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Maternal Use of Selective Serotonin Reuptake Inhibitors, Fetal Growth, and Risk of Adverse Birth Outcomes

Hanan El Marroun, PhD; Vincent W. V. Jaddoe, MD, PhD; James J. Hudziak, MD; Sabine J. Roza, MD, PhD; Eric A. P. Steegers, MD, PhD; Albert Hofman, MD, PhD; Frank C. Verhulst, MD, PhD; Tonya J. H. White, MD, PhD; Bruno H. C. Stricker, MD, PhD; Henning Tiemeier, MD, PhD

Context: Selective serotonin reuptake inhibitors (SSRIs) are frequently prescribed to pregnant women, but knowledge about their unintended effects on child health is scarce.

Objective: To examine the effects of maternal SSRI use during pregnancy on fetal growth and birth outcomes.

Design: The study was embedded in the Generation R Study, a prospective population-based study from fetal life onward.

Participants: Seven thousand six hundred ninety-six pregnant women were included. Selective serotonin reuptake inhibitor use was assessed by questionnaires in each trimester and verified by pharmacy records. Using depressive symptom scores from the Brief Symptom Inventory, 7027 pregnant mothers (91.3%) had no or low depressive symptoms, 570 pregnant mothers (7.4%) had clinically relevant depressive symptoms and used no SSRIs, and 99 pregnant mothers (1.3%) used SSRIs.

Main Outcome Measures: Fetal ultrasonography was performed in each trimester. We determined fetal body and head growth with repeated assessments of body and

head size. The birth outcomes studied were preterm birth, small for gestational age, and low birth weight.

Results: Fetuses from mothers with prenatal depressive symptoms showed reduced body growth ($\beta = -4.4$ g/wk; 95% CI: -6.3 to -2.4 ; $P < .001$) and head growth ($\beta = -0.08$ mm/wk; 95% CI: -0.14 to -0.03 ; $P = .003$). Mothers using SSRIs during pregnancy had fewer depressive symptoms than mothers in the clinical symptom range. Prenatal SSRI use was not associated with reduced body growth but was associated with reduced fetal head growth ($\beta = -0.18$ mm/wk; 95% CI: -0.32 to -0.07 ; $P = .003$). The SSRI-exposed children were at higher risk for preterm birth (odds ratio = 2.14; 95% CI: 1.08 to 4.25; $P = .03$).

Conclusions: Untreated maternal depression was associated with slower rates of fetal body and head growth. Pregnant mothers treated with SSRIs had fewer depressive symptoms and their fetuses had no delay in body growth but had delayed head growth and were at increased risk for preterm birth. Further research on the implications of these findings is needed.

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Author Affiliations: Department of Child and Adolescent Psychiatry, Sophia Children's Hospital (Drs El Marroun, Hudziak, Roza, Verhulst, White, and Tiemeier), Departments of Epidemiology (Drs Jaddoe, Hofman, Stricker, and Tiemeier), Pediatrics (Dr Jaddoe), Psychiatry (Drs Roza and Tiemeier), Obstetrics and Gynecology (Dr Steegers), and Radiology (Dr White), and the Generation R Study Group (Drs El Marroun and Jaddoe), Erasmus MC, Rotterdam, the Netherlands; and Department of Psychiatry, College of Medicine, University of Vermont, Burlington (Dr Hudziak).

THE IMPORTANCE OF TREATING maternal depression during pregnancy is well known. Selective serotonin reuptake inhibitors (SSRIs) are commonly prescribed medications to treat depression^{1,2} because they have been shown to be both efficacious and safe.³ Selective serotonin reuptake inhibitors are also frequently prescribed to pregnant women, but knowledge about their potential unintended effects on health of the unborn child is scarce.⁴ Thus, trying to balance the possible negative consequences of untreated maternal depression with the unknown potential negative consequences of SSRIs remains an open debate.

Animal studies demonstrated that serotonin plays an important role during prenatal brain development; serotonin regulates neuronal proliferation, differentiation, migration, and synaptogenesis.^{5,6} Serotonin modulates its own synthesis and the number of serotonin receptors.^{7,8} Also, prenatal exposure to SSRIs was related to smaller head size in mice.⁹ In serotonin transporter (5-HTT) knockout mice, high levels of serotonin lead to abnormal structural organization of the somatosensory cortex and the corticolimbic circuits in the brain.¹⁰ These neuroanatomical deficits were also associated with disturbed behavioral functioning later in life.¹¹

Human studies showed that SSRIs pass the placenta; SSRIs and metabolite con-

centrations up to 72% of the maternal levels have been detected in umbilical cord blood.^{12,13} Some studies reported malformations at birth, persistent pulmonary hypertension, and long-term effects on neurodevelopment due to prenatal SSRI exposure in children, but results are conflicting.¹⁴⁻¹⁷ High-quality studies with good controls are sparse, but prenatal exposure to SSRIs has been associated with delayed motor milestone development, albeit a delay that was within the normal range of motor development. This may suggest subtle effects of prenatal SSRI use on offspring brain development.¹⁷⁻²¹ However, none of these studies focused on the development of the brain or head during pregnancy.

