Psychiatria Danubina, 2017; Vol. 29, Suppl. 3, pp 629-644 *Conference paper*

WHAT ARE THE RISKS ASSOCIATED WITH DIFFERENT SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS (SSRIS) TO TREAT DEPRESSION AND ANXIETY IN PREGNANCY? AN EVALUATION OF CURRENT EVIDENCE

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SUMMARY

A literature review was conducted to elucidate the respective reproductive safety profiles of different SSRIs to inform the prescribing practices of doctors treating pregnant women with anxiety and depression.

***Background:** Women are most likely to be diagnosed with depression or anxiety between the ages of 25 and 44 years, which are also the years of childbearing potential (Burke et al., 1991). Therefore a substantial number of women face a decision about whether or not to take an antidepressant or anxiolytic during pregnancy. There are no psychotropic medications that have UK marketing authorisation (NICE, 2014), no clear clinical consensus has been reached regarding the use of SSRIs in pregnancy, and clinicians lack a resource which discusses the reproductive safety profiles of different SSRIs rather than the class of drugs as a whole.*

***Subjects and methods:** We performed a search for the English language literature indexed on MEDLINE/PubMed for the period 2012 to 2017, using the following key terms: fluoxetine, prozac, paxil, oxactin, paroxetine, seroxat, sertraline, lustral, citalopram, cipramil, escitalopram, cipralex, fluvoxamine, faverin, with 'pregnant woman', 'pregnant women', pregnancy. We excluded general SSRI and pregnancy articles (although we did read these papers for valuable background information) because we are interested in elucidating the differences between the drugs in this class, rather than the general effects of the SRRI class as a whole.*

***Results:** The literature shows that paroxetine and fluoxetine have the strongest association with negative outcomes (significant malformations, PPHN and PNAS) whilst the associations between sertraline and citalopram with negative outcomes remains mixed and generally unsubstantiated when studies that show an association are controlled for the effects of maternal depression and associated factors. There are too few studies to draw definite conclusions regarding the safety of escitalopram and fluvoxamine.*

***Conclusions:** Sertraline and citalopram should be first-line drug treatments for anxiety and depression in pregnant women in the SSRI class. Sertraline can be continued in breast-feeding as the concentration found in breast milk is very low and has not been linked to infant complications. Furthermore, it would be useful to assess GPs current knowledge and confidence levels about prescribing, to see whether further education is needed in this area to encourage an open discussion of the risks and benefits of medication or no medication. It would also be useful to conduct further research on escitalopram which is likely to grow in popularity in the coming years as it came off patent in 2012. When these holes are filled, a clinical protocol for treating anxiety and depression in pregnant women should be created and implemented for the UK population.*

Key words: *depression - anxiety - SSRIs - pregnancy - paroxetine - fluoxetine - citalopram - excitalopram - fluvoxamine - sertraline - malformations - teratogenic - PPHN - PNAS*

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INTRODUCTION

Women are most likely to be diagnosed with depression or anxiety between the ages of 25 and 45 years, which are also the years of childbearing potential (Burke et al. 1991). Therefore a substantial number of women face a decision about whether or not to take an antidepressant or anxiolytic during pregnancy (Einarson 2012). Data varies widely about the estimated number of pregnant women in the UK who have a diagnosis requiring administration of SSRIs. According to the NICE guidelines on antenatal and postnatal mental health, depression and anxiety are the most common mental health problems during pregnancy. Prevalence of maternal depression in pregnancy has been estimated at between 7% and 15% (Bennett et al. 2004, Llewellyn et al. 1997), and anxiety disorders have been diagnosed in 4% to 39% of all pregnant women (the size of the interval here suggests the inaccuracy of these estimations). Some estimates are even higher, stating that 18.4% of women suffer from antenatal depression. Anxiety disorders are also common at this time, with a prevalence of 21.7% among pregnant women by the 3rd trimester of pregnancy (Borriet al. 2008, Reck et al. 2008).

Studies have argued that anxiety or depression is more common in pregnancy than at other times in an individual's life (Biaggiet al. 2016), not just because women are generally more likely than men to suffer from these two mental health conditions, but also because hormone concentrations change during pregnancy and in the puerperium. These altered concentrations are hypothesized to cause potential alterations in a woman's mental wellbeing. However, Chaudron argues that there is little evidence to support such a theory regarding the etiology or symptoms of depression being distinct in pregnancy when compared to other periods in a woman's life (Chaudron 2013).

Despite the significant burden of mental health problems in pregnancy, when compared to postpartum depression and postpartum anxiety, pre-natal depression and anxiety have attracted less research scrutiny and less media attention. A resilient myth that pregnancy is protective against depression has fuelled this neglect. According to the NICE guidelines on antenatal and postnatal mental health, between 2006 and 2008 there were 1.27 maternal deaths per 100,000 maternal deliveries in the UK due to mental health issues. Furthermore, mental health problems are not well recognised and therefore not effectively treated, potentially having repercussions far beyond pregnancy (NICE Guidance for Antenatal and postnatal mental health: clinical management and service guidance, 2014 & updated 2017)

Valid ethical concerns about randomised control trials involving pregnant women has contributed to a thin evidence base about the treatments potentially available to women in pregnancy to help alleviate mental health problems. Practically, this means that there are no psychotropic medications that have UK marketing authorisation (NICE 2014). The current guidance states that the prescriber must take full responsibility for off-license use and the patient must be fully informed of such 'un-authorised' prescribing and consent. The guidance further states that the prescriber should take into account (1) the woman's previous response to treatments, (2) her stage of pregnancy, and (3) current literature on different drugs and their reproductive safety. The guidance highlights only paroxetine as being particularly associated with discontinuation symptoms in the woman, and neonatal adaptation syndrome in the baby. Other SSRIs are simply described as showing some risk of these complications. In short, the NICE guidance leaves it up to the individual doctor to decide with the patient what action (or inaction) is safest. Furthermore, the complex environment of the fetus in utero, as well as multifactorial post-natal environment, have meant that associations between a mother's mental health and infant outcomes are hard to quantify. Many confounding factors, including socioeconomic status of the mother, substance use and comorbidities (particularly co-existing mental illness) further complicate the clinical picture (Chaudron 2013).

Beyond the disputed scale of need for mental health treatments in pregnancy, a wide range of estimates regarding the number of women who actually end up taking SSRIs during these 9 months have been circulated. SSRIs are the mainstay treatment for moderate to severe peripartum depression. In a randomized controlled trial comparing antidepressants with community-based psychosocial intervention for peripartum depression, SSRIs were superior with a number needed to treat of 4 at four weeks (Goodhead & Langan 2016).

Studies suggest that perceptions of the risk that maternal SSRI use poses to the fetus vary widely between patients and health professionals (Widnes 2013). Pregnant women were shown to have significantly higher perceptions of teratogenic risks associated with SSRIs and other antidepressants, and lower confidence in the use of such medicines, when compared with general practitioners. Amongst the range of drugs (which included medications for pain and other indications as well as an SSRI) differences in teratogenic risk perception and confidence in use were highest for escitalopram, perhaps because this drug is not widely used as it has only recently been removed from patent in 2012. This study highlights the importance of educating health professionals about the specific risks of SSRIs, as well as educating them about how to counsel women about the associated risks. Moreover, the wording of information leaflets for SSRI medications have been shown to influence teratogenic risk perception, and thus the prescription of medicines as well as affecting patient adherence. In a recent study, 69% of women thought it was definitely or probably acceptable to take such drugs when not pregnant or not breast feeding; but only 33% of women thought that it was definitely or probably acceptable to do so when pregnant (Reefhuis et al. 2015).

However, SSRIs are increasingly used by women of reproductive age and during pregnancy, despite reported concern and uncertainty about their safety. Prescribing patterns in the NHS suggest that women are increasingly seeking treatment for depression and anxiety even while pregnant, and more SSRIs are being prescribed by their doctors than in previous decades. One study found that use of antidepressant medication in pregnancy has increased by over 100% in the last 20 years (Bérard et al. 2017), and the UK has one of the highest international rates of antidepressant prescriptions for pregnant women.

As in the general population, SSRIs are the most frequently prescribed antidepressants and anxiolytics for pregnant women in the NHS, followed by SNRIs and tricyclic antidepressants (TCAs). The number of women taking SSRIs declines with each trimester, meaning that prescription rates in the third trimester are lower than the first (Yonkers et al. 2014). This may be due to an acknowledged association between third-trimester exposure to SSRIs and poor neonatal adaptation syndrome (PNAS) (Byatt et al. 2013). Moreover, SSRI treatment of pregnant women is too often at lower doses than recommended; it is reported that almost 8% of pregnant women are not receiving an adequate therapeutic dose. Failure to reach an effective dose may be due to patient and doctor concerns about a dose-dependent relationship between SSRI exposure and poor neonatal outcomes (Oliver et al. 2013).

On the other hand, many women do decide to discontinue antidepressants in pregnancy (Ruddock, 2004). Few studies have researched the effect of discontinuing SSRIs (or initiating SSRIs) during pregnancy compared to either abstaining from the time of conception or staying on the medication throughout the 9 months (Roca et al. 2013). Studies suggest that women who discontinue depression or anxiety medication are at a signi-

ficantly higher risk of recurring mental illness either prenatally or soon after delivery (Altshuler et al. 2000). In one study, women who discontinued their antidepressants were three times more likely to relapse compared with women who continued their antidepressants throughout the pregnancy (Marcus & Heringhausen 2009).

