Should Antidepressants be Avoided in Pregnancy?

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Abstract

Many (> 40%) women discontinue antidepressants during pregnancy because of concerns about effects on the foetus, based on information from inadequately-controlled studies. The sibling-control study design provides the best control for confounding factors, notably maternal depression. The purpose of this review was to investigate the evidence from sibling-control analyses for adverse outcomes in offspring associated with antidepressant exposure during pregnancy. Fourteen sibling-control studies were identified through searches of PubMed and Embase. Outcomes included preterm birth, small for gestational age, neonatal size, birth defects, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), behavioural problems, neurodevelopmental deficits, and scholastic attainment. For the majority of these outcomes, no statistically significant associations were found when comparing exposed and unexposed siblings. Single studies reported associations with preterm birth, reduced gestational age, ADHD, anxiety at 36 months, and lower mathematics test scores, which persisted in the sibling-control analyses. However, differences were small and possibly not clinically significant. Moreover, effects of residual confounding could not be excluded. These findings provide evidence that many of the previously reported associations between prenatal antidepressant exposure and adverse outcomes in offspring are no longer statistically significant when exposed offspring are compared with unexposed siblings. The few statistically significant differences in sibling-control analyses were generally small with doubtful clinical significance. Decisions on antidepressant treatment during pregnancy should be made individually, based on evidence from properly controlled studies, not on misleading information based on studies that have not controlled adequately for confounding factors.

Key Points

A sibling-control analysis provides more reliable information on the effects on offspring of antidepressant exposure during pregnancy than comparisons with the general population.

In most cases, associations between antidepressant exposure during pregnancy and adverse outcomes in offspring are weakened or disappear when comparing siblings born to the same mother where one sibling was prenatally exposed to antidepressants and the other was not.

Relatively few studies of adverse outcomes in offspring with prenatal exposure to antidepressants have included comparisons between exposed and unexposed siblings.

More information is needed on the possible effects of dose, timing of exposure and antidepressant type, to assist clinicians and women with depression to make informed decisions on the best treatment during pregnancy.

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1 Introduction

The risk of depression in women is greatest during their childbearing years, with a peak prevalence between the ages of 25 and 34 years [1]. Pregnancy can be a period of particularly increased risk for new-onset depression or depressive relapse [2–4]. Recent estimates suggest that worldwide, 11.9% of women will be affected by depression during the perinatal period [5]. However, perinatal depression is likely both to be underdiagnosed and to be undertreated [6, 7], in particular in low-income and middle-income countries [5]. Untreated or inadequately treated prenatal or postnatal depression is associated with adverse outcomes for the mother, foetus and child, including an increased risk of maternal suicide [8], subsequent depressive relapse [9], substance abuse [10, 11], preeclampsia [12], spontaneous abortion [13], preterm birth [14, 15], low birth weight [14, 16], admission to neonatal intensive care [17], poorer child emotional, behavioural and cognitive development [11, 18, 19] and impaired mother-child interactions [11, 18, 20]. Untreated prenatal depression is associated with depression in the postnatal period [21, 22]. Despite these risks, uncertainty regarding the potential adverse effects of antidepressant medication on their offspring has led to a reluctance among many women to commence or adhere to treatment while pregnant, with more than 40% discontinuing medication [23], with an increasingly lower adherence as pregnancy progresses. While depression rates during the first, second and third trimesters have been estimated as 7.4%, 12.8% and 12.0%, respectively [24], antidepressant use falls, for example, in an analysis by Zoega et al., from 2.1% in the first trimester, to 1.7% in the second trimester and 1.3% in the third trimester [25]. Prescribing medication to any patient, especially a pregnant woman, should only be undertaken if necessary. Before prescribing an antidepressant, non-medication interventions such as cognitive behavioural therapy should be implemented, if feasible. Further guidance is available from national organisations, for example, in the UK, the National Institute for Health and Care Excellence [26].

The decision as to whether to maintain or initiate antidepressant treatment during pregnancy is frequently influenced strongly by clinician guidance [27]. In many countries, however, there are no national clinical practice guidelines for the management of perinatal depression [28]. Among the guidelines that do exist, recommendations are inconsistent. A 2018 systematic review found that among 16 clinical guidelines from 12 countries, four advised continuation of antidepressant treatment during the perinatal period, while five neither specifically advised nor discouraged continuation. Recommendations for the treatment of new episodes of depression were in agreement with psychotherapy as the preferred option for mild-to-moderate depression and

antidepressants reserved for severe episodes [29]. More recently, a review of European clinical practice guidelines reported a consensus with regard to recommending or "mentioning the possibility" of continuing antidepressant treatment for pre-existing moderate-to-severe depression. Most of the guidelines advised initiating antidepressants for new episodes of moderate-to-severe depression [28]. Consideration of the individual risk-benefit ratio in each case is also widely emphasised [28]. Concern about the supposed potential risks to the foetus appears to be the most common reason for discontinuation [30].

Antidepressants transfer to the foetus across the placenta [31, 32] and are found in both amniotic fluid [33–35] and cord blood [35, 36]. Foetal exposure may be as high as 80% of maternal serum levels [37]. Antidepressants can also cross the foetal blood–brain barrier [38]. Animal models have reported altered brain development and abnormal behaviour in offspring [39–42] (see Creeley and Denton [43], for a review). Although not necessarily indicating a similar risk in humans, such studies raise the possibility of an effect of in utero antidepressant exposure on foetal development, possibly as a result of disrupted serotonergic signalling during early gestation [44]. Serotonin acts as a neural growth factor at a critical period for foetal brain development and mediates processes involved in neuronal maturation, migration, synaptogenesis and differentiation of neural crest cells [38, 45, 46].

While the relevance of animal studies to human perinatal outcomes remains questionable, widely cited studies have suggested associations between foetal antidepressant exposure and a spectrum of physical and neurodevelopmental conditions in humans, notably congenital malformations [47–51], autism [52–55] and ADHD [56–59]. Frequently, however, such associations are attenuated or disappear when adjusting for potential confounding factors such as maternal depression and genetic propensity.

A 2014 report by the US Agency for Healthcare Research and Quality [60, 61], which evaluated pregnancy and postnatal outcomes in women receiving antidepressants, concluded that the available evidence was "largely inadequate to allow well-informed decisions about treatment", partly owing to the failure to control for potential confounding. This led to the recommendation that future studies should control for possible confounding factors, including maternal depression and severity of depression.

