Medicines Adverse Reactions Committee

Meeting date	3/12/2020	Agenda item	3.2.4
Title	**Tricyclic antidepressants and the risk of congenital malformations**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Amitriptyline	**Arrow-Amitriptyline Film coated tablet, 10 mg, 25 mg & 50 mg**		Teva Pharm (NZ) Ltd
	Amirol Film coated tablet, 10 mg & 25 mg		AFT Pharmaceuticals Ltd
Clomipramine	**Apo-Clomipramine Film coated tablet, 10 mg & 25 mg**		Apotex NZ Ltd
	Anafranil Tablet, 10 mg		*Section 29*
Dosulepin	**Dosulepin Mylan Film coated tablet, 75 mg**		Mylan New Zealand Ltd
	Dosulepin Mylan Capsule, 25 mg		*Section 29*
Doxepin	Anten 50 Capsule, 50 mg		Mylan New Zealand Ltd
Imipramine	**Tofranil Coated tablet, 10 mg & 25 mg**		AFT Pharmaceuticals Ltd
Nortriptyline	**Norpress Tablet, 10 mg & 25 mg**		Mylan New Zealand Ltd
PHARMAC funding	Product highlighted in bold above are funded on the Community Schedule. Two products (shown in italics) are funded but only available under Section 29 of the Medicines Act (ie, the products have not been approved by Medsafe).		
Previous MARC meetings	In utero exposure to serotonin reuptake inhibitors and risk of congenital abnormalities 141st meeting March 2010		
International action	None		
Prescriber Update	The use of antidepressants in pregnancy September 2010		
Classification	Prescription medicine		
Usage data	The following pregnancy usage data for 2019 was obtained from the National Collections using the Pharmaceutical Dispensing in Pregnancy application in Qlik. The table shows the total number of dispensings, repeat dispensings and number of pregnancies exposed during first trimester (defined as 30 days prior to the estimated pregnancy start date to week 13) for pregnancies that ended in 2019.		
Advice sought	**The Committee is asked to advise:** • Whether the current evidence supports an association between first trimester exposure to tricyclic antidepressants and an increased risk of congenital malformations in the infant.		

Tricyclic antidepressant	dispensings	repeat dispensings	pregnancies
Amitriptyline	605	359	240
Clomipramine	32	17	12
Dosulepin [Dothiepin]	38	22	12
Doxepin	14	9	5
Nortriptyline	349	177	166

	• Whether there is a need to update the data sheets for tricyclic antidepressants about the risk to the fetus.

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1 PURPOSE

The current New Zealand data sheets for tricyclic antidepressant (TCA) medicines contain conflicting information about the risk to the fetus if used in pregnancy. The data sheet wording is discussed below in Section 2.2. It is important that the information in the data sheets reflect the current evidence about the risk to the fetus as the information may influence women's decisions about pregnancy.

This paper aims to review the available information on the risk of congenital malformation associated with the use of tricyclic antidepressants in the first trimester of pregnancy, and to identify data sheet wording that is inconsistent with the current evidence.

2 BACKGROUND

2.1 Tricyclic antidepressants

TCAs have been used to treat depression since the late 1950s [1]. The US Food and Drug Administration (FDA) approved the first TCA, imipramine (Tofranil), for major depressive disorder in 1959 [2]. Many other TCAs were subsequently developed, including amitriptyline, amoxapine, clomipramine, desipramine, dosulepin (formerly called dothiepin), doxepin, nortriptyline, protriptyline and trimipramine.

TCAs work by inhibiting the neuronal reuptake of serotonin and noradrenalin. The mechanism of action was unknown at the time of discovery, so the TCAs were named for their structure, which includes an iminodibenzyl (tricyclic) molecular core (Figure 1). Subtle structural differences between the different TCAs affect their affinity for serotonin and noradrenaline transporters and therefore their relative ability to inhibit serotonin and noradrenaline reuptake [3].

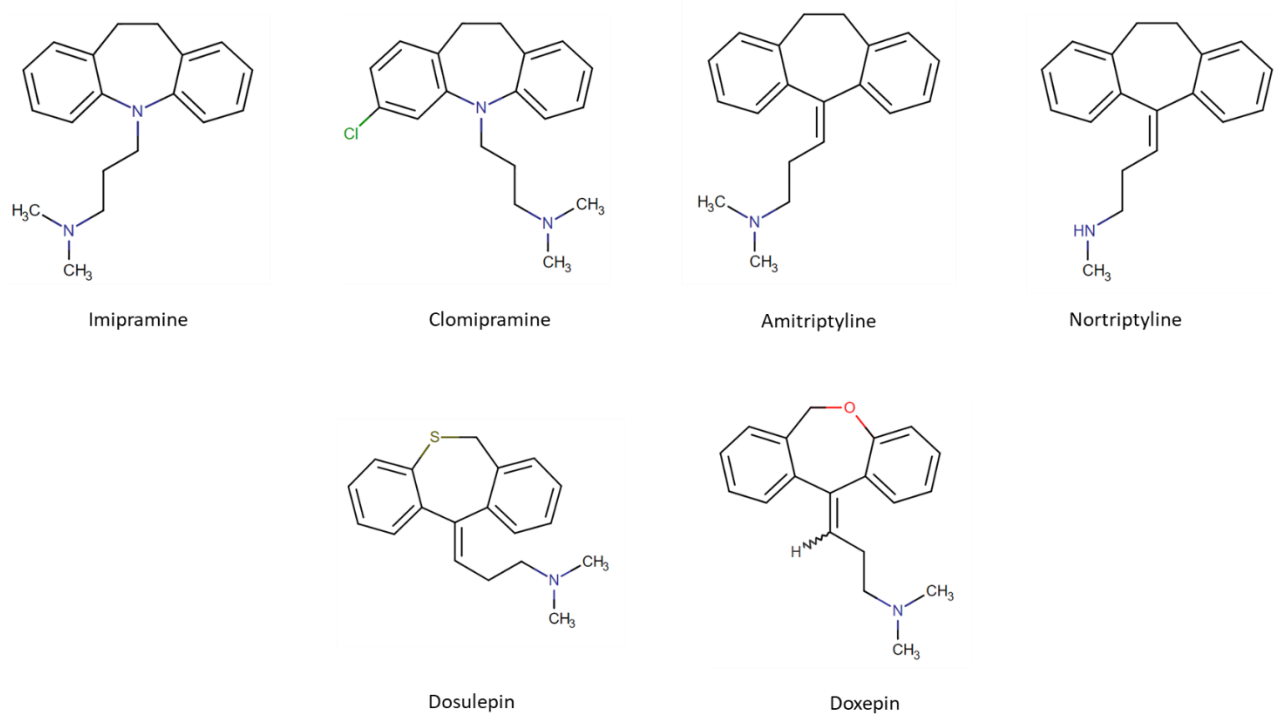

Figure 1. Molecular structure of currently approved tricyclic antidepressants (source: DrugBank [4])

Amitriptyline inhibits the uptake of noradrenaline and serotonin equally. It is metabolised to nortriptyline, which is a stronger inhibitor of noradrenaline than of serotonin uptake. Clomipramine is a strong, but not completely selective serotonin reuptake inhibitor, as the active main metabolite desmethyclomipramine acts preferably as an inhibitor of noradrenaline reuptake. [5-7]

TCAs undergo hepatic metabolism through the cytochrome p450 system, predominantly as a substrate for CYP 2D6. Genetic polymorphisms of CYP 2D6 affect the metabolism of TCAs, such that poor metabolisers are at increased risk of elevated serum levels, drug interactions and reduced levels of active metabolites [5-8].

