What challenges do clinicians face when prescribing psychotropic medication in pregnancy?

Perinatal Psychiatry Essay 2013

Alexandra Nowbar

5th year medical student

Word count: 2924

Alexandra.nowbar09imperial.ac.uk

Table of Contents

Introduction

Mental disorder in pregnancy is a significant public health challenge. Data from the 2000-2002 Confidential Enquiries into Maternal Deaths found that suicide was the leading cause of maternal deaths(1) and, while the data for 2006-2008 shows this is no longer the case, suicide remains one of the major causes of maternal death(2). Depression and anxiety are particularly prevalent in pregnancy(3,4).

Mental disorders may be treated with psychotropic medications such as anti-depressants, mood stabilisers and antipsychotics which have a myriad of possible adverse effects in pregnancy including preterm birth, birth defects and poor neonatal adaptation. Risks due to the mental disorder itself can be as worrying as or more worrying than the risks of the medications for example, preterm birth, pre-eclampsia and heavy use of alcohol(5-7). The clinician must balance the risks of the specific individual's illness with the risks of taking the relevant medication. Three scenarios based on real patients are shown in Table 1 to illustrate the potential issues.

Table 1. Dilemmas about psychotropic medication in pregnancy based on real patients

Case 1: Maria

Maria is a 19 year old lady admitted to a mental health unit and found to be 19 weeks pregnant. This is thought to be an episode of acute and transient psychosis. She has no previous psychiatric history. She does not currently have capacity to make a decision about treatment. Should she be started on medication?

Case 2: Sarah

Sarah is a 39 year old with a diagnosis of bipolar affective disorder. She is on lithium and olanzapine. When manic she binge drinks but she rarely drinks otherwise. She is planning to get pregnant. Should the medication be continued?

Case 3: Alice

Alice is a 23 year old with a history of depression, self-harm and impulsive behaviour. She has been on paroxetine for a year but has just found out she is 10 weeks pregnant. Should the paroxetine be stopped?

Effects of mental health disorders in pregnancy

Depression, bipolar disorder, affective psychosis and schizophrenia are all associated with low birth weight and preterm birth(7-10). The most commonly occurring mental disorders in pregnancy, depression and anxiety, are associated with poor obstetric, foetal and neonatal outcomes(11). Furthermore, prenatal depression is a risk factor for post-partum depression(12). Maternal depression may have a significant impact on the behaviour and development of the infant(13). Table 2 describes many possible links between features of mental disorders and harm to mother and baby.

Table 2. Features of mental disorders which may have adverse effects in pregnancy

	Feature	Possible adverse consequences
Biological	Malnourishment	Low birth weight
	Lack of sleep	Preterm birth, difficult labour
	Stress	Pre-eclampsia
Psychological	Suicidal ideation	Suicide
	Obsessive thoughts	Infanticide
	Low mood	Postpartum depression, poor maternal attachment to infant
	Delusions e.g. denial of pregnancy	Inadequate weight gain, no recognition of signs of labour
Social	Non-compliance with medication e.g. folic acid	Neural tube defects
	Non-attendance to appointments	Late detection of complications
	Illicit drug use e.g. cocaine, cannabis	Birth defects
	Alcohol use	Foetal alcohol syndrome
	Loss of inhibitions e.g. unprotected sex	Congenital infections
	Antisocial behaviour	Social isolation
	Unemployment	Financial difficulties
	Smoking	Preterm birth, low birth weight, obstetric complications

These risks are a compelling argument for treating mental disorders in pregnancy but there is evidence that psychotropic medications are not always effective at reducing these risks. Antidepressants may prevent relapse of major depression(14) or they may not(15) and they may increase or decrease the risk of pre-eclampsia in depression in pregnancy(6,16). Similarly it is unclear whether mood stabilisers for bipolar disorder or antipsychotics for schizophrenia improve outcomes in pregnancy(17,18).

