Medicines Adverse Reactions Committee

Meeting date	10/03/2022	Agenda item	3.2.2
Title	**Venlafaxine use in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Venlafaxine	Efexor-XR Modified release capsule	Viatris Limited
	Enlafax XR Modified release capsule	Viatris Limited

PHARMAC funding	The *Enlafax* brand is the fully PHARMAC-funded brand in New Zealand.
Previous MARC meetings	Paroxetine and use in pregnancy - Sept 2005 (123rd meeting) SSRIs and use in pregnancy: watching brief review – June 2006 (126th meeting) SSRI antidepressants and use in pregnancy (including developmental delay): watching brief review – June 2007 (130th meeting) *In utero* exposure to serotonin reuptake inhibitors and risk of congenital abnormalities – March 2010 (141st meeting) – Annex 1
Prescriber Update	The use of antidepressants in pregnancy (September 2010) Medicines and Use in Pregnancy (June 2013) SSRI Use in Pregnancy – Collaborative Decision-Making is Key (May 2008)
Classification	Prescription medicine
Usage data	The table below shows the number of people (NumPpl) that received a dispensing of venlafaxine from a pharmacy at least once during the specified year (includes people who only received a repeat dispensing during the year). This includes pregnant women. Data source is from the Ministry of Health's Pharmaceutical Collection (extracted 26 November 2021).

Year	**NumPpl**	**NumPreg**
2016	46,804	409
2017	51,307	436
2018	50,986	436
2019	50,181	371
2020	51,650	N/A

Advice sought	**The Committee is asked to advise whether:** • the current evidence supports an association between venlafaxine use in pregnancy and the increased risk of congenital malformations/birth defects • the current evidence supports an association between venlafaxine use in pregnancy and the contribution to gestational hypertension • the information in the New Zealand data sheet with regards to birth defects and gestational hypertension is sufficient or an update is necessary • the topic requires further communication other than MARC's Remarks in Prescriber Update

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1 PURPOSE

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI) available and fully funded in New Zealand. It is used to treat depression and anxiety.

In August 2020, a multicentre case-control study, (Anderson et al) [1] was published where the objective was to assess whether there were any associations between maternal antidepressant use and specific birth defects. The results of the study suggested some associations, with venlafaxine having the highest risk of being associated with congenital anomalies.

In addition to this, dose-related hypertension is a recognised adverse drug effect of venlafaxine and there is current evidence that suggests an association between antidepressant use during pregnancy and the risk of developing gestational hypertension. A retrospective cohort study, Zakiyah et al, 2018 [2] showed that there appeared to be associations between exposure to antidepressants and gestational hypertension.

The purpose of this report is to review the available evidence of birth defects and gestational hypertension with the use of venlafaxine in pregnancy. The report will also review the New Zealand data sheets to determine whether there is a need for updates to these or any other communication.

2 BACKGROUND

2.1 Venlafaxine

2.1.1 Serotonin and noradrenaline re-uptake inhibitors

This report will only consider venlafaxine as this is the only approved serotonin and noradrenaline reuptake inhibitor (SNRI) in New Zealand. SNRI medicines appear to treat depression by initially blocking presynaptic serotonin and norepinephrine transport proteins. This then inhibits the reuptake of serotonin and noradrenaline, which changes various homeostatic mechanisms and ultimately increases the stimulation of postsynaptic receptors.

It is important to note that SNRI medicines are "dual action agents" meaning that the degree to which reuptake of serotonin and noradrenaline is inhibited depends on the dose administered. At lower doses (75mg), venlafaxine is a selective serotonin reuptake inhibitor (SSRI), but at higher doses (between 225mg and 375mg), venlafaxine has significant effects on noradrenaline transporters [3].

2.1.2 Usage

Venlafaxine is a first line alternative to SSRIs or second line in case of SSRI failure [4].

It is indicated for the treatment of:

- Major depression
- Generalised anxiety disorder
- Social anxiety disorder
- Panic disorder.

Venlafaxine is also indicated (where appropriate) for the prevention of

- Relapse of major depression
- Recurrence of major depression [5,6].

2.1.3 Depression in pregnancy

Antenatal depression is depression that happens during pregnancy. The 'Growing up in New Zealand' study found that out of 5,664 women who were pregnant in 2009, 12% of women experienced symptoms of antenatal depression in their third trimester [7].

Similar figures are seen internationally with 12% of women experiencing antenatal depression [7].

Dadi et al 2020, a systematic review of reviews finds a high prevalence of antenatal depression in the world with a prevalence ranging from between 15 to 65% [8].

Antenatal depression affects maternal quality of life and is a major cause of disease burden in both developed and developing countries. At an individual level, the risk of low birth weight, preterm birth, intrauterine growth restriction, and pregnancy complications are all known to be higher in association with antenatal depression.

Therefore, untreated depression during pregnancy can cause serious harm to both the mother and baby and it is essential that women receive treatment appropriately and when necessary.

2.1.4 Pharmacological Treatment

Anderson et al 2020 approximates that 10 to 15% of US reproductive-aged women are prescribed antidepressants annually [1].

Antenatal depression management is like depression in other stages of life, but with the additional considerations of the pregnancy and fetus. Mild depression can be treated with behavioural and psychological interventions and moderate to severe depression or persistent depression is usually treated with a combination of behavioural, psychological interventions and medicines, usually an antidepressant.

Currently, women are advised, and should be reassured, that appropriate indications of adequately prescribed antidepressants generally outweigh the risks. If a woman is already taking an antidepressant it is recommended that they keep taking the same medicine[7].

The bpac guidelines state that venlafaxine may be a treatment option in women who have not responded to a SSRI and should be considered if safer treatment options have not been successful. If SSRI's are ineffective or not tolerated, tricyclic antidepressants (TCAs) are second-line. Venlafaxine may be a treatment option for women who have not responded to a SSRI. The guidelines further state that due to an increased risk of neonatal withdrawal (including seizures), venlafaxine is only considered if safer treatment options have not been successful [7]. Furthermore, the management of pre-pregnancy use of anti-depressants and continuation throughout pregnancy is another important consideration. If a woman already taking an antidepressant becomes pregnant, it is recommended that she continue taking the same medicine while being informed that there is a high level of uncertainty regarding the risks of withdrawing pharmacological treatment during pregnancy [7].

2.2 Birth defects/congenital malformations

Congenital anomalies are defined as 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 (e.g., heart, brain, foot) and can occur at any stage of pregnancy [9].

They can be identified prenatally, at birth, or sometimes may only be detected later in infancy. Congenital anomalies are also known as birth defects, congenital disorders, or congenital malformations.

2.3 Hypertension in pregnancy

High blood pressure or hypertension in pregnancy can be classified into three types

1. Pre-existing hypertension or chronic hypertension
2. Pregnancy-induced hypertension or gestational hypertension
3. Pre-eclampsia which is characterized by high blood pressure (with or without proteinuria), and end-organ dysfunction, most often kidneys or liver [10].

Eclampsia is a severe complication of pre-eclampsia that is characterized by the development of a grand mal seizure in the absence of other neurological conditions that could account for the seizure [10].

2.4 [redacted]

[redacted]

2.5 The New Zealand data sheet

There are currently two data sheets in New Zealand that are published on the Medsafe website. They are for the Enlafax and Efexor-XR brands [5,6]. Both data sheets contain the same information regarding the usage of venlafaxine in pregnancy. The relevant sections in the NZ data sheet are highlighted below.

Sustained hypertension (in section 4.4 Special warnings and precautions for use)

Dose-related increases in blood pressure have been reported in some patients treated with venlafaxine.

Among patients treated with 75 to 375 mg per day of EFEXOR-XR in pre-marketing depression studies, 3% (19/705) experienced sustained hypertension [defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits].

Among patients treated with 37.5 to 225 mg per day of EFEXOR-XR in pre-marketing GAD studies, 0.5% (5/1011) experienced sustained hypertension. Experience with the immediate-release venlafaxine showed that sustained hypertension was dose-related, increasing from 3 to 7% at 100 to 300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of EFEXOR-XR over 300 mg per day to fully evaluate the incidence of sustained increases in blood pressure at these higher doses.

In placebo-controlled pre-marketing depression studies with EFEXOR-XR 75 to 225 mg per day, a final on-drug mean increase in supine diastolic blood pressure (SDBP) of 1.2 mm Hg was observed for EFEXOR-XR treated patients compared with a mean decrease of 0.2 mm Hg for placebo-treated patients. In placebo-controlled pre-marketing GAD studies with EFEXORXR 37.5 to 225 mg per day up to 8 weeks or up to 6 months, a final on-drug mean increase in SDBP of 0.3 mm Hg was observed for EFEXOR-XR treated patients compared with a mean decrease of 0.9 and 0.8 mm Hg, respectively, for placebo-treated patients. In pre-marketing Social Anxiety Disorder studies up to 12 weeks, the final on-therapy mean change from baseline in SDBP was small - an increase of 0.78 mmHg, compared to a decrease of 1.41 mm Hg in placebo-treated patients. In a 6-month study, the final on-therapy mean increase from baseline in SDBP with EFEXOR-XR 150 to 225 mg was 1.49 mmHg. The increase was significantly different from the 0.6 mm Hg decrease with placebo and the 0.2 mmHg decrease with EFEXOR-XR 75 mg.