TCAs are indicated for the treatment of depression. Additionally, nortriptyline is indicated as an aid to smoking cessation. Clomipramine is indicated for the treatment of obsessive-compulsive syndromes, phobias and panic attacks, cataplexy accompanying narcolepsy, and chronic painful conditions.

NZ treatment guidelines [9] recommend TCAs as second line therapy in the treatment of depression, largely due to their toxicity in overdose, anticholinergic side-effects, superseded by SSRIs and SNRIs.

2.2 Safety of TCAs in pregnancy

The prevalence of major depression and bipolar disorder peak during the childbearing years. Key considerations in the management of mood disorders in women of child-bearing age are the neurodevelopmental effects of the illness and its treatment on the developing fetus, infant and mother-infant relationship. Maternal depression during pregnancy has been associated with an increased risk of premature delivery, low birth weight, gestational hypertension and perinatal death. Maternal depression may also adversely affect the infant's emotional and cognitive development. [9]

It is important to treat depression in pregnancy. The *Royal Australian and New Zealand College of Psychiatrists Antidepressant clinical practice guidelines for mood disorders* recommend a careful assessment of the benefits and risks to the mother and fetus before using an antidepressant medicine in women who are pregnant [9].

A systematic review and meta-analysis examining associations between the use of any antidepressant medicine and congenital malformations found that, overall, antidepressant exposure was not associated with congenital malformations or major malformations. A small but statistically significant increased risk was found for cardiovascular malformations and septal heart defects, but the clinically significant threshold (determined to be an RR ≥ 2) was not met. [10]

Serotonin is necessary for healthy fetal development during embryogenesis. Antidepressants that block serotonin reuptake such as selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenalin reuptake inhibitors (SNRIs) and to some extent TCAs, which cross the placental barrier, interfere with the free movement of serotonin during this critical phase of development. Disruption of serotonin signalling early in pregnancy has the potential to result in a wide variety of malformations [11].

The UK Teratology Information Service (UKTIS), a member of the European Network of Teratology Information Services (ENTIS), provides evidence-based information on fetal risk following pharmacological and other potentially toxic pregnancy exposures. UKTIS provides the following information about the risk to the fetus of TCAs:

> *'Tricyclic antidepressants (TCAs) block the re-uptake of both serotonin and noradrenaline and are used in the management of depression, anxiety disorders and neuropathic pain. Currently available TCAs include amitriptyline, clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline and trimipramine.*
>
> *The available data provides no strong evidence of an association between maternal use of TCAs as a class during pregnancy and an increased risk of congenital malformation overall, or of any specific malformations. There is limited or no information on use of specific TCAs, therefore an increased risk of malformations cannot be ruled out. A possible association between in utero clomipramine exposure and cardiac malformations has been suggested but remains to be confirmed. Other findings are conflicting; however possible associations with spontaneous abortion, preterm delivery, preeclampsia, and autism spectrum disorder have been identified.*

An increased incidence of neonatal complications has been reported in the offspring of women with psychiatric illnesses; however, the relative contributions of the underlying maternal condition and specific drug treatments have not been clearly defined. Use of TCAs throughout pregnancy or near delivery may be associated with withdrawal symptoms in the neonate and/or poor neonatal adaptation syndrome (PNAS). These symptoms are likely to be more severe in infants exposed in utero to more than one CNS acting drug.

It is important to ensure that maternal mental health disorders are treated appropriately during pregnancy. Where a patient is stabilised on a TCA, either prior to conception or during pregnancy, the risk of discontinuing or changing medication, or reducing the dose, should be carefully weighed against the risk of relapse of the maternal condition.

The currently available data do not support the need for any additional fetal monitoring following in utero exposure to TCAs; however, data on individual TCAs is limited and the need for additional monitoring should therefore be determined on a case-by-case basis. Other risk factors may also be present in individual cases which may independently increase the risk of adverse pregnancy outcome. Clinicians are reminded of the importance of consideration of such factors when performing case-specific risk assessments.' [12]

2.3 Data sheets

2.3.1 New Zealand

The Medsafe website hosts seven data sheets for TCA medicines (Table 1). Most of the current TCA data sheets state that the medicines are classified as Category C in the Australian categorisation system for prescribing medicines in pregnancy. Category C is defined as:

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.

Five data sheets also state that epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy. Four data sheets note that there is evidence of reproductive toxicity in animals. These statements appear to conflict with the Category C classification.

All the data sheets include a statement to the effect that the medicine should only be used during pregnancy if the benefits clearly outweigh the risks.

Table 1. Pregnancy information in the current New Zealand data sheets for approved tricyclic antidepressant medicines

Trade name	Active ingredient	Pregnancy Statements									
		1	2	3	4	5	6	7	8	9	10
Arrow-Amitriptyline	amitriptyline	•	•		•				•		
Amirol	amitriptyline			•			•	•	•		•
Apo-Clomipramine	clomipramine	•	•						•	•	
Dosulepin Mylan	dosulepin	•		•		•	•	•	•		•
Anten	doxepin	•		•		•	•	•	•		•
Tofranil	imipramine	•	•				•	•	•	•	•
Norpress	nortriptyline	•		•		•	•	•	•		•

Pregnancy Statement Key

1. Category C.
2. Not recommended during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.
3. Should only be used in pregnancy if considered necessary, taking into account the risks of untreated depression, and under the close supervision of a physician.
4. Animal studies have shown reproductive toxicity
5. There is evidence of interference with central monoamine neurotransmission in rats.
6. Epidemiological studies have suggested an increased risk of congenital abnormalities associated with use of tricyclic antidepressants in pregnancy
7. Neonates should be observed if maternal use of [drug name] has continued into the later stages of pregnancy, particularly into the third trimester.
8. Neonates exposed to tricyclic antidepressants, late in the third trimester have showed drug withdrawal symptoms such as dyspnoea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms.
9. To avoid such symptoms, gradually withdraw at least 7 weeks before the calculated date of confinement.
10. Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in pre-term delivery.

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Anderson et al, 2020 (JAMA Psychiatry)

Maternal Use of Specific Antidepressant Medications During Early Pregnancy and the Risk of Selected Birth Defects [13]

Objectives

Few studies have examined associations between individual antidepressants and specific birth defects. Most analyses have focused on selective serotonin reuptake inhibitors (SSRIs). This study aimed to examine associations between antidepressants and birth defects, and to account for potential confounding by underlying conditions and environmental factors.

Methods

The National Birth Defects Prevention Study (NBDPS) was a US population-based, multicentre (across 10 States) case-control study that examined risk factors for major structural birth defects. Cases with selected birth defects were identified from surveillance systems using standard case definitions and included live births, still births and terminations. Data were abstracted from medical records for pregnancies ending on or after 1 October 1997 to those with an estimated delivery date (EDD) on or before 31 December 2011. Infants with known single-gene disorders or chromosomal abnormalities were excluded. Controls were randomly sampled live-born infants without major birth defects from the same birth month and geographic catchment area as cases.

Mothers participated in a computer-assisted telephone interview 6 weeks to 24 months after the EDD, with a median time to interview of 11 months for case and 9 months for controls. Participation rates were 67 % for cases and 65% for controls.

