Psychopharmacology
DOI 10.1007/s00213-013-3029-5

ORIGINAL INVESTIGATION

The effects of maternal depression and use of antidepressants during pregnancy on risk of a child small for gestational age

Hans Mørch Jensen · Randi Grøn · Øjvind Lidegaard · Lars Henning Pedersen · Per Kragh Andersen · Lars Vedel Kessing

Received: 10 December 2012 / Accepted: 4 February 2013

Abstract
Rationale Use of antidepressants during pregnancy has been associated with an increased rate of children small for gestational age (SGA), but it is unclear whether this is due to an effect of the underlying depressive disorder.
Objectives This study aimed to investigate the effect of antidepressants on SGA in a nationwide sample and to separate the effect of exposure to antidepressants in utero from the effect of maternal depression.
Methods A register study was conducted on all pregnant women in Denmark from 1996 to 2006 linking nationwide individualized data from the Medical Birth Register, the Psychiatric Central Register, and a prescription database. The rate of SGA (birth weight below the 10 percentile at given gestational week) was investigated for children exposed in utero to antidepressants or to a maternal psychiatric diagnosis of depression compared to children not prenatally exposed to antidepressants or maternal diagnosis.
Results A total of 673,853 pregnancies were included in the study of which 35.737 women had a diagnosis of depression and/or used antidepressants before end of pregnancy. Antidepressant use during pregnancy was weakly associated with SGA (hazard ratios (HR)=1.19; 95 % confidence interval (CI), 1.11–1.28), whereas a psychiatric diagnosis before or during pregnancy was not (HR= 1.02; 95 % CI, 0.92–1.13). The association for use during pregnancy was found for selective serotonin reuptake inhibitors and newer antidepressants, but not for older antidepressants.
Conclusions The use of antidepressants during pregnancy slightly increases the rate of SGA. The association seems unrelated to the underlying maternal depressive disorder.

Keywords Pregnancy · Depression · Small for gestational age · Antidepressants

Introduction

Depression is common among pregnant women with an estimated prevalence of 7–13 % (Bennett et al. 2004; Evans et al. 2001) and the use of antidepressants during pregnancy has increased in Western countries (Cooper et al. 2007; Alwan et al. 2011). Antidepressants pass the placental barrier (Heikkine et al. 2002; Heikkinen et al. 2002; Hendrick et al. 2003) and neonatal complications, such as tremors, jitteriness, increased muscle tone (Moses-Kolko et al. 2005), and low Apgar score (Kallen 2004; Lund et al. 2009; Oberlander et al. 2008; Simon et al. 2002; Wisner et al. 2009; Jensen et al. 2013) associated with exposure to antidepressants have been widely reported. Exposure in utero to antidepressants has further been associated with low birth weight (Ericson et al. 1999; Simon et al. 2002; Kallen 2004), preterm delivery (Simon et al. 2002; Hendrick et al. 2003), and children small for gestational age (Simon et al. 2002; Ramos et al. 2010).

H. M. Jensen · L. V. Kessing (✉)
Psychiatric Centre Copenhagen, Rigshospitalet,
Copenhagen University Hospital, Blegdamsvej 9,
2100 Copenhagen Ø, Denmark
e-mail: lars.vedel.kessing@regionh.dk

R. Grøn · P. K. Andersen
Department of Biostatistics, University of Copenhagen,
Copenhagen, Denmark

Ø. Lidegaard
Department of Obstetrics and Gynecology, Rigshospitalet,
University of Copenhagen, Copenhagen, Denmark

L. H. Pedersen
Department of Obstetrics and Gynecology, Institute of Clinical
Medicine, Aarhus University, Aarhus, Denmark