In pre-marketing depression studies, 0.7% (5/705) of the EFEXOR-XR treated patients discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 16 mm Hg, SDBP). In pre-marketing GAD studies up to 8 weeks and up to 6 months, 0.7% (10/1381) and 1.3% (7/535) of the EFEXOR-XR treated patients, respectively, discontinued treatment because of elevated blood pressure. Among these patients, most of the blood pressure increases were in a modest range (12 to 25 mm Hg, SDBP up to 8 weeks; 8 to 28 mm Hg up to 6 months).

Cases of elevated blood pressure requiring immediate treatment have been reported in post-marketing experience. Sustained increases of SDBP could have adverse consequences. Therefore it is recommended that patients receiving EFEXOR-XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered. Pre-existing hypertension should be controlled before treatment with venlafaxine.

Caution should be exercised in patients whose underlying conditions might be compromised by increases in blood pressure.

Usage in pregnancy (in section 4.6 Fertility, pregnancy, and lactation)

Pregnancy: Category B2.

The safety of venlafaxine in human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Venlafaxine must be administered to pregnant women only if the expected benefits outweigh the possible risks. Patients should be advised to notify their physician if they

become pregnant or intend to become pregnant during therapy. If venlafaxine is used until or shortly before birth, discontinuation effects in the newborn should be considered.

Some neonates exposed to venlafaxine, other SNRIs, or SSRIs, late in the third trimester have developed complications requiring prolonged hospitalisation, respiratory support, or tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnoea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycaemia, hypotonia, hypertonia, hyper-reflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome.

Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of SSRIs and SNRIs in pregnancy. The relevance for venlafaxine treatment remains unknown.

Some epidemiological data suggests that the use of SSRIs and SNRIs in pregnancy may be associated with a small but statistically significant increase in pre-term delivery.

A prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy showed that women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

Exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia, and exposure to SNRIs near delivery may increase the risk for postpartum haemorrhage.

Comments

There is relevant information within the New Zealand data sheet regarding venlafaxine use in pregnancy and the outcomes of interest.

For congenital abnormalities, the data sheet states that there are some epidemiological studies that suggest an increased risk of congenital abnormalities associated with SNRIs in pregnancy, but the relevance of these studies for venlafaxine treatment remain unknown.

In section 4.4 (Special warnings and precautions) the data states that dose-related increases in blood pressure can occur and that sustained increases of SDBP could have adverse consequences. Regular monitoring should be carried out as well as caution in patients with underlying conditions who might be compromised by increases in blood pressure. This may be of relevance for venlafaxine use in pregnancy.

The data sheet says that women may be at an increased risk of preeclampsia with exposure to SNRIs in mid to late pregnancy.

2.6 Pregnancy information in the New Zealand Formulary (NZF)

Pregnancy Summary

The NZF summarises that neither the animal reproduction data nor the human pregnancy experience suggests that venlafaxine is a major risk for structural anomalies. However, venlafaxine, as well as selective serotonin reuptake inhibitors (SSRIs), have been associated with developmental toxicity, including spontaneous abortions (SABs), low birth weight, prematurity, neonatal serotonin syndrome, neonatal behavioural syndrome (withdrawal including seizures), possibly sustained abnormal neurobehaviour beyond the neonatal period, and respiratory distress. Persistent pulmonary hypertension of the newborn (PPHN) is an additional potential risk, but confirmation is needed.

2.7 International data sheet review

A review was carried out on the 9 February 2022 to see what information was contained within the venlafaxine data sheets/product information documents on the use of venlafaxine in pregnancy and whether there was any information with regards to birth defects, blood pressure and/or pre-eclampsia outcomes.

The relevant wordings in each of the data sheets are summarised in the table below.

Table 1: International data sheet review (as of 9 February 2022)

Country/ Product	Use in Pregnancy	Birth Defects	Blood Pressure/Pre-eclampsia
Australia			
Australian Product Information - Effexor-XR (Venlafaxine HCl [11]	Safety not established Use if benefit outweighs risk Information regarding discontinuation of antidepressant medicines, more likely to have a relapse of major depression.	Animal teratogenicity information included	Includes information regarding dose-related hypertension Recommends regular monitoring of blood pressure Pre-existing hypertension should be controlled Take caution in patients with underlying conditions Epidemiological studies suggest that exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia
UK			
Summary of Product Characteristics – UK (Efexor) [12]	No adequate data - safety not established Use if benefit outweighs risk in pregnant woman.	Studies in animals have shown reproductive toxicity	Blood pressure should be monitored and controlled before the initiation of treatment and reviewed periodically.
Summary of Product Characteristics – UK (Depfex) [13]	No adequate data – use if benefit outweighs risk in pregnant women.	Studies in animals have some reproductive toxicity	Blood pressure should be monitored and controlled before the initiation of treatment and reviewed periodically.
FDA			
Effexor XR (venlafaxine Extended-Release) capsules [14]	There are no adequate and well-controlled studies in pregnant women. Should only be used in the potential benefit outweighs the potential risk to the foetus.	Teratogenic animal study results listed, no adequate or well-controlled studies in pregnant women.	Under 'Warnings and precautions' – elevations in blood pressure. Monitor blood pressure regularly during treatment, use in caution in patients with pre-existing hypertension. Sustained blood pressure elevation can lead to adverse health outcomes.

Comments
The information regarding the use of venlafaxine in pregnancy is the same in NZ and in the international product information. Only in the NZ data sheet there is information about epidemiological studies suggesting an increased risk in congenital abnormalities. All countries list dose-related hypertension and only NZ and Australia mentioning the possible risk of preeclampsia.

3 SCIENTIFIC INFORMATION

This section provides summaries of published literature.

Section 3.1 includes the published literature on birth defects/congenital malformations and begins with a table showing a summary of their studies, venlafaxine comparators and conclusions.

Section 3.2 includes the published literature on gestational hypertension.

3.1 Published literature on birth defects/congenital malformations

Table 2: Summary of results of literature exploring pregnancy outcome after exposure to venlafaxine

Study/design	Venlafaxine exposure	Results/conclusions
3.1.1 Anderson et al 2020 (US) Case-control study (multi-centre)	During early pregnancy: the month before conception through the third pregnancy month. Exposure information of various antidepressants obtained by telephone interview with mother 6 weeks to 24 months after estimated date of delivery (EDD).	Varied risks for specific birth defects observed with venlafaxine having the highest proportion of elevated birth defect risks.
3.1.2 Bellantuono et al 2015 Comprehensive review	Five out of twenty-nine studies focused on the association between major malformations and exposure to venlafaxine.	The authors found that prenatal venlafaxine exposure may be considered relatively safe for neonates. In the studies that found a small increase in relative risk, the authors could not rule out whether this was because of residual confounding factors or other variables.
3.1.3 Furu et al 2015 Multi-country population-based cohort study	Women were exposed if they filled a prescription from 30 days before the first day of the last menstrual period until the end of the first trimester Registers were used to identify major birth defects diagnosed with 365 days of birth	No significant association was found between venlafaxine and birth defects.
3.1.4 Lassen et al 2015 Systematic review	Includes one case series and four cohort studies	The authors conclude that the corresponding relative risk estimates of major malformations deny that venlafaxine is associated with an increased risk of major malformations.
3.1.5 Kolding et al 2021 Register-based study	Antidepressant exposure was measured using redeemed prescriptions, outcomes were pregnancies with severe cardiac malformations.	The authors conclude that first-trimester exposure to venlafaxine was associated with an increased risk of severe cardiac malformations but with a low absolute risk
3.1.6 Polen et al 2013 Population based case-control study	Exposure was measured using redeemed prescriptions and cases were mothers of pregnancies affected by one of 30 selected birth defects	Statistically significant results were found for specified birth defects but due to the small sample sizes, and wide CIs the authors conclude that more studies are needed to confirm results
3.1.7 Berard et al 2016 Longitudinal prospective cohort study	Antidepressant exposure was identified with prescription fillings and relevant exposure time window was the first trimester (0-14 weeks of gestation). The reference category were depressed/anxious women that were not using any antidepressants during the relevant time window.	Antidepressants with serotonin reuptake inhibition effect increased the risk of certain organ-specific defects with venlafaxine being associated with respiratory defects.

