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The Risk of Relapse of Depression During Pregnancy After Discontinuation of Antidepressants:

A Systematic Review and Meta-Analysis

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ABSTRACT

Objective: The aim of this systematic review and meta-analysis was to determine the effect of antidepressant discontinuation on the risk of relapse of depression during pregnancy.

Data Sources: MEDLINE, EMBASE, CINAHL, and PsycInfo were searched from the inception of each database through March 2019 using keywords such as *antidepressants*, *pregnancy*, *preconception*, *discontinuation*, *stop*, *recurrence*, *reintroduction*, and *relapse*.

Study Selection: Original studies that involved pregnant women who discontinued antidepressants during preconception (ie, 3 months prior to pregnancy) or pregnancy and examined the relapse of depression during pregnancy (ie, the reemergence of depression or reintroduction of medication) and published in English were included. A total of 2,172 records were identified, and the full texts of 37 articles were reviewed. Eight studies met the inclusion criteria, 6 of which fulfilled the quality criteria, with 4 studies providing data for the meta-analysis.

Data Extraction: Data were extracted using a data extraction form developed for the purpose of this study. The Cochrane Collaboration Review Manager software version 5.3 was used to conduct the meta-analysis.

Results: Pooled data did not show higher risk of relapse of depression during pregnancy for women who discontinued antidepressants than for those who continued antidepressants (risk ratio [RR] = 1.74; 95% CI, 0.97 to 3.10; $P = .06$). In the subanalysis based on the severity and recurrence of depression in the study populations, the risk of relapse was significantly higher for populations suggestive of severe or recurrent depression (RR = 2.30; 95% CI, 1.58 to 3.35) but not for populations suggestive of mild or moderate depression severity (RR = 1.59; 95% CI, 0.83 to 3.04).

Conclusions: Women with severe or recurrent depression should be informed about the increased risk of relapse following antidepressant discontinuation, and those who discontinue antidepressants should be monitored for relapse.

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Depression is common during pregnancy with an overall prevalence rate of 12%.[1] The rate of antidepressant use among pregnant women varies between 1.8% and 8% in different countries and settings.[2–4] Pregnancy is a major factor for antidepressant discontinuation,[5] as pregnant recipients are 5 times more likely to discontinue use than nonpregnant recipients.[2,5] Only 1 in 4 women undergoing antidepressant treatment before conception reports taking antidepressants in the third trimester.[6] Avoiding fetal exposure is the main reason women discontinue antidepressants.[5]

There are increased risks of adverse pregnancy and child outcomes associated with untreated depression.[7–9] Prenatal exposure to antidepressants might also increase the risk of the adverse outcomes.[10,11] However, it is challenging to disentangle the risk of exposure to antidepressants from underlying clinical and social factors associated with the indication of use.[12] While numerous studies have been conducted to examine the risks associated with prenatal exposure to antidepressants, the effects of antidepressant discontinuation, including the risk of relapse, remain unclear. In 2006, in a prospective cohort study of 201 women, Cohen et al[13] reported an overall relapse rate of 43% during pregnancy. They found that women who discontinued medication were more likely to experience a relapse of major depression than those who maintained their medication. However, another prospective study conducted in 2011[14] did not replicate such findings. It found that the risk for onset of a major depressive episode was similar between women who continued and those who discontinued antidepressants. In the general population, a 2015 meta-analysis[15] showed a 2-fold increased risk of relapse after antidepressant discontinuation. Another systematic review[16] among the general population showed that antidepressant discontinuation is associated with an increased risk of suicide attempts. Similar evidence during the perinatal period is scarce. A recent international review[17] of the practice guidelines for the treatment of depression and the use of antidepressants during pregnancy revealed that 4 guidelines advised continuing antidepressants while 5 other guidelines did not explicitly advise or discourage continuation.

The aim of this systematic review and meta-analysis was to identify the current evidence in this area and determine the pooled effect of antidepressant discontinuation on the risk of relapse of depression during pregnancy. We also synthesized the identified evidence to determine factors contributing to

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Clinical Points

- In the literature, the risk of relapse of depression during pregnancy after antidepressant discontinuation is unclear.
- Populations with mild and moderate depression severity or recurrence did not appear to experience significant relapse during pregnancy following antidepressant discontinuation.
- Populations with severe or recurrent depression were at increased risk of relapse during pregnancy following antidepressant discontinuation.

antidepressant discontinuation and relapse of depression and the risk of suicidal ideation or suicide attempts after antidepressant discontinuation. This knowledge can aid decision-making regarding antidepressant use during pregnancy.

METHODS

Sources

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[18] An electronic literature search that included keywords such as *antidepressants*, *pregnancy*, *preconception*, *discontinuation*, *stop*, *recurrence*, *reintroduction*, and *relapse* was conducted using MEDLINE, EMBASE, CINAHL, and PsycINFO for studies dating from the inception of each database to March 2019 (see Supplementary Appendix 1 for the complete list of search strategies and results). The reference lists of the included articles and trial registries in ClinicalTrials.gov were reviewed for additional citations. Gray literature and unpublished studies were not retrieved. Since this was a systematic review, an institutional ethics board approval was not required.

Study Selection

We included original studies that (1) involved pregnant women who discontinued antidepressants during preconception (ie, 3 months prior to pregnancy)[19] or pregnancy, (2) assessed relapse of depression during pregnancy, and (3) were published in English. If a study met the inclusion criteria but did not report relapse rates, the authors of the study were contacted. The presence of a comparison group was not an inclusion criterion; however, only studies with a comparison group were included in the meta-analysis. The exclusion criteria were case reports and studies that used other interventions for depression treatment or medication adherence. The main outcome was the rate of relapse of depression during pregnancy after antidepressant discontinuation. Relapse was defined as the reemergence of depression (ascertained by a clinical diagnosis or valid tools) or reintroduction of medication after discontinuation. Secondary outcomes included factors contributing to antidepressant discontinuation and relapse of depression and the risk of suicide ideation/attempts after discontinuation. Three authors (H.B., A.K., M.B.) independently reviewed the abstracts and full text of articles and extracted the data. Disagreements were resolved by discussion.