The aim of this review is to summarise the evidence for adverse outcomes in offspring from studies in which the analysis attempted to control for confounding, specifically by means of comparisons between siblings born to the same mother where one sibling was prenatally exposed to antidepressants, and the other was not (see below). Antidepressant medication is also commonly prescribed for indications other than depression, such as anxiety and

obsessive-compulsive disorder; discussion of these data, while important, is beyond the scope of this review.

2 What Types of Study Are to Be Preferred?

Major ethical issues effectively preclude using standard randomised controlled studies for investigating the effect of antidepressant treatment on perinatal outcomes. Instead, observational studies have been conducted, in the form of either cohort or case-control studies. These studies provide a lower level of evidence than randomised controlled trials and are subject to multiple potential sources of bias and confounding. In addition to known potential risk factors for adverse outcomes, such as maternal age, smoking, alcohol use, obesity and diabetes mellitus, which are often, but not always or consistently, adjusted for, findings may be influenced by unknown, unmeasured, or inadequately measured factors [62, 63]. As recent reviews and commentaries have highlighted, there is an important effect of a comparator group on estimates of the relative risk of adverse outcomes between antidepressant-exposed and unexposed pregnancies that should be considered when interpreting the findings of observational studies [62, 64–68]. In particular, comparisons with outcomes in the general population are unlikely to be valid owing to the potential for confounding by indication because the indication for treatment, namely maternal depression, is independently associated with the outcome of interest.

In a 2019 review, Sujan et al. [62] described methods for controlling for known and unknown confounders. Table 1 summarises the strengths and limitations of these approaches. Of these, the "discordant sibling" design probably provides the best, although not perfect, control for confounding factors. Discordant sibling analyses have been used to investigate the effects on offspring of prenatal exposure to various drugs used by the mother during pregnancy including medication for ADHD [69], benzodiazepines [70] and acetaminophen [71, 72], as well as the effects of maternal smoking [73, 74] and alcohol use [75].

In discordant sibling studies, the outcomes of different pregnancies in the same mother, with and without the exposure of interest , are compared. This still does not control for all potential confounders, for example, in the case of antidepressant exposure, it might not control for differences in the severity of depression between different pregnancies. Furthermore, although the siblings in these studies have the same mother, they do not always have the same father, implying inadequate control for genetic factors (see later). However, because the "discordant sibling" design appears to offer the best control for important confounding factors, the remainder of the current review will concentrate on these studies.

To highlight the influence of a comparator group on risk estimates, we have also considered the findings of a number of recent meta-analyses that do not solely use the sibling-control design. These are summarised in Table 2.

3 Methods

We searched PubMed and Embase for studies investigating adverse outcomes for the foetus or child following prenatal antidepressant exposure, using the search terms listed in Fig. 1. The results were screened to identify studies that included a sibling-control analysis. We also reviewed the texts of recent systematic reviews and meta-analyses.

4 Results

Fourteen sibling-control studies were identified. As the findings from many of these studies have been summarised in previously published systematic reviews and meta-analyses [62, 76–80], they are only discussed briefly in the current review (see Sect. 4.2 and Table 3). Instead, the following section focuses in detail on the findings from the sibling-control analyses in the four most recent studies that investigated the effects of antidepressant exposure on the risk of ADHD, seizures, cognitive ability and ASD, respectively.

4.1 Recent Studies

Esen et al. [81] used data on children born between 1997 and 2017 from the Danish Medical Birth Registry to investigate the association between the use of any antidepressant during pregnancy and ADHD in offspring. Data for children born during this period were screened for ADHD diagnoses to the end of 2018. Antidepressant exposure was defined as the redemption of one or more antidepressant prescription for maternal depression from 30 days before the date of conception to the date of childbirth. Analysis of relative risk between exposed and non-exposed children was based on a "triangulation" approach, which compared results from an overall analysis, a negative control analysis (paternal antidepressant use), a discordant sibling analysis and a former-user analysis, in order to investigate potential sources of bias. For each approach, incidence rate ratios (IRRs), incidence rate differences and risk differences and their 95% confidence intervals (CIs) were calculated. Sensitivity analyses were designed to control for confounding by indication and possible exposure misclassification, and to evaluate the effects of antidepressant class and trimester of exposure.

Data for 1,253,362 children were analysed, 28,910 of whom had in utero exposure to antidepressants. Of these, 1411 (4.9%) had a diagnosis of ADHD, compared with

Table 1 Study designs for controlling for confounding factors (adapted from Sujan et al. [62])

Comparator	Confounders	Interpretation	Limitations
Untreated maternal depression	Confounding by indication	Controls for the effect of maternal depression on the outcome of interest No difference between groups suggests the observed effect might be accounted for by factors associated with maternal depression, or maternal depression itself	Does not control for severity of depression
Maternal past antidepressant use	Confounding by indication Confounding by other shared perinatal factors	Controls for the effect of maternal depression on the outcome of interest No difference between groups suggests the observed effect might be accounted for by factors associated with maternal depression, or maternal depression itself	Assumes past antidepressant use is not associated with outcome of interest Does not control for severity of depression or other factors that might differ between women who discontinue antidepressant treatment during pregnancy and those who maintain treatment Past antidepressant use may be indicative of remission from depression
Paternal antidepressant use	Genetic risk Shared familial environmental factors	Paternal antidepressant use acts as a "negative control" as it is unlikely directly to expose the foetus to medication but is subject to the same genetic and familial confounders as the exposure group (maternal antidepressant use) Evidence of an effect in the paternal antidepressant group suggests residual confounding in the exposure group	Assumes the same confounding factors are associated with both maternal and paternal antidepressant use
Maternal use of alt. psychotropic medication	Unmeasured confounders associated with use of either medication (e.g. common indication)	No difference between groups suggests that prenatal exposure to antidepressant treatment is not associated with the outcome of interest	Assumes comparator medication is not associated with the outcome of interest In practice, identifying patients with depression who are treated with medication other than antidepressants may not be possible, with the exception of comparisons between antidepressant classes
Discordant sibling	Genetic risk Shared familial environmental factors	No difference between siblings with and without prenatal antidepressant exposure suggests treatment is not associated with the outcome of interest	Does not control for factors that vary between pregnancies Assumes no "carry-over" effects between exposed and unexposed siblings Possible increased risk of bias due to exposure misclassification Large patient samples required