Safety of psychotropic medications in pregnancy

Prescription of psychotropic medications in pregnancy is a highly emotive topic, particularly because of the risk of birth defects. Many perceive psychotropic medications to be highly teratogenic. Over 80% of women rated as "very important" the following three concerns about use of psychopharmacological medication in pregnancy: harm to the foetus, infant development and long-term effect on the child(20).

Antidepressants

Antidepressants are commonly prescribed in pregnancy(21) and selective serotonin reuptake inhibitors (SSRIs) are the most commonly used. Many women stop taking their antidepressants before or after they get pregnant; recently a large cohort study found that 75% of women who filled antidepressant prescriptions before pregnancy discontinued use before or during the first trimester(22). Their perception of a high level of risk may not be accurate.

Birth defects are one of the most feared risks of antidepressant use in pregnancy but results of meta-analyses have been varied. One meta-analysis found an association between antidepressant use and cardiovascular malformations but no association with congenital malformations overall(23). Another meta-analysis synthesized data on individual SSRIs and found that fluoxetine and paroxetine are associated with increased risk of major malformations and paroxetine with cardiac malformations while sertraline and citalopram are not associated with congenital malformations(24). The risk of birth defects is thought to be highest with antidepressant use in the first trimester as the foetus is in a stage of early development. The background risk of birth defects has been stated to be 3 in 100 and paroxetine has been shown to raise the risk to 4 in 100(25). Paroxetine also increases the risk of heart defects from 1 in 100 to 2 in 100(25). Thus paroxetine is contraindicated in

pregnancy. According to National Institute of Clinical Excellence (NICE) guidelines, the risk with other antidepressants is lower than paroxetine and therefore they can be used in pregnancy with caution(26).

Maternal antidepressant use is strongly associated with increased risk of poor neonatal adaptation(27). This risk may be related to timing (that is, late in the pregnancy)(28) or duration of use(29). Poor neonatal adaptation is a transient condition that is usually mild. Its features include jitteriness, respiratory distress and seizures. It may be prevented by discontinuation of the medication prior to delivery but timing of delivery can be unpredictable, discontinuation is likely to result in relapse of the mental disorder and there is no evidence for its efficacy.

A large recent study found that use of SSRIs in late pregnancy increased the risk of persistent pulmonary hypertension of the newborn from 1.2 in 1000 to 3 in 1000(30). While this was a statistically significant difference, one could argue that it is not a clinically significant increase in risk.

Other adverse effects of antidepressant use during pregnancy may include spontaneous abortion(31), postpartum haemorrhage(32), low birth weight(33), preterm birth(33,34), pulmonary diseases(35) and autistic spectrum disorder(36). Exposure to antidepressants in utero is not thought to affect child neurodevelopment(37).

Tricyclic antidepressants (TCAs) are generally considered safer than SSRIs; NICE guidelines state that TCAs have "lower known risks during pregnancy than other antidepressants"(26). Studies have not shown a risk of birth defects with use of TCAs in pregnancy but there is a risk of poor neonatal adaptation(38). Serotonin-noradrenaline reuptake inhibitors such as duloxetine do not appear to increase the risk of major malformations(39).

Mood stabilisers

Lithium is a first-line mood stabiliser for bipolar disorder. The risks of lithium include floppy infant syndrome and heart defects, particularly Ebstein's anomaly(40). The risk of Ebstein's anomaly is especially high when lithium is taken early in the first trimester(41). Anti-epileptics such as sodium valproate, carbamazepine and lamotrigine are often used as mood stabilisers second-line. There is a high risk of major congenital malformations with use of

these anti-epileptics during pregnancy(42). Sodium valproate has the highest rate of congenital malformations of the medications used for bipolar disorder, particularly neural tube defects(43). Sodium valproate is also associated developmental delay(43). Carbamezpine and lamotrigine have teratogenic effects, particularly on the nervous system, gastrointestinal tract and heart(26).