The following data were extracted from each included study: study design, participant eligibility criteria, sample size and characteristics (eg, age at the first onset of depression, number of depressive episodes, medication types), and outcomes. Extracted data were synthesized by two reviewers independently (H.B., A.K.) to identify the rates of relapse, factors contributing to antidepressant discontinuation and relapse, and the risk of suicidal ideation or suicide attempts after antidepressant discontinuation. To quantify and determine the risk of relapse of depression after antidepressant discontinuation, we conducted a meta-analysis using the Cochrane Collaboration Review Manager software version 5.3.[20] The rates of relapse of depression for the discontinued and maintained antidepressant groups were compared, and the risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using random-effects models. Statistical heterogeneity was examined using I^2 values.

We also performed a predefined subgroup analysis by stratifying the results based on the depression severity and recurrence of the study population. In previous research,[21] the number of prior episodes of illness has been used to classify depression severity as mild or severe. In this review, in addition to the number of prior episodes, we used the age at the first onset and recruitment setting as extra indicators of illness severity and recurrence. Depression severity and recurrence were determined post hoc based on the following indicators: recruitment setting (regular prenatal clinics vs specialized psychiatric clinics), age at the first onset of depression (> 18 years), and the number of recurrent episodes. Using these characteristics when available, two reviewers (H.B. and A.K.) independently categorized the studies into two groups: studies whose populations had mild or moderate depression and studies whose populations had high depression severity or recurrence of depression (ie, severe/recurrent depression). Quality appraisal was performed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology checklist.[22] This checklist includes 14 items, 12 of which evaluate various biases, including selection, performance, attrition, and detection. Two reviewers (H.B. and A.K.) independently determined the risk of each type of bias by evaluating the corresponding items in the SIGN methodology checklist. The Cochrane Collaboration Review Manager risk-of-bias graph was adopted to present this information (Supplementary Appendix 1).

RESULTS

A total of 2,172 records were identified. After removal of duplicates and screening of titles and abstracts, the full text of 37 articles was retrieved and reviewed. Using a PRISMA flow diagram, Figure 1 illustrates the search and selection processes and reasons for exclusion at each review stage. Ten studies met the inclusion criteria, 3 of which did not provide relapse data,[14,23,24] and the authors were

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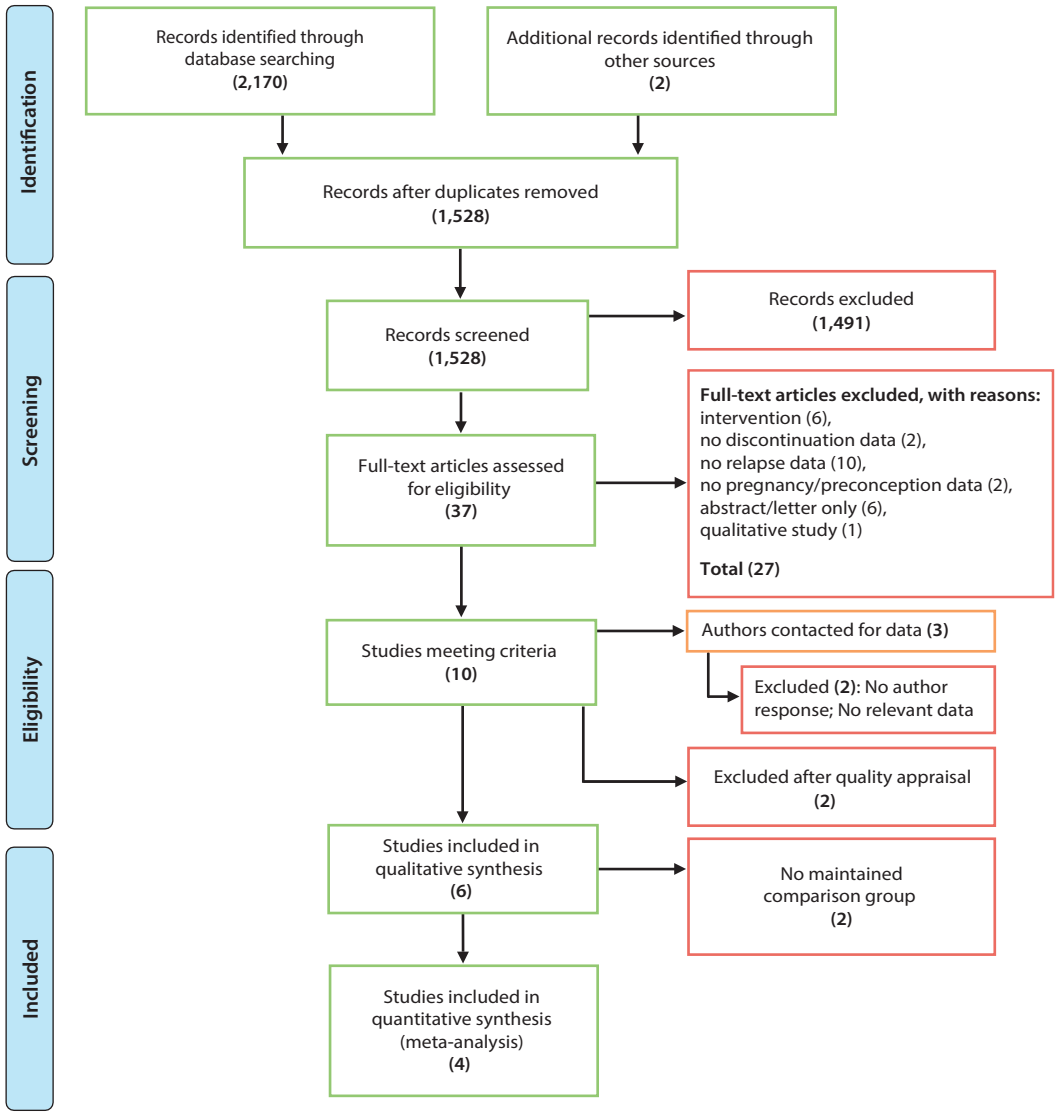
Figure 1. PRISMA Flow Diagram of Article Collection Throughout the Systematic Review