Study/design	Venlafaxine exposure	Results/conclusions
3.1.8 Desai et al 2019 Retrospective review	Antidepressant exposure confirmed with chart reviews and identified pregnant women that underwent fetal echocardiography because of an in-utero exposure to either SSRIs or SNRIs.	This was a very small sample size out of a single centre and does not consider any other variables. Two out of 40 cases identified with congenital heart disease were on venlafaxine.
3.1.9 Richardson et al 2019 Prospective, observational comparative cohort study	Data collected from UK Teratology Information Service which included venlafaxine-exposed pregnancies with unexposed and SSRI exposed pregnancies.	No statistically significant increased risks of other adverse pregnancy or fetal outcomes were observed following the study of gestational venlafaxine use.
3.1.10 Ankarfeldt et al 2021 Population based observational study	Exposure was defined a redeemed prescription at a pharmacy with the time window being from last menstrual period (LMP) to 90 days after LMP, corresponding to the first trimester of pregnancy	When duloxetine-exposed was compared to comparator groups of SSRI exposed, venlafaxine exposed, and duloxetine discontinuers, some point estimates indicated an increased risk however the wide confidence interval suggests a great uncertainty.
3.1.11 Selmer et al 2016 Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy	This study is a reanalysis on 2.3 million births in a Nordic register-based cohort study. Venlafaxine is one of the antidepressants in the article.	The reanalysis on the estimated effect of SSRI/venlafaxine on risk of cardiovascular birth defects did not differ substantially between a fixed effects meta-analysis and the analyses of a pooled individual-based dataset.

3.1.1 Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects - Anderson et al 2020 [1]

This was a population-based, multicentre case-control study which included cases with selected birth defects from December 2011 to October 2017 that were identified using surveillance systems. Controls were randomly sampled live-born infants without major birth defects. The objective of the study was to examine the association between individual antidepressants and specific birth defects with and without attempts to partially account for potential confounding by underlying conditions. The study included 30,630 case mothers of infants with birth defects and 11,478 control mothers (aged 12–53 years).

Mothers participated in a computer-assisted telephone interview 6 weeks to 24 months after estimated date of delivery (EDD) and were asked about the use of citalopram, fluoxetine, paroxetine, sertraline, venlafaxine, and bupropion during the 3 months before conception or during pregnancy. Mothers were not asked specifically about depressive or anxiety diagnoses.

Early pregnancy exposure: defined as maternal report of using 1 or more medication product(s) in these classes in any dose, duration, or frequency from the month before conception through the third pregnancy month; the month before conception was included in early pregnancy estimates to account for the imprecision of conception date estimates and medication exposure dates.

Women were considered unexposed if they reported no antidepressant use during the 3 months before conception through their pregnancy's end.

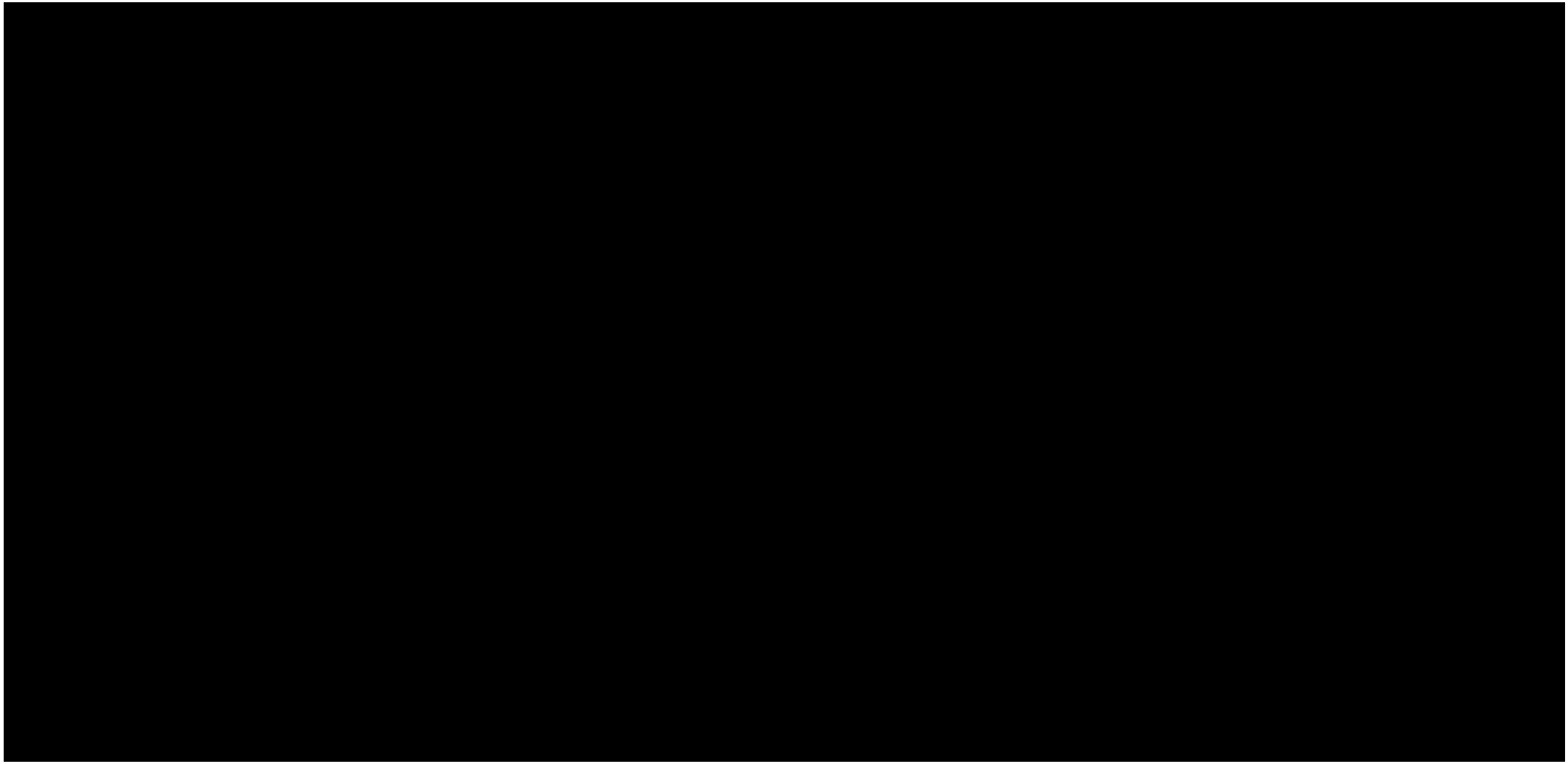
The study used x^2 tests to examine the distributions of characteristics among control mothers with any early pregnancy monotherapy or polytherapy antidepressant exposure compared with (1) unexposed control mothers and (2) control mothers whose only exposure to an antidepressant(s) occurred outside of early pregnancy. Multivariable logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals for NBDPS-eligible birth defects with 4 or more exposed cases.

Early pregnancy antidepressant use was reported by 1562 cases (5.1%) and 467 control mothers (4.1%) among control mothers. In Set 1 Birth defects analyses where they compared early pregnancy antidepressant-exposed women with women unexposed to antidepressants before and during pregnancy, they found that mothers who used venlafaxine had elevated aORs for most examined defects. These models were adjusted for maternal race/ethnicity, pre-pregnancy body mass index, education, and early pregnancy smoking and alcohol use.

Set 2 Birth defects analyses: compared early pregnancy antidepressant-exposed women with women exposed only to an antidepressant outside of early pregnancy, models were adjusted for maternal education. After accounting for the underlying condition, the elevated venlafaxine aORs persisted for most defects; in some instances, the association strength increased (anencephaly and craniorachischisis aOR, 6.50; 95% CI, 1.85-22.88).

Table 3 below shows the risk for specific birth defects after early pregnancy exposure to common antidepressant medications, compared to women who were exposed to an antidepressant outside of early pregnancy. These figures are partially accounted for confounding by the underlying condition.

Table 3. Risk for specific selected birth defects after early pregnancy exposure to common antidepressant medicines compared to women who were only exposed outside of early pregnancy (which at least partially accounts for confounding by the underlying condition, National Birth Defects Prevention Study, 1997-2011.



The authors conclude that their findings show and suggest varied risks for specific birth defects after early pregnancy use of individual SSRIs, venlafaxine, and bupropion. The results indicate that venlafaxine had the highest proportion of elevated birth defect risks and further conclude that the shown associations may be useful when making risk-benefit decision-making between antidepressants.

Comments
Exposure to antidepressants were self-reported, it is important to consider the role of recall bias. Interview did not ascertain diagnoses with treatment, which limits the ability to account directly for mental health conditions. Selection bias also needs to be considered as being selected as either a case or control mother affected participation. The results with regards to venlafaxine need to be interpreted with caution, as the numbers exposed are small, therefore have wide confidence intervals.

3.1.2 The safety of serotonin-noradrenaline reuptake inhibitors SNRIs in pregnancy and breastfeeding: a comprehensive review – Bellantuono et al 2015 [15]

This review is a comprehensive review of the existing literature on the safety of SNRI medicines in pregnancy and lactation. A search was undertaken for medical literature published in English reporting data on the safety of venlafaxine and duloxetine in pregnancy and lactation. Studies were identified searching MEDLINE/PubMed, PsycINFO, and EMBASE.

