

**Mari Grepstad, Victoria Tzouma,
Federico Grimaccia and Panos Kanavos**

**Treating schizophrenia during pregnancy: A
systematic literature review of the impact of
drug treatment on mother and foetus**

Treating schizophrenia during pregnancy: a systematic literature review of the impact of drug treatment on mother and foetus

Mari Grepstad¹, Victoria Tzouma¹, Federico Grimaccia¹ and Panos Kanavos²

¹ Medical Technology Research Group, LSE Health, London School of Economics and Political Science

² LSE Health, London School of Economics and Political Science

Working Paper No. 41/2015

First published in January 2015 by:
LSE Health
The London School of Economics and Political Science
Houghton Street
London WC2A 2AE

© Mari Grepstad, Victoria Tzouma, Federico Grimaccia, Panos Kanavos

All rights reserved. No part of this paper may be reprinted or reproduced or utilised in any form or by any electronic, mechanical or other means, now known or hereafter invented, including photocopying and recording, or in any information storage or retrieve system, without permission in writing from the publishers.

British Library Cataloguing in Publication Data. A catalogue record for this publication is available from the British Library.

ISSN 2047-8879

Corresponding Author:
Panos Kanavos
Department of Social Policy
Old Building
London School of Economics and Political Science
Houghton Street
London WC2A 2AE
p.g.kanavos@lse.ac.uk

Abstract

Background: There is an increasing need to understand the impact of drug use in pregnant women with schizophrenia as women are conceiving later in life and newer antipsychotics have proved to make women more fertile than older treatment regimes. However, the risks associated with prenatal exposure to antipsychotics remains largely unknown. Ethical considerations related to schizophrenia and parenthood further complicates family planning for these women.

Objective: The aim of this systematic review is to provide an update of current knowledge in the field by critically summarising the literature on the effects of drug use for the treatment of schizophrenia on mother, foetus and newborn, to study the ethical considerations related to childbearing for women with schizophrenia, and to explore the economic impact of drug use during pregnancy for women with schizophrenia, their families and society.

Methods: A systematic literature review was performed following the PICO approach. Medline and Scopus were searched for articles providing primary estimates of the clinical impact of drug use on mother and foetus, ethical issues around childbearing for women with schizophrenia, and economic impact of drug use during pregnancy for these women.

Results: Nineteen studies were identified, most of which were case reports exploring the use of atypical antipsychotics. Evidence of foetal malformations was found in nine cases. When reported, delivery mode, term time and birth weight were most often normal. About half of the studies discussed the ethics of schizophrenia and childbearing. Supportive care and services, informed consent and educational interventions were seen as effective non-drug measures. Despite the economic impact of pregnancy in women with schizophrenia remaining largely unknown, there are increased costs associated with the adverse outcomes associated with pregnancy in woman with schizophrenia.

Conclusion: The review confirms the paucity of scientific evidence on the impact of drug use during pregnancy in women with schizophrenia. Case reports continue to play a valuable source of evidence for the development of guidelines. The risk of congenital malformation due to drug exposure must be balanced against the risk of relapse and psychosis in pregnant women whose treatment regimens are changed. Non-drug interventions may provide cost-

effective measures to decrease the risk of adverse outcomes. Better insight into the economics of pregnancy for woman with chronic diseases will improve care and value for money in obstetric healthcare.

Keywords: schizophrenia, pregnancy, pharmaceuticals

Contents

| | |
|---|-----------|
| Abstract..... | 2 |
| Contents | 4 |
| Abbreviations | 5 |
| 1. Background | 6 |
| 2. Methods..... | 8 |
| 2.1 Search strategy | 8 |
| 2.2 Search terms..... | 8 |
| 2.3 Inclusion criteria | 8 |
| 2.4 Data Extraction and Endpoints of Analysis | 10 |
| 2.5 Limitations of the method..... | 10 |
| 3. Results | 10 |
| 3.1 Clinical impact..... | 14 |
| 3.1.1 The effect of typical antipsychotics | 14 |
| 3.1.2 The effect of atypical psychotics and endpoints of interest..... | 15 |
| 3.1.3 The effect of other drugs and non-specified antipsychotics | 17 |
| 3.2 Ethical issues..... | 17 |
| 3.3 Economic implications..... | 18 |
| 4. Discussion..... | 19 |
| 4.1 Outcomes for the mother: disease activity and complications of pregnancy..... | 19 |
| 4.2 Outcomes for the foetus: abnormal foetal growth and development..... | 20 |
| 4.3 Ethical considerations for patients, families and professionals | 21 |
| 4.4 Economic aspects for individuals and society | 22 |
| 5. Conclusions..... | 24 |
| References..... | 26 |
| Appendix..... | 29 |

Abbreviations

| | |
|--------|--|
| FDA | Food and Drug Administration |
| OECD | Organisation of Economic Cooperation and Development |
| PICOS | Population Intervention Comparator Outcome Study design |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| RCT | Randomised Controlled Trial |

1. Background

Schizophrenia is a chronic mental illness characterised by a breakdown of thought processes and impaired emotional responses. The disease has a median age of onset in the late twenties for women.

Managing chronic diseases during pregnancy requires a careful evaluation of the risks for both mother and foetus. In the case of schizophrenia, drug management is particularly difficult as the control of psychotic symptoms during pregnancy is complicated by a reduction in drug plasma concentration due to increased hepatic metabolism and volume of distribution. But while drug management is difficult, a discontinuation of antipsychotic medication poses an equally difficult dilemma as this can lead to a relapse of psychosis (Duran et al. 2008).

For ethical reasons such as the tragedy of thalidomide in the 1950s and 1960s, strict regulations apply to the testing of medicines on pregnant women. This has led to a paucity of clinical research on drug use in pregnant women with schizophrenia. Consequently, most evidence is available through case reports. While this anecdotal body of literature is important, conclusions on the causal effects of drug use during pregnancy cannot be drawn. In the meantime, women in Organisation of Economic Cooperation and Development (OECD) countries are conceiving at an increasingly older age, when they are more likely to have developed a chronic condition. The average conception age of women in OECD countries was 27.8 years in 2009 (OECD 2009). As a result, the management of chronic diseases during pregnancy poses increasingly challenging for policy makers and physicians.

Although there is a disagreement in the literature about fertility among women with schizophrenia (Howard 2005; McCullough et al. 2002), recent drug developments in the treatment of schizophrenia have made family planning for schizophrenic women easier. Recent years have seen a substantial increase in the use of atypical antipsychotics before and throughout pregnancy (Toh et al. 2013). These drugs have been known to cause hyperprolactinemia, which may lower fertility. This side effect is less likely to appear with atypical antipsychotics, although two atypical antipsychotics (risperidone and amisulpride) induce hyperprolactinaemia similarly to the typical antipsychotics. New drugs such as clozapine and quetiapine may therefore lead to higher birth rates in patients with psychotic

disorders, increasing the need for reliable data on the pharmacological impact on mother and foetus.

The ethical considerations around family planning in couples where women with schizophrenia are considering becoming pregnant are strong. Genetic factors are thought to be important in the development of schizophrenia, and individuals with a close family member with schizophrenia are 10 times more likely to develop the condition. Research has shown that not only is the woman and her child at risk of obstetric complications, stillbirth and neonatal deaths, but mothers with psychotic disorders also have parenting difficulties and may lose custody over their children (Howard 2005; Miller 1997). Studies have showed that schizophrenia and bipolar disorder may result in loss of empathy, difficulty in understanding and expressing feelings and lack of impulse control and cognitive functions. These skills are seen as crucial for parenting (Stotland 2001).