contacted. Deidentified data from the study by Yonkers et al[14] were obtained through an agreement between the University-Industry Liaison Office at the University of British Columbia and the Office of Sponsored Projects at Yale University. Relapse rates in the study by Molenaar et al[24] were confirmed through e-mail correspondence with the first author. However, discontinuation of antidepressants in this study took place anytime during pregnancy and 3 months postpartum; thus, this study was excluded. The authors of the third study[23] did not respond. Overall, 8 studies[2,13,14,21,25–28] were considered for quality appraisal and the risk-of-bias assessment. All studies were observational studies, and we used the SIGN methodology checklist. Based on the criteria listed in this checklist, the quality of 6 studies[13,14,21,25,26,28] was rated high or acceptable, and the quality of 2 studies[2,27] was rated low. The risk of bias was low in 1 study.[13] Five studies[14,21,25,26,28] had a moderate/unclear risk of bias, 3 of which[25,26,28] did not provide sufficient methodological details; thus, several areas were coded as unclear. Two studies[2,27] had a high risk of performance and detection biases with unclear selection and attrition biases and were excluded.

Synthesis of the Review Findings

All 6 included studies were observational cohort studies; 4 were prospective studies,[13,14,21,28] and 2 were retrospective studies.[25,26] Four studies were conducted in the United States,[13,14,21,26] 1 in Spain,[28] and 1 in Japan.[25] At baseline, the presence or absence of depression was examined using *DSM-III-R*[21] or *DSM-IV* criteria,[13,26,28] the World Mental Health Composite International Diagnostic Interview,[14] or a psychiatric specialist's diagnosis.[25] All prospective studies[13,14,21,28] included at least 2 study visits; 1 study[21] required a visit every trimester, and 1 study[13] required monthly study visits. The study characteristics are presented in Table 1.

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Table 1. Characteristics of the Included Studies

Study, Country, Design, Duration	Sample Size	Inclusion Criteria	Exclusion Criteria	Baseline Diagnosis	Follow-Up Frequency	Assessments	Discontinuation Timing	Medication Type
Cohen et al 2004a,[26] US, retrospective, duration not reported	N = 54	Was euthymic at the time of conception; discontinued antidepressant treatment no earlier than 6 wk prior to conception and no later than 7 wk after conception (9 wk of gestation)	Not applicable	*DSM-IV* criteria	Not applicable	Not applicable	Between 6 wk prior to conception and 7 wk after conception	Not applicable
Cohen et al 2004b,[21] US, prospective, duration not reported	N = 32	Pregnant with a history of recurrent major depression; was euthymic at the time of conception; was treated with antidepressant for at least 3 mo; discontinued or attempted to discontinue antidepressants within 15 wk prior to conception and 9 wk gestation	Not applicable	SCID-P for *DSM-III-R*	Each trimester	SCID-P for *DSM-III-R*, HDRS, CGI, BDI	Between 15 wk prior to conception and 9 wk of gestation	SSRI (n = 19) TCA (n = 4) Other antidepressants (n = 9)
Cohen et al 2006,[13] US, prospective, 1999–2003	N = 201	Had a history of major depression; underwent less than 16 wk of gestation; was euthymic for ≥ 3 mo prior to LMP; was receiving or recently received antidepressants	Was suicidal; met *DSM-IV* criteria for: organic mental, substance use, bipolar, delusional, or current psychotic disorder or schizophrenia; had a positive urine drug screen for toxic substances; had a medical condition associated with depressive symptomatology	SCID-I/P for *DSM-IV*	Monthly	HDRS, SCID-I/P for *DSM-IV*, CGI	Between 3 mo prior to LMP and 16 wk of gestation	TCA (n = 28) SSRI/SNRI (n = 142) Combination (n = 22) Other monotherapy (n = 9)
Roca et al 2013,[28] Spain, prospective, 2005–2008	N = 132	Met *DSM-IV* criteria for depression or anxiety disorders; was receiving treatment with SSRIs at the time of conception	Had a psychotic or bipolar disorder; met criteria for dependence on alcohol or illicit substances; had illiteracy and presence of serious medical illness	SCID-I/P for *DSM-IV* EPDS and BMQ	< 20 wk of pregnancy Between 34 and 36 wk	EPDS, STAI	Upon confirmation of pregnancy	All SSRI (n = 132)
Suzuki and Kato 2017,[25] Japan, retrospective, 2009–2015	N = 146	All singleton deliveries were beyond 22 wk of gestation; the mother was diagnosed with depression before pregnancy by Japanese psychiatric specialists	Not applicable	Psychiatric specialist diagnosis	Not reported	Depression relapse; suicidal ideation; obstetric outcomes	First trimester	Not reported
Yonkers et al 2011,[14] US, prospective, 2005–2009	N = 778	Was aged 18 y or older and had not yet completed the 17th wk of pregnancy	Had a known multifetal pregnancy or insulin-dependent diabetes; did not speak English or Spanish; did not have access to a telephone; planned to relocate; intended to terminate pregnancy	WMH-CIDI	< 17 wk of gestation 28 (± 2) wk of gestation 8 (± 4) wk postpartum	Depressive disorder, PTSD, generalized anxiety disorder, and panic disorder modules of the WMH-CIDI	During the study (we included data for discontinuation between month before pregnancy and first trimester)	SSRI/SNRI (n = 127) TCA (n = 1) Other (n = 22)

Abbreviations: BDI = Beck Depression Inventory; BMQ = Beliefs about Medicine Questionnaire, specific version; CGI = Clinical Global Impressions scale; EPDS = Edinburgh Postnatal Depression Scale; HDRS = Hamilton Depression Rating Scale; LMP = last menstrual period; PTSD = posttraumatic stress disorder; SCID-I/P = Structured Clinical Interview for *DSM-IV*, Patient Edition; SCID-P = Structured Clinical Interview for *DSM-III-R*, Patient Edition; SSRI = selective serotonin reuptake inhibitor; STAI = Spielberger State-Trait Anxiety Inventory; WMH-CIDI = World Mental Health Composite International Diagnostic Interview.