Published online: 02 March 2013

However, depression per se may increase the risk of birth complications (O'Keane and Marsh 2007b; Nakano et al. 2004; Lorenzo et al. 2011; Koren and Nordeng 2012). It is possible that increased placental secretion of corticotrophin-releasing hormone resulting in increased activity within the gestational cortisol system (Wadhwa et al. 2002) as well as unhealthy behavior related to depression such as smoking and poor attendance to obstetric care may have adverse effects (Andrade et al. 2008; Alwan et al. 2011; O'Keane and Marsh 2007a). So far, only few studies have attempted to discriminate between the effects of maternal disease and use of antidepressants in relation to birth outcomes revealing increased risk of low birth weight, respiratory distress (Oberlander et al. 2006), preterm birth (El Marroun et al. 2012), and low Apgar score (Jensen et al. 2013), even when maternal illness severity was accounted for.

The present paper reports from a register-based study investigating the rate of small for gestational age (SGA) and other outcomes in different groups according to maternal depression before or during pregnancy and to exposure to antidepressants. We have been previously using a similar data set and design reported on Apgar score as an outcome (Jensen et al. 2013). In the present paper, we aimed to determine the potential isolated effects of prenatal antidepressant exposure and antenatal maternal depression on fetal growth. We chose SGA as the outcome measure, as SGA is a combined measure of gestational age and birth weight and as SGA seems to be associated with detrimental consequences later on in life. Children born with SGA have a small, yet increased risk of developing psychiatric disorders during adolescence and young adulthood (Laursen et al. 2007; Mathiasen et al. 2011) and lower academic achievement and professional attainment as adults (Strauss 2000).

The hypothesis of the present study was that birth complications, as reflected in SGA, are explained by the effect of the maternal disease.

Methods

Danish register data

Data on all pregnancies from 1996 to 2006 were obtained from the Medical Birth Register and linked with data from the National Psychiatric Central Register, the Medicinal Product Statistics Register, and Statistics Denmark.

The Medical Birth Register (Knudsen and Olsen 1998) includes information on birth date, gestational age, birth weight, maternal smoking status at first pregnancy visit, parity, and age of mother at delivery. Only singleton deliveries with a gestational age of at least 22 weeks during the period 1996–2006 were included.

The Medicinal Product Statistics is a nationwide prescription database containing information on all redeemed prescriptions from all Danish pharmacies from 1994 and onwards, validated from 1995. The drugs in the register are coded by the Anatomical Therapeutical Chemical classification system (ATC) codes (World Health Organization 2003), and we received information on antidepressants, antipsychotics, antiepileptics, and all other kinds of drugs. Antidepressants were classified into selective serotonin reuptake inhibitors (SSRIs; ATC N06AB03-10), newer antidepressants (ATC N06AX06, N06AX06-11, N06AX06-16, N06AX06-18, and N06AX06-21) and older antidepressants consisting mainly of tricyclic antidepressants (ATC N06AA02-7, N06AA09-12, N06AA16-17, N06AA21, N06AX03, N06AF01, and N06AG02).

The Danish Psychiatric Central Register is a nationwide psychiatric register (Mors et al. 2011) with data from all public mental health services for inpatients as well as outpatients. The included depression diagnosis codes were: ICD-8 codes 296.09 and 296.29 and from 1994 the ICD-10 codes DF32.00-DF33.99.

Statistics Denmark provided data on annually updated social background of the women included grouping them into either working, unemployed, disability or age pension, student, children under the age of 18, or other (Statistics Denmark 2011).

Statistical analyses

Data on diagnosis of depression and medication were available as time-dependent variables from 1996 to 2006. Pregnant women were divided into eight exposure groups according to the exposure of a diagnosis of depression before end of pregnancy, use of antidepressants before pregnancy, and antidepressant use during pregnancy (Table 2, model 1). Poisson regression analyses were performed to estimate the relative risk by calculating hazard ratios (HR) for SGA. Additional analyses were done using a simpler characterization of exposure groups using three binary variables: diagnosis in DPC before giving birth (yes/no), use of antidepressants before pregnancy (yes/no), and use of antidepressants during pregnancy (yes/low) (see lower part of Table 2, model 2).

