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 SSRIs 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 SSRI 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 remain 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 - escitalopram - fluvoxamine - sertraline - malformations - teratogenic - PPHN - PNAS

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 (Einaron 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 (Borret 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-authorisation (NICE 2014). The current guidance states no psychotropic medications that have UK marketing authorisation (NICE 2014). The current guidance states that the prescriber must take full responsibility for off-authorisation (NICE 2014). The current guidance states that the prescriber must take full responsibility for off-authorisation (NICE 2014).

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 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-authorisation (NICE 2014). The current guidance states that the prescriber must take full responsibility for off-authorisation (NICE 2014). The current guidance states that the prescriber must take full responsibility for off-authorisation (NICE 2014).

The treatment prioritises the woman’s well-being and 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 (Wisnes 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 SSRI) 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 (Altschuler 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, Reehuis 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 SSRIs 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. SSRIs 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 (PHPHN) 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; Reehuis 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-adrenal (HPA) axis. Normally, levels of gonadal hormones and progesterone increase during pregnancy. Placental corticotropin-releasing hormone (CRH), cortisol, human chorionic gonadotropin (HCG), prolactin, ȕ-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 varying extents. Average fluoxetine metabolite ratio levels decrease between 20 to 26 weeks, and between 30 to 36 weeks’ gestation (Deligiannidis et al.
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 (Deli-giannidiset 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 (Grigo-riadi set 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. Summary results

<table>
<thead>
<tr>
<th></th>
<th>Prenatal effects</th>
<th>Perinatal outcome</th>
<th>Malformations – GI, neuro</th>
<th>Cardiac malformations</th>
<th>PNAS*</th>
<th>PPIN</th>
<th>Autism</th>
<th>ADHD</th>
<th>Neurological development/ fine motor skills</th>
<th>SUMMARY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>No increased risk for miscarriage</td>
<td>Mixed evidence for Low birth weight, preterm birth and small for gestational age</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed evidence - insignificant association with negative outcomes. Also very low concentrations in breast milk.</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>No increased risk for miscarriage</td>
<td>Mixed evidence for Low birth weight, preterm birth and small for gestational age</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed evidence - insignificant association with negative outcomes</td>
<td></td>
</tr>
<tr>
<td>Escitalopram**</td>
<td>No increased risk for miscarriage</td>
<td>Mixed evidence for Low birth weight, preterm birth and small for gestational age</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed evidence – insignificant association with negative outcomes; also lack of studies</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>No increased risk for miscarriage</td>
<td>Mixed evidence for Low birth weight, preterm birth and small for gestational age</td>
<td>Neural tube defects - Anencephaly, Gastrochisis, Omphalocele</td>
<td>Septal defects - RV outflow obstruction</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Repeated associations with significant malformations, particularly cardiac defects</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>No increased risk for miscarriage</td>
<td>Limited evidence</td>
<td>Limited evidence</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Not enough data to inform decision-making</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>No increased risk for miscarriage</td>
<td>Mixed evidence for Low birth weight, preterm birth and small for gestational age</td>
<td>Craniosynostosis</td>
<td>RV outflow obstruction - VSDs &amp; Tetralogy of Fallot</td>
<td>Yes</td>
<td>Yes</td>
<td>Mixed</td>
<td>Mixed</td>
<td>Repeated associations with significant malformations</td>
<td></td>
</tr>
</tbody>
</table>
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, paroxetine, sertraline, 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 SSRI 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 summary 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 gastrochisis 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; gastrochisis 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, prematurely 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 therapeutic effect. 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.

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 socio-economic 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 (sertraline, 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 (significantly 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.

Contribution of individual authors:
First authors: Kate Womersley & Katherine Ripullone
Supervisor: Mark Agius