Deciding whether to treat pre-existing or new-onset depression or anxiety with medication poses a challenge: on the one hand, SSRIs have been linked with fetal complications (Kovich 2015, Larsen et al. 2015, Alwan et al. 2016, Byatt et al. 2013, Reefhuis et al. 2015, Bravo et al. 2016, Eleftheriou 2013, Forsberg et al 2014); on the other, untreated maternal depression and anxiety has been associated with potential risk to the wellbeing of both the mother as well as the fetus (Davalos et al. 2012). M.K. Seo et al. (2016) have shown that early life stress (ELS) of the fetus – due to the stress of the mother altering the uterine environment –may exert long-lasting epigenetic influences on the fetal brain. This is hypothesized to leave the individual susceptible to depression later in life. Their explanations are incomplete about whether ELS and later chronic stress as an adult can be explained via the involvement of epigenetic mechanisms in utero linked to maternal mental illness, whether untreated or otherwise (Seo et al. 2016).

Conflicting data has led to uncertainty and variation in prescribing patterns amongst doctors, and confusion amongst the public, regarding the safety of SSRI use during pregnancy. Concern for fetal safety hinges on the fact that all SSRIs pass through the placenta into the fetal circulation (Velasquez et al. 2013). Moreover, the fetus has additional exposure through the amniotic fluid, which has the potential to increase serotonin concentrations in the fetus as it develops (Hostetter et al. 2000, Loughhead et al. 2006). Increased serotonin concentrations may affect the baby's cardiovascular, respiratory and neurological development, all of which involve serotonin.

Short- and long-term effects of SSRIs on the fetus have been reported in the literature. SSRI exposure in utero has been linked to negative birth outcomes, such as higher numbers of spontaneous abortion, low birth weight, preterm birth, persistent pulmonary hypertension (PPHN) and postnatal adaptation syndrome (PNAS). Immediately post-partum, these PNAS symptoms include infant irritability, excessive crying, a tremor, lethargy, under-activity, reduced feeding, tachypnea and respiratory distress (AK 2015; Larsen et al. 2015; Alwan et al. 2016; Byatt et al. 2013; Reefhuis et al. 2015; Bravo K et al. 2016; Eleftheriou 2013; Forsberg et al. 2014). Speculative associations have also been made between maternal SSRI use and their children developing autism spectrum disorder and impaired neurocognitive function into adulthood (Kovich 2015, HM 2012, Alwan et al. 2016).

Untreated depression and anxiety carry abuse a risk for mothers, and may not be the safest option for baby either. Maternal depression in pregnancy is associated with adverse perinatal outcomes. Pregnant women who do not receive treatment for depression or anxiety are more likely to abuse recreational drugs and other substances such as tobacco, alcohol and caffeine while pregnant (Flynn et al. 2008), all of which have been shown to be directly harmful to the fetus, particularly in excess. A recent study found that repeated episodes of binge drinking in early pregnancy increases the likelihood of cardiac defects, which becomes even more risky when combined with maternal smoking. Other effects include insufficient maternal weight gain (Bodnaret al. 2009), decisions to terminate the pregnancy (Suri et al. 2004), preeclampsia (Cripe et al. 2011), preterm birth (Istvan 1986), intra-uterine growth restriction, increased risk for delivery of a low birth weight infant (Grote et al. 2010), anxiety and postpartum depression (Gotlib et al. 1991), and infant cognitive and emotional complications postnatally. Fetal distress (Jablensky et al. 2005) and increased risk of neonatal care unit admission as well as Caesarian section delivery (Chung et al. 2001) are linked to maternal depression.

Theories have been posited as to how maternal depression, stress and anxiety affect the fetus if untreated. The impact of depression on fetal wellbeing may be through direct or indirect effects on the hypothalamic-pituitary-ovarian (HPO) axis and the hypothalamic-pituitary-adrenal (HPA) axis. Normally, levels of gonadal hormones and progesterone increase during pregnancy. Placental corticotropin-releasing hormone (CRH), cortisol, human chorionic gonadotropin (HCG), prolactin, β-endorphin, and thyroid hormone-binding globulin concentrations also normally increase over the 9 months. Complex feedback systems exist and disruptions of these interactions, usually via suppression due to stress, anxiety and low mood are potentially significant (Ahokas et al. 2005, Giesbrecht et al. 2012).

As well as the physiological changes in pregnancy that might be altered by depression and anxiety, such changes can interfere with the pharmacokinetics of SSRIs. Pregnancy-associated changes in absorption, distribution, metabolism and elimination may result in lower SSRI concentrations and therefore potentially reduced therapeutic effects, particularly in the third trimester of pregnancy (Feghali et al., 2015). Reported mechanisms affected by pregnancy include changes in both phase 1 hepatic cytochrome P450, and phase 2 uridine diphosphate glucuronosyltransferase enzyme activities, changes in hepatic and renal blood flow and glomerular filtration rate (Deligiannidis et al. 2014). Increased metabolism of SSRIs in the third trimester may require consideration of a higher dose in this later stage in order to reach sufficient therapeutic effect.

During pregnancy, the concentrations of different SSRIs in the mother's blood are affected in different ways and to varying extents. Average fluoxetine metabolite ratio levels decrease between 20 to 26 weeks, and between 30 to 36 weeks' gestation (Deligiannidis et al.

2014). An increase in sertraline dose is often required early in the third trimester to treat new-onset depressive symptoms, with some women experiencing increased drug metabolism from second to third trimester. Regarding paroxetine, decreasing plasma levels and worsening depressive symptoms can occur in pregnancy if the woman has a CYP2D6-extensive or ultra-rapid metabolizer genotype. By contrast, antidepressant accumulation can happen in low and intermediate metabolizers, an effect which could potentially have adverse outcomes for the fetus. Citalopram plasma concentration lowers, as does the concentration of metabolites during pregnancy, but there is a higher mean es-methylcitalopram metabolic ratio when compared to 8 weeks postpartum. Such a difference suggests faster rate of escitalopram metabolism during pregnancy (Deligiannidiset al. 2014). Decreased dose ratios are associated with lowered drug efficacy and therefore a higher dose requirement in the second half of gestation. No studies exist on the metabolic changes of fluvoxamine in pregnancy. Therefore, therapeutic SSRI monitoring is essential in women who do decide to take an SSRI drug in pregnancy.

Since Thalidomide in the 1950s, a pharmacological 'martyrdom' has been encouraged in pregnant women: there is a popular assumption that mothers should give up psychoactive medication for the sake of the fetus. This is compounded by conflicting advice from obstetricians, primary care doctors and psychiatric professionals, and too often discussion regarding the advisability of taking SSRIs in pregnancy has lacked nuance. Counseling and education of pregnant women, or those hoping to conceive, must take into account the severity of each woman's mental health diagnosis, her wishes and values, her socio-economic situation as well as available support structures and her emotional stability. The mother's medical and mental health history, as well as considerations of any previous risk-taking behaviours, are essential to inform this decision.

To this end, health professionals must also be well-informed about the differences that exist between the 6 medications in the SSRI class currently available on prescription in the NHS. Many studies have been undertaken which analyse general effects of SSRIs as a family of drugs, but these lack a subgroup analysis examine specific effects of individual drugs in the class which might influence the risk-benefit analysis.

In general, SSRIs have been linked to many complications for infants as well as in later childhood. In 2006, the FDA issued a health advisory for SSRI use after the 20th week of gestation because of a reported increased risk of persistent pulmonary hypertension of the newborn (PPHN). This recommendation was revised in 2011, and now states that conflicting findings leave it unclear whether use of SSRIs during pregnancy can cause PPHN (Kovich 2015). A recent meta-analysis of five trials supported the link between late pregnancy exposure to SSRIs and PPHN (Grigoriadis et al. 2014). A large case-control study reported a 600% increase in risk of PPHN among infants born to mothers taking an SSRI in late pregnancy (FDA study published in the New England Journal of Medicine). A correlation has also been made between SSRI use in pregnancy and lower Apgar scores of the infant at delivery (Jensen et al. 2013). Other associations include miscarriage, premature delivery, neonatal complications and birth defects (specifically cardiac defects) (Kovich 2015; Larsen et al. 2015; Alwan et al. 2016; Byatt et al. 2013; Reefhuis et al. 2015; Bravo et al. 2016; Eleftheriou 2013; Forsberg et al. 2014). Late in utero exposure to SSRIs has been suggested as a risk factor for impaired neonatal adaptation (PNAS) (Byatt et al., 2013). Infants born to mothers treated with SSRIs prior to delivery were reportedly more likely to suffer from respiratory distress, body temperature instability, feeding problems, jitteriness and restlessness, convulsions, rigidity, hypoglycemia, jaundice, and other symptoms of abnormal neonatal adaptation. Symptoms appear to be worse and more common with high-dose maternal SSRI treatment late in pregnancy.

More recently, neurodevelopmental disorders in childhood, specifically autism spectrum disorders have been connected to maternal SSRI use (Kovich 2015; Larsen et al. 2015; Alwan et al. 2016; Byatt et al. 2013; Reefhuis et al. 2015; Bravo et al. 2016; Eleftheriou 2013; Forsberg et al. 2014). Later-emerging conditions including attention-deficit/hyperactivity disorder and speech delay have been reported, but it is worth noting that high-quality evidence to support these general claims is lacking. Conflicting findings about any association between prenatal SSRI exposure and a child developing autism mean that the issue remains speculative. The observed risk of SSRIs in pregnancy with autism of the infant is probably confounded by severity of maternal illness, and there is inconclusive evidence for delayed psychomotor and slow fine motor development.

Given this backdrop of controversy, without differentiating between the respective risks of particular drugs rather than the SSRI drug class as a whole, we were interested to assess current research differentiating 6 different SSRIs: paroxetine, fluoxetine, sertraline, citalopram, escitalopram and fluvoxamine. By analyzing the different risks and benefits of each of these drugs, our intention is to give health professionals a clearer picture of what differentiates the 6 SSRIs, so that doctors and nurses can assist women and their partners to make an informed choice about the various risks and benefits of each particular SSRI. By assessing and distilling the current plethora of evidence, we hope to enable more accurate risk assessment, better patient education and empowerment to make a truly collaborative decision about whether medication per se, and which medication in particular, is best suited for each individual woman in pregnancy.