SGA was defined as birth weight below the 10 percentile of birth weight at a given gestational week (between weeks 22 and 45). The analyses on the effect of antidepressants and diagnoses of depression were corrected for the woman's age at delivery, calendar year of delivery (in 1-year categories), sex of newborn, use of antiepileptics (yes/no), antipsychotics (yes/no), and other types of medicine (yes/no) during pregnancy, smoking status (nonsmoker, quit smoking, smoking, and unknown), and social status (student or employed vs. unemployed, disability pension or retired, and others).

Results

We aimed to include all singleton deliveries with a gestational age of at least 22 weeks during the period 1996–2006 in Denmark. Over the 11-year study period, we recorded 963,585 pregnancies including miscarriages, live, and stillbirths. After removing pregnancies terminated at a gestational age of less than 22 weeks, the study cohort included 673,853 pregnancies, 672,601 live-born children by 440,835 mothers, and 1,252 stillbirths by 1,234 women. A total of 671,175 of the children were born at a gestational age of 28 to 44 weeks (i.e., third trimester) and 1,426 children were born at a gestational age of less than 28 weeks.

The women had a diagnosis of depression during pregnancy coded in the Danish Psychiatric Central Register in 3,966 of the pregnancies (0.6 % of all pregnancies). In 8,511 pregnancies (1.3 %), the women cashed a prescription of antidepressant medication during pregnancy. In 7,510 (1.1 %) pregnancies, the women cashed a prescription during first trimester, in 3,837 (0.6 %) during second trimester, and in 3,300 (0.5 %) cases during third trimester. The total number of pregnancies where the woman had cashed antidepressants before pregnancy was 33,599 (5.0 %). Antiepileptics were used in 2,936 (0.4 %) pregnancies, prescriptions on antipsychotics in 1,300 (0.2 %) pregnancies, and prescriptions on lithium in 59 (0.01 %) pregnancies. Prescriptions of "other" medication were recorded in 457,185 (67.9 %) pregnancies. Table 1 shows the characteristics of the pregnant women according to antidepressant therapy and depressive diagnosis.

The distribution of pregnancies within the eight exposure groups (observed at the end of pregnancy) and the adjusted rate of small children are presented in Table 2 (upper part, model 1). Pregnancy end points were stillbirth (N=1,252; 0.2 %), term delivery with SGA (N=64,716; 9.6 %), preterm delivery before 37 full weeks of gestation (N=32,240; 4.8 %), or preterm delivery before full 32 weeks of gestation (N=4,074; 0.6 %). Treatment with antidepressants during pregnancy was associated with increased risk of SGA (exposure groups 3, 4, and 8). No increased risk for SGA was observed among women with depression who did not use antidepressants during pregnancy (exposure groups 5 and 6). The risk was also increased for exposure group 2 using antidepressants before pregnancy.

Additional analyses using a simpler characterization of exposure groups (lower part of Table 2, model 2) showed that compared to not being prenatally exposed to antidepressants or maternal diagnosis, taking antidepressants during pregnancy was associated with increased risk of SGA (HR=1.19; 95 % confidence interval (CI), 1.11–1.28). A depressive diagnosis before or during pregnancy was not associated with SGA (HR=1.02; 95 % CI 0.92–1.13); however, the use of antidepressants before pregnancy had a comparable point estimate with a CI excluding the null (HR=1.06; 95 % CI, 1.02–1.10).

Comparing women without a depressive episode and taking antidepressants during pregnancy to women with a diagnosis but not taking antidepressants during pregnancy resulted in HR=1.19/1.02=1.17 (95 % CI, 1.01–1.32).

