BJPsych The British Journal of Psychiatry (2014)
205, 95–102. doi: 10.1192/bjp.bp.113.127746

Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness symptoms of autism: population-based study of young children†

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Background
Selective serotonin reuptake inhibitors (SSRIs) are considered safe and are frequently used during pregnancy. However, two case–control studies suggested an association between prenatal SSRI exposure with childhood autism.

Aims
To prospectively determine whether intra-uterine SSSRI exposure is associated with childhood autistic symptoms in a population-based study.

Method
A total of 376 children prenatally exposed to maternal depressive symptoms (no SSRI exposure), 69 children prenatally exposed to SSRIs and 5531 unexposed children were included. Child pervasive developmental and affective problems were assessed by parental report with the Child Behavior Checklist at ages 1.5, 3 and 6. At age 6, we assessed autistic traits using the Social Responsiveness Scale ($n = 4264$).

Results
Prenatal exposure to maternal depressive symptoms without SSRIs was related to both pervasive developmental (odds ratio (OR) = 1.44, 95% CI 1.07–1.93) and affective problems (OR = 1.44, 95% CI 1.15–1.81). Compared with unexposed children, those prenatally exposed to SSRIs also were at higher risk for developing pervasive developmental problems (OR = 1.91, 95% CI 1.13–3.47), but not for affective problems. Children prenatally exposed to SSRIs also had more autistic traits ($B = 0.15$, 95% CI 0.08–0.22) compared with those exposed to depressive symptoms only.

Conclusions
Our results suggest an association between prenatal SSRI exposure and autistic traits in children. Prenatal depressive symptoms without SSRI use were also associated with autistic traits, albeit this was weaker and less specific. Long-term drug safety trials are needed before evidence-based recommendations are possible.

Declaration of interest
F.C.V. is head of the Department of Child and Adolescent Psychiatry at Erasmus Medical Centre, which publishes the Achenbach System of Empirically Based Assessment (ASEBA) and from which the department receives remuneration.

Selective serotonin reuptake inhibitors (SSRIs) are efficacious and safe[1] and have become the most commonly prescribed medications to treat depression and to prevent recurrence of depression.[2] These drugs are also used to treat and prevent depression in pregnant women, but their safety during pregnancy is less well established.[3] Short-term consequences on newborn health, such as neonatal abstinence syndrome characterised by convulsions, irritability, abnormal crying and tremor have been described.[4,5] However, the possible long-term consequences of prenatal SSRI exposure on child neurodevelopment are uncertain. Recently, two case–control studies, a retrospective and a prospective one, suggested that prenatal SSRI exposure increased the risk of childhood autism spectrum disorder.[6,7] More specifically the study of Rai and colleagues demonstrated that SSRI use was related to autism spectrum disorder without intellectual disability.[6] However, prospectively few studies examined potential long-term effects of prenatal SSRI exposure, and often study samples are relatively small and results are conflicting.[8–11] Previously, we demonstrated that prenatal SSRI exposure was associated with decreased fetal head growth,[12] which was in line with a previous animal study.[13] In addition, comparable with previous human studies investigating SSRI exposure and birth outcomes,[14–17] we demonstrated a higher risk of preterm birth.[12] In the current study, the objective was to prospectively investigate the association of SSRI use and depressive symptoms during pregnancy with child autistic symptoms in a population-based setting. Child affective problems were also investigated to examine the specificity of any observed effect of SSRIs. Finally, we investigated whether fetal head size mediated any effect on autistic symptoms.

Method

Setting and population

The present study is embedded in an ongoing population-based cohort, the Generation R Study.[18] All pregnant women resident in Rotterdam were invited to participate. In total, 8880 mothers were enrolled during pregnancy (delivery from April 2002 to January 2006). The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, approved the study. Written informed consent was obtained from all participants. For the present analyses, only children who participated in the pre- and postnatal follow-up ($n = 8098$) were considered. Of these, 650 children were excluded, as information on maternal SSRI use was unavailable. Information on child behavioural and emotional problems was obtained in 6122 (82.2%) children during follow-up. Use of SSRIs before pregnancy only was recorded in 146 (2.4%) women; these individuals were excluded as a spillover effect cannot be ruled out. Thus, 5976 children formed the study population.

†See invited commentaries, pp. 103–106, this issue.

Exposure to SSRIs and depressive symptoms during pregnancy

In this study, we assessed exposure to SSRIs and depressive symptoms during pregnancy. It is essential to contrast any effect of prenatal SSRI exposure with the known long-term consequences of untreated prenatal depression on child development.[19]

To optimise ascertainment of maternal SSRI use in pregnancy, we used two sources of information: (a) self-report assessed with questionnaires and (b) prescription records from pharmacies. In each trimester, pregnant mothers filled out the type of medication taken and when it was used. From these questionnaires, SSRI exposure before or during pregnancy was assessed.