Table 1. Summry results

	Prenatal effects	Perinatal Outcome	Malformations – GI, neuro	Cardiac malformations	PNAS*	PPHN	Autism	ADHD	Neurological development/fine motor skills	SUMMARY
Sertraline	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence - insignificant association with negative outcomes. Also very low concentrations in breast milk.
Citalopram	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence - insignificant association with negative outcomes
Escitalopram**	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	No	No	Yes	Yes	Mixed	Mixed	Mixed	Mixed evidence – insignificant association with negative outcomes; also lack of studies
Paroxetine	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	Neural tube defects - Anencephaly Gastrochisis Omphalocele	Septal defects RV outflow obstruction	Yes	Yes	Mixed	Mixed	Mixed	Repeated associations with significant malformations, particularly cardiac defects
Fluvoxamine	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	Limited evidence	Limited evidence	Yes	Yes	Mixed	Mixed	Mixed	Not enough data to inform decision-making
Fluoxetine	No increased risk for miscarriage	*Mixed evidence for Low birth weight, preterm birth and small for gestational age*	Craniosynostosis	RV outflow obstruction VSDs	Yes	Yes	Mixed	Mixed	Mixed	Repeated associations with significant malformations

* All studies examined showed a positive association between PNAS and SSRI exposure in utero, but these studies have been criticised for being low powered, and prone to prejudicial bias;

** Whilst there are more studies on escitalopram than on Fluvoxamine, making trends in findings easier to discern, there is still limited evidence on the safety of escitalopram when compared to other SSRIs

METHOD

We performed a search for the English language literature indexed on MEDLINE/PubMed for the period 2012 to 2017, using the following key terms: fluoxetine, prozac, paxil, oxactin, paroxetine, seroxat, sertraline, lustral, citalopram, cipramil, escitalopram, cipralex, fluvoxamine, faverin, with 'pregnant woman', 'pregnant women', pregnancy. We searched for both the SSRI generic name and any brand names. To ensure that all relevant articles were identified, which might have been missed in our initial search, all articles were cross-referenced. We included animal studies that provided a model for human physiology, observational studies, case reports and case series.

We excluded general SSRI and pregnancy articles (although we did read these papers for valuable background information) because we are interested in elucidating the differences between the drugs in this class, rather than the general effects of the SRRI class as a whole. We also excluded all papers about antidepressants and anxiolytics in other drugs classes, such as SNRIs and TCAs. We also did not analyze in detail papers which focus on patient adherence to medication regimens, or presentation and symptomatology of prenatal depression and anxiety. Other excluded papers proved to be irrelevant to our research question.

RESULTS

Full results table as an appendix and summry results are in Table 1.

Fluoxetine (OR 1.14, 95% CI 1.01–1.30) and paroxetine (OR 1.29, 95% CI 1.11–1.49) are associated with increased risk of major malformations (Ban et al., 2014). Paroxetine is associated with increased risk of cardiac malformations (OR 1.44, 95% CI 1.12–1.86), which is in-line with the 2005 FDA decision to classify paroxetine as pregnancy category D (of high risk but not entirely contra-indicated) because of this concern about congenital cardiac malformations (Myles et al. 2013). Sertraline and citalopram are not significantly associated with congenital malformation.

A meta-analysis suggests that children exposed to SSRI medications in utero have increased risk of developing major congenital malformations, not including cardiac or minor congenital malformations (Myles et al. 2013). However, subgroup analysis suggested that the aggregate effect for major malformation is driven specifically by paroxetine (OR 1.29, p=0.001) and fluoxetine (OR 1.14, p=0.04), with citalopram and sertraline exerting a non-significant impact on effect size Myles et al. 2013).

A Bayesian analysis suggests that none of the five previously reported birth defects associations with sertraline was confirmed. The analysis confirmed reported associations between right ventricular outflow tract obstruction and other cardiac defects in infants with maternal use of fluoxetine or paroxetine early in pregnancy, and between anencephaly or atrial septal defects in infants and maternal use of paroxetine. The Bayesian analysis also confirmed associations between gastroschisis and omphalocele with paroxetine, and between craniosynostosis with fluoxetine. There have been 9 previously reported associations between maternal SSRI use and birth defects in infants, but findings were consistent with no association (Reefhuis et al. 2015). Here, the high posterior odds ratios excluding the null value were observed for five birth defects with paroxetine (anencephaly 3.2, 95% credible interval 1.6 to 6.2; atrial septal defects 1.8, 1.1 to 3.0; right ventricular outflow tract obstruction defects 2.4, 1.4 to 3.9; gastroschisis 2.5, 1.2 to 4.8 and omphalocele 3.5, 1.3 to 8.0) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.1 and craniosynostosis 1.9, 1.1 to 3.0). These data are reassuring for some SSRIs but suggest that some birth defects occur 2 to 3 times more frequently among infants of women treated with paroxetine or fluoxetine in first trimester of pregnancy (Reefhuis et al. 2015).

DISCUSSION

Clinical Applications

Sertraline and citalopram should be first-line drug treatments in the SSRI class for pregnant women. The advantage of sertraline over citalopram is that it can be continued into breast-feeding, as the concentration found in breast milk is very low and has not been linked to infant complications. Paroxetine should be avoided if possible, as there is the strongest link between this SSRI and fetal malformations. Paroxetine is associated with an increased prevalence of cardiac and GI malformations as well as neonatal complications postpartum. Escitalopram does not pose any reported problems during pregnancy, but the volume of evidence is limited. Fluvoxamine cannot be actively recommended because there the data is too scarce for conclusions to be made as to its safety.

Planning and discussion with women taking SSRIs for anxiety or depression should begin before conception, if possible. Prescription and control of the patient's treatment should ideally be carried out collaboratively with a psychiatry specialist. If a woman has become pregnant and is already on an SSRI, she may be advised to come off medication or switch. Discontinuation of SSRIs is not recommended if the treatment is still indicated, due to increased risk of maternal relapse into depression or anxiety during pregnancy or soon postpartum. Data suggests that treatment with fluoxetine or fluvoxamine might be advisedly discontinued if this is considered safe in relation to the preferences of the patient, and changed to another SSRI or taken off medication altogether (and then, psychotherapy offered if appropriate and necessary). Paroxetine should be

discontinued unless there is a very strong indication why a patient should stay on this drug in preference to other options, within or outside the SSRI class. If taking escitalopram, current evidence suggests a pregnant woman may continue this medication without excessive risk to her or the infant.

Although not the focus of this paper, SSRI choice in pregnancy should also consider breastfeeding intention. If a woman anticipates that she will breastfeed the baby post-partum, sertraline and paroxetine are recommended as they have the fewest reported side-effects and the smallest transfer into breast milk. Of the two, prenatally sertraline has the lower risk profile, so may well be the best option. By comparison, residual fluoxetine in nursed infants has been reported, as well as symptoms in the baby from maternal use of fluoxetine and citalopram, and these drugs are therefore not recommended when breastfeeding. Again, a risk-benefit analysis should be applied to women who are breastfeeding. SSRI treatment can continue after delivery and during breast-feeding as long as sufficient information about the potential side effects in the infant is communicated to the mother. Specifically, the child's wellbeing and predicted weight gain should be closely monitored. If doubt arises about possible side effects in the child, the SSRI concentration can be measured in the baby's blood.

Additionally, pregnant women exposed to SSRIs in early pregnancy should be offered options for prenatal diagnosis through ultrasound imaging and fetal echocardiography to detect presence of birth defects. Tapering off SSRI use or changing to another therapy in early pregnancy, if appropriate for the individual, may also be considered on a case-by-case basis.

Limitations of studies

Much of the research in this field has insufficient power and reliability to be applied to clinical practice. Several of the studies' poor design that did not control for co-morbid maternal illness, that did not prove ingestion of prescribed SSRI medication, or assess response to treatment. Also, studies such as (Ban et al 2014; Grigoriadis et al. 2014) were careless not to highlight the difference between increased risk and absolute risk, a distinction which is crucial when making decisions about whether or not to take SSRIs in pregnancy. A further limitation is that pharmacy records are used in studies such as (Dawson et al. 2016) to assume treatment, and then also to assume therapeutic effect.

The flaw of publication and citation bias is also possible here, as positive scientific finds are easier to publish than negative ones. Therefore studies that show particular SSRIs to be safe without risk of malformation or without negative effect on the baby, are less attention-grabbing than reports of negative effect. It is important to note that studies often report a scarcity of information about true adherence to prescription regimens during pregnancy, including a lack of accurate information about doses, duration and exact timing of fetal exposure.

Some of the studies looked at presentation of the child at birth, including vague symptoms of fussiness, crying and distress, all of which were subjectively assessed and so were prone to false positives. Also, cardiac abnormalities are relatively common in the general population, and often prove insignificant and remain un-detected. However, when purposely searched for, small variations appear to be malformations which also increases the positive association in a false manner.

Because the effects of depression and anxiety are manifold, many studies point-out how hard it is to differentiate between effects of treatment and effects of the mental health condition being treated. Causation is a much harder thing to prove than an association, and it is challenging to differentiate between effects of SSRIs and the effects of being depressed (e.g. reduced social interaction with the baby postnatally, low socioeconomic status and negative lifestyle variables). When these factors are accounted for, many studies' findings lose their statistical significance (Byatt et al. 2013 HM 2012, Grigoriadis et al. 2017, Alwan et al. 2016).