Mothers were specifically asked about the use of citalopram, fluoxetine paroxetine, sertraline, venlafaxine and bupropion during the e months before conception or during pregnancy. Other antidepressants could be reported when women were asked about any other medicines taken during

the period of interest. Information collected included stop and start dates, duration and frequency of use. Timing before or during pregnancy was calculated in pregnancy months (consecutive 30-day intervals from the estimated conception date (ECD). Medicines were coded using the Slone Drug Dictionary. Antidepressants from the following classes were identified: SSRI, SNRI, TCAs and other norepinephrine inhibitor, monoamine oxidase inhibitor, and other antidepressants.

The NBDPS included 32300 case and 11829 control mothers. After exclusions for incomplete medicine history, pre-pregnancy diabetes, or use of a known teratogenic medicine during the period of interest, 30630 cases and 11478 controls were included in the analysis.

Antidepressant use in early pregnancy was estimated for each antidepressant and broader medicine class for case and control mothers separately. To identify associations between early pregnancy antidepressant use and specific birth defects, multivariate logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals for birth defects with four or more exposed cases To account for potential confounding due to the underlying condition, mothers exposed to each antidepressant during early pregnancy were compared with (1) unexposed mothers and to (2) mothers only exposed to an antidepressant outside of early pregnancy.

Results

Early pregnancy antidepressant use was reported by 1562 cases (5.1%) and 467 controls mothers (4.1%). Antidepressant use among case and control mothers is shown in (Table 2)

Elevated aORs were observed for individual selective serotonin reuptake inhibitors (SSRIs) and selected congenital heart defects (CHD) (eg, fluoxetine and anomalous pulmonary venous return: aOR, 2.56; 95%CI, 1.10-5.93; this association was attenuated after partially accounting for underlying conditions: aOR, 1.89; 95%CI, 0.56-6.42). This pattern was observed for many SSRI-CHD combinations.

Associations between SSRIs and non-CHD birth defects often persisted or strengthened after partially accounting for underlying conditions (eg, citalopram and diaphragmatic hernia: aOR, 5.11; 95%CI, 1.29-20.24). Venlafaxine had elevated associations with multiple defects that persisted after partially accounting for underlying conditions (eg, anencephaly and craniorachischisis: aOR, 9.14; 95%CI, 1.91-43.83).

No specific analyses were performed for TCAs, which were included only as concurrent medicines.

Comments:

This recently published study of congenital malformations associated with antidepressant use in pregnancy did not specifically look at TCAs. The study focused on SSRIs, SNRIs, and bupropion.

There was no useful analysis of congenital malformations in patients using TCAs concurrently

Table 2 Antidepressant Medication Use Prevalence Among US Women Before and During Pregnancy in the National Birth Defects Prevention Study From 1997 to 2011

3.1.2 Bérard et al, 2017 (BMJ Open)

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 [11]

Objective

To determine the association between first trimester-exposure to antidepressants and the risk of major congenital malformations in a cohort of women with depression and/or anxiety.

Methods

Register-based cohort study using data from the Quebec Pregnancy Cohort (QPC). The QPC is an ongoing population-based cohort with prospective data for all pregnancies that occurred between January 1998 and December 2009 in the province of Quebec.

Eligible pregnancies had (1) continuous prescription drug insurance coverage for at least 12 months before the first day of gestation and during pregnancy, (2) a diagnosis of depression and/or anxiety and exposed to antidepressants in the 12 months before pregnancy and (3) resulted in a live-born singleton.

Pregnancies with an antidepressant dispensed during the first trimester (0-14 weeks gestation) confirmed by ultrasound or before pregnancy but with the duration overlapping the first day of the last menstrual period were defined as exposed.

The primary analysis examined four mutually exclusive active comparison groups: SSRI, SNRI, TCA and other AD. Secondary analyses considered eight mutually exclusive active comparison groups: monotherapy exposure to (1) paroxetine, (2) sertraline, (3) citalopram, (4) fluoxetine, (5) fluvoxamine, (6) venlafaxine, (7) TCA (amitriptyline, desipramine, doxepin, imipramine, nortriptyline, trimipramine, clomipramine) and (8) other antidepressants (AD; L-tryptophan, trazodone, bupropion, moclobemide, buspirone, mirtazapine) during the relevant time window. For all analyses, the reference category was pregnancies with no exposure to any antidepressant during the time window of interest (ie, women with depression/anxiety who were not using an antidepressant during the first trimester).

Major congenital malformations (MCMs) diagnosed in the first year of life were identified in the patient registries and defined by ICD-9 or ICD-10 codes. The MCMs were grouped according to the European Registration of Congenital Anomalies and Twins (EUROCAT) Registry.

Separate analyses for overall congenital malformations and for each organ system malformation. Pregnancy was the unit of analysis. Potential confounders considered in the analyses were (1) sociodemographic variables (maternal age, maternal marital status, welfare status, education level and place of residence on first day of gestation), (2) maternal chronic comorbidities during the 12 months prior to pregnancy (including hypertension, diabetes and asthma)

Results

Of 289,688 women in the QPC, 18,487 pregnant women met the inclusion criteria. Before exclusions, the prevalence of maternal depression was 7.3% (21,175 pregnancies).

Of the 18487 women (pregnancies) in the study population, 3640 were exposed to an antidepressant during the first trimester: SSRIs 2327, SNRI 738, TCA 382 and other ADs 193. There were 14,847 unexposed pregnancies.

Antidepressant users were older, more likely to be living alone and be welfare recipients compared to non-users. AD users had more comorbidities (asthma, diabetes and hypertension) and more health service usage. Infants of antidepressant users had lower birthweight.

Crude and adjusted estimates for the association between first trimester exposure and the risk of overall MCM by antidepressant class are show in Table 3. MCMs were diagnosed in 51 of the 382 pregnancies exposed to TCAs, but the crude and adjusted ORs were not statistically significant compared to non-exposed pregnancies.

Table 3. Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women

[redacted]

Tricyclic antidepressants were significantly associated with malformations of the eye, ear, face and neck (aOR 2.45; 95% CI 1.05 to 5.72) and digestive system (aOR 2.55; 1.40 to 4.66), Table 4.

Other significant associations identified in the analysis were: citalopram and MCMs overall (aOR 1.36; 1.08 to 1.73), musculoskeletal system malformations (aOR 1.92; 1.40 to 2.62), and craniosynostosis (aOR 3.95; 2.08 to 7.52); venlafaxine and respiratory system malformations (aOR 2.17; 1.07 to 4.38); paroxetine and cardiac malformations (aOR 1.45; 1.12 to 1.88) and ventricular/atrial septal defects (aOR 1.39; 1.00 to 1.93).

Table 4. Tricyclic antidepressant use during pregnancy and major congenital malformations and organ-specific malformations in a cohort of depressed women compared to non-exposed.

[redacted]

Limitations

Information on potentially important confounders such as smoking, folic acid intake and alcohol intake was not available. Psychiatrist visits were used as a proxy for disease severity. The study had low statistical power for detecting specific malformations.

Conclusions

Antidepressants with effects on serotonin reuptake during embryogenesis increased the risk of some organ-specific malformations in this population-wide cohort study. Infants were at an increased risk of cardiac, musculoskeletal, craniofacial, digestive and respiratory defects, and craniosynostosis from in utero exposure to serotonin inhibitor drugs (SSRI, SNRI and some TCAs).

Given that the effectiveness of antidepressants during pregnancy for the treatment of mild to moderate depression is marginal, there is a need for caution with antidepressant use during pregnancy and alternative non-drug options should be considered.

Comments:

The study identified an increased risk of digestive and ENT malformations in pregnancies exposed to TCAs. The congenital malformations were aggregated at system level and the actual malformations are not specified.