References


47. Leung EY: A report from #BlueJC: is prozac going to affect my baby’s development? BJOG 2015; 122:866.
## Appendix. Part 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Key Findings/Results</th>
<th>SSRIs Associated</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. L. (2017). Common Questions about the Pharmacological Management of Depression in Adults. - Published in JNC, Klini, Health mkr.</td>
<td>Literature review</td>
<td>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.</td>
<td>All SSRIs</td>
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<tr>
<td></td>
<td></td>
<td>Antidepressants are the most commonly prescribed antidepressants for pregnant women.</td>
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<td>In 2005, the FDA issued a public health advisory for SSRI use after the 2003 WHO statement because of concerns about potential case reports. 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 case reports.</td>
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<td>In 2009, the FDA issued a health advisory for SSRI use after the 2009 WHO statement because of concerns about increased risk of permanent pulmonary hypertension in newborns (PPIH). This advisory was revised in 2011, and currently states that umbilical findings should not be misinterpreted as evidence of SSRI exposure during pregnancy can cause PPHN.</td>
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<td>A recent meta-analysis of five trials supported the link between late exposure to SSRI's and PPHN. With these trials combined, there is evidence that PPHN is seen in recipients of SSRI's during pregnancy.</td>
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<td>Outconflicting findings on the association between prenatal SSRI exposure and outcomes.</td>
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<td></td>
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<td>Breastfeeding:</td>
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<td></td>
<td>There is little evidence to support any causal link between antidepressant use in breastfeeding mothers and adverse effects in infants.</td>
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<td></td>
<td></td>
<td>Antidepressants may transfer to low concentrations in breast milk.</td>
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<td></td>
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<td>Paroxetine and sertraline (Citalopram) transfer to lower concentrations than other antidepressants, and produce measurable breast tumor levels.</td>
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<td>Fluoxetine (Prozac) and venlafaxine produce the highest breast tumor concentrations.</td>
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<td>Potential adverse effects in infants exposed to SSRIs via breast milk have been documented only in case reports.</td>
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<td></td>
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<td>There is a need for long-term neurodevelopmental effects.</td>
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<tr>
<td>A. L. (2018). Identification and Management of Postpartum Depression. - Published in JNC, Klini, Health mkr.</td>
<td>Literature review</td>
<td>SSRIs are a main treatment for severe postpartum depression. It is recommended that all pregnant women and breastfeeding mothers are treated with antidepressants, regardless of whether or not they are breastfeeding. Cases with depression or postpartum psychosis have a lower risk of responsiveness.</td>
<td>All SSRIs</td>
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<td>In addition to evidence supporting the use of one SSRIs over another, ECT. If the patient has a history of</td>
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<td>response to a particular SSRIs, it is reasonable to use that medication initially.</td>
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<td></td>
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<td>Antidepressants may require higher doses of medications because of larger volumes of distribution.</td>
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<td>If the patient is breastfeeding, it is reasonable to consider the relative transfer of a medication into breast milk.</td>
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<td>Moderately safe medications in the American Academy of Pediatrics (AAP) guidelines can be considered safe seroquel levels that reached 10% of maternal serum levels. Often, although the AAP guideline does not classify all antidepressants as safe, it is a guide for a specific category, the AAP places these in the most low-risk category.</td>
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<td>Antidepressants may cause symptoms of antidepressant toxicity in the infant, such as lethargy, irritability, or severe neonatal depression, and impaired feeding.</td>
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<tr>
<td>P. L. (2018). The safety of escitalopram during pregnancy and breastfeeding: a comprehensive review. - Published in JNC, Klini, Health mkr.</td>
<td>Literature review</td>
<td>EDC exposure seems to be significantly associated with some PC and lower rates of breastfeeding. There is no evidence that breastfeeding and low birth weight are related to the use of escitalopram.</td>
<td>Escitalopram</td>
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<td></td>
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<td>Sertraline and escitalopram are recommended for breastfeeding. There is no evidence of significant differences in the safety and efficacy of escitalopram.</td>
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<td>Data coming from ESCGBF center are consistent with the literature. All women were full term, all newborns were healthy, and no misdiagnosis were reported. Only one case of mild withdrawal were reported in a newborn who was also exposed to benzodiazepines and born at term in pregnancy. Two infants exposed to escitalopram also developed an infantile disorder from exposure, as shown by the following data:</td>
<td></td>
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<tr>
<td>E. A. (2018). Antidepressant Prescribing Choices Among Reproductive-Aged Women Using Primary Health Insurance - United States 2006-2016. - Published in JNC, Klini, Health mkr.</td>
<td>Secondary data analysis</td>
<td>There was a 29% increase in the proportion of women filling an antidepressant prescription for an antidepressant class as a prescription for an antidepressant from an index antidepressant class as an index antidepressant class of antidepressant.</td>
<td>Sertraline, citalopram, escitalopram, fluoxetine</td>
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<td>Data coming from the CDCH were consistent with the literature. All women were full term, all newborns were healthy, and no misdiagnosis were reported. Only one case of mild withdrawal were reported in a newborn who was also exposed to benzodiazepines and born at term in pregnancy. Two infants exposed to escitalopram also developed an infantile disorder from exposure, as shown by the following data:</td>
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<td>There was a 29% increase in the proportion of women filling an antidepressant prescription for an antidepressant</td>
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<td>There was a 29% increase in the proportion of women filling an antidepressant prescription for an antidepressant</td>
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<td>There was a 29% increase in the proportion of women filling an antidepressant prescription for an antidepressant</td>
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Appendix. Part 2