Antipsychotic medications that control symptoms may make the mother less responsive to her child, causing disillusioned thinking and inappropriate behaviour that can impact the relationship between mother and child as well as her relationship with her partner (d'Orb 1979) (Falkov and Britain 1996). Suicide, suicide attempts and self-harm during pregnancy due to psychotic disorders appear to be rare (Howard 2005).

While some evidence suggests that healthcare costs and accessibility of care for pregnant women with a chronic disease compared with pregnant women without chronic diseases are similar (Chatterjee et al. 2008), adverse outcomes relevant for pregnancy in women with schizophrenia calls for concern from an economic perspective. Exploring these economic implications helps make better informed policy decisions and provides better estimates of budget impact for healthcare payers.

This review was conducted in order to gauge the level of understanding of the impact of drug use during pregnancy in women with schizophrenia so as to develop better informed guidelines for disease management during pregnancy. The objectives were threefold: to explore the evidence of drug use during pregnancy in women with schizophrenia and the likely impact of the drug on mother and foetus, to investigate the ethical considerations related to the management of the disease and the pregnancy, and to explore the economic implications for the mother, her family and the society as a whole. The article is structured as

follows. First, the methodology employed is presented. Second, an overview of the results is given, followed by a discussion. Finally, some concluding remarks are made and implications for policy provided.

2. Methods

A review of the literature on the use of drug treatment for schizophrenia during pregnancy and the effects on mother, foetus and new-born was conducted in September 2013. For this review we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009) for the identification, screening, eligibility and inclusion of articles in the review.

2.1 Search strategy

Searches were performed for papers published between January 2000 and June 2013 in relevant databases (PubMed and Scopus). Reference list in the papers meeting the articles included in the review were searched to identify further eligible papers.

2.2 Search terms

Search terms and the combinations used in the search are set out in Table 1. Databases were searched using the primary term “schizophrenia” in combination with either “pregnancy” or “pregnant” plus one term associated with drug treatment (column 3 of Table 1).

2.3 Inclusion criteria

Articles were considered eligible if they met the inclusion criteria set out in the PICOS framework as described in table 2. First, the articles were screened for evidence on the primary endpoint of the review: any clinical outcome for mother, foetus and newborn due to drug use for the treatment of schizophrenia. Secondly, we searched in the identified literature

for any reference or material to ethical considerations and costs related to drug use during pregnancy in women with schizophrenia. Only studies that presented primary data were considered eligible.

Due to the absence of pregnant women in randomised controlled trials (RCT), it was anticipated that no such studies would be retrieved from the search. Consequently, cohort studies, case reports, surveys and registry studies were considered for inclusion in the review. Although case reports are prone to bias (M. Doherty 1994), these studies were expected to enable the identification of relevant information to the subject under investigation, particularly in light of the strong ethical considerations concerning drug use in pregnancy.

Table 1. Search terms

| <i>Column 1</i> | <i>Column 2 Combined with (individually)</i> | <i>Column 3 Combined with (individually)</i> |
|-----------------|--|--|
| schizophrenia | pregnancy | “drug use” |
| | pregnant | “medication use” |
| | | drugs |
| | | medication(s) |
| | | treatment |
| | | therapy |
| | | pharmacotherapy |
| | | “pharmaceutical use” |
| | | management |

Table 2. Inclusion criteria

| | | |
|----------|----------------------------|--|
| P | Population | Pregnant women diagnosed with schizophrenia before pregnancy |
| I | Intervention/ treatment | Any drug intervention or combination of drug interventions or lack of drug intervention given for the treatment of schizophrenia |
| C | Comparator | N/A |
| O | Outcome | Any clinical outcome for mother, foetus and newborn, ethical considerations, socio economic implications and costs |
| S | Study design | Cohort studies, clinical trials, registry studies, case studies, surveys/ interviews. |

2.4 Data Extraction and Endpoints of Analysis

The review included articles using both quantitative and qualitative research methods. Therefore, we undertook an aggregative synthesis (Dixon-Woods et al. 2006) in which the data was extracted into an Excel spreadsheet using predefined categories. The data collected for each article included (a) information about the study (study design, study objective, country of origin, year of data collection, sample size); (b) baseline characteristics of the study population (maternal age), (c) interventions (treatment regimens studied); (d) primary endpoints (clinical outcomes: disease-related outcome, birth outcome, foetal complications); and (e) secondary endpoints (ethical considerations, economic implications).

2.5 Limitations of the method

The limitations of the method employed in the review should be noted. The relationship between psychotic disorders and substance and alcohol abuse was outside the scope of this review. These are comorbidities that are often overseen by the general practitioner (Howard 2005), and while the effect of substance and alcohol abuse is unknown it could be an additional risk factor for the development of the foetus. Future reviews should explore the effects of alcohol and substance abuse with regards to the clinical aspects as well as social stigma experienced by women in these situations. Future research should aim to explore the social economic status of the patients as this may impact not only the women's conditions and abilities to make decisions, but also their supportive network and the access to treatment and care. Reviews including earlier studies may have resulted in more literature on typical antipsychotics. However, given the more favourable conditions for pregnancy with atypical antipsychotics, the time frame chosen for this review is likely to be more relevant to current treatment patterns.

3. Results

The flow of articles in the study selection process of the review is depicted in Figure 1. A total of 278 articles was identified from Medline and SCOPUS databases. After duplicates

(n=80) were removed, the remaining 198 studies were reviewed in terms of title and abstract to gauge their suitability following the inclusion criteria presented in Table 2. A number of studies were excluded (n=170) as they comprised studies conducted on animals (n=40), did not present primary data (n=44) or did not relate to schizophrenia in pregnant women but rather explored risk factors in pregnancy leading to schizophrenia in the offspring (n=40). Further articles (n=46) were excluded because they did not provide disaggregated data for schizophrenia, or they did not provide information on pregnant women with schizophrenia or drug use other than illicit substance abuse. The articles that were found to be relevant (n=28) were then downloaded and read in full for further assessment. This resulted in the exclusion of another ten articles due to irrelevant study design (n=4), irrelevant topic (n=2), no data available on drug treatment (n=2), no disaggregated data available for patients with schizophrenia and studies that could not be obtained (n=2). Finally, nineteen studies, including one article identified from the included articles' reference lists were included in the review.