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Table 2. Frequency of Antidepressant Discontinuation and Depression Relapse

Study	N	Groups	Relapse Definition	Discontinuation Frequency, % (n)	Relapse Frequency, % (n)
Cohen et al 2004a[26]	54	Discontinued	Reintroduction	100 (54)	42 (23)
Cohen et al 2004b[21]	32	Discontinued	MDD (SCID-P for *DSM-III-R*)	78 (25)	68 (17)
		Discontinuation attempt		22 (7)	100 (7)
Cohen et al 2006[13]	201	Discontinued	MDD (SCID-I/P for *DSM-IV*)	32 (65)	68 (44)
		Decreased dose		17 (34)	35 (12)
		Increased dose		10 (20)	45 (9)
		Maintained		41 (82)	26 (21)
Roca et al 2013[28]	132	Discontinued	Reintroduction/dose increase	53 (70)	57 (40)
		Maintained		47 (62)	18 (11)
Suzuki and Kato 2017[25]	146	Discontinued (specialist discretion)	Diagnosis by psychiatric specialists	12 (18)	61 (11)
		Discontinued (self-interruption)		13 (19)	63 (12)
		No medications		41 (60)	5 (3)
		Maintained		34 (49)	16 (8)
Yonkers et al 2011[14]	153	Discontinued	*DSM-IV* criteria for depression	22 (34)	15 (5)
		Maintained		78 (119)	16 (19)

Abbreviations: MDD (SCID-I/P for *DSM-IV*) = Structured Clinical Interview for *DSM-IV*, Mood Module; MDD (SCID-P for *DSM-III-R*) = Structured Clinical Interview for *DSM-III-R*, Mood Module.

All studies except 1[26] included at least 1 comparison group. The control group in 1 of these studies[21] consisted of women who decreased the antidepressant dose. Three studies included additional comparison groups consisting of patients who intended to taper use or attempted discontinuation,[21] increased or decreased the medication dose,[13] or interrupted medication based on the discretion of psychiatric specialists or by self-interruption.[25] The frequency of discontinuation (Table 2) varied from 22%[14] to 78%.[21] A fear of the influence of antidepressant medications on the fetus was the main reason for interrupted medication use as reported in 1 included study.[25] The types of medications were reported in 4 studies.[13,14,21,28] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) were the most common types of medications, constituting between 59%[21] and 71%[13] of the prescribed medications. For example, in the 2006 study by Cohen et al,[13] 142 of 201 women reported taking SSRIs or SNRIs. Women who maintained their medication were more likely to be receiving an SSRI regimen than women who chose to alter their therapy regimen.[13] Single pregnant women[13] or those with an unplanned pregnancy[28] were more likely to discontinue treatment. Other factors did not differ significantly between the maintained and discontinued antidepressant groups.[13,28]

Studies defined relapse of depression as a fulfillment of *DSM* criteria,[13,14,21] a diagnosis ascertained by a psychiatric specialist,[25] an increase in the antidepressant dose,[28] or a reintroduction of antidepressant medication.[26] The frequency of relapse ranged from 15%[14] to 68%,[13,21] with 4 studies[13,21,25,28] reporting a relapse frequency of approximately 60% or greater. All studies reported that the highest relapse rates occurred in the first trimester. Younger (< 32 years of age)[13] nulliparous women[25] were at greater risk of relapse. Cohen et al (2006)[13] also observed that single women tended to have a higher risk of relapse than married women. No significant associations between ethnicity, educational level, baseline antidepressant treatment, and the risk of relapse were reported.[13] The chronicity of illness was the most commonly reported predictor of relapse.[13,21,26] Women with a duration of depressive illness of more than 5 years had nearly a 3-fold increased risk of relapse.[13] Women with a history of severe depression also tended to relapse more quickly than women with mild depression (80% vs 38%).[21] Other predictors of relapse included the number of recurrent episodes,[13,14] high Edinburgh Postnatal Depression Scale scores during early pregnancy,[28] and history of suicide attempts.[26] Two studies[13,21] examined the effect of tapering medication or decreasing dose on relapse of depression. In a study of 32 participants,[21] all women who decreased the antidepressant dose from the dosage used to maintain euthymia experienced relapse. In another study with 201 participants,[13] the women who decreased their medication had a 35% rate of relapse, which was between the rate of those who maintained (26%) and those who discontinued (68%) antidepressants.

Only 1 study[25] examined the effect of relapse on obstetric outcomes, and the effect was null. Among the women who experienced relapse after discontinuing antidepressants, depression was improved by the resumption of medications.[25] Medication reintroduction also reduced the risk of relapse; however, the risk remained substantially greater than that for women who retained their medication regimen throughout pregnancy.[13] Suzuki and Kato[25] reported that 3 in 37 women in the discontinued antidepressant group had suicidal ideations, while 1 in 49 women in the continued antidepressant group had suicidal ideations. The difference was not statistically significant. Cohen et al (2006)[13] reported no suicidal attempts among the participants during the course of the study.

Meta-Analysis

Four studies[13,14,25,28] had a comparison group consisting of women who maintained antidepressants and were included in the meta-analysis. The total sample included 518 women; 302 women in the maintained group and 206

