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Lithium Exposure During Pregnancy and the Postpartum Period: A Systematic Review and Meta-Analysis of Safety and Efficacy Outcomes

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Abstract

Objective:

Uncertainty surrounds the risks of lithium use during pregnancy in women with bipolar disorder. The authors sought to provide a critical appraisal of the evidence related to the efficacy and safety of lithium treatment during the peripartum period, focusing on women with bipolar disorder and their offspring.

Methods:

The authors conducted a systematic review and random-effects meta-analysis assessing case-control, cohort, and interventional studies reporting on the safety (primary outcome, any congenital anomaly) or efficacy (primary outcome, mood relapse prevention) of lithium treatment during pregnancy and the postpartum period. The Newcastle-Ottawa Scale and the Cochrane risk of bias tools were used to assess the quality of available PubMed and Scopus records through October 2018.

Results:

Twenty-nine studies were included in the analyses (20 studies were of good quality, and six were of poor quality; one study had an unclear risk of bias, and two had a high risk of bias). Thirteen of the 29 studies could be included in the quantitative analysis. Lithium prescribed during pregnancy was associated with higher odds of any congenital anomaly (N=23,300, k=11; prevalence=4.1%, k=11; odds ratio=1.81, 95% CI=1.35–2.41; number needed to harm (NNH)=33, 95% CI=22–77) and of cardiac anomalies (N=1,348,475, k=12; prevalence=1.2%, k=9; odds ratio=1.86, 95% CI=1.16–2.96; NNH=71, 95% CI=48–167). Lithium exposure during the first trimester was associated with higher odds of spontaneous abortion (N=1,289, k=3, prevalence=8.1%; odds ratio=3.77, 95% CI=1.15–12.39; NNH=15, 95% CI=8–111). Comparing lithium-exposed with unexposed pregnancies, significance remained for any malformation (exposure during any pregnancy period or the first trimester) and cardiac malformations (exposure during the first trimester), but not for spontaneous abortion (exposure during the first trimester) and cardiac malformations (exposure during any pregnancy period). Lithium was more effective than no lithium in preventing postpartum relapse (N=48, k=2; odds ratio=0.16, 95% CI=0.03–0.89; number needed to treat=3, 95% CI=1–12). The qualitative synthesis showed that mothers with serum lithium levels <0.64 mEq/L and dosages <600 mg/day had more reactive newborns without an increased risk of cardiac malformations.

Conclusions:

The risk associated with lithium exposure at any time during pregnancy is low, and the risk is higher for first-trimester or higher-dosage exposure. Ideally, pregnancy should be planned during remission from bipolar disorder and lithium prescribed within the lowest therapeutic range throughout pregnancy, particularly during the first trimester and the days immediately preceding delivery, balancing the safety and efficacy profile for the individual patient.

The management of women with bipolar disorder during both the antenatal and postnatal periods is associated with major obstetric and mental health concerns because of the inherent risks related to bipolar disorder itself as well as its treatment (1). Balancing the benefits and risks of intervention for

bipolar disorder is therefore crucial. This is particularly so because women with bipolar disorder are typically young at illness onset, placing them at risk for episodes throughout their reproductive years (2), although fertility rates among women with bipolar disorder are lower than those among the general population (3).

Women with bipolar disorder often exhibit a rapid-cycling course, which is also associated with a lifetime predominance of depression with mixed features, as well as long latency between treatment initiation and the onset of therapeutic effects for a wide range of mood-stabilizing medications, including lithium (4). Both bipolar disorder itself and the abrupt discontinuation of lithium at any time before conception, during pregnancy, or during the breastfeeding period carry a significant risk for relapse and recurrence (5), potentially increasing the risk for suicide as well as of psychosocial and general medical deterioration (6, 7). Medico-legal issues, as well as concerns about potential detrimental effects on fetal development associated with lithium exposure during pregnancy and the lack of a consistent position across most guidelines, may lead to the premature and often abrupt interruption of lithium treatment. In fact, the prescribing clinician or the insufficiently informed patient may discontinue lithium without carefully weighing the risk-benefit profile for the mother and the offspring.

According to a recent meta-analysis assessing maternal and infant outcomes associated with lithium use during pregnancy from six international cohorts (8), lithium exposure during the first trimester was associated with a relative 171% increase in the odds of a major malformation (an absolute risk of 7.4% with lithium, compared with 4.3% in offspring not exposed to lithium), and a 162% increase in the odds of neonatal readmission rates within 4 weeks of birth compared with an unexposed mood disorder reference group (an absolute risk of 27.5% in offspring exposed to lithium, compared with 14.3% in offspring not exposed). In contrast, the odds for major malformations in exposed offspring, especially neural tube defects and Ebstein's anomaly (downward displacement of the tricuspid valve into the right ventricle and variable levels of right ventricle hypoplasia) did not significantly differ from those in unexposed offspring (8). Aside from lithium teratogenicity, neonatal toxicity events may occur in offspring exposed to lithium during labor, including the so-called floppy baby syndrome (characterized by cyanosis and hypotonicity), neonatal hypothyroidism, and nephrogenic diabetes insipidus (9). Nonetheless, the appraisal of the risk for long-term adverse neurodevelopmental consequences of intrauterine exposure to lithium is hampered by the fact that most studies have compared exposed children with children from unaffected populations, which did not allow for correction of the potential influence of genetic predisposition or parental psychiatric illness (10).