Table 2 Summary of findings from recent meta-analyses (N.B. These findings are included for comparison only. Because general population comparisons do not adjust adequately for confounding, they should not be used as a sole basis for making clinical decisions, see discussion)

Study (year)	Outcomes	N	AD type	Psychiatric control	Sibling control	Main findings
Kautzky (2022) [106]	PNAS	17	SSRI, SNRI	Y	N	Statistically significant associations with preterm birth (OR = 2.36, 95% CI 1.35–4.15), admission to neonatal intensive care (OR = 2.64, 95% CI 1.58–4.40), respiratory problems (OR = 2.85, 95% CI 1.26–6.43), lower gestational age (MD = −0.36, 95% CI −0.81 to 0.08), and lower 5-minute Apgar score (MD = −0.32, 95% CI −0.54 to −0.11) in untreated maternal depression comparisons
Vlenterie (2022) [107]	GA, BW, SGA, Apgar score	215	Any	N	N	In general population comparisons, preterm birth associated with prenatal depression (OR = 1.6, 95% CI 1.2–2.1), untreated prenatal depression (OR = 2.2, 95% CI 1.7–3.0), and prenatal antidepressant use for any indication (OR = 1.4, 95% CI 1.1–1.8) Low (<5) 5-minute Apgar score associated with prenatal depression (OR = 1.5, 95% CI 1.3–1.7), and prenatal antidepressant use for any indication (OR = 1.6, 95% CI 1.1–2.5) but not untreated prenatal depression Preterm birth associated with prenatal SSRI use for depression (OR = 1.6, 95% CI 1.0–2.5) and prenatal SSRI use for any indication (OR = 1.9, 95% CI 1.2–2.8) Low 5-minute Apgar score associated with prenatal SSRI use for any indication (OR = 1.7, 95% CI 1.1–2.8) AD use during pregnancy not associated with low BW or SGA
De Vries (2021) [108]	Congenital heart defects[a]	20	Any	N	N	In general population comparisons, statistically significant association between prenatal AD exposure and congenital heart defects (OR = 1.28, 95% CI 1.17–1.41) Statistically significant associations for SSRIs (OR = 1.25, 95% CI 1.15–1.37), SNRIs (OR = 1.69, 95% CI 1.37–2.10), paroxetine (OR = 1.57, 95% CI 1.20–1.97), fluoxetine (OR = 1.36, 95% CI 1.08–1.72), sertraline (OR = 1.29, 95% CI 1.14–1.45), and bupropion (OR = 1.23, 95% CI 1.01–1.49). TCAs, citalopram, escitalopram, and venlafaxine not associated with an increased risk
Leung (2021) [109]	Seizures	13	Any	N	N	In general population comparisons, overall analysis found statistically significant association between prenatal AD use and seizures in offspring (RR = 2.30, 95% CI 1.63–3.24). Adjusted analysis limited to 6 studies also statistically significant (RR = 2.42, 95% CI 1.30–4.49). Similar risk estimates for SSRIs (RR = 1.63, 95% CI 1.42–1.87) and TCAs (RR = 1.61, 95% CI 1.40–1.84) Statistically significant associations with first trimester exposure (RR = 1.43, 95% CI 1.08–1.88) and exposure later in pregnancy (RR = 2.40, 95% CI 1.45–3.97) No adjustment for maternal epilepsy in most studies

Table 2 (continued)

Study (year)	Outcomes	N	AD type	Psychiatric control	Sibling control	Main findings
Vega (2020) [78]	ASD	14	Any	Y	Y	In general population comparisons, prenatal AD exposure statistically significantly associated with ASD (HR = 1.42, 95% CI 1.18–1.70; OR = 1.58, 95% CI 1.25–1.99) No statistically significant association in psychiatric control comparison (HR = 1.14, 95% CI 0.84–1.53; OR = 1.24, 95% CI 0.93–1.66) or discordant sibling comparison (HR = 0.97, 95% CI 0.68–1.37; OR = 0.85, 95% CI 0.54–1.35) Summary effect estimates for each sibling-control study were <1
Halvorsen (2019) [79]	Psychiatric and behavioural	18	SSRI	N	N	In general population comparisons, prenatal SSRI exposure was associated with ASD (HR = 1.27, 95% CI 1.10–1.47), ADHD (HR = 1.33, 95% CI 1.06–1.66), and ID (HR = 1.41, 95% CI 1.03–1.91) Risk estimates reported in 5/7 studies that controlled for untreated maternal depression and/or genetic and familial factors were not individually statistically significant. No meta-analysis was possible on these results
Masarwa (2019) [110]	PPHN	11	SSRI, SNRI	N	N	In general population comparisons, the risk of PPHN was associated with SRI use in any trimester (OR = 1.82, 95% CI 1.31–2.54) and SRI use from 20 weeks gestation only (OR = 2.08, 95% CI 1.44–3.01)
Gao (2018) [111]	Congenital malformations[a]	18	SSRI	Y	N	In general population comparisons, first trimester SSRI exposure was associated with increased risk of major congenital malformations (RR = 1.11, 95% CI 1.03–1.19) and congenital heart defects (RR = 1.24, 95% CI 1.11–1.37) No statistically significant association for either outcome in psychiatric control comparisons
Man (2018) [80]	ADHD	7	Any	Y	Y	Statistically significant association between prenatal AD use and ADHD compared to AD non-use (general population) for AD use any time during pregnancy (RR = 1.39, 95% CI 1.21–1.61), and for AD use during the first and second trimester (RR = 1.42, 95% CI 1.18–1.73), but not for AD use during the third trimester (RR = 1.05, 95% CI 0.74–1.48) AD use before pregnancy only was also associated with ADHD compared with AD non-use (RR = 1.56, 95% CI 1.25–1.95) AD use during pregnancy was not associated with increased risk of ADHD in sibling-control analysis comparing siblings with and without prenatal AD exposure (RR = 0.94, 95% CI 0.75–1.16)