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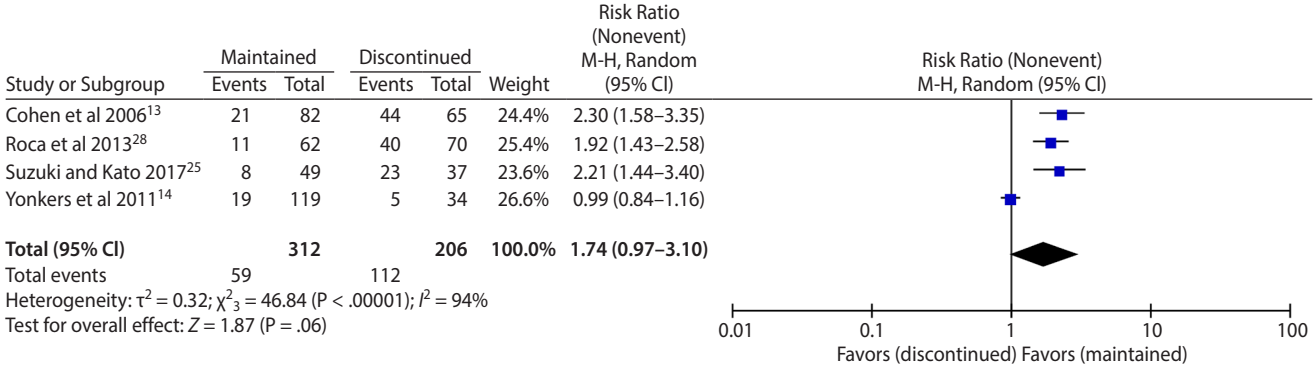
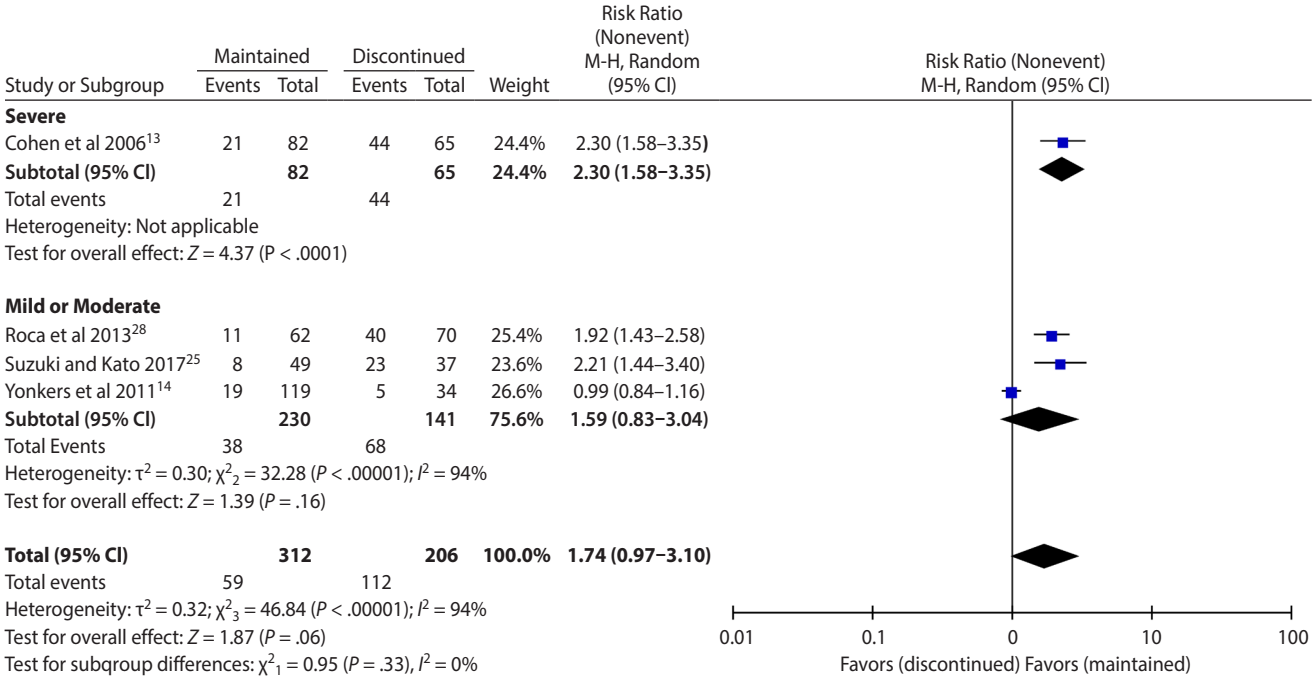
Figure 2. Pooled Analysis of Risk of Relapse for Women Who Discontinued Antidepressants Versus Those Who Continued Antidepressants



Abbreviation: M-H = Mantel-Haenszel test.

Figure 3. Pooled Analysis of Risk of Relapse for Women With Severe Depression and Those With Mild or Moderate Depression



Abbreviation: M-H = Mantel-Haenszel test.

women in the discontinued group. In the first analysis, we compared the risk of relapse among women who maintained antidepressants to that of women who discontinued antidepressants using random-effects models. Pooled data from all studies did not show higher risk of relapse for women who discontinued antidepressants than for those who continued antidepressants (RR = 1.74; 95% CI, 0.97 to 3.10; *P* = .06; Figure 2). For the subanalysis based on the severity or recurrence of depression, 3 studies[14,25,28] met the criteria for populations suggestive of mild or moderate severity and 1 study[13] included a population suggestive of severe/recurrent depression. In this analysis, the risk of relapse was significantly higher for population suggestive of severe/recurrent depression (RR = 2.30; 95% CI, 1.58 to 3.35) but not for those of mild or moderate severity (RR = 1.59; 95% CI, 0.83 to 3.04) (Figure 3). Tests for funnel plot asymmetry to determine publication bias were not performed due to the small number of included studies (ie, < 10).[29]

DISCUSSION

The findings of this meta-analysis showed that, overall, the discontinuation of antidepressants is not associated with a significant increased risk of relapse of depression during

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pregnancy. In this review, the main predictors of relapse included the illness chronicity,[13,21,26] number of previous recurrent episodes,[13,14] and history of suicide attempts,[26] suggesting that greater depressive illness severity may contribute to an increased risk of relapse. In the subgroup analysis based on depression severity or recurrence, the risk of relapse among studies with populations suggestive of mild or moderate depression remained nonsignificant. However, for the population suggestive of severe/recurrent depression, the risk of relapse after discontinuation of antidepressants was more than 2 times higher than those who maintained treatment. A meta-analysis of 72 trials of major depressive disorders in the general population[15] showed a greater risk of relapse or recurrence of a depressive disorder in participants who received a placebo than those who received medications (RR = 1.90; 95% CI, 1.73 to 2.08).