Kate Womersley, Katherine Ripullone & Mark Agius: 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
Psychiatria Danubina, 2017; Vol. 29, Suppl. 3, pp 629-644

Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of study</th>
<th>Key findings/results</th>
<th>SSRIs of concern</th>
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<tbody>
<tr>
<td>Dellaportas, K., Brat N., &amp; Prenov, M. (2014). Pharmacotherapy for Mood Disorders in Pregnancy. Journal of Clinical Psychopharmacology, 34(2), 244-255. doi: 10.1097/JCP.0b013e3182e60667</td>
<td>Literature review</td>
<td>- Pregnancy-associated changes in absorption, distribution, metabolism, and elimination may result in lowered psychotrophic drug levels and possibly treatment failure, particularly in late pregnancy. - Mechanisms for changes in both plasma 1 hepatic and brain drowsiness, dizziness, blurred vision, and impaired cognitive function.</td>
<td>Fluoxetine, Sertraline, Paroxetine, Citalopram, Fluvoxamine</td>
</tr>
</tbody>
</table>

Appendix. Part 2


Case report | Late-onset exposure to cholinesterase inhibitors may be associated with a nonmelanoma skin cancer and may be related to nonmelanoma skin cancer. A long-term weight loss was defined 40 weeks gestation. The mother had been taking cholinesterase inhibitor for more than 2 months postpartum, with the indication for treatment during pregnancy. Increased levels of oxytocin are associated with lowered drug efficacy and increased disease progression in the second half of gestation. | Cholinesterase |


Literature review | Unrelated events seem to be associated with nonmelanoma skin cancer in the second half of gestation. A significant number of oxytocin was not significantly different between the groups. Individual factors such as maternal and infant characteristics of nonmelanoma skin cancer in the second half of gestation. | Cholinesterase |


Retrospective cohort study | Majority of all infants born to mothers with SSRI or SNRI treatment during pregnancy are healthy in the neonatal period. Only 1% developed severe neonatal abstinence syndrome and 2% infants of maternal abstinence, the symptoms mainly arising from the central nervous system. | Cholinesterase, Serotonin, Noradrenaline, Dopamine |


Animal model | SSRI treatment in rat infants decreased serum serotonin, but had little effect on serum serotonin and decreased the expression of serotonin transporter-Specific markers during development. | Cholinesterase, Serotonin, Noradrenaline, Dopamine |