It has been shown that lithium is the most effective prophylactic treatment option for bipolar disorder (as well as other psychiatric disorders, including recurrent major depression and schizoaffective disorder), even during the perinatal period if properly used, and that its side effect profile is more favorable than generally assumed (11). Moreover, the U.S. Food and Drug Administration (FDA) issued a warning about the use of antipsychotics during the peripartum period (12), and the risk of fetal valproate and carbamazepine syndrome (and the confirmed neurodevelopmental teratogenicity of valproate) contraindicates the use of such medications during this phase of the female reproductive cycle (13). Further complicating the clinical decision is the fact that most evidence on medications other than lithium is anecdotal or outdated. While specific guidelines, such as the National Institute for Health and Care Excellence guidelines (14), state that the use of lithium is contraindicated, especially during the first trimester of pregnancy, "evidence-based" guidelines are not necessarily concordant with "consensus-based" guidelines, which need to weight and integrate evidence for efficacy and safety (1). Such a difference is particularly true for suggested algorithms, which can change dramatically depending on whether safety or efficacy is

prioritized, shifting the ultimate question for the clinician from whether or not to use lithium during the peripartum period in women with bipolar disorder to how to use lithium optimally in this population (15).

Our aim in this systematic review and meta-analysis was to provide a critical appraisal of the evidence of both the efficacy and the safety of lithium during the peripartum period, focusing on women with bipolar disorder and their offspring, in order to inform prescribing clinicians.

Methods

We followed the procedures outlined in the 2015 update of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (http://www.prisma-statement.org/) (16) and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (17), following an a priori (but unpublished) protocol.

Search Strategy

Four authors divided into two teams (E.M., E.S., M.F., A.A.) independently searched the PubMed and Scopus databases for records since database inception through October 18, 2018. The following search strings were used in PubMed and then adapted for Scopus: search 1: "(pregnancy OR pregnant OR pre-natal OR prenatal OR peri-natal OR perinatal OR post-natal OR postnatal OR delivery OR pre-partum OR prepartum OR peri-partum OR peripartum OR post-partum OR postpartum)"; search 2: lithium; search 3: searches 1 AND 2 with the filter "humans." Finally, the results of the electronic searches were augmented by a manual search and cross-referencing of the reference lists of relevant studies.

Eligibility Criteria

We limited our search to original studies (of any design) reporting quantitative data on the efficacy and safety outcomes of women treated with lithium during pregnancy and the postpartum period, and/or lithium exposure to the fetus and/or the newborn. However, we did not focus on risks for the newborn related to lithium treatment during breastfeeding (see reference 18 for a review).

We excluded review articles, case reports or series (i.e., N<10 subjects), expert opinion, animal studies, and studies without quantitative data. In the case of multidiagnostic samples, we excluded studies that did not provide data separately for women with bipolar disorder. We included studies without a control group for the qualitative synthesis of the evidence, whereas the quantitative extraction was performed only on those studies that used a control group, allowing an effect size computation.

Meta-Analysis Primary and Secondary Outcomes, and Qualitative Synthesis

In the meta-analysis, the primary safety outcome was the risk of any malformation; the primary efficacy outcome was "relapse prevention" (whether during pregnancy or in the postpartum period). Except for lactation-related outcomes, we included any other safety and primary outcomes during pregnancy and the postpartum period that were reported in eligible studies (secondary outcomes). In the qualitative synthesis, we also extracted the main safety and efficacy outcomes during pregnancy and the postpartum period from studies without a control group, and we provided a narrative synthesis of eligible studies' findings grouped by study safety and efficacy and study design.

Data Extraction

The retrieved records were independently assessed by two authors (M.S., M.F.) at the title and abstract level, followed by a detailed evaluation of the full text. Any inconsistencies were resolved by consensus or inclusion of a third reviewer blind to the other reviewers' decisions (A.A.).

The following information was extracted independently by two authors (E.S., E.M.) for the lithium and control groups: author, publication year, study design, study aim (efficacy, safety), pregnancy (including gestational week) or postpartum period, and sample size. We extracted quantitative outcome measures related to efficacy and safety, as well as the description of the main findings.

We also extracted the information needed to assess the quality of the included studies with the Newcastle-Ottawa Scale (19) for observational studies and the Cochrane risk of bias tool for randomized studies (20). We adopted the thresholds for converting Newcastle-Ottawa Scale scores into "good," "fair," and "poor" quality criteria, previously described by systematic reviews (21).

Evidence Synthesis

We conducted a narrative synthesis of the results of the studies that fulfilled the predetermined eligibility criteria. We performed a random-effects meta-analysis (22) of outcomes reported in at least two studies, given the population heterogeneity, using the Comprehensive Meta-Analysis package, version 2 (23). Effect sizes and their 95% confidence intervals were computed on the basis of the type of results reported in each study; adjusted effect sizes were prioritized whenever both adjusted and unadjusted estimates were available. Publication bias was assessed when at least three studies provided results for a given outcome, using visual inspection of funnel plots and Egger's test (whereby $p<0.05$ indicates significant publication bias) (24). We calculated the number needed to harm (NNH) or the number needed to treat (NNT) for harm or benefit, respectively, by dividing 1 by the risk difference of event rates in each group. Finally, we calculated the prevalence of adverse health outcomes from cohort studies to put association metrics into an epidemiologic context.