The HRs for antidepressant use by trimester were: 1.07 for the first trimester (95 % CI, 0.98–1.16), 1.15 for the second trimester (95 % CI, 0.97–1.35), and 1.18 for the third trimester (95 % CI, 1.00–1.40). For women who cashed in prescriptions of antidepressants during pregnancy, the SSRIs were associated with SGA (HR=1.22; 95 % CI, 1.13–1.32) and a comparable point estimate for the rate of SGA, but including the null, was found for newer antidepressants (HR=1.16; 95 % CI, 0.97–1.40). For older antidepressants, the estimate did not suggest an association (HR=0.96; 95 % CI, 0.78–1.20). Taking antidepressants before pregnancy was associated with slightly increased SGA for newer and older antidepressants, but not for SSRIs (see Table 3).

The study controlled for maternal age. Compared to pregnant women aged 25–30 years old, the rates of SGA were: HR=1.36 for <20 years old (95 % CI, 1.31–1.41), HR=1.14 for 20–25 years old (95 % CI, 1.12–1.17), HR=0.98 for 30–35 years old (95 % CI, 0.96–1.00), and HR=1.12 for 36+ years old (95 % CI, 1.09–1.15).

The use of antidepressant medication among pregnant women generally increased during the study period (Danish National Board of Health 2007), but this study demonstrated no systematic increase in hazard ratio with calendar year (results not presented).

Discussion

This study found an increased risk of SGA among women taking antidepressants during pregnancy. Conversely, we found no increased risk for SGA among women with depression who did not use antidepressants during pregnancy. The finding of SGA related to antidepressants is in accordance with findings in some previous studies (Simon et al. 2002; Ramos et al. 2010). An elevated risk of SGA has been shown for SSRIs but not for tricyclic antidepressants (Simon et al. 2002), and one study showed an *increase* in gestational age-specific birth weight in infants of women who used non-SSRI drugs (Ericson et al. 1999). In the present study, we controlled for important confounders including age of mother, smoking status, social status, calendar year, and treatment with other medication than antidepressants. The fact that the rate of SGA was drug class-dependent further supports that the effect relates to the medication and not the disease.

The slightly increased risk of SGA among women taking antidepressants before but not during pregnancy and without

Table 1 Characteristics of pregnant women according to antidepressant therapy and depressive diagnosis

Maternal characteristics	Antidepressant medication before pregnancy	Antidepressant medication during pregnancy	Depression diagnosis before end of pregnancy	All pregnant women
Age (years), median, quartiles	30 (26–33)	30 (26–33)	29 (25–33)	29 (26–32)
Gestational age (weeks), median, quartiles	39 (38–40)	39 (38–40)	39 (38–40)	40 (39–41)
Smoking status (%)				
Nonsmoker	63.8	57.3	60.5	68.6
Smoking	27.1	31.4	29.1	16.1
Quit smoking	2.7	2.8	3.0	1.8
Unknown	6.4	8.5	7.4	13.5
Lithium treatment (%)				
No	99.9	99.8	99.6	99.99
Yes	0.1	0.2	0.4	0.01
Antiepileptic treatment (%)				
No	98.7	97.3	97.9	99.6
Yes	1.3	2.8	2.2	0.4
Antipsychotic treatment (%)				
No	98.0	94.3	95.3	99.8
Yes	2.0	5.7	4.7	0.2
Other medication (%)				
No	21.5	17.5	20.1	32.2
Yes	78.5	82.5	80.0	67.8

Each of the three columns is binary (antidepressant medication before pregnancy (yes/no), antidepressant medication during pregnancy (yes/no), and depression diagnosis before end of pregnancy (yes/no)) and presents data for those patients fulfilling the criteria (yes). The columns are not mutually exclusive

Table 2 The adjusted rate of SGA according to a depressive diagnosis and antidepressant therapy before or during pregnancy

