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Maternal depression, antidepressant use in pregnancy and Apgar scores in infants

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Background
Use of antidepressants during pregnancy has been associated with a low Apgar score in infants but a contribution from the underlying depressive disorder might influence this association.

Aims
To estimate the effects of maternal depression and use of antidepressants during pregnancy on low Apgar scores (<7) 5 min after birth.

Method
Register study on all pregnant women in Denmark from 1996 to 2006 linking nationwide individualised data from the Medical Birth Register, the Psychiatric Central Register and the National Prescription database.

Results
Infants exposed to antidepressants during pregnancy had an increased rate of a low Apgar score (odds ratio (OR) = 1.72, 95% CI 1.34–2.20). The increased rate was only found among infants exposed to selective serotonin reuptake inhibitors (SSRIs) (OR = 1.96, 95% CI 1.52–2.54), not among those exposed to newer (OR = 0.83, 95% CI 0.40–1.74) or older antidepressants (OR = 0.53, 95% CI 0.19–1.45). 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). Women who had only used antidepressants prior to pregnancy had no increased rate of a low Apgar score in their subsequent pregnancy, regardless of depression status.

Conclusions
Use of SSRIs during pregnancy increases the risk of a low Apgar score independently of maternal depression.

Declaration of interest
H.M.J has been a consultant for Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Astra-Zeneca, Lundbeck, Servier, Merck Sharp & Dohme and Schering-Plough. Ø.L. has received honoraria for speeches including fees from Bayer Pharma Denmark, MSD Denmark and Theramex, Monaco, and has been expert witness for a plaintiff in a legal US case in 2011. L.V.K. has been a consultant for Bristol-Myers Squibb, Eli Lilly, Lundbeck, Astra-Zeneca, Pfizer, Wyeth, Servier and Janssen-Cilag.

A substantial number of pregnant women experience depressive symptoms during pregnancy with prevalence rates of depression in the range 7–13%[1,2] and 4–7.6% of pregnant women are treated with antidepressants.[1,3] Mental disorders and psychotropic drugs may influence the development of the fetus, but the associations are unclear, and mechanisms are poorly understood. Antidepressants readily cross the placenta barrier potentially affecting fetal development[4] but maternal depressive illness may also cause adverse effects on pregnancy outcome. Increased placental secretion of corticotrophin-releasing hormone resulting in increased activity within the gestational cortisol system,[5] as well as unhealthy behaviour related to depression such as smoking and poor attendance for obstetric care, may have adverse effects.[2,3,6] The importance of differentiating the effects of exposure to maternal depression from the effects of antidepressants has been highlighted in recent reviews[6–9] but, so far, studies have not sufficiently discriminated between the effects of maternal disease and use of drugs in relation to birth outcomes, except from one study[10] that revealed an increased risk of low birth weight and respiratory distress even when maternal illness severity was accounted for. The hypothesis of the present study was that birth complications, as reflected in a low Apgar score, are explained by the effect of the maternal disease. We compared the Apgar score in eight risk groups, classified according to maternal depression and exposure to antidepressants, in a nationwide register linkage study.

The Apgar score at 5 min after birth is a clear index of problems in adult life; recent studies have shown that infants with low Apgar scores (<7 at 5 min) are at increased risk of a low IQ score at age 18,[11] never receiving graduation grades[12] or attending university and are more likely to have no income from work than those born with an Apgar score of 7–10.[13] Further, an Apgar score <7 at 5 min has been associated with neurological disability, including cerebral palsy, epilepsy and cognitive impairment that persists many years postnatally.[14,15]

Method

Danish register data

We linked data on all pregnancies from 1996 to 2006 from the Medical Birth Register with data from the Psychiatric Central Register, the Medicinal Product Statistics register and Statistics Denmark.

The Medical Birth Register[16] includes data on date of birth, gestational age, Apgar score 5 min after birth, birth weight, length of fetus, maternal smoking status during pregnancy, parity and maternal age on all deliveries in Denmark. Data from births of more than one child from 1996 to 2006 were included whereas twin births were excluded, implying that the same woman could be included more than once.