Maternal depression during pregnancy can also adversely affect fetal development; it has been associated with an increased risk of poor pregnancy outcomes and neonatal complications.²²⁻²⁴ Moreover, prenatal depression has been associated with adverse neurodevelopmental outcomes, such as language delay.²⁵⁻²⁷

In this population-based study, we examined the association of depressive symptoms and maternal SSRI use during pregnancy with fetal body and head growth assessed by repeated ultrasonography and birth outcomes (birth weight, gestational age at birth, and head circumference at birth).

METHODS

SETTING AND POPULATION

The present study is part of the Generation R Study,²⁸ a population-based prospective cohort study from early fetal life onward in Rotterdam, the Netherlands. The Medical Ethics Committee of the Erasmus Medical Centre Rotterdam reviewed and approved the study. Written informed consent for both maternal and child data was obtained from all mothers.

Briefly, all pregnant women who resided in Rotterdam and whose delivery date was between April 2002 and January 2006 were invited to participate. In total, 9778 mothers were enrolled in Generation R (8880 during pregnancy and 898 after birth of their child).

For the present analyses, only mothers enrolled during pregnancy (8880) were considered. We excluded 104 fetal deaths (1 exposed to SSRIs) and 93 twin pregnancies. Selective serotonin reuptake inhibitor use only before pregnancy was recorded in 188 women; they were excluded from analyses because spillover effects could not be ruled out. The remaining 8495 mothers were eligible. There were 45 mothers lost to follow-up during pregnancy, and in 754 (8.9%) of the eligible mothers, information on SSRI use was unavailable. Thus, 7696 mothers were included in the analyses.

MATERNAL USE OF SSRIs AND MATERNAL DEPRESSION DURING PREGNANCY

To minimize misclassification of maternal SSRI use during pregnancy, we used 2 sources of information: (1) self-reports assessed with questionnaires and (2) prescription records from pharmacies.

In each trimester, participants reported whether they had used any medication (7129 [92.7%] provided information). In the first trimester, the mothers were asked whether they used medications within the past 6 months. The mothers filled out the type of medication and when it was used (during preg-

nancy, only before pregnancy, or stopped when I knew I was pregnant). In the second and third trimesters, we asked which medications were used in the preceding 3 months. From these questionnaires, we assessed SSRI exposure and timing (before or during pregnancy).

To validate the use of filled prescriptions, we asked women for permission to contact their pharmacy. For the large majority, permission was obtained and data were requested, but prescription records were only available in 56.4% (n=4870) of our study sample. The records screened for SSRI use provided information on the type of SSRIs, duration, and dose. The agreement between self-reports and prescription records was high; Yule's Y as a measure of agreement was 0.94. Pharmacy records confirmed many self-reports (68.5%) and added 10 exposed participants.

Depressive symptoms were assessed with the Brief Symptom Inventory at, on average, 20.6 weeks of gestation. The Brief Symptom Inventory is a validated self-report questionnaire with 53 items^{29,30} and these items define a spectrum of psychiatric symptoms; we used the 6-item Depression Scale. According to the manual, mothers with a score higher than 0.75 were defined to have clinically relevant depressive symptoms.³⁰

Based on the information about depressive symptoms and SSRI use, we classified the pregnant mothers into 3 groups:

1. Women not using SSRIs with low depressive symptoms (7027 [91.3%]), ie, the control group.
2. Women with clinically relevant depressive symptoms and not using SSRIs (570 [7.4%]).
3. Women using SSRIs during pregnancy (99 [1.3%]).

