihydrogesterone	Overall cardiac malformations Aortic insufficiency Spina bifida Hydrocephalus Hypospadias Cryptorchidism
Isotretinoin	Facial and ear defects Lalate defects Spinal cord defects Thymus abnormalities Cognitive defects Overall cardiac defects
Alcohol	Cognitive and behavioural abnormalities Facial dysmorphology Cardiac defects: septal

601–900 mg/day, and 3.22 for doses larger than 900 mg/day. The prevalence of right ventricular outflow tract obstruction defects was 0.6% among lithium-exposed infants versus 0.18% among unexposed controls (adjusted risk ration 2.66, 95% CI: 1.00–7.06).

These dose-dependent characteristics are novel and clinically important because many women who did not require the higher end of the dose were counselled until now to avoid using lithium altogether even if clinically important.

A common error in managing pregnant women on lithium is discontinuing the medication for the whole pregnancy, despite of the fact that it cannot produce a malformation after the completion of embryogenesis. Another potential misconception is regarding the dose, because in the second and third trimesters of pregnancy there is a marked increase in glomerular filtration rate, the elimination of lithium through the kidney is enhanced, and the pregnant patient may need higher doses to stay in the therapeutic range [7]. For many clinicians the idea of giving more drug in late pregnancy is unpalatable.

Antidepressants

Depression affects up to 20% of pregnant women, and many of them need pharmacotherapy to keep themselves in good health. Since their introduction, selective serotonin and serotonin- norepinephrine reuptake inhibitors (SSRI and SNRI) have become the drugs of choice for this condition, and they are prescribed to millions of pregnant women worldwide [8]. Initial observational studies have been reassuring, not showing malformation risks. On the other hand, their use was associated with neonatal discontinuation syndrome, in a pattern quite similar to what happens to an adult patient abruptly discontinuing SSRI/SNRI use [9]. Quite commonly women received very low, suboptimal doses due to fears of malformations. However, after 15 years of reassuring data, new reports based on large databases claimed an excess in cardiac malformations, mostly with paroxetine, leading the Food and Drug Administration (FDA) to establish warning labels. The results of additional studies and meta-analyses were contradictory. To try to resolve this issue, we conducted a prospective observational study with over 1000 prospectively collected paroxetine cases, showing only 0.7% of cardiac malformations, a rate similar to that in the unexposed control group, and congruent with textbook rates of congenital cardiac malformations [10]. This discrepancy led to focusing on potential sources of uncontrolled bias in studies based on large administrative databases.

We subsequently showed that depressed women are significantly more likely to see physicians, to have fetal echocardiogram and ultrasound, and have their young children visiting emergency rooms [11], all of which result in a much greater likelihood of detecting a cardiac malformation than among healthy women. Moreover, because most ventricular septal defects (VSD) close spontaneously at a young age, early detection of cardiac malformation in the depressed group of women will yield more cases than among unsuspected controls. This type of ascertainment bias has not been previous explored in pregnancy. Our hypothesis was proven by a large cohort study covering over 800,000 births in Denmark [12]. Children exposed to SSRI had a twofold higher risk for VSD but so did babies born to depressed mothers who chose not to take any antidepressant during pregnancy.

Valproic acid

The association between valproic acid and neural tube defects was first established in 1980 [13]. Over the ensuing decades more and more teratogenic risks have been identified. In a cumulative and conventional meta analyses of 59 cohort studies, the following signals emerged: neural tube defects were confirmed in 1992, genitourinary and musculoskeletal in 2005, congenital heart defects in 2006, and cognitive defects in 2010 [14]. Presently, despite being a first-line drug for generalised seizures and bipolar disorder, there have been warnings against

its use in an increasing number of countries, in pregnant women or in those planning pregnancy.

Similarly to lithium, recent research strongly suggests a dose dependency with a threshold for teratogenicity at a daily dose of 1000 mg/day [15].