Results

Synthesis of the Search Results and Main Characteristics of the Included Studies

The search flow and the main results are reported in Figure 1. Of 3,067 unduplicated records, 57 full-text articles were retrieved and assessed for eligibility. (The list of studies excluded after full-text assessment, with the reasons, is available from the authors on request.) Of these, 33 articles were excluded because they did not report data on the safety or efficacy of lithium (14 articles), were reviews (14 articles), were not published in English (three articles), or were case reports (two articles) (see Table S1 and references in the online supplement). The remaining 24 articles covered 29 studies that reported qualitative information on either the safety or the efficacy of lithium during pregnancy or the postpartum period for the exposed women and/or on safety for the fetus or newborn, suitable for the narrative synthesis, and 13 studies (covered by eight articles) were suitable for the meta-analysis.

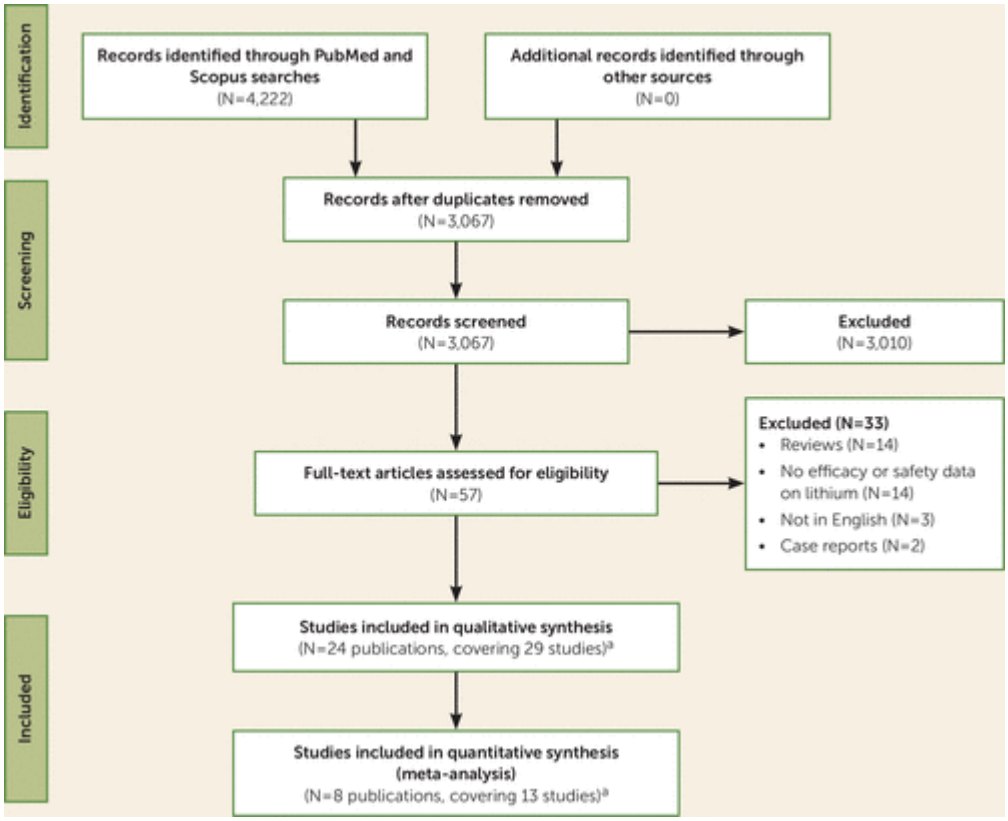

FIGURE 1. Flow diagram of study selection for qualitative synthesis and a meta-analysis

[a] One publication covered six original cohort studies.

The characteristics of the included studies, together with a narrative synthesis of the study results, are reported in Table 1, and the quality of the appraised evidence is outlined in Table S2 in the online supplement. Briefly, besides previous studies that represent the first attempts to quantify the effects of lithium in pregnancy and were of poor quality, relevant information on lithium dosage and related safety are presented in Table S2 from more recent studies.

TABLE 1. Characteristics of included studies and narrative synthesis of results

Enlarge table

Quality of the Included Studies

Overall, among case-control studies and cohort studies, 20 had “good” quality and six were of “poor” quality overall, based on the Newcastle-Ottawa Scale (see Table S2 in the online supplement), according to systematic reviews (21). The Cochrane risk of bias tool indicated an unclear risk for bias for one interventional study, and two had a high risk of bias (two randomized controlled trials, one trial without a control group). All studies included in the meta-analysis on safety outcomes had good quality on the Newcastle-Ottawa Scale, and studies included in the efficacy outcomes meta-analysis had a high risk of bias.