To validate the use of filled prescription, we asked women for permission to contact their pharmacy. For the large majority, permission to contact their pharmacy was obtained and data were requested. However, because of a delay in linkage not everything could be retrieved; prescription records were available in 60.2% ($n = 3684$) of our sample. Records screened for SSRI use provided information on the type of SSRI, duration and dose. Agreement between self-report and information from prescription records was high; Yule's Y was 0.93. Yule's Y, also called the coefficient of colligation for dichotomous variables, is equivalent to kappa of agreement,[20] but is less dependent on the prevalence, which provides a more accurate estimation of the agreement between self-reports and information from prescription records when the prevalence of SSRI use is low.

Of the 69 women who used SSRIs during pregnancy, 35 women used SSRIs in the first trimester only and 34 women used them in the first and also in one or two other trimesters. The SSRIs used were paroxetine ($n = 38$), fluoxetine ($n = 17$), sertraline ($n = 11$), fluvoxamine ($n = 6$) and citalopram ($n = 4$); these numbers add up to 76 as some pregnant women used multiple SSRIs. Mean duration of SSRI use was 257 days (8.4 months). Reasons for use of SSRIs were (previous) depression ($n = 52$) or (previous) anxiety ($n = 4$); in 13 cases reasons for use were unknown.

Depressive symptoms were assessed with the Brief Symptom Inventory (BSI)[21,22] at, on average, 20.6 weeks of gestation. The BSI is a validated self-report questionnaire with 53 items, [21,22] which define a spectrum of psychiatric symptoms; we used the 6-item depression scale. Mothers with a score higher than 0.75 have clinically relevant depressive symptoms according to the Dutch norm data.[22]

Within a Generation R subgroup of 905 women, we tested the BSI's ability to identify clinical depression using the applied cut-off score. Data on clinical depression during the past year were obtained in this subgroup with the Composite International Diagnostic Interview (CIDI).[23] The CIDI is a structured interview based on DSM-IV criteria.[24] Good reliability and validity have been reported.[23] Research assistants conducted the home interviews during pregnancy. We calculated the positive likelihood ratio (LR+) as it accounts for a low prevalence and the LR+ was equal to 7.29. This demonstrates moderate quality of the cut-off as an indicator of certainty of diagnosis.

For the same subgroup we tested the BSI's ability to identify postpartum depression. Data on postpartum depression were obtained with the Edinburgh Postnatal Depression Scale (EPDS), a widely used 10-item self-report scale that has been validated for the Dutch population.[25,26] The EPDS sum score ranges from 0 to 30, with higher scores indicating more depressive symptoms. We used the validated cut-off score of more than 12 on the EPDS. Previous research indicated that this cut-off score has a sensitivity of over 80% and a specificity of 95% for identifying women with clinically diagnosed postpartum depression in a community sample.[26] We calculated the LR+, which was equal to 28.68. This demonstrates good quality of the BSI cut-off as an indicator of depression as measured with the EPDS.

Based on maternal depressive symptoms and SSRI use, children were classified into three groups:

(a) no exposure to SSRIs and a low score of maternal depressive symptoms (92.5%, $n = 5531$), referred to as 'reference group';

(b) exposure to clinically relevant depressive symptoms and no maternal SSRI use (6.3%, $n = 376$), referred to as 'exposed to depression'; and

(c) exposure to SSRIs during pregnancy (1.2%, $n = 69$), referred to as 'exposed to SSRIs'.

Head size

Fetal ultrasound assessments were performed in the first (median 12.8 weeks), second (median 20.3 weeks) and third (median 30.1 weeks) trimester of pregnancy.[27] The ultrasound examinations were used for both assessing gestational age (first trimester measurement), as well as for fetal growth characteristics (second and third trimester), including head circumference. The intra-observer and inter-observer reliabilities of fetal biometry within Generation R were excellent, with all intraclass correlation coefficients greater than 0.99.[27] Head circumference was also measured directly after birth or at child healthcare centres at age 3 weeks (mean post-conception age: 42.9 weeks).

Autistic symptoms

We assessed parent-reported autistic symptoms using two instruments: the pervasive developmental problems subscale of the Child Behavior Checklist for ages 1.5–5 (CBCL 1.5–5),[28] and the Social Responsiveness Scale (SRS).[29,30] The CBCL 1.5–5 is a standardised assessment instrument, which covers a broad age range. Parents filled out the CBCL 1.5–5 for toddlers[28] to measure emotional and behavioural problems repeatedly at age 1.5, 3 and 6 years. At age 6 years, parents also completed the SRS, which focused specifically on the various dimensions important in autism spectrum disorder.