The evidence on the risk of suicide following antidepressant discontinuation during pregnancy is scarce. A few case studies[30,31] have reported suicide incidents following antenatal antidepressant discontinuation. In a small study of 36 women, Einarson et al[32] reported suicidal ideation in almost one-third of the patients after antidepressant discontinuation. Among the general population, antidepressant discontinuation is associated with an increased risk of suicide attempts (odds ratio = 1.61; 95% CI, 1.34 to 1.92).[16] In this review, only 2 studies[13,25] reported data on suicidal ideation or attempts following antidepressant discontinuation, and both studies reported no significant differences. Suzuki and Kato[25] observed that women who discontinued antidepressants tended to have a higher risk of suicidal ideation than those who continued (8% vs 2%). This finding is noteworthy given that suicide is a rare outcome and that women who discontinued antidepressants were more likely to experience severe depression[25] or remain at higher risk for relapse despite the resumption of medication.[13]

Many women discontinue antidepressants during pregnancy, mostly to prevent fetal exposure.[25] There are increased risks of adverse pregnancy and child outcomes associated with prenatal exposure to antidepressants.[10,11,33] On the other hand, untreated depression can also increase the risk of poor pregnancy and child outcomes.[7–9] Nonetheless, there is not strong evidence that the use of antidepressants to treat depression during pregnancy can improve these outcomes,[34] prevent postpartum depression,[35–37] or improve infant-mother attachment.[38] A recent systematic review[34] that examined the comparative effects of antidepressant medications and untreated major depression found that the risk of low birth weight (LBW) and related pregnancy outcomes did not differ between antidepressant-treated women and untreated depressed women. In a large population-based study, there were no significant differences in the risk of preterm birth (PTB) and LBW among women who received either SSRIs or other antidepressants during pregnancy and that of women who discontinued antidepressants before pregnancy. Both groups had a higher risk of PTB and LBW than those who never received antidepressants.[39] Similarly, there is not strong evidence that the use of non-pharmacologic interventions for depression is effective in improving birth outcomes.[40,41] In a randomized controlled trial of 226 pregnant women,[40] no significant differences in the gestational age, birth weight, or Apgar scores were found when comparing the cognitive-behavioral therapy (CBT) group with the care-as-usual group. In this review, only 1 study[25] examined pregnancy outcomes associated with antidepressant discontinuation, and the study reported no significant differences between the PTB and cesarean birth of women who discontinued antidepressants or relapsed and those of women who continued medications.

In this review, the rate of relapse despite maintaining antidepressants varied between 7% and 26%. A recent study[42] reported that 20% of pregnant women receiving antidepressants remained depressed. Cohen et al[13] reported that 10% of pregnant women in their study required an increase in their antidepressant dose. This group appeared distinct from those who maintained their antidepressant treatment, as this group had a higher risk of relapse of depression (45% vs 26%) and a more rapid time to relapse. In another study,[43] two-thirds of women required an increase in their daily dose, mostly around 27 weeks of gestation, to maintain euthymia. No associations were detected between age, educational level, or personal and familial psychiatric history and dose adjustment. Antidepressant metabolism during pregnancy can vary among individuals based on the expression of certain genes.[44] In a recent study,[42] a significantly higher proportion of women in the fast metabolizer group had depressive symptoms in the first trimester than that of women in the slow metabolizer group. This evidence highlights the heterogeneity of pregnant women in terms of their response to antidepressants and suggests that each individual, depending on her unique genotypes and personal history, may require specific changes in antidepressant dosage to maintain therapeutic plasma levels. The practice of precision medicine has been encouraged, but genetic testing is currently not mandatory to initiate treatment.[42,45] A further understanding of the interactions between phenotypes and genotypes can have important implications to inform appropriate treatment adjustments during pregnancy.

Two studies[13,21] examined the relapse risk after tapering antidepressants. Among women who decreased their medication dose from a previous optimal dose or discontinued 1 antidepressant from a combination regimen, the relapse risk was slightly higher than that of women who maintained consistent antidepressant therapy throughout pregnancy, but the relapse risk was lower than that of women who discontinued antidepressants (35%, 26%, and 68%, respectively).[13] In a smaller study,[21] all women who decreased the antidepressant dose experienced relapse. Recent trials among the general population have demonstrated that the tapering of antidepressants combined with preventive CBT can be as effective as the continuation of the same dose.[46] Similar evidence during the perinatal

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period is scarce but emerging; in an open preliminary study of CBT for the prevention of depression recurrence among pregnant women who discontinued antidepressant treatment,[47] 75% of the women did not relapse after the completion of 12 CBT sessions. In a recent trial on the treatment of postpartum depression,[48] a combination of psychotherapeutic interventions (ie, detached mindfulness and stress management training) with a standard SSRI was shown to be superior to and have a longer-lasting improvement than the use of only antidepressants.

The use of clinical diagnostic interviews to ascertain relapse in the majority of included studies is one of the strengths of our findings. Other strengths include the application of strict criteria for quality appraisal and risk-of-bias assessment and the involvement of 3 reviewers in most stages of the review. Several limitations of this review should be considered when interpreting the findings. The number of included studies and their sample sizes were relatively small. There was significant heterogeneity among the included studies. Only 1 study[13] had a low risk of bias, and it was the only study in the subanalysis that met the criteria for the category of populations with severe/recurrent depression. The included studies did not specifically report the severity of prior episodes of depression. Thus, we used the number of prior episodes, age at the first onset of depression, and recruitment setting as proxy to estimate depression severity or recurrence. Being euthymic at the time of recruitment was an inclusion criterion in 3 studies. Two studies used reintroduction as an indicator for relapse.[21,28] However, the sensitivity analysis did not change the direction of the total effect (results not shown). Only 1[13] of the included studies in the meta-analysis reported relapse information for subgroups of maintained group based on medication dosage (ie, no change, decrease, increase).

Every person receiving antidepressants who is planning a pregnancy or becomes pregnant encounters a difficult dilemma. The absence of confirmative evidence regarding the effectiveness of depression treatments to improve birth outcomes intensifies this dilemma by necessitating the weighing of the maternal benefits of using antidepressants with the risk of prenatal exposure. The findings of our review showed that the discontinuation of antidepressants did not increase the risk of relapse during pregnancy; however, there was a trend toward the increased risk of relapse ($P = .06$). A significant number of pregnant women (up to 75%) discontinue antidepressants.[6] Women may choose to discontinue antidepressants on their own or after consulting a health professional.[32] While further studies are required to compare the relapse risk of these two groups, the limited available data show that the risk of relapse increases after discontinuation regardless of how the decision was made.[25]

The general consensus among clinical practice guidelines is that the potential harms and benefits of antidepressants should be discussed with pregnant women so they can make well-informed decisions.[17] Beliefs about the necessity of medications and the perception that the benefits of antidepressants outweigh the risks are important factors in the continuation of and adherence to medications.[23,24,49] As Miller[50] noted when explaining the risks of antidepressants during pregnancy, maternity care providers should avoid errors of omission by explaining the risks of discontinuing treatment. While the effectiveness and safety of psychotherapy interventions as a complete alternate therapy for women who discontinue antidepressants remain to be further examined, there is evidence that a combination of psychotherapy and pharmacotherapy interventions is as effective as antidepressants when tapering off medications,[46,51] is more effective than the use of antidepressants alone,[46,48] and can increase medication adherence.[32,52] Women with severe/recurrent depression should be informed about the increased risk of relapse following antidepressant discontinuation, and those who discontinue antidepressants should be monitored for relapse.