Meta-Analysis

The available information from eight studies reporting on 13 comparisons (k) between lithium-exposed and unexposed control subjects (both in the general population and patients with affective disorders not exposed to lithium) (2, 8, 11, 25–29) (N=1,349,563 pregnancies) allowed pooling of data on the effects of antenatal exposure to lithium regarding risk of spontaneous abortion (two

studies, N=1,289), preterm birth (usually defined as a gestation period <37 weeks) (six studies, N=23,695), low birth weight (three studies, N=23,238), any congenital anomaly (four studies, N=23,046), and cardiac congenital anomalies (four studies, N=1,348,475).

Available data allowed additional analyses comparing lithium-exposed pregnancies with unexposed general-population pregnancies regarding preterm birth (two studies, N=845) and any congenital anomaly (two studies, N=1,003). The data also allowed comparisons between lithium-exposed and unexposed pregnancies in women with affective disorders regarding spontaneous abortion (two studies, N=441), preterm birth (six studies, N=23,001), low birth weight (three studies, N=22,527), any congenital anomaly (four studies, N=22,225), and cardiac anomalies (four studies, N=24,699) (Table 2).

TABLE 2. Random-effects meta-analysis of the safety and efficacy outcomes of lithium exposure during any time of pregnancy and during the postpartum period[a]

Enlarge table

Spontaneous abortion.

Lithium exposure during the first trimester of pregnancy was associated with a significantly increased risk of spontaneous abortion (2, 26) (two studies, k=3, N=1,289; odds ratio=3.77, 95% CI=1.15–12.39; I^2=86.56%; NNH=15, 95% CI=8–111, p=0.03; I^2=56.17%) when compared with any unexposed group. When compared with unexposed patients with affective disorders, the difference was not significant (two studies, k=2, N=541; odds ratio=2.46, 95% CI=0.56–10.77; I^2=82.1%) (Tables 2 and 3 and Figure 2).

TABLE 3. Random-effects meta-analysis of the safety outcomes of lithium exposure during the first trimester of pregnancy[a]

Enlarge table

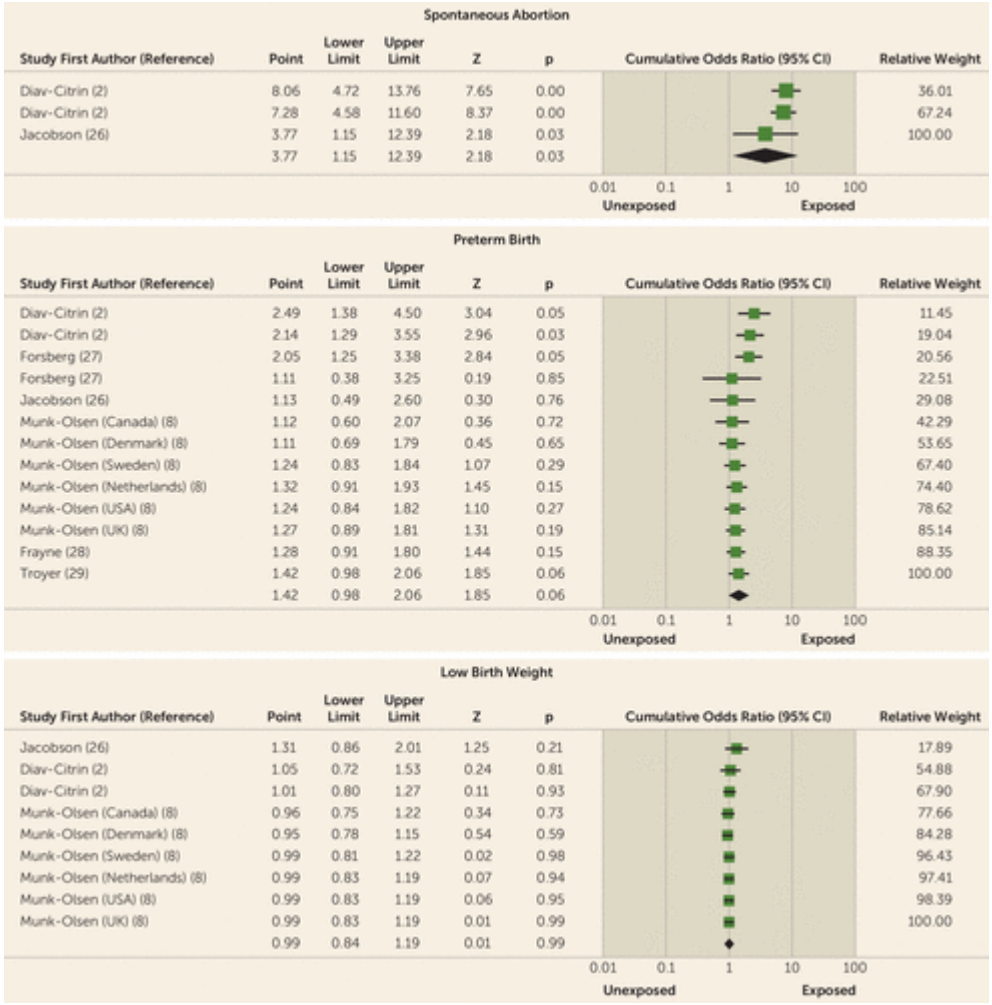

FIGURE 2. Risk of spontaneous abortion, preterm birth, and low birth weight associated with lithium exposure at any time during pregnancy

Preterm birth and low birth weight.