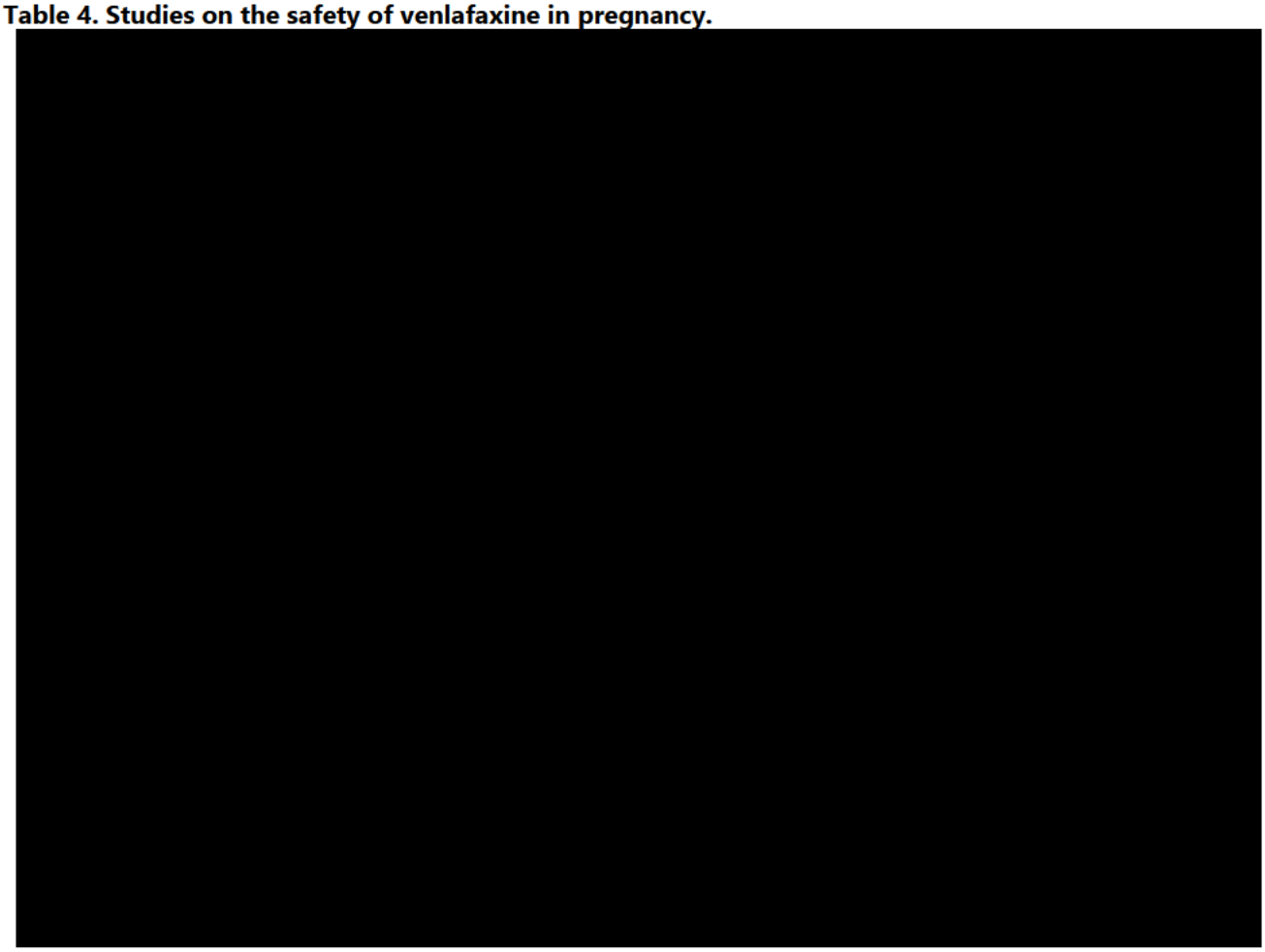
Twenty-nine studies were included in this review with the aim to review the results of the studies focusing on the safety of SNRIs in new-borns exposed to such drugs during pregnancy. Of these studies, five studies focused on the association between major malformations and venlafaxine exposure, see Table 4.

- Einarson et al (2009) found that out of 928 women exposed to antidepressants during the first trimester of pregnancy, 154 had been exposed to venlafaxine with 2 of these infants presenting with major malformations (club foot and hypospadias). No increased risk for major malformations was observed above the baseline.
- Lennestal et al (2007) found no increased risk for stillbirth or major malformations.
- Einarson et al (2001) included 150 pregnant women exposed to venlafaxine and in two new-borns, hypospadias and neural tube defects with clubfoot were reported. The study found that no differences between venlafaxine and the two comparison groups emerged in the endpoints investigated.
- Lind et al (2013) found that out of 1697 infants with hypospadias identified, 9 infants had been exposed to venlafaxine. Out of the antidepressants prescribed, an increase of relative risk only for venlafaxine was seen (OR 2.4; 95% CI:1.0-6.0).
- Polen et al (2013) found that an increased risk of major malformations with statistically significant associations. This study is further discussed in section 3.1.6.

Of the data analysed for venlafaxine, the study finds that prenatal venlafaxine exposure may be considered relatively safe for neonates. Of the five studies included that reported the occurrence of major malformations, three of the studies reported a rate ranging from 1.3% to 3.4% which is within the range of major malformations reported in the general population.

Of the two more recent case-control studies a small increase in relative risk was found, but the authors could not conclude whether these findings could have been affected by residual confounding factors, which they were not able to account for, particularly the severity of maternal depression.

Table 4. Studies on the safety of venlafaxine in pregnancy.



The authors further conclude that the results of these studies need to be interpreted in the context of some limitations such as incomplete information about daily dosage and concomitant drug use.

3.1.3 SSRIs and venlafaxine in early pregnancy and risk of birth defects: population-based cohort study and sibling design – Furu et al 2015 [16]

The objective of this study was to assess whether specific SSRIs or venlafaxine use in early pregnancy is associated with an increased risk of birth defects, with an emphasis on cardiovascular birth defects even when accounting for lifestyle or other familial confounding.

This was a multi-country population-based cohort study with sibling-controlled analysis across five Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden).

Women who gave birth to a live singleton infant between 1996 and 2010 were included and siblings born to the same mother were also identified during these periods. Infants were considered exposed in utero if they were born to women who filled a prescription for an SSRI or venlafaxine from 30 days before the first day of the last menstrual period until the end of the first trimester (defined as 97 days after the last menstrual period).

Using medical birth, patient, and malformation registers, data on maternal characteristics, the pregnancy and delivery, and major birth defects diagnosed within 365 days after birth was retrieved.

Included potential confounders: country of residence, maternal age at delivery, calendar year of delivery, birth order, maternal smoking during pregnancy, maternal diabetes and concurrent drug use.

Concurrent drugs considered to be confounders included antiepileptics, anxiolytics, hypnotics, and agents acting on the renin-angiotensin system dispensed from 30 days before the first day of the last menstrual period until 97 days after the last menstrual period.

For statistical analyses, logistic regression analysis was used to estimate odds ratio with 95% confidence intervals for all major and specific types of birth defects according to exposure status. Primary analyses were the assessment of odds ratios for birth defects by exposure in pregnancy to venlafaxine, with the reference group comprising of births of infants not exposed to any antidepressant in utero.

Out of the full study cohort, 36,772 infants (1.6%) infants were exposed to a SSRI or venlafaxine in the first trimester. And 1357 (3.7%) had a diagnosis of a major birth defect compared with 74,374 (3.2%) of the 2,266,875 unexposed infants, see Figure 2.

Figure 2: SSRI or venlafaxine in early pregnancy and risk of birth defects. *Adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs (antiepileptics (ATC code N03), anxiolytics and hypnotics (N05B and N05C), and angiotensin converting enzyme inhibitors (C09))

The prevalence of overall cardiac birth defects was 1.5% among infants exposed to any SSRI or venlafaxine compared with 1.2% among infants in the unexposed group (1.15, 1.05 to 1.26).

Findings with regards to venlafaxine:

- Cardiac defects had a crude odds ratio (95% CI) 1.23 (0.90 to 1.68) and an adjusted odds ratio of 1.14 (0.82 to 1.57)
- Atrial and ventricular septal defects 1.17 (0.79 to 1.74) with an adjusted odds ratio of 1.10 (0.73 to 1.64).
- With non-cardiac birth defects, hypospadias, there were 7 with the birth defect (2.5 per 1,000) had a crude odds ratio of 1.27 (0.60 to 2.67) with an adjusted odds ratio of 1.13 (0.54 to 2.38).

Note that adjusted odds ratio was adjusted for maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs, anxiolytics and hypnotics, and angiotensin converting enzyme inhibitors.

However, when looking at individual antidepressants, no significant association was found between venlafaxine and birth defects. The authors conclude that the results from their covariate adjusted analyses and the sibling-controlled analyses point against a substantial teratogenic effect of SSRIs and they did not suggest a teratogenic effect of venlafaxine either.

Comments

This study was based on large numbers that allowed the authors to study individual antidepressants and specific birth defects with independent ascertainment of exposure and outcome up to 1 year of age without any risk of recall bias. Although the cohort was large, the numbers of outcomes were low which is reflected in the relatively wide confidence intervals.

Non-adherence to the dispensed antidepressants may have yielded misclassification of the exposure and therefore biased results.