Ondansetron

Ondansetron has emerged as a leading medication for nausea and vomiting in pregnancy, despite the fact that it is not FDA approved for use during pregnancy. The data on different malformations have been controversial among different studies [16]. However, oral clefts and cardiovascular malformations repeatedly showed a positive signal.

In a study from the Swedish Medical Birth Register, the authors identified 1349 infants born to women who had taken ondansetron in early pregnancy between 1998 and 2012 [17]. After adjustment for the year of delivery, maternal age, parity, smoking in early pregnancy, and pre-pregnancy body weight, no statistically significant increased risk for major malformations in general was found. In contrast, the risk for cardiovascular birth defects and, notably, cardiac septum defects was increased (OR = 1.62, 95% CI: 1.04–2.14). In a recent American study, first-trimester exposure to either intravenous or oral ondansetron and risk of major malformations was sought among 33,677 deliveries, with 3733 (11%) receiving the drug in the first trimester in doses ranging between 2.4 and 1008 mg [18]. Ondansetron was associated with risk ratios ranging from 1.7–2.1 for neonatal VSD. This risk corresponds to one additional case of VSD for every 330 pregnancies exposed to the drug in the first trimester. Of importance, the association was dose dependent with an RR of 3.2 (95% CI: 1.0–9.9) among women receiving the highest cumulative dose.

Another recent study investigated the risk of specific structural birth defects associated with ondansetron exposure during the first trimester in a large, US, commercially insured population including 864,083 mother-infant pairs from 2000 to 2014 [19]. First-trimester exposure to ondansetron was associated with increased risk of cardiac (OR = 1.52, 95% CI: 1.35–1.70) and orofacial cleft defects (OR = 1.32, 95% CI: 0.76–2.28) in offspring when compared to women with no antiemetic exposure during pregnancy.

While there were also studies not showing increased teratogenic risk, in 2019 the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended that ondansetron should not be used by women during the first trimester of pregnancy because they can increase the risk of oral cleft or cardiovascular malformations. Moreover, the agency suggested that women using the drug prior to pregnancy should use effective contraception [20].

Topiramate

This antiepileptic and antimigraine agent has shown a clear signal for increased risk of oral cleft when used at high doses (> 100 mg/day), and a less consistent signal for other malformations. Using four healthcare databases, Tennis *et al.* searched for common malformations, showing that conotruncal heart defects, ventricular septal defects, coarctation of the aorta, and ductus arteriosus all had a prevalence ratio greater than 1.5 [21]. Topiramate is contraindicated during pregnancy because of its association with oral clefts.

Methylphenidate

While for decades attention-deficit/hyperactivity disorder (ADHD) was regarded as mostly a paediatric condition, it is apparent that many adults continue to be afflicted by this condition, and presently an estimated 30–40% of patients continue with ADHD symptomatology into adulthood. With more adults using stimulants for ADHD, there is evidence of increased numbers using ADHD medications in pregnancy. Methylphenidate has been a first-line treatment for ADHD, with relatively large numbers of users. In a scoping review and meta-analysis of observational cohort studies, we recently compared malformation rates among offspring exposed to methylphenidate during early pregnancy to the rates in the general population. A meta-analysis of four cohort studies, with almost 3000 women exposed to methylphenidate only and almost 3 million unexposed controls, yielded an OR of 1.26 (95% CI: 1.05–1.51) for major malformations and 1.59 (95% CI: 1.02–2.49) for cardiac malformations. Hence, methylphenidate exposure in early pregnancy is associated with a small but significant increased risk for major malformations, which can be attributed mostly to increased risk of cardiac malformations. Presently, while the risk to the unborn fetus of methylphenidate requires further study, it may be advisable to consider fetal echocardiography in women using methylphenidate during pregnancy [22].