Lithium exposure during pregnancy was not associated with a significantly increased risk of preterm birth (2, 8, 26–29) when compared with any unexposed group (six studies, k=13, N=23,695; odds ratio=1.42, 95% CI=0.98–2.06; I^2=60.6%), with unexposed patients with affective disorders (six studies, k=11, N=23,001; odds ratio=1.34, 95% CI=0.89–2.01; I^2=62.8%), or with the unexposed general population (two studies, k=2, N=845; odds ratio=2.22, 95% CI=0.99–4.97; I^2=6.68%) (Table 2). Lithium exposure during pregnancy was not significantly associated with low birth weight (2, 8, 26) when compared with any unexposed group (three studies, k=9, N=23,238; odds ratio=0.99, 95% CI=0.84–1.19; I^2=0%) or with unexposed patients with affective disorders (three studies, k=8, N=22,527; odds ratio=1.07, 95% CI=0.85–1.34; I^2=0%) (Table 2 and Figure 2). Results were similar when exposure occurred specifically during the first trimester (Table 3).

Any congenital anomaly.

Lithium exposure during pregnancy was associated with a significantly increased risk of any congenital anomaly (2, 8, 25, 26) when compared with any unexposed group (four studies, k=11, N=23,300; odds ratio=1.81, 95% CI=1.35–2.41; I^2=0%; NNH=33, 95% CI=22–77, p<0.001; I^2=6.6%). The association was significant in analyses restricted to patients with affective disorders (four studies, k=9, N=22,297; odds ratio=1.75, 95% CI=1.21–2.52; I^2=15.4%; NNH=38, 95% CI=20–333, p=0.03;

I^2=29.3%) and when the referent was the unexposed general population (two studies, k=2, N=1,003; odds ratio=2.03, 95% CI=1.03–3.99; I^2=0%; NNH=22, 95% CI=12–200, p=0.03; I^2=0%) (Table 2 and Figure 3). Results were similar for first-trimester exposure (Table 3 and Figure 3). Finally, the major malformations considered were those diagnosed by age 1 year, including singular and combined structural defects, syndromes, sequences (groups of related anomalies that generally stem from a single initial major anomaly that alters the development of other surrounding or related tissues or structures), and associations—such as cardiovascular defects, neural tube defects, hypospadias, and epispadias. Major cardiac malformations were defined as atrial and atrioventricular septal defects and Ebstein's anomaly, but excluding atrial septal defect, and excluding patent ductus arteriosus in infants born before 37 weeks of gestation, according to the European Surveillance of Congenital Anomalies guide (30).

FIGURE 3. Risk of any congenital anomaly associated with lithium exposure at any time during pregnancy and during the first trimester compared with unexposed women (either bipolar disorder or general-population controls)

Cardiac anomalies.

Lithium exposure during pregnancy was associated with a significantly increased risk of cardiac malformations (2, 8, 11, 25) (four studies, k=12, N=1,348,475; odds ratio=1.86, 95% CI=1.16–2.96; I^2=40.16%; NNH=71, 95% CI=48–167, p<0.001; I^2=4.62%) when compared with any unexposed group and with the general population (three studies, k=3, N=1,324,591; odds ratio=4.00, 95% CI=1.19–13.4, p=0.03; I^2=63.2%; NNH=37, 95% CI=19–1000, p=0.04; I^2=46.4%). When compared with unexposed patients with affective disorders, the difference was not significant (four studies, k=9, N=24,699; odds ratio=1.59, 95% CI=0.91–2.77; I^2=35.4%) (Table 2 and Figure 4).