3.1.4 First-Trimester Pregnancy Exposure to Venlafaxine or Duloxetine and Risk of Major Congenital Malformations: A Systematic Review – Lassen et al 2015 [17]

This is a systematic review that looked at the use of venlafaxine and duloxetine during the first trimester and the risk of congenital malformations and estimated the relative risks using background population malformation rate as a reference. A literature search was conducted following PRISMA guidelines, and the databases included were PubMed (Medline) and EMBASE and were searched from inception to the end of April 2015.

There was one case report/series reporting nine live births exposed to venlafaxine during first trimester with none of these babies born with major malformations.

Four included cohort studies held data on venlafaxine exposure during the first trimester of pregnancy. To summarise, the authors identified 3186 exposed infants of whom 107 infants were born with major malformations, which resulted in a malformation rate of 3.36%. The relative risk estimate and 95% CI are 1.12 (0.92-1.35).

The authors report a pooled malformation rate and an estimation of the relative risk with 95% confidence intervals (CI) of major malformations among live births after exposure to venlafaxine or duloxetine during pregnancy using a population reference value of 3% for major congenital malformations by exact binominal distribution.

Table 5 below displays the characteristic of eligible studies and Table 6 displays cumulated numbers of exposed, malformations, malformation rates and relative risks.

Table 5: Characteristics of eligible studies

Table 6: Cumulated number of exposed, cumulated number of malformations, malformation rate and relative risk for each drug

The authors conclude that the corresponding relative risk estimates of major malformations deny that venlafaxine is associated with an increased risk of major malformations. The reference population estimate of major congenital malformations is reported within the range of 2.5-3.5%.

3.1.5 Antidepressant use in pregnancy and severe cardiac malformations: Danish register-based study – Kolding et al 2021 [18]

This study was a Danish register-based study that investigated the association between antidepressant use in pregnancy and severe cardiac malformations (SCM). The study population consisted of all clinically recognised singleton pregnancies with fetuses alive at the nuchal scan from 11 completed gestational weeks, with estimated conception dates from 1 Nov 2007 to 1 Feb 2014.

Exposure to antidepressants were measured using redeemed prescriptions through linkage to the Danish Health Services Prescription Database. First-trimester exposure was defined as two or more redeemed prescriptions from 28 days before through 70 days after conception date with the unexposed group being defined by the absence of redemptions for an antidepressant in the same window, combined with absence of former use.

Outcomes were pregnancies with cardiac malformations that end in miscarriage, termination, stillbirth, postnatal death, or cardiac surgery <1 year of birth were classified as severe cardiac malformations (SCM).

The authors used log-binomial regression to estimate the association between antidepressants and the cardiac malformation outcomes by prevalence ratios (PRs) with 95% confidence intervals (CI).

Results: the fully adjusted PRs for SCM were 1.31 (95% CI 0.78-2.22) for any antidepressant, 2.13 (95% CI 0.89-5.13) for venlafaxine. Most PRs became attenuated in response both to improved covariate adjustment and using the former as a comparator, but the association with venlafaxine persisted even after exclusion of pregnancies exposed to other psychiatric medication, see Table 7.

Table 7. Non-SCM in first trimester exposed (>prescriptions) compared with unexposed and former use.

The authors conclude that first-trimester exposure to venlafaxine was associated with an increased risk of severe cardiac malformations but with a low absolute risk. Among malformations in all clinically recognised pregnancies, regardless of fetal survival, first-trimester exposure to venlafaxine was associated with a 2.1-fold increased PR of SCM, a 1.7-fold increase PR of other cardiac malformations, and a 17-fold increase in a specific type of severe heart malformation, HLHS, but with a low absolute risk with an NNH of 225.

They conclude that these results are potentially important for the clinical management of women but recognise that a limitation to their study is low prevalence of malformations which limits the power of the analyses, in particular the analyses of the specific malformations.

The authors further conclude that their results need to be interpreted with caution as venlafaxine is often a second-line treatment and therefore potentially a marker for depression severity.

Comments
This study includes data from both prenatal and postnatal diagnoses of cardiac malformations, which addresses the limitation of other previous studies with just live births as this could mean that a protective effect could be seen if most exposed cases do not survive to term.

3.1.6 Association between Reported Venlafaxine use in early pregnancy and birth defects, National Birth Defects Prevention Study 1997-2007 – Polen et al 2013 [19]

The objective of this study is to determine whether the use of venlafaxine during pregnancy is associated with specific birth defects. Data was used from the National Birth Defects Prevention Study (NBDPS), a population-based, case-control study in the United States. The NBDPS is an ongoing, population-based case-control study designed to investigate genetic and environment risk factors for major structural birth defect. Birth defects data are collected by 10 birth defects surveillance systems in the United States and cases included live births, stillbirths (≥20 weeks), and elective terminations diagnosed with one or more than 30 selected major birth defects.

The analysis included mothers with pregnancies affected by one of 30 selected birth defects (cases) and babies without birth defects (controls) with estimated dates of delivery between 1997 and 2007.

Mothers of case and control infants are contacted within 6 weeks to 24 months after the estimated date of delivery (EDD) to participate in a telephone interview where specific exposures and behaviours are ascertained throughout pregnancy and the 3 months preconception.

Exposure was reported as use of venlafaxine from 1 month preconception through the third month of pregnancy and women were classified as unexposed if they did not report use of any antidepressant from 3 months before conception through the end of pregnancy.

For statistical analysis, the authors calculated adjusted odds ratios (aORs) and 95% Fisher Exact confidence intervals (Cis) for 24 birth defect groups for which at least 400 case mothers were interviewed. The adjusted analyses controlled for only two variables; these were maternal age and race/ethnicity due to the small number of exposed mothers.

Among mothers who met the inclusion criteria, 0.17% (14/8002) of control mothers and 0.40% (77/19,043) of case mothers reported any periconceptional use of venlafaxine. The duration of use ranged from 1 to 120 days, but 54% of mothers reported using venlafaxine for the entire period of 1 month before pregnancy through the end of the first trimester.

Results: As shown in Table 8, statistically significant associations were found for anencephaly, atrial septal defect (ASD) secundum, or ASD not otherwise specified, coarctation of the aorta, cleft palate, and gastroschisis. The data suggests associations between periconceptional use of venlafaxine and some birth defects. However, sample sizes were small, CIs were wide, and therefore additional studies are needed to confirm these results.

Table 8: Association between use of venlafaxine just before and during Early Pregnancy and the Occurrence of Certain Birth Defects, National Birth Defects Prevention Study, 1997-2007

Comments
Due to the small numbers of women exposed to venlafaxine during early pregnancy has led to imprecise estimates with wide CIs.

3.1.7 Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort – Berard et al 2016 [20]

This was a register-based longitudinal prospective cohort study with an aim to determine the association between first-trimester exposure to antidepressants and the risk of major congenital malformations in a cohort of depressed/anxious women.

Data was obtained from the Quebec Pregnancy Cohort with all pregnancies with a diagnosis of depression or anxiety or exposed to antidepressants in the 12 months before pregnancy and ending with a live-born singleton were included.

Major congenital malformations overall and organ-specific malformations in the first year of life were identified. Antidepressant classes and types were studied specifically as well to quantify the risk of organ-specific defects.

Exposures: antidepressant exposure was identified with prescription fillings for any antidepressant dispensed to women in the study cohort from the Quebec Public Prescription Drug Insurance Database, with the timing

of exposure determined between the dispensed date and duration of prescription. The relevant exposure time window was the first trimester (0-14 weeks of gestation) confirmed by ultrasound.

Statistical analysis: separate analyses were conducted for overall major congenital malformations, and for each organ system malformation. Crude and adjusted ORs (aORs) with 95% CIs were calculated for each outcome.

Results: among users of antidepressants, there were 738 (20.3%) of SNRI (all users of venlafaxine). Table 9 below presents the crude and adjusted estimates for the association between the use of antidepressant classes during the first trimester and the risk of overall major congenital malformations. Adjusting for potential confounders the use of SNRI was not associated with an increased risk of major malformation, compared with non-use in the study population of depressed pregnant women.

Table 9: Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed women

The authors present the use of antidepressants and the risk of organ-specific defects, stratified by types of malformations, showing that venlafaxine use during early pregnancy was associated with an increased risk of respiratory defects (aOR 2.17, 95% CI 1.07 to 4.38, 9 exposed cases).

Comments

Indication bias can be of concern in pharmacoepidemiological studies, so using a group of depressed/anxious pregnant women not using antidepressants as a reference category enabled for the adjustment of the indication (depression/anxiety).

Results could potentially be underestimated as it is known that antidepressants increase the risk of spontaneous abortions and spontaneous abortion is a determinant of severe malformations. Only live births were included.

3.1.8 Risk of congenital heart disease in Newborns with Prenatal Exposure to Anti-depressant Medications – Desai et al 2019 [21]

This study is a retrospective review of institutional medical records at Children's Hospital of New Orleans from Jan 1st 2009 to Dec 31st 2014 and identified all pregnant women that underwent fetal echocardiography because of an in-utero exposure to either SSRIs or SNRIs.

A total of 40 pregnant women were identified and 31 (77.5%) were receiving SSRIs, six (15%) SNRIs and three (7.5%) were on a combination of drugs. Among the six that were on SNRI's, two were on venlafaxine, see table 10.