Antipsychotics

Antipsychotics in pregnancy do not appear to be associated with birth defects(44). On the other hand, antipsychotics such as olanzapine may increase the risk of gestational diabetes(17). Gestational diabetes is a serious condition associated with increased risk of pre-eclampsia, macrosomia (large for gestational age) and caesarean delivery(45). There is also an increased risk of type 2 diabetes mellitus and metabolic syndrome in the mother(46). Risk factors for gestational diabetes and weight gain such as current weight, ethnicity and family history should be taken into account when prescribing olanzapine to a pregnant woman(26) such as Sarah (Table 1).

Clozapine should not be prescribed in pregnancy because of the risk of agranulocytosis in the foetus. Use of typical antipsychotics in pregnancy can result in extra-pyramidal side-effects in the neonate(47). Atypical antipsychotics do not appear to be associated with birth defects but may be associated with postnatal disorders such as jitteriness and seizures(48). Data is lacking on the safety of depot medications in pregnancy.

In some cases, more than one psychotropic medication may need to be prescribed. Evidence suggests that such combinations may be harmful(49). However, mono-therapy may be insufficient to adequately treat the mother.

Discussion

Risk-benefit analysis

A detailed risk-benefit analysis is required to determine whether psychotropic medication should be started or continued in pregnancy. Many factors may play a role in the clinician's decision (Table 3). It is important to establish the biological, psychological and social impact of the mother's illness to determine whether it would be safe not to treat with medication

(Table 2). The past, current and future circumstances of the mother and her family should also be taken into consideration.

Table 3. Factors to consider when prescribing psychotropic medications in pregnancy

Suicidal intent
Lack of capacity
History of overdose
Lack of family support
Number of weeks gestation
Strategies for dealing with stress
Frequency and severity of relapse
Family history of congenital disorders
History of violent behaviour and aggression
Known substance misuse and alcohol abuse when not treated
Maternal desire not to take any medications during pregnancy
Severe depressive episodes associated with previous pregnancies

The psychiatric interview, background and collateral history are invaluable in assessing risk. Patients with their first presentation to mental health services may be more challenging to assess such as Maria in Case 1 (Table 1). Without a previous psychiatric history, it is unclear how long Maria's episode is likely to last and what the chances of relapse are. Family history and identification of triggers for this episode may shed light on the course of the illness. In Maria's case, antipsychotic medication is likely to be warranted to treat her current psychotic episode in the hope that her mental state will improve and she will regain capacity to make a decision about her treatment.

Case 2 (Table 1) is another example where a complex risk assessment is required. It is important to know the nature of Sarah's manic episodes, how frequently they occur, what triggers them, her functioning in between episodes and how she plans to cope during future episodes (particularly regarding use of alcohol). The risk of foetal alcohol syndrome is greater than the risks of the medication but if her manic episodes occur only once a year the alcohol intake is unlikely to cause harm. It is important to enquire further about the alcohol use and her current social circumstances. For example, Sarah may have had success with a

detoxification programme, been abstinent for 6 months with the support of a partner and having a child may be a protective factor for her. Under these circumstances, not using medication may be justifiable. Gauging the chances of relapse and the possible consequences is therefore an essential part of the clinician's assessment.

Minimising risk

Given the potential risks of psychotropic medications in pregnancy, psychological therapies should first be considered. PROMISES is a randomised controlled trial currently underway in women with depression and/or anxiety. This trial will evaluate the effect of cognitive behavioural therapy (CBT) during pregnancy on emotional and behavioural problems in the child at 18 months compared with usual care(50). However, this trial does not look at obstetric or neonatal outcomes. Psychological therapies such as CBT could be a useful alternative for women on antidepressants who are planning pregnancy.

