Medicines Adverse Reactions Committee

Meeting date	9/06/2022	Agenda item	3.2.2
Title	**Methylphenidate and risk of birth defects**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Methylphenidate	Concerta Extended Release Tablets Modified release tablet (Class B2 Controlled Drug) 18mg*, 27mg*, 36mg*, 54mg*	Janssen-Cilag (New Zealand) Ltd
	Methylphenidate Extended Release Modified release tablet, Teva (Class B2 Controlled Drug) 18mg*, 27mg*, 36mg*, 54mg*	Teva Pharma (New Zealand) Limited
	Ritalin Tablet, 10mg* (Class B2 Controlled Drug)	Novartis New Zealand Ltd
	Ritalin LA Modified release capsule (Class B2 Controlled Drug) 10mg*, 20mg*, 30mg*, 40mg*, 60mg	
	Rubifen Tablet (Class B2 Controlled Drug) 10mg*, 20mg*, 5mg*	AFT Pharmaceuticals Ltd
	Rubifen SR Modified release tablet (Class B2 Controlled Drug) 20mg*	

PHARMAC funding	*Products are funded by PHARMAC with special authority on the Community Schedule.
International action	EMA: PRAC recommendations for update of product information (July 2019) TGA: Updates to product information for methylphenidate products with new information about use in pregnancy (July 2021)
Classification	Prescription medicine
Usage data	The table below shows the number of people (NumPpl) that received a dispensing of methylphenidate from a pharmacy at least once during the specified year (includes people who received a repeat dispensing during the year). This includes pregnant women. The (NumPreg) is also shown in the table. Data source is from the Ministry of Health's Pharmaceutical Collection and the Qlik PoC Dispensing in Pregnancy Application.

Year	**NumPpl Methylphenidate hydrochloride**	**NumPpl Methylphenidate hydrochloride Extended release**	[redacted]
2016	12,390	9,246	[redacted]
2017	13,603	10,351	[redacted]
2018	15,325	11,527	[redacted]
2019	17,217	13,057	[redacted]
2020	19,650	14,754	[redacted]

Advice sought	**The Committee is asked to advise:** • If the current evidence supports an association between first trimester exposure to methylphenidate and an increased risk of congenital malformations in the baby? • If there is a need to include information in the data sheets for methylphenidate regarding congenital malformations for methylphenidate? • Whether the topic requires further communication, other than MARC's Remarks in *Prescriber Update*?

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1 PURPOSE

In 2019, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended that the Summary of Product Characteristics (SmPC) for methylphenidate-containing products be updated with information on birth defects [1].

In July 2021, the Therapeutic Goods Administration (TGA) subsequently changed their pregnancy category for methylphenidate products and updated their Product Information (PI) to reflect this change [2].

The purpose of this report is to review the information on methylphenidate-containing products and the risk of birth defects when used in pregnant women.

2 BACKGROUND

2.1 Methylphenidate

Methylphenidate is a medicine used to treat Attention Deficit Hyperactivity Disorder (ADHD) and narcolepsy [3]. The exact mechanism of action of stimulants in ADHD is unknown, but they affect the dopaminergic and noradrenergic systems. This causes the release of catecholamines from storage sites at CNS synapses. Stimulants have been used to treat ADHD since the 1930s [4].

2.1.1 Indications

Concerta ER Modified release Tablets [5]

- Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Methylphenidate Extended Release (Teva) Tablets [6]

- Treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Ritalin Tablets, Ritalin LA Capsules [7]

- Attention-Deficit/Hyperactivity Disorder (ADHD, DSM-IV)
- Special Diagnostic Considerations for ADHD in children
- Special Diagnostic Considerations for ADHD in adults
- Narcolepsy (Ritalin only)

Rubifen and Rubifen SR Tablets [8]

- Attention Deficit/Hyperactivity Disorder (ADHD)
- Special Diagnostic Considerations for ADHD
- Narcolepsy

2.1.2 Attention Deficit Hyperactivity Disorder [9]

ADHD is a common neuropsychiatric disorder of childhood and adolescence and often persists into adulthood. The pathogenesis is unknown, and deficits are related to frontal-subcortical dysfunction and deal with executive function. Adults with ADHD also suffer from impairments such as memory or information processing speed deficits.

2.2 Birth defects/congenital malformations

Congenital anomalies/birth defects are structural or functional anomalies that occur during intrauterine life. They are structural changes present at birth that can affect almost any part or parts of the body (eg, heart, brain, foot) and can occur at any stage of pregnancy [10].

The Pharmacovigilance Risk Assessment Committee (PRAC) recommended that all Product Information (PI) for methylphenidate containing products be updated with information on birth defects are below (SmPC section 4.6) [1].

(new text **underlined and in bold,** deleted text ~~strike through~~)

SmPC Section 4.6

~~There is limited amount of data from the use of methylphenidate in pregnant women.~~

Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

SmPC Section 4.8 it should be added:

- SOC "Psychiatric disorders": bruxism (frequency: *common*)
- SOC "Renal and urinary disorders": incontinence (frequency: *unknown*)
- SOC "Musculoskeletal and connective tissue disorders": trismus (frequency: *unknown*)

Methylphenidate products with indication(s) in Adults:

The frequency of "hyperhidrosis" should be updated to: common*

***ADR from clinical trials in adult patients that were reported with a higher frequency than in children and adolescents**

Package Leaflet

All MPH products:

2. What you need to know before you take [TRANDNAME]

Pregnancy, breast-feeding and contraception

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

~~It is not known if methylphenidate will affect an unborn baby.~~

Available data do not suggest an increased risk of overall birth defects, whilst a small increase in the risk of malformations of the heart when used during the first three months of pregnancy could not be ruled out. Your doctor will be able to give you more information about this risk. Tell your doctor or pharmacist before using methylphenidate if you or your daughter:

- is sexually active. Your doctor will discuss contraception.
- is pregnant or think might be pregnant. Your doctor will decide whether methylphenidate should be taken.

In July 2021, the Australian Therapeutic Goods Association (TGA) changed the methylphenidate pregnancy category from Category B3 to Category D (see below for category definitions). This change aligns with that recommended by the PRAC and was due to the small increased occurrence seen in observational studies of fetal cardiac malformations in births where women who exposed to methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies. In addition, the Patient Information (PIs) have also been updated to include this new information in their respective '4.6 Fertility, Pregnancy and Lactation' sections [2].

Following the PRAC recommendations, Medsafe reviewed this safety concern in May 2020. At the time of the review, no relevant cases were reported in New Zealand and was given low priority however the recent changes from the TGA has prompted this review.

2.2.1 Australian pregnancy categorisation system [11]

The Australian pregnancy category definitions are shown in Table 1. Note that this system is no longer in use in New Zealand. However, many NZ data sheets still include the pregnancy information because the same products are used in the Australia and the data sheets are harmonised.

Table 1: Australian pregnancy category definitions for prescribing medicines

Category	Definition
A	Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.
B1	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation of other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
B2	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation of other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
B3	Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.
D	Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damaged. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
X	Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

2.3 Data sheets

New Zealand

Table 2 shows a summary of information in the New Zealand-approved data sheets. See Annex 1 for the full information.

All data sheets state that the safety of methylphenidate has not been established in pregnancy and no studies are available on the use of methylphenidate in pregnant women. There is no information about congenital malformations.

Table 2: Comparison of information relating to use in pregnancy in the New Zealand methylphenidate data sheets

Product Name	Use in Pregnancy?	Risk Benefit Statement	Congenital Malformations	Animal Teratogenicity
Concerta	Safety not established	Use only if potential benefit outweighs potential risk	No	Yes
Methylphenidate Extended Release (Teva)	Safety not established	Use only if potential benefit outweighs potential risk	No	Yes
Ritalin and Ritalin LA	No data/insufficient experience	Use only if potential benefit outweighs potential risk	No	Yes
Rubifen and Rubifen SR	No data/insufficient experience	Use only if potential benefit outweighs potential risk	No	Yes

2.3.1 International product information

Relevant information from the Australian, UK and US methylphenidate prescribing information is summarised below. The text relating to congenital malformations is highlighted in yellow.