The source data does not provide information on tobacco, alcohol, illicit drug use, or folic acid use, which are significant confounders for congenital malformations.

3.1.3 Ban et al, 2014 (BJOG)

Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study [14]

Objective

To estimate: (1) the absolute and relative risks of congenital anomaly and system-specific anomalies in children born to women without depression, with unmedicated depression during the first trimester of pregnancy, and with SSRIs or TCAs in the first trimester; (2) drug class-related risks for specific heart anomalies; and (3) system-specific congenital anomaly risks for individual SSRIs.

Methods

A UK population-based cohort study using The Health Improvement Network (THIN), a nationally representative database of electronic primary care records. The study population included all singleton live births for women aged 15-45 years between 1990 and 2009. Children were excluded whose mothers had bipolar disorder, schizophrenia, other serious psychotic disorders, or prescriptions for antimanic or antipsychotic drugs before childbirth.

All diagnoses of MCAs were identified in the children's medical records using Read codes, classified into 14 system specific groups according to the EUROCAT subgroups (which are based on ICD-10 codes, mainly Q00-Q99). Children were excluded with records of genetic anomalies or anomalies attributed to known teratogens (eg, maternal infections or fetal alcohol syndrome). Specific types of major heart anomaly were also assessed.

Maternal depression was defined as diagnoses of depression during the year before conception or in the first trimester. Antenatal exposure to SSRIs and TCAs during the first trimester of pregnancy was defined as a prescription record for the relevant drug from 4 weeks before to 12 weeks after the first day of the estimated last menstrual period (LMP). Children were grouped into five mutually exclusive exposure groups: (1) no clinical record of maternal depression, (2) maternal depression in the year before conception to end of first trimester but with no antidepressants in the first trimester (unmedicated depression), (3) first-trimester exposure to SSRIs alone, (4) first-trimester exposure to TCAs alone, and (5) exposure to both SSRIs and TCAs in the first trimester.

The absolute risk (AR, per 10,000 live births) were calculated for the whole study population and for children in each of the five defined antenatal exposure groups for overall MCA disease burden and for each system-specific subgroup. Logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (95% CIs) for MCA overall, and for each system-specific subgroup associated with unmedicated maternal depression, each class of antidepressants, and individual SSRIs during the first trimester of pregnancy. In the primary analysis, the comparison was with children whose mothers did not have clinically recognised depression. Secondary analyses used children whose mothers had diagnosed but unmedicated depression for the comparison.

Multivariable analyses were used to adjust all models for maternal characteristics that were prospectively recorded in women's records before delivery. These were: maternal age, smoking before or during pregnancy, body mass index (BMI) recorded before pregnancy, and socio-economic deprivation.

Models were also adjusted for maternal diabetes, hypertension, asthma, and epilepsy in the year before conception or during pregnancy, as these comorbidities could be associated with an increased risk of congenital anomalies in off-spring.

Results

The study included 349,127 liveborn singletons. The overall prevalence of MCA was 2.7%.

There were similar demographic profiles for mothers of children with and without MCA, but chronic medical comorbidities were more prevalent in mothers of children with MCA than in those of children with no MCA.

First-trimester TCA exposure was present in 2428 children, of which 74 (305/10,000) had diagnosis of MCA (Table 5).

In comparisons with children of women without depression, there were no statistically significant associations between first-trimester TCA exposure and any subgroup categories of malformation (Table 6), or any specific heart anomalies (Table 7).

In comparisons with children of women with unmedicated depression, there were no statistically significant associations between first-trimester TCA exposure and anomalies of the heart, limb or genital system (Table 8).

Table 5. Absolute risks (per 10,000 live births) of major congenital anomalies in children according to first-trimester exposure to unmedicated depression and antidepressant medications

Table 6. Adjusted odds ratios for major congenital anomalies in children with first-trimester exposure to unmedicated maternal depression and antidepressant medications (n = 349 127 children, 9397 with major congenital anomalies) – compared to children of women without depression

Table 7. Absolute risks (per 10,000 live births) and adjusted odds ratios for specific heart anomalies in children with first-trimester exposure to unmedicated maternal depression and antidepressant medications (n = 349,127 children, 2646 with heart anomalies) - compared to children of women without depression

Table 8. Adjusted odds ratios for major congenital anomalies in children with first-trimester exposure to different antidepressant medications, compared with children of women with unmedicated depression (n = 23 833 children, 666 with major congenital anomalies)

Limitations

The authors note that power was inevitably reduced when examining system-specific groups, and given the number of comparisons conducted, random error cannot be ruled out.

MCAs among pregnancies ending in spontaneous or induced abortions are not included, which may underestimate teratogenicity

Conclusions

Overall MCA risk did not increase with maternal depression or with antidepressant prescriptions. Paroxetine was associated with increases of heart anomalies, although this could represent a chance finding from the many comparisons that were undertaken.

Comments:

This study aimed to account for indication bias by comparing exposed pregnancies with unexposed pregnancies in women with depression. First trimester TCA exposure was not associated with MCA or subgroup anomalies when compared to no depression or unmedicated depression.

3.1.4 Huybrechts et al, 2014 (NEJM)

Antidepressant use in pregnancy and the risk of cardiac defects [15]

Objective

To assess the risk of congenital cardiac defects after the use of specific antidepressants, with attention to the potential for confounding by the underlying depression and associated factors, using a large national database of publicly insured pregnant women and adolescents in the United States.

Methods

The study cohort was drawn from the Medicaid Analytic eXtract for 46 U.S. states and Washington, D.C., for the period of 2000 through 2007. The dataset contains individual-level demographic and Medicaid enrolment information, data on all physician services and hospitalisations, diagnoses and procedures and filled outpatient prescriptions.

All completed pregnancies in women and adolescents aged 12-55 years were linked to their liveborn infants. Using a validated algorithm, the date of LMP was estimated based on delivery date and diagnostic codes for preterm delivery. Women who were eligible for Medicaid, without supplementary private insurance or

restricted benefits, from 3 months before the last menstrual period through 1 month after delivery were included. Pregnancies in which the infant had received a diagnosis of a chromosomal abnormality (1609 pregnancies) and pregnancies in which the mother had been treated with known teratogens during the first trimester (i.e., lithium, antineoplastic agents, retinoids, and thalidomide; 2476 pregnancies) were excluded.

The exposure window of interest was from the date of the LMP through to day 90 of pregnancy (ie, first trimester). Maternal use of antidepressants was determined using pharmacy dispensing records. Exposure categories were any SSRI, paroxetine, sertraline, fluoxetine, tricyclic antidepressants, serotonin– norepinephrine reuptake inhibitors (SNRIs), bupropion, and other antidepressants. The reference group was women without exposure to antidepressants during the first trimester.

Cardiac malformations were identified based on ICD-9 diagnostic codes in the maternal or infant records during the first 90 days after delivery. Outcomes were grouped as: any cardiac malformation, right ventricular outflow tract obstruction, ventricular septal defect, and other cardiac malformation. Anomalies related to prematurity (e.g., patent ductus arteriosus, pulmonary-valve stenosis, and anomalies of the pulmonary artery in preterm infants) were excluded.

Covariates considered in the analysis were: sociodemographic information (year of delivery, state of residence, age, race, and parity), known or suspected risk factors for congenital cardiac malformations and proxies for such risk factors including multiple gestation, chronic maternal illness (hypertension, diabetes, epilepsy, and renal disease), use of suspected teratogenic medications, use of other psychotropic medications (anticonvulsant, antipsychotic, anxiolytic, and hypnotic agents; other benzodiazepines; and barbiturates), use of antidiabetic and antihypertensive medications, and the number of distinct prescription drugs used, excluding antidepressants, as a general marker of coexisting conditions.