The Dutch version of the CBCL 1.5–5 is reliable and well validated,[31] and the subscales for syndromes derived from the CBCL 1.5–5 had good fit in 23 international studies across diverse societies.[32] The affective and the pervasive developmental problems subscales are two of the five scales that can be derived from the CBCL 1.5–5, consistent with the DSM-IV diagnostic categories. These DSM-oriented scales could not be normalised, and therefore we dichotomised the scores. An established norm cut-off score (above the 93rd percentile) was used that indicates clinically meaningful problems.[31] The subscale cut-off in the Dutch norm (93rd percentile) for pervasive developmental problems is 7, which in our sample corresponded to the 95th percentile. The subscale cut-off in the Dutch norm for affective problems is 4, which in our sample corresponded to the 89th percentile. The pervasive developmental problems subscale of the CBCL 1.5–5 has been shown to be a useful screening instrument to identify children with autism spectrum disorder when compared with the Autism Diagnostic Observation Schedule – Generic.[33] It has a good predictive validity to identify preschoolers at risk of autism spectrum disorder.[34]

Although 40% of children were 6 years or older at the time of assessment (mean age 72.8 months (s.d. = 5.8), range 57.7–108.9), we used the CBCL 1.5–5 (preschool version) for reasons of continuity. At the age of 1.5, 3 and 6 years, mothers completed the CBCL. At age 3, fathers also rated the child. All correlations between the different CBCL measurements fell in the expected

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press

range, based on a mean correlation ($r = 0.60$) in a meta-analysis of parental ratings.[35]

To assess autistic traits, mothers filled out the adapted 18-item version of the SRS at age 6 years, which is a quantitative measure of autistic traits for children aged between 4 and 18 years.[29,30] The SRS covers various dimensions of interpersonal behaviour, communication and repetitive/stereotypic behaviour characteristic of autism spectrum disorder. A Likert-scale response format was used, producing a scale that is sensitive and reliable across a wide range of symptom severity. The 18-item questionnaire in the current study contained items from three subscales: social cognition, social communication and autistic mannerism. The (weighted) sum score of autistic traits ranged between 0 and 2.83. In our study, the Crohnbach's alpha indicated high inter-item reliability for the SRS ($\alpha = 0.79$). The SRS correlated well with the pervasive developmental problems scale of the CBCL 1.5–5 ($r = 0.59$, $P < 0.001$).

Covariates

Based on previous literature potential confounders were selected.[36] Information on maternal and paternal age, ethnicity and education was based on self-report. Parental ethnicity was defined according to the classification of Statistics Netherlands and categorised into Dutch, non-Dutch Western and non-Dutch non-Western based on the country of birth of their parents.[37] Educational level was categorised into three levels: primary, secondary and higher education.[38] Information about maternal prenatal smoking and alcohol use was categorised based on repeated questionnaires in each trimester of pregnancy as 'no', 'until pregnancy was known' and 'continued during pregnancy'; detailed information about the frequency of smoking and drinking was collected using six categorical answer options.[39,40] Postnatal maternal depressive symptoms at child age 3 years, as for prenatal depressive symptoms, were assessed using the BSI.[21] Information on maternal benzodiazepine use, as for information on maternal SSRI use during pregnancy, was collected with mailed questionnaires in each trimester and prescription records.[12] Benzodiazepines were used by 75 women; 33 used benzodiazepines in early pregnancy and 42 women in two or more trimesters. The most commonly used benzodiazepines included diazepam, oxazepam and temazepam. Mean duration of benzodiazepine use was 49.9 days (1.6 months).

Statistical analyses

We used analysis of variance (ANOVA) and chi-squared statistics to compare characteristics of SSRI-exposed children, children exposed to depressive symptoms and the non-exposed reference group. We used the generalised estimating equation (GEE) procedure to analyse the relationship of exposure to prenatal SSRI use or maternal depressive symptoms with pervasive developmental and affective problems, which combines ratings at multiple time points (1.5, 3 and 6 years). The GEE procedure adjusts for within-participant correlation. Also, this procedure provides a more precise effect estimate and reduces the error derived from multiple comparisons.[41] It was not our aim to test for differences between two informants or possible age trends in child symptoms. To examine the relationship of exposure to prenatal SSRI use or maternal depressive symptoms with pervasive developmental and affective problems as reported by the father, we used linear regression analyses.

To analyse the relationship between prenatal SSRI exposure and autistic traits as measured with the SRS we used linear regression. The effects of exposure to SSRI and depressive symptoms on autistic traits were compared by calculating the difference between the two effects and the 95% confidence interval.[42,43]

Models were adjusted for maternal age, education, ethnicity, smoking habits, postnatal depressive symptoms at 3 years, child gender and gestational age. Based on the change-in-estimate method[44,45] age of the biological father, maternal drinking habits and use of benzodiazepine were not used as covariates as it did not affect the association. Likewise, birth weight did not confound the association tested if gestational age was controlled for.

Additional analyses accounting for the level of prenatal depressive symptoms and fetal head growth were performed. Supplemental sensitivity analyses were performed, examining first trimester SSRI exposure and multiple trimester SSRI exposure separately. Finally, additional analyses were performed where we used the level of depressive symptoms as a continuous measure, rather than using it as a categorical variable with three groups.