Due to the ethical challenges of conducting research on pregnant women, the vast majority of studies included are not prospective and do not have matched controls. Moreover, blinding is not done in pregnancy for similar ethical reasons, but this remains a limitation about the evidence.

Unbiased counseling, based on a thorough understanding of the nuances in existing data, in a supportive therapeutic professional relationship will be best for mother and baby. Doctors must be careful to counsel such that, if a woman does require an SSRI in the future she does not see this as a failure, or believes that the risk is out of proportion to what the evidence actually shows. Informed consent should include the risks of maternal psychiatric symptoms and treatments. Focus should be on SSRIs within the many treatment options.

Suggestions for future research questions

This analysis has pointed out the important holes in current research, which, if filled, could improve the decision-making process regarding SSRIs in pregnancy for doctors and patients. It would be useful to assess GPs current knowledge and confidence levels about prescribing, to see whether further education is needed in this area to encourage an open discussion of the risks and benefits of medication versus no medication. One study has compared perceptions between pregnant women and GPs, but not directly looking into GP confidence and knowledge, and no such research was found that specifically looked at these issues amongst UK patients and GPs

It would also be useful to conduct further research on escitalopram, which is likely to grow in popularity in coming years as its patent expired in 2012. Escitalopram

is often chosen in preference to citalopram due to a reduced profile of side effects, and this is likely to be preferable in pregnancy too. There is also a need for further research into the specific effects of fluvoxamine, which is under-studied but is quite rarely prescribed in the NHS.

After such gaps in knowledge are filled, it would be useful to create a protocol regarding the choice of SSRIs in pregnancy. Only one study to-date has attempted to create a protocol for treating depressed pregnant women, which differentiated between the SSRI drugs for prescription in Denmark. A similar protocol would be usefully adapted and implemented for the UK population.

Role of psychotherapy

There is an important role for psychotherapy in the majority of cases of depression and anxiety, and this is no different in pregnancy. GPs should endeavour to connect women who would like this treatment as well as showing need for it, to a psychotherapist or CBT practitioner. However, it would be wrong to assume that psychotherapy is sufficient for all women without pharmacological treatment. SSRIs are the primary treatment for moderate to severe peripartum depression, and in a randomized controlled trial comparing antidepressants with community-based psychosocial intervention for peripartum depression, SSRIs were superior, with a number needed to treat of 4 at four weeks (Langanet al. 2016).

CONCLUSIONS

Anxiety and depression are the most common mental health issues faced by pregnant women. Furthermore, an increasing number of women of reproductive age are fulfilling prescriptions for SSRIs to treat these conditions. Yet, no clear clinical consensus has been reached regarding the use of SSRIs in pregnancy. In this review we have examined the available evidence pertaining to individual SSRIs (sertaline, citalopram, fluoxetine, fluvoxamine, paroxetine, escitalopram) and their associations with negative fetal outcomes. The literature shows that paroxetine and fluoxetine have the strongest association with negative outcomes (significant malformations, PPHN and PNAS) whilst the associations between sertraline and citalopram and negative outcomes remains mixed and generally unsubstantiated when studies are controlled for maternal depression and associated factors. There are too few studies to draw definite conclusions regarding the safety of escitalopram and fluvoxamine. We have summarised these results into initial clinical guidance for UK medical practitioners. There are several holes in existing research and these should be filled to arrive at a more complete clinical protocol for treating anxiety and depression in pregnant women.

Acknowledgements: None

Conflict of interest: *None to declare.*

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Appendix. Part 1

Paper	Type of study	Key findings/results	SSRI of interest
A, K. (2015). *Common Questions About the Pharmacologic Management of Depression in Adults. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26176368	literature review	**Pregnancy** • Depression during pregnancy is associated with premature birth and decreased initiation of breastfeeding. Antidepressant use during pregnancy has not been shown to improve these outcomes, and may increase the risk of preterm delivery compared with untreated women who have depression. • SSRIs are the most commonly prescribed antidepressants for pregnant women. • In 2005, the FDA classified paroxetine (Paxil) as pregnancy category D because of concerns about congenital cardiac malformations. More recently, however, a population-based cohort study of nearly 1 million pregnant women suggested that there is no link between first trimester antidepressant use and cardiac malformations. • In 2006, the FDA issued a health advisory for SSRI use after the 20th week of gestation because of concerns about increased risk of persistent pulmonary hypertension of the newborn (PPHN). This advisory was revised in 2011, and currently states that conflicting findings make it unclear whether use of SSRIs during pregnancy can cause PPHN. • A recent meta-analysis of five trials supported the link between late pregnancy exposure to SSRIs and PPHN, with a number needed to harm of 286 to 351.34 Studies have also suggested a correlation between antidepressant use in pregnancy and lower Apgar scores, attention-deficit/hyperactivity disorder, and speech delay, although high-quality evidence is lacking. • Conflicting findings on the association between prenatal SSRI exposure and autism. **Breastfeeding** • There is little evidence to support any causal link between antidepressant use in breastfeeding mothers and adverse effects in infants • Antidepressants transfer in low concentrations into breast milk. • Paroxetine and sertraline (Zoloft) transfer in lower concentrations than other antidepressants, and produce undetectable infant plasma levels. • Fluoxetine (Prozac) and venlafaxine produce the highest infant plasma concentrations. • Potential adverse effects in infants exposed to SSRIs via breast milk have been documented only in case reports and are recorded more often after exposure to fluoxetine and citalopram (Celexa) than other drugs. These effects are nonspecific and include irritability and decreased feeding. • There are no data on long-term neurocognitive effects.	**All SSRIs**
AJ, L. (2016). *Identification and Management of Peripartum Depression. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/27175720	literature review	• SSRIs are main treatment for moderate to severe peripartum depression - In a randomized controlled trial comparing antidepressants with community-based psychosocial intervention for peripartum depression, SSRIs were superior, with a number needed to treat of 4 at four weeks. • no substantial evidence supports the use of one SSRI over another, BUT: If the patient has a history of response to a particular SSRI, it is reasonable to use that medication initially • pregnant women often require higher doses of medications because of larger volumes of distribution • If the patient is breastfeeding, it is reasonable to consider the relative transfer of a medication into breast milk. • Moderately safe medications in the ACOG guideline correspond to infant serum medication levels that reach at least 10% of maternal serum levels. Of note, although the ACOG guideline lists fluvoxamine, nortriptyline (Pamelor), and sertraline in the safer category, the AAP places them in the next higher risk category because of serum medication levels. • clinicians should be attentive to symptoms of antidepressant toxicity in the infant, such as lethargy, irritability unresponsive to normal comfort measures, and impaired feeding.	All SSRIs
Bellantuono C, e. (2012). *The safety of escitalopram during pregnancy and breastfeeding: a comprehensive review. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23044635	Literature review	• ESC exposure seems to be significantly associated with some PC such as lower rates of live births and higher rates of newborns with low birth weight. • No short-term adverse effects in newborns were reported in the 5 studies evaluating the safety of ESC during breastfeeding. • Data coming from DEGRA Center are consistent with the literature: all pregnancy were full term, all newborns were healthy and obtained normal APGAR score; no MM or miscarriage were reported. Only one case of mild withdrawal syndrome was reported in a newborn who was also exposed to benzodiazepines and paroxetine late in pregnancy. Two infants exposed to ESC also during the lactation did not reported any adverse effects at short-term. • Data coming from published studies and from our cases seem to support the notion that ESC might be considered safe during pregnancy and breastfeeding, particularly as far as MM is concerned • There are very few cases analysed and the paucity of the studies so far published, there are no definitive conclusions	Escitalopram
Dawson AL, e. (2016). *Antidepressant Prescription Claims Among Reproductive-Aged Women With Private Employer-Sponsored Insurance - United States 2008-2013. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26821271	Secondary data analysis	• During 2008–2013, on average, 15.4% of reproductive-aged women (range = 15.3% to15.6%) filled a prescription for an antidepressant from an outpatient pharmacy each year; • The most commonly filled antidepressant prescriptions by reproductive-aged women each year were for sertraline (filled by an average of 3.3% of reproductive-aged women each year), bupropion (2.7%), citalopram (2.6%), escitalopram (2.5%), and fluoxetine (2.3%) • By age group, the percentage of reproductive-aged women who filled a prescription for an antidepressant ranged from an average of 8.3% among women aged 15–19 years to 20.9% among women aged 40–44 years. • Women aged 15–24 years represented 12.5% of women filling prescriptions for duloxetine but 24.0% of women filling prescriptions for fluoxetine • There was less variation in the proportion of women filling an antidepressant who were aged 25–34 years, ranging from 26.8% (for trazodone) to 32.9% (for sertraline) • Women aged 35–44 years accounted for the largest proportion of reproductive-aged women filling prescriptions for all common antidepressant types, including 44.0% who filled prescriptions for sertraline and 60.3% who filled prescriptions for duloxetin	Sertraline, citalopram, escitalopram, fluoxetine