To assess confounding by underlying indication, proxies for depression severity, and other indications for antidepressant use were considered.

Results

There were 949,504 eligible pregnancies. Women could have contributed more than one pregnancy to the cohort. During the first trimester, 64,389 women (6.8%) used an antidepressant: 46,144 women (4.9%) were exposed to an SSRI, 5954 (0.6%) to a tricyclic antidepressant, 6904 (0.7%) to an SNRI, 8856 (0.9%) to bupropion, and 7055 (0.7%) to other antidepressants.

Compared with women who took no antidepressant, women who filled a prescription for an antidepressant were older, had greater health care utilization, and were more likely to be white, to use other psychotropic medications, to have a chronic illness (in particular, hypertension or diabetes), and to use suspected teratogenic medications. Baseline characteristics were more homogeneous in analyses comparing users of various antidepressant classes than in analyses comparing users of antidepressants with nonusers.

Overall, cardiac malformations were diagnosed in 6403 infants who were not exposed to an antidepressant during the first trimester (72.3 cardiac malformations per 10,000 infants), compared with 580 infants who were exposed (90.1 cardiac malformations per 10,000 infants). This higher unadjusted risk among exposed infants was observed for each of the specific types of malformations considered.

The absolute risk of congenital malformations for each exposure group is presented in Table 9. For TCAs, the relative risk of any cardiac malformation in unadjusted analyses was 0.98 (95% CI, 0.72 to 1.32).

The ORs for cardiac malformations overall or for specific cardiac malformations in TCA exposed infants were not statistically significant in the unadjusted analysis, depression restricted analysis or with propensity score stratification. Figure 2 and Figure 3

Table 9. Absolute Risk of Congenital Cardiac Malformations among Infants Born to Mothers with Antidepressant Exposure and Infants Born to Mothers without Exposure, According to Antidepressant Category in the Overall Cohort.*

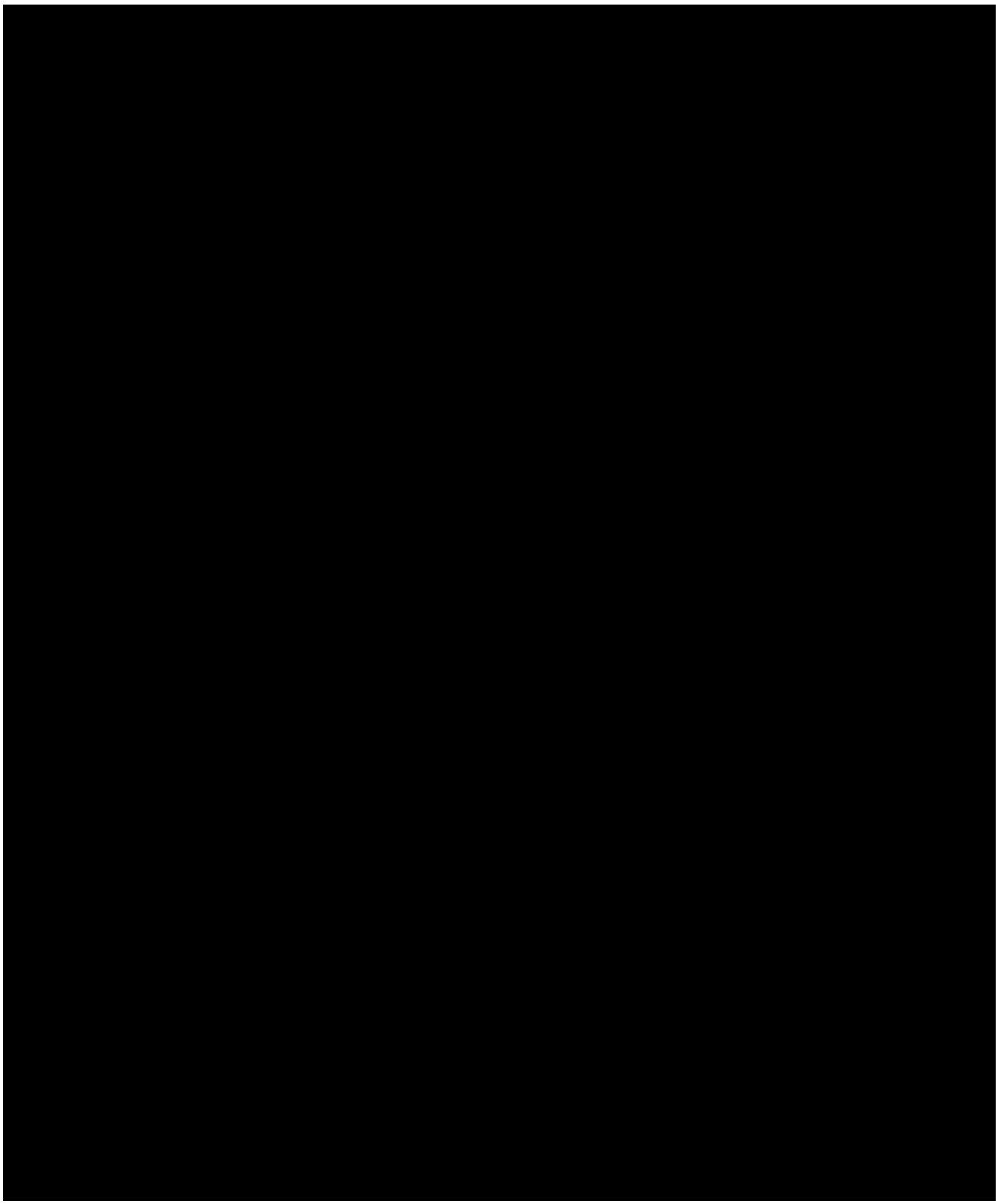

Figure 2. Risk of Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Figure 3. Risk of Specific Cardiac Malformation in Infants, According to Maternal Exposure to Antidepressants.

Limitations

The cohort included only live births, so severe malformations that resulted in spontaneous abortion, still birth or termination of pregnancy are not captured in this data. Potential for misclassification due to missing or incomplete data on factors such as smoking, obesity, alcohol and drug use, BMI

Conclusions

The use of antidepressants during the first trimester does not substantively increase the risk of specific cardiac defects. The accumulated evidence implies low absolute risks and argues against important cardiac teratogenic effects associated with the most used antidepressant medications.

Comments:

As noted by the authors, this study includes a very large population-based cohort, objective assessment of drug exposure, linkable clinical information, access to medical records, and availability of information on multiple pregnancy outcomes and on a wide range of potential confounders. Medicaid covers the medical expenses for more than 40% of births in the United States. Medicaid-eligible pregnant women are a young, racially diverse, vulnerable population.

The study did not find an association between first-trimester exposure to TCAs as a group and any cardiac malformation. Individual TCAs were not studied.

3.1.5 Reis and Källén, 2010 (Psychol Med)

Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data [16]

Objective

To update previously published data from Swedish national health registries on delivery outcomes following the use of antidepressants in pregnancy.

Methods

The study is based on data from the Swedish Medical Birth Register (MBR) from 1 July 1995 to 2007. The MBR contains information on 98-99% of deliveries in Sweden and includes data collected during prenatal care, delivery and the paediatric examination of the newborn infant. Information on drug use is based partly on an interview conducted by the midwife at the first antenatal visit, which occurs before the end of the first trimester in 90% of cases and the majority during weeks 10-12 ('early use'), and partly on information from the antenatal care for drugs prescribed during the pregnancy ('later use'). Drugs are coded using the ATC codes. Information on exact timing , dose and duration of drugs used is incomplete. Information on congenital malformations was obtained from the Register of Birth Defects and the patient Register. Registers were linked using the patient's personal identification number.