The Medicinal Product Statistics is a nationwide prescription database containing individual information on all prescriptions filled at all Danish pharmacies from 1995 and onwards.[17] Data included and distinguished between ATC codes (Anatomical Therapeutical Chemical classification system) for antidepressant, antipsychotics, anti-epileptics and 'other kinds of drugs'. Antidepressants were classified as selective serotonin reuptake inhibitors (SSRIs: fluoxetine, citalopram, escitalopram, paroxetine, sertraline, fluvoxamine: ATC N06AB03–10), newer antidepressants (nefazodone, mirtazapine, venlafaxine, reboxetine: ATC N06AX06,

–11, –16, –18 and –21) or older antidepressants consisting mainly of tricyclic antidepressants (imipramine, clomipramine, trimipramine, lofepramine, amitriptyline, nortriptyline, doxepin, dosulepin, amoxapine, maprotiline; mianserin, isocarboxazid, moclobemide: ATC N06AA02–7, N06AA09–12, N06AA16–17, N06AA21, N06AX03, N06AF01 and N06AG02).

The Danish Psychiatric Central Register is a nationwide psychiatric register[18] with data from all public mental health services both as in- and out-patients. Data extracted were ICD-8[19] and ICD-10[20] codes for depression (i.e. ICD-8 codes 29609 and 29629, ICD-10 codes DF32.00-DF33.99). Statistics Denmark provided data on employment status on a yearly basis for the women included.[21]

Statistical analyses

Pregnant women were divided into eight risk groups according to their exposure to a diagnosis of depression before the end of pregnancy, use of antidepressants before pregnancy and antidepressant use during pregnancy (see Table 2, Model 1). Group 1 was the reference group.

Additional analyses were done using three binary variables ($\pm$ diagnosis before end of pregnancy; $\pm$ antidepressants before pregnancy; $\pm$ antidepressants during pregnancy; see Table 1 and lower part of Table 2, Model 2).

To avoid assumptions of linearity, Apgar score at 5 min was divided into two groups: Apgar score from 0 to 6 and 7 to 10 in accordance with the dichotomisation in prior studies showing poorer intellectual, cognitive, social and clinical outcome related to an Apgar score <7 at 5 min.[11–15]

Logistic regression analyses were applied with Apgar score as the outcome and risk group as the variable of interest. The analyses were adjusted for the effect of calendar periods (1996, 1997, 1998 etc. to 2006), maternal age, parity (first child, second child, child number three or more), employment status (employed, unemployed, disability pension and retired, student, child and others), smoking status (non-smoker, quit smoking, smoking, unknown), gestational age, gender of the child, birth weight and use of other medication during pregnancy, including use of lithium (yes/no), anti-epileptics (yes/no), antipsychotics (yes/no) and other kinds of medication than antidepressants, lithium, anti-epileptics or antipsychotics (yes/no). In the analysis, employment status was dichotomised into 'working and students' *v.* the remaining groups.

To account for the fact that some women contributed with more than one live birth, robust standard errors were compared with the model-based standard errors. Since the impact of this adjustment was minimal, only model-based standard errors are reported.

Results

The data-set included all pregnant women in Denmark from 1996 to 2006. Infants with a gestational age of less than 22 weeks were excluded from the data resulting in a total of 672 601 live births. Data on birth weight were available from 668 144 live births (99.3%) and data on Apgar score at 5 min were available for 665 399 live births (98.93 % of all live births) resulting in 664 089 live births with full data on Apgar score and other

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

Maternal characteristics	Antidepressant medication before pregnancy[a] ($n=33\,084$)	Antidepressant medication during pregnancy[a] ($n=8375$)	Depression diagnosis before end of pregnancy[a] ($n=3916$)	All pregnancies ($n=664\,089$)
Age, years: median (IQR)	30 (27–34)	30 (27–34)	30 (26–34)	30 (26–33)
Parity, %				
First child	41.7	43.1	41.2	42.8
Second child	34.4	32.1	36.5	37.6
⩾Third child	23.9	24.9	22.3	19.7
Smoking status, %				
Non-smoker	64.2	57.7	60.8	68.9
Smoking	27.2	31.5	29.1	16.2
Quit smoking	2.7	2.8	3.1	1.8
Unknown	5.9	8.0	7.0	13.1
Lithium-treatment, %				
No	99.9	99.8	99.6	100.0
Yes	0.1	0.2	0.4	0.01
Anti-epileptic treatment, %				
No	98.7	97.2	97.9	99.6
Yes	1.3	2.8	2.1	0.4
Antipsychotic treatment, %				
No	98.1	94.3	95.3	99.8
Yes	2.0	5.7	4.7	0.2
Other medication, %				
No	21.5	17.5	20.0	32.1
Yes	78.5	82.6	80.1	67.9
Characteristics child, %				
Female child	48.4	48.1	48.3	48.7
Gestational age, weeks: median (IQR)	39 (38–40)	39 (38–40)	39 (38–40)	39 (39–39)
Apgar score, %				
⩾7	99.3	98.9	99.4	99.4
<7	0.7	1.1	0.6	0.6

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

predictive variables included in the analysis. Among the 664 089 children, 22 155 (3.34%) had a birth weight below 2500 g, and 4076 children (0.61%) had an Apgar score after 5 min between 0 and 6 whereas 660 013 children had an Apgar score from 7 to 10.