The Australian PI and UK SmPC have information about the risk of congenital malformations because of the recommendation from PRAC. The US labels state that safety has not been established, with the Ritalin label stating that a drug-associated risk has not been identified.

2.3.1.1 Australia

Ritalin 10/Ritalin LA [12]

Section 4.6: Fertility, pregnancy and lactation

Women of child-bearing potential

Methylphenidate should not be prescribed for women of childbearing age unless, in the opinion of the physician, the potential benefits outweigh the possible risks (see Use in Pregnancy).

Use in pregnancy

Category D

The safety of methylphenidate for use during human pregnancy has not been established. Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations in women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Methylphenidate should not be prescribed for pregnant women unless, in the opinion of the physician, the potential benefits outweigh the possible risks. As a general rule, no drugs should be taken during the first 3 months of pregnancy, and the benefits and risks of taking drugs should be carefully considered throughout the whole of the pregnancy.

2.3.1.2 United Kingdom

Ritalin 10mg Tablets UK SmPC and Concerta XL Prolonged-release tablets UK SmPC [13, 14]

4.6 Fertility, pregnancy and lactation: Pregnancy

Data from a cohort study of in total approximately 3,400 pregnancies exposed in the first trimester do not suggest an increased risk of overall birth defects. There was a small increased occurrence of cardiac malformations (pooled adjusted relative risk, 1.3; 95 % CI, 1.0-1.6) corresponding to 3 additional infants born with congenital cardiac malformations for every 1000 women who receive methylphenidate during the first trimester of pregnancy, compared with non-exposed pregnancies.

Cases of neonatal cardiorespiratory toxicity, specifically foetal tachycardia and respiratory distress have been reported in spontaneous reports.

Studies in animals have only shown evidence of reproductive toxicity at maternally toxic doses. (See Section 5.3, Preclinical Safety Data).

Methylphenidate is not recommended for use during pregnancy unless a clinical decision is made that postponing treatment may pose a greater risk to the pregnancy.

2.3.1.3 United States

Ritalin Label [15]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy - Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ADHD medications, including RITALIN and RITALIN-SR, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for ADHD Medications at 1-866-961-2388 or visit https://womensmentalhealth.org/adhd-medications/.

Risk Summary

Published studies and postmarketing reports on methylphenidate use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There may be risks to the fetus associated with the use of CNS stimulants use during pregnancy (see Clinical Considerations).

No effects on morphological development were observed in embryo-fetal development studies with oral administration of methylphenidate to pregnant rats and rabbits during organogenesis at doses up to 10 and 15 times, respectively, the maximum recommended human dose (MRHD) of 60 mg/day given to adolescents on a mg/m2 basis. However, spina bifida was observed in rabbits at a dose 52 times the MRHD given to adolescents. A decrease in pup body weight was observed in a pre- and post-natal development study with oral administration of methylphenidate to rats throughout pregnancy and lactation at doses 6 times the MRHD given to adolescents (see Data).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively

Concerta Label (methylphenidate HCl) Extended-Release [16]
Section 8.1

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m2 basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA on a mg/kg and mg/m2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

2.4 Usage

Note that the data provided below is only for PHARMAC-funded medicines dispensed in community pharmacy and therefore does not capture medicines dispensed in the hospital.

2.4.1 General usage

The Pharmaceutical Web Data Tool from the Ministry of Health was queried for usage data on methylphenidate. This tool provides summary data from the Pharmaceutical Collection about prescriptions and dispensings that were dispensed in the community and funded by the New Zealand Government. It does not provide the indication for use, nor whether the patient took their dispensed medicine as prescribed.

Table 3 below shows the number of people (NumPpl) that received a prescription of methylphenidate or methylphenidate extended release between 2016 and 2020.

Table 3: Number of people (NumPpl) that received a prescription of Methylphenidate hydrochloride and Methylphenidate extended release, year 2016-2020

Year	NumPpl Methylphenidate hydrochloride	NumPpl Methylphenidate hydrochloride Extended release
2016	12,390	9,246
2017	13,603	10,351
2018	15,325	11,527
2019	17,217	13,057
2020	19,650	14,754

Source: Ministry of Health. 2021. Pharmaceutical Data web tool version 13 January 2022 (data extracted from Pharmaceutical Collection on 26 November 2021). URL: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 21 March 2022).

Comments
The data shows that in recent years, the usage for both methylphenidate and methylphenidate extended release is increasing.

The Ministry of Health Qlik Data Analysis Tool (Pharmaceutical dispensings PoC) was queried to look at demographic information about people that received a dispensing of methylphenidate. Table 4 shows the number of dispensings by gender and Figure 1 shows the age at dispensing.

Between 2017 and 2019, there was greater use of methylphenidate in males compared to females and the greatest number of dispensings occurred in the 10- to 14-year-old age group.

Table 4: Number of dispensings by gender, years 2017 to 2019

Figure 1: Age of people that received a dispensing of methylphenidate hydrochloride and methylphenidate hydrochloride extended release, by five-year age group, 2017 to 2019

[redacted]

[redacted]

[redacted]

3 SCIENTIFIC INFORMATION

Author [Ref No.]	Study Design	Objective	Exposure	Outcome	Summary of Findings
9.1 Anderson et al. 2020. **[17]**	Observational case-control study	To look at associations between early pregnancy ADHD use and risk for 12 *specific* selected birth defects.	Maternal report via computer-assisted telephone interview. Mothers were asked about start/stop dates, duration and frequency of medication use during the three months before and during pregnancy using calendar dates or pregnancy months.	64 cases and 20 control mothers exposed during the month before conception through the third month of pregnancy.	Early pregnancy ADHD medicine use was associated with 3 out of 12 selected birth defects (gastroschisis, omphalocele and transverse limb deficiency).
9.2 Auffret et al. 2019. **[18]**	Systematic review and meta-analysis	An updated quantitative meta-analysis of the risk of major congenital malformations (MCM) associated with methylphenidate exposure in the first trimester of pregnancy.	Published reports and meeting abstracts were searched for in MEDLINE, Web of Science and PsychInfo up to Dec 2018	Five studies met the inclusion criteria, totalling 4,356,318 pregnancies and 4,132 exposed to methylphenidate. All studies were retrospective or prospective cohorts.	Did not show an association between methylphenidate exposure in the first trimester of pregnancy and an increased risk of MCM. However, a lack of power cannot be ruled out. An increased risk of cardiac malformations was found and needs to be further evaluated.
9.3 Bolea-Alamanac 2013. **[19]**	Systematic review	To summarise scientific evidence about risks of using methylphenidate for ADHD in pregnancy.	Three articles were found on methylphenidate use in pregnancy. 40 exposed mothers and 41 infants.	Total sample of 41 children exposed to methylphenidate in pregnancy. Malformations reported included congenital heart defects (n=2), finger abnormalities (syndactyly, adactyly and polydactyly n=2) and limb malformations (n=1). Other problems included premature birth, asphyxia, and growth retardation.	Only three studies were identified, and they were not representative of the population taking methylphenidate. Therefore, because of this review, the risk to the unborn foetus due to methylphenidate remains undetermined.
9.4 Bro et al 2015. **[20]**	Population-based cohort study	To determine if prenatal exposure to methylphenidate or atomoxetine increases the risk of adverse pregnancy outcomes in women with ADHD.	Exposure information from all redeemed prescriptions in Denmark registry.	Congenital abnormalities occurred in 2 children (3.8%) from the exposed ADHD cohort, in 7 children (6.9%) in the unexposed ADHD cohort, and in 39,557 children (5.7%) in the reference group.	Very few cases of congenital malformations were found and authors were not able to calculate RRs.
9.5 Damer et al. 2021. **[21]**	Retrospective observational cohort study	To determine safety for the offspring of exposure to methylphenidate during pregnancy.	A cohort of pregnant women who continued MPD treatment during pregnancy and a cohort of women who discontinued MPD treatment during pregnancy.	Secondary endpoint: neonatal malformations, at 20 weeks ultrasound	There were no significant differences found in frequency of neonatal malformations at the 20-week ultrasound.
9.6 Diav-Citrin et al. 2016. **[22]**	Multicentre, prospective, comparative observational study	To evaluate the risk of major abnormalities after early pregnancy exposure to methylphenidate.	Exposure during pregnancy was obtained either with a telephone interview with mother or questionnaire.	382 methylphenidate-exposed pregnancies and a similar number of pregnancies in women counselled for non-teratogenic exposure were prospectively followed up. Of these 89.5% of exposures to methylphenidate occurred at least in the first trimester.	The authors found that methylphenidate treatment, in the context of medical indications or for cognitive enhancement, is not associated with an increased risk of major anomalies or cardiovascular anomalies.