Unadjusted mean values for pervasive developmental problems, affective problems and autistic traits for each group at each measurement (1.5, 3 and 6 years of age are presented in online Table DS1). On average, 5.9% of data across all variables were missing. To avoid the bias of complete case analysis, we accounted for missing information on the confounders (determinants and outcomes were not imputed) by using multiple imputation methods; five imputed data-sets were generated using a fully conditional specified model to handle missing values. Imputations were based on the relations between all covariates in the study.[46] The associations in the complete-case data-set (with no missing data imputed) were very similar to the associations found in the imputed data-sets. We only reported the pooled estimates of the analyses of these five imputed data-sets.

Non-response analyses

We compared the characteristics of the 5976 women included in the analyses of the CBCL to those of 2122 mothers not included. The non-responders were younger (28.1 years (s.d. = 5.6)) than responders (30.6 years (s.d. = 4.9), $t = 19.4$, $P < 0.001$) were more likely to be of non-Dutch origin (26.2% *v.* 55.8% Dutch, $\chi^2 = 1020.2$, $P < 0.001$), less educated (17.4% *v.* 48.2% higher education; $\chi^2 = 1067.7$, $P < 0.001$) and smoked more often in pregnancy (43.4% *v.* 69.3% never smoked in pregnancy, $\chi^2 = 791.3$, $P < 0.001$).

Non-response analyses of those included in the analyses of autistic traits ($n = 4264$) compared with non-responders ($n = 3834$ of whom $n = 1712$ were included in the CBCL analyses) showed very similar differences.

Results

Mothers with depression but no SSRI treatment during pregnancy were younger, less educated, more often of non-Dutch origin and smoked more often during pregnancy than the reference group (Table 1). Compared with the reference group, mothers taking SSRIs during pregnancy were less educated and smoked more often (Table 1). Additionally, we compared the SSRI-exposed group with the group exposed to depression. Mothers taking SSRIs were significantly older ($t = 3.36$, $P < 0.001$) and more likely to be of Dutch origin ($\chi^2 = 47.2$, $P < 0.001$). Furthermore, mothers taking SSRIs had significantly fewer depressive symptoms prenatally (0.74 *v.* 1.38, $t = 9.00$, $P < 0.001$) and also postnatally (0.34 *v.* 0.47, $t = 2.51$, $P = 0.01$) than mothers with clinically relevant depressive symptoms.

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press

Table 1 Descriptive statistics of the study population[a]

	Reference group ($n=5531$)	Exposed to depression ($n=376$)	*P*	Exposed to SSRIs ($n=69$)	*P*
Maternal characteristics					
Maternal age at intake, years: mean (s.e.)	30.7 (0.06)	28.4 (0.29)	<0.001	30.9 (0.72)	0.69
Educational level, %					
Primary education	7.7	16.8	<0.001	10.1	0.05
Secondary education	41.3	59.0		53.9	
Higher education	51.0	24.2		36.0	
Maternal ethnicity, %					
Dutch	57.9	26.4	<0.001	65.2	0.04
Non-Dutch Western	9.0	8.3		14.5	
Non-Dutch non-Western	33.1	65.3		20.3	
Smoking habits,[b] %					
Never smoked in pregnancy	75.1	59.6	<0.001	48.4	<0.001
Smoked in early pregnancy	12.0	12.2		16.5	
Smoked throughout pregnancy	12.9	28.2		35.1	
Drinking habits,[b] %					
Never drank in pregnancy	42.4	59.6	0.002	34.2	0.07
Drank in early pregnancy	17.3	12.2		27.8	
Drank throughout pregnancy	40.3	28.2		38.0	
Used benzodiazepine in pregnancy, %	0.9	2.1	0.02	24.6	<0.001
Depressive symptoms, mean (s.e.)					
Prenatal scores	0.12 (0.01)	1.38 (0.03)	<0.001	0.68 (0.09)	<0.001
Postnatal scores	0.15 (0.01)	0.47 (0.03)	<0.001	0.38 (0.06)	<0.001
Child characteristics					
Gender of the child, % boys	49.7	52.9	0.23	39.1	0.08
Birth weight, g: mean (s.e.)	3430 (7.6)	3341 (29.3)	0.003	3292 (82.0)	0.04
Gestational age at birth, weeks: mean (s.e.)	39.9 (0.02)	39.8 (0.10)	0.88	39.2 (0.32)	0.004

SSRI, selective serotonin reuptake inhibitor.
a. Reference group: no SSRI use, low score on depression symptoms scale during pregnancy; exposed to depression group: children exposed to clinically relevant depressive symptoms during pregnancy; exposed to SSRIs group: children exposed to SSRIs during pregnancy. *P*-values are derived from ANOVAs for parametric continuous variables, Kruskal–Wallis tests for non-parametric continuous variables and χ^2-tests for categorical variables with reference group as the comparison group. There were no missing data on these variables as they were imputed using multiple imputation methods.
b. Smoking ten or more cigarettes per day fluctuated between 19.1 and 9.3% throughout pregnancy, with the highest percentage in the first trimester. Drinking more than one drink per day varied between 4.8 and 0.9% throughout pregnancy, with the highest percentage in the first trimester.