Risk group (*n*)	Diagnosis before end of pregnancy	Antidepressants before pregnancy	Antidepressants during pregnancy	HR[a] (95 % CI)
Model 1				
1 (*n*=638,116)	−	−	−	1 (reference)
2 (*n*=24,560)	−	+	−	1.07 (1.03–1.11)
3 (*n*=1,232)	−	−	+	1.27 (1.09–1.48)
4 (*n*=5,979)	−	+	+	1.22 (1.13–1.32)
5 (*n*=740)	+	−	−	0.91 (0.72–1.16)
6 (*n*=1,926)	+	+	−	1.04 (0.92–1.20)
7 (*n*=166)	+	−	+	1.44 (0.89–2.31)
8 (*n*=1,134)	+	+	+	1.42 (1.20–1.68)
Antiepileptics during pregnancy				1.24 (1.12–1.37)
Antipsychotics during pregnancy				1.11 (0.96–1.29)
Other medication during pregnancy				0.99 (0.97–1.00)
Model 2				
Antidepressants before pregnancy				1.06 (1.02–1.10)
Antidepressants during pregnancy				1.19 (1.11–1.28)
Diagnosis of depression before end of pregnancy				1.02 (0.92–1.13)

The eight groups in model 1 are mutually exclusive and sum up to 100 %. Group 1 is the group unexposed to a diagnosis of depression as well as to antidepressants (the reference group). Groups 2, 4, 6, and 8 are exposed to antidepressants before pregnancy. Groups 3, 4, 7, and 8 are exposed to antidepressants during pregnancy. Groups 5–8 include patients with a diagnosis of depression before end of pregnancy. The three groups in model 2 are not mutually exclusive

[a] In both models, HRs are adjusted for maternal age, smoking status, social status, calendar year, sex of newborn, and use of antiepileptics, antipsychotics, and other types of medication

Table 3 Associations between risk of SGA child and use of different classes of antidepressants

	HR (95 % CI)
SSRIs during pregnancy	1.22 (1.13–1.32)
Newer antidepressants during pregnancy	1.16 (0.97–1.40)
Older antidepressants during pregnancy	0.96 (0.78–1.20)
SSRIs before pregnancy	1.00 (0.96–1.04)
Newer antidepressants before pregnancy	1.14 (1.05–1.24)
Older antidepressants before pregnancy	1.14 (1.05–1.24)
Diagnosis before pregnancy	0.99 (0.90–1.10)

HRs are adjusted for maternal age, smoking status, social status, calendar year, sex of newborn, and use of antiepileptics, antipsychotics, and other types of medication

a diagnosis of depression (exposure group 2 and model 2 in Table 2) and among women using newer or older antidepressants before pregnancy (Table 3) may be explained by use of antidepressants during early pregnancy even if they were prescribed prior to pregnancy (as some prescription may cover many months). This type of exposure misclassification would lead to an underestimation of the effect. Exposure during the early stage could theoretically interfere with placentation and subsequently lead to intrauterine growth restriction and thus an increased occurrence of SGA at birth. The association between use of antidepressants during pregnancy and SGA seems unrelated to timing during pregnancy; however, the study had limitations in determining the precise timing of intake.

We found a much lower prevalence of depression during pregnancy (0.7 %) than previously described due to the use of a hospital-based register that does not include information from general practitioners or private psychiatrists. As a consequence, only more severe forms of depression were included. For these women, we found no association between depression and the rate of SGA and thus believe that effects of milder forms of depression are unlikely.

The proportion of women with a prescription of antidepressants during pregnancy was low at 1.3 % because it was uncommon to treat pregnant women with antidepressants in the early years of the study period (Danish National Board of Health 2007). The prevalence of pregnant women undergoing treatment has since increased substantially (Danish National Board of Health 2007). Our study does not suggest any possible etiology concerning the effect of antidepressants and rate of SGA but demonstrated an association between the two. Lower birth weight and gestational age correlate with decreased cognitive function among school-aged children (Bhutta et al. 2002) and children born with SGA have a small, yet increased risk of developing psychiatric disorders during adolescence and young adulthood (Laursen et al. 2007; Mathiasen et al. 2011). Findings of the present study add to the growing body of evidence in the area and address the clinically important question of whether a woman taking antidepressants and planning pregnancy should consider tapering off the medication or continue the medication.