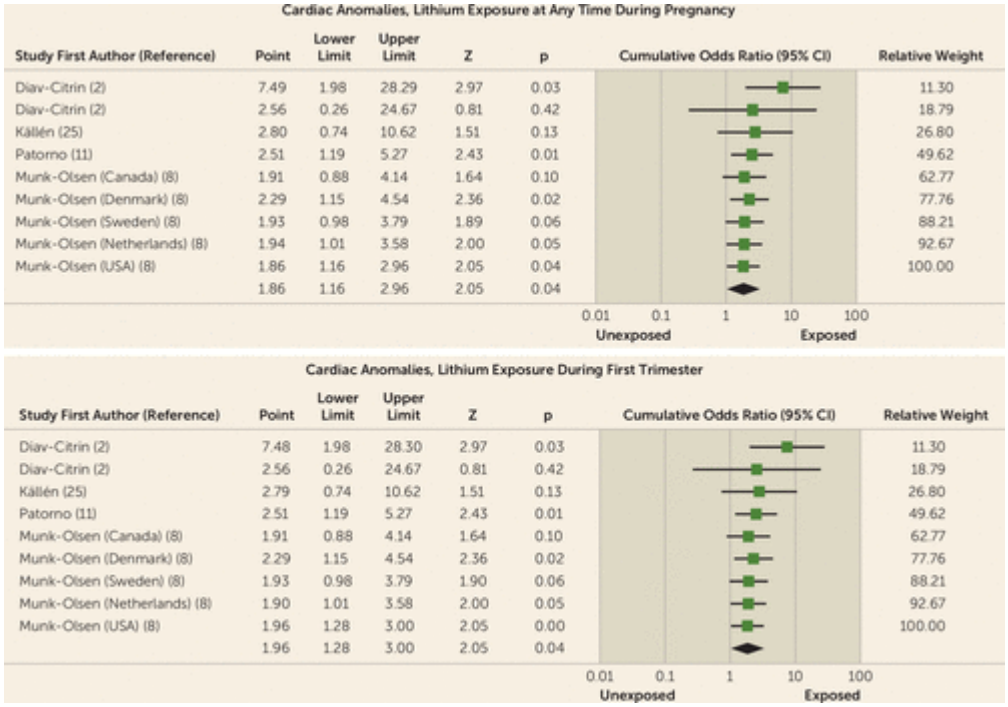

FIGURE 4. Risk of cardiac anomalies associated with lithium exposure at any time during pregnancy and during the first trimester compared with unexposed women (either bipolar disorder or general-population controls)

In the analysis of exposure during the first trimester, lithium was associated with an increased risk of cardiac malformations compared with any unexposed group (four studies, k=11, N=1,348,403; odds ratio=1.96, 95% CI=1.28–3.00; I^2=29.92%; NNH=71, 95% CI=48–143, p≤0.001; I^2=11.8%). The risk was identical to that for exposure during any pregnancy period (as all studies investigated exposure during the first trimester) compared with the general population, and was again significantly increased compared with unexposed patients with affective disorders (four studies, k=8, N=24,627; odds ratio=1.75, 95% CI=1.08–2.84; I^2=19.99%; NNH=83, 95% CI=48–333, p=0.01; I^2=0%) (Table 3 and Figure 4).

Relapse.

Lithium was significantly more effective than no prophylaxis in preventing postpartum mood episodes (any polarity; follow-up range, 4 weeks to 2 years) in women with mood disorders (two studies, k=2, N=48; odds ratio=0.16, 95% CI=0.03–0.89; I^2=52.7%; NNT=3, 95% CI=1–12, p=0.12; I^2=52.7%). The risk of relapse during pregnancies with lithium exposure could not be computed because of insufficient data.

Discussion

Our aim in this systematic review was to summarize the evidence on the safety and efficacy of lithium use during pregnancy and the postpartum period. The quantitative synthesis showed that lithium exposure at any time during pregnancy was associated with a significantly increased risk of spontaneous abortion, any congenital anomaly, and cardiac anomalies, but it was not related to preterm delivery and low birth weight when compared with women with bipolar disorder unexposed to lithium or with the general population. When the control group was matched for the presence of an underlying mood disorder, lithium use during the first trimester of pregnancy was not associated

with an increased risk for spontaneous abortion but was still associated with a significantly increased risk for any congenital malformations and cardiac malformations, yet with low absolute risk.

During the first trimester of pregnancy, the risk of any congenital anomaly retained statistical significance on stratification of any comparison groups (odds ratio=1.75; 95% CI=1.23–2.48, p=0.002; and odds ratio=1.81; 95% CI=1.35–2.41, p≤0.001). However, such association, although clinically relevant, should be balanced against several unhealthy behavioral factors, such as smoking and alcohol consumption among others, that are known to be associated with mood disorders and illness episodes (either depressive or manic) and which could themselves have a detrimental effect on both the mother and the fetus or newborn.

Consistent with the timing of organogenesis, the risk of cardiac anomalies was significantly higher in children of lithium-exposed than unexposed patients with bipolar disorder during the first trimester of pregnancy, but not in those of mothers exposed at any time of pregnancy. In contrast, the meta-analysis by Munk-Olsen et al. (8) documented a statistically significant increased risk for major malformations during the first trimester of pregnancy, but not for major cardiac malformations. This discrepancy could be due to the inclusion of larger samples in our analysis, especially those provided by Patorno et al. (11). In this sense, we acknowledge that some outcomes pooled in the present analyses should be considered preliminary, especially in the context of few comparisons and high between- and within-study heterogeneity as well as our inability to systematically stratify for study design.

It is worth noting, however, that while we were able to expand the sample size and strengthen the statistical power of our analysis, the previous study by Munk-Olsen et al. (8) also documented the rate of neonatal readmission within 28 days of birth, which was seen to be increased in the lithium-exposed group compared with the unexposed mood disorder group. On the other hand, our meta-analysis included the outcome “spontaneous abortion” (which yielded a statistically significant increased risk among lithium-exposed women with bipolar disorder during any time and the first trimester of pregnancy when compared with overall control subjects: odds ratio=3.77, 95% CI=1.48–12.39, p=0.03), also allowing comparison with general-population controls beyond that of lithium-exposed women with bipolar disorder (8).