FETAL OUTCOMES

Fetal ultrasonography assessments were performed in the first (median 12.8 weeks [90% range: 11.0-16.6 weeks]), second (median 20.3 weeks [90% range: 19.1-22.0 weeks]), and third (median 30.1 weeks [90% range: 29.0-32.0 weeks]) trimesters.³¹ The ultrasonography examinations were used for both establishing gestational age and assessing fetal growth characteristics. Crown-rump length, femur length, abdominal circumference, and head circumference were measured using standardized procedures. Fetal weight was then estimated using femur length and head and abdominal circumference in the formula of Hadlock.³² Estimated fetal weight and head circumference were correlated; the correlation coefficients were 0.90 in the first measurement but only 0.72 in the third measurement. The intraobserver and interobserver reliabilities of fetal biometry in early pregnancy within Generation R were excellent, with all intraclass correlation coefficients greater than 0.98.³³ Gestational age and weight at birth were extracted from medical records.

PREGNANCY COMPLICATIONS AND BIRTH OUTCOMES

Prematurity was defined as birth before 37.0 weeks of gestation and low birth weight was defined as a birth weight smaller than 2500 g. Small for gestational age was defined as a standard deviation score smaller than -2.0 and based on standard deviation curves derived from the whole Generation R cohort.³¹ Head circumference after birth was measured directly by the midwife or at child health care centers at the age of 2 weeks (mean postconception age was 42.9 weeks).

COVARIATES

Important covariates were selected based on previous literature and change-in-estimate criteria.³⁴ Maternal body mass index and

height were measured during the first visit to the research center. Demographic information such as maternal age, ethnicity, education, and obstetric information were based on self-report. Ethnicity of the parents was defined according to the classification of Statistics Netherlands³⁵; a mother was classified as being non-Dutch if one of her parents was born abroad. If both of her parents were born abroad, the country of birth of the mother's mother determined maternal national origin. Among non-Dutch mothers in this study, we identified persons of Western origin (such as European, American, and Australian) and non-Western origins (Cape Verdean, Dutch Antillean, Indonesian, Moroccan, Surinamese, Turkish, and other non-Western). Educational level was categorized into 3 levels: primary (no or primary education), secondary (lower and intermediate vocational training), and higher (higher vocational education and university) education.³⁶ Family income, defined by the total net monthly income of the household, was categorized as less than €1200 (US \$1551) (below social security level), €1200 to €2000 (US \$1551-US \$2586), and more than €2000 (US \$2586) (more than modal income). Maternal prenatal smoking and alcohol use was obtained by questionnaires in each trimester and categorized into "no," "until pregnancy was known," and "continued during pregnancy," as described previously.³⁷ Information on cannabis use during pregnancy was obtained by a questionnaire in early pregnancy and by urine samples and was categorized into "not in pregnancy" and "during pregnancy" and has been described previously.³⁸ Information on maternal benzodiazepine use, like information on maternal SSRI use during pregnancy, was collected with mailed questionnaires in each trimester and prescription records.

STATISTICAL ANALYSES

We determined differences in the demographic data of the 3 groups using the χ^2 test, analysis of variance, and the Kruskal-Wallis test.

Based on multiple ultrasonography assessments of body size (estimated fetal weight) and head size (head circumference), we examined fetal growth. Since body size was not measured reliably in the first measurement, the body growth analyses were conducted with the second and third ultrasonography measurements and birth measures (gestational age range: 18.0-43.6 weeks). For head growth, we used head circumference from each measurement in pregnancy (gestational age range: 7.1-39.2 weeks). The associations between maternal depressive symptoms and antidepressant use with fetal weight gain and head growth were analyzed using longitudinal multilevel analyses.³⁹ The multilevel models take between-subject and within-subject changes over time into account. Using the repeated ultrasonography measures in flexible mixed models with polynomials provides a more accurate estimation as compared with a single measurement in the analysis. These analyses involved 2 steps. First, the best-fitting model with the outcome as a function of gestational age was constructed using fractional polynomials.⁴⁰ Second, maternal depressive symptoms or antidepressant use was brought into the model. The final curve was fitted with random effects for both the intercept and gestational age. The interaction term of depressive symptoms/maternal antidepressant use with gestational age was included in the model to compare the slope of the curves between the different groups defined by depressive symptoms and SSRI use. Using the same strategy, linear models were constructed for standard deviation scores of the growth characteristics.³¹ All analyses were adjusted for body mass index, educational level, maternal smoking habits, maternal age, ethnicity, fetal sex, parity, and maternal use of benzodiazepines, but not maternal drinking habits and cannabis use because these variables did not change the observed associations.³⁴ These adjust-

ments in the multilevel models were performed for random effects on the intercept. When analyzing the effects of depressive symptoms and SSRI use on head growth, we also corrected the fetal body size measures in the models to test specificity. We also tested whether results changed if we additionally adjusted the model for random effects on the slope using the following interaction terms: depressive symptoms score with gestational age, smoking with gestational age, maternal ethnicity with gestational age, and maternal use of benzodiazepines with gestational age. We added the interaction term maternal ethnicity with gestational age to control for any difference in fetal growth by ethnicity that may be related to SSRI use. We compared the effects of exposure to depressive symptoms with the effects of SSRI exposure using standard methods calculating the difference between the 2 effects and a standard error, which provided a 95% confidence interval with a *P* value.^{41,42}

We examined the association of depression and SSRI use during pregnancy with birth outcomes using linear and logistic regression analyses. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc), including the PROC MIXED module for longitudinal multilevel analyses.

NONRESPONSE ANALYSES

We compared the characteristics of the 7694 women included in the analyses with those of 799 mothers without SSRI information or lost to follow-up. Women without information on medication use were somewhat younger (*n*=799; mean [SD] age, 28.7 [5.8] years) than those with information (*n*=7696; mean [SD] age, 29.7 [5.3] years; *t*=5.35; *P*<.001), tended to be less educated (18.8% higher education vs 40.2%; χ^2 =816.4; *P*<.001), and smoked more often (18.1% never smoked in pregnancy vs 67.8%; χ^2 =799.0; *P*<.001). Children of mothers without information on medication use were born with a shorter gestational age (mean [SD] age, 39.6 [2.2] vs 39.8 [1.8] weeks; *t*=2.54; *P*=.01) and had a somewhat lower birth weight (mean [SD], 3348 [595] vs 3416 [558] g; *P*=.002).

RESULTS

DESCRIPTIVE STATISTICS

Table 1 shows that women with depressive symptoms not using SSRIs in pregnancy were younger, less educated, more often of non-Dutch origin, and more likely to smoke and drink alcohol during pregnancy as compared with the controls. As compared with the control group, women using SSRIs in pregnancy were less educated, more often of Dutch origin, and more likely to smoke and drink alcohol during pregnancy (Table 1). In addition, we compared the SSRI-using group with the group with depressive symptoms; the SSRI-using group was significantly older (*t*=5.51; *P*<.001).

Mean depression scores were 0.10, 1.45, and 0.74 for the control group, the group with depressive symptoms, and the SSRI-using group, respectively (Table 1). The SSRI-using group demonstrated a significantly lower score on the depressive symptoms scale than the group with depressive symptoms not using SSRIs (*t*=-9.43; *P*<.001).

Of the 99 women who used SSRIs during pregnancy, 28 had clinically relevant depressive symptoms. Moreover, 47 women used SSRIs in the first trimester only, and 52 pregnant women used SSRIs in the first trimester plus at least 1 additional trimester.

Table 1. Descriptive Characteristics of the Study Population^a

	Control Group (n = 7027)	Group With Depressive Symptoms Not Using SSRIs (n = 570)	P Value	SSRI-Using Group (n = 99)	P Value
Maternal characteristics, mean (SD)					
Maternal age at intake, y	29.8 (5.2)	27.1 (5.7)	<.001	30.4 (5.7)	.33
Maternal BMI	24.8 (4.5)	25.1 (4.7)	.17	26.0 (5.2)	.008
Parity	0.62 (0.87)	0.65 (0.93)	.42	0.66 (0.86)	.71
Educational level, %					
Primary education	10.8	18.6	<.001	15.8	.01
Secondary education	44.4	63.2		56.9	
Higher education	44.8	18.2		27.3	
Maternal ethnicity, %					
Dutch	52.0	21.8	<.001	59.4	.03
Non-Dutch Western	8.7	6.7		13.5	
Non-Dutch non-Western	39.3	71.5		27.1	
Smoking habits, %					
Never smoked in pregnancy	76.4	59.8	<.001	49.4	<.001
Smoked in early pregnancy	8.5	7.6		11.5	
Smoked throughout pregnancy	15.1	32.6		39.1	
Drinking habits, %					
Never drank in pregnancy	48.5	57.1	.001	48.3	.04
Drank in early pregnancy	13.8	11.5		23.0	
Drank throughout pregnancy	37.7	31.4		28.7	
Cannabis use habits, %					
Used during pregnancy	2.3	5.9	<.001	5.1	.15
Benzodiazepine use, %					
Used during pregnancy	1.0	1.8	.09	22.2	<.001
Family income, %					
<€1200 (US \$1551)	17.4	50.0	<.001	29.9	.01
€1200-€2000 (US \$1551-US \$2586)	17.8	25.0		22.1	
>€2000 (US \$2586)	64.8	25.0		48.1	
Psychopathology score, mean (SD)					
Depression	0.10 (0.15)	1.45 (0.69)	<.001	0.74 (0.79)	<.001
Anxiety	0.20 (0.25)	1.06 (0.75)	<.001	0.89 (0.92)	<.001
Child characteristics					
Sex of the child, % of boys	50	53.2	.16	41.2	.09
Birth weight, g, mean (SD)	3424 (556)	3333 (541)	<.001	3235 (654)	.001
Gestational age at birth, y, mean (SD)	39.8 (1.9)	39.9 (1.7)	.65	39.2 (2.5)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); SSRI, selective serotonin reuptake inhibitor.

^a P values are derived from analyses of variance for parametric continuous variables, Kruskal-Wallis tests for nonparametric continuous variables, and χ^2 tests for categorical variables. Reference group: no SSRI use, low score on Brief Symptom Inventory.

Table 2. Associations of Maternal SSRI Use and Depressive Symptoms in Pregnancy With Fetal Growth Characteristics^a

Groups	Fetal Weight Gain		Fetal Head Growth ^b	
	β (95% CI) ^c	P Value	β (95% CI) ^c	P Value
Control group	1 [Reference]		1 [Reference]	
Group with depressive symptoms not using SSRIs	-4.4 (-6.3 to -2.4)	<.001	-0.08 (-0.14 to -0.03)	.003
SSRI-using group	-2.3 (-7.0 to 2.3)	.32	-0.18 (-0.32 to -0.07)	.003

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

^a Longitudinal multilevel models were constructed using fractional polynomials for gestational age. All values were adjusted for maternal age, maternal body mass index, parity, sex of the child, maternal educational level and ethnicity, and maternal smoking habits and benzodiazepine use.

^b The model for fetal head growth was also corrected for estimated fetal weight measures to test for specificity.

^c β represents the decrease of fetal size characteristics in grams (fetal weight) and millimeters (head circumference) per week in the subgroups using the control group as the reference.

FETAL GROWTH

Table 2 demonstrates that children in the group with depressive symptoms not using SSRIs showed a slower rate of

fetal weight gain of approximately 4.4 g per week (95% CI: -6.3 to -2.4). In contrast, children in the SSRI-using group did not show a reduction in fetal growth as measured by fetal weight gain (slope β = -2.3; 95% CI: -7.0 to 2.3).

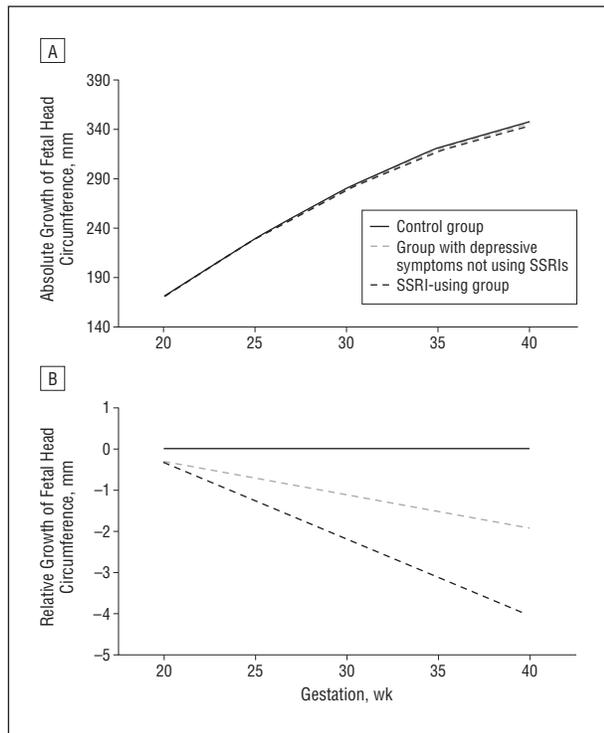


Figure. The absolute (A) and relative (B) growth of fetal head circumference in 3 groups: fetuses exposed to selective serotonin reuptake inhibitors (SSRIs) during pregnancy, fetuses exposed to high levels of depressive symptoms during pregnancy, and fetuses in the control group. Estimates were obtained from fitting a fractional polynomial model adjusted for maternal age, maternal body mass index, parity, sex of the child, maternal educational level and ethnicity, and maternal smoking habits and benzodiazepine use.

Children of mothers with depressive symptoms not using SSRIs also showed a reduced growth of head circumference (slope $\beta = -0.08$; 95% CI: -0.14 to -0.03). Children of mothers using SSRIs, however, had a more pronounced reduced head circumference growth of $\beta = -0.18$ mm per week (95% CI: -0.32 to -0.07). A direct comparison of the effect estimates of SSRI use and depressive symptoms showed a trend but it did not reach statistical significance ($\beta = -0.10$; 95% CI: -0.24 to 0.04 ; $P = .07$). Performing an additional adjustment for the depressive symptom scores, the decreased head growth remained present in the SSRI-using group ($\beta = -0.15$; 95% CI: -0.27 to -0.02 ; $P = .02$). Taking into account the effects of maternal ethnicity and smoking habits on the slope (interaction terms: ethnicity with gestational age and smoking with gestational age) did not attenuate the effect of SSRI exposure on head growth ($\beta = -0.17$; 95% CI: -0.29 to -0.04 ; $P = .008$). Moreover, taking into account the effects of maternal use of benzodiazepines on the slope (interaction term: benzodiazepine use with gestational age) did not attenuate the effect of SSRI exposure on head growth ($\beta = -0.19$; 95% CI: -0.32 to -0.06 ; $P = .003$). Finally, when we excluded the 28 SSRI-using women with high depressive symptoms, the association between maternal SSRI use and fetal head growth ($\beta = -0.17$ mm/wk; 95% CI: -0.31 to -0.03 ; $P = .02$) remained the same. Supplementary analyses using the standard deviation scores of fetal growth and head growth yielded very similar results (data not shown).

The **Figure** demonstrates the fetal head growth trajectories; Figure, A shows the absolute growth of head circumference and Figure, B shows the relative fetal head growth (ie, the difference of fetal head circumference growth between the groups). The graph demonstrates that the growth rate of the fetal head was high, varying from 171 mm at 20 weeks of gestation to 345 mm at 40 weeks of gestation. It also demonstrates that the effect of maternal SSRI use on head growth was rather small, up to a 4.0-mm difference in head circumference. The total effect size of SSRI use during pregnancy on fetal head circumference varied from 0.24% (at 20 weeks of gestation) to 1.19% (at 40 weeks of gestation).

BIRTH OUTCOMES

Table 3 shows that children of mothers with depressive symptoms not using SSRIs were born after a slightly longer (on average 1 day) gestational duration ($\beta = 0.18$; 95% CI: 0.01 to 0.34) compared with the controls. In contrast, children in the SSRI-using group were born with a shorter gestational duration as compared with the controls ($\beta = -0.60$; 95% CI: -0.97 to -0.21). Moreover, children in the SSRI-using group were twice as likely to be born preterm (odds ratio = 2.14; 95% CI: 1.08 to 4.25), as compared with the controls. The absolute numbers for preterm birth were 355 (5.1%), 36 (6.3%), and 10 (10.1%) for the control children, children of mothers with depressive symptoms, and children of mothers in the SSRI-using group, respectively.

Also, Table 3 demonstrates that the low birth weight of children of mothers using SSRIs during pregnancy (unadjusted in Table 1) was explained by the shorter gestational duration and other covariates. There was no evidence for a relationship between SSRI use and being small for gestational age (odds ratio = 0.89; 95% CI: 0.28 to 2.87).

Table 4 demonstrates that children of mothers who had depressive symptoms during pregnancy but did not use SSRIs had no reduced head circumference at birth ($\beta = 0.05$; 95% CI: -3.48 to 4.43), while SSRI-exposed children did have a smaller head circumference at birth ($\beta = -5.88$; 95% CI: -11.45 to -0.30) compared with children in the control group.

COMMENT

In this prospective population-based study, we examined the association of maternal depression and SSRI use during pregnancy with fetal growth. Untreated depressive symptoms were associated with a reduction in total body growth, including the fetal head, during pregnancy. In contrast, prenatal SSRI use was related to a reduced growth of the fetal head, whereas prenatal SSRI use did not affect growth of the fetal body. Our results indicate a rather specific effect of SSRI use during pregnancy, which differs from depressive symptoms on the fetus.

Although our findings add to current knowledge about the consequences of SSRI use (or nonuse) in women with depressive symptoms during pregnancy, they are not conclusive. Most importantly, untreated women with depressive symptoms also have children with reduced

Table 3. Association Between SSRI Exposure in Pregnancy and Birth Outcomes^a

Group	Gestational Age at Birth: Model A ^b		Birth Weight: Model B ^c	
	β (95% CI)	P Value	β (95% CI)	P Value
Control group	1 [Reference]		1 [Reference]	
Group with depressive symptoms not using SSRIs	0.18 (0.01 to 0.34)	.03	-28.4 (-65.9 to 9.2)	.13
SSRI-using group	-0.60 (-0.97 to -0.21)	.002	-53.5 (-141.3 to 34.3)	.23

Group	Preterm Birth (<37 wk): Model A ^b		Low Birth Weight (<2500 g): Model B ^c	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Control group	1 [Reference]		1 [Reference]	
Group with depressive symptoms not using SSRIs	1.10 (0.77 to 1.59)	.61	0.96 (0.65 to 1.42)	.82
SSRI-using group	2.14 (1.08 to 4.25)	.03	1.65 (0.77 to 3.56)	.20

Abbreviations: OR, odds ratio; SSRI, selective serotonin reuptake inhibitor.

^aModels were constructed using linear regression models. β represents the increase or decrease in gestational age in weeks and in birth weight in grams in the subgroups as compared with the control group.

^bModel A was adjusted for maternal age at intake, sex of the child, maternal education, ethnicity, maternal smoking and drinking habits, body mass index, parity, and maternal benzodiazepine use.

^cModel B was adjusted for the same variables as model A with additional adjustment for gestational age at birth.

growth of the fetal head, albeit less prominently. Nevertheless, our findings are of important value because there is a paucity of data regarding safety of SSRI use during pregnancy and possible consequences on fetal health. Importantly, a recent review characterized the unwanted effects of prenatal SSRI exposure as the prenatal antidepressant exposure syndrome, which included pregnancy complications and negative neurological, gastrointestinal, metabolic, respiratory, and cardiac symptoms at birth.²¹ However, this syndrome does not include decreased fetal head growth.

Several possible explanations for our results are conceivable. First, SSRIs are prescribed to treat depression; thus, the association between prenatal SSRI exposure and fetal head growth could be explained by these residual depressive symptoms. We tried to account for confounding by indication with a contrast group of women not pharmacologically treated for their depressive symptoms. However, confounding by severity of the disease might still be present, because women treated with antidepressants during pregnancy might have initially had more severe depression. On the other hand, women taking SSRIs have lower depression scores during pregnancy as compared with the women not treated pharmacologically, which possibly is consistent with the intended antidepressant effect (Table 1), and adjusting for depressive symptoms in the SSRI-using group did not attenuate the association between SSRI exposure and fetal head growth. Although most women started SSRI use well before pregnancy and had lower depressive symptom scores during pregnancy, it is possible that past depression affects maternal physiology lastingly and thus could also affect fetal development.

Second, serotonin is known to play an important role in prenatal brain development,^{3,6} and manipulation of serotonin levels with SSRIs in utero may directly affect fetal brain growth. Pharmacological animal studies demonstrated decreased brain maturation; animals exposed to SSRIs had fewer dendritic branches, shorter dendritic length, and a smaller dendritic field in the somatosen-

Table 4. Association Between SSRI Exposure in Pregnancy and Head Circumference at Birth^a

Groups	Head Circumference at Birth: Model A ^b	
	β (95% CI)	P Value
Control group (n = 5431)	1 [Reference]	
Group with depressive symptoms not using SSRIs (n = 425)	0.05 (-3.48 to 4.43)	.81
SSRI-using group (n = 71)	-5.88 (-11.45 to -0.30)	.04

Abbreviation: SSRI, selective serotonin reuptake inhibitor.

^aModels were constructed using linear regression models. β represents the increase or decrease in millimeters in the subgroups as compared with the control group.

^bModel A was adjusted for maternal age at intake, sex of the child, maternal education, ethnicity, maternal smoking and drinking habits, body mass index, parity, and maternal benzodiazepine use.

sory barrel cortex.^{11,43-45} Also, Rayburn et al⁹ demonstrated that newborn mice exposed to paroxetine were more likely to have narrower heads. In that study, therapeutic doses were used to mimic the human levels in the fetal mouse brain.⁹

A third potential mechanism to explain the association between maternal SSRI use and fetal head growth is the presence of epiphenomena of SSRI use, eg, smoking or drinking during pregnancy and low socioeconomic status. These risk factors have been shown to affect fetal growth.^{37,46} We attempted to adjust for these epiphenomena in our analyses, but unmeasured residual confounding (eg, use of other medication or illicit drugs in pregnancy, malnutrition, genetic susceptibility, family stress) could still be present. However, such epiphenomena are less likely to explain a specific effect on head size. If fetal growth is compromised, head growth is typically impaired last; this is termed the *brain-sparing effect*.⁴⁷

Our results demonstrated that children of mothers with depressive symptoms not using SSRIs were born after a slightly longer gestational duration (1 day) but within

normal range of childbirth. In addition, we found no association between depressive symptoms and low birth weight. These results are in agreement with the meta-analytic study of Grote and coworkers⁴⁸ demonstrating no increased risk for preterm birth when using a continuous measure of depression and no increased risk of low birth weight in European countries. Interestingly, the meta-analyses showed that in the United States antenatal depression was associated with an increased risk for low birth weight. One potential explanation for this discrepancy is that mental health care in Western Europe, including nonpharmacological depression treatment, is more accessible.

Selective serotonin reuptake inhibitor exposure during pregnancy was associated with a shorter gestational age at birth, which was in line with previous studies.⁴⁹⁻⁵² These studies were based on hospital, health insurance, or patient data and demonstrated consistently that SSRI use is associated with preterm birth or a shorter gestational duration.⁴⁹⁻⁵² The effect of SSRI use during pregnancy on birth weight in the present study was explained by the shorter gestational duration, consistent with the observations of Simon and colleagues.⁵¹

To place the magnitude of the observed effects of prenatal SSRI use on fetal head circumference in perspective, we compared our results with 2 previous studies of head growth. These studies showed that prenatal tobacco (-0.13 mm/wk) and prenatal cannabis (-0.21 mm/wk) exposure negatively affected growth of fetal head circumference.^{37,53}

The strengths of our study include the large population recruited prospectively and precise and sensitive measure of fetal growth obtained with repeated ultrasonography measurements. Furthermore, we used both self-reported information and prescription records to determine prenatal SSRI use. Moreover, we contrasted the effects of SSRIs and depressive symptoms on fetal growth. Thus, the current study meets the methodological criteria proposed for studies on the effects of prenatal antidepressant exposure, ie, the distinction of different exposed and unexposed groups.⁵⁴ However, 1 group, the women treated with SSRIs who failed to achieve remission ($n=28$), was too small to study separately. We could only exclude these women in additional analyses to rule out that this group, in particular, explained the observed effect of SSRI use. Nevertheless, several limitations must be discussed. For example, it would be useful to have pretreatment or preconception depression scores to better match the SSRI and depressive symptom groups. Such data would only be available in preconception cohorts. Moreover, because of small numbers, we could not study period-specific effects of SSRI use and were not able to assess prenatal effects related to exposure to specific SSRIs. Furthermore, this small sample could be the reason why the reduction in fetal weight in the SSRI-using group did not reach significance. Because of logistical reasons, pharmacy records were not available in many participants. This was most likely random, but further information could have reduced any misclassification of SSRI exposure. Finally, we cannot rule out selection bias because the nonresponse analyses demonstrated that nonresponders were younger,

tended to be less educated, and smoked more often. Their children were more likely to be born with a shorter gestational duration and had a somewhat lower birth weight.

Prescribing antidepressant medication to pregnant women is a major controversy in current psychiatry.⁵⁵ Whereas the use of SSRIs among pregnant women has increased from 1.5% in 1996 to 6.2% in 2005,⁵⁶ studies using detailed measures of fetal and child developmental outcomes to examine potential long-term consequences are sparse. Our study shows a rather specific effect of maternal SSRI use on fetal head growth, one of the best prenatal markers of brain volume. Fetal head circumference in early life has been shown to be an accurate indicator of brain weight.^{57,58} Small head size in neonates predicts behavioral problems and psychiatric disorders, such as internalizing problems, anxiety and attention-deficit/hyperactivity disorder, and poorer cognitive performance later in life.⁵⁹⁻⁶² Importantly, a recent study demonstrated that prenatal exposure to SSRIs might increase the risk of autism spectrum disorders.⁶³ Nonetheless, we must be careful not to infer an association of SSRI use in pregnancy with future developmental problems. Therefore, more long-term drug safety studies are needed before evidence-based recommendations can be derived.

Our findings further raise the question whether maternal SSRI treatment during pregnancy is better or worse for the fetus than untreated maternal depression. Clinicians must carefully weigh the known risks of untreated depression during pregnancy and the possible adverse effects of SSRIs. Ideally, preconception health promotion and prevention programs should be developed to improve health of pregnant women and to reduce the risk of developing prenatal depression. However, these programs will doubtless be ineffective for some women with prenatal depression in whom the benefits of antidepressant treatment with SSRIs probably outweigh the risks.

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Correspondence: Henning Tiemeier, MD, PhD, The Department of Child and Adolescent Psychiatry, Erasmus MC, Sophia Children's Hospital, 3000 CB Rotterdam, the Netherlands (h.tiemeier@erasmusmc.nl).

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