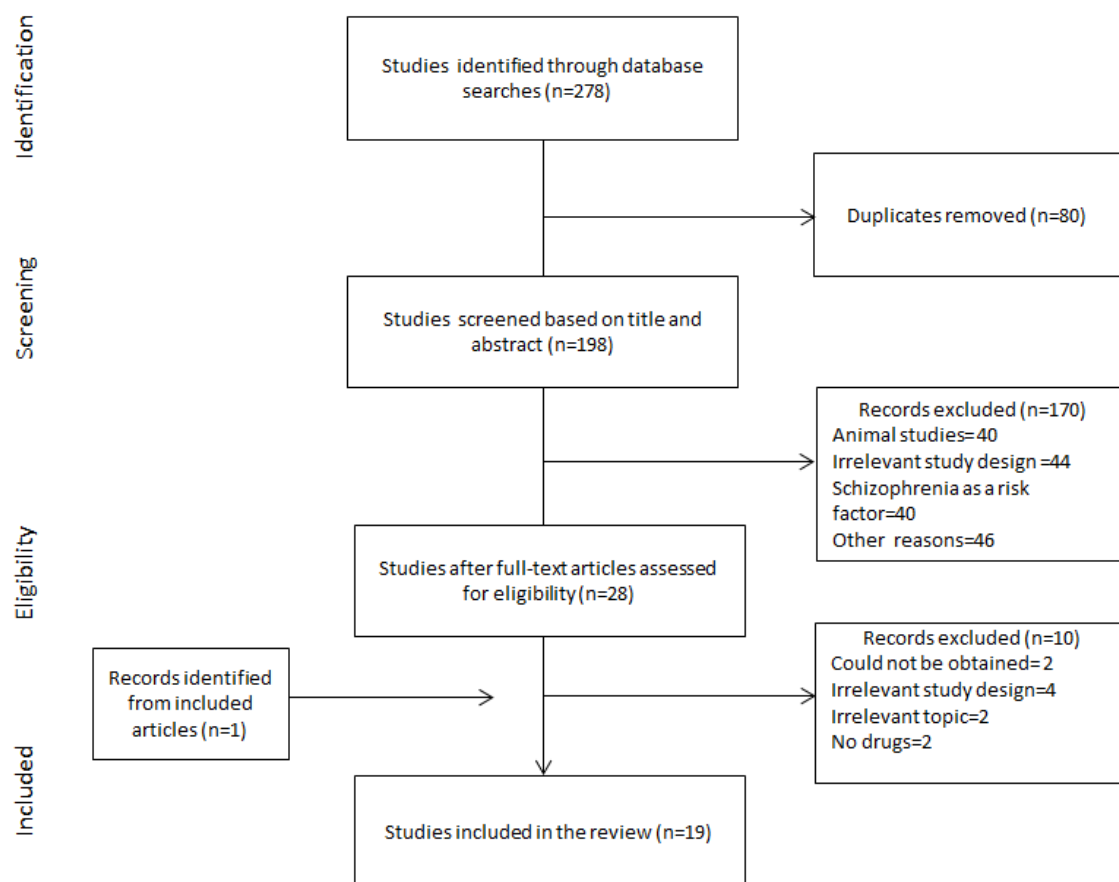


Figure 1. Flow chart of the study selection process.

Table 3. Study characteristics of included articles

| Author | Title | Study country | Study design | Sample Size |
|--------------------------------|--|---------------|--------------|-------------|
| Doherty et al. 2006 | Implications for anaesthesia in a patient established on clozapine treatment | Ireland | Case study | 1 |
| Dudzinski et al. 2004 | When agreeing with the patient is not enough: a schizophrenic woman requests pregnancy termination | USA? | Case study | 1 |
| Duran et al. 2008 | Clozapine use in two women with schizophrenia during pregnancy | Turkey | Case study | 2 |
| Hironaka et al. 2008 | Maternal mental disorders and pregnancy outcomes: a clinical study in a Japanese population | Japan | Cohort study | 15 |
| Janjic et al. 2013 | Zuclopenthixol decanoate in pregnancy: Successful outcomes in two consecutive off springs of the same mother | Serbia | Case study | 1 |
| Klys et al. 2007 | Neonatal death following clozapine self-poisoning in late pregnancy. An unusual case report | Poland | Case study | 1 |
| Lin et al. 2010 | Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference? | Taiwan | Cohort study | 696* |
| Mendhekar et al. 2008 | Risperidone therapy in two successive pregnancies | India | Case study | 1 |
| Nako et al. 2001 | Neonatal thrombocytosis resulting from the maternal use of non-narcotic antischizophrenic drugs during pregnancy | Japan | Case study | 1 |
| Nishizawa et al. 2007 | Effectiveness of comprehensive supports for schizophrenic women during pregnancy and puerperium: Preliminary study | Japan | Cohort study | 20 |
| Vučić Peitl et al. 2010 | Ziprasidone as a possible cause of cleft palate in a newborn | Croatia | Case study | 1 |
| Ružić et al. 2009 | Pregnancy and atypical antipsychotics | Croatia | Case study | 1 |
| Su et al. 2001 | Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient | Taiwan | Case study | 1 |
| Yaeger et al. 2006 | Atypical antipsychotics in the treatment of schizophrenia during pregnancy and the postpartum | USA? | Case study | 1 |
| Yaris et al. 2004 | Use of polypharmacotherapy in pregnancy: a prospective outcome in a case | Turkey | Case study | 1 |
| Bursalioglu et al. 2013 | The Correlation Between Psychiatric Disorders and Women's Lives | Turkey | Survey | 61 |
| Tenyi et al. 2002 | Quetiapine and Pregnancy | ? | Case study | 1 |
| Kim et al. 2007 | Use of long acting injectible risperidone before and throughout pregnancy in schizophrenia | Korea | Case study | 1 |
| Coppola et al. 2007 | Evaluating the postmarketing experience of risperidone use during pregnancy | worldwide | Case studies | 713 |

* 242 patients were on antipsychotics

The characteristics of the studies included in the review are presented in Table 3. The majority of the studies were case studies (n=15), followed by cohort studies (n=3) and a survey study (n=1). One study (Coppola et al. 2007) reporting on a series of case studies as

part of the post-marketing evidence safety database of the pharmaceutical company Johnson and Johnson's was included. These represented unpublished data and the publication was therefore considered primary data, making it eligible for the review.

Sample sizes varied between one and 713. Studies were conducted in the following countries: Japan (n=3), Turkey (n=3), Croatia (n=2), Taiwan (n=2), USA (n=2), India (n=1), Poland (n=1), Serbia (n=1), Korea (n=1). In one study, the location was unknown. A comprehensive overview of the data extracted can be found in the Appendix.

Table 4. Endpoints addressed in the studies included in the review

| Author | Disease related outcomes | Birth outcomes | Foetal complications | Ethical considerations | Economic implications |
|-------------------------|--------------------------|----------------|----------------------|------------------------|-----------------------|
| Doherty et al. 2006 | | x | | | |
| Dudzinski et al. 2004 | | | | x | |
| Duran et al. 2008 | | x | | x | |
| Hironaka et al. 2008 | x | x | | | |
| Janjic et al. 2013 | | x | | | x |
| Kłys et al. 2007 | x | x | x | | |
| Lin et al. 2010 | | x | | x | |
| Mendhekar et al. 2008 | | x | | | |
| Nako et al. 2001 | | x | x | | |
| Nishizawa et al. 2007 | x | x | x | x | |
| Vučić Peitl et al. 2010 | | x | x | x | |
| Ružić et al. 2009 | | x | | x | |
| Su et al. 2001 | x | | | | |
| Yaeger et al. 2006 | | | | x | |
| Yaris et al. 2004 | | x | | x | |
| Bursalioglu et al. 2013 | x | | | x | x |
| Tenyi et al. 2002 | x | x | | | |
| Kim et al. (2002) | x | x | | x | |
| Coppola et al. 2007 | | x | x | | |

The main endpoints addressed in the studies included in the review are shown in Table 4. Seven studies dealt with disease related outcomes, fifteen studies explored birth outcomes including mode of delivery, five studies had information on foetal complications, ten studies

discussed the ethical considerations related to women with schizophrenia and pregnancy, and two studies provided information on the economic implications.

3.1 Clinical impact

3.1.1 The effect of typical antipsychotics

Two case studies and two cohort studies investigated the effect of typical antipsychotic drugs for the treatment of schizophrenia in pregnant women. One case study described a thirty-five year old woman suffering from schizophrenia who became pregnant twice, had uncomplicated pregnancies and gave birth to healthy girls while taking zuclopenthixol at an initial dose of 400mg /day, with a reduction to 200mg /day when the improvements in her mental condition were observed (Janjić et al. 2013). The mother's psychiatric status was found to improve significantly during pregnancy and remained stable after giving birth. In another case study, a twenty-five year old woman with schizophrenia was treated with chlorpromazine (50mg /day), haloperidol (12mg /day) biperiden (5mg /day), promethazine hydrochloride (25mg /day) and nitrazepam (5mg /day). She had an uneventful pregnancy and normal delivery, giving birth to a baby whose weight at birth was 2,540g (Nako et al. 2001). Due to the risk of neonatal drug withdrawal syndrome, the baby was admitted to the neonatal ward, where he developed neonatal thrombocytosis that lasted for three months. It is not known which of the five drugs prescribed caused the thrombocytosis.