9.8 Dideriksen et al. 2013. **[23]**	Systematic MiniReview	To review of available data on birth outcomes after human *in utero* exposure to methylphenidate.	Six articles were retrieved for full text review. These included case reports and cohort studies.	This review identified 183 children exposed to methylphenidate *in utero.* Among these, 7 children with malformations were observed.	Both data quantity and quality are unimpressive, and the review concludes that methylphenidate exposure in pregnancy does not appear to be associated with a substantially increased risk of congenital malformations.
9.8 Huybrechts et al. 2018. **[24]**	Cohort study	To examine the risk of congenital malformations with intrauterine exposure to stimulants.	Methylphenidate and amphetamines dispensed during the first trimester (if a women filled a prescription for a stimulant during the first 90 days of pregnancy).	Major congenital malformations and subgroup of cardiac malformations.	Detected a small increase in the risk of cardiac malformations.
9.9 Kolding et al. 2021. **[25]**	Registry-based study	To examine the association between ADHD medication and overall malformations.	ADHD medication was measured using redeemed prescriptions through linkage to the Danish Health Services Database. First-trimester exposure was defined as 1 or more redeemed prescriptions from 28 days before conception date through 70 days after conception date	The primary outcome was major malformations overall, and secondary outcomes were malformations of the central nervous system or the heart.	No association between ADHD medication and overall malformations was found.
9.10 Nörby et al. 2017. **[26]**	Register-based study	To analyse perinatal outcomes after maternal use of ADHD medicines during pregnancy.	Drug exposure was collected for stimulant medication and categorised into three exposure categories. Stimulant drugs constituted 1464 of the exposures, with ~90% methylphenidate.	Congenital malformations were identified no later than 1 month after the birth of the child from data reported from the clinics to the Medical Birth Register. Congenital malformations were then coded according to ICD-10.	The authors did not detect any association between ADHD medication and the overall rate of congenital malformations.
9.11 Pottegard et al. 2014. **[27]**	Register-based cohort study	To compare prevalence proportion of malformations in a cohort of pregnancies exposed to methylphenidate matched with a cohort of pregnancies during which the mother had not used psychostimulants.	Mother was required to redeem 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester.	The two study endpoints were major malformations and major cardiac malformations. Major malformations and subgroupings were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) system guide v1.3, based on ICD-10 discharge diagnoses from the Danish National Patient Register.	The authors conclude that out of the 240 women that were exposed to methylphenidate in the first trimester of pregnancy, 222 women entered the final cohort for analysis. They found no indication of increased overall risk of major congenital malformations. However, they do add that current data is quite sparse to allow risk estimates for specific malformations.

3.1 Published literature

3.1.1 Anderson et al. 2020. ADHD Medication Use During Pregnancy and Risk for Selected Birth Defects: National Birth Defects Prevention Study, 1998-2011 [17]

Aim: To examine prevalence and maternal characteristics associated with ADHD medicine use before and during pregnancy, as well as associations between early pregnancy ADHD medicine use and the risk for 12 selected birth defects.

Methods: Data was analysed from the National Birth Defects Prevention Study (NBDPS) (1998-2011), a US population-based multi-site case-control study examining risk factors for major structural birth defects.

Mothers were invited to participate in a computer-assisted telephone interview 6 weeks to 24 months after the mother's estimated date of delivery (EDD). Mothers were asked to report the start and stop dates, duration, and frequency of medication use during the three months before and during pregnancy using calendar dates or pregnancy months. ADHD medication exposure was defined as maternal report of use of ≥1 product(s) in any dose, duration, or frequency that included any of the following: amphetamine, dextroamphetamine, combination amphetamine/dextroamphetamine, lisdexamfetamine, dexmethylphenidate, methylphenidate, methamphetamine, pemoline or atomoxetine.

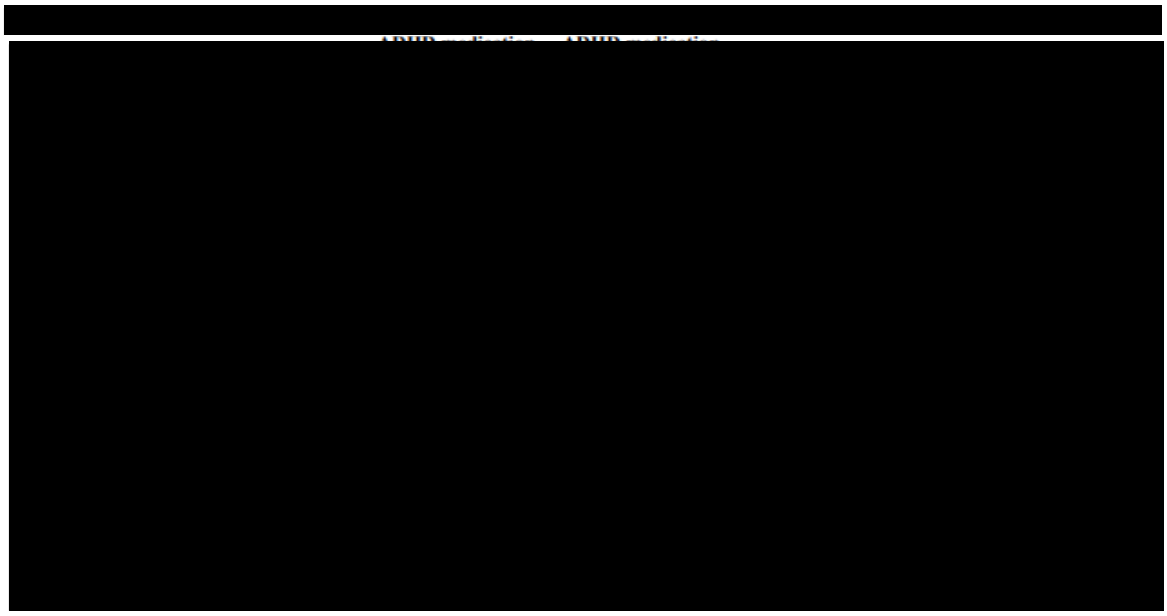
Logistic regression was used by the authors to estimate crude odds ratios (cORs) and corresponding 95% confidence intervals (CIs) to assess the association between any early pregnancy ADHD medication exposure and selected birth defects. Early pregnancy was defined as the month before conception through the third month of pregnancy. Except for gastroschisis, the authors were unable to adjust for potential confounders using multivariable models due to low statistical power.

Results: ADHD medication use in the 3 months before conception through the end of pregnancy was rare: 0.2% (98/42,667) of case and control mothers reported use during this period. The prevalence was the same for case mothers (0.2%; 74/31,213) and control mothers (0.2%; 24/11,454).