In case 3 (Table 1), Alice has already been on paroxetine for most of her first trimester. NICE guidelines recommend she be taken off paroxetine and another antidepressant started, perhaps a TCA(26). However, if Alice's risk is deemed to be low perhaps she could gradually be taken off antidepressants altogether. Previous response to treatment can help guide the decision whether or not to continue using an antidepressant. Discontinuing the paroxetine should be accompanied by frequent monitoring of Alice's mental state and a contingency plan in the event of relapse. Sudden discontinuation of paroxetine should be avoided to prevent relapse and withdrawal symptoms. Unfortunately stopping the paroxetine does not mean a congenital malformation will not occur and this must be carefully explained to Alice. NICE guidelines recommend avoiding use of psychotropic medications with known teratogenic risk, such as paroxetine and valproate, in women of child-bearing age so this type of event does not occur(26).

Another method of limiting possible harm of psychotropic medication is to start at the lowest dose and slowly increase it because some risks are dose-related(51). However, it is important to ensure the dose is sufficiently high at the end of titration as many women have been found to be treated sub-optimally(52). Avoidance of poly-therapy has also been recommended to reduce the risk of harm(26) but severity of the disorder may mean that multiple medications are required.

Communicating with the pregnant woman

It is helpful to first elicit the mother's opinions and values. Naturally mothers value the safety of their unborn children highly and may believe that psychotropic medications are not safe to be taken during pregnancy(20). This perception may be reinforced by media coverage of research findings and lawsuits(19). These women may not be aware of the ways in which their illness may affect the foetus. In this situation, educating the mother is a priority including highlighting behaviours that could be harmful to the foetus such as smoking and drinking alcohol.

A good rapport is helpful when communicating the risk to the mother and explaining the advantages of taking the medication. Sometimes trust can break down between the mother and the clinician and other medical professionals such as pharmacists or nurses may act as providers of information. Provision of leaflets or other written material may also be helpful. One useful communication technique is to describe risk using natural frequencies rather than percentages and using a common denominator such as 100(26).

Once fully informed of the risks of taking and not taking the medication the mother may still refuse the medication. In this event, the medical team must accept her decision not to take the medication even if they think this decision is unwise, unless there is reason to believe she does not have capacity. It may be necessary to use the Mental Capacity Act 2005 to assess capacity. A meeting with the family and medical professionals is likely to help determine best interests, for example in Maria's case (Table 1).

Ethics

The clinician may face an ethical dilemma in making their decision. Clinicians have a duty not to harm and may believe that therefore, deliberately increasing risk to the foetus is morally wrong. However, practically the risk of the medication to the foetus cannot be considered in isolation. The effects of the disorder on the mother and the foetus must be considered at the same time as the risk of the medication. Guidelines take a more consequentialist approach, that is weighing up the risks and benefits to determine what would result in the best outcome overall.

Study design

Associations found in observational studies such as the link between SSRIs and PPHN may be the result of uncontrolled confounding factors. Only randomised controlled trials can reconcile the conflicting results about the type and level of risk of psychotropic medications in pregnancy and equip clinicians with information to guide decision-making. Some argue that it is not ethical to expose pregnant women to medications which may cause birth defects but a systematic review by Coverdale et al suggests that randomised controlled trials of antidepressants in pregnant women are ethically justified(53).

Conclusion

Mental health disorders are a significant cause of maternal morbidity and mortality and poor neonatal outcomes. NICE guidelines indicate that antidepressants can be used in pregnancy despite increases in risks of birth defects and poor neonatal adaptation. However paroxetine should be not be used in pregnancy as it significantly increases risk of birth defects, especially heart defects. TCAs are thought to be safer than SSRIs. If an SSRI must be used, sertraline or citalopram are preferred. Some mood stabilisers can be used in pregnancy but valproate should not be used due to the high risk of neural tube defects. Antipsychotics can be used in pregnancy although there is an increased risk of gestational diabetes. However clozapine should not be used in pregnancy due to the potential risk of agranulocytosis(26).