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Author contributions: Dr Bayrampour conceptualized the study; acquired, analyzed, and interpreted the data; and drafted the manuscript. Dr Kapoor conducted the literature search; acquired, analyzed, and interpreted the data; and drafted parts of the Methods and Results sections of the manuscript. Ms Bunka acquired and interpreted the data and revised the manuscript for important intellectual content. Dr Ryan contributed to the study design and interpretation of data and revised the manuscript for important intellectual content. All authors have approved the final version of the manuscript.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Women's Mental Health section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

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Supplementary Material

Article Title: The Risk of Relapse of Depression During Pregnancy After Discontinuation of Antidepressants: A Systematic Review and Meta-Analysis

Author(s): Hamideh Bayrampour, MSc, PhD; Arunima Kapoor, MSc, PhD; Mary Bunka, BA; and Deirdre Ryan, MD, FRCPC

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List of Supplementary Material for the article

1. Appendix 1 Search Strategies and Results
2. Figure 1 Assessment of risk of bias in included studies

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Appendix 1. Search Strategies and Results

A. Search Strategy on Medline

Search ID #	Search Terms or Options	Results
1	Pregnant Women/ or Pregnancy/	838594
2	Prenatal Care/ or Perinatal Care/ or Preconception Care/ or Maternal Welfare/	36197
3	(pregnant or pregnanc* or prenatal or perinatal or preconception or conceive or antenatal or antepartum).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1001789
4	Maternal-Fetal Exchange/	29026
5	or/ 1-4 [pregnant]	1003918
6	Depression/ or Depression Disorder, Major/	107155
7	Mood Disorders/	13510
8	(depressi* or affect*disorder or mood disorder).mp.	428397
9	or/ 6-8 [depression]	435837
10	Antidepressive Agents/	40974
11	Depressive Disorder, Major/ dt [Drug Therapy]	8012
12	Serotonin Uptake Inhibitors/	18633
13	(antidepress*).mp	86041
14	(tricyclic or TCA or selective serotonin reuptake inhibitor or SSRI or serotonin norepinephrine reuptake inhibitor or SNRI). Mp	38333
15	Sertraline/ or Paroxetine/ or Citalopram/ or Fluoxetine/ or Desipramine/ or Imipramine/ or Nortriptyline/	32720
16	or/ 10-15 [antidepressants]	125266
17	5 and 9 and 16 [population]	1866

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18	Medication Adherence/ or Treatment Refusal/ or Withholding Treatment/	37262
19	(discontinu* or end or stop or decrease or maintain* or withhold* or adhere* or refus*).mp	2412555
20	Recurrence/	174479
21	Substance Withdrawal Syndrome/	20746
22	(relapse or reintroduc* or recurrence or withdraw*).mp	647866
23	or/ 18-22 [outcome]	2969502
24	17 and 23 [population, outcome]	414

B. Search strategy on EMBASE

Search ID #	Search Terms or Options	Results
1	pregnant woman/ or exp pregnancy/	654166
2	prenatal care/ or perinatal care/ or prepregnancy care/ or maternal welfare/ or maternal care/	73517
3	(pregnant or pregnanc* or prenatal or perinatal or prepregnancy or antenatal or antepartum).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1023153
4	or/1-3 [pregnant]	1034395
5	depression/	332274
6	mood disorder/	39618
7	antenatal depression/	346
8	(depressi* or affect*disorder or mood disorder).mp.	657689
9	maternal disease/	6449
10	or/ 5-9 [depression]	663585

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11	antidepressant agent/	89977
12	major depression/dt [Drug Therapy]	14752
13	serotonin uptake inhibitor/	45260
14	tricyclic antidepressant agent/	32494
15	(antidepress*).mp	150229
16	(tricyclic or TCA or selective serotonin reuptake inhibitor or SSRI or serotonin norepinephrine reuptake inhibitor or SNRI).mp	69294
17	sertraline/ or paroxetine/ or citalopram/ or fluoxetine/ or desipramine/ or imipramine/ or nortriptyline/	109406
18	prenatal drug exposure/	9308
19	or/ 11-18 [antidepressants]	254389
20	4 and 10 and 19 [population]	4518
21	medication compliance/ or treatment refusal/ or treatment withdrawal/	58047
22	(discontinu* or end or stop or decrease or maintain* or withhold* or adhere* or refus*).mp	3215604
23	relapse/	131197
24	recurrent disease/ or recurrence risk/	224708
25	(relapse or reintroduc* or recurrence or withdraw*).mp	995236
26	drug withdrawal/ or withdrawal syndrome/	195342
27	or/ 21-26 [outcome]	4116339
28	20 and 27 [population, outcome]	1281

C. Search strategy on PSYCInfo

Search ID #	Search Terms	Search Options	Results

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1	pregnant or pregnanc* or prenatal or perinatal or preconception or conceive or antenatal or antepartum	80,054
2	depressi* or affect*disorder or mood disorder	344,301
3	antidepress* or tricyclic or TCA or selective serotonin reuptake inhibitor or SSRI or serotonin norepinephrine reuptake inhibitor or SNRI or sertraline or paroxetine or citalopram or fluoxetine or desipramine or imipramine or nortriptyline	58,360
4	discontinu* or end or stop or decrease or maintain* or withhold* or adhere* or refus* or relapse or reintroduc* or recurrence or withdraw*	490,982
5	1 and 2 and 3 and 4	274