Compared with the reference group (33.5 years (s.d. = .07)), fathers of children exposed to SSRIs (32.2 years (s.d. = 0.64), $P=0.04$) and fathers of children exposed to maternal depression were younger (31.6 years (s.d. = 0.33), $P<0.001$).

Pervasive developmental problems

Children exposed to maternal prenatal depressive symptoms (but not SSRIs) had more pervasive developmental problems in the clinical range (odds ratio (OR) = 2.02, 95% CI 1.53–2.66, $P<0.001$) than the reference group across childhood. This association was partially as a result of higher postnatal maternal depressive symptoms (Table 2).

Children exposed to SSRIs during pregnancy were also more likely to have pervasive developmental problems (OR = 2.58, 95% CI 1.46–4.54, $P=0.001$) than the reference group. This association was not explained by postnatal maternal depressive symptoms (Table 2). This association between prenatal SSRI exposure and pervasive developmental problems was also independent of depressive symptoms during pregnancy

Table 2 Prenatal selective serotonin reuptake inhibitor (SSRI) use, depressive symptoms and pervasive developmental problems and autistic symptoms[a]

Maternal depressive symptoms and SSRI use	Pervasive developmental problems, categorical, age 1.5–6 years			Autistic traits, continuous, age 6 years		
	n	OR (95% CI)	*P*	*n*	β (95% CI)	*P*
Model I						
Reference group	5531	1.0		3992	1.0	
Exposed to depression	376	2.02 (1.53–2.66)	<0.001	222	0.08 (0.04–0.11)	<0.001
Exposed to SSRIs	69	2.58 (1.46–4.54)	0.001	50	0.17 (0.10–0.24)	<0.001
Model I + postnatal depressive symptoms (II)						
Reference group	5531	1.0	Reference	3992	1.0	
Exposed to depression	376	1.44 (1.07–1.93)	0.02	222	0.05 (0.01–0.08)	0.01[b]
Exposed to SSRIs	69	1.91 (1.13–3.47)	0.03	50	0.15 (0.08–0.22)	<0.001

a. Models were constructed using generalised estimating equations models or linear regression models. Odds ratios (ORs) represent the increased or decreased risk for pervasive developmental problems (1.5–6 years) as measured with the Child Behavior Checklist in the subgroups as compared with the reference group. Betas (βs) represent the increased or decreased risk for autistic traits as measured with the Social Responsiveness Scale (at 6 years) in the subgroups as compared with the reference group. Reference group: no SSRI use, low score on depression symptoms scale during pregnancy; exposed to depression: children exposed to clinically relevant depressive symptoms during pregnancy; exposed to SSRIs: children exposed to SSRIs during pregnancy. Model I was adjusted for maternal age at intake, gender of the child, maternal education, ethnicity, maternal smoking habits, and gestational age at birth. Model II was additionally adjusted for maternal depressive symptoms at 3 years.
b. A direct comparison of the effect estimates of SSRI use and depressive symptoms without SSRI use showed a statistical significance (β = 0.10, 95% CI 0.02–0.18, $P<0.01$).

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press

(OR = 1.96, 95% CI 1.09–3.52, $P = 0.02$). The effect estimate for pervasive developmental problems in SSRI-exposed children did not differ significantly from the effect observed in children exposed to depression (OR for comparison 1.33, 95% CI 0.68–2.57, $P = 0.41$).

Adjustment for head size during pregnancy or at birth did not change the association between SSRI use and pervasive developmental problems. Consistent results were observed when only the father-rated pervasive developmental problems (OR for SSRI exposure 2.98, 95% CI 1.07–8.28, $P = 0.04$) were analysed. In contrast, the effect of prenatal exposure to maternal depressive symptoms was not significant when analyses were based on the father's ratings (OR = 1.63, 95% CI 0.93–2.88, $P = 0.09$). Furthermore, the sensitivity analyses demonstrated an increased risk for pervasive developmental problems when exposed to SSRIs in the first trimester of pregnancy only (OR = 2.15, 95% CI 1.02–4.55, $P = 0.047$) and a trend for and increased risk when exposed to SSRIs in multiple trimesters (OR = 2.03, 95% CI 0.82–5.03, $P = 0.13$). Finally, we used the level of depressive symptoms as a continuous variable and the analyses showed that prenatal depressive symptoms were not associated with an increased risk for pervasive developmental problems (OR = 1.19, 95% CI 0.93–1.53, $P = 0.16$).