Table 1 shows the characteristics of the 664 089 births according to the mother's antidepressant therapy and depressive diagnosis. As can be seen from Table 1, for 3916 live births the mother had a diagnosis of depression before the end of pregnancy. For a total of 8375 live births the mother redeemed a prescription for antidepressants during pregnancy (Table 1). In 2941 of these cases only one prescription was redeemed whereas, in 5434 cases, two or more prescriptions were redeemed; for 7208 live births the mother redeemed a prescription for an SSRI, 982 for a newer antidepressant and 780 for an older antidepressant. Among the 664 089 children included, in 7389 (1.11%) cases the mother redeemed a prescription for an antidepressant during the first trimester, 3780 (0.57%) during the second trimester and 3246 (0.49%) during the third trimester.

Prior to pregnancy, 33 084 (4.98%) women redeemed prescriptions for antidepressants (Table 1), 59 (0.01%) lithium, 2884 (0.43%) anti-epileptics, 1278 (0.19%) antipsychotics and 450 712 (67.87%) women redeemed prescriptions for other drugs.

Table 2 shows the adjusted odds for a low Apgar score (0–6 *v.* 7–10) in the risk groups according to logistic regression analyses (Model 1). The only risk group with a significantly increased risk for a low Apgar score 5 min after birth compared with the reference group was risk group 4, i.e. children born of women without a diagnosis of depression, who had redeemed a prescription for antidepressants before and during pregnancy (OR = 1.72, 95% CI 1.34–2.20). Odds ratios for risk group 3 (no diagnosis + antidepressants during pregnancy) and risk group 8 (a diagnosis of depression + antidepressants before and during pregnancy) were also increased but did not differ significantly from the reference group. If the mother had taken medication other than antidepressants, lithium, anti-epileptics or antipsychotics, the OR for a low Apgar score was slightly increased (OR = 1.11, 95% CI 1.04–1.19).

All analyses were repeated without correcting for gestational age and birth weight. These analyses resulted in the same findings as when correcting for gestational age and birth weight with ORs within the same ranges.

Additional analyses using three binary variables confirmed the results as only children of women using antidepressants during pregnancy had an increased risk of a low Apgar score (OR = 1.67, 95% CI 1.30–2.14); unadjusted OR = 1.87 (95% CI 1.41– 2.47) whereas there was no effect of use of antidepressants before pregnancy or a diagnosis of depression (see lower part of Table 2, Model 2). These results did not change, resulting in ORs within the same ranges, when Model 2 was repeated with exclusion of preterm births, i.e. gestational age <36 weeks (antidepressants before pregnancy: OR = 0.95, 95% CI 0.79–1.14; antidepressants during pregnancy: OR = 1.87, 95% CI 1.41–2.47; diagnosis of depression before end of pregnancy: OR = 0.69, 95% CI 0.41–1.15).

Further analyses of subtypes of antidepressants showed that only use of SSRIs during pregnancy increased the OR of a low Apgar score whereas there was no effect of use of newer antidepressants or older antidepressants during pregnancy (Table 3, although a formal test of homogeneity resulted in only a borderline significant difference, $P = 0.052$). Using antidepressants before conception did not significantly increase the OR for a low Apgar score regardless of the type of antidepressant.

There was no differential effect of timing of the use of antidepressants during various trimesters (first trimester: OR = 1.16, 95% CI 0.83– 1.63; second trimester: OR = 1.51, 95% CI 0.90–2.53; third trimester: OR = 1.42, 95% CI 0.85– 2.38), which may be explained by the limited sample size in these analyses.

Discussion

We found that a low Apgar score was attributed to the use of SSRIs during pregnancy and not to the effect of the disease or associated lifestyle factors. Non-SSRI antidepressants were not associated with a low Apgar score. No increased rates were found among women who used antidepressants prior to pregnancy (but not during; risk group 2) or who had a diagnosis of depression but used no antidepressants during pregnancy (risk groups 5 and 6).