There were 64 case and 20 control mothers exposed to any ADHD medication anytime during the month before conception through the third month of pregnancy. There were 12 specific birth defects with at least three exposed cases (see Figure 4). ADHD medication use in early pregnancy was more commonly reported by mothers of infants/fetuses with gastroschisis (cOR: 2.9; 95% CI: 1.2–6.9), omphalocele (cOR: 4.0; 95% CI: 1.2–13.6), and transverse limb deficiency (cOR: 3.3; 95% CI: 1.1–9.6).

No other statistically significant associations between ADHD medication use and the nine other birth defects examined were observed. These findings persisted when examining any early pregnancy stimulant ADHD medication use only.

Figure 4: Associations between ADHD medication use from one month before conception through the third month of pregnancy and selected birth defects, National Birth Defects Prevention Study, 1998-2011.



Author's conclusions: The strengths of this study are that the analysis includes the use of a large, population-based case-control study of major structural birth defects. This meant that the authors could examine the association between early pregnancy ADHD medication use and risk for specific birth defects. Limitations were that despite the large sample, there were only a few women exposed to ADHD medications which reduced statistical power. Recall bias is another limitation as use was ascertained with maternal report/recall up to 24 months after the EDD, and exposure was not verified from other sources.

Comments
The numbers of cases were quite small therefore the study is lacking in power. The study looked at many ADHD medicines rather than just methylphenidate. Therefore, the relevance of the study to the methylphenidate safety concern is difficult to ascertain. Some of medicines in the study are not approved or available in New Zealand. Also, atomoxetine is not a stimulant medicine.

3.1.2 Auffret et al. 2019. Methylphenidate during pregnancy and the risk of congenital major malformations: A systematic review and analysis [18]

Comments
The full article could not be obtained and so the abstract is included below.

Introduction: The objective of this study is to perform an updated quantitative meta-analysis of the risk of major congenital malformations (MCM) associated with methylphenidate exposure in the first trimester of pregnancy. This is because use of methylphenidate in adults or during pregnancy is increasing in the USA and Europe. Therefore, computerising safety data in this population group is important.

Methods: The authors conducted a systematic review and meta-analysis. Published reports and meeting abstracts were searched for in MEDLINE, Web of Science and Psych Info up to December 2018. Bibliographic references list of all found studies, meta-analyses and reviews were hand-searched in order to identify additional eligible articles.

All comparative cohort and case-control studies investigating the risk of MCM after methylphenidate exposure in early pregnancy were included. Pooled effect sizes with corresponding 95% CI were calculated using

random effects models, comparing the risk of MCM between methylphenidate exposed and non-exposed pregnancies.

Results: Five studies met the inclusion criteria, totalling 4,356,318 pregnancies and 4,132 exposed to methylphenidate. All studies were retrospective or prospective cohorts. First trimester exposure to methylphenidate was not significantly associated with an increased risk of MCM (pooled OR: 1.01; 95% CI: 0.83–1.24). For cardiac malformations, an increased risk was found (pooled OR: 1.31; 95% CI: 1.04–1.66). No heterogeneity between studies was observed (I2 = 0%). Funnel plot was suggestive of publication bias.

Author's conclusion: This meta-analysis did not show an association between methylphenidate exposure in the first trimester of pregnancy and an increased risk of MCM. However, a lack of power cannot be ruled out. An increased risk of cardiac malformations was found and needs to be further evaluated.

Comments
The study methods are not known, so the author's conclusion needs to be interpreted with caution.

3.1.3 Bolea-Alamanac et al. 2014. Methylphenidate use in pregnancy and lactation: a systematic review of evidence [19]

Aims: To summarise the scientific evidence about the risks of using methylphenidate for ADHD in pregnancy and lactation.

Methods: Pubmed, Psychinfo, Web of Science, Embase, Biosis and Medline were searched.

Results: Only two case reports and a case series were identified. In the case series, 38 mothers abusing methylphenidate and IV pentazocine, and two congenital anomalies were found. The congenital anomalies were polydactyly and a heart septal defect, and involved exposure to methylphenidate with other drugs. Figure 5 shows a summary of clinical studies of methylphenidate in pregnancy.

Figure 5: Summary of clinical studies of methylphenidate in pregnancy classified according to level of evidence.

Author's conclusion: The three articles encompass 40 exposed mothers and 41 infants. While all children were assessed for malformations, follow-up was only available for 32 infants of the initial sample. Only one of the case reports involved methylphenidate as a prescribed drug and the rest were exposures due to drug abuse, therefore these cases are not representative of methylphenidate exposure in the general population.

3.1.4 Bro et al. 2015. Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy [19]

Aim: To determine if prenatal exposure to methylphenidate (MPH) or atomoxetine (ATX) increases the risk of adverse pregnancy outcomes in women with ADHD. This is a population-based cohort study of all pregnancies in Denmark from 1997 to 2008.

Methods: Information on use of ADHD medication, ADHD diagnosis, and pregnancy outcomes was obtained from nationwide registers.

The cohort compromised of all clinically recognised pregnancies in Denmark with estimated time of conception and an observed pregnancy outcome in the period from 1 February 2007 to 31 December 2008. Information was obtained from Danish administrative health registries, including the Danish Medical Birth Registry (MBR) and the Danish National Hospital Discharge Register (NHDR), and data were linked through the personal identification number unique to each person with a permanent address in Denmark.

Exposures: Obtained from information on all redeemed prescriptions in Denmark from the Registry of Medicinal Product Statistics. For live births and stillbirths, the exposure window spanned from 30 days before the estimated day of conception until the day prior to birth. Women who had redeemed a prescription for MPH/ATX within the exposure window were defined as "the exposed ADHD cohort". Women with an ADHD diagnosis who had not redeemed a prescription for MPH/ATX within the exposure window were defined as "the unexposed ADHD cohort".

Results: The study population consisted of 989,932 pregnant women, of whom 186 (0.02%) used MPH and/or ATX (the exposed cohort) and 275 (0.03%) who had a history of an ADHD diagnosis but received no treatment with MPH/ATX (the unexposed ADHD cohort) during pregnancy.

The reference group consisted of women without MPH/ATX use and no ADHD diagnosis. In the exposed ADHD cohort, 67% (35%) had a hospital diagnosis of ADHD, 166 (89%) used MPH, 18 (9.7%) used ATX, and two (1.1%) used both ATX and MPH. Congenital abnormalities occurred in two children (3.8%) from the exposed ADHD cohort, in seven children (6.9%) in the unexposed ADHD cohort, and in 39,557 children (5.7%) in the reference group (Figure 6).

Figure 6: Pregnancy and birth outcomes according to ADHD medcation use and ADHD hospital contact

Comments
This study looked at adverse pregnancy outcomes and there were very few congenital abnormalities. The study is lacking in power due to very small numbers.

3.1.5 Damer et al. 2021. Fifteen years' experience with methylphenidate for attention-deficit disorder during pregnancy: Effects on birth weight, Apgar score and congenital malformation rates [21]

Aim: This retrospective observational study looked at the safety for the offspring of exposure to methylphenidate in pregnancy. A cohort of pregnant women who continued methylphenidate during pregnancy and a cohort of women who discontinued methylphenidate treatment during pregnancy (the control group) was studied.

Methods: The study was carried out in a Netherlands hospital from 1 January 2005 to 1 June 2020 where patients were in a specialised outpatient clinic for pregnant women with psychiatric disease. Only pregnancies resulting in live births were used in this study, defined as a gestation period of at least 24 weeks.

Data for mothers and neonates was manually extracted from the electronic patient records of the hospital. Methylphenidate exposure was defined as taking methylphenidate from the first day of the last menstrual period (LMP). Exposure was methylphenidate use, in any trimester and dosage. Frequency, dose, and duration of use were determined. One of the secondary endpoints was neonatal malformations at the 20-week ultrasound.

Results: 149 pregnancies were identified, of which 114 resulted in live birth and 35 resulted in miscarriage. 32 pregnancies exposed to methylphenidate in any dosage resulted in 26 live births. Twenty-two patients (mothers) were exposed to methylphenidate in the first trimester, four patients in the second and third trimester.