The weighing up of the relative risks of the mental disorder versus the risks of the medication in pregnancy is complex for two reasons. Firstly, many factors contribute to the assessment of the risk posed by the disorder itself including the nature of past episodes and likely future social circumstances. Secondly, there is a lack of data available about the safety of a variety of psychotropic medications during pregnancy and no randomised controlled trials. However, the available data support the use of numerous psychotropic medications in pregnancy.

References

(1) Confidential Enquiry into Maternal and Child Health. *Why Mothers Die 2000–2002: The Sixth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom.* London: RCOG Press; 2004.

(2) Lewis Ge. *Saving Mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008.The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom.* London: CMACE; 2011.

(3) Andersson L, Sundstrom-Poromaa I, Bixo M, Wulff M, Bondestam K, aStrom M. Point prevalence of psychiatric disorders during the second trimester of pregnancy: a population-based study. *American Journal of Obstetrics and Gynecology* 2003;189(1) 148-154.

(4) Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Prevalence of depression during pregnancy: systematic review. *Obstetrics and gynecology* 2004;103(4) 698-709.

(5) Zuckerman B, Amaro H, Bauchner H, Cabral H. Depressive symptoms during pregnancy: relationship to poor health behaviors. *American Journal of Obstetrics and Gynecology* 1989;160(5 Pt 1) 1107-1111.

(6) Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. *Obstetrics and gynecology* 2000;95(4) 487-490.

(7) Grote NK, Bridge JA, Gavin AR, Melville JL, Iyengar S, Katon WJ. A meta-analysis of depression during pregnancy and the risk of preterm birth, low birth weight, and intrauterine growth restriction. *Archives of General Psychiatry* 2010;67(10) 1012-1024.

(8) Boden R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H. Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. *BMJ (Clinical research ed.)* 2012;345 e7085.

(9) MacCabe JH, Martinsson L, Lichtenstein P, Nilsson E, Cnattingius S, Murray RM, Hultman CM. Adverse pregnancy outcomes in mothers with affective psychosis. *Bipolar disorders* 2007;9(3) 305-309.

(10) Nilsson E, Lichtenstein P, Cnattingius S, Murray RM, Hultman CM. Women with schizophrenia: pregnancy outcome and infant death among their offspring. *Schizophrenia research* 2002;58(2-3) 221-229.

(11) Alder J, Fink N, Bitzer J, Hosli I, Holzgreve W. Depression and anxiety during pregnancy: a risk factor for obstetric, fetal and neonatal outcome? A critical review of the literature. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2007;20(3) 189-209.

(12) Beck CT. Predictors of postpartum depression: an update. *Nursing research* 2001;50(5) 275-285.

(13) Beck CT. The effects of postpartum depression on maternal-infant interaction: a meta-analysis. *Nursing research* 1995;44(5) 298-304.

(14) Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, Suri R, Burt VK, Hendrick V, Reminick AM, Loughead A, Vitonis AF, Stowe ZN. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. *JAMA : the journal of the American Medical Association* 2006;295(5) 499-507.

(15) Yonkers KA, Gotman N, Smith MV, Forray A, Belanger K, Brunetto WL, Lin H, Burkman RT, Zelop CM, Lockwood CJ. Does antidepressant use attenuate the risk of a major depressive episode in pregnancy? *Epidemiology (Cambridge, Mass.)* 2011;22(6) 848-854.

(16) Palmsten K, Setoguchi S, Margulis AV, Patrick AR, Hernandez-Diaz S. Elevated risk of preeclampsia in pregnant women with depression: depression or antidepressants? *American Journal of Epidemiology* 2012;175(10) 988-997.

(17) Boden R, Lundgren M, Brandt L, Reutfors J, Kieler H. Antipsychotics during pregnancy: relation to fetal and maternal metabolic effects. *Archives of General Psychiatry* 2012;69(7) 715-721.

(18) Lin HC, Chen IJ, Chen YH, Lee HC, Wu FJ. Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? *Schizophrenia research* 2010;116(1) 55-60.