Strengths

The register data were collected prospectively on a routine basis and not specifically as part of this study. This is the case in relation to data from all four registers included in the study (the Medical Birth Register, the National Psychiatric Central Register, the Medicinal Product Statistics Register, and Statistics Denmark) and for all variables included in the analyses (outcome, exposure, and confounders). Using such prospectively collected routine data, recall bias is excluded, which is a major strength of the study.

The number of pregnancies added up to 673,853, of which 35.737 women had a diagnosis of depression and/or used antidepressants before the end of pregnancy resulting in a subsequent substantial statistical power, as expressed in the narrow confidence intervals. The study controlled for a number of confounders known to impact the rate of SGA. The data set is almost complete, as only 24 women could not be identified in the Medical Birth Register and data on gestational age were missing or invalid for only 3,545 (0.5 %) live births. The paramount strength of the study is, however, the ability to at least partly separate the effect of the disease from the effect of the treatment owing to the design with various exposure groups. The number of pregnancies at which the woman was diagnosed with depression before the end of pregnancy but at which they did not use antidepressants during pregnancy was rather large (groups 5 and 6, N=2.666 cases) and we should therefore reveal an association between the illness and risk of SGA, if there truly was such an association. Women with a diagnosis of depression did not differ from users of antidepressant medication before or during pregnancy with respect to several risk factors for SGA, including smoking status, minimizing the risk of important residual confounding (see Table 1). In this way, it is less likely that the finding of an increased rate of SGA associated with the use of antidepressants during pregnancy is due to confounding by indication.

We have been previously using a similar data set and design reported on Apgar score as an outcome suggesting that the use of SSRIs during pregnancy increased the risk of low Apgar score independently of maternal depression (Jensen et al. 2013). Children exposed to antidepressants during pregnancy had an increased rate of low Apgar score (odds ratio (OR)=1.72; 95 % CI, 1.34–2.20), whereas maternal depression before or during pregnancy, without prescription of antidepressants, was not associated with a low Apgar score (OR=0.44; 95 % CI, 0.11–1.74). These

findings with Apgar score as the outcome are rather similar to those of the present study with SGA as the outcome.

Limitations

The study did not control for alcohol consumption or severity of depression, as these data were not available. Further, there are a number of other potential confounding factors, for instance food intake, sleep pattern, and other lifestyle factors, that we were not able to take into account. In this way, residual confounding is possible due to the rather crude models. We did, however, attempt to adjust for these factors in the design of the study with several exposure groups. Importantly, exposure misclassification is possible arising from women noncompliant with cashed prescriptions or from women using medication cashed before the study period. The amount of misclassification may be difficult to calculate, as it depends on unobserved factors, but, importantly, the direction of the biases can be predicted. For bias from noncompliance to prescriptions during pregnancy, this would normally lead to bias toward the null (as exposed women would be coded as unexposed) and does not explain the association between antidepressants and SGA. In addition, the majority of women in this group had repeated prescriptions, which is reassuring. Concerning bias arising from medication prescribed prior to pregnancy and used during pregnancy, this bias would be away from the null given a biological effect and does not explain the lack of association for depression without pharmacological treatment.