AD antidepressant, *ADHD* attention-deficit hyperactivity disorder, *ASD* autism spectrum disorder, *BW* birth weight, *GA* gestational age, *HR* hazard ratio, *N* no, *OR* odds ratio, *PNAS*= poor neonatal adaptation syndrome, *PPHN* persistent pulmonary hypertension of the newborn, *RR* rate ratio, *SGA* small for gestational age, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SRI* serotonin reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant, *Y* yes
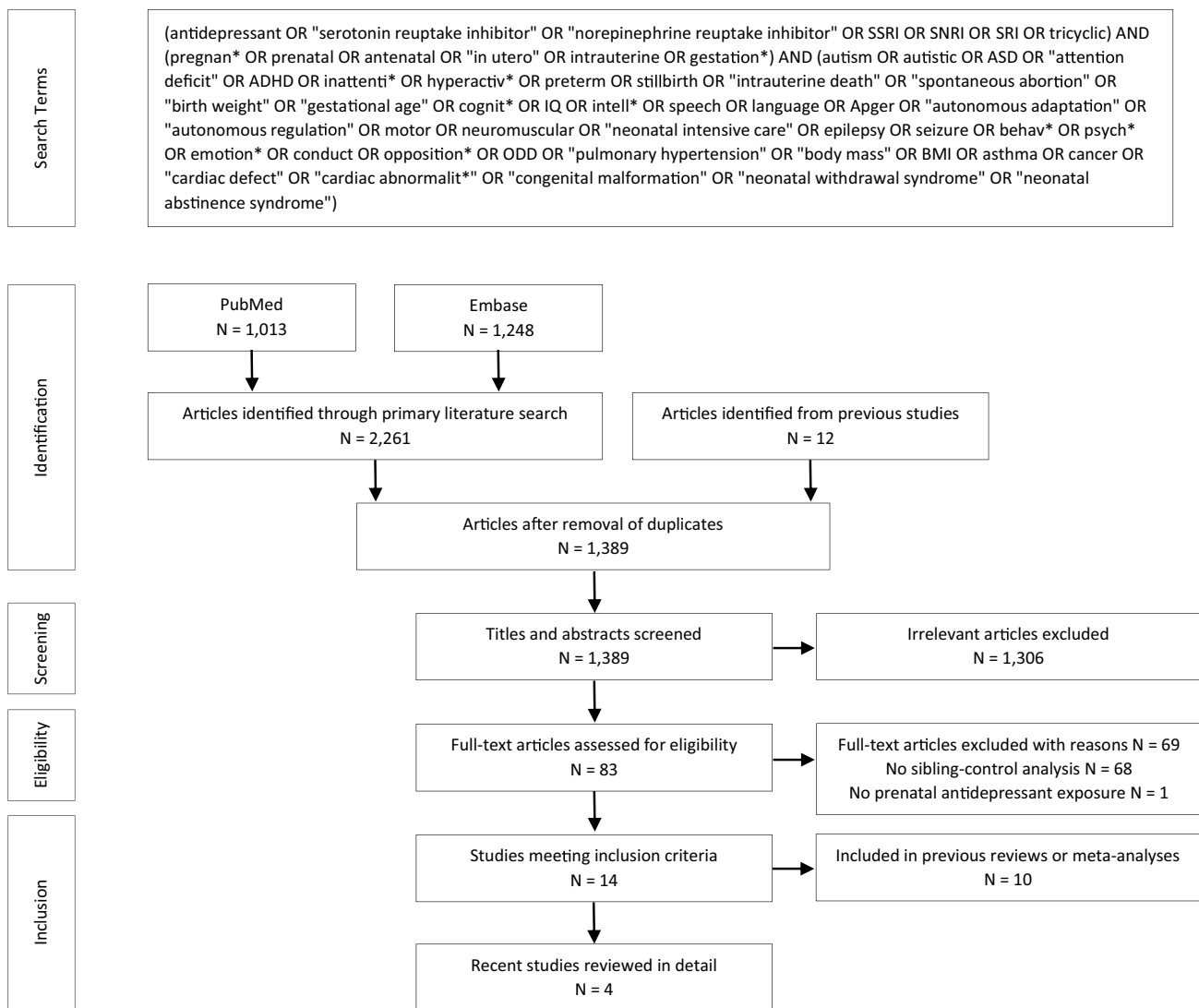
[a]First-trimester exposure

Fig. 1 Search flow diagram

37,196 (3.0%) in the unexposed group. The sibling-control analysis included data for 31,624 children.

In the overall analysis that adjusted only for measured confounders, the adjusted IRR for ADHD was 1.36 (95% CI 1.25–1.49). However, the result of the negative control analysis, which investigated the effect of paternal antidepressant prescription, indicated residual confounding in the main analysis (adjusted IRR = 1.24, 95% CI 1.14–1.36). In the discordant sibling analysis, the adjusted IRR was 1.15 (95% CI 1.02–1.29) and in the former-user analysis was 1.09 (95% CI 0.99–1.20). Adjusted incidence rate differences (cases/1000 years) were 1.50 (95% CI 1.15–1.87) for the overall analysis, 0.86 (95% CI 0.57–1.16) for the negative control analysis, 0.73 (95% CI 0.09–1.38) for the discordant sibling analysis and 0.47 (95% CI −0.13 to 1.07) for the former-user analysis. Adjusted risk differences were

3.4% (95% CI 2.3–4.4) for the overall analysis, and 2.0% (95% CI 1.2–2.8), 0.9% (95% CI −0.8 to 2.6) and 2.2% (95% CI 0.5–4.0) for the negative control, discordant sibling and former-user analyses, respectively. The IRR for the active comparator analysis, designed to address confounding by indication, was 1.19 (95% CI 1.09–1.29).

Triangulating the results from the four separate analyses resulted in an estimated IRR for ADHD of 1.09 (95% CI 0.99–1.20) to 1.15 (95% CI 1.02–1.29), a small incidence rate difference of less than 1 case/1000 person-years, and a risk difference over a period of up to 18 years of 0.9–2.2%. In the opinion of the current authors, the slightly increased risk represented by these estimates might not be considered to be clinically relevant. Esen et al. noted that the possible influence of residual biases could not be discounted.