(19) BBC. *Antidepressants 'could be risk to unborn babies'*. [Online] Available from: http://www.bbc.co.uk/news/health-23005367 [Accessed 12 October 2013].

(20) Price SK, Bentley KJ. Psychopharmacology decision-making among pregnant and postpartum women and health providers: informing compassionate and collaborative care women's health. *Women & health* 2013;53(2) 154-172.

(21) Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. *Journal of clinical psychopharmacology* 2012;32(2) 186-194.

(22) Hayes RM, Wu P, Shelton RC, Cooper WO, Dupont WD, Mitchel E, Hartert TV. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. *American Journal of Obstetrics and Gynecology* 2012;207(1) 49.e1-49.e9.

(23) Grigoriadis S, VonderPorten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Radford K, Martinovic J, Ross LE. The impact of maternal depression during pregnancy on perinatal outcomes: a systematic review and meta-analysis. *The Journal of clinical psychiatry* 2013;74(4) e321-41.

(24) Myles N, Newall H, Ward H, Large M. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. *The Australian and New Zealand Journal of Psychiatry* 2013.

(25) Medicines and Healthcare Products Regulatory Agency. *MHRA update on the risks of birth defects in babies born to mothers taking paroxetine – Q&A* . [Online] Available from: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con2022700.pdf [Accessed 13 October 2013].

(26) National Institute for Clinical Excellence. *Antenatal and postnatal mental health (NICE clinical guideline 45).* [Online] Available from: http://www.nice.org.uk/nicemedia/live/11004/30433/30433.pdf [Accessed 13 October 2013].

(27) Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A, Ross LE. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. *The Journal of clinical psychiatry* 2013;74(4) e309-20.

(28) Sivojelezova A, Shuhaiber S, Sarkissian L, Einarson A, Koren G. Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. *American Journal of Obstetrics and Gynecology* 2005;193(6) 2004-2009.

(29) Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. *The British journal of psychiatry : the journal of mental science* 2008;192(5) 338-343.

(30) Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M, Nielsen RB, Norgaard M, Stephansson O, Valdimarsdottir U, Zoega H, Haglund B. Selective serotonin reuptake inhibitors during pregnancy and risk of

persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. *BMJ (Clinical research ed.)* 2012;344 d8012.

(31) Nikfar S, Rahimi R, Hendoiee N, Abdollahi M. Increasing the risk of spontaneous abortion and major malformations in newborns following use of serotonin reuptake inhibitors during pregnancy: A systematic review and updated meta-analysis. *Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences* 2012;20(1) 75-2231-20-75.

(32) Palmsten K, Hernandez-Diaz S, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, Mogun H, Setoguchi S. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *BMJ (Clinical research ed.)* 2013;347 f4877.

(33) Huang H, Coleman S, Bridge JA, Yonkers K, Katon W. A meta-analysis of the relationship between antidepressant use in pregnancy and the risk of preterm birth and low birth weight. *General hospital psychiatry* 2013.

(34) Ross LE, Grigoriadis S, Mamisashvili L, Vonderporten EH, Roerecke M, Rehm J, Dennis CL, Koren G, Steiner M, Mousmanis P, Cheung A. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. *JAMA psychiatry (Chicago, Ill.)* 2013;70(4) 436-443.

(35) ter Horst PG, Bos HJ, de Jong-van de Berg LT, Wilffert B. In utero exposure to antidepressants and the use of drugs for pulmonary diseases in children. *European journal of clinical pharmacology* 2013;69(3) 541-547.

(36) Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. *BMJ (Clinical research ed.)* 2013;346 f2059.

(37) Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JG, Kulin N, Koren G. Neurodevelopment of children exposed in utero to antidepressant drugs. *The New England journal of medicine* 1997;336(4) 258-262.