Conclusions: No significant association found between methylphenidate exposure or neonatal malformations.

Comments
The relevance of this study to the risk is limited, due to both the low numbers of patients and malformations. Also, only 20-week ultrasound data was available; therefore, neonatal malformations may have been missed. In addition, only live births were included (miscarriage and induced abortion) was excluded therefore the true number of congenital malformations in this study population may have been underestimated.

3.1.6 Diav-Citrin et al. 2016. Methylphenidate in Pregnancy: A multicentre, prospective, comparative, observational study [22]

Aim: To evaluate the risk of major abnormalities after early pregnancy exposure to methylphenidate.

Methods: Pregnant women who contacted 1 of 4 selected Teratology Information Service (TIS) providers: Israeli TIS (Jerusalem, Israel), the Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy (Berlin, Germany), the United Kingdom TIS (Newcastle upon Tyne, England), or the Motherisk Program (Toronto, Canada) – between 1996 and 2013 regarding gestational exposure to methylphenidate were enrolled.

Exposure during pregnancy was defined from conception until the end of pregnancy. Exposure to methylphenidate during the period of organogenesis was defined when the woman took the medication during pregnancy between 4 and 13 completed weeks from her last menstrual period. Exposure details were collected at the initial contact with the TIS before pregnancy outcome was known.

Outcome: Pregnancy outcome was actively sought after estimated date of delivery (EDD) in both the exposed and comparison groups. At least two physical examinations were performed in the neonatal period. Follow-up was conducted by a telephone interview with the woman or by a questionnaire mailed to the woman.

Details sought were gestational age at delivery, birth weight, congenital anomalies, and neonatal complications. For congenital anomalies, the authors attempted to obtain medical records. Major anomalies were defined in this study as structural anomalies in the offspring that have serious medical, surgical or cosmetic consequences.

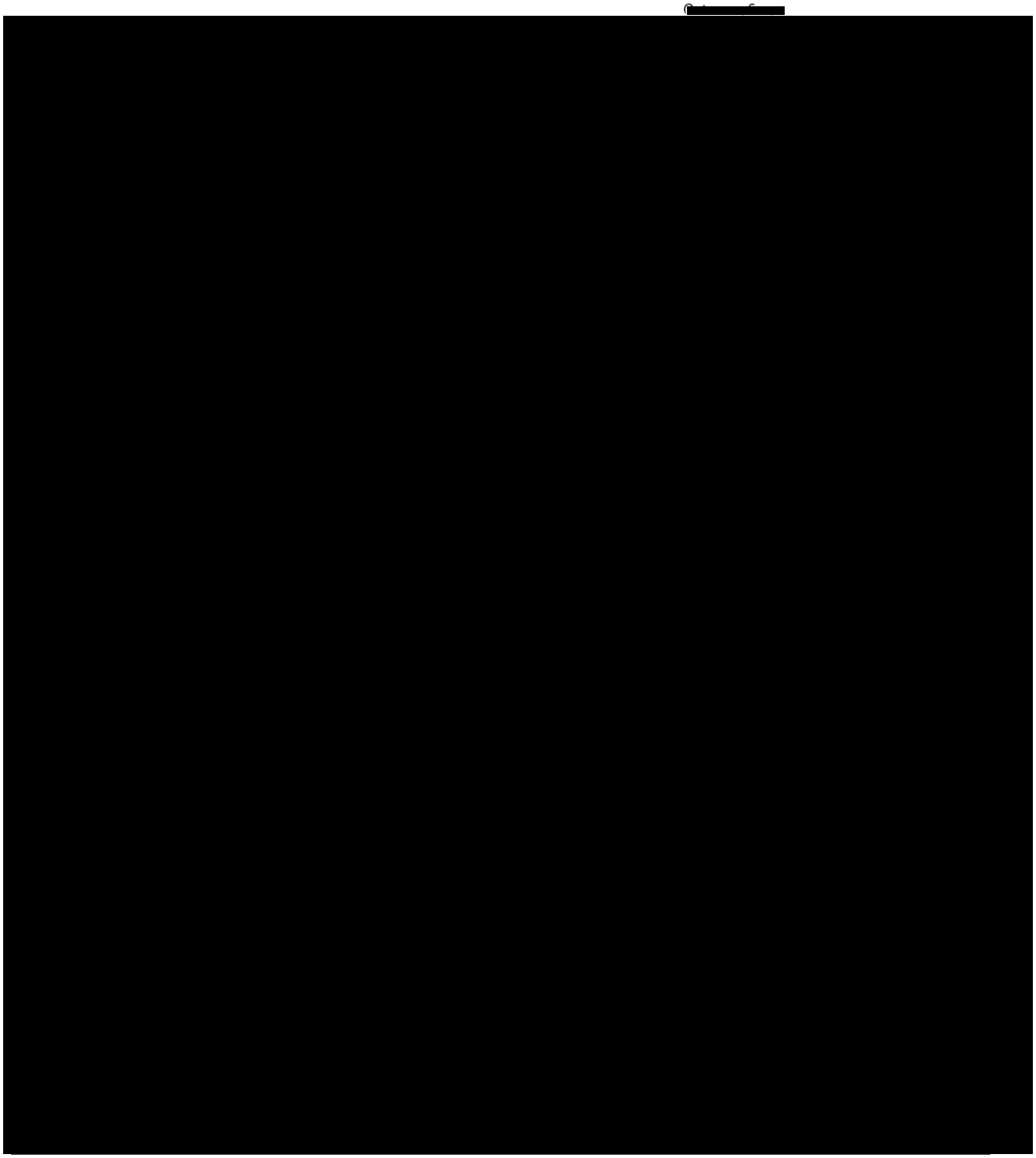
Results: A total of 382 methylphenidate-exposed pregnancies and a similar number of pregnancies in women counselled for non-teratogenic exposure (NTE) were prospectively followed up. Of these, 89.5% of the exposures to methylphenidate occurred at least in the first trimester. Exposure occurred in all three trimesters in 15.2% of pregnancies. Over 95% of women started treatment with methylphenidate before pregnancy.

Elective terminations of pregnancy were performed due to prenatally diagnosed anomalies in 3 of 31 and in 4 of 10 cases of the methylphenidate and comparison groups, respectively.

The rate of overall major anomalies was similar between the 2 groups (3.2% methylphenidate, 3.6% NTE, p=0.780). The difference remained nonsignificant (2.3% methylphenidate, 3.4% NTE, p=0.400) even after a reanalysis excluding genetic or cytogenetic anomalies. Also, this rate did not significantly differ when the analysis was limited to pregnancies exposed to methylphenidate during the period of organogenesis (2.4% methylphenidate, 3.4% NTE, p=0.511). The cardiovascular anomaly rate also remained similar.

Figure 7 lists the reported major anomalies and the details of exposures in the methylphenidate and NTE groups. The authors note that there is no specific pattern of anomalies in the methylphenidate group.

Figure 7: List of Major Anomalies in the Methylphenidate and Comparison Groups



Author's conclusion: The study shows that methylphenidate treatment, in the context of medical indications or for cognitive enhancement, is not associated with an increased risk of major anomalies or cardiovascular anomalies. The rate between the methylphenidate and NTE group did not differ considerably. The authors note that the study is not powered to find an increase in the rate of specific rare anomalies. The study population is from a TIS population, so may not be representative of the general population.

3.1.7 Dideriksen et al. 2013. First trimester in utero exposure to methylphenidate [23]

Aim: a systematic mini review of available data on birth outcomes after human *in utero* exposure to methylphenidate.

Methods: From origin until 2012, PubMed/Embase searches were performed. Additional data was also extracted from other available sources: Michigan Medicaid Cohort, Swedish Birth Registry and Danish Ministry of Health (adverse reaction database).

Results: Six articles reporting data from methylphenidate exposure during pregnancy were retrieved for full-text review.