The Apgar score 5 min after birth is a clear index of problems in adult life; studies have shown that infants with low Apgar scores (<7 at 5 min) are at increased risk of a low IQ score at age 18 (OR = 1.35, 95% CI 1.07–1.69),[11] never receiving graduation grades (OR = 1.93, 95% CI 1.75–2.14),[12] never attending university

Table 2 Adjusted odds rate of a low Apgar score (0–6 *v.* 7–10) according to depressive diagnosis and antidepressant therapy before or during pregnancy[a]

	Diagnosis before end of pregnancy	Antidepressants before pregnancy	Antidepressants during pregnancy	*n*	Unadjusted OR (95% CI)	OR[b] (95%CI)
Model 1						
Risk group						
1	–	–	–	628 898		1 (reference)
2	–	+	–	24 185		0.96 (0.81–1.14)
3	–	–	+	1 212		1.53 (0.86–2.72)
4	–	+	+	5 878		1.72 (1.34–2.20)
5	+	–	–	731		0.44 (0.11–1.77)
6	+	+	–	1 900		1.03 (0.58–1.83)
7	+	–	+	164		0
8	+	+	+	1 121		1.35 (0.74–2.47)
Anti-epileptics during pregnancy						1.24 (0.84–1.82)
Antipsychotics during pregnancy						1.26 (0.74–2.13)
Other medication during pregnancy						1.11 (1.04–1.19)
Model 2						
Antidepressants before pregnancy					0.95 (0.79–1.14)	1.00 (0.85–1.17)
Antidepressants during pregnancy					1.87 (1.41–2.47)	1.67 (1.30–2.14)
Diagnosis of depression before end of pregnancy					0.69 (0.41–1.15)	0.80 (0.53–1.20)

a. The eight groups in Model 1 are mutually exclusive and sum up to 100%. The three groups in Model 2 are not mutually exclusive.
b. Odds ratio adjusted for: maternal age, social status, smoking status, calendar year, gender of newborn, and use of anti-epileptics, antipsychotics and other types of medication.

Table 3 Subtypes of antidepressants[a] and risk of a low Apgar score (0–6 *v.* 7–10)

	n	OR (95% CI)[b]
During pregnancy		
Selective serotonin reuptake inhibitors	7 208	1.96 (1.52–2.54)
Newer antidepressants	982	0.83 (0.40–1.74)
Older antidepressants	780	0.53 (0.19–1.45)
Before pregnancy		
Selective serotonin reuptake inhibitors	27 466	0.93 (0.78–1.12)
Newer antidepressants	5 875	1.21 (0.88–1.67)
Older antidepressants	6 282	1.14 (0.85–1.54)

a. According to the Anatomical Therapeutical Chemical (ATC) classification system.
b. Odds ratios adjusted for: maternal age, social status, smoking status, calendar year, gender of newborn, and use of anti-epileptics, antipsychotics and other types of medication.

(OR = 1.14, 95% CI 1.05–1.23) and are more likely to have no income from work (OR = 1.19, 95% CI 1.07–1.32) than those born with an Apgar score of 7–10.[13] Further, an Apgar score <7 at 5 min has been associated with neurological disability, including cerebral palsy, epilepsy and cognitive impairment that seems to persist many years postnatally.[14,15]

A number of studies have demonstrated low Apgar scores in children exposed to SSRIs *in utero*[22–26] whereas the effects of newer and older antidepressants have not been investigated.[27] We found that the risk of a low Apgar score was associated specifically with the use of SSRIs during pregnancy whereas there was no increased risk in relation to the use of newer antidepressants or older antidepressants (mainly tricyclic antidepressants; Table 3). A recent review[28] suggests that antenatal exposure to antidepressants is associated with a higher risk of neonatal adaptation difficulties.[22,29] A possible explanation could be a direct effect of SSRIs on the development of the fetal brain. The serotonergic network projects from the raphe nuclei and arborises over large areas to an array of other nuclei[30] comprising functionally diverse targets; it interacts with other neurotransmitter systems[31] and plays a role in regulation and developmental signalling in the organisation of developing neural networks in the central nervous system (CNS).[32] Antidepressants readily cross the placental barrier, exposing the fetal CNS, which from even a very early embryonic stage, displays a serotonergic network,[4] and effects in offspring after maternal exposure to antidepressants have been demonstrated in rodents.[33,34]