Table 3 Summary of results from sibling-control analyses

ADHD

Study (year)	Study design	AD indication[a]	AD type	Data source	Sibling definition	N[b]	Risk estimates for AD exposed vs unexposed siblings[c]	P-value[d]
Esen (2022) [81]	Cohort (prospectively collected data)	Not clearly stated	Any	Danish Medical Registries	Not clearly defined	13,628/17,996	**IRR = 1.15 (95% CI 1.02–1.29)**	
							IRD = 0.73/1000 person-years	
Man (2017) [56]	Population-based cohort	Any psychiatric	Any	Hong Kong CDARS	Not clearly defined	53,616[e]	HR = 0.54 (95% CI 0.17–1.74)	0.30
Sujan (2017) [57]	Retrospective cohort	Not clearly stated	Any	Swedish Medical Registries	Not clearly defined	10,975/13,994	OR = 0.99 (95% CI 0.79–1.25)	
Laugesen (2013) [90]	Cohort	Any	Any	Danish Medical Birth Registry	Same mother	348/519	OR = 0.7 (95% CI 0.4–1.4)	
ASD								
W-Hagberg (2018) [84]	Cohort (nested sibling case-control)	Any	Any	UK CPRD	Same mother	531/601[f]	RR = 1.53 (95% CI 0.89–2.62)	
Brown (2017) [87]	Retrospective cohort	Any	SSRI, SNRI	Ontario Medical Databases	Not clearly defined	620/620	HR = 1.60 (95% CI 0.69–3.74)	
							IRD = 1.35/1000 person-years (95% CI 0.63–3.60)	
Rai (2017) [88]	Population-based cohort	Any psychiatric	Any	Stockholm Youth Cohort	Not clearly defined	3038[g]	OR_{ASD} = 1.36 (95% CI 0.84–2.20)	
						2408[g]	$OR_{ASD\ Without\ ID}$ = 1.57 (95% CI 0.92–2.66)	
						630[g]	$OR_{ASD\ With\ ID}$ = 0.78 (95% CI 0.24–2.54)	
Sujan (2017) [57]	Retrospective cohort	Not clearly stated	Any	Swedish Medical Registries	Not clearly defined	10,975/13,994	OR = 0.83 (95% CI 0.62–1.13)	
Sørensen (2013) [89]	Population-based cohort	Any	Any	Danish Medical Registries	Full siblings	96/6046	HR_{Any} = 1.1 (95% CI 0.5–2.3)	
						81/6036	HR_{SSRI} = 0.9 (95% CI 0.4–2.0)	
Behavioural problems								
Brandlistuen (2015) [92]	Prospective cohort	Depression/anxiety	Any	Norwegian Mother Child Cohort	Not clearly defined	20,180[e, h]	$\beta_{Internalising}$ = 0.16 (95% CI −0.14 to 0.46)[j]	
							$\beta_{Anxiety}$ = 0.14 (95% CI −0.19 to 0.47)[j]	
							$\beta_{Emotional\ Reactivity}$ = 0.05 (95% CI −0.28 to 0.38)[j]	
							$\beta_{Somatic}$ = −0.05 (95% CI −0.41 to 0.30)[j]	

Table 3 (continued)

ADHD

Study (year)	Study design	AD indication[a]	AD type	Data source	Sibling definition	N[b]	Risk estimates for AD exposed vs unexposed siblings[c]	P-value[d]
							$\beta_{Sleep} = 0.20$ (95% CI -0.11 to 0.51)[j]	
							$\beta_{Externalising} = 0.26$ (95% CI -0.05 to 0.56)[j]	
							$\beta_{Attention} = 0.15$ (95% CI -0.16 to 0.47)[j]	
							$\beta_{Aggression} = 0.30$ (95% CI -0.03 to 0.64)[j]	
						14,352[e, i]	$\beta_{Internalising} = 0.34$ (95% CI -0.01 to 0.68)[j]	
							$\boldsymbol{\beta_{Anxiety} = 0.64}$ **(95% CI 0.26–1.02)[j]**	**<0.05**
							$\beta_{Emotional\ Reactivity} = -0.06$ (95% CI -0.42 to 0.30)[j]	
							$\beta_{Somatic} = 0.04$ (95% CI -0.36 to 0.43)[j]	
							$\beta_{Sleep} = 0.25$ (95% CI -0.11 to 0.60)[j]	
							$\beta_{Externalising} = -0.08$ (95% CI -0.44 to 0.27)[j]	
							$\beta_{Attention} = -0.01$ (95% CI -0.38 to 0.36)[j]	
							$\beta_{Aggression} = -0.11$ (95% CI -0.49 to 0.27)[j]	
Nulman (2015) [91]	Prospective cohort	Depression	SSRI, SNRI	Toronto Motherisk Database		45/90	$\%_{CBCL-IP}$ Exp. = 11.1%, Non-Exp. = 6.7%, $p = 0.46$[k]	0.46
							$\%_{CBCL-EP}$ Exp. = 11.1%, Non-Exp. = 11.1%, $p = 1.00$[k]	1.00
							$\%_{CBCL-TP}$ Exp. = 13.3%, Non-Exp. = 8.9%, $p = 0.48$[k]	0.48
Birth defects								
Furu (2015) [86]	Population-based cohort	Not clearly stated	SSRI, VEN	Multinational Health Registers	Same mother	980/1,308	$OR_{Birth\ Defect} = 1.13$ (95% CI 0.91–1.24)	
						422/569	$OR_{Cardiac\ Defect} = 0.92$ (95% CI 0.72–1.17)	
						48/67	$OR_{Right\ Ventricular\ Outflow\ Tract\ Obs.} = 0.56$ (95% CI 0.21–1.49)	
IQ								
Nulman (2015) [91]	Prospective cohort	Depression	SSRI, SNRI	Toronto Motherisk Database	Not clearly defined	45/90	$MD_{Full\ Scale\ IQ} = -3.0$ (95% CI -7.06 to 2.21)	0.30
							$MD_{Visual\ IQ} = -3.0$ (95% CI -7.48 to 1.97)	0.25
							$MD_{Performance\ IQ} = -2.0$ (95 CI -5.84 to 1.71)	0.28
Preterm birth								
Sujan (2017) [57]	Retrospective cohort	Not clearly stated	Any	Swedish Medical Registries	Not clearly defined	-	**OR = 1.34 (95% CI 1.18–1.52)**	**<0.001**

Table 3 (continued)