Appendix. Part 2

Paper	Type of study	Key findings/results	SSRI of interest
Deligiannidis, K., Byatt, N., & Freeman, M. (2014). Pharmacotherapy for Mood Disorders in Pregnancy. *Journal Of Clinical Psychopharmacology*, *34*(2), 244-255. doi:10.1097/jcp.0000000000000087	Literature review	**Summary** • Pregnancy-associated changes in absorption, distribution, metabolism, and elimination may result in lowered psychotropic drug levels and possible treatment effects, particularly in late pregnancy. • Mechanisms include changes in both phase 1 hepatic cytochrome P450 and phase 2 uridine diphosphate glucuronosyltransferase enzyme activities, changes in hepatic and renal blood flow, and glomerular filtration rate **Specific results** • increased metabolism of SSRIs in late pregnancy may require higher dosing, especially during the third trimester to maintain clinical benefits. • **Fluoxetine:** Mean fluoxetine-metabolite ratio levels decrease between 20 to 26 weeks and 30 to 36 weeks' gestation, suggesting increased clearance during pregnancy, whereas postpartum fluoxetine-metabolite ratio levels increase, suggesting reduced clearance after delivery. higher maternal serum concentrations of fluoxetine and norfluoxetine (metabolite) in the postpartum period, compared with the third trimester, have been reported in women taking the same fluoxetine dose during both periods. • **Sertraline:** Dose increases are often required early in the third trimester to treat emergent depressive symptoms or maintain euthymia with some women experiencing increased drug metabolism from second to third trimester. • **Paroxetine**: Steadily decreasing plasma levels of paroxetine and increasing depressive symptoms can occur in pregnancy in women with the CYP2D6-extensive or ultra-rapid metabolizer genotype. Antidepressant accumulation in poor and intermediate metabolizers could potentially have adverse effects on the fetus. • **Citalopram**: Doses of citalopram result in low trough plasma concentrations and metabolites during pregnancy but a significantly higher mean methylcitalopramcitalopram metabolic ratio compared with 2 months postpartum, suggesting induced metabolism during pregnancy. Decreased level/dose ratios are associated with lowered drug efficacy and increased dose requirements in the second half of gestation. • **Fluvoxamine** - no studies found - CYP2D6 activity has been shown to be increased during the third trimester and associated with decreased plasma drug concentrations and possibly diminished efficacy. This effect may be offset by the decreased CYP1A2 activity seen throughout pregnancy.	**Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine**
Eleftheriou G, e. (2013). *Neonatal toxicity following maternal citalopram treatment. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23438790	Case report	• Late gestational exposure to citalopram, may be associated with a neonatal toxicity syndrome with immediate onset at birth or soon after birth and sometimes may be mistaken for neonatal withdrawal syndrome. • A normal weight infant was delivered at 40 weeks gestation. The mother had been taking citalopram 20 mg/day until the day of delivery. Fifteen minutes after birth, the baby became hypertonic. Neonatal serotonin toxicity due to citalopram seems the most likely mechanism, though an important differential diagnosis is a citalopram withdrawal syndrome. • Neonatal withdrawal syndrome may follow citalopram serotonin toxicity.	Citalopram
F, U. (2015). *A pharmacological approach to panic disorder during pregnancy. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26043642	Literature review	• Untreated PD seems to be associated with several negative outcomes in the pregnancy. • sertraline, citalopram, imipramine and clomipramine at low doses for pure PD, and venlafaxine appeared to be more favorable than the other potential drugs • controlled studies examining optimum dosing, efficacy of antipanic medications and risk-benefit profile of intrauterine exposure to treated or untreated PD are urgently needed.	Sertaline, Citalopram
Forsberg, L., Navér, L., Gustafsson, L., & Wide, K. (2014). Neonatal Adaptation in Infants Prenatally Exposed to Antidepressants-Clinical Monitoring Using Neonatal Abstinence Score. *Plos ONE*, *9*(11), e111327. doi:10.1371/journal.pone.0111327	Retrospective cohort study	• 'Majority of all infants born to mothers with SSRI or SNRI treatment during pregnancy are healthy in the neonatal period. Only 3% developed a severe abstinence syndrome and 22% signs of mild abstinence, the symptoms mainly arising from the central nervous system' • Seventy seven women (35%) used citalopram, 76 used (35%) sertraline, 34 (15%) fluoxetine and 33 (15%) other SSRI/SNRI. • 'Different antidepressants have different pharmacokinetic properties. This may, in theory, influence the timing of symptoms of abstinence or serotonergic overstimulation in exposed neonates. Time to peak value (NAS) was therefore analyzed but failed to show any significant differences between the groups. Individual factors such as metabolic and transporter capacity of SSRI/SNRI in mother and child as well as placenta may be of greater influence on the occurrence of maladaptation and timing of symptoms.'	Citalopram, sertraline, fluoxetine
Fraher D, e. (2016). *Citalopram and sertraline exposure compromises embryonic bone development. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26347317	Animal model	• SSRI treatment in zebrafish decreased bone mineralization, visualized by alizarin red staining and decreased the expression of mature osteoblast-specific markers during embryogenesis • 'In differentiating human MSCs, we observed a decrease in osteoblast activity that was associated with a decrease in expression of the osteoblast-specific genes Runx2, Sparc and Spp1, measured with quantitative real-time PCR (qRT-PCR). Similar to the developing zebrafish, no increase in expression of the apoptotic marker Caspase 3 was observed' • SSRIs inhibit bone development by affecting osteoblast maturation during embryonic development and MSC differentiation	Citalopram, Sertraline
Larsen ER, e. (2015). *Use of psychotropic drugs during pregnancy and breast-feeding. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26344706	Literature review	• no increased risk for miscarriage, still birth or neonatal death with SSRI use in pregnancy (did not differentiate between different SSRIs) • no overall increased risk of congenital abnormalities was found, RR 0.93 (CI: 0.85–1.02) • **Cardiac malformations:** slightly increased risk was found when cardiac malformations were included , RR 1.36 (CI: 1.08–1.71). A significant part of this signal is carried by septal defects, RR1.40 (CI: 1.10–1.77) - most studies point to paroxetine and fluoxetine (but not all studies reviewed) • atrial and ventricular septal defects were more frequent in mothers treated w/ SSRIs (but not when they were described as 'general heart malformations')-Among non-medicated women, the risk was 0.5%, whereas it was 0.8% among those taking SSRI • 'Number needed to treat, one to harm, (NNH) was calculated to 246. This means that more than 246 women must be treated with SSRI to cause one additional case of septal defect **cannot be ruled out that many septal defects were only found, because the foetuses known to have been exposed to SSRI during pregnancy were examined extra carefully**' • **Reduced foetal development and premature birth** – 'Some studies, but not all, suggest that the treatment with SSRI during pregnancy can lead to pre-mature birth and that children born at term are smaller. However, it is difficult to estimate as some studies show that untreated depression in itself may result in premature birth and low birthweight. • **Complications in connection with birth** – 'Between 15 and 30% of children whose mothers have taken a SSRI will show symptoms, which possibly are discontinuation symptoms (irritability, quivering, limpness, and trouble to suck or sleep). Symptoms cease spontaneously and require generally no treatment… In principle, the symptoms can occur in connection with all types ofSSRI, but one study has found paroxetine to be particularly frequently associated with these' • **PPHN** - risk is increased if mother is on SSRIs – 'The frequency of PPHN among non-exposed children was 1.2 per 1000, whereas among children exposed to SSRIs after week 20, it was 3 per 1000. This gives an adjusted odds ratio of 2.1 (95% CI 1.5–3.0).The risk was increased roughly in the same degree for all types of SSRI, which implies that it is a class effect…A new meta-analysis of PPHN showed that early exposure to SSRI does not increase the risk, whereas exposure late in the pregnancy (after week 20) increases the risk by a factor 2.50 (95% CI 1.32–4.73), the absolute frequency was 2.9 to 3.5 per 1000 newborns, which lead to NNH being between 286 and 351' • **Brain development and emotional development** - no correlation between SSRIs and brain development of the foetus measured with regard to intelligence and on a number of emotional and motor parameters. Studies that look at this are difficult to interpret as depression in the mother can influence these variables (by affecting the social environment).	All SSRIs