One cohort study compared forty-six women taking atypical antipsychotics with 190 women in their mid to late twenties taking typical antipsychotics for the treatment of schizophrenia (Lin et al. 2010). The results showed no significant difference in low birth weight or gestational age between the two treatment arms. However, preterm babies were observed more frequently in women on antipsychotics compared to women not taking antipsychotics. Another cohort study investigated twenty pregnant women with schizophrenia in their mid to late thirties taking chlorpromazine and other antipsychotics (Nishizawa et al. 2007). Patients were divided into two groups, the first comprising women with psychotic deterioration who received an increasing dosage of chlorpromazine (twelve patients), and the second comprising women whose disease was stable and at a higher dosage of chlorpromazine (eight patients). The authors found that patients on an increasing dosage were at higher risk of a

worsening mental status: seven patients (58%) were admitted to the hospital with unstable mental status compared to only two patients (25%) in the stable group. Five of the twenty women (25%) underwent caesarean section due to obstetric complications and five neonates had minor abnormalities such as difficulty in feeding, respiratory acidosis and low birth weight.

3.1.2 The effect of atypical psychotics and endpoints of interest

The majority of studies investigated the use of atypical antipsychotics during pregnancy (14 of 19 studies).

Clozapine

Three case studies reported on the use of clozapine during pregnancy. One study described a thirty-three year old woman who took clozapine, went into early labour and underwent caesarean section under general anaesthesia (J. Doherty et al. 2006). She had a healthy baby boy. Similar findings were reported in a study on one woman taking clozapine at 200mg/day and another taking clozapine at 400mg/day, reduced to 200mg/day (Duran et al. 2008). Both women had normal and full term deliveries, and their babies had normal birth weights. The third case study described a twenty-seven year old woman whose baby suffered neonatal death following clozapine poisoning when the mother attempted to commit suicide in late pregnancy (Kłys et al. 2007). Clozapine was discontinued in the first trimester, and the patient was on valproate, promethazine, risperidone and fluoxetine. In week thirty-nine, the patient took an overdose of clozapine that she had accumulated during her prior treatment. Following vacuum assisted delivery she gave birth to a boy whose health state was very poor (Apgar score of 1 at 1 minute). The boy was placed on assisted aspiration but died less than an hour later.

Ziprasidone

Two case studies reported on women taking ziprasidone during pregnancy. In one case, the woman was taking 120mg/day, which was lowered to 80mg/day during the pregnancy and finally further reduced to 40mg/day until child birth (Vučić Peitl et al. 2010). She experienced a normal delivery and had a baby with a normal birth weight and cleft palate. It

was not known whether the malformation was caused by ziprasidone or not. The other case was uneventful and resulted in a healthy baby boy (Ružić et al. 2009).

Risperidone

The use of risperidone during pregnancy was described in three case studies, as well as in a study reporting on eighteen individual cases. The first case study reported on a woman who was given 3mg/day during the first pregnancy and 2mg/day after the first delivery and throughout the second delivery (Mendhekar and Lohia 2008). Both pregnancies resulted in healthy babies, with normal deliveries and normal birth weights. The second case study reported on a woman taking risperidone, quetiapine as well as thirteen other drugs (Yaris et al. 2004). She gave birth to a healthy baby in week thirty-seven, and the birth weight was normal. The third study reported a woman who was given 2mg/day of risperidone when becoming pregnant (Kim et al. 2007). She had an induced abortion due to fear of congenital malformation resulting from the medication. Shortly after, she was switched to long acting injectable risperidone and became pregnant again. She gave birth to a healthy baby girl in week thirty-six.

One study looking at the post marketing use of risperidone as reported in the Benefit Risk Management Safety Database of Johnson and Johnson Pharmaceutical Research and Development, described eighteen individual cases of women with schizophrenia taking risperidone during pregnancy (Coppola et al. 2007). Nine cases reported incidence of congenital malformations, seven in which risperidone was reported taken during the first trimester of pregnancy. In one case, a baby was born with major organ malformations, with abnormalities consistent with Ivemark's Syndrome. The remaining eight cases of malformation included cleft lip and palate, right-auricular achondroplasia, Pierre Robin syndrome, corpus callosum agenesis, moyamoya disease, ventricular cyst in the brain and patent foramen oval. Drug withdrawal syndrome was reported in eight cases, including somnolence, jitteriness, hypersensitivity, convulsion, feeding problems and depressed levels of consciousness. Three cases of perinatal syndrome was reported, including jaundice, respiratory difficulties, neonatal asphyxia, subarachnoid/subdural haemorrhage and shoulder dystocia, cyanosis, shock, retracted breathing, decreased muscle tone, congenital brain damage, unilateral facial palsy, metabolic acidosis and hyperbilirubinemia.

Olanzapine and Quetiapine

One case study described a woman wanting to become pregnant who was switched from quetiapine to olanzapine (Yaeger et al. 2006). Within three months the patient had gained 20 lb, was depressed, lethargic, anhedonic, and had severe memory and concentration difficulties. She was finally switched back on quetiapine which led to great improvements in terms of weight loss and improved mental state. In another case, quetiapine was taken in pregnancy during which the woman experienced remission of symptoms, and at week thirty-eight gave birth to a healthy boy (Tényi et al. 2002). Mode of delivery and birth weight were normal.

One cohort study explored the use of atypical antipsychotics and benzodiazepine in fifteen women with schizophrenia in their early thirties and found that those on drug treatment had significant increases in weight gain compared to patients with schizophrenia who did not receive drug treatment (Hironaka et al. 2011). They also observed shorter gestational age in those on drugs compared to women not on drug treatment.

3.1.3 The effect of other drugs and non-specified antipsychotics

One case study described a woman with schizophrenia experiencing an episode of acute exacerbation of psychotic symptoms during pregnancy, but showed great improvement after being enrolled in an open trial of omega-3 PUFAs therapy (Su et al. 2001). A survey of sixty-one women with schizophrenia investigated the number of abortions for the purpose of resuming psychiatric treatment, and found that five patients had seven abortions (Bursalioglu et al. 2013).

3.2 Ethical issues

Ten studies touched upon the ethical issues around schizophrenia and pregnancy. One case study dealt with the ethical dilemma of assisting a woman who interchangeably requested termination and continuation of her pregnancy (Dudzinski and Sullivan 2004). The woman lacked decision-making capacity, and the authors discussed the dilemma of the physician attempting to balance the obligations to protect the patient from harm while also respecting

her preferences and decisions. In another case study, the woman on a daily dosage of 400 mg clozapine expressed a wish to become pregnant, to which health professionals responded by recommending her to use contraception (Duran et al. 2008). The authors did not elaborate on the reason why she was recommended birth control; however it is assumed that this was because of the teratogenic risk to the women and her baby.

In two studies, women underwent abortions due to the potential risks of congenital malformations (Kim et al. 2007; Yaeger et al. 2006). Three case studies described discussions between health professionals and the patient as well as her partner and family on the ethical issues. The importance of making sure that all parties involved understood the risks and consequences of drug use during pregnancy was emphasised (Kim et al. 2007; Ružić et al. 2009; Vučić Peitl et al. 2010). In one of these case studies, the patient signed an informed consent to confirm that she was aware of the risks (Vučić Peitl et al. 2010). In another study, the validity of the informed consent signed on behalf of the patient by her husband to continue treatment with atypical antipsychotics was questioned (Yaris et al. 2004). In a third study, the woman's husband gave informed consent to continue drug treatment after having been explained the risks and benefits (Kim et al. 2007). One study investigated women with mental illnesses and their perception of their own ability to be good parents (Bursalioglu et al. 2013). The authors found that the sense of inefficiency in parenting was highest among patients with schizophrenia and bipolar disorder.