Table 10: Characteristics of two patients with venlafaxine exposure

Patient number	Gestational age at echo (weeks)	Anti-depressant medications during pregnancy	Fetal echocardiography findings
4	27	Venlafaxine	Two mid-muscular VSDs
5	33.5	Venlafaxine	Ductal constriction with doppler velocity of 2.38m/sec

The authors conclude that fetal echocardiographic abnormalities were found in 18% of fetuses, whereas the incidence of CHD is 1% in the general population.

Comments
This was a very small retrospective review out of a single centre and with a relatively small sample size. It does not take into any other variables. However, antidepressant exposure was confirmed via chart reviews, not telephone interviews.

3.1.9 Pregnancy outcomes following maternal venlafaxine use; a prospective observational comparative cohort study – Richardson et al 2019 [22]

This prospective, observational comparative cohort study utilised data collected by the UK Teratology Information Service (UKTIS) between 1995 and 2018. The study sample included 281 venlafaxine-exposed pregnancies matched to antidepressant unexposed (n=1,405) and SSRI exposed (n=843) comparator groups.

The main aim of this study was to look and pregnancy outcomes, in particular spontaneous abortion risks following gestational venlafaxine use, with secondary outcomes to investigate congenital malformations and other adverse pregnancy outcome risks.

The study sample consists of non-duplicate pregnancy/fetal outcomes collected by the service following reports of maternal exposures between Sept 1995 and August 2018.

The exposed study group included pregnancies in which mothers had used venlafaxine at any stage of pregnancy. 281 venlafaxine-exposed pregnancies were identified and matched to 1,405 antidepressant unexposed pregnancies and 843 SSRI exposed pregnancies. In all but 4 pregnancies, gestational venlafaxine exposure occurred in at least the first trimester for the majority of the venlafaxine exposed study group, with treatment being initiated before the 24th gestational week of pregnancy. Out of these pregnancies, seven venlafaxine-exposed infants were reported to have congenital malformations with four infants with major malformations and three minor malformations. Table 11 shows a comparison of crude pregnancy and fetal outcome rates between the venlafaxine, antidepressant unexposed and SSRI exposed study groups.

Table 11: Comparison of crude pregnancy and fetal outcome rates between the venlafaxine, antidepressant unexposed and SSRI exposed study groups.

Results: when comparing crude malformation rates there were no statistically significant differences in major malformation rates following exposure. Furthermore, adding co-variable estimates to carry out adjusted analyses did not alter statistical significance.

The authors conclude that no statistically significant increased risks of other adverse pregnancy or fetal outcomes were observed following the study of gestational venlafaxine use.

Comments
It is important to consider that the request for outcomes was not standardised and therefore this may be an additional source of outcome variation. Outcomes were requested shortly after the estimated delivery date, however congenital malformations may be diagnosed by one year of age rather than at six months. In addition, this analysis is based on surveillance data therefore outcome detection may also be heterogenous and not standardised as differences between healthcare professionals, responder clinical knowledge and experience exist.

3.1.10 Exposure to duloxetine during pregnancy and risk of congenital malformations and stillbirth: A nationwide cohort study in Denmark and Sweden – Ankarfeldt et al 2021 [23]

Study type: population-based observational study. The aim of this study is to evaluate the association of exposure to duloxetine during pregnancy and the risk of major or minor congenital malformations and the risk of stillbirths. The study was based on data from registers in Sweden and Denmark, including all registered births and stillbirths in the medical birth registers between 2004 and 2016, and malformation diagnoses were identified up to 1 year after birth.

The prescription registers, containing electronically submitted information on prescriptions dispensed by pharmacies, classified according to the global ATC system. Duloxetine exposed women were compared with 4 comparators, one being venlafaxine-exposed women.

Maternal exposure to medication was defined as a redeemed prescription at a pharmacy and the exposure time window was from last menstrual period (LMP) to 90 days after LMP, corresponding to the first trimester of pregnancy. Major and minor malformations were classified according the EUROCAT classification of congenital malformations version 1.4.

For statistical analysis: unadjusted, adjusted multiple regression, and a propensity score (PS)-matched analysis were performed. The results are shown in Figure 3.

Figure 3: Risk of major and minor malformation. Duloxetine vs. 4 comparators.

Results: for major malformations, all odds ratio (OR) point estimates based on unadjusted, adjusted or PS-matched analyses across all 4 comparator groups are centred around 1, suggesting no increased risk. For minor malformations, the unadjusted analysis shows increased risk but when adjusted and PS-matched, the risk was lower and showed no statistically significant increase.

When duloxetine-exposed was compared to comparator groups of SSRI exposed, venlafaxine exposed, and duloxetine discontinuers, some point estimates indicated an increased risk however the wide confidence interval suggests a great uncertainty.

This observational study found no increased risk of congenital minor or major malformations among women exposed to duloxetine during pregnancy. For minor malformations, there was some tendency for an increased risk, however the estimates of associations had wide CIs and the tendency decreased when duloxetine exposed were compared with venlafaxine exposed or duloxetine discontinuers as well as in adjusted and PS-matched analyses.

Comments

The strengths of this study were that it included register data and so there was no risk of recall bias. Also, they were using nationwide registers so selection bias was kept at a minimum. There was no information regarding congenital malformations among abortions and stillbirth which could lead to an underestimation of risk.

Another important consideration is for major malformation subtypes, adjusted analyses could not be consistently carried out due to the low number of outcome events despite the cohort including more than 2 million births.

Duloxetine is not available in NZ and it is important to note that in this study, the indication for duloxetine was not available as a recorded covariate as duloxetine is indicated for other conditions, not just depression as is the case for venlafaxine also.

3.1.11 Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy – Selmer et al 2016 [24]

This study is a reanalysis on 2.3 million births in a Nordic register-based cohort study (Furu et al, 2015, discussed in section 3.1.3). The main purpose was to compare individual-based analyses of a pooled dataset with the results from aggregate fixed effects meta-analysis Out of the births, 27,309 infants were born with a cardiovascular birth defect.

Statistical analysis: for any cardiovascular birth defect the inverse variance method in the fixed effects meta-analyses is weighting the country-specific log-odds ratios (ORs) by the inverse of the within-countries' variances. A similar analysis was performed for the rare outcome right ventricular outflow tract obstructions (RVOTO). Logistic regression was used to adjust for confounders in both the individual-based pooled analysis and the country-specific analysis.

Results:

- Country adjusted OR (95%CI) for any cardiovascular birth defect in the individual-based pooled analysis was 1.27 (1.17–1.39), 1.17 (1.07–1.27) adjusted for common covariates and 1.15 (1.05–1.26) adjusted for all covariates.
- The pooled OR from the meta-analysis was 1.29 (1.19-1.41) for CV defects, based on crude data. After adjustment for common covariates (age, birth order, diabetes, and co-medication), all ORs were slightly reduced and further reduced after country optimized adjustment. After country-optimized adjustment, the pooled OR from the fixed effect model was 1.16 (1.06-1.27). There was statistically significant heterogeneity between the countries. The random effects result was a pooled OR of 1.07 (0.87-1.32).
- Country-specific adjusted analyses at the substance level were not possible for RVOTO.

The estimated ORs in the fixed effects models for any cardiovascular defect both for exposure to any SSRI/venlafaxine and for exposure to specific substances were close to the estimated odds ratio based on logistic regression of the individual-based pooled dataset. There was no statistically significant heterogeneity between countries for specific substances.

The authors conclude that their reanalysis on the estimated effect of SSRI/venlafaxine on risk of cardiovascular birth defects did not differ substantially between a fixed effects meta-analysis and the analyses of a pooled individual-based dataset.

Comments
A fixed effects model assumes that all the studies included in a meta-analysis are estimating a single true underlying effect. Note that this model is only appropriate if there is no statistical heterogeneity among the effect sizes. The authors included a heterogeneity test.

3.2 Published literature on gestational hypertension

3.2.1 Antidepressant Use and Risk for Preeclampsia – Palmsten et al 2013 [25]

The objective of this cohort study was to compare specific antidepressants and the risk for preeclampsia.

Study population: Pregnancy cohort was identified from 2000-2007 US nationwide Medicaid Analytic eXtract (MAX) data. This study used US nationwide Medicaid eXtract (MAX) data to identify 100,942 pregnant women and their inpatient/outpatient medical records as well as pharmacy dispensing records to ascertain exposure to antidepressants (SSRI, SNRI, tricyclic, bupropion or other antidepressant (mirtazapine, nefazodone, trazodone, mono-or polutherapy) to associate relative risks (RR) and 95% confidence intervals (CI).

Exposure: The primary exposure window was from 90 to 225 gestational days (i.e., the second trimester through the end of the first half of the third trimester). Women were classified as exposed if they had an antidepressant dispensed during the exposure window, and unexposed if there was no antidepressant dispensed between the LMP and the end of the window.

Preeclampsia was defined as any inpatient or outpatient ICD-9 code for preeclampsia or eclampsia after 140 gestational days and within 30 days after the delivery date.

Methods: The primary analysis compared the risk for preeclampsia between exposed women (according to antidepressant class) and unexposed women and then secondly in a comparative-safety analysis, the study compared other exposure groups to the SSRI monotherapy group.