Appendix. Part 3

Paper	Type of study	Key findings/results	SSRI of interest
Myles N, e. (2013). *Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23761574	Meta-analysis	• 'Fluoxetine (OR 1.14, 95% CI 1.01–1.30) and paroxetine (OR 1.29, 95% CI 1.11–1.49) were associated with increased risk of major malformations. Paroxetine was associated with increased risk of cardiac malformations (OR 1.44, 95% CI 1.12–1.86)' • Sertraline and citalopram were not significantly associated with congenital malformation. • 'meta-analysis suggests that children exposed in utero to SSRI medications have increased odds of developing major congenital malformations, although not cardiac or minor congenital malformations BUT Subgroup analysis suggests that the aggregate effect for major malformation is driven specifically by paroxetine (OR 1.29, p=0.001) and fluoxetine (OR 1.14, p=0.04), with citalopram and sertraline exerting a non-significant impact on effect size. '	All SSRIs
N, N. (2013). *[Citalopram taken during pregnancy and the child born with Hirschsprung's disease]. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25353330	Case report	'A woman treated with citalopram during the entirety of her pregnancy bore a child with Hirschsprung's disease…Epidemiological studies confirm a correlation between pregnant women's use of SSRIs and congenital malformations of their children's digestive system, but not specifically Hirschsprung's disease. Certain limitations in these studies might explain this lack of specificity'	Citalopram
Reefhuis J, e. (2015). *Specific SSRIs and birth defects: Bayesian analysis to interpret new data in the context of previous reports. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26156519	Bayesian analysis	• Sertraline was the most commonly reported SSRI, but none of the five previously reported birth defects associations with sertraline was confirmed. • confirmed previously reported associations between right ventricular outflow tract obstruction cardiac defects in infants and maternal use of fluoxetine or paroxetine early in pregnancy, and between anencephaly or atrial septal defects in infants and maternal use of paroxetine. • confirmed associations between gastroschisis or omphalocele and paroxetine and between craniosynostosis and fluoxetine • For nine previously reported associations between maternal SSRI use and birth defect in infants, findings were consistent with no association. • High posterior odds ratios excluding the null value were observed for five birth defects with paroxetine (anencephaly 3.2, 95% credible interval 1.6 to 6.2; atrial septal defects 1.8, 1.1 to 3.0; right ventricular flu tract obstruction defects 2.4, 1.4 to 3.9; gastroschisis 2.5, 1.2 to 4.8 and omphalocele 3.5, 1.3 to 8.0) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.1 and craniosynostosis 1.9, 1.1 to 3.0). • reassuring evidence for some SSRIs but suggest that some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.	Citalopram, escitalopram, fluoxetine, paroxetine, or sertraline
Seo MK, e. (2016). *Early life stress increases stress vulnerability through BDNF gene epigenetic changes in the rat hippocampus. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26877199	Animal model	• Rat pups were separated from their dams (3 h/day from P1-P21). When the pups reached adulthood (8 weeks old), we introduced RS (2 h/day for 3 weeks) followed by escitalopram treatment. • 'both the MS and RS groups showed decreased levels of acetylated histone H3 and H4 at BDNF promoter IV, and RS exacerbated MS-induced decreases of H3 and H4 acetylation. Both the MS and RS groups had increased MeCP2 levels at BDNF promoter IV, as well as increased HDAC5 mRNA, and the combination of MS and RS exerted a greater effect on these parameters than did RS alone. In the forced swimming test, the immobility time of the MS + RS group was significantly higher than that of the RS group' • chronic escitalopram treatment recovered changes. • 'results suggest that postnatal MS and subsequent adult RS modulate epigenetic changes in the BDNF gene, and that these changes may be related to behavioral phenotype. These epigenetic mechanisms are involved in escitalopram action.'	Escitalopram
Vitale SG, e. (2016). *Psychopharmacotherapy in Pregnancy and Breastfeeding. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/28005135	Review of literature and clinical guidelines	• only paroxetine lead to an increased risk of malformations, whereas fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram and venlafaxine do not appear to increase this risk	Paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram
Yazdy, M., Mitchell, A., Louik, C., & Werler, M. (2014). Use of Selective Serotonin-Reuptake Inhibitors During Pregnancy and the Risk of Clubfoot. *Epidemiology*, *25*(6), 859-865. doi:10.1097/ede.0000000000000157	Secondary data analysis	• 'For the 2nd or 3rd lunar month of pregnancy (the relevant gestational period), SSRI use for a period of more than 30 days was higher in case mothers (5%) than control mothers (3%). After adjustment for maternal smoking and body mass index, the OR for any SSRI use and clubfoot was 1.8 (95% CI = 1.1-2.8).' • When individual SSRIs were examined, ORs were elevated for sertraline (1.6 [0.8-3.2]), paroxetine (9.2 [0.7-484.6]), and escitalopram (2.9 [1.1-7.2]). • 'data suggest an increased risk of clubfoot occurrence in relation to SSRI use. Drug-specific risks varied widely, and some estimates were unstable'	Citalopram, escitalopram, fluvoxamine, paroxetine, sertraline, fluoxetine
Widnes SF, e. (2013). *Teratogenic risk perception and confidence in use of medicines in pairs of pregnant women and general practitioners based on patient information le... - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23539202	Cross-sectional	• 'Pregnant women had significantly higher perceptions of teratogenic risks and lower confidence in use of medicines compared to GPs. ' • 'Differences in teratogenic risk perceptions and confidence in use were highest for escitalopram and lowest for dexchlorpheniramine, representing texts with different phrasing and length. Neither pregnant women nor GPs were confident in using Valeriana officinalis.' • 'Perceptions of teratogenic risks and confidence in use of medicines during pregnancy differ within pairs of pregnant women and their GP when they assess PILs. Phrasing of medicines information texts can influence teratogenic risk perceptions and thereby prescribing of medicines and adherence'	
H, M. (2012). *Prenatal exposure to selective serotonin reuptake inhibitors and infant outcome. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23042258	Literature Review	• 'Fluoxetine and paroxetine use in early pregnancy has been associated with a small increased risk for specific cardiovascular malformations in some studies, fluoxetine with ventricular septal defects and paroxetine with right ventricular outflow tract defects. The observed absolute risk for these specific malformations is small. ' • 'Data on preterm birth, low birth weight, and being small for gestational age have been conflicting; and mother's underlying depression is obviously an important confounder. ' • 'Respiratory distress and neonatal adaptation problems are common in prenatally exposed infants, and an increased risk for persistent pulmonary hypertension of the newborn has been observed in several studies.' • 'several studies have not confirmed an increased risk for adverse neurodevelopment, a recent study observed an increased risk for autism spectrum disorders in prenatally exposed offspring'	All SSRIs
Porzionato A, e. (2012). *Fluoxetine may worsen hyperoxia-induced lung damage in neonatal rats. - PubMed - NCBI . Ncbi.nlm.nih.gov*. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23059890	Animal model	• 'Hyperoxia resulted in significant reduction in alveolar density and an increase in pulmonary endocrine cells, as well as increases in muscle layer areas of bronchi and arteries.' • 'Fluoxetine treatment generated a further increase in muscularisation and did not significantly modify the hyperoxia-induced reductions in alveolar density and increases in the endocrine cells.' • 'In hyperoxia, Real-Time PCR showed a lower pulmonary expression of vascular endothelial growth factor (VEGF) with no significant changes in the expression of matrix metalloproteinases (MMP) 2 and 12.' • 'Fluoxetine did not affect VEGF or MMP-2 expression but it significantly increased MMP-12 mRNA in both normoxic and hyperoxic groups.' • 'Zymographic analysis of MMP-2 activity in bronchoalveolar fluid showed a significantly reduced MMP-2 activity in hyperoxia, while fluoxetine treatment restored MMP-2 activity to levels comparable with the normoxic group.' • 'fluoxetine may worsen bronchial and arterial muscularisation during development of BPD and may up-regulate MMP expression or activity.'	Fluoxetine

