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

Michele Fornaro, M.D., Ph.D., Elena Maritan, M.D., Roberta Ferranti, M.D., Leonardo Zaninotto, M.D., Ph.D., Alessandro Miola, M.D., Annalisa Anastasia, M.D., Andrea Murru, M.D., Ph.D., Eva Solé, M.D., Brendon Stubbs, Ph.D., André F. Carvalho, M.D., Ph.D., Alessandro Serretti, M.D., Ph.D., Eduard Vieta, M.D., Ph.D., Paolo Fusar-Poli, M.D., Ph.D., Philip McGuire, F.R.C.Psych., F.Med.Sci., Allan H. Young, M.D., Ph.D., Paola Dazzan, M.D., Ph.D., Simone N. Vigod, M.D., Christoph U. Correll, M.D., Marco Solmi, M.D., Ph.D.

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.

AJP in Advance (doi: 10.1176/appi.ajp.2019.19030228)

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). Medicolegal 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.

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.

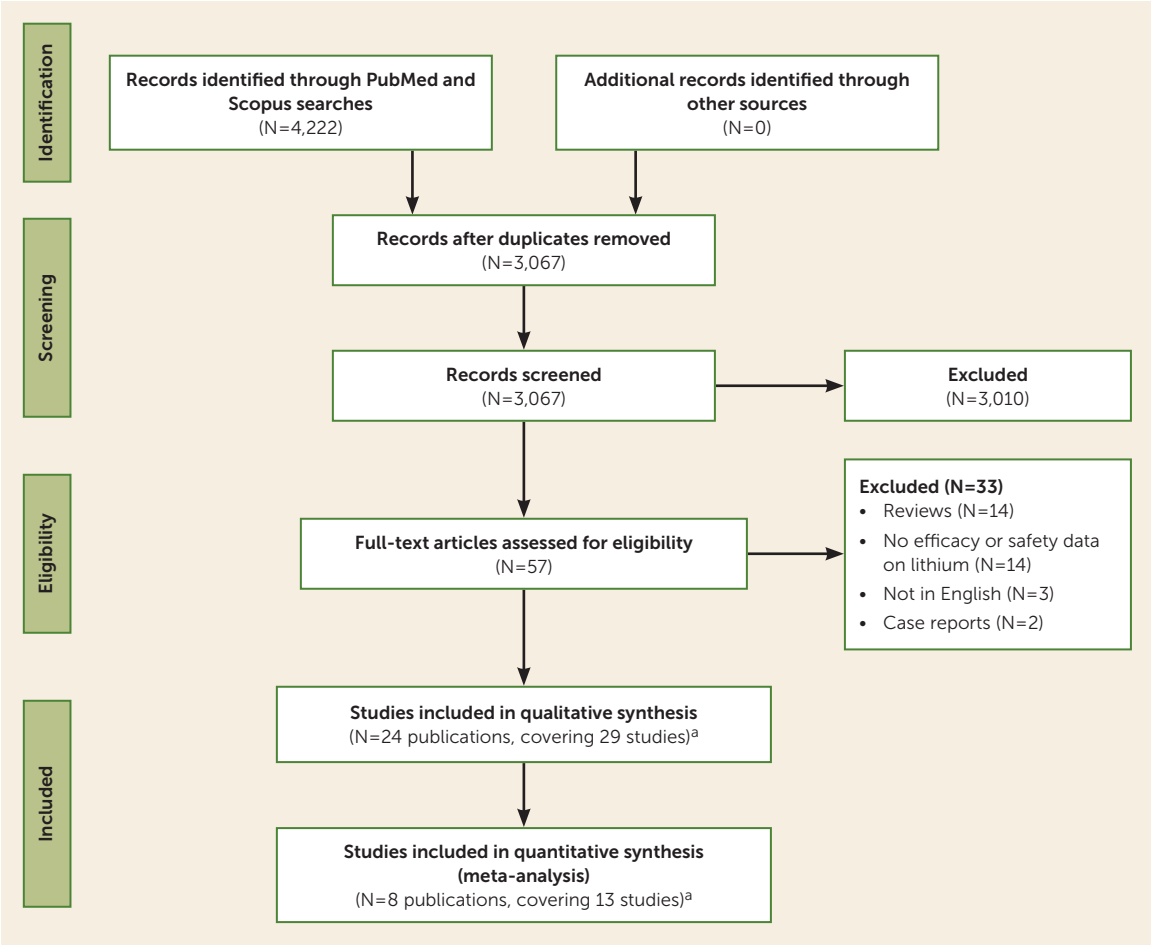
Quality of the Included Studies

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

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



[a] One publication covered six original cohort studies.

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).

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).

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).

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

First Author, Year (Reference)	Sample Size (N)	Source	Lithium Exposure	Comparison	Main Safety or Tolerability Results (Systematic Qualitative Review)
Safety: case-control studies					
Edmonds 1990 (38)	68	Birth Defects Monitoring Program (USA)	Pregnancy	Lithium exposure in births with versus without Ebstein's anomaly	Among the 34 infants with confirmed Ebstein's anomaly and the infants in the control group, we found none whose mother had a history of manic-depressive illnesses or lithium use during pregnancy.
Zalzstein 1990 (39)	227	Department of Pediatrics and the Research Institute, Hospital for Sick Children, Toronto