Statistical analysis: relative risk (RR) and their corresponding 95% CIs were estimated with models being adjusted for delivery year, preeclampsia risk factors, depression-severity proxies, other indications, other medicines, and healthcare utilization.

Results: the risk of preeclampsia was 5.4% among women with depression and no antidepressant exposure. For the SNSR-group, compared to these women, the risk for preeclampsia was higher among those receiving SNRI (RR: 1.52, 95% CI: 1.26-1.83). When compared to SSRI monotherapy, the risk of preeclampsia was higher among women with SNRI monotherapy (RR: 1.57, 95% CI: 1.29-1.91).

When the primary analysis was repeated by the study authors to include both women with and without depression, the associations changed slightly with the RR 1.53 for SNRI (1.33-1.76). The median antidepressant days supply during exposure window was 77 for SNRI and only women with high or medium cumulative duration had an increased risk for preeclampsia when compared with unexposed women. The relative risks are shown in Table 12 and 13.

Table 12. Relative risks and 95% Confidence Intervals Comparing the Risk for Preeclampsia Between Women with and without Antidepressant Exposure by Class, Restricted to Women with Depression: Medicaid Analytic eXtract, 2000-2007.

Table 13: Relative Risks and 95% Confidence Intervals Comparing the Risk for Preeclampsia Between Women in the Monotherapy Exposure Groups with Specific Antidepressant Exposures and Women without Antidepressant Exposure, Restricted to Women with Depression: Medicaid Analytic eXtract, 2000-2007

The authors conclude that women who used SNRIs during mid-pregnancy had an approximately 1.5-fold increased risk of preeclampsia. Also, the comparative-safety analysis estimates showed a moderate increased risk with SNRI compared with SSRIs. However, the magnitude of the SNRI relation were smaller in this study than previous studies.

The limitations discussed by the author include misclassification bias due to exposure being measured with pharmacy records and claims. They also could not rule out the possibility that results from any of the analyses reflect residual confounding by unmeasured lifestyle factors, such as other antidepressant medicines or depression severity. In addition, they were also unable to measure for obesity, which is a strongly and positively associated with preeclampsia. The best estimate that the authors have for the RR is between 1.3-1.7 for SNRIs.

Comments
In this population, SNRI use throughout mid-pregnancy was associated with a higher risk of preeclampsia than SSRIs.

3.2.2 Antidepressant use during pregnancy and the risk of developing gestational hypertension: a retrospective cohort study – Zakiyah et al 2018 [26]

The aim of this retrospective cohort study was to assess the association between the use of antidepressants during pregnancy and the risk of developing gestational hypertension.

The study was performed with a large mother-infant subset referred to as a "pregnancy database". Singleton pregnant women that were registered in this database during 1994 to 2015 were included in this study. Women who had gestational hypertension in a previous pregnancy, using anti-thrombotic medicines and low-dose acetylsalicylic acid were excluded.

Women using antidiabetic drugs prior to conception, at least one dispensing of antihypertensive drugs, thiazides, beta-blocking agents, ACE-II antagonists, CCB's in the period of 6 months before conception until twenty completed weeks of gestation were also excluded.

Exposure: defined as at least one dispensing record of an antidepressant (ATC code N06A) between the theoretical conception date and 20 completed weeks of gestation. The non-exposed group were pregnant women that were without antidepressant prescriptions in the period of six months prior to the theoretical conception date until 20 completed weeks of gestation.

Methods: Multivariate logistic regression was performed to estimate the odds ratio (OR) and their corresponding 95% confidence intervals. In multivariate analysis, ORs were adjusted for variables that were significantly associated with the outcome in univariate analyses, to assess if there was a significant difference in distribution ($p<0.05$) in the frequency or means of the covariates between exposed and unexposed.

To examine whether association varied by type of antidepressant, the authors subsequently stratified different classes of antidepressants. They also stratified exposure by the total amount of antidepressants dispensed during pregnancy.

Outcome: determined by identifying dispensed antihypertensive drugs to treat gestational hypertension. A woman was considered to have gestational hypertension when she had at least one prescription for methyldopa, nifedipine, labetalol, ketanserin, or nicardipine between 20 completed weeks of gestation and 14 days after delivery.

Results: out of 28,020 pregnant women, 539 (1.9%) were exposed to antidepressants between the theoretical gestation date and twenty completed weeks of gestation. Within the exposed group, 22 (4.1%) suffered from a

medically treated hypertension, whereas 571 (2.1%) of the non-exposed pregnant women were prescribed antihypertensive drugs in the period of twenty completed weeks of gestation until 14 days after delivery.

After adjusting for age, use of benzodiazepines, use of antibiotics and the exposure to antidepressants during pregnancy was associated with significant increased odds for developing gestational hypertension.

Prolonged exposure to antidepressants seemed to significantly increase the odds of developing gestational hypertension, with aOR of 2.13 (95% CI 1.36–3.34), 2.36 (95% CI 1.35–4.12) and 2.66 (95% CI 1.52–4.65) for exposure in the period of 0–10 weeks of gestation including both women with and without ongoing exposure,11–20 weeks of gestation, and both periods, respectively.

The authors conclude that the risk of developing gestational hypertension is higher among women who were exposed to SSRIs and with DDDs (Defined Daily Dose) more than 30. Prolonged use of antidepressants during both the first and second trimesters seemed to further increase this risk.

Covariates that could potentially confound the association were assessed. These were maternal age at delivery, other medications before conception and during pregnancy (i.e. the use of fertility treatment), maternal antibiotic prescriptions. The authors also took into consideration potential underlying condition that might affect the risk of developing preeclampsia – such as mood disorders.

Comments
The main antidepressant that was used in this analysis were SSRIs therefore the relevance of this study to venlafaxine is not known. However, it is important to note that venlafaxine is a 'dual agent' and at lower doses such as 75mg, venlafaxine is a selective serotonin reuptake inhibitor (SSRI).

3.2.3 Antidepressant use during pregnancy and the risk of pregnancy-induced hypertension – De Vera and Berard 2012 [27]

This was a nested case-control study to evaluate the impact of antidepressant use during pregnancy on the risk of pregnancy-induced hypertension. Data was used form the Quebec Pregnancy Registry which is a longitudinal cohort established with the linkage of three administrative databases.

Cases of pregnancy-induced hypertension were defined as women with a diagnosis of gestational hypertension, pre-eclampsia, or eclampsia. Using nested case-control design, controls were selected among women who did not have a diagnosis of pregnancy-induced hypertension.

Statistical analysis was done using conditional logistic regression models and crude and adjusted odds ratios (OR) with 95% confidence intervals were calculated. Multivariate analysis was also carried out.

Out of 61,735 women who met the study criteria, 1216 cases of pregnancy-induced hypertension were identified. Overall, 345 women filled at least one prescription for an antidepressant during pregnancy, 45 (3.7%) were cases and 300 (2.5%) were controls.

The results are shown in table 14. Following modelling exposure according to antidepressant class, the study found that use of SSRIs alone was significantly associated with the risk of pregnancy-induced hypertension (adjusted OR 1.60, 95% CI 1.00, 2.55) and the use of other antidepressants (serotonin modulators, monoamine oxidase inhibitors, tetracyclic piperazino-azepines, and dopamine and norepinephrine re-uptake inhibitors) was also significantly associated with risk of pregnancy-induced hypertension adjusted OR 3.71, 95% CI 1.25, 10.98.

Table 14: Risk of pregnancy-induced hypertension with antidepressants during pregnancy by medicine class and type.

Comments
This study has only 2 cases (0.2%) of women that were on venlafaxine, therefore the unadjusted and adjusted OR has to be interpreted with caution, especially as they have wide CIs.

3.2.4 Newport, 2016 – Prenatal psychostimulant and antidepressant exposure and risk of hypertensive disorders of pregnancy – Newport, 2016 [28]

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

OBJECTIVE: To investigate the association, if any, of prenatal mental illness and psychotropic exposure with the risk of hypertensive disorders of pregnancy (HDP).

METHODS: A case-cohort analysis was conducted of 686 pregnant women participating in prospective, longitudinal observational studies in a tertiary referral centre between January 1998 and May 2012. Risk estimates were produced using multivariate logistic regression modelling. Medication- and diagnosis-specific data were utilized to conduct post hoc confirmatory analyses of the risk estimates.