Appendix. Part 4

Paper	Type of study	Key findings/results	SSRI of interest
Grigoriadis S, e. (2017). *Antidepressant exposure during pregnancy and congenital malformations: is there an association? A systematic review and meta-analysis of the best e... - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23656855	Systematic Review & Meta-analysis	• Antidepressant exposure was not associated with congenital malformations (RR = 0.93; 95% CI, 0.85-1.02; P = .113) or major malformations (RR = 1.07; 95% CI, 0.99-1.17; P = .095). • 'increased risk for cardiovascular malformations (RR = 1.36; 95% CI, 1.08-1.71; P = .008) and septal heart defects (RR = 1.40; 95% CI, 1.10-1.77; P = .005) were found; the RR for ventral septal defects was similar to septal defects, although not significant (RR = 1.54; 95% CI, 0.71-3.33; P = .274). Pooled effects were significant for paroxetine and cardiovascular malformations (RR = 1.43; 95% CI, 1.08-1.88; P = .012).' • 'overall antidepressants do not appear to be associated with an increased risk of congenital malformations, but statistical significance was found for cardiovascular malformations.' • RRs are marginal, therefore they may be the result of uncontrolled confounders. 'Although the RRs were statistically significant, none reached clinically significant levels. '	All SSRIs
Riggin L, e. (2013). *The fetal safety of fluoxetine: a systematic review and meta-analysis. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23660045	Systematic Review & Meta analysis	• Odds ratio for major malformations associated with maternal fluoxetine use was 1.12 (95% CI 0.98 to 1.28) • Fifteen cohort studies evaluated cardiac malformation and yielded an OR of 1.6 (95% CI 1.31 to 1.95)	Fluoxetine
Kiryanova V, e. (2013). *Long-term outcomes of developmental exposure to fluoxetine: a review of the animal literature. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/24247012	Literature Review – Animal models	• 'early FLX exposure in non-human animals can alter the development of the brain in ways that are relevant to behaviour in adulthood, decreasing exploration and social interaction, and in some cases altering anxiety- and depression-like behaviours'	Fluoxetine
Sousa-Ferreira, L., Aveleira, C., Botelho, M., Álvaro, A., Pereira de Almeida, L., & Cavadas, C. (2014). Fluoxetine Induces Proliferation and Inhibits Differentiation of Hypothalamic Neuroprogenitor Cells In Vitro. Plos ONE, 9(3), e88917. doi:10.1371/journal.pone.0088917	Cellular Mechanism	• 'fluoxetine inhibits the differentiation of hypothalamic neuroprogenitor cells, as demonstrated by decreased number of mature neurons (Neu-N+ cells) and increased number of undifferentiated cells (SOX-2+ cells)' • fluoxetine-induced proliferation and maintenance of hypothalamic neuroprogenitor cells leads to changes in the mRNA levels of appetite regulator neuropeptides, including Neuropeptide Y (NPY) and Cocaine-and-Amphetamine-Regulated-Transcript (CART).' • first evidence that SSRIs affect the development of hypothalamic neuroprogenitor cells in vitro with consequent alterations on appetite neuropeptides	Fluoxetine
Rayen I, e. (2015). *Developmental exposure to SSRIs, in addition to maternal stress, has long-term sex-dependent effects on hippocampal plasticity. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25304865	Animal Model	• 'Developmental fluoxetine exposure to prenatally stressed offspring reversed the effect of prenatal stress or fluoxetine exposure alone on the number of immature neurons.' • 'Prenatal stress alone, regardless of developmental exposure to fluoxetine, markedly decreased hippocampal cell proliferation and tended to decrease new cell survival.' • 'in adult female offspring, developmental fluoxetine exposure greatly increased new cell survival and significantly decreased synaptophysin density in the granule cell layer.' • 'There are long-term effects of developmental SSRI exposure on hippocampal plasticity that is differentially affected by expose to maternal adversity and offspring sex.'	Fluoxetine
Silva AP, e. (2015). *Clinical and cytogenetic features of a Brazilian sample of patients with phenotype of oculo-auriculo-vertebral spectrum: a cross-sectional study. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25337663	Cross-sectional study	• 'Cytogenetic abnormalities were observed in three cases (13%) and consisted of: 47,XX,+mar; mos 47,XX,+mar/46,XX; and 46,XX,t(6;10)(q13; q24). ' • 'observed cases of OAVS with histories of gestational exposition to fluoxetine, retinoic acid and crack. One of our patients was a discordant monozygotic twin who had shown asymmetrical growth restriction during pregnancy'	Fluoxetine
Ewing, G., Tatarchuk, Y., Appleby, D., Schwartz, N., & Kim, D. (2015). Placental Transfer of Antidepressant Medications: Implications for Postnatal Adaptation Syndrome. *Clinical Pharmacokinetics, 54*(4), 359-370. doi:10.1007/s40262-014-0233-3	Systematic review	• 'Ultimately, from this data there is no pattern in which PNAS is related to placental transfer of antidepressant medications. In general, there is large interindividual variability for each type of antidepressant. To make the most clinically informed decisions about the use of antidepressants in pregnancy, studies that link maternal, placental and fetal genetic polymorphisms, placental transfer rates and infant outcomes are needed'	All SSRis
Morris, R., & Matthes, J. (2015). Serotonin syndrome in a breast-fed neonate. *Case Reports, 2015*(may06 1), bcr2015209418-bcr2015209418. doi:10.1136/bcr-2015-209418	Case report	• 'A late preterm presented with tachypnoea, jitteriness, irritability and low grade fever. Blood gas showed a compensated metabolic acidosis. His mother was taking the selective serotonin reuptake inhibitor (SSRI) fluoxetine, 60 mg/day, and he was exclusively breast-fed.' • 'The baby's serum level of fluoxetine on day 8 was within the adult therapeutic range and his symptoms were ascribed to fluoxetine toxicity. On changing to formula feeds, his symptoms resolved. ' • 'SSRIs are commonly administered during pregnancy, but SSRI toxicity in infants is rarely reported. It is possible that this condition is under diagnosed or, alternatively, misdiagnosed as SSRI withdrawal in breast fed infants whose mothers are on SSRIs. ' • 'There is limited research looking at serotonin excess in neonates, making case reports such as this important in our learning. Increased awareness may prompt more frequent measurements of blood levels in breast-fed infants whose mothers are on SSRIs.'	Fluoxetine
Wemakor A, e. (2015). *Selective serotonin reuptake inhibitor antidepressant use in first trimester pregnancy and risk of specific congenital anomalies: a European regist... - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26148560	Case-control study	• 'SSRI exposure in first trimester pregnancy was associated with CHD overall (OR adjusted for registry 1.41, 95% CI 1.07-1.86, fluoxetine adj OR 1.43 95% CI 0.85-2.40, paroxetine adjOR 1.53, 95% CI 0.91-2.58) and with severe CHD (adjOR 1.56, 95% CI 1.02-2.39), particularly Tetralogy of Fallot (adjOR 3.16, 95% CI 1.52-6.58) and Ebstein's anomaly (adjOR 8.23, 95% CI 2.92-23.16).' • 'Significant associations with SSRI exposure were also found for ano-rectal atresia/stenosis (adjOR 2.46, 95% CI 1.06-5.68), gastroschisis (adjOR 2.42, 95% CI 1.10-5.29), renal dysplasia (adjOR 3.01, 95% CI 1.61-5.61), and clubfoot (adjOR 2.41, 95% CI 1.59-3.65). ' • support a teratogenic effect of SSRIs specific to certain anomalies, but cannot exclude confounding by indication or associated factors	Fluoxetine, paroxetine
Dalmizrak O, e. (2016). *Fluoxetine-induced toxicity results in human placental glutathione S-transferase-π (GST-π) dysfunction. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26872722**	Pharmacokinetic	• 'Vm, at variable [CDNB] (142 ± 16 U/mg protein) was 3 times higher than the Vm obtained at variable [GSH] (49 ± 4 U/mg protein). On the other hand, the Km for CDNB was ~10 times higher than the Km for GSH (1.99 ± 0.36 mM versus 0.21 ± 0.06 mM). The IC50 value for FLU was 8.6 mM. Both at constant [CDNB] and variable [GSH] and at constant [GSH] and variable [CDNB] the inhibition types were competitive with the Ki values of 5.62 ± 4.37 and 8.09 ± 1.27 mM, respectively.'	Fluoxetine
Bravo K, e. (2016). *Perinatal Fluoxetine Exposure Impairs the CO2 Chemoreflex. Implications for Sudden Infant Death Syndrome. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/27018763**	Animal model	• 'Prenatal-perinatal fluoxetine did not affect litter size, birth weight, or the postnatal growth curve.' • 'Ventilation under eucapnic normoxic conditions was similar to that of control offspring. Fluoxetine exposure reduced ventilatory responses to hypercapnia at P8-P40 ($P < 0.001$) but not at P0-P5. At P8, it reduced hypercapnia-induced neuronal activation in raphe nuclei ($P < 0.05$) and nucleus tractus solitarius ($P < 0.01$) and the acidosis-induced increase in the respiratory frequency in brainstem slices ($P < 0.05$)' • 'Fluoxetine applied acutely on control slices did not modify their respiratory response to acidosis.' • 'We concluded that prenatal-perinatal fluoxetine treatment impairs central respiratory chemoreception during postnatal life. These results are relevant in understanding the pathogenesis of respiratory failures, such as sudden infant death syndrome, associated with brainstem serotonin abnormalities and the failure of respiratory chemoreflexes.'	Fluoxetine

Appendix. Part 5

Paper	Type of study	Key findings/results	SSRI of interest
Alwan S, e. (2016). *Safety of Selective Serotonin Reuptake Inhibitors in Pregnancy: A Review of Current Evidence. - PubMed - NCBI . Ncbi.nlm.nih.gov.* Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/27138915	Literature review	• 'we recommend that pregnant women exposed to any SSRI in early pregnancy be offered options for prenatal diagnosis through ultrasound examinations and fetal echocardiography to detect the presence of birth defects. Tapering off or switching to other therapy in early pregnancy, if appropriate for the individual, may also be considered on a case-by-case basis.' • **late exposure –** "large case–control study reported a sixfold increase in the risk of PPHN among infants born to mothers treated with an SSRI in late pregnancy. Late in utero exposure to SSRIs has been identified as a risk factor for impaired neonatal adaptation. Reported findings among newborn infants whose mothers had been treated with SSRIs prior to delivery include respiratory distress, temperature instability, feeding difficulties, jitteriness, restlessness, convulsions, rigidity, hypoglycemia, jaundice, and other symptoms of abnormal neonatal adaptation. These symptoms appear to be especially common with high-dose maternal treatment late in pregnancy, particularly with paroxetine' • **Development –** 'mixed evidence for ASD and ADHD - authors suggested that the observed risk of antidepressants in pregnancy with ASD in the infant is probably confounded by the severity of maternal illness. Mixed evidence for delayed psychomotor and fine motor development'	
EY, L. (2014). A report from #BlueJC: is prozac going to affect my baby's development? - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from **https://www.ncbi.nlm.nih.gov/pubmed/25892473**	prospective pregnancy cohort study	• Prolonged use of SSRI during pregnancy associated with lower language competence in children by age three independently of depression • Data suggest that human fetal brain development is susceptible to SSRI exposure. • The adjusted relative risk ratios of language delay were 0.86 (0.42-1.76) for short-term and 2.30 (1.21-4.37) for long-term use • Only 57% of the children exposed to SSRIs during at least two periods fell in the best language competence category, compared with 77% in children who were not exposed • Moderate delay, that is, use of two- to three-word phrases, was also more common among children exposed to SSRI during at least two periods (7%) than among unexposed children (3%) • very few children could be classified as having clinically impaired language even after long-term prenatal exposure to SSRI	All SSRIs
Marchesi C, e. (2016). Clinical management of perinatal anxiety disorders: A systematic review. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/26671104	Systematic Review	• CBT should be first line, but SSRIs can represent a first line treatment strategy, and not exclusively in cases where AnxD is refractory to CBT	SSRIs for anxiety
Potter, P., John, N., & Coffey, D. (2012). Onset of Abnormal Movements and Cardiovascular Symptoms after Acute Change in Complex Polypharmacy in a Child with Attention-Deficit/Hyperactivity Disorder and Mood Symptoms. Journal Of Child And Adolescent Psychopharmacology, 22(5), 388-392. doi:10.1089/cap.2012.2253	Case report	• Mother had taken paroxetine during the pregnancy and smoked cigarettes. • No firm conclusions about paroxetine's role	Paroxetine
Byatt, N., Deligiannidis, K., & Freeman, M. (2013). Antidepressant use in pregnancy: a critical review focused on risks and controversies. Acta Psychiatrica Scandinavica, 127(2), 94-114. doi:10.1111/acps.12042	Meta-analysis and Systematic review	• "Prior to 2005, studies had not suggested an increased risk of major congenital malformations with in utero exposure to SSRIs. These studies, as well as those since, were generally limited by insufficient power, confounding variables, concerns with the method of birth outcome classification, and limited exposure information" • "Discrepant findings have fueled confusion, and it is unclear whether un-replicated results represent true associations." • "One example of conflicting findings is the retrospective case–control studies by Alwan et al. and Louik et al. that linked the use of SSRI drugs with rare malformations. Both studies carry a risk for recall bias and have a high rate of non-responders" • "Other studies are so small that they lack statistical power to detect anything, but extreme risk increases that are unlikely to occur with SSRI exposure." • "specific patterns of congenital malformations have not been demonstrated with SSRIs across studies, and teratogenicity is usually determined by a consistent risk and pattern of malformation." • "Specific individual studies have found malformations associated with specific SSRIs as isolated reports. These include hypertrophic stenosis, congenital heart defects, and other major abnormalities with fluoxetine, omphalocele and cardiac septal defects with sertraline, and omphalocele, congenital heart defects, and neural tube defects with citalopram. Other studies, however, have not suggested an association between fluoxetine, sertraline, or citalopram and major congenital abnormalities. While the data are very limited, escitalopram has not been associated with risk of major malformation." • "Five meta-analyses have investigated the risk for major malformations in association with antidepressant use during pregnancy. Four of these studies found no statistically significant increased risk of major malformations in the first trimester of pregnancy." • PAROXETINE - "multiple studies, although not all, have found an association between prenatal paroxetine exposure and an increased risk of congenital malformations, yet the causality and magnitude of that risk are unclear", "recent meta-analysis based on research prior to 2006 found that paroxetine was associated with 1.7-fold risk increase of cardiac malformation"; "authors concluded that first-trimester paroxetine exposure is associated with an increased prevalence of combined cardiac defects [prevalence odds ratio (POR) = 1.46%; 95% CI 1.17–1.82] and aggregated defects (POR = 1.24; 95% CI 1.08–1.43)." • PNAS - "1996, Chambers et al. [35] published the first cohort study examining PNAS and found that late pregnancy exposure to fluoxetine was associated with an increased special care nursery admission rate when compared with exposure earlier in pregnancy.", "Another study that prospectively compared neonatal complications in infants found that third-trimester paroxetine exposure had a high rate of neonatal complications compared with controls (22% vs. 5.5%, respectively)"; "PNAS appears to be multifactorial in nature, with late pregnancy antidepressant use accounting, in part, for neonatal symptoms." • PPHN - Although studies have also reported an association between mode of delivery and PPHN, several were small and lacked control groups.	All SSRIs
Nagai M, e. (2017). Characterization of transplacental transfer of paroxetine in perfused human placenta: development of a pharmacokinetic model to evaluate tapered do... - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/24046332	Pharmacokinetic	• Paroxetine showed a larger distribution volume in placental tissue and a smaller transplacental transfer as compared with antipyrine, a passive diffusion marker.	Paroxetine
Meunier MR, e. (2013). Use of antidepressant medication in the United States during pregnancy, 2002-2010. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/24185537	Retrospective	• Despite controversy over possible negative effects, prescribing of antidepressants during pregnancy increased between 2002 and 2010 • Prescribing of paroxetine, likely in response to warnings by the U.S. Food and Drug Administration, dropped dramatically	All SSRIs, Paroxetine
Ban, L., Gibson, J., West, J., Fiaschi, L., Sokal, R., & Smeeth, L. et al. (2014). Maternal depression, antidepressant prescriptions, and congenital anomaly risk in offspring: a population-based cohort study. BJOG: An International Journal Of Obstetrics & Gynaecology, 121(12), 1471-1481. doi:10.1111/1471-0528.12682	Cohort study	• "Absolute risks of MCA were 2.7% (95% confidence interval, 95% CI, 2.6-2.8%) in children of mothers without diagnosed depression, 2.8% (95% CI 2.5-3.2%) in children of mothers with unmedicated depression, and 2.7% (95% CI 2.2-3.2%) and 3.1% (95% CI 2.2-4.1%) in children of mothers with SSRIs or TCAs, respectively. • Compared with women without depression, MCA overall was not associated with unmedicated depression (aOR 1.07, 95% CI 0.96-1.18), SSRIs (aOR 1.01, 95% CI 0.88-1.17), or TCAs (aOR 1.09, 95% CI 0.87-1.38). • Paroxetine was associated with increased heart anomalies (absolute risk 1.4% in the exposed group compared with 0.8% in women without depression; aOR 1.78, 95% CI 1.09-2.88), which decreased marginally when compared with women with diagnosed but unmedicated depression (aOR 1.67, 95% CI 1.00-2.80)."	All SSRIs