3.3 Economic implications

Only two studies touched upon issues of economic implications related to pregnancy and women with schizophrenia. One study argued that patients' and physicians' preference for Zuclopenthixol was due to its low acquisition price compared to the newer generation of antipsychotics (Janjic et al. 2013). Another pointed out that gender plays a key role in determining the socio-economic position, the access to resources and the social status, impacting mental health, including schizophrenia (Bursalioglu et al. 2013). Associations were drawn between the low use of contraceptives and the lower levels of socioeconomic conditions in women with schizophrenia.

4. Discussion

The findings of the review can be grouped into four main categories to discuss the relevant risks of drug use in pregnancy for women with schizophrenia and the evidence to support it: a) outcomes for the mother, b) outcomes for the foetus, c) ethical considerations related to pregnancy and family planning for these women, and d) the implications for costs.

4.1 Outcomes for the mother: disease activity and complications of pregnancy

While changes in treatment regimens due to fear of harming the foetus may impact the woman and her illness, evidence of serious adverse impact on disease activity as a result of the pregnancy itself was not found. However, weight gains proved to be more prominent in patients taking antipsychotics compared to women *not* on antipsychotics (Hironaka et al. 2011). Obesity has been identified as an adverse effect of drug treatment during pregnancy for women with schizophrenia, and may lead to other complications for both mother and foetus. In a review by Gentile (2010) gestational diabetes was found to be related to the drug treatment in several cases. A study meeting all but one of the inclusion criteria for this review discussed the risk of neural tube defects of infants born to women taking atypical antipsychotics and showed that these women's babies were at higher risk of neural tube defects due to the low intake of folate and obesity in the mother (Koren et al. 2002).

Relapse during or after pregnancy due to changes in antipsychotics treatment or discontinuation may lead to adverse effects. Stopping antipsychotic treatment may lead to relapse or psychosis in up to 65% of the women, as well as poor nutrition, increased use of over the counter drugs, and alcohol and substance abuse (Coppola et al. 2007). These complications expose the foetus to further risk. While pregnancy is often a less symptomatic time for the woman, relapses are frequent post-partum (Grigoriadis and Seeman 2002). A meta-analysis of the post-partum period of women with schizophrenia found that the post-partum period was characterised by a high risk of psychotic relapse (Matevosyan 2011). In the case of paused treatment regime during pregnancy, medication should be started again after delivery, as relapse of the disease can lead to child neglect or custody loss, or fatal outcomes. Fatal consequences for both mother and foetus due to changes in treatment regimes in pregnancy are illustrated in the literature reviewed in this study. A mother took overdose on the remaining supplies of clozapine after discontinuation of the treatment during

pregnancy (Kłys et al. 2007). This caused her serious poisoning and resulted in the neonatal death of her son. The case illustrates the difficulties in changing treatment regimens and the need for close follow-up of the patient when changes are made.

4.2 Outcomes for the foetus: abnormal foetal growth and development

Women with schizophrenia, depression or panic disorders have been found to be at higher risk of having preterm delivery and low birth weight babies (Bánhidý et al. 2006; MacCabe et al. 2007; Nilsson et al. 2002). Nevertheless, birth weight and time of delivery reported in this review were normal in the majority of cases. However, one study did report low birth weight as part of transient abnormalities, together with difficulties in feeding, respiratory acidosis, cyanosis with hypoxemia and polycythaemia (Nishizawa et al. 2007). Also, Apgar scores were normal in five out of six cases reported in the reviewed literature.

The United States' Food and Drug Administration's (FDA) Classification System rates clozapine as the only antipsychotic drug in group B, indicating no evidence of risk in humans when administered during pregnancy, while all other antipsychotics are classified as group C, indicating a risk when used during pregnancy. This distinction is highly in favour of clozapine, a view which has been challenged (Trixler et al. 2005). The literature reviewed showed mixed results on clozapine. Pregnancy and birth outcomes were normal and resulting in healthy babies in two of the three cases, whereas in the third case they were serious and fatal. In this case the mother took an overdose of clozapine obtained from previous treatment regimes, resulting in the death of her new born son.

Following the outcome classification by Gentile (2010), all nine malformations reported in the review are to be considered major malformations, many of which are expected to need surgery, including cleft lip and palate in three cases. While foetal malformation is a serious potential complication of drug use during pregnancy in women with schizophrenia, some of the adverse outcomes reported showed to be less serious in the long run. For a number of babies, the situation stabilised during a post birth follow-up period. Further, the lack of relationship between the adverse outcome and the drug was stressed by physicians in several cases.

4.3 Ethical considerations for patients, families and professionals

Schizophrenia is more common among relatives with schizophrenia than in the general population (McGuffin et al. 1995). However, despite the genetic component in developing schizophrenia, heredity was not an issue in any of the cases explored in this review. Ethical considerations related largely to other potential adverse outcomes for the foetus and the mother's ability to parent her child.

Coverdale and colleagues have discussed ethical strategies for managing pregnancy in patients with schizophrenia. They recommend preventive strategies by means of assisted and surrogate decision making with the aim of diminishing chronically and variably impaired autonomy (Coverdale et al. 2004). Similar strategies were discussed in the reviewed literature (Dudzinski and Sullivan 2004). The patient's exercise of autonomy in making a decision should be treated as a major ethical consideration. Given a certain level of decision-making capacity, the woman must decide, based on her values, beliefs and preferences, whether or not the foetus should be considered as a patient (Coverdale et al. 2004).

The patient's capacity to exercise autonomy relies on her ability to achieve cognitive understanding and appreciation, meaning she must understand the consequences of what could happen to her and her baby (Coverdale et al. 2004). Further, she should be able to evaluate the consequences following her own values and beliefs, referred to as *evaluative understanding* (White 1994). Finally, the patient must be able to communicate a voluntary decision. While informed consent was given in three studies (Kim et al. 2007; Vučić Peitl et al. 2010; Yaris et al. 2004), its validity was questioned in one of the reports (Vučić Peitl et al. 2010). In order to mitigate vulnerability, decision making could be shared with a responsible surrogate decision makers, and informed consent should be obtained from the patient's surrogate, as well as herself (Dudzinski and Sullivan 2004). Surrogate decision making should be based on information about the patient's longstanding values and preferences, and the surrogate should try to make the decision that the patient would make had she been able to do so. If this is not possible to identify, decisions should be made in a way that protects and promotes the patient's health (Buchanan and Brock 1986).

A review of the impact of antipsychotics during pregnancy stressed the importance of healthcare professionals to provide women with schizophrenia with information about the advantages of accepting a modest increase in teratogenic risk in order to maintain a stable mental status during pregnancy. Also, women should be informed that foetal malformation is a relatively common obstetric complication in the general population (Gentile 2010). But while information and educational interventions are important to improve the patient's autonomy in the decision making process, medication provides an important response to impaired decision making as a result of psychotic conditions. Adequate treatment regimens may improve the patients' ability to make informed decisions (Gentile 2010).

Psychiatric disorders represent the fourth leading cause of maternal death in the first year post-partum (Oates 1996). Policies should be aimed at providing better support to these vulnerable women and their new born babies. Measures such as longer hospitalisation after birth for women with schizophrenia have shown to improve outcomes (Muqtadir et al. 1986). A more cost-effective measure to consider is the reinforcement of non-medical initiatives such as specialised consultation units for mothers and their families. However, while close liaison has been pointed out as important to provide better management of care for these women with high risk pregnancies, women with mental illnesses have also avoided services being afraid of losing custody over their children (Howard 2005). Furthermore, as most pregnancies are unplanned, pregnancy counselling for women with schizophrenia is important to make decisions as to whether or not pregnancy and treatment should be continued or terminated. However, this proves to be difficult in practice. As illustrated by the studies in this review, women often present with relatively advanced pregnancies (Tényi et al. 2002; Vučić Peitl et al. 2010).