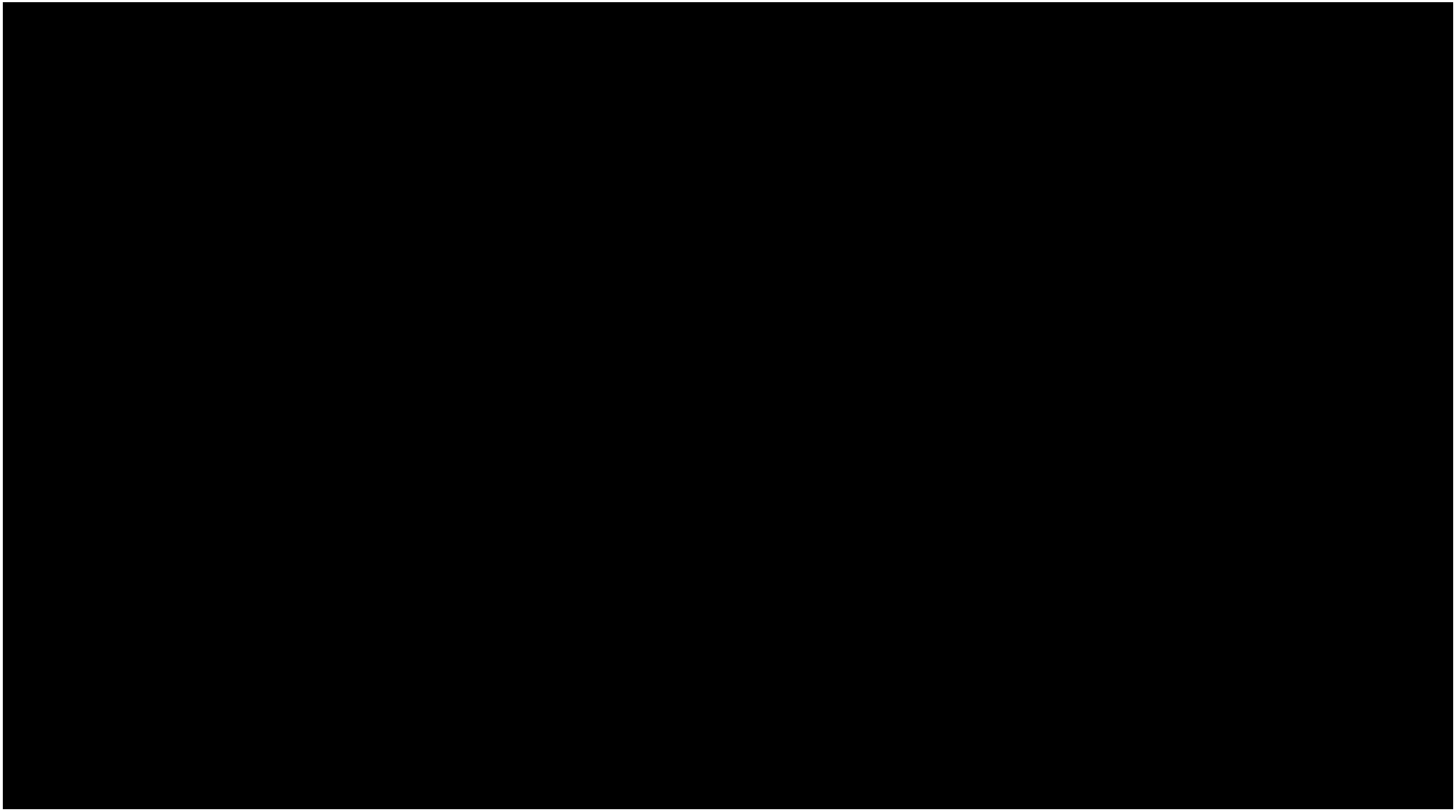
RESULTS: After adjustment for confounders, HDP were significantly associated with psychostimulant (odds ratio [OR] = 6.11; 95% CI, 1.79-20.9) and serotonin-norepinephrine reuptake inhibitor (SNRI) (OR = 2.57; 95%, 1.34-4.93) exposure following the 20th week of gestation and lifetime histories of cocaine dependence (OR = 2.99; 95% CI, 1.12-7.98) and panic disorder (OR = 1.78; 95% CI, 1.06-2.98) using DSM-IV diagnostic criteria. HDP risk was not associated with prenatal selective serotonin reuptake inhibitor exposure or other psychiatric disorders. Post hoc analyses demonstrated an increased risk for HDP with higher maternal daily doses of amphetamine psychostimulants and the SNRI venlafaxine.

CONCLUSIONS: These data indicate that psychostimulant and SNRI exposure following the 20th week of gestation conveys considerable risk for the emergence of HDP. Overall, the findings suggest that heightened vascular reactivity to noradrenergic, rather than serotonergic, stimulation may be pivotal to HDP risk among women with psychiatric illness.

Comments
Due to the abstract only being available, although the authors conclude that psychostimulant and SNRI exposure following the 20th week shows a considerable risk of hypertensive disorders in pregnancy, this needs to be interpreted with caution for this report as study methods are not known.

3.3 External comments [redacted]

[redacted]



3.4 CARM Data - NZ Spontaneous Data

New Zealand spontaneous data was requested from the Centre for Adverse Reactions Monitoring (CARM) but was not received before the release of this report. Data will be tabled at the MARC meeting.

3.5 [redacted]

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

This report reviews the use of venlafaxine in pregnancy and the possible associations with birth defects and potential contribution to hypertensive disorders in pregnancy (gestational hypertension, pre-eclampsia, and eclampsia).

Untreated depression can cause serious harm to both mother and baby and for women that are already on antidepressants, there is a high level of uncertainty with regards to withdrawing pharmacological treatment during pregnancy. It is therefore essential that pregnant women receive appropriate care

Congenital Malformations/Birth Defects

There are several studies with an aim to measure and assess the risk of congenital malformations if the mother was exposed to venlafaxine. Many of the studies investigate several different outcomes as there are a wide range of congenital abnormalities, and because of the often-small numbers of venlafaxine-exposed mothers the studies are often unable to give reliable evidence, with large confidence intervals.

The results of the studies are conflicting and not consistent, with some of the studies showing no statistically significant increased risks associated with venlafaxine use (Furu et al 2015, Richardson et al 2019).

Two reviews were included in this paper, Bellantuono et al 2015, a comprehensive review which included five studies relating to venlafaxine found that prenatal venlafaxine exposure may be considered relatively safe for neonates and Lassen et al 2015 also do not consider that venlafaxine is associated with an increased risk of major malformations.

There are other studies providing evidence of an association between venlafaxine use and malformation and also some specific malformations such as respiratory defects (Berard et al 2016). Polen at al 2013 and Ankarfeldt et al 2021 also show increased risk for specified birth defects in venlafaxine-exposed mothers however due to small sample sizes and wide CIs the results do suggest a level of uncertainty and therefore the results need to be interpreted with caution.

The results of the studies may have been affected by methodological biases and/or confounding. Methodological biases include when antidepressant exposure is measured by telephone or interview where recall bias is likely as mothers that are case are more likely to remember exposure. In the studies that used pharmacy and dispensing registers to measure exposure there is a degree of uncertainty with regards to whether the women took the medicine or not. Confounding by indication and the unmeasured disease severity is also not accounted for in some of these studies.

At the time of writing this report, the data sheet in New Zealand states that (with regards to congenital abnormalities) that "Some epidemiological studies have suggested an increased risk of congenital abnormalities associated with the use of SSRIs and SNRIs in pregnancy. The relevance for venlafaxine treatment remains unknown" and the pregnancy summary in the NZF states that human pregnancy experience does not suggest that venlafaxine is a major risk for structural anomalies.

Hypertension in Pregnancy

The literature surrounding the association with hypertension in pregnancy and venlafaxine use is limited. Palmsten et al 2013 shows that women who used SNRIs mid-pregnancy had an increased risk of pre-eclampsia than compared with other SSRIs. De Vera and Berard 2012 also found that SNRI's were significantly associated with the risk of pregnancy-induced hypertension.

The length of exposure in these studies are significantly different. One of the studies define exposure as one dispensing record of an antidepressant between the theoretical conception date and 20 completed weeks of gestation while another study defines primary exposure window from 90 to 225 gestational days (the second trimester through the end of the first half of the third trimester).

It is important that these results should be interpreted with caution however as the numbers exposed to venlafaxine are low with wide CIs. In addition, other limitations that need to be considered include misclassification bias and the possibility that results from the analyses reflect residual confounding from factors such as concomitant medicines and lifestyle factors such as obesity.

The NZ data sheet with regards to pre-eclampsia lists that 'exposure to SNRIs in mid to late pregnancy may increase the risk for preeclampsia'

5 ADVICE SOUGHT

The Committee is asked to advise whether

- the current evidence supports an association between venlafaxine use in pregnancy and the increased risk of congenital malformations/birth defects
- the current evidence supports an association between venlafaxine use in pregnancy and the contribution to gestational hypertension
- the information in the New Zealand data sheet with regards to birth defects and gestational hypertension is sufficient or an update is necessary
- the topic requires further communication other than MARC's Remarks in Prescriber Update

6 ANNEXES

- Annex 1 - *In utero* exposure to serotonin reuptake inhibitors and risk of congenital abnormalities – Paper present to Medicines Adverse Reactions Committee (MARC) at the 141st meeting in March 2010.
- Annex 2 – Anderson et al 2020
- Annex 3 – Bellantuono et al 2015
- Annex 4 – Furu et al 2015
- Annex 5 – Lassen et al 2016
- Annex 6 – Kolding et al 2021
- Annex 7 – Polen et al 2013
- Annex 8 – Berard et al 2016
- Annex 9 – Richardson et al 2019
- Annex 10 – Palmsten et al 2013
- Annex 11 – Zakiyah et al 2018
- Annex 12 – De Vera and Berard 2012

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