ADHD

Study (year)	Study design	AD indication[a]	AD type	Data source	Sibling definition	N[b]	Risk estimates for AD exposed vs unexposed siblings[c]	P-value[d]
Viktorin (2016) [85]	Population-based cohort	Depression	SSRI	Swedish Medical Registries	Full siblings	501/506	OR = 1.36 (95% CI 0.77–2.42)	
							MD_{GAB} = −2.27 days (95% CI −3.79 to −0.75)	**0.004**
Seizures								
Wang (2022) [82]	Cohort	Not clearly stated	Any	Hong Kong CDARS	Not clearly defined	Not stated	wHR = 1.16 (95% CI 0.75–1.77)	
Size at birth								
Sujan (2017) [57]	Retrospective cohort	Not clearly stated	Any	Swedish Medical Registries	Not clearly defined	-	OR_{SGA} = 1.01 (95% CI 0.81–1.25)	
Viktorin (2016) [85]	Population-based cohort	Depression	SSRI	Swedish Medical Registries	Full siblings	501/506	Δ_{BW} = 0.05 (95% CI −0.05 to 0.14)[l]	
							Δ_{BL} = 0.01 (95% CI −0.1 to 0.11)[l]	
							Δ_{BHC} = −0.03 (95% CI −0.14 to 0.08)[l]	
Standardised test scores								
Christensen (2021) [83]	Retrospective cohort	Not clearly stated	Any	Danish Medical Birth Register	Not clearly defined	4235/357,833	**MD_{Maths} = −2.8 (95% CI −4.5 to −1.2)**	
							MD_{Lang} = −0.3 (95% CI −1.9 to 1.2)	

ADHD attention-deficit hyperactivity disorder, *ASD* autism spectrum disorder, *BHC* birth head circumference, *BL* birth length, *BW* birth weight, *CBCL* Child Behaviour Checklist, *CDARS* Clinical Data Analysis and Reporting System, *CI* confidence interval, *CPRD* Clinical Practice Research Datalink, *EP* externalising problems, *GAB* gestational age at birth, *HR* hazard ratio, *ID* intellectual disability, *IP* internalising problems, *IRD* incidence rate difference, *IRR* incidence rate ratio, *MD* mean difference, *OR* odds ratio, *RR* relative risk, *SGA* small for gestational age, *SNRI* serotonin-norepinephrine reuptake inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TP* total problems, *VEN* venlafaxine, *wHR* weighted hazard ratio

[a]Individuals included in overall analyses

[b]Number of exposed siblings/number of unexposed siblings (unless otherwise indicated)

[c]Fully adjusted analysis (statistically significant results in **bold**)

[d]P-values where stated in original studies

[e]Total number of siblings analysed

[f]Siblings with ASD (cases)/same-sex siblings without ASD (controls)

[g]Affected sibling sets

[h]Outcomes at 18 months

[i]Outcomes at 36 months

[j]β coefficient represents standardised mean difference adjusting for familial factors and observed confounders. Interpreted as for Cohen's d

[k]Percentage meeting clinical threshold (CBCL ≥65)

[l]Standardised values adjusted for gestational age

In a second study by Wang et al. [82], the authors examined the risk of seizure in offspring with prenatal antidepressant exposure using data for children born between 2001 and 2015 from the Hong Kong Clinical Data Analysis and Reporting System. At least 1 year of follow-up data were available for each child. Antidepressant exposure was inferred based on maternal prescribing records. Exposure for each pregnancy was classified as either "maternal gestational

use", "maternal gestational non-use", "maternal past use" or "maternal non-use ever". Hazard ratios (HRs) were calculated for comparisons between "maternal gestational use" and each of the comparator groups. In addition, confounding by indication was investigated by comparing children born to mothers with "past use" to children born to mothers with "non-use ever". A discordant sibling analysis was performed to control for genetic and familial factors.

Data for 412,796 mother-child pairs were analysed with a mean follow-up time for offspring of 6.59 ± 3.91 years. Seizure diagnosis rates in children in the "maternal gestational use" and "maternal gestational non-use" groups were 6.75% and 4.46%, respectively, corresponding to a 23% greater risk in exposed children (propensity score-weighted HR [wHR] = 1.23, 95% CI 1.02–1.48). However, the association was no longer evident when comparing "maternal gestational use" with "maternal past use" (wHR = 1.13, 95% CI 0.88–1.44), suggesting confounding by indication. Limiting the analysis to children with "maternal non-use ever", children born to mothers with a diagnosis of psychiatric disorder had a greater risk of seizure than those born to mothers without a psychiatric diagnosis (wHR = 1.44, 95% CI 1.25–1.67). Controlling for genetic and familial variables, the discordant sibling analysis showed no difference between exposed and non-exposed siblings (wHR = 1.16, 95% CI 0.75–1.77). The authors concluded that the results of their analysis suggested the association between prenatal antidepressant exposure and seizure in offspring observed in the overall analysis might be explained by confounding factors.

A third study by Christensen et al. [83] investigated the effect of prenatal antidepressant exposure on language and mathematical abilities in school-aged children born in Denmark between 1997 and 2009. Language and mathematical ability were determined with reference to scores in the Danish National School Test Program.

Data were available for 575,369 children between the ages of 8.9 ± 0.4 years and 14.9 ± 0.4 years at the time of testing. Of these, it was inferred that 10,198 children had prenatal exposure to antidepressants, based on maternal medication prescribing records indicating one or more antidepressant prescription redemption from 30 days before the date of the last menstrual period to the day before childbirth.

Mean test scores for mathematics were 52.1 (95% CI 51.7–52.6) for exposed children and 57.4 (95% CI 57.3–57.4) for unexposed children on a 100-point scale. In language tests, the mean scores were 53.4 (95% CI 53.1–53.7) for exposed children and 56.6 (95% CI 56.5–56.6) for unexposed children. In the fully adjusted analysis, scores for mathematics (mean difference, MD = −2.2, 95% CI −2.7 to −1.6) but not language (MD = −0.1, 95% CI −0.6 to 0.3) remained significantly lower in exposed children. When analysed by class, statistically significant differences in mathematics scores were found for selective serotonin reuptake

inhibitors, serotonin-norepinephrine reuptake inhibitors and "other antidepressants", but not for tricyclic antidepressants.

The results of sensitivity analyses, which controlled for potential confounding factors including maternal depression diagnosis, genetic and familial factors, and child psychiatric disorder, were consistent with the fully adjusted main analysis, but showed a generally weaker association between antidepressant exposure and lower test scores. The exception was the sibling-control analysis, which resulted in greater adjusted MDs between exposed and non-exposed siblings for both mathematics (MD = −2.8, 95% CI −4.5 to −1.2) and for language (MD = −0.3, 95% CI −1.9 to 1.2). Sequential adjustment for each of the identified potential confounders suggested that maternal education and maternal psychiatric disorders had the greatest influence.