Besides the period of exposure, lithium dosage also seems to play a role in determining health outcomes of the fetus and newborn. As outlined by our qualitative synthesis here, the risk of cardiac malformations seems to triple with dosages >900 mg/day compared with dosages ≤600 mg/day (11), and a median lithium serum level >0.64 mEq/L seems to increase the risk of neonatal complications, such as CNS, cardiac, thyroid, hepatic, neuromuscular, renal, and respiratory complications. Lowering the lithium dosage during the first trimester, yet keeping it within the therapeutic range, could minimize both the risk of malformations (compared with higher dosages) and the risk of relapse compared with lithium withdrawal. However, beyond safety concerns, it is important to note that lowering the lithium dosage toward the lower end of the therapeutic range (usually defined as 0.6–1.2 mEq/L) may result in suboptimal dosages for patients who respond to concentrations ≥0.8 mEq/L. This potential complication is crucial especially for the most severe cases of bipolar disorder (e.g., those with psychotic features and/or high risk for suicidal behavior). Lowering lithium levels on the days immediately before delivery (yet with prompt dosage resumption immediately after delivery) may minimize neonatal complications, with the newborn more vital and less sedated, with recommendations on this topic varying slightly across the international guidelines that we reviewed (31). However, currently, it is impossible to determine what the potential harmfulness of lithium exposure to the newborn during the delivery may be compared with exposure during pregnancy. In other words, the recommendation to swiftly resume the patient’s regular lithium dosage soon after

delivery may need to be decided on a case-by-case basis, also keeping in mind the slight increase of lithium serum levels in the postpartum period compared with the last trimester of pregnancy. Since different women benefit from different lithium dosages, lithium dosing needs to be individualized on the basis of prepregnancy relationships between lithium dosage, serum level, efficacy, and tolerability, which must be ascertained anamnestically and, ideally, via periodic sampling of lithium serum levels during pregnancy (32).

Clinicians need to be aware of and consider that lithium serum levels fluctuate during pregnancy. Specifically, an increased glomerular filtration rate leads to a 24% mean reduction in lithium blood levels during the first trimester, 36% during the second trimester, and 21% during the last trimester of pregnancy; in contrast, the serum levels of lithium may rise by 9% during the postpartum period, as detailed elsewhere (32). Close monitoring of the pregnant woman's serum lithium levels is therefore crucial to inform clinical choices on the basis of the physiological fluctuations occurring during pregnancy to avoid suboptimal therapeutic dosing for the pregnant woman, or potentially toxic doses thereafter, especially for the infant, in whom the adverse neonatal effects of lithium, such as hypoglycemia, cardiac arrhythmia, thyroid dysfunction, and neonatal lithium toxicity, are dose related (32).

However, considering the significant publication bias on the matter (and the virtual underrepresentation of most outdated studies because of stringent PRISMA criteria) and the chance of inflated cumulative effect sizes because of comparison of a handful of studies featuring disproportionate sample sizes and designs for selected outcomes, no firm recommendation on the need for lithium dosage adjustment can be provided at this time, and some women may require a steady dosage of lithium whenever sudden relapse is a concern and the harm to the newborn is considered negligible or nil by the prescribing clinician. In addition, abrupt discontinuation should be avoided whenever possible, in line with the recently released FDA labeling rules for pregnancy and lactation emphasizing the risks posed by the untreated disorder if medication is discontinued (33), considering the lack of sufficient quantitative information allowing any reliable meta-analytic pooling on the matter at the time of writing.

Although on the question of relapse our analysis could include only two studies, lithium was significantly more effective for the prevention of mood episode relapse in the postpartum period than no lithium prophylaxis. This finding is highly clinically relevant because the risk of bipolar disorder relapse during pregnancy has been estimated to be almost three times higher than in nonpregnant women (7). Nevertheless, our analyses indicated that lithium has a relatively favorable risk-benefit profile, with an NNT of 3 ("prevention of mood episode relapse during any time of pregnancy") counterbalanced by an NNH of 33 ("risk of any congenital anomaly at any time during pregnancy").

The results of this systematic review and meta-analysis must be interpreted within their limitations. First, only a few studies were available for quantitative meta-analysis. This lack of data, most pronounced for efficacy outcomes associated with lithium maintenance treatment during pregnancy, precluded any meta-regression or subgroup analyses and therefore may have yielded results that are not definitive. This limitation pertains mainly to the exploratory meta-analysis of the outcome "spontaneous abortion," which included only a handful of comparisons, and those outcomes with high heterogeneity. Therefore, findings in this admittedly challenging-to-study population need to be followed up by more large controlled and nationwide database studies, such as those considered in the recent meta-analysis by Munk-Olsen et al. (8). Furthermore, a publication or reporting bias may be present concerning some of the outcomes other than major cardiac malformations (e.g., birth weight) that were not systematically documented in the appraised literature. With few notable

exceptions (8), the assessed studies were unclear on whether they excluded per protocol women who were taking potentially teratogenic medications other than lithium, were taking other psychotropic medications, or had substance or alcohol misuse and other maternal conditions potentially influencing fetal or newborn health outcomes.

Moreover, no quantitative data regarding serum lithium concentration and temporal lithium exposure were available aside from the information provided by a single study (34). Future studies should systematically record lithium dosages during the peripartum period, also taking into account that serum levels may fluctuate during pregnancy (35). Furthermore, the data were inadequate for further stratifying the lithium-unexposed bipolar disorder control subjects by exposure to alternative mood-stabilizing agents, as well as by additional confounding factors (e.g., type of bipolar disorder).

Strengths of this study include the large sample size and the resulting high statistical power, the stratified comparison between lithium-exposed and unexposed patients with bipolar disorder and between lithium-exposed patients and the general population whenever both control groups were available, as well as the stratification of the analysis between any time during pregnancy and exposure during the first trimester only, whenever possible.