Case reports

Three case reports were identified.

- An infant with microtia after *in utero* exposure to methylphenidate from the third to the sixth week of pregnancy was reported in a study from 1962 (using material from Liverpool abnormalities register 1962).
- A case report from 1975 described an infant delivered at 30 weeks gestation, with multiple limb malformations. The infant had been exposed to haloperidol, methylphenidate and phenytoin during the first 7 weeks of pregnancy. The infant died at 2 hours of age of a subdural haemorrhage.
- Pregnancy-related adverse effects reported to the Danish Medicines Agency include one congenital malformation (myelomeningocele), three spontaneous abortions, one pre-eclampsia and one unintended pregnancy during administration of an oral contraceptive.

Cohort data

Four cohorts were identified describing birth outcome after *in utero* exposure to methylphenidate (Figure 8).

Figure 8: Source, exposure and congenital malformations in four cohort studies

- Eleven mother-child pairs with first-trimester exposure to methylphenidate were monitored as part of The Collaborative Perinatal Project including 50,282 women. No significant increase in malformations was observed for this group.
- A surveillance study of Michigan Medicaid recipients involving 229,101 pregnancies between 1985-1992 reported 12 newborns exposed to methylphenidate during the first trimester of pregnancy. Among these, one major malformation (cardiac defect) was found.

- The Israeli TIS was a prospective comparative cohort study. Out of 52 methylphenidate-exposed pregnancies, no malformations were observed.
- Swedish Birth Register holds 104 reports on children exposed to methylphenidate *in utero* in early pregnancy. Three children had congenital malformations (2-3 expected). Two children had ventricular septal and one child was born with a univentricular heart.

Four malformations among 180 exposed children yields a rate of 2.2% with 95% confidence interval of 0.6-5.6% (exact binomial distribution). Assuming a spontaneous malformation rate of 3.5%, this corresponds to a relative risk of 0.6 with confidence limits of 0.2-1.6.

Author's conclusion: The authors in this review identified 183 children exposed to methylphenidate *in utero* and observed seven children with malformations. The authors note that the data quantity and quality is unimpressive along with the level of confounder control. They also mention the possibility of publication bias. They conclude that methylphenidate exposure during pregnancy does not appear to be associated with a substantially (ie, more than twofold) increased risk of congenital malformations.

3.1.8 Huybrechts et al. 2018. Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study from the International Pregnancy Safety Study Consortium [24]

Aim: The study was carried out to examine the risk of congenital malformations with intrauterine exposure to stimulants. The study included a total of 1,813,894 publicly insured pregnancies in the US and 2,560,069 singleton pregnancies in the 5 Nordic countries ending in live births were included.

Exposures: Methylphenidate and amphetamines dispensed during the first trimester: if a woman filled a prescription for a stimulant during the first 90 days of pregnancy.

Two exposure groups were characterised: methylphenidate, and amphetamine and dextroamphetamine (referred to hereafter as amphetamines for brevity). A pregnancy was considered unexposed if a woman did not fill a prescription for any ADHD medicine from 3 months before the LMP to the end of the first trimester.

Outcomes: Major congenital malformations and subgroup of cardiac malformations. An infant was considered to have a major congenital malformation if any of 13 specific malformation groups (central nervous system, ear, eye, cardiovascular, other vascular, respiratory oral cleft, gastrointestinal, genital, urinary, musculoskeletal, limb, and other) were present. Note: subgroup of cardiovascular malformations was also evaluated separately.

Methods: Primary analyses were conducted using the pregnancy cohort nested in the 2000-2013 nationwide Medicaid Analytic eXtract. To be eligible for the study, pregnant women aged 12 to 55 years were required to be continuously enrolled in Medicaid from 3 months before the date of their last menstrual period (LMP) to 1 month after delivery; their live born infants were required to be enrolled for the first 3 months of life or until death. Pregnancies with exposure to a known teratogenic medication during the first trimester (n=3562) and pregnancies with a fetal chromosomal abnormality (n=3156) were excluded.

Statistical Analysis: Relative risks were estimated accounting for underlying psychiatric disorders and other potential confounders. Relative risk estimates for the US and Nordic data were pooled using a fixed-effects meta-analytic approach. Baseline characteristics of women who received vs did not receive stimulants.

The authors then calculated the prevalence of any congenital malformation and the subgroup of cardiac malformations in their infants as well as unadjusted RRs (prevalence ratios) with 95% CIs. Analyses were performed with 2 levels of adjustment: (1) adjustment for psychiatric and neurologic conditions and use of psychotropic medications to control for the possible effect of the underlying indication and associated factors, and (2) adjustment for all potential confounding variables.

Results: A total of 1,813,894 pregnancies ending in live birth met the cohort selection criteria. Among these women, 2072 women (0.11%) filled a prescription for methylphenidate and 5571 women (0.31%) filled a prescription for an amphetamine during their first trimester. There were 1,797,938 women without exposure to any ADHD medication during the 3 months before their LMP or during the first trimester.

Malformations were diagnosed in 62,966 infants who were not exposed to a stimulant during the first trimester (35.0 malformations per 1,000 infants). The prevalence was higher among methylphenidate-exposed (n=95; 45.9 per 1,000) and amphetamine-exposed (n=253; 45.4 per 1,000 infants). The prevalence of cardiovascular malformations was increased among methylphenidate-exposed infants (18.8 vs 12.7 per 1,000 unexposed infants) and to a lesser degree among amphetamine-exposed infants (15.4 per 1,000 infants).

In the unadjusted analyses, the RRs for any malformation and for cardiovascular malformations were elevated for both methylphenidate and amphetamine exposure. After adjustment for psychiatric morbidity, the associations with malformations overall were reduced for both methylphenidate (RR: 1.16; 95% CI: 0.95-1.41) and amphetamines (RR: 1.18; 95% CI: 1.04-1.33). The risk for cardiovascular malformations remained slightly elevated for methylphenidate (RR: 1.27; 95% CI: 0.93-1.73), but not for amphetamines (RR: 1.07; 95% CI: 0.86-1.32).

In fully adjusted analyses, the associations with malformations overall and with cardiovascular malformations were null for amphetamines: RR: 1.05 (95% CI: 0.93-1.19) for any malformations and 0.96 (95% CI: 0.78-1.19) for cardiac malformations.

The fully adjusted RRs for methylphenidate were 1.11 (95% CI: 0.91-1.35) for any malformation and 1.28 (95% CI: 0.94-1.74) for cardiac malformations.

These results were unchanged following adjustment with additional confounders or changing the exposure or outcome definition.

For the risk of specific cardiac defects for methylphenidate, the most strongly increased risk was for conotruncal defects (adjusted RR: 3.44; 95% CI: 1.54-7.65), but this finding is based on less than 11 exposed events.

None of the specific cardiac defects were associated with amphetamine use. When the authors removed (1) patent ductus arteriosus and (2) patent ductus arteriosus and patent foramen ovale/osteum secundum type atrial septal defects, the associations strengthened somewhat for methylphenidate: RR 1.32 (95% CI: 0.96-1.82) and 1.50 (95% CI: 1.05-2.14), respectively but remained null for amphetamines.

Conclusions: The authors conclude that their study allowed them to detect a small increase in the risk of cardiac malformations that prior studies may have been underpowered to detect. Although the absolute risk is small, it is important evidence to consider when weighing the potential risks and benefits of different treatment strategies.

3.1.9 Kolding et al. 2021. Associations Between ADHD Medication Use in Pregnancy and Severe Malformations Based on Prenatal and Postnatal Diagnoses: A Danish Registry-Based Study [25]

Aim: To evaluate the associations between ADHD medication use in pregnancy and severe malformations. This was a nation-wide registry-based study where the study population included all clinically recognised singleton pregnancies with a live fetus at the first-trimester scan from 11 gestational weeks, with conception dates from 1 November 2017 to 1 February 2014.