Literature review | - an increased risk for miscarriage, stillbirth or neonatal death with SSRI use in pregnancy did not differ from the one for different SSRIs. - an increased risk of congenital anomalies was found, RR: 1.03 (CI: 1.01 – 1.05). | All SSRIs |
<table>
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<tr>
<th>Title</th>
<th>Type of study</th>
<th>Key findings/research results</th>
<th>SRM of interest</th>
</tr>
</thead>
</table>
| Moya et al. (2013)                                                    | Meta-analysis                                                                  | + Fluoxetine (CB 1.34, 95% CI 0.66–1.31) and paroxetine (CB 1.29, 95% CI 1.11–1.50) were associated with increased risk of major malformations. Paroxetine was associated with increased risk of cardiac malformations (OR 1.41, 95% CI 1.12–1.80).  
+ Sertraline and citalopram were not significantly associated with congenital malformations. + Tests analysis suggested that children exposed to in utero SSRIs medications had increased odds of developing major congenital malformations, although cardiac or minor congenital malformations but Subgroup analysis suggested that the aggregate effect for major malformations is driven specificity by paroxetine (CB 1.27, 95% CI 0.70–2.31) and fluoxetine (CB 1.14, 95% CI 0.38–3.08), with citalopram and sertraline creating a non-significant effect on sex risk. | All SSRIs        |
| N. K. (2013)                                                          | Case report                                                                    | A woman treated with citalopram during the entirety of her pregnancy bore a child with Hirschspring’s disease. + A prospective study confirmed a correlation between pregnant women’s use of SSRIs and congenital malformations of their children’s digestive system, but not specifically Hirschspring’s disease. Certain limitations in these studies might explain this lack of specificity | Citalopram      |
| Reddick et al. (2013)                                                 | Bayesian analysis                                                              | + Paroxetine was the most commonly reported SSRI, but none of the five previously reported both defects associations with citalopram 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 nonsyndromic or isolated septal defects in infants and maternal use of paroxetine. + Confirmed associations between genitourinary or umbilical defects and paroxetine and between cardiomyopathy and fluoxetine.  
+ Forantin previously reported associations between maternal SSRI use and birth defects in infants, findings were consistent with an association. + High posterior odds ratios excluding the null value were observed for birth defects with paroxetine (0.73, 95% credible interval 0.61–0.86), right ventricular outflow tract obstruction defects 2.14, 1.4 to 3.9; gynecomastia 2.75, 1.2 to 6.18 and emphysema 1.53, 1.3 to 1.80) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.5 and cardiomyopathies 1.51, 1.1 to 2.0). + Cumberland incidence for some SSRIs but suggests that birth defects occur 2.5 to 3 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy. | Citalopram, fluoxetine, paroxetine, or sertraline |
| Seo et al. (2014)                                                      | Animal model                                                                   | + Rat pups were separated from their dams (3 days following birth). When the pups reached adulthood (8 weeks old), we introduced RS (2 mg/kg for 3 weeks) followed by escitalopram treatment.  
+ Both the MS and RS groups showed decreased levels of intestinal histone H1 and H4 (DNMT) promoter IV, and B-cell associated MS reduced decrease of H1 and H4 acetylation. Both the MS and RS groups had increased MHC class II levels at increased (DNMT) DNA, while the MS group showed a greater effect than the values parameters than those rats alone. In the immunostaining, the positivity rate of MS vs RS groups was significantly higher than that of the RS group.  
+ Chronic escitalopram treatment rescued changes.  
+ Results suggest that mesial MS and subsequent adult MS model epigenetic changes in the DNMT4 gene, and that these changes may be related to behavioral phenotype. These epigenetic mechanisms are involved in escitalopram action. | Escitalopram      |
| Vikale SG. (2016)                                                     | Review of literature and clinical guidelines                                    | Only paroxetine lead to an increased risk of malformations, whereas fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram and escitalopram have no apparent risk to increase the risk.  
+ Paroxetine, fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram. | Paroxetine       |
| Vassy M, Mitchell A, Leadh C, & Wirten M. (2014)                     | Secondary data analysis                                                        | For the 2nd or 3rd leaf of pregnancy (the relevant gestational period), SSRI use for a period of more than 4 weeks was higher in cases mothers (%) than control mothers (%). After adjustment for maternal smoking and body mass index, the OR for any SSRI use and childbirth was 1.89 (95% CI: 1.12–3.19).  
+ When individual SSRI were examined, ORs were elevated for sertraline (1.6 [95% CI: 1.0–2.8]), paroxetine (9.2 [9.74–63]), and escitalopram (2.5 [1.7–3.7]). + Data suggest an increased risk of childhood occurrence in relation to SSRI use. Drug-specific risks varied widely, and some estimates were unreliable. | Citalopram, fluoxetine, escitalopram, paroxetine, fluvoxamine, sertraline, citalopram |
| Wilkens SF. et al. (2010)                                             | Cross-section/mixed model                                                      | Prepregnant women had significantly higher perceptions of therapeutic risks and lower confidence in use of medicine compared to CPs.  
+ Differences in therapeutic risk perceptions and confidence in use were highest for escitalopram and lowest for desipramine, representing tests with different profiles and lengths. Neither pregrenant women using CPs were more confident in use Valium efficacies.  
+ Perceptions of therapeutic risks and confidence in use of medications during pregnancy differ within pairs of pregnant women and their CPs when they receive PPA. PPIs of effective information can influence therapeutic risk perceptions and thereby prescribing of medications and their harms. | All SSRIs         |
| H. M. (2012)                                                          | Literature Review                                                              | Fluoxetine and paroxetine use in early pregnancy has been associated with a small increased risk for specific cardiac and musculoskeletal malformations in some studies, fluoxetine with ventricular septal defects and paroxysm with atrial septal defects. The observed absolute risk for these specific malformations was small.  
+ Data on premenopausal, low birth weight, and being small for gestational age may be conflicting, and mother’s smoking depression is obviously an important confounder.  
+ Temporaneous difficulties and neonatal adaptation problems are common in prenatally exposed infants, and an increased risk for peripartum palsy syndrome of the neonate has been observed in several studies.  
+ Ultrasound studies have not confirmed an increased risk for adverse neurodevelopmental, a recent study observed an increased risk for autism spectrum disorders improperly exposed offspring. | All SSRIs         |
| Portimano A. et al. (2012)                                           | Animal model                                                                   | + Hypereactivity in significant reduction in overall body mass and an increase in pulmonary cardiovasal cells, as well as increases in mouse heart mass.  
+ Fluoxetine treatment provided further increase in mass and did not significantly modify the hypereactivity induced reductions in body fat mass and thus increases in the mice cells.  
+ In hypoxia, H2O2 40% PFC showed a lower pulmonary expression of vascule endothelial growth factor (VEGF) with no significant changes in the expression of matrix metalloproteinase (MMP) 2 and 12.  
+ Fluoxetine induced effect VEGF and MMP-2 expression but it significantly increased MMP-12 Na+.  
+ Both ssaemic and hypertensive groups.  
+ Cardioprotective activity of MPP-2 activity in bronchial fluid showed a significant reduction of MMP-2 activity in hypertensive, while fluoxetine treatment restored MMP-2 activity to levels comparable with the ssaemic group.  
+ Fluoxetine may worsen bronchial and arterial malformations during development of BPD and may up-regulate MMP expression or activity. | Fluoxetine       |
Appendix. Part 4