4.4 Economic aspects for individuals and society

The reviewed literature provided little information on the economic aspects of drug use during pregnancy with specific regard to women with schizophrenia. Therefore, the economic implications related to pregnancy in women with mental health problems, as well as those resulting from adverse effects associated with pregnancy in schizophrenic women were explored.

A study comparing the direct healthcare costs, during and after pregnancy, between women who continued treatment on antidepressants during the course of the pregnancy and those who discontinued the treatment during the first trimester found that healthcare costs were significantly higher for women continuing drug therapy. However, it was also thought that the women using antidepressants during pregnancy were likely to have disorders of greater severity compared to those who discontinued the treatment (Ramos et al. 2007).

Discontinuation of treatments for psychiatric disorders may lead to increased healthcare costs for intensive care services such as hospital stays, emergency department visits, and community physician services such as emergency department visits and hospital stays. The mean total healthcare costs for women continuing treatment was 1.6 times higher than those discontinuing treatment, however, when the costs associated with prescription medications were excluded, there were no differences in healthcare costs during and after pregnancy between the two groups (Ramos et al. 2007).

Evidence suggests that adverse outcomes for the foetus and newborn are associated with increased costs. In the United States, the healthcare costs for children with disabilities resulting from birth defects have been estimated to exceed USD 1.4 billion every year annually (PCRM 2014). A study which estimated the hospital costs of preterm and low birth weight babies in the United States in 2001 found that costs per infant hospitalisation were highest for very preterm babies (Russell et al. 2007). It was also estimated that preterm/low birth weight babies accounted for half of infant hospitalisation costs and one quarter of paediatric costs. This suggests that substantial savings can be made from preventing preterm birth among women with schizophrenia.

While no clinical guidelines in the United Kingdom exist for drug management in pregnant women with schizophrenia, guidelines do exist for antenatal and postnatal mental health (NICE 2007). The costing report accompanying the clinical guidelines for implementation purposes estimated costs in three areas of care identified as having the greatest resource impact. Costs of psychological therapy for pregnant women not meeting defined diagnostic criteria were estimated to £1,122 000, costs of core staff to manage clinical networks for perinatal mental health services were estimated at £1,673 000, and costs of additional mother and baby unit beds were estimated at £6,924 000. The report discussed the benefits of perinatal managed networks supporting the woman within the community, potentially leading

to reductions in the number of admissions to specialist services. The unit cost of an average bed day in a mental health service mother and baby unit was estimated to be £514, £271 more compared to a normal inpatient bed day unit cost. These estimates illustrate the potential economic burden of adverse outcomes relevant for pregnant woman with schizophrenia, and must be taken into account when planning obstetric care for optimal use of resources.

5. Conclusions

The review of the literature on drug use in pregnant women with schizophrenia clearly illustrates the abundance of anecdotal evidence in this field. This calls for better registries to document the use and effect on women and their babies. Until then, case reports will continue to play a valuable source of information regarding the effect of drug treatment for mental illnesses during pregnancy.

Continuing, discontinuing or changing drug treatment for schizophrenia in pregnant women pose several clinical and ethical dilemmas, and must be carefully investigated before a decision can be made. The risk of foetal malformation due to drug exposure must be balanced against the risk of relapse in the pregnant women whose treatment regimens are changed. Further, it should be stressed that the risk of foetal malformation, abortion, unintended delivery modes and low birth weight also occur in the general population.

Although the mother's ability to parent and nurse her child after birth may in some cases be questioned, non-drug treatment and support through specialised consultation and follow-up represent important measures to protect the mother and her baby, and should take place both before and after the baby is born. Consultation services should also aim to assist patients' partners and families. Further, potential carers for the baby should be identified. Finally, the women should be helped reintegrating into society.

The present review illustrates the need for further research into the economic implications for the individual and the healthcare system of drug therapy during pregnancy for women with schizophrenia. Better insight into the economics of pregnancy for women with chronic diseases will help improve patterns of care and provide better value for money in obstetric healthcare. In particular, the costs and efficacy of non-drug treatment and support before,

during and after pregnancy for women with schizophrenia should be explored with the aim to inform policy.

Recent drug developments and the emergence of atypical antipsychotics in the treatment of schizophrenia have made family planning for women with schizophrenia easier. While the risks associated with pregnancy and birth outcomes are unclear, even less is known about the long term effects of these new atypical antipsychotics. With higher fertility rates among women with schizophrenia, the need for more research on drug use in the treatment of schizophrenia during pregnancy is more pressing than ever.

References

- Bánhid, Ferenc, et al. (2006), 'Association between maternal panic disorders and pregnancy complications and delivery outcomes', *European Journal of Obstetrics & Gynecology and Reproductive Biology*, 124 (1), 47-52.
- Buchanan, Allen and Brock, Dan W (1986), 'Deciding for others', *The Milbank Quarterly*, 17-94.
- Bursalioglu, Fusun Sevimli, et al. (2013), 'The Correlation Between Psychiatric Disorders and Women's Lives', *Journal of clinical and diagnostic research: JCDR*, 7 (4), 695.
- Chatterjee, Sharmila, Kotelchuck, Milton, and Sambamoorthi, Usha (2008), 'Prevalence of chronic illness in pregnancy, access to care, and health care costs: implications for interconception care', *Women's Health Issues*, 18 (6), S107-S116.
- Coppola, Danielle, et al. (2007), 'Evaluating the postmarketing experience of risperidone use during pregnancy', *Drug Safety*, 30 (3), 247-64.
- Coverdale, John H, McCullough, Laurence B, and Chervenak, Frank A (2004), 'Assisted and surrogate decision making for pregnant patients who have schizophrenia', *Schizophrenia Bulletin*, 30 (3), 659-64.
- d'Orb, PT (1979), 'Women who kill their children', *The British journal of psychiatry*, 134 (6), 560-71.
- Dixon-Woods, Mary, et al. (2006), 'How can systematic reviews incorporate qualitative research? A critical perspective', *Qualitative research*, 6 (1), 27-44.
- Doherty, J, Bell, PF, and King, DJ (2006), 'Implications for anaesthesia in a patient established on clozapine treatment', *International Journal of Obstetric Anesthesia*, 15 (1), 59-62.
- Doherty, Michael (1994), 'What value case reports?', *Annals of the Rheumatic Diseases*, 53 (1), 1.
- Dudzinski, Denise M and Sullivan, Mark (2004), 'When agreeing with the patient is not enough: a schizophrenic woman requests pregnancy termination', *General Hospital Psychiatry*, 26 (6), 475-80.
- Duran, Alaattin, et al. (2008), 'Case Report: Clozapine use in two women with schizophrenia during pregnancy', *Journal of Psychopharmacology*, 22 (1), 111-13.
- Falkov, Adrian and Britain, Great (1996), *Study of Working Together Part 8'Reports Fatal Child Abuse and Parental Psychiatric Disorders: An Analysis of 100 Area Child Protection Committee Case Reviews Conducted Under the Terms of Part 8 of Working Together Under the Childrens Act 1989* (Department of Health).
- Gentile, Salvatore (2010), 'Antipsychotic therapy during early and late pregnancy. A systematic review', *Schizophrenia Bulletin*, 36 (3), 518-44.
- Grigoriadis, S. and Seeman, M. V. (2002), 'The role of estrogen in schizophrenia: implications for schizophrenia practice guidelines for women', *Can J Psychiatry*, 47 (5), 437-42.
- Hironaka, Masae, et al. (2011), 'Maternal mental disorders and pregnancy outcomes: A clinical study in a Japanese population', *Journal of Obstetrics and Gynaecology Research*, 37 (10), 1283-89.
- Howard, L. M. (2005), 'Fertility and pregnancy in women with psychotic disorders', *Eur J Obstet Gynecol Reprod Biol*, 119 (1), 3-10.
- Janjic, V., et al. (2013), 'Zuclopenthixol decanoate in pregnancy: Successful outcomes in two consecutive off springs of the same mother', *Zuklopentiksol dekanat u trudnoci: Uspešan ishod dve uzastopne trudnoce iste majke*, 70 (5), 526-29.