Methods: Exposure to ADHD medication was measured using redeemed prescriptions through linkage to the Danish Health Services Database. First-trimester exposure was defined as 1 or more redeemed prescriptions from 28 days before conception date through 70 days after conception date. The unexposed group had no redemptions for an ADHD medication (former use). Medications were analysed as any ADHD medication and as specific drugs (methylphenidate, modafinil, atomoxetine).

Major malformations were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) classification. The primary outcome was major malformations overall, and secondary outcomes were malformations of the central nervous system or the heart.

Results: 366,489 eligible pregnancies were identified during the study period and 364,012 were included in the study population. The prevalence of first-trimester exposure to ADHD medication was 0.16% (n=569) on

average. Over the study period, this increased more than 5-fold. Note that most exposed pregnancies were to methylphenidate (473/569).

Prevalence for malformations in the exposed group was 5.1% and the unexposed group was 4.6%. For cardiac malformations, this was 2.1% among the methylphenidate exposed and 1.0% among the unexposed. After confounding, most prevalence rate (PR) estimates were attenuated. For methylphenidate, the fully adjusted PRs were 1.04 (95% CI: 0.70-1.55) for malformations overall, 1.65 (95% CI: 0.89-3.05) for cardiac malformations, and 2.59 (95% CI: 0.98-6.90) for severe cardiac malformations (SCM). Out of the 12 cases of exposed cardiac malformations, there were septal defects in 10 cases.

Figure 9: Pregnancy outcome for exposure to ADHD Medication During First Trimester and Unexposed

Author's conclusion: The authors did not find an association between ADHD medication and overall malformations. A strength of this study was that prenatal data added 233 cases of cardiac malformations that were not in live births (terminated, miscarriage, or stillborn). Out of these, only 1 case was exposed to ADHD medication, which resulted in unchanged estimates in cardiac malformations. The authors found that pregnancies exposed to ADHD medication were 4 times more likely to end in a termination of pregnancy than unexposed pregnancies.

3.1.10 Nörby et al. 2017. Perinatal outcomes after treatment with ADHD medication during pregnancy [26]

Aim: To analyse perinatal outcomes after maternal use of ADHD medicines during pregnancy. This was done by analysing population level data from Swedish health and neonatal quality registers.

Methods: Data was obtained from four registers in Sweden and singleton births between 1 July 2006 and 31 December 2014 were identified Congenital malformations are coded according to the ICD-10. The data reported from the clinics to the MBR (Medical Birth Register) was no later than 1 month after the birth of the child.

To control for confounding by indication, the infants exposed during pregnancy were compared with infants whose mothers used ADHD medication before or after the pregnancy, in addition to the general population.

Drug exposure: Collected for the following stimulant medications: methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine, modafinil and atomoxetine. Use was categorised into 3 categories: use during pregnancy (self-reported use according to the MBR and/or registered in the Prescribed Drug Register

(PDR) during pregnancy or 1 month before); use but not during pregnancy (ADHD medication registered in the PDR anytime during the study period, except during the interval 1 month before pregnancy until delivery); and no use (no records of ADHD medication). Data on birth defects were collected and defined with ICD-10 diagnoses.

Results: The study population consisted of 964,734 singleton births with 1,591 women exposed to ADHD medication during pregnancy. Stimulant drugs constituted 1464 of the exposures (~90% methylphenidate). Most women were treated with ADHD medication during early pregnancy: 251 (15.8%) of the infants were exposed during the last 90 days of pregnancy. Women who used ADHD medication before or after (but not during) pregnancy gave birth to 9,475 (1.0%) of infants.

Figure 10: Perinatal Morbidity Among Infants Exposed to ADHD Medication During Pregnancy Compared with Infants whose mothers used ADHD Medication Before or After Pregnancy and With Infants whose mothers used these drugs

Author's conclusion: The authors did not detect any association between ADHD medication and the overall rate of congenital malformations.

Comments
Only malformations diagnosed during the neonatal period were included. This could mean that there could be an increased risk later as some conditions take some time to detect.

3.1.11 Pottegard et al. 2014. First-trimester exposure to methylphenidate: a population-based cohort study [27]

Aim: This is a register-based nationwide cohort study where the authors compared the prevalence proportion of malformations in a cohort of pregnancies exposed to methylphenidate in the first trimester to a propensity score-matched cohort of pregnancies during which the mother had never used psychostimulants.

Method: Data was obtained from 1 January 1995 to 31 December 2012 from 4 Danish nationwide registries. Pregnancies were identified using the Medical Birth Registry.

Exposures: To be included in the cohort of pregnancies exposed to methylphenidate in the first trimester, the mother was required to redeem 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester.

The unexposed cohort included pregnancies in which the mother had not redeemed a prescription for a psychostimulant at any time point prior to the end of the pregnancy. For each pregnancy in the exposed cohort, the authors matched 10 pregnancies from the unexposed cohort.

The two study endpoints were major malformations and major cardiac malformations. Major malformations and subgroupings were classified according to the European Surveillance of Congenital Anomalies (EUROCAT) system guide v1.3, based on ICD-10 discharge diagnoses from the Danish National Patient Register.

Results: Out of 460,323 pregnancies resulting in live births, 240 pregnancies were identified in this period. 222 women then entered the final cohort for analysis. Among the exposed, the authors observed 7 (3.2%) major malformations, 3 (1.4%) of which were cardiac. Among the unexposed, the corresponding numbers were 86 (3.9%) and 32 (1.4%). These rates are comparable to those observed in the random sample of unexposed pregnancies (3.7% and 1.1%, respectively).

Comparison of the exposed and unexposed cohorts yielded point prevalence ratios of 0.8 (95% CI: 0.3-1.8) for all major malformations and 0.9 (95% CI: 0.2-3.0) for cardiac malformations (Figure 11). There was no sign of aggregation of single malformations. Sensitivity analyses stratifying by maternal age and excluding users of potentially confounding drugs did not result in materially different risk estimates. Covariates were still well balanced among exposed and unexposed subjects within these subgroups.

Figure 11: Fetal Outcomes and Point Prevalence Ratios (PPRs) Comparing the Exposed to the Unexposed Cohort, Overall, and by Subgroup

Author's conclusion: No indication of increased overall risk of major congenital malformations. However, they do add that current data is quite sparse to allow risk estimates for specific malformations.

[redacted]

3.3 New Zealand – CARM data

Up to 30 March 2022, CARM had received a total of 294 case reports for methylphenidate, methylphenidate SR and methylphenidate ER (see Annex 2).

There was one case of birth/congenital defects reported in 1972. There is limited information available about this case. The mother took Phenergan 10mg three times a day, Valium 2mg three times a day and Ritalin twice a day (no dose stated) during her pregnancy. The exposed baby was diagnosed with an eye abnormality (cataracts) seven months after birth.

4 DISCUSSION AND CONCLUSIONS

This report was prompted by the PRAC recommendation in 2019 and the TGA's pregnancy change and reviews the use of methylphenidate in pregnancy and the risk of congenital malformations.

There were several studies found in the literature with an aim to measure and assess the risk of birth defects if the mother was exposed to methylphenidate. Many of the studies investigated several different outcomes, and some grouped medicines used to treat ADHD together.

Most studies were observational, with exposures measured either with maternal reporting or dispensing records. The results of the literature are conflicting with most concluding that there are no associations between methylphenidate use and congenital malformations. However, some of the more recent studies show a small increase in association of cardiac malformations or specific birth defects.

Some studies were lacking in power due to small numbers of cases and many of the authors conclude that risk estimates are unable to be calculated for specific malformations.

At the time of writing this report, the New Zealand data sheets do not include any information regarding congenital malformations or cardiac abnormalities. In comparison, the Australian PI and UK SmPC contain information about this risk because of the PRAC recommendation. The US labels state that safety has not been established, with the Ritalin label stating that a drug-associated risk has not been identified.