The timing of maternal depression varied in the study and the extent to which women presented with depressive symptoms before compared to during depression may be unclear. In fact, 3,287 got a diagnosis of depression before pregnancy (with a median period from the time of diagnosis to pregnancy of 802 days (quartiles, 345, 1,568)) and 929 got a diagnosis during pregnancy. It is likely that the former group may have presented with depressive symptoms of various severity during pregnancy although only 27 % of this group got antidepressants during pregnancy. Nevertheless, we can only conclude from our results that suffering from a depressive disorder at one point of time before end of pregnancy were not associated with increased risk of SGA when the pregnant women did not use antidepressants during pregnancy (risk groups 5 and 6 in Table 2). We cannot exclude the possibility that the risk of SGA would have been increased for these groups if our sample had included more pregnant women who got a diagnosis of depression during pregnancy. In parallel to this, it is a limitation that we do not have a measure of severity of depression prior to and during pregnancy but such data are not available on a routine basis from the register data.

Generalizability

Antidepressants are used in the study population for a variety of illnesses not confined to depression. We therefore believe that the findings can be generalized to all women taking antidepressants regardless of the indication for treatment or the severity of illness. A differentiated response to antidepressants depending on the underlying disease would suggest that antidepressants affected the fetus differently in women with, e.g., anxiety compared to depression. We are aware of no such interaction mechanism.

Conclusion

The rate of SGA is slightly increased in pregnant woman taking SSRIs during pregnancy. The association seems unrelated to the underlying disorder. However, untreated depression during pregnancy may have severe detrimental effects on the mother and the offspring, and these factors are crucial to consider when treating women with depression during pregnancy.

Acknowledgements This study was supported by the Lundbeck Foundation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest Hans Mørch Jensen has been a consultant for Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Astra-Zeneca, Lundbeck, Servier, Merck Sharp and Dohme, and Schering-Plough. Øjvind Lidegaard has received honoraria for speeches including fees from Bayer Pharma Denmark, MSD Denmark, and Theramex, Monaco and has been an expert witness for plaintiff in a legal US case in 2011. Lars Vedel Kessing has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, Astra-Zeneca, Pfizer, Wyeth, Servier, and Janssen-Cilag. Randi Grøn, Lars Henning Pedersen, and Per Kragh Andersen have no financial disclosure or competing interests.

References

Alwan S, Reefhuis J, Rasmussen SA, Friedman JM (2011) Patterns of antidepressant medication use among pregnant women in a United States population. J Clin Pharmacol 51:264–270

Andrade SE, Raebel MA, Brown J, Lane K, Livingston J, Boudreau D, Rolnick SJ, Roblin D, Smith DH, Willy ME, Staffa JA, Platt R (2008) Use of antidepressant medications during pregnancy: a multisite study. Am J Obstet Gynecol 198:194–195

Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR (2004) Prevalence of depression during pregnancy: systematic review. Obstet Gynecol 103(4):698–709, Erratum in Obstet Gynecol. 2004 Jun;103(6):1344

Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ (2002) Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA 288:728–737

Cooper WO, Willy ME, Pont SJ, Ray WA (2007) Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 196:544–545

Danish National Board of Health 2007. Use of antidepressant medication during pregnancy and labor 1997–2006. *Nye tal fra Sundhedsstyrelsen*: Danish National Board of Health

El Marroun H, Jaddoe VW, Hudziak JJ, Roza SJ, Steegers EA, Hofman A, Verhulst FC, White TJ, Stricker BH, Tiemeier H (2012) Maternal use of selective serotonin reuptake inhibitors, fetal growth, and risk of adverse birth outcomes. Arch Gen Psychiatry 69:706–714

Ericson A, Kallen B, Wiholm B (1999) Delivery outcome after the use of antidepressants in early pregnancy. Eur J Clin Pharmacol 55:503–508

Evans J, Heron J, Francomb H, Oke S, Golding O (2001) Cohort study of depressed mood during pregnancy and after childbirth. Br Med J 323:257–260

Heikkine T, Ekblad U, Laine K (2002) Transplacental transfer of citalopram, fluoxetine and their primary demethylated metabolites in isolated perfused human placenta. BJOG 109:1003–1008

Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K (2002) Citalopram in pregnancy and lactation. Clin Pharmacol Ther 72:184–191