While lower scores in mathematics, but not language, remained after adjustment for confounding factors, the small difference in scores between exposed and unexposed children was considered by the study's authors not to be clinically relevant on an individual basis. See also the commentary on this study by Andrade [64].

Finally, Hagberg et al. [84] used data from the UK Clinical Practice Research Datalink database to conduct a cohort study and nested sibling case-control analysis of ASD risk. Data for 194,494 mother-baby pairs, with a minimum of 12 months predelivery maternal history and 3 months postdelivery follow-up, were analysed. Of these, 40,387 had prenatal exposure to any antidepressant medication, prenatal exposure to maternal depression, or both, and 154,107 were matched mother-baby pairs without exposure to either prenatal maternal depression or antidepressants (defined as "unexposed"). Among all mother-baby pairs, 2154 cases of ASD were identified. The prevalence of ASD per 1000 pregnancies was 9.7 (95% CI 9.3–10.2) for unexposed pregnancies, 15.1 (95% CI 13.1–17.3) for untreated depression, 17.3 (95% CI 15.8–19.0) for treated depression and 7.4 (95% CI 4.0–12.6) for antidepressant treatment for other indications. In the sibling case-control analysis adjusted for birth year, birth order and maternal age at delivery, estimates of the relative risk of ASD were 1.18 (95% CI 0.64–2.20) for untreated depression during pregnancy, and 1.53 (95% CI 0.89–2.62) for treated depression during pregnancy, in same-sex matched siblings, compared with unexposed pregnancies.

Overall, the investigators concluded that the results of their analysis did not support an association between antidepressant exposure and an increased risk of ASD, in light of the absence of an association with prenatal antidepressant use for indications other than depression. It was considered that differences in apparent risk might be accounted for by differences in the severity of maternal depression, or by genetic factors.

4.2 Earlier Studies

Results of earlier sibling-control studies are summarised in Table 3. In a large majority of cases, these studies have not found statistically significant associations between prenatal antidepressant exposure and adverse outcomes for the child, including preterm birth [85], small for gestational age [57], smaller size at birth [85], birth defects [86], ASD [57, 87–89], ADHD [56, 57, 90], neurodevelopmental deficits [91] and behavioural problems [92] in discordant sibling analyses. Single studies have reported statistically significant associations with preterm birth [57], lower gestational age at delivery [85] and child anxiety at 36 months [92] that persisted in the sibling-control analyses. Sujan et al. [57] found a slightly increased risk of preterm birth (odds ratio [OR] = 1.34, 95% CI 1.18–1.52) with first-trimester antidepressant exposure. However, no associations were found for small for gestational age, ASD, or ADHD. Infants with prenatal selective serotonin reuptake inhibitor exposure in an analysis by Viktorin et al. [85] had a lower by 2.27 days (95% CI 0.75–3.79) mean gestational age at birth compared with unexposed siblings. In the opinion of the current authors, this small reduction in mean gestational age would probably not be clinically significant, but this does not exclude the possibility that some individual pregnancies were of much shorter duration that could have been of clinical significance. Brandlistuen et al. [92] found evidence of higher anxiety symptoms at 36 months of age in children with prenatal selective serotonin reuptake inhibitor exposure compared with unexposed siblings, based on Child Behaviour Checklist scores (adjusted standardised MD = 0.64, 95% CI 0.26–1.02, $p < 0.05$). Biases due to self-selection of participants, and self-reporting of antidepressant use and symptoms of depression, were highlighted by the authors as potential limitations. Although the results of sibling-control analyses in these studies suggested an increased risk with prenatal antidepressant exposure, it was considered that residual confounding by indication or other factors might partially explain the associations.

4.3 Summary of Sibling-Control Studies

A consistent pattern in these studies is that associations observed in general population comparisons, which do not control for potential sources of confounding and bias, are attenuated or are no longer evident when the analysis is designed to adjust for these factors. Given the limitations of observational data, associations that persist in adjusted analyses may be indicative of residual confounding or be the product of bias, for example due to misattribution of exposure (either for depression or antidepressant use) or ascertainment bias, whereby children born to mothers with depression and/or those who use antidepressants might be more likely to be screened for adverse outcomes. Discordant sibling analyses can help to address the latter [78] but may be more susceptible to the former [93]. Despite their many advantages, neither sibling nor psychiatric controls are likely to control adequately for the severity of depression, or for the presence of acute depression during pregnancy, especially where the analysis is based on retrospective data. In their recent meta-analysis of ASD risk, Vega et al. noted that all of the included studies relied on indications of a lifetime diagnosis of depression and were not able to ascertain depression during the index pregnancy [78]. This is likely to be a problem common to most studies of this type.

Of note, in the majority of these studies, the exact nature of the relationship between siblings is not clearly defined. Only two studies stated that comparisons were between full siblings [85, 89]. Three other studies defined siblings as children born to the same mother [84, 86, 90]. This has implications for the completeness of controlling for genetic factors, as in some cases children defined as siblings may be maternal half-siblings. Ideally, sibling controls would be same-sex children sharing both mother and father. This may be an additional limitation of retrospective studies where details of paternity or sex-parity of the offspring may not always be available in the data.

5 Risk of Adverse Outcomes for Mother and Offspring Following Antidepressant Discontinuation During Pregnancy

Whereas the risk of adverse foetal outcomes with prenatal antidepressant exposure is likely to have been overstated by reference only to the findings from uncontrolled analyses, anxiety over possible harm to the foetus has been cited as the most common reason for discontinuation [30] and may also influence decisions on whether to initiate treatment during pregnancy. Only one in four women taking antidepressants before conception maintain treatment through the third trimester [94]. However, untreated or inadequately treated depression during the perinatal period is also associated with negative outcomes for the child [17], as well as an increased risk of morbidity and mortality for the mother [8, 95]. A review of adverse perinatal outcomes associated with untreated prenatal depression [11] found evidence of increased risks for preeclampsia, spontaneous abortion, low Apgar score, admission to neonatal intensive care, neonatal growth retardation, foetal death, low birth weight, small for gestational age and preterm birth. In women who have been treated with antidepressants up to the time of conception, there also appears to be a substantial risk of depressive relapse following discontinuation [9, 27], which may increase the risks of poor maternal prenatal self-care, poor maternal and, therefore, foetal, nutrition, maternal substance