Congenital malformations were identified with ICD codes: ICD-9 codes 740-759 or later ICD-10 codes Q00-Q99. The analysis first determined the presence of any type of malformation. Common, less significant malformations (pre-auricular appendage, tongue ties, patent ductus in a preterm infant, single umbilical artery, undescended testicle, hip subluxation, and nevus) were then excluded. The remaining congenital malformations were considered 'relatively severe'. Infants with known chromosomal anomalies were excluded. Specific types of malformation were analysed separately, irrespective of whether other malformations were also present.

'Early use' and 'later use' exposure to antidepressant was compared with all other women in the MBR register using Mantel-Haenszel analysis after adjustment for: year of delivery, maternal age, parity, smoking and BMI. Odds ratios were calculated with 95% confidence intervals. When the expected number of outcomes was < 10, risk ratios (observed/expected) were calculated instead using Poisson distributions.

Results

During the study period, 14,821 women were exposed to antidepressants during pregnancy: 12,914 had early exposure, 5987 had later exposure and 4080 had both early and late exposure. The total number of infants born following antidepressant exposure in pregnancy was 15,017, including 13,080 with early exposure, 6066 with late exposure and 4127 with both early and late exposure. There were 1,062,190 unexposed women and unexposed 1,236,053 infants in the MBR during the study period.

Early exposure to TCAs occurred in 1662 pregnancies, of which 1208 were exposed to clomipramine and 379 were exposed to amitriptyline (Table 10).

Women using an antidepressant were older and had lower parity, were more often smokers and had a high BMI. The pattern of use of other drugs in early pregnancy differed from other women. The most significant differences were for the use of other psycho-active drugs with very high usage of sedatives and hypnotics, and neuroleptics, drugs for migraine and anticonvulsants [1].

Congenital malformations were diagnosed in 4.3% of the population, and a 'relatively severe malformation' occurred in 2.9%. The risks for a relatively severe malformation, for any cardiovascular defect, and for a ventricular (VSD) or atrial septal defect (ASD) were significantly increased only for TCAs (primarily clomipramine). Table 11

[1] Data on concurrent use of other medicines was published in an appendix and was not available for this review.

Table 10. Number of women using specific antidepressant drugs either before the first antenatal visit ('early') or prescribed the drugs during pregnancy ('Later')

[redacted]

Table 11. Five groups of congenital malformations where risks seemed to differ with the group of antidepressants used. Odds ratios (ORs) with 95% confidence interval (CIs) adjusted for year of birth, maternal age, parity, smoking and body mass index (BMI)

[redacted]

To eliminate possible confounding factors from concomitant use of drugs with potential teratogenic properties or use of drugs given for conditions that may harm the embryo, infants were removed from the analysis if the mother had also reported taking any one of the following: insulin, antihypertensive drugs, drugs for asthma, systemic corticoids, drugs for thyroid disease. This left 88–90% of the cases for analysis. There were only minor changes in OR estimates but the OR for relatively severe malformations after exposure to fluoxetine decreased slightly (to 1.26) and lost statistical significance (95% CI 0.96–1.65) whereas the OR after exposure to paroxetine increased slightly to 1.31 and approached statistical significance (95% CI 0.98–1.76).

Conclusions

Women using antidepressants during pregnancy and their infants have increased pathology. It is not clear how much of this is due to drug use or underlying pathology. Use of TCAs was found to carry a higher risk than other antidepressants and paroxetine seems to be associated with a specific teratogenic property.

Comments:

In this Swedish register-based study it is surprising that medicine exposure was based on maternal recall, albeit recorded prospectively at the antenatal visit, rather than on pharmaceutical dispensing data, which has been used in similar Swedish studies for pregnancy exposure outcomes. It would have been useful if the authors had correlated the maternal history with dispensing data to rule out the possibility of recall bias.

Confounding by indication cannot be excluded as the comparison group is women who were not taking any antidepressant with no information about depression.

A sensitivity analysis was performed by removing the use of potential confounding factors (concomitant drugs with known teratogenic effects and drugs used to treat conditions that may adversely affect the embryo). No change to the ORs for TCAs were reported.

The use of other psychoactive drugs was noted to be higher in women taking antidepressants, but their contribution to the occurrence of congenital malformations in the offspring is not further explored.

3.2 CARM data

As at 30 September 2020, the Centre for Adverse Reactions Monitoring (CARM) database contains 20 reports of a congenital abnormality or adverse neonatal outcome associated with pregnancy exposure to a TCA. The reports span the years 1966 to 2016, but 16 of the cases were reported before 1995. The most frequently reported TCA is amitriptyline (8 reports) followed by nortriptyline (4 reports), clomipramine (2 reports). Desipramine, dothiepin, imipramine, maprotiline and protriptyline were each reported once. One further report includes both amitriptyline and protriptyline. The reports are summarised in Table 12.

Fifteen reports included congenital abnormalities. One of these reports concerned an infant born with spina bifida who was exposed to protriptyline and diazepam [redacted], after the period for neural tube defects. The remaining 14 reports included one or more of the following congenital malformations:

Cleft palate, clubfoot, heart malformation, hydrocephalus, syndactyly (2 reports each), congenital brain damage, cataract, epispadias, hypospadias, chest wall haematoma, cord malformation, gross trunk deformity, intestinal perforation, limb malformation, congenital nevus and patent ductus arteriosus (1 report each).

One of the cases (report ID 000418), from 1966, reports a very high dose of amitriptyline [redacted]. The infant was born live with limb and heart malformations, cleft palate, hypospadias and syndactyly.

Three cases (one each for amitriptyline, clomipramine and nortriptyline) report neonatal withdrawal syndrome.

In 13 reports, the pregnancy resulted in a live birth. Adverse pregnancy outcomes were reported in the remaining seven cases, [redacted] The pregnancy outcome was not reported for one case.

Table 12. CARM reports for congenital malformations and adverse pregnancy outcomes associated with TCA exposure during pregnancy

Report ID	Year	Medicine	[redacted]	[redacted]	Adverse events	[redacted]
000418	1966	Amitriptyline	[redacted]	[redacted]	Limb malformation Heart malformation Cleft palate Hypospadias Syndactyly	[redacted]
000615	1966	Amitriptyline	[redacted]	[redacted]	Heart malformation	[redacted]
002321	1970	Amitriptyline Protriptyline	[redacted]	[redacted]	Brain damage congenital	[redacted]
002466	1971	Amitriptyline	[redacted]	[redacted]	Cleft palate	[redacted]
003681	1972	Amitriptyline	[redacted]		Pericarditis Hepatitis cholestatic Intestinal perforation Fetal distress	[redacted]
004732	1974	Amitriptyline	[redacted]	[redacted]	Hydrocephalus Spina bifida Clubfoot Stillbirth	[redacted]
226779	1994	Amitriptyline	[redacted]	[redacted]	Hydrocephalus Clubfoot Elective abortion	[redacted]
074394	2007	Amitriptyline Mexiletine Methadone		[redacted]	Hypertension pulmonary - neonate	[redacted]
097131	2011	Amitriptyline		[redacted]	Withdrawal syndrome neonatal	[redacted]
009853	1981	Clomipramine	[redacted]	[redacted]	Withdrawal syndrome neonatal	[redacted]
012180	1983	Clomipramine Trifluoperazine	[redacted]	[redacted]	Fetal disorders (chest wall haematoma, cord malformation) Birth premature	[redacted]
006100	1977	Desipramine Trifluoperazine Procyclidine	[redacted]	[redacted]	Nevus (fetal)	[redacted]
044072	2000	Dothiepin		[redacted]	Epispadias	[redacted]
000532	1966	Imipramine Thioridazine		[redacted]	Patent ductus arteriosus Death neonatal	[redacted]
013285	1985	Maprotiline	[redacted]	[redacted]	Abortion	[redacted]
000957	1967	Nortriptyline Diazepam	[redacted]	[redacted]	Fetal disorders (grossly deformed body stalk)	[redacted]