Autistic traits

Prenatal exposure to depression (with no SSRI use) was associated with slightly higher scores for autistic traits (β = 0.05, 95% CI 0.01–0.08, $P = 0.01$). The relationship between prenatal SSRI exposure and autistic traits was more pronounced (β = 0.15, 95% CI 0.08–0.22, $P < 0.001$). A direct comparison of the effect estimates of SSRI use and depressive symptoms without SSRI use showed a significant difference (β for comparison 0.10, 95% CI 0.02–0.18, $P < 0.01$). Higher trait scores of SSRI-exposed than of non-exposed children were observed in every domain of autism: social cognition (β = 0.13, 95% CI 0.03–0.23, $P = 0.01$), social communication (β = 0.17, 95% CI 0.09–0.25, $P < 0.001$) and autistic mannerism (β = 0.12, 95% CI 0.05–0.20, $P = 0.006$, Table 3).

Adjustment for head size during pregnancy or at birth did not change the association between prenatal SSRI use and autistic traits. Sensitivity analyses demonstrated that children exposed to SSRIs in the first trimester only had higher scores on the autistic traits scale (β = 0.11, 95% CI 0.01–0.21, $P = 0.03$), like those exposed to SSRIs in multiple trimesters (β = 0.19, 95% CI 0.09–0.28, $P < 0.001$). Supplemental analyses demonstrated that prenatal depressive symptoms (continuous scores) were associated with slightly increased autistic traits (β = 0.05, 95% CI 0.03–0.07, $P < 0.001$).

Affective problems

To study the specificity of the observed effects of maternal SSRI use and depressive symptoms, we also studied child affective problems in childhood. Children exposed to maternal depressive symptoms (without SSRIs) were more likely to have affective problems (OR = 1.44, 95% CI 1.15–1.81, $P = 0.001$), whereas prenatal SSRI exposure was not associated with child affective problems (OR = 1.37, 95% CI 0.87–2.16, $P = 0.17$). Again, consistent results were observed if father ratings of child affective problems were analysed (OR for SSRI exposure 1.04, 95% 0.39–2.76, $P = 0.95$). The effect of prenatal exposure to maternal depressive symptoms on child affective problems was significant as rated by the father (OR for exposure to maternal depressive symptoms 1.60, 95% CI 1.05–2.45, $P = 0.03$).

Furthermore, prenatal depressive symptoms (as a continuous measure) were associated with an increased risk for affective problems in young children (OR = 1.35, 95% CI 1.13–1.61, $P = 0.001$).

Head size

Online Table DS2 demonstrates an association between a smaller head size in mid pregnancy and pervasive developmental problems (OR = 0.91, 95% CI 0.83–0.99, $P = 0.04$), whereas in late pregnancy no association was observed (OR = 0.93, 95% CI 0.87–1.01, $P = 0.09$). Around birth, the direction of the association between head size and pervasive developmental problems reversed: a larger head was associated with a higher risk of pervasive developmental problems (OR = 1.14, 95% CI 1.06–1.24, $P = 0.001$). When we stratified the children by exposure (reference group, prenatal depression and prenatal SSRI exposure) it became clear that the association of head size at birth with pervasive developmental problems is similar and consistent across the groups (online Table DS2).

Discussion

Main findings

In this population-based study, we found that prenatal SSRI exposure was associated with autistic traits, but not with affective

Table 3 Prenatal selective serotonin reuptake inhibitor (SSRI) use, depressive symptoms and specific autistic symptoms[a]

Maternal depressive symptoms and SSRI use	*n*	Social cognition, continuous, age 6 years		Social communication, continuous, age 6 years		Autistic mannerism, continuous, age 6 years	
		β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Model I							
Reference group	3992	0		0		0	
Exposed to depression	222	0.08 (0.03 to 0.13)	0.002	0.08 (0.04 to 0.12)	<0.001	0.06 (0.03 to 0.10)	0.001
Exposed to SSRIs	50	0.15 (0.05 to 0.25)	0.001	0.19 (0.12 to 0.27)	<0.001	0.14 (0.07 to 0.22)	<0.001
Model I + postnatal depressive symptoms (II)							
Reference group	3992	0		0		0	
Exposed to depression	222	0.05 (−0.01 to 0.04)	0.07	0.05 (0.01 to 0.09)	0.02[b]	0.04 (−0.01 to 0.07)	0.07[b]
Exposed to SSRIs	50	0.13 (0.03 to 0.23)	0.01	0.17 (0.09 to 0.25)	<0.001	0.12 (0.05 to 0.20)	0.006

a. Models were constructed using linear regression models. Betas (βs) represent the increased or decreased risk for autistic traits as measured with the Social Responsiveness Scale (at 6 years) in the subgroups as compared with the reference group. Reference group: no SSRI use, low score on depression symptoms scale during pregnancy; exposed to depression: children exposed to clinically relevant depressive symptoms during pregnancy; exposed to SSRIs: children exposed to SSRIs during pregnancy. Model I was adjusted for maternal age at intake, gender of the child, maternal education, ethnicity, maternal smoking habits and gestational age at birth. Model II was additionally adjusted for maternal depressive symptoms at 3 years.
b. A direct comparison of the effect estimates of SSRI use and depressive symptoms without SSRI use showed a statistical significance for social communication (β = 0.12, 95% CI 0.03 to 0.21, $P < 0.01$) and autistic mannerism (β = 0.09, 95% CI 0.01 to 0.17, $P = 0.04$) and a trend for social cognition (β = 0.10, 95% CI −0.02 to 0.22, $P = 0.09$).