Dydrogesterone

The progestin dydrogesterone (DYD) has been widely used since 1961 and is indicated for threatened or repeated miscarriages, luteal insufficiency, dysmenorrhoea, and premenstrual syndrome. Repeated studies have demonstrated efficacy equivalent to micronised vaginal progesterone, with about one third of success in maintaining a pregnancy. In contrast, fetal safety has been only sparsely investigated because, typically, reports by fertility scientists are ended after confirming the pregnancy rather than after the birth of the child. The introduction of the oral contraceptive pill in the 1960s raised serious concerns regarding sexual abnormalities in male fetuses. However, numerous studies and repeated meta-analyses have confirmed the fetal safety of "the pill" [23]. Because DYD is substantially more potent than most progestins, one cannot extrapolate from the fetal safety of the oral contraceptive pill to DYD.

In 2015, a case control study from Gaza, Palestine compared neonates born to women treated with DYD to untreated controls showing a 2.5-fold increased risk for cardiac malformations [24]. This study, published in the journal Paediatric Cardiology, would probably have gone unnoticed had "The Lancet" not chosen to republish it.

To address this safety question, we utilised Maccabi Health Services in Israel, with more than 2.1 million insured members [25]. We identified all cases of pregnant women receiving DYD

Table 2. Odds ratios (95% confidence interval) of selected congenital malformations in children exposed in utero to DYD vs. an unexposed control group, after excluding those exposed also to IVF/ART, or when combined with those exposed to IVF/ART, and after adjusting for potential confounders

Congenital malformations	Dydrogesterone	DYD + IVF/ART
Hypospadias	1.28 (1.06–1.55)	1.56 (1.31–1.85)
Undescended testis cryptorchidism	1.0 (0.85 –1.19)	1.37 (1.19–1.58)
Cong. hip dislocation	0.9 (0.78–1.04)	1.58 (1.42–1.78)
Fallot tetralogy	1.1 (0.72–1.33)	
VSD	1.02 (0.91– 1.32)	1.07 (0.86–1.34)
Renal dysplasia	1.04 (0.85–1.33)	2.16 (1.22–3.82)
Cong. pylorus stenosis	1.04 (0.84–1.18)	1.25 (0.86–1.82)
PDA	1.27 (0.96–1.67)	1.51 (1.17–1.95)
Cong. aortic insufficiency	1.65 (1.008–2.71)	1.96 (1.25–3.1)
Pulm. stenosis	0.95 (0.81–1.48)	1.21 (0.81–1.81)
Cong. cataract	1.52 (0.84–2.76)	1.52 (0.84–2.76)
Spina bifida	2.29 (1.32–3.97)	2.29 (1.32–3.97)
Cong. hydrocephalus	1.75 (1.03–1.96)	2.04 (1.28–3.25)
TGA	2.03 (0.75–5.4)	2.03 (0.75–5.4)
Overall cardiovascular malformations	1.18 (1.06–1.33)	1.31 (1.12–1.42)

PDA – patent ductus arteriosus, TGA – transposition of great arteries

between 1 January 1999 and 31 December 2016. We identified all purchases of DYD from participants medical records, including the dose and number of packs during the nine months preceding the birth date of the child and verified first-trimester exposure to DYD. We searched whether, in addition to DYD, the woman underwent in vitro fertilisation (IVF) or other methods of assisted reproductive technology (ART), because these procedures have been associated with increased risk of birth defects. Women exposed to IVF or ART were excluded from the primary analysis but were included in a secondary sensitivity analysis. The control group consisted of all women giving birth to children in the same time frame, who did not receive DYD. All major malformations were identified using the International Classification of Diseases (ICD9).

Overall 8508 children were born after maternal use of DYD during pregnancy (4417 boys, 4091 girls). After removing those who were also on ART, we had 7728 infants. Overall, during this period 777,422 children were born in Maccabi (399,391 boys and 378,031 girls). Women receiving DYD were twice as likely to have undergone IVF than the control group women (9% vs. 4%, respectively; $p < 0.0001$). Children exposed in utero to DYD had a slightly lower birth weight (3096 ±631 g vs. 3222 ±536 g, respectively; $p < 0.0001$) and shorter gestation (38.5 ±wk. vs. 39.0 ±1.95 wk., respectively; $p < 0.0001$).