003917	1972	Nortriptyline Diazepam Methylphenidate Promethazine	[redacted]	[redacted]	Cataract	[redacted]
045558	2000	Nortriptyline		[redacted]	Lethargy Hypotonia neonatal Withdrawal syndrome neonatal	[redacted]
119714	2016	Nortriptyline Venlafaxine		[redacted]	Syndactyly	[redacted]
001358	1968	Protriptyline Diazepam		[redacted]	Spina bifida	[redacted]

[redacted]

3.3 National Collections data

A newly developed application for Pharmaceutical Dispensing in Pregnancy in the Ministry of Health's Qlik Sense data analysis tool was used to query the National Collections data for pregnancy exposure to TCAs and congenital abnormalities. The proof-of-concept application, which is currently available for internal Ministry of Health use only, links data from the National Maternity Collection (MAT), Pharmaceutical Collection (PHARMS) and the National Minimum Dataset (NMDS). The application includes data on:

- Pregnancies: grouped by year of delivery (sourced from MAT) for the latest 10-year period based on the date of birth. The data was last refreshed on 29 October 2020 and covers the period 2010-2019.
- Pharmaceutical exposure: PHARMAC subsidised medicines dispensed during pregnancy (from PHARMS).
- Congenital conditions (ICD-10 codes Q00-Q99): diagnosed during publicly funded inpatient hospitalisations within the first year of life (from NMDS)[2].

Pregnancy exposure to TCAs has remained relatively constant over the period 2010-2019, with amitriptyline and nortriptyline the most used TCAs in pregnancy. For all TCAs, first trimester exposure occurs more often than exposure in later trimesters. (Figure 4, Figure 5 and Appendix 1)

[2] NMDS data for babies born in 2019 is currently incomplete for 12-month outcomes.

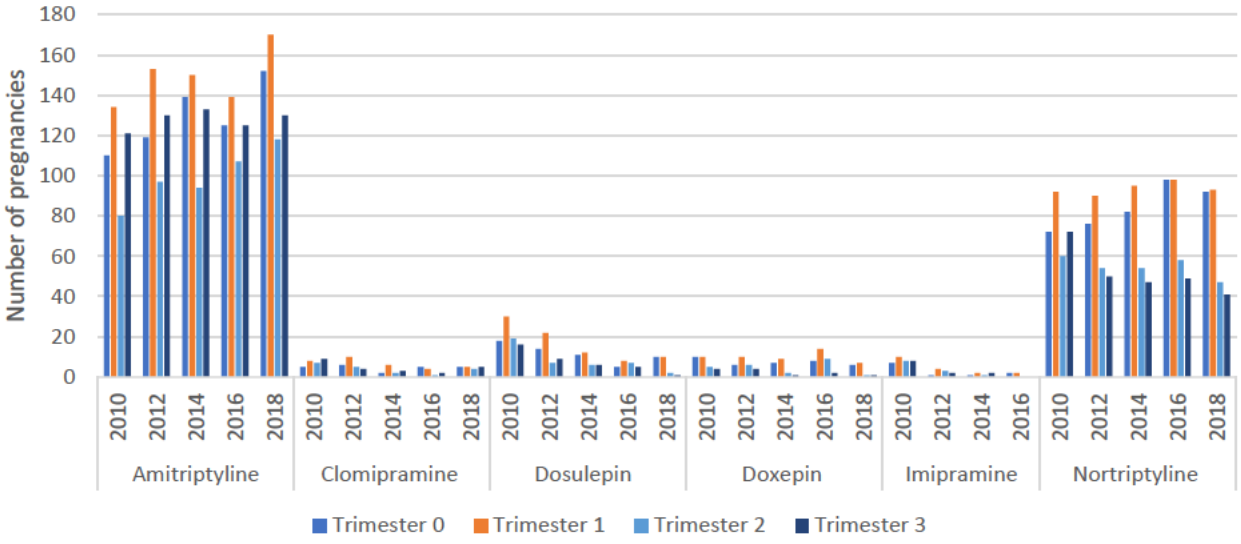

Figure 4. Number of pregnancies exposed to a TCA by trimester for alternate years from 2010 to 2018

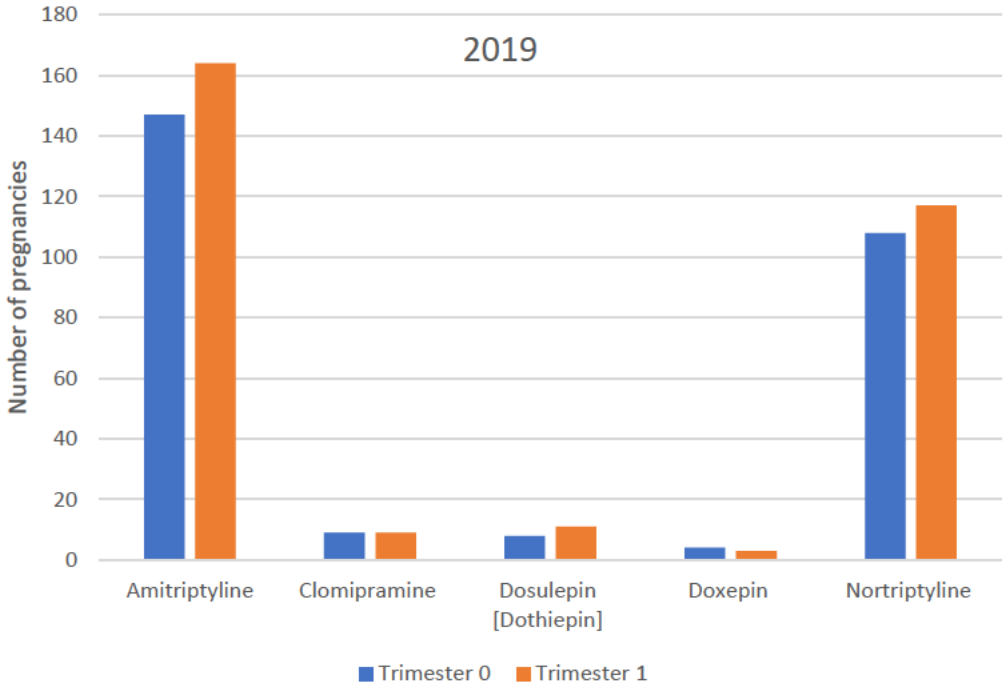

Figure 5. Number of pregnancies exposed to a tricyclic antidepressant in trimesters 0 and 1 in 2019

Overall, for the period 2010-2019, 8.9% of pregnancies exposed to a TCA were associated with a congenital condition (ICD-10 code Q00-Q99) compared to 7.6% of pregnancies that were not exposed to any TCA (OR 1.19). This proportion was the same for both amitriptyline and nortriptyline, which together comprise 90.8% of first-trimester TCA exposures over the 10-year period. Table 13

Table 13. Proportion of infants diagnosed with congenital malformation, deformation or chromosomal abnormality (ICD-10 codes Q00-Q99) by 12 months of age by first trimester exposure to TCAs for period 2010-2019.