In conclusion, pregnancies in women affected by bipolar disorder should ideally be planned in order to gradually reduce the lithium dosage to the lower extreme of the therapeutic range, in particular during the first trimester, given that a rapid decrease of lithium dosage increases the risk of relapse during pregnancy (7). Pregnancy should not be considered an absolute contraindication to lithium prescription, given the relatively small increase in risk for any malformation or cardiac malformations, and given that such events, fortunately, remain rare (prevalences of 4.2% for any malformation and 1.2% for cardiac malformations), as opposed to the frequent relapse of mood episodes during pregnancy and in the postpartum period (20%–70% over 12 months) (36, 37), which can themselves have severe health implications for both mother and fetus or newborn. In particular, women with affective disorders who are currently stable on lithium or who have benefited from lithium and who experienced suboptimal outcomes with treatments other than lithium should be treated with lithium, and at the lowest effective dosages according to guidelines (11, 34). Finally, as eloquently noted by Snellen and Malhi (1), while “the aim is always to achieve the minimum effective dosage, emphasis needs to be on effective rather than minimal, and this is often not the case … and, half treatment represents the worst possible scenario, as it exposes the fetus to the risks of treatment and maternal mental illness.”

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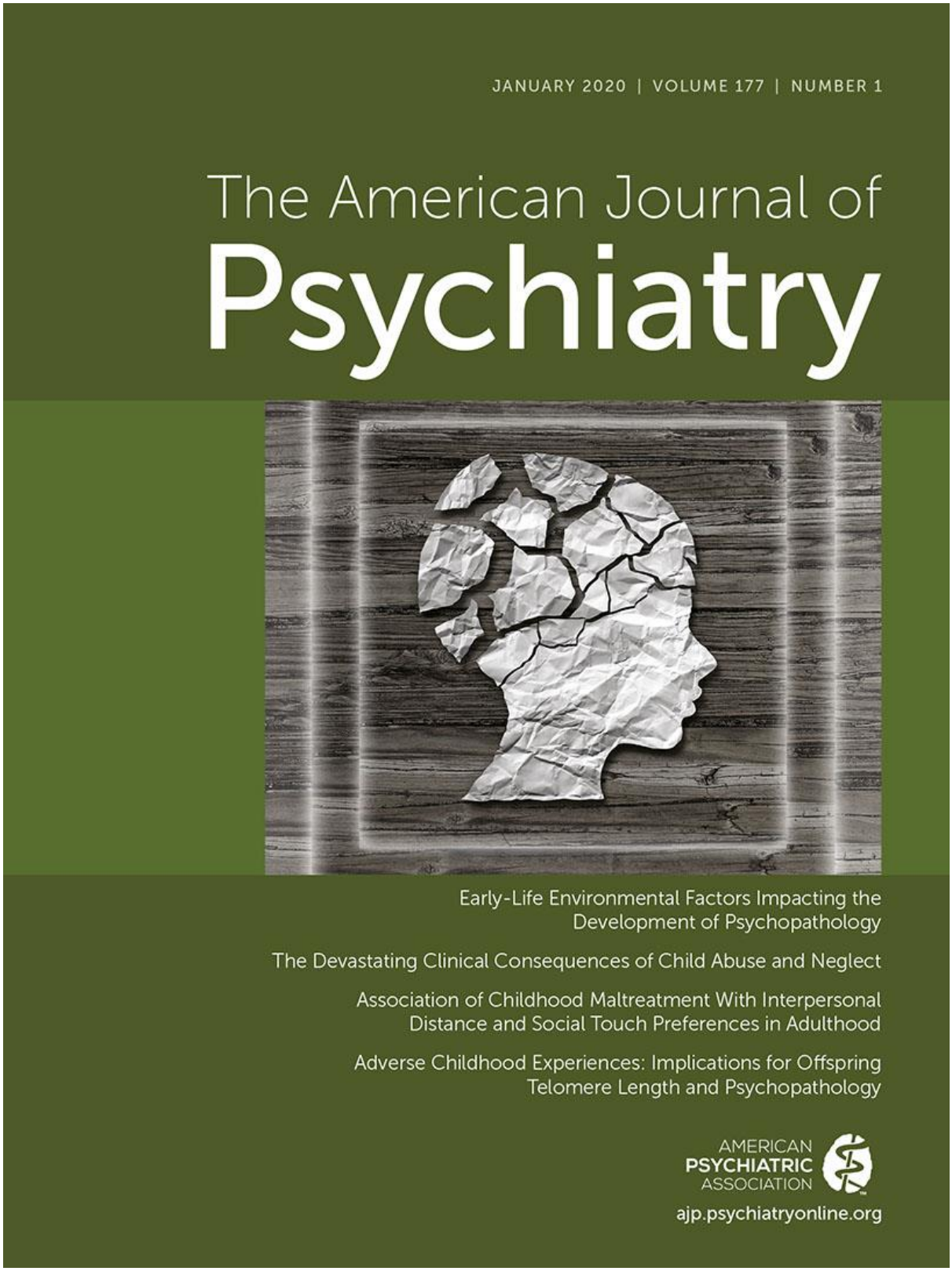

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