The CARM database only contains one report of congenital abnormality associated with methylphenidate. A causal association could not be determined due to lack of information and other suspect medicines.

Methylphenidate is a first line treatment for ADHD. Data from the National Collections data shows that the use of methylphenidate is increasing. It is important that details on risk/benefit are clear for both medical practitioners and women so that informed decisions can be made regarding the use of this medicine throughout pregnancy.

5 ADVICE SOUGHT

The Committee is asked to advise:

- If the current evidence supports an association between first trimester exposure to methylphenidate and an increased risk of congenital malformations in the baby?
- If there is a need to include information in the data sheets for methylphenidate regarding congenital malformations for methylphenidate?
- Whether the topic requires further communication, other than MARC's Remarks in *Prescriber Update*?

6 ANNEXES

Annex 1 – New Zealand data sheet review for methylphenidate-containing products
Annex 2 – CARM data

7 REFERENCES

1. European Medicines Agency (EMA). 2019. *Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)* June 2019. URL: https://www.ema.europa.eu/en/documents/psusa/methylphenidate-cmdh-scientific-conclusions-grounds-variation-amendments-product-information/00002024/201810_en.pdf (accessed 20 May 2022).
2. Therapeutic Goods Administration (TGA). 2021. *Methylphenidate - use in pregnancy* 22 July 2021. URL: https://www.tga.gov.au/publication-issue/methylphenidate-use-pregnancy (accessed 17 May 2022).
3. New Zealand Formulary (NZF). 2022. *NZF v117: Methylphenidate hydrochloride* 1 March 2022. URL: https://nzf.org.nz/nzf_2334 (accessed 21 March 2022).
4. Krull K. 2022. Pharmacology of drugs used to treat attention deficit hyperactivity disorder in children and adolescents. In: *UpToDate* 19 January 2022. URL: https://www.uptodate.com/contents/pharmacology-of-drugs-used-to-treat-attention-deficit-hyperactivity-disorder-in-children-and-adolescents (accessed 5 May 2022).
5. Janssen-Cilag (New Zealand) Ltd. 2021. *Concerta New Zealand Data Sheet* 29 October 2021. URL: https://medsafe.govt.nz/profs/Datasheet/c/Concertatab.pdf (accessed 21 March 2022).
6. Limited TPNZ. 2021. *Methylphenidate Extended Release (Teva), extended release tablets New Zealand Data Sheet* 2 June 2021. URL: https://medsafe.govt.nz/profs/Datasheet/m/methylphenidateTevatab.pdf (accessed 21 March 2022).
7. Novartis New Zealand Limited. 2022. *Ritalin New Zealand Data sheet* 8 February 2022. URL: https://medsafe.govt.nz/profs/Datasheet/r/RitalintabSRtabLAtab.pdf (accessed 21 March 2022).
8. AFT Pharmaceuticals Ltd. 2020. *Rubifen and Rubifen SR New Zealand data sheet* 19 June 2020. URL: https://medsafe.govt.nz/profs/Datasheet/r/rubifentabsrtab.pdf (accessed 21 March 2022).
9. Bukstein O. 2022. Attention deficit hyperactivity disorder in adults: Epidemiology, pathogenesis, clinical features, course, assessment, and diagnosis. In: *UpToDate* 7 April 2022. URL: https://www.uptodate.com/contents/attention-deficit-hyperactivity-disorder-in-adults-epidemiology-pathogenesis-clinical-features-course-assessment-and-diagnosis (accessed 17 May 2022).
10. Centers for Disease Control and Prevention. 2021. *What are Birth Defects?* 5 November 2021. URL: https://www.cdc.gov/ncbddd/birthdefects/facts.html (accessed 21 March 2022).
11. Therapeutic Goods Administration (TGA). 2011. *Australian categorisation system for prescribing medicines in pregnancy* 4 May 2011. URL: https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy (accessed 17 May 2022).
12. Novartis Pharmaceuticals Australia Pty Limited. 2022. *Australian Product Information Ritalin 10/Ritalin LA* 6 April 2022. URL: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-03175-3&d=20220428172310101 (accessed 28 April 2022).
13. Novartis Pharmaceuticals UK Ltd. 2021. *Ritalin 10mg Tablets SmPC* 6 July 2021. URL: https://www.medicines.org.uk/emc/product/1035/smpc (accessed 28 April 2022).
14. Janssen-Cilag Ltd. 2020. *Concerta XL 18mg prolonged-release tablets SmPC* 14 October 2020. URL: https://www.medicines.org.uk/emc/product/6872/smpc (accessed 28 April 2022).
15. Novartis Pharmaceuticals Corporation. 2019. *Ritalin Label* November 2019. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/010187s093lbl.pdf (accessed 2 May 2022).
16. Janssen-Cilag Manufacturing L. 2017. *CONCERTA Label (methylphenidate HCl) Extended release* January 2017. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021121s038lbl.pdf (accessed 28 April 2022).

17. Anderson KN, Dutton AC, Broussard CS, et al. 2020. ADHD Medication Use During Pregnancy and Risk for Selected Birth Defects: National Birth Defects Prevention Study, 1998-2011. *J Atten Disord* 24(3): 479-89. DOI: 10.1177/1087054718759753 (accessed 12 April 2022).
18. Auffret M. 2019. Methylphenidate during pregnancy and the risk of congenital major malformations: a systematic review and meta-analysis. *Service hospitalo-universitaire de pharmacotoxicologie*: (accessed 20 April 2022).
19. Bolea-Alamanac BM, Green A, Verma G, et al. 2014. Methylphenidate use in pregnancy and lactation: a systematic review of evidence. *Br J Clin Pharmacol* 77(1): 96-101. DOI: 10.1111/bcp.12138 (accessed 12 April 2022).
20. Bro SP, Kjaersgaard MI, Parner ET, et al. 2015. Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. *Clin Epidemiol* 7: 139-47. DOI: 10.2147/clep.S72906 (accessed 12 April 2022).
21. Damer EA, Edens MA, van der Loos MLM, et al. 2021. Fifteen years' experience with methylphenidate for attention-deficit disorder during pregnancy: Effects on birth weight, Apgar score and congenital malformation rates. *Gen Hosp Psychiatry* 73: 9-15. DOI: 10.1016/j.genhosppsych.2021.09.003 (accessed 12 April 2022).
22. Diav-Citrin O, Shechtman S, Arnon J, et al. 2016. Methylphenidate in Pregnancy: A Multicenter, Prospective, Comparative, Observational Study. *J Clin Psychiatry* 77(9): 1176-1181. DOI: 10.4088/JCP.15m10083
23. Dideriksen D, Pottegård A, Hallas J, et al. 2013. First trimester in utero exposure to methylphenidate. *Basic Clin Pharmacol Toxicol* 112(2): 73-6. DOI: 10.1111/bcpt.12034 (accessed 12 April 2022).
24. Huybrechts KF, Bröms G, Christensen LB, et al. 2018. Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study From the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 75(2): 167-175. DOI: 10.1001/jamapsychiatry.2017.3644 (accessed 14 April 2022).
25. Kolding L, Ehrenstein V, Pedersen L, et al. 2021. Associations Between ADHD Medication Use in Pregnancy and Severe Malformations Based on Prenatal and Postnatal Diagnoses: A Danish Registry-Based Study. *J Clin Psychiatry* 82(1): DOI: 10.4088/JCP.20m13458 (accessed 14 April 2022).
26. Nörby U, Winbladh B and Källén K. 2017. Perinatal Outcomes After Treatment With ADHD Medication During Pregnancy. *Pediatrics* 140(6): DOI: 10.1542/peds.2017-0747 (accessed 12 April 2022).
27. Pottegård A, Hallas J, Andersen JT, et al. 2014. First-trimester exposure to methylphenidate: a population-based cohort study. *J Clin Psychiatry* 75(1): e88-93. DOI: 10.4088/JCP.13m08708 (accessed 14 April 2022).