Appendix. Part 6

Paper	Type of study	Key findings/results	SSRI of interest
Dinlen N, e. (2014). Treacher Collins syndrome with multiple congenital heart defects after paroxetine exposure: case report. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/24783649	Case report	• Prenatal paroxetine exposure may enhance the risks of major malformation, particularly cardiac defects	Paroxetine
McDonagh MS, e. (2014). Depression drug treatment outcomes in pregnancy and the postpartum period: a systematic review and meta-analysis. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25004304	Systematic review & Meta-analysis	• Low-strength evidence suggested neonates of pregnant women with depression taking SSRIs had higher risk of respiratory distress than neonates of untreated women (13.9% compared with 7.8%; P<.001) No difference in risk of neonatal convulsions (0.14% compared with 0.11%; P=.64) or preterm birth (17% compared with 10%; P=.07). • Evidence was insufficient for other outcomes, including depression symptoms, functional capacity, breastfeeding, and infant and child development.	All SSRIs
Charlton RA, e. (2015). Selective serotonin reuptake inhibitor prescribing before, during and after pregnancy: a population-based study in six European regions. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25352424	Descriptive	• In the year preceding pregnancy, prevalence of SSRI prescribing was highest in Wales [9.6%; 95% confidence interval (CI95), 9.4-9.8%] and lowest in Emilia Romagna (3.3%; CI95 , 3.2-3.4%). • During pregnancy, SSRI prescribing had dropped to between 1.2% (CI95 , 1.1-1.3%) in Emilia Romagna and 4.5% (CI95 , 4.3-4.6%) in Wales. • higher SSRI prescribing rates in the UK, compared with other European regions • Paroxetine was more commonly prescribed in the Netherlands and Italian regions than in Denmark and the UK.	All SSRIs
Bérard, A., Iessa, N., Chaabane, S., Muanda, F., Boukhris, T., & Zhao, J. (2016). The risk of major cardiac malformations associated with paroxetine use during the first trimester of pregnancy: a systematic review and meta-analysis. British Journal Of Clinical Pharmacology, 81(4), 589-604. doi:10.1111/bcp.12849	Systematic Review & Meta-analysis	• Compared with non-exposure to paroxetine, first trimester use of paroxetine was associated with an increased risk of any major congenital malformations combined (pooled OR 1.23, 95% CI 1.10, 1.38; n = 15 studies), major cardiac malformations (pooled OR 1.28, 95% CI 1.11, 1.47; n = 18 studies), specifically bulbus cordis anomalies and anomalies of cardiac septal closure (pooled OR 1.42, 95% CI 1.07, 1.89; n = 8 studies), atrial septal defects (pooled OR 2.38, 95% CI 1.14, 4.97; n = 4 studies) and right ventricular outflow track defect (pooled OR 2.29, 95% CI 1.06, 4.93; n = 4 studies). • trend towards increased risk	Paroxetine
Müller MJ, e. (2013). Serotonergic overstimulation in a preterm infant after sertraline intake via breastmilk. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23249132	Case report	• A preterm infant was exposed to sertraline in utero and via breastmilk. • Beyond the first 48 hours after birth, the infant developed increasing clinical signs of serotonergic overstimulation associated with substance intake via breastmilk, until breastfeeding was discontinued on postnatal Day 9. • Despite low calculated daily substance intake via breastmilk, the serum substance levels of the preterm infant were within the therapeutic range of adults. Serotonergic overstimulation may be explained by the limited metabolic capacity of the infant and the immaturity of the blood-brain barrier	Sertraline
LH, Chaudron. (2013). Complex challenges in treating depression during pregnancy. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/23288385	General Review	• "Similar to the effects of depression on the fetal environment, antidepressants have the potential to affect the fetus in many ways, including pregnancy loss (38, 39), growth reduction (reduced head growth, low birth weight, small for gestational age) (25, 40–43), preterm birth (43, 44), and malformations (43, 45–50). • In addition, antidepressants may have an impact on neonates, as suggested by recent studies of neonatal adaption (41, 51), neonatal and infant motor development (52, 53), persistent pulmonary hypertension (45, 54–57), and infant and child behavioral effects (58–60). • Finally, antidepressants may also affect the mother's health (61, 62). While some of these studies have shown associations between antidepressant use and outcomes, often others have not. It is difficult to determine cause and effect, as well as the increased likelihood and absolute risk, on the basis of these studies."	All SSRIs
TA, Furukawa. (2017). Adverse effects of antidepressants during pregnancy. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25326493	Case report and literature review	• "strong data to suggest that antidepressants overall and sertraline in particular are not associated with increased risk of cardiac malformations in the newborns" • "theoretically maximum harm could be one additional malformation per 9000 pregnant women taking antidepressants." • "continuing the antidepressant may decrease the possibility of depression recurrence from 80–60% to 40–30%."	Sertraline
Bérard A, e. (2015). Sertraline use during pregnancy and the risk of major malformations. - PubMed - NCBI . Ncbi.nlm.nih.gov. Retrieved 13 August 2017, from https://www.ncbi.nlm.nih.gov/pubmed/25637841	Cohort Study	• 18,493 eligible pregnancies, 366 were exposed to sertraline, 1963 to other SSRIs • Sertraline use was not statistically significantly associated with risk of overall major malformations when compared to nonuse of antidepressants. • sertraline exposure was associated with an increased risk of atrial/ventricular defects specifically (risk ratio [RR], 1.34; 95% CI, 1.02–1.76; 9 exposed cases), and craniosynostosis (RR, 2.03; 95% CI, 1.09–3.75; 3 exposed cases). • Exposure to SSRIs other than sertraline during the first trimester of pregnancy was associated with craniosynostosis (RR, 2.43; 95% CI, 1.44–4.11; 19 exposed cases), and musculoskeletal defects (RR, 1.28; 95% CI, 1.03–1.58; 104 exposed cases).	All SSRIs, Sertraline

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