Tricyclic antidepressant	Exposed in 1st trimester [a]			Not exposed in 1st trimester				
	Number of pregnancies	Infants with congenital condition	%	Number of pregnancies	Infants with congenital condition	%	RR	OR
Amitriptyline	2152	191	8.9	433149	32,732	7.6	1.17	1.19
Clomipramine	68	5	7.4	435233	32,918	7.6	0.97	0.97
Dosulepin	174	21	12.1	435127	32,902	7.6	1.60	1.68
Doxepin	122	8	6.6	435179	32,915	7.6	0.87	0.86
Imipramine	33	2	6.1	435268	32,921	7.6	0.80	0.79
Mianserin	4	0	0	435297	32,923	7.6	0	0
Nortriptyline	1381	123	8.9	433920	32,800	7.6	1.18	1.2
Any TCA [b]	3893	345	8.9	431408	32,578	7.6	1.17	1.19

Notes:

a) Includes 30 days prior to estimated pregnancy start date and first 13 weeks of pregnancy.
b) Exposure to 'Any TCA' is less than the sum of all TCA exposures as in some cases more than one type of TCA may have been dispensed during the exposure period of interest.

Table 14 gives an overview of the types of congenital malformations diagnosed within 12 months of birth in infants who were exposed to a TCA in the first trimester. A full list of the ICD-10 diagnoses for each TCA is provided in Appendix 2.

Table 14. Congenital malformations (grouped by ICD-10 sub-chapter) diagnosed within 12 months of birth for infants born 2010-2019 [a] who were exposed to a TCA in the first trimester [b]

ICD-10 sub-chapter	Amitriptyline	Clomipramine	Dosulepin	Doxepin	Imipramine	Nortriptyline	Total (sub-chapter)
Q00-Q07 Congenital malformations of the nervous system	6		1	1		7	**15**
Q10-Q18 Congenital malformations of eye, ear, face and neck	15		1			7	**23**
Q20-Q28 Congenital malformations of the circulatory system	77		12		2	44	**135**
Q30-Q34 Congenital malformations of the respiratory system	16		2			11	**29**
Q35-Q37 Cleft lip and cleft palate	7					8	**15**
Q38-Q45 Other congenital malformations of the digestive system	71	4	13	5		48	**141**
Q50-Q56 Congenital malformations of genital organs	22		1			6	**29**

Q60-Q64 Congenital malformations of the urinary system	9		2	1		7	**19**
Q65-Q79 Congenital malformations and deformations of the musculoskeletal system	38	1	3	1	1	34	**78**
Q80-Q89 Other congenital malformations	9		4	1		6	**20**
Q90-Q99 Chromosomal abnormalities, not elsewhere classified	6					3	**9**
Total for medicine	**276**	**5**	**39**	**9**	**3**	**181**	**513**

Notes:

a) The 12-month diagnosis data for infants born in 2019 may be incomplete
b) Includes 30 days prior to estimated pregnancy start date and first 13 weeks of pregnancy.

The most frequent congenital malformation recorded within the first 12 months of birth for the TCA medicine class is Q381 ankyloglossia, followed by patent ducts arteriosus and congenital laryngomalacia (Appendix 3).

4 DISCUSSION AND CONCLUSIONS

TCAs have been used to treat depression since the 1950s but have now largely been superseded by SSRIs and SNRIs due to their more favourable adverse effect and overdose toxicity profile.

Studies of the safety of TCAs in pregnancy have produced conflicting results and the information in the current data sheets reflects this uncertainty. Most of the current TCA data sheets state that the medicine is classified as Category C under the Australian categorisation system for prescribing medicines in pregnancy. A Category C classification indicates that the medicine may cause harmful effects on the fetus without causing malformations and that the effects may be reversible. However, this statement appears to be contradicted in some data sheets by statements that epidemiological studies have suggested an increased risk of congenital abnormalities and that animal studies have shown reproductive toxicity.

A search of the recent literature identified five observational studies of congenital malformations and first-trimester exposure to anti-depressant medicines that included TCA exposures. There is no consensus between these studies: two studies reported an association [11, 16], two reported no association [14, 15], and one study was non-contributory as it did not specifically look at TCA exposure and outcomes [13].

Bérard et al (2017) [11] examined first trimester-exposure to antidepressants and the risk of major congenital malformations in the Quebec Pregnancy Cohort. Of the 382 TCA-exposed pregnancies, 51 (13.4%) had major congenital malformations, but neither the crude nor adjusted ORs were statistically significant when compared to unexposed pregnancies. However, further analysis of congenital malformations by subgroup, identified a statistically significant increase in digestive system (aOR 2.55, 95% CI 1.40 to 4.66) and eye, ear, face and neck malformations (aOR 2.45, 95% CI 1.05 to 5.72). Information on important confounders was not available for the analysis.

Reis and Källén (2010) [16] used data from the Swedish Medical Birth Register and Register of Birth Defects to identify congenital malformations in infants exposed to antidepressants in the first trimester. This study found a statistically significantly association for TCA exposure and 'relatively severe malformation' (OR 1.36, 95% CI 1.07 to 1.72) any cardiovascular defect (OR 1.63, 95% CI 1.12 to 2.36) and VSD and/or ASD (OR 1.84, 95% CI 1.13 to 2.97). However, this study did not adjust for the use of other psychoactive drugs, which was noted to be higher in women taking antidepressants, and confounding by indication could not be excluded.

Ban et al (2014) [14] undertook a population-based cohort study using THIN. To address the issue of indication bias, the study included comparisons with unexposed mothers who did not have depression and with unexposed mothers with unmedicated depression. First trimester TCA exposure was not associated with MCA or subgroup anomalies when compared to no depression or unmedicated depression.

Huybrechts et al (2014) [15] examined the risk of congenital malformations associated with first trimester antidepressant exposure in a large US public insurance database. No statistically significant associations were

identified for TCAs cardiac malformations overall or specific cardiac malformations in the unadjusted analysis, depression restricted analysis or with propensity score stratification.

The most recent study, by Anderson et al (2020) [13] examined congenital malformations associated with first-trimester antidepressant use in a large US population-based birth cohort. Information on antidepressant use was obtained by interview within 6 weeks to 24 months after delivery. Use of TCAs was not specifically sought but information about their use was captured under 'other medicines'. Very few exposures were reported, and no specific analyses for congenital malformations were performed for TCAs.

The CARM database contains 15 reports of congenital abnormality associated with TCA use, but a causal association is difficult to determine from the available information.

The National Collections data shows relatively stable use of TCAs in pregnancy over the past 10 years, with amitriptyline and nortriptyline the most used. Overall, first trimester use of a TCA was associated with a congenital malformation in 8.9% of exposed infants, compared to 7.6% of unexposed infants, with OR 1.19 (confidence interval not calculated). This data does not consider concurrent use of other medicines or risk factors for congenital malformation.

In summary, the evidence for any association between first-trimester TCA use and an increased risk of congenital malformation is weak.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the current evidence supports an association between first trimester exposure to tricyclic antidepressants and an increased risk of congenital malformations in the infant.
- Whether there is a need to update the data sheets for tricyclic antidepressants about the risk to the fetus.

6 ANNEXES

None

7 REFERENCES

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