Hendrick V, Smith LM, Suri R, Hwang S, Haynes D, Altshuler L (2003) Birth outcomes after prenatal exposure to antidepressant medication. Am J Obstet Gynecol 188:812–815

Jensen, H.M., grøn, R., Lidegaard, Ø., Pedersen, L.H., Andersen, P.K., and Kessing, L.V. (2013) Maternal depression, antidepressant use in pregnancy and Apgar scores in infants. Brit J Psychiat. doi:10.1192/bjp.bp.112.115931

Kallen B (2004) Neonate characteristics after maternal use of antidepressants in late pregnancy. Arch Pediatr Adolesc Med 158:312–316

Knudsen LB, Olsen J (1998) The Danish medical birth registry. Dan Med Bull 45:320–323

Koren G, Nordeng H (2012) Antidepressant use during pregnancy: the benefit-risk ratio. Am J Obstet Gynecol 207(3):157–163

Laursen TM, Munk-Olsen T, Nordentoft M, Bo MP (2007) A comparison of selected risk factors for unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia from a Danish population-based cohort. J Clin Psychiatry 68:1673–1681

Lorenzo L, Byers B, Einarson A (2011) Antidepressant use in pregnancy. Expert Opin Drug Saf 10:883–889

Lund N, Pedersen LH, Henriksen TB (2009) Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med 163:949–954

Mathiasen R, Hansen BM, Forman JL, Kessing LV, Greisen G (2011) The risk of psychiatric disorders in individuals born prematurely in Denmark from 1974 to 1996. Acta Paediatr 100:691–699

Mors O, Perto GP, Mortensen PB (2011) The Danish Psychiatric Central Research Register. Scand J Public Health 39:54–57

Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B, Wisner KL (2005) Neonatal signs after late in utero exposure to serotonin reuptake inhibitors—literature review and implications for clinical applications. Jama-J Am Med Assoc 293:2372–2383

Nakano Y, Oshima M, Sugiura-Ogasawara M, Aoki K, Kitamura T, Furukawa TA (2004) Psychosocial predictors of successful delivery after unexplained recurrent spontaneous abortions: a cohort study. Acta Psychiatr Scand 109:440–446

O'Keane V, Marsh MS (2007a) Depression during pregnancy. BMJ 334:1003–1005

O'Keane V, Marsh MS (2007b) Pregnancy plus—depression during pregnancy. Bri Med J 334:1003–1005

Oberlander TF, Bonaguro RJ, Misri S, Papsdorf M, Ross CJ, Simpson EM (2008) Infant serotonin transporter (SLC6A4) promoter genotype is associated with adverse neonatal outcomes after prenatal exposure to serotonin reuptake inhibitor medications. Mol Psychiatry 13:65–73

Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C (2006) Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry 63:898–906

Ramos E, St-Andre M, Berard A (2010) Association between antidepressant use during pregnancy and infants born small for gestational age. Can J Psychiatry 55:643–652

Simon GE, Cunningham ML, Davis RL (2002) Outcomes of prenatal antidepressant exposure. Am J Psychiatry 159:2055–2061

Statistics Denmark (2011) Statistics Denmark. http://www.dst.dk/HomeUK.aspx. Accessed 26 Feb 2013

Strauss RS (2000) Adult functional outcome of those born small for gestational age: twenty-six-year follow-up of the 1970 British Birth Cohort. JAMA 283:625–632

Wadhwa PD, Glynn L, Hobel CJ, Garite TJ, Porto M, Chicz-Demet A, Wiglesworth AK, Sandman CA (2002) Behavioral perinatology: biobehavioral processes in human fetal development. Regul Pept 108:149–157

Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, Perel JM, Jones-Ivy S, Bodnar LM, Singer LT (2009) Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. Am J Psychiatry 166:557–566

World Health Organization (2003) World Health Organization CCfDSM. The anatomical therapeutic chemical classification system with defined daily doses. World Health Organization, Geneva