- Janjić, Vladimir, et al. (2013), 'Zuclopenthixol decanoate in pregnancy: Successful outcomes in two consecutive off springs of the same mother', *Vojnosanitetski pregled*, 70 (5), 526-29.
- Kim, Sung-Wan, et al. (2007), 'Use of long-acting injectable risperidone before and throughout pregnancy in schizophrenia', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 31 (2), 543-45.
- Kłys, Małgorzata, Rojek, Sebastian, and Rzepecka-Woźniak, Ewa (2007), 'Neonatal death following clozapine self-poisoning in late pregnancy: an unusual case report', *Forensic Science International*, 171 (1), e5-e10.
- Koren, Gideon, et al. (2002), 'Use of atypical antipsychotics during pregnancy and the risk of neural tube defects in infants', *American Journal of Psychiatry*, 159 (1), 136-37.
- Lin, Herng-Ching, et al. (2010), 'Maternal schizophrenia and pregnancy outcome: does the use of antipsychotics make a difference?', *Schizophrenia Research*, 116 (1), 55-60.
- MacCabe, James H, et al. (2007), 'Adverse pregnancy outcomes in mothers with affective psychosis', *Bipolar disorders*, 9 (3), 305-09.
- Matevosyan, Naira Roland (2011), 'Pregnancy and postpartum specifics in women with schizophrenia: a meta-study', *Archives of Gynecology and Obstetrics*, 283 (2), 141-47.
- McCullough, Laurence B, Coverdale, John H, and Chervenak, Frank A (2002), 'Ethical challenges of decision making with pregnant patients who have schizophrenia', *American Journal of Obstetrics and Gynecology*, 187 (3), 696-702.
- McGuffin, Peter, Owen, MichaelJ, and Farmer, AnneE (1995), 'Genetic basis of schizophrenia', *The Lancet*, 346 (8976), 678-82.
- Mendhekar, Dattatreya and Lohia, Deep (2008), 'Risperidone therapy in two successive pregnancies', *The Journal of neuropsychiatry and clinical neurosciences*, 20 (4), 485-86.
- Miller, Laura J (1997), 'Sexuality, reproduction, and family planning in women with schizophrenia', *Schizophrenia Bulletin*, 23 (4), 623.
- Moher, D., et al. (2009), 'Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement', *Journal of Clinical Epidemiology*, 62 (10), 1006-12.
- Muqtadir, Syeda, Hamann, Martin W, and Molnar, George (1986), 'Management of psychotic pregnantpatients in a medical-psychiatricunit', *Psychosomatics*, 27 (1), 31-33.
- Nako, Y, et al. (2001), 'Neonatal thrombocytosis resulting from the maternal use of non-narcotic antischizophrenic drugs during pregnancy', *Archives of Disease in Childhood-Fetal and Neonatal Edition*, 84 (3), F198-F200.
- NICE, National Institute for Health and Clinical Excellence (2007), 'Antenatal and postnatal mental health', in National Institute for Health and Clinical Excellence NICE (ed.), *NICE clinical guideline* (London: NICE, National Institute for Health and Clinical Excellence).
- Nilsson, Emma, et al. (2002), 'Women with schizophrenia: pregnancy outcome and infant death among their offspring', *Schizophrenia Research*, 58 (2), 221-29.
- Nishizawa, Osamu, et al. (2007), 'Effectiveness of comprehensive supports for schizophrenic women during pregnancy and puerperium: Preliminary study', *Psychiatry and Clinical Neurosciences*, 61 (6), 665-71.
- Oates, Margaret (1996), 'Psychiatric services for women following childbirth', *International Review of Psychiatry*, 8 (1), 87-98.
- OECD (2009), 'Mean age of mothers at first child birth. OECD Family Database: OECD Social Policy Division'.
- PCRM (2014), 'Birth Defect Statistics', in Physicians Committee for responsible Medicine (ed.), (Washington).

- Ramos, E, et al. (2007), 'Antidepressant therapy during pregnancy: an insight on its potential healthcare costs', *The Canadian journal of clinical pharmacology= Journal canadien de pharmacologie clinique*, 15 (3), e398-410.
- Russell, Rebecca B, et al. (2007), 'Cost of hospitalization for preterm and low birth weight infants in the United States', *Pediatrics*, 120 (1), e1-e9.
- Ružić, Klementina, et al. (2009), 'Pregnancy and atypical antipsychotics', *Psychiatria Danubina*, 21 (3), 368-70.
- Stotland, NL (2001), 'Psychiatric aspects of induced abortion', *Archives of Women's Mental Health*, 4 (1), 27-31.
- Su, Kuan-Pin, Shen, Winston W, and Huang, Shih-Yi (2001), 'Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient', *European Neuropsychopharmacology*, 11 (4), 295-99.
- Tényi, Tamás, Trixler, Mátyás, and Keresztes, Zsuzsanna (2002), 'Quetiapine and pregnancy', *American Journal of Psychiatry*, 159 (4), 674-74.
- Toh, Sengwee, et al. (2013), 'Prevalence and trends in the use of antipsychotic medications during pregnancy in the US, 2001–2007: a population-based study of 585,615 deliveries', *Archives of Women's Mental Health*, 1-9.
- Trixler, Mátyás, et al. (2005), 'Use of antipsychotics in the management of schizophrenia during pregnancy', *Drugs*, 65 (9), 1193-206.
- Vučić Peitl, Marija, Petrić, Daniela, and Peitl, Vjekoslav (2010), 'Ziprasidone as a possible cause of cleft palate in a newborn', *Psychiatria Danubina*, 22 (1), 117-19.
- White, Becky (1994), *Competence to consent* (Georgetown University Press).
- Yaeger, Deborah, Smith, Healy, and Altshuler, Lori (2006), 'Atypical antipsychotics in the treatment of schizophrenia during pregnancy and the postpartum', *American Journal of Psychiatry*, 163 (12), 2064-70.
- Yaris, Fusun, et al. (2004), 'Use of polypharmacotherapy in pregnancy: a prospective outcome in a case', *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 28 (3), 603-05.

Appendix

Overview of the clinical outcomes compiled for the review

| Study | Sample size | Age | Drug, daily dose, timing of exposure during pregnancy | Gest. Complications | Pregnancy outcomes (delivery, term) | Birth weight | Foetal malformations | Foetal and neonatal outcomes | Comments |
|---------------------|-------------|-----|---|---------------------|--|----------------|---|---|---|
| Coppola et al. 2007 | 1 | 35 | risperidone | | | | | Somnolence, Jitteriness, slow to suckle | Mother occasionally drank during pregnancy. Possibly Withdrawal or perinatal syndrome |
| Coppola et al. 2007 | 1 | 35 | risperidone, lormetazepam, first trimester | | | Normal (2900g) | Multiple major malformations (pulmonary artery stenosis, abdominal heterotaxy, splenic agenesis (Ivemark's syndrome)) | | |
| Coppola et al. 2007 | 1 | 27 | risperidone, first trimester | | | | Cleft lip and palate | | Malformations detected on ultrasound evaluation at 25 weeks |
| Coppola et al. 2007 | 1 | 30 | risperidone, first trimester | | | | Right-auricular achondroplasia | | At 3 month follow up infant was well with no abnormal findings |
| Coppola et al. 2007 | 1 | 33 | risperidone, first trimester | | | | Pierre Robin syndrom, (micrognathia, glossotosis and cleft palate) | | |
| Coppola et al. 2007 | 1 | 34 | risperidone, first trimester | | Cesarian, week 32 (due to pre-eclampsia) | | Corpus callosum agenesis | | |