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press

problems in childhood. Prenatal depressive symptoms without SSRI use were also associated with autistic traits, albeit weaker, and were also associated with affective problems in children. In addition, the association between prenatal SSRI exposure and more pervasive developmental symptoms was consistent across parental informants. In contrast, exposure to maternal depressive symptoms during pregnancy and pervasive developmental problems were not associated if the child's symptoms were reported by the father. This suggests that mothers with depressive symptoms particularly may overestimate the problems of their children.

Strengths and weaknesses

Despite the strengths of our study, such as the prospective nature of the study, the information on child problems at multiple time points and two informants, and the use of two different measures of autistic symptoms, some limitations need to be discussed. Women treated with SSRIs could systematically overestimate the problems of their child. However, this potential overestimation is not in line with the lack of association with affective problems. And, when we used the ratings of the father only, we also observed that children exposed to SSRIs were more likely to have pervasive developmental problems. Second, it was not feasible to obtain clinical diagnoses in such a large number of children in a population-based setting. These children were too young to be assessed by teachers or other informants, thus we had to rely on parental ratings. We did not use clinical assessments, but validated instruments for the general population; these have been shown to be reliable in such young children.[28,47] Third, we did not have any information about the autistic traits of the parents. Fourth, we did not assess clinical diagnoses of depression in pregnancy with a diagnostic instrument. Rather, pregnant mothers reported psychological symptoms by questionnaire. However, it has been shown that the BSI is reliable and valid.[21] In a subgroup of the Generation R cohort, we demonstrated that the depression subscale of the BSI was a moderate indicator of a depression diagnosis. Fifth, the number of SSRI-exposed children was small, and therefore we could not study dose-dependent effects of SSRI use in pregnancy. Finally, no observational study can rule out residual confounding, i.e. unmeasured factors associated with both SSRI use and autism.

Interpretation of the findings

Little evidence of the possible consequences of prenatal SSRI use on child development beyond the neonatal or early postnatal period is available. The current study demonstrates an association between prenatal SSRI exposure and childhood autistic symptoms, independent of the level of depressive symptoms during or after pregnancy, and showed that this association was specific; no association was found between prenatal SSRI exposure and affective problems, in line with a previous study of 4-year-olds.[9] These findings extend the previously published case–control studies, demonstrating that prenatal SSRI exposure was associated with an increased risk for autism spectrum disorder.[6,7] The effect estimates are strikingly similar – the investigators also reported a twofold higher risk of autism spectrum disorder associated with SSRI treatment.[6,7]

Several explanations are plausible. First, serotonin is known to play an important role in prenatal brain development[48] and manipulation of serotonin levels with SSRIs *in utero* may cause long-term consequences. In animal models, prenatal treatment with fluoxetine during early brain development produced abnormal behaviours in offspring.[49,50] Furthermore, it has been suggested that abnormalities in serotonin levels and serotonergic pathways may play a role in autism.[51] Indeed, perinatal SSRI exposure in rats affect myelination in the corpus callosum, which also corresponds to the pathophysiology of autism.[52] Recently, a study demonstrated that prenatal exposure to SSRIs affected fetal neurobehavioral functioning.[53]

Second, we previously showed that prenatal SSRI exposure was associated with decreased fetal head growth,[12] and we investigated whether this reduced head growth mediated the association between prenatal SSRI exposure and pervasive developmental problems. We demonstrated that a larger head size at birth was related to pervasive developmental problems. When we stratified the analyses, it became clear that the association of a larger head size at birth and childhood pervasive developmental problems was similar and consistent among the groups. This is in agreement with studies demonstrating overgrowth of the brain in children with autism in the first 3 years of life.[54] It has been proposed that this early brain overgrowth might be as a result of an excess of neurons resulting from cell-cycle dysregulation and/or failure of naturally occurring apoptosis.[55] This also implies that the observed effect of SSRIs, which are most likely mediated by the fetal serotonergic system, could not be explained by head growth and probably is an independent mechanism increasing the risk of autistic symptoms.

Finally, SSRIs are mainly prescribed to treat depression, thus the association between prenatal SSRI exposure and pervasive developmental problems could be explained by these residual depressive symptoms. We accounted for confounding by indication (i.e. those who take a drug may differ from those who do not according to the medical indication for which the drug was prescribed) with a contrast group of women not pharmacologically treated for their depressive symptoms. Some confounding by severity might still be present, because pregnant women treated with antidepressants might have experienced more severe depression in the past, although this cannot easily affect child development during pregnancy. Moreover, pregnant women taking SSRIs had lower depression scores compared with women not treated pharmacologically and correcting for prenatal depressive symptoms did not change the association of maternal SSRI use in pregnancy with pervasive developmental problems.