(38) Kruger S. Psychopharmacological treatment of mood and anxiety disorders during pregnancy. *Handbook of Experimental Pharmacology* 2012;(214):279-305. doi(214) 279-305.

(39) Einarson A, Smart K, Vial T, Diav-Citrin O, Yates L, Stephens S, Pistelli A, Kennedy D, Taylor T, Panchaud A, Malm H, Koren G, Einarson TR. Rates of major malformations in infants following exposure to duloxetine during pregnancy: a preliminary report. *The Journal of clinical psychiatry* 2012;73(11) 1471.

(40) Gentile S. Lithium in pregnancy: the need to treat, the duty to ensure safety. *Expert opinion on drug safety* 2012;11(3) 425-437.

(41) Pinelli JM, Symington AJ, Cunningham KA, Paes BA. Case report and review of the perinatal implications of maternal lithium use. *American Journal of Obstetrics and Gynecology* 2002;187(1) 245-249.

(42) Campbell E, Kennedy F, Irwin B, Morrison P, Delanty N, Hunt S, Craig J, Morrow J. Malformation Risks of Antiepileptic Drug Monotherapies in Pregnancy. *Journal of neurology, neurosurgery, and psychiatry* 2013;84(11) e2.

(43) Nguyen HT, Sharma V, McIntyre RS. Teratogenesis associated with antibipolar agents. *Advances in Therapy* 2009;26(3) 281-294.

(44) Einarson A, Boskovic R. Use and safety of antipsychotic drugs during pregnancy. *Journal of psychiatric practice* 2009;15(3) 183-192.

(45) Wendland EM, Torloni MR, Falavigna M, Trujillo J, Dode MA, Campos MA, Duncan BB, Schmidt MI. Gestational diabetes and pregnancy outcomes--a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC pregnancy and childbirth* 2012;12 23-2393-12-23.

(46) Reece EA. The fetal and maternal consequences of gestational diabetes mellitus. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians* 2010;23(3) 199-203.

(47) Collins KO, Comer JB. Maternal haloperidol therapy associated with dyskinesia in a newborn. *American Journal of Health-System Pharmacy : AJHP : Official Journal of the American Society of Health-System Pharmacists* 2003;60(21) 2253-2255.

(48) Habermann F, Fritzsche J, Fuhlbruck F, Wacker E, Allignol A, Weber-Schoendorfer C, Meister R, Schaefer C. Atypical antipsychotic drugs and pregnancy outcome: a prospective, cohort study. *Journal of clinical psychopharmacology* 2013;33(4) 453-462.

(49) Sadowski A, Todorow M, Yazdani Brojeni P, Koren G, Nulman I. Pregnancy outcomes following maternal exposure to second-generation antipsychotics given with other psychotropic drugs: a cohort study. *BMJ open* 2013;3(7) 10.1136/bmjopen-2013-003062. Print 2013.

(50) Meijer JL, Bockting CL, Beijers C, Verbeek T, Stant AD, Ormel J, Stolk RP, de Jonge P, van Pampus MG, Burger H. PRegnancy Outcomes after a Maternity Intervention for Stressful EmotionS (PROMISES): study protocol for a randomised controlled trial. *Trials* 2011;12 157-6215-12-157.

(51) Roca A, Garcia-Esteve L, Imaz ML, Torres A, Hernandez S, Botet F, Gelabert E, Subira S, Plaza A, Valdes M, Martin-Santos R. Obstetrical and neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitors: the relevance of dose. *Journal of affective disorders* 2011;135(1-3) 208-215.

(52) Flynn HA, Blow FC, Marcus SM. Rates and predictors of depression treatment among pregnant women in hospital-affiliated obstetrics practices. *General hospital psychiatry* 2006;28(4) 289-295.

(53) Coverdale JH, McCullough LB, Chervenak FA. The ethics of randomized placebo-controlled trials of antidepressants with pregnant women: a systematic review. *Obstetrics and gynecology* 2008;112(6) 1361-1368.