| | | | | | | |
|----------------------------|---|-----|--|-----------------------|-------------------------------|---|
| Coppola et al. 2007 | 1 | 35 | risperidone | | Moyamoya disease | Infant had cerebral infarction causing hemiplegia on the left side 8 months after birth. Paralysis disappeared after surgery and she recovered completely |
| Coppola et al. 2007 | 1 | 35 | risperidone | Preterm (by 10 weeks) | Ventricular cyst in the brain | Child developed normally although head circumference was above the 97th percentile |
| Coppola et al. 2007 | 1 | n/a | risperidone, first trimester | | Patent foramen ovale | Severity of defect outcome was not reported |
| Coppola et al. 2007 | 1 | 35 | risperidone, 12mg/day, from 3 days prior to delivery, then ↓ to 10mg/day for 2 days, then ↓ to 8mg/day | | | Withdrawal syndrome (somnolence, jitteriness, slow to suckle) |
| Coppola et al. 2007 | 1 | 32 | risperidone, 4mg/day (long-term treatment) | | | Withdrawal syndrome, hypertonia, jitteriness) |
| Coppola et al. 2007 | 1 | 24 | risperidone, 1mg/day during the last 4 months | | | Withdrawal syndrome (hypersensitivity, choking, irritability and jitteriness) |
| Coppola et al. 2007 | 1 | n/a | risperidone, 4mg/day | | | Withdrawal syndrome (jitteriness) |
| Coppola et al. 2007 | 1 | 29 | risperidone | | | Withdrawal syndrome (convulsion, feeding problems) |
| Coppola et al. 2007 | 1 | 35 | risperidone, 1mg/day throughout pregnancy | | | Withdrawal syndrome (somnolence, depressed level of consciousness, hypersalivation) |

| | | | | | | | | |
|------------------------------|----|----------|---|--------------|--|--|---|--|
| Coppola et al. 2007 | 1 | 31 | risperidone, 6mg/day during the second and third trimesters | | Full term | Normal (3600g) | Perinatal syndrome (respiratory difficulties) | According to the physician the event was not related to risperidone |
| Coppola et al. 2007 | 1 | n/a | risperidone, 12mg/day, duration unknown | | Full term | Normal (3700g) | Perinatal syndrome (neonatal asphyxia, subsarachnoid/subdural haemorrhage and shoulder dystocia, cyanosis, shock, retractive breathing, decreased muscle tone, congenital brain damage, unilateral facial palsy, metabolic acidosis and hyperbilirubemia) | |
| Coppola et al. 2007 | 1 | 33 | risperidone | | Full term | Normal (3800g) | Perinatal syndrome (jaundice) | Physician reported that a causal association with risperidone was doubtful |
| Doherty et al. 2006 | 1 | 33 | clozapine | | Cesarean, early labour | | Healthy, Apgar: 9@1min, 10@5min | |
| Dudzinski et al. 2004 | 1 | 34 | haliperidole, injection once a month | | | | | |
| Duran et al. 2008 | 2 | n/a | Case 1: clozapine, 200mg/day. Case 2: clozapine 400mg/day, then ↓ to 200gm/day | | Case 1 and 2: normal delivery, full term | Normal (Case 1: normal 2900g, 3000g, Case 2: 3100g, 2940g) | Healthy, Apgar: 9@1min, 10@5min | |
| Hironaka et al. 2008 | 15 | 32 | Benzodiazepine and atypical antipsychotics | Weight gains | Shorter gestational age | | Apgar scores similar (normal) in treatment and control group | |
| Janjic et al. 2013 | 1 | Mid-aged | zuclopenthixol decaonate, injection 400mg/2weeks, then ↓ to 200mg/month | | 2 deliveries, normal, full term | Normal (3750g, 3700g) | Healthy, both babies had Apgar: 9 | |
| Klys et al. 2007 | 1 | 27 | clozapine discontinued in the first trimester, switched to valproate, promethazine, | | | | Neonatal death following clozapine poisoning, Apgar: 1 | |

| | | | | | | | |
|------------------------------|------|-------|---|---|---------------------------------------|--------------|---|
| risperidone, fluoxetine | | | | | | | |
| Lin et al. 2010 | 236* | 25-29 | atypical (n=46), typical (n=190) | Preterm observed more frequently in patients receiving typical antipsychotics | | | No difference in birth weight between babies of mothers on atypical vs typical antipsychotics |
| Mendhekar et al. 2008 | 1 | 23 | risperidone, 3mg/day during first pregnancy, then ↓ to 2mg/day | 2 deliveries, normal, full term | Normal (3200g, 3000g) | | |
| Nako et al. 2001 | 1 | 25 | chlorpromazine 50mg/day, haloperidol 12mg/day, biperiden 5mg/day, promethazine hydrochloride 25mg/day, nitrazepam 5mg/day | Normal, week 35 | Normal (2540g (appropriate for date)) | | Thrombocytosis (3 months), Apgar: 7@1min, 8@5min |
| Nishizawa et al. 2007 | 20 | 33/39 | chlorpromazine, other antipsychotics (not specified) | Caesarean due to obstetric complication (n=5) | Low birth weight (n=5) | | Transient abnormalities (difficulties in feeding, respiratory asidosis) (n=5) |
| Peitl et al. 2010 | 1 | 33 | ziprasidone, 120mg/day, ↓ to 80mg/day, ↓ to 40mg/day until childbirth | Normal, full term | Normal (3070g) | Cleft palate | Authors not sure if the cleft palate was a result of use of ziprasidone |
| Ružić et al. 2009 | 1 | 40 | ziprasidone | Normal, full term | Normal (4210g) | | Healthy |
| Su et al. 2001 | 1 | 30 | omega 3 fatty acid, throughout pregnancy | Improvement in disease symptoms | | | |
| Yaeger et al. 2006 | 1 | 38 | quetiapine, 300mg/day | Induced abortion | | | |

| | | | | | | | |
|--------------------------------|----|----|--|-----------|---|----------------|---|
| Yaris et al. 2004 | 1 | 36 | risperidone, quetiapine, other drugs (n=13) | | Normal, week 37 | Normal (3000g) | Healthy, Apgar: 8-9@1min and 5min |
| Bursalioglu et al. 2013 | 61 | 30 | Antipsychotics (not specified) | | 5 woman had 7 abortion in order to resume therapy | | No postnatal complications in babies due to the psychotic medication taken by the mother during pregnancy |
| Tenyi et al 2002 | 1 | 38 | quetiapine, 300mg/day, then ↓ to 200mg/day, then↓ to 150mg/day | Remission | Normal, full term | Normal (3120g) | Apgar: 9@1min, 10@5min |
| Kim et al | 1 | ? | risperidone, 2mg/day, switched to long acting injectible risperidone | | 1st pregnancy: Induced abortion (when on risperidone), 2nd pregnancy: membrane abruptly ruptured, week 36 | | Healthy |

*Out of a total of 242 women treated with antipsychotic for schizophrenia during pregnancy, 236 were treated in monotherapy.

**For further information on this or any of the
Health publications contact:**

Anthony Kelly
Managing Editor
LSE Health
The London School of Economics and Political Science
Houghton Street
London WC2A 2AE

Tel: + 44 (0)20 7955 7392

Fax: + 44 (0)20 7955 6090

Email: a.p.kelly1@lse.ac.uk

Website: www.lse.ac.uk/collections/LSEHealth/