D. Search strategy on CINAHL

Search ID #	Search Terms	Search Options	Results
1	(MH "Expectant Mothers")		5,640
2	(MH "Pregnancy+") OR (MH "Pregnancy Complications, Psychiatric+")		179,465
3	(MH "Prenatal Care") OR (MH "Prenatal Diagnosis+")		30,062
4	(MH "Perinatal Care") OR (MH "Prepregnancy Care")		5,019
5	(MH "Maternal Welfare") OR (MH "Maternal Behavior")		4,217
6	or/ 1-5		189,802
7	pregnant or pregnanc* or prenatal or perinatal or preconception or conceive or antenatal or antepartum		221,772
8	6 or 7 [pregnancy]		232,202

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9	(MH "Depression+")		95,246
10	(MH "Affective Disorders+")		100,685
11	9 or 10		100,685
12	depressi* or affect*disorder or mood disorder		149,131
13	11 or 12 [depression]		152,867
14	(MH "Antidepressive Agents+")		20,380
15	(MH "Antidepressive Agents, Tricyclic+") OR (MH "Antidepressive Agents, Second Generation+")		7,476
16	(MH "Serotonin Uptake Inhibitors+")		10,060
17	(MH "Sertraline Hydrochloride") OR (MH "Paroxetine") OR (MH "Citalopram") OR (MH "Fluoxetine+") OR (MH "Desipramine") OR (MH "Imipramine") OR (MH "Nortriptyline")		4,588
18	(MH "Substance Abuse, Perinatal")		1,472
19	14 or 15 or 16 or 17 or 18		25,232
20	antidepress* or tricyclic or TCA or selective serotonin reuptake inhibitor or SSRI or serotonin norepinephrine reuptake inhibitor or SNRI		23,174
21	19 or 20 [antidepressants]		31,579
22	8 and 13 and 21 [population]		1,010
23	(MH "Medication Compliance") OR (MH "Treatment Refusal") OR (MH "Treatment Termination") OR (MH "Treatment Complications, Delayed")		23,943
24	discontinu* or end or stop or decrease or maintain* or withhold* or adhere* or refus*		392,703
25	(MH "Recurrence") OR (MH "Substance Withdrawal Syndrome+")		43,779
26	relapse or reintroduc* or recurrence or withdraw*		113,395
27	or/ 23-26 [outcome]		498,921

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28	22 and 27 [population, outcome]	201

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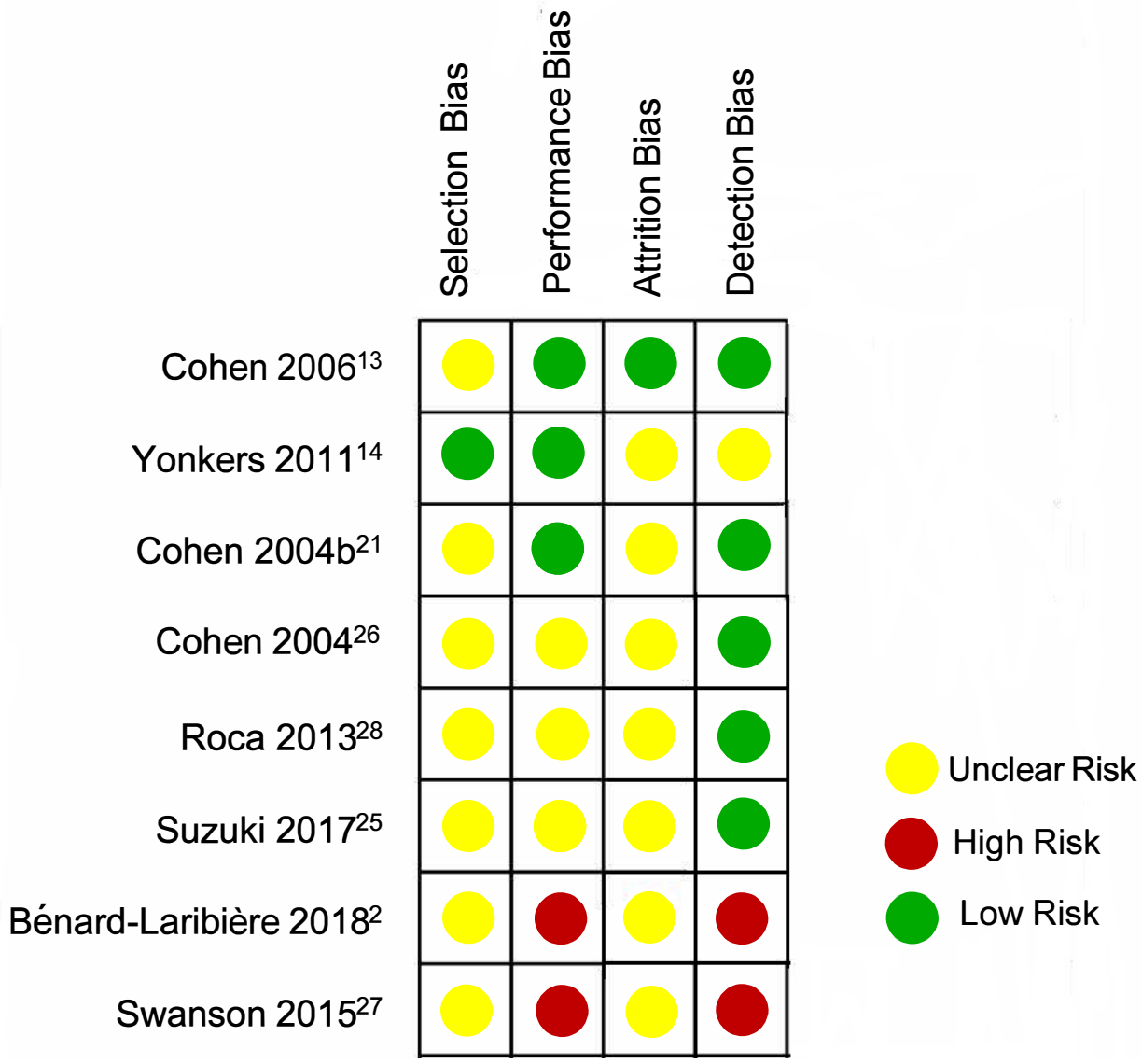
Figure 1. Assessment of risk of bias in included studies



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