We were able to take into account other possible risk factors for a low Apgar score (i.e. parity, maternal social status, maternal smoking status, calendar year, other medication and gestational age). In our models, these factors did not explain the higher ORs for a low Apgar score for children born of mothers using antidepressants during pregnancy. This finding was independent of whether the mother had a diagnosis of depression or not. Confounding by unmeasured factors or residual confounding is, however, still possible but would have to act specifically on the women with depression and who took medication and not on the non-medicated controls to explain our main result (see below). The aim of this study was not to determine whether pregnant women with depression should be treated with antidepressants or not. The study shows that treating depression does have consequences that should be taken into consideration when a physician informs a female patient about risk factors enabling her to make an evidence-based decision. Thus, although the probability of a low Apgar score was increased more than 70% in children whose mother had used SSRIs during pregnancy, compared with healthy women, the absolute prevalence of a low Apgar score was still low (1.14%, Table 1). Further, treatment with antidepressants during pregnancy has been associated with a number of other birth complications such as low birth weight[35–37] and preterm delivery,[38,39] but it should be noted that none of these studies has taken the potential effect of the depressive illness into account.

We found a lower prevalence of depression (i.e. 0.6%) than previously reported as we used data from nationwide databases, which only include information from hospital-based psychiatric facilities and not from general practitioners. Consequently, we had data on a diagnosis of depression only for women with more severe and complicated depressive illnesses. For these women, we found no association between depression and Apgar score and thus believe that the effects of milder forms of depression are unlikely. We have no reason to suspect a reverse dose–response relationship between depression and birth outcome. Further, the impact of antidepressants on birth outcome seems to be independent of severity of depression.[27]

In the present study, only 1.26% of the pregnant women were treated with antidepressants. The low percentage is explained by the fact that data were gathered from 1996 at which time it was uncommon to treat pregnant women with antidepressants. The number of women treated with antidepressants during pregnancy in the sample increased steadily each year from 232 in 1996 to 1453 in 2005. The increase in prevalence of pregnant women undergoing treatment is also found in other countries, for example in the USA.[1,3]

Strengths

We used information from national registers with longitudinal data on inhabitants from an entire country. The data in these registries are collected prospectively and therefore recall bias is excluded. In contrast, in retrospective studies the recall of potential treatment with antidepressants during pregnancy may be influenced by the prevalence of birth complications. The study presents data from almost 665 000 births and is able to adjust for a number of potential confounders including all medication other than antidepressants. We had almost complete data with, for example, information on the Apgar scores for 98.9% of infants. The number of women who did not use antidepressants during pregnancy but who previously had used antidepressants or had a diagnosis of depression was rather large and consequently the statistical power to detect an association between depressive illness *per se* and a low Apgar score was high, as reflected by the narrow 95% confidence intervals (Table 2).

Limitations

Redeeming a prescription does not necessarily mean that the woman actually took the medication, although having paid for it at a pharmacy increases the possibility. The potential exposure misclassification tends to underestimate the effect of antidepressant drugs or overestimate the effect of depression among women that we coded as unexposed.

The timing of maternal depression varied in the study and the extent to which women presented with depressive symptoms before compared with during pregnancy may be unclear. In fact, 3245 women received a diagnosis of depression before pregnancy (with a median period from the time of diagnosis to pregnancy of 801 days (quartiles: 346, 1568)) and 918 received a diagnosis during pregnancy. It is likely that the former group may have presented with depressive symptoms of differing severity during pregnancy although only 27% of this group got antidepressants during pregnancy. Nevertheless, we can only conclude from our results that having a depressive disorder at one point in time before the end of pregnancy was not associated with an increased risk of a low Apgar score 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 a low Apgar score would have been increased for these groups if our sample had included more pregnant women who received a diagnosis of depression during pregnancy.

It is unlikely that the association between antidepressants and a low Apgar score is the result of congenital abnormalities such as heart defects owing to the low prevalence of these. In any case, if an Apgar score <7 in some cases is a consequence of a congenital heart defect, this further emphasises the clinical importance of the Apgar score measure. The study does not control for alcohol consumption, for age of the father or severity of depression, as these data were not available.

Generalisability

It is most likely that the findings can be generalised to all women taking antidepressants regardless of the indication for treatment (depression, anxiety, etc.) or the severity of illness.

In conclusion, women who are treated with SSRIs during pregnancy have an increased risk of giving birth to an infant with an Apgar score of 6 or lower 5 min after birth. The effect seems to be attributable to treatment and not to the disease.

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