Rayon L, et al. (2013). Developmental exposure to SSRIs, in addition to maternal stress, has long-term adverse effects on hippocampal plasticity. - Psychiatr Danubina, 2013; 25, Suppl. 3, pp 81-91


Rayon L, et al. (2013). Developmental exposure to SSRIs, in addition to maternal stress, has long-term adverse effects on hippocampal plasticity. - Psychiatr Danubina, 2013; 25, Suppl. 3, pp 81-91


Appendix.

Part 5


Pharmacokinet

Paroxetine showed a larger distribution volume in placental tissue and a small or transplacental transfer as compared with antipyrine, a passive diffusion marker. All SSRI, Paroxetine


Describing

Despite controversy over possible negative effects, prescribing of antidepressants during pregnancy increased between 2002 and 2016. All SSRI, Paroxetine


Colhod study

"Absence of risk of MAC was 3% (95% confidence interval, 1.9% to 4.2%) in children of mothers without antidepressant exposure, and 2.2% (95% CI 1.9-2.4%) in children of mothers with antidepressant exposure. All SSRI, Paroxetine"
### Appendix. Part 6

<table>
<thead>
<tr>
<th>Page</th>
<th>Type of study</th>
<th>Key findings/results</th>
<th>SSRI of interest</th>
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</thead>
<tbody>
<tr>
<td>644</td>
<td>Case report</td>
<td>Premature paroxysmal exposure may enhance the risks of major malformation, particularly cardiac defects</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>644</td>
<td>Systematic review &amp; Meta-analysis</td>
<td>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&lt;0.001) No difference in risk of major malformations (1.4% compared with 0.1%; P=0.14) or preterm birth (17% compared with 10%, P=0.27). Evidence was insufficient for other outcomes, including depression symptoms, functional capacity, breastfeeding, and infant and child development.</td>
<td>All SSRIs</td>
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<td>644</td>
<td>Descriptive</td>
<td>In the year preceding pregnancy, prevalence of SSRIs prescribing was higher in Wales (15%: 95% confidence interval (CI) 9–21%) and lowest in Emilia-Romagna (0.3%; CI 0–3.9%). During pregnancy, SSRIs prescribing had dropped to between 1% (CI 0.5–1.3%) in Emilia-Romagna and 4.3% (CI 3.4–5.6%) in Wales. Higher SSRIs 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.</td>
<td>All SSRIs</td>
</tr>
<tr>
<td>644</td>
<td>Case report</td>
<td>Premature 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 3. Despite low calculated daily substance intake via breastmilk, the serum substance levels of the premature 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.</td>
<td>Sertraline</td>
</tr>
<tr>
<td>644</td>
<td>General Review</td>
<td>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 (SGA) (25–40%), preterm birth (43–48%), and malformations (43–48%). In addition, antidepressants may have an impact on neonates, as suggested by recent studies of neonatal ablation (41–51), neonatal and infant motor development (52–53), persistent pulmonary hypertension (44–54–57), and infant and child behavioral effects (56–60). 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.</td>
<td>All SSRIs</td>
</tr>
<tr>
<td>644</td>
<td>Case report and literature review</td>
<td>&quot;Strong data to suggest that antidepressants overall and sertraline in particular are not associated with increased risk of major malformations in the newborns&quot; &quot;Theoretically maximum harm could be one additional malformation per 1000 pregnant women taking antidepressants.&quot; &quot;Continuing the antidepressant may decrease the possibility of depression recurrence from 60–65% to 40–53%.”</td>
<td>Sertraline</td>
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Lady Margaret Road, Cambridge, UK
E-mail: kw310@cam.ac.uk