With DYD exposure only, there were increased teratogenic risks for congenital aortic insufficiency and overall cardiac malformations, as well as for hypospadias, spina bifida, and congenital hydrocephalus. When DYD was combined with IVF/ART, there was also increased risk for cryptorchidism, hip dislocation, and renal dysplasia (Table 2).

The increased risk of cardiovascular defects was consistent with the case control study reported from Gaza [24]. The increased risks of hypospadias and cryptorchidism were consistent with the biological effects of a potent progestin on male genitalia. The increased risk for spina bifida was consistent with the documented effects of oral contraceptives on lowering of plasma folic acid levels [26]. We also detected increased risk of hydrocephalus without neural tube defects.

The cumulative evidence suggests that DYD increases the risk of specific congenital malformations, including several serious cardiovascular anomalies.

Isotretinoin

Isotretinoin was introduced in the early 1980s to treat cystic recalcitrant acne vulgaris. Soon after its introduction, similar to animal studies, this vitamin A analogue was recognised as the most notorious teratogen since thalidomide, adversely affecting the development of the brain, face, palate, heart, spinal cord, ear, and thymus [27]. The rate of major malformation was originally reported at almost 30%, and isotretinoin-exposed fetuses exhibited 30% mental retardation even in the absence of gross malformations and up to 60% poor performance in neuropsychological tests. Despite being on the market for over 40 years, we could not locate a study that addressed the incidence and exact nature of the cardiac malformations produced.

Ethyl alcohol

Since the discovery of prenatal exposure to ethyl alcohol by maternal drinking, it has become evident that, in addition to the core findings of in utero and postpartum growth restrictions, typical facial changes, and a spectrum of damages in brain function, fetal alcohol spectrum disorder (FASD) also causes damage to the developing heart. In 12 case series studies of subjects with FASD, the proportion of cases with atrial (ASD) and ventricular (VSD) septal defects, as well as less common effects, ranged from 33% to 100%. In an analysis of 14 retrospective studies, the rate of septal defects was 21%, other structural defects 6%, and unspecified defects 12%. In two case-control studies, the odds of congenital heart defects ranged from 1.0 (mild symptoms) to 18.0 (full-blown fetal alcohol syndrome). Children with FASD need increased levels of attention to prenatal alcohol exposure as a potential aetiology of congenital heart disease [28].

Counselling women about teratogenic risk

Owing to high levels of anxiety among pregnant women – and because half of all pregnancies are unplanned – every year many thousands of women need counselling about fetal exposure to medications. Clinicians providing such counselling to planning or pregnant women must ensure that their information is up to date and evidence based, and that the woman

understands that the baseline teratogenic risk in pregnancy (i.e. the risk of a neonatal abnormality in the absence of any known teratogenic exposure) is about 3%. It is also critical to address the maternal-fetal risks of the untreated condition if a medication is avoided. Recent studies have shown serious morbidity in pregnant women who discontinued selective serotonin reuptake inhibitor therapy for depression due to fears of teratogenicity.

A woman who needs antiepileptic therapy and who is well controlled on valproic acid should discuss other therapeutic options and initiate the alternative drug optimally well before conception. If a woman takes the drug through the first trimester, she should be advised on the attendant fetal risks and tests that can be performed during pregnancy. Because we are dealing in this paper with drugs causing cardiac birth defects, it is important to consider ultrasound, echocardiogram, electrocardiogram, and other diagnostic tests that can get closer to a specific diagnosis. Because valproic acid, lithium, and ondansetron appear to cause dose-dependent teratogenicity, the clinician should examine whether the dose is in excess of the known safety limit. Presently, though, the safety limit is defined as a total daily dose, and it is not yet corrected for body weight.

In the case of DYD, it is important to explain to women requiring the medication the potential increase of cardiovascular malformations and the ability to detect a proportion of them prenatally.

Conflict of interest

The author declares no conflict of interest.

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