abuse [43] and postnatal depression [96]. In many cases, postnatal depression may represent a continuation or recurrence of prenatal depression [96, 97]. In addition to its deleterious effects on maternal well-being, postnatal depression may contribute to impaired mother-child interactions [18, 98], and is associated with poorer cognitive, emotional and behavioural development in the child [99, 100]. A multinational European study [95] that investigated the association between prenatal depression and postnatal depression severity in mothers with a psychiatric disorder found that those who were treated with antidepressants at any time during pregnancy had a significant reduction in postnatal symptom severity (based on Edinburgh Postnatal Depression Scale scores) compared with those who did not receive medication (adjusted $\beta = -0.34$, 95% CI -0.66 to -0.02), with the effect greatest during the first 6 months after childbirth (adjusted $\beta = -0.74$, 95% CI -1.24 to -0.24). Somewhat surprisingly, a recent systematic review and meta-analysis on the effect of antidepressant discontinuation before conception or during pregnancy [101] found no increased risk of relapse for women who discontinued antidepressant treatment (risk ratio = 1.74, 95% CI 0.97–3.10) except when the analysis was restricted to cases indicative of severe or recurrent depression (risk ratio = 2.30, 95% CI 1.58–3.35). However, these findings were not consistent with those of a study by Bérard et al. [27], which suggested that women with predominantly mild-to-moderate depression who discontinued treatment during pregnancy were at a greater risk of depression during the second half of pregnancy than those who continued treatment without dose adjustment, compared with non-users (discontinued adjusted OR = 5.95, 95% CI 1.54–23.02; continued adjusted OR = 4.59, 95% CI 1.44–14.64). Albeit not statistically significant, women who discontinued antidepressant treatment during the second half of pregnancy were more likely to have depression during the remainder of the pregnancy than women who continued treatment (adjusted OR = 1.34, 95% CI 0.49–3.65). There is remarkably little information on the risk of suicide in women during the perinatal period [101], or how the risk of suicide during pregnancy and following childbirth might be affected by discontinuation of antidepressant treatment. However, suicide represents a greater risk for mortality for women during the perinatal period than either haemorrhage or preeclampsia [102] and is responsible for 5–20% of maternal deaths during pregnancy and the first year after childbirth [8]. A 1997 consensus statement by the National Depressive and Manic-Depressive Association reported that 15% of women with untreated prenatal depression attempt suicide [103]. In the general population, antidepressant discontinuation is associated with a significant risk of suicide attempts [104]. A 2016 study of suicide in pregnant and postnatal women that analysed data from the UK National Confidential Inquiry into Suicides and Homicides by People with Mental Illness [8] found that women who died by suicide during the perinatal period were more likely to have been diagnosed with depression (adjusted OR = 2.19, 95% CI 1.43–3.34) and less likely to have been receiving active treatment (adjusted OR = 0.46, 95% CI 0.24– 0.89) than women who died by suicide at other times.

Related to consideration of the risk:benefit ratio of maternal antidepressant treatment in the perinatal period is the potential for exposure of infants to antidepressants in breast milk. A recent Cochrane Review [105] on antidepressant treatment for postnatal depression found limited data on outcomes in breastfed infants but there were no reports of adverse effects up to 12 months postpartum in the included randomised controlled trials. None of the sibling-control studies identified in the current review considered the possible effect of exposure via breast milk on outcomes in children. However, the majority of these studies based their analysis on data from medical databases, which are unlikely to include data on breastfeeding. We are not aware of any sibling-control studies that have specifically investigated this question.

Treatment decisions during the perinatal period should be made on a case-by-case basis, with consideration of each individual's circumstances and preferences. Clinicians and expectant mothers should be assisted in making these decisions by providing them with the best available evidence on the relative risks to the mother and child of continuing or discontinuing treatment, or initiating antidepressants for new episodes of depression. It is concerning that population-based studies that have found associations between prenatal antidepressant exposure and adverse outcomes in analyses that have not accounted for confounding factors have tended to achieve the greatest prominence, while evidence that many of the risks attributed to prenatal antidepressant exposure might be explained to a large degree by other (confounding) associations is less widely recognised. Sibling-control studies are an imperfect method for elucidating these associations. In combination with other comparator group analyses, however, they offer a more reliable assessment of the risks associated with antidepressant exposure. Women considering discontinuing antidepressant treatment, or who are reluctant to commence treatment, owing to concerns over the potential risks to their child should be reassured that increasing evidence from well-designed studies suggests that these risks are largely unfounded.

Although the sibling-controlled study eliminates many of the major confounding factors that have invalidated previous studies, the number of sibling-controlled studies is still relatively small and does not allow definitive answers to several important questions. These questions include whether different risks are associated with various antidepressants and whether factors such as dose, timing of treatment during pregnancy and duration of treatment are important factors.

It is recommended that these factors are examined in more detail in future sibling-controlled studies.

6 Conclusions

Many previous, inadequately controlled studies have suggested that treatment with antidepressant medication during pregnancy is associated with a range of adverse outcomes for the mother, foetus or child. More recent studies have attempted to control for confounding factors through a range of analytical techniques. Many of the associations lose statistical significance when confounders, in particular maternal depression, genetic susceptibility and familial factors, are adequately controlled for. An overemphasis on effects observed in studies that do not adjust for these factors is likely to result in misleading conclusions with regard to the true risk of adverse outcomes, and potentially to poorly informed decisions on whether to continue or initiate treatment. Where statistically significant associations persist after adjustment for confounders, the absolute risk often remains small, as many of the outcomes have very low rates in the general population. A slightly increased risk of an infrequent adverse event may often be outweighed by the risk to the mother, foetus and/or child of discontinuing or declining treatment. The risks for the mother and child of untreated depression during pregnancy are well documented and, although perhaps less widely recognised, may have severe and lasting consequences. There remains a limited number of sibling-control studies investigating outcomes in children with prenatal antidepressant exposure, and few data from studies of this type on differential risk according to timing of exposure, or for individual antidepressants or classes of antidepressant. Further studies to elucidate these relationships are warranted. Assessment of the risks and benefits of continued treatment or discontinuation should be made on a case-by-case basis and decisions taken in consultation with the individual, with consideration for their preferences. However, to enable the individual to make an informed decision, it is essential to provide accurate information from properly controlled studies and not be influenced by the many past studies that were misleading because of an inadequate study design.

Declarations

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