Implications

Prescribing antidepressant medication to pregnant women is a matter of debate in current psychiatry. Although the use of SSRIs among pregnant women has increased from 1.5% in 1996 to 6.2% in 2005,[56] studies with detailed measures of child developmental outcomes are sparse and conflicting. We demonstrated an effect of SSRIs on autistic symptoms in young children, which was not mediated by impaired fetal head growth. These findings suggest that very different mechanisms may be involved in developing autistic symptoms; increased brain growth and imbalanced serotonin levels in prenatal life are most likely independent risk factors. Nevertheless, we must be careful when interpreting these results, as this prospective study was not a randomised controlled trial. Further long-term drug safety studies are needed before evidence-based recommendations can be developed.

Funding

The Sophia Children's Hospital Fund (SSWO-616) supported this work financially. The first phase of the Generation R Study was made possible by financial support from the Erasmus Medical Centre and The Netherlands Organization for Health Research and Development (Zon MW Geestkracht Program 10.000.1003 & ZonMw TOP 40-00812-98-11021, NWO Brain & Cognition Program Grant 433-09-311 and VIDI Grant 017.106.370).

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press

Acknowledgements

The Generation R Study is conducted by the Erasmus Medical Centre in close collaboration with the Municipal Health Service Rotterdam area, the Rotterdam Homecare Foundation and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR), Rotterdam. We gratefully acknowledge the contribution of general practitioners, hospitals, midwives and pharmacies in Rotterdam.

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First received 14 Feb 2013, final revision 1 Aug 2013, accepted 5 Sep 2013

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EXTRA CONTENT ONLINE

reflection

Man's Search for Meaning by Victor Frankl

Jeremy Holmes

Contra Brecht, happy the age that has its heroes. Your author's psychiatric pantheon includes Pinel, Tuke, Freud, Meyer, Schneider, Jaspers, Menninger, Lewis, Bowlby, Laing, Lambo; the living await the verdict of history. But alongside intellectual and organisational greatness, a species of fame comes from adversity overcome, a life lived well, from unimpeachable integrity and moral courage. Gandhi, Mandela, Ahkmatova – and the psychiatrist Victor Frankl – come immediately to mind.

Frankl survived 3 years in Auschwitz and Dachau, entering the camps clutching a half-completed manuscript which contained the seeds of his famous 'third Viennese school of psychology'. Logotherapy's Schopenhauerian guiding philosophy is the 'will to meaning', in contrast to Freud's pleasure, and Adler's power principles. Logotherapy can be reframed relationally as connectedness and communication, verbal and non-verbal.

In the camps Frankl found practical confirmation of his precepts. Man can live, even without bread alone, if he has a framework of meaning to sustain him and give him hope, whether this be religious or political. Suffering is inescapable; to the extent one can accept suffering as 'an ineradicable part of life, even as fate or death', one is buttressed against adversity. Even in the worst of situations, man is always free to choose his perspective. There is no overall 'meaning of life', only specific meanings in particular situations. Our choices represent 'footprints in the sands of time' – so choose wisely, as though living life for the second time, and 'had acted as wrongly the first time as you about to act now'. Clarity is all: 'emotion, which is suffering, ceases to be suffering as soon as we form a clear and precise picture of it'.

For all its best-seller status, *Man's Search for Meaning* is something of a hodge-podge, consisting of three unrelated essays, the first the compelling story of Frankl's incarceration, the second a brief account of logotherapy, the third a statement of his guiding philosophy, 'the search for ''tragic optimism'' '. Re-reading it 40 years on was not easy – its upbeat message notwithstanding, man's inhumanity to man feels even more unbearable now than in mortality-denying youth. An interesting aspect is that here psychotherapy saved not the patient's life, but the therapist's; for a while Frankl was befriended by a troubled 'Capo', patiently listening to this brutal man's domestic troubles, so was protected from the worst jobs which would have meant almost certain death. Another ironic survival factor was Frankl's determination to accept whatever fate dealt him, and to stick by those who depended on him – his parents during the Anschluss, and his cholera patients in the camps – rather than pursue illusory dreams and escape plans. Thus, this founder of 'existential therapy' found a way to trust life, and accept the reality of death, even in extreme circumstances. His survival story is one which every psychiatrist should read, not just as a vivid window into the supreme horror of the 20th century, but as a parable for the transcendence of, and recovery from, the worst of human cruelty and destructiveness.

The British Journal of Psychiatry (2014) 205, 102. doi: 10.1192/bjp.bp.113.133520

https://doi.org/10.1192/bjp.bp.113.127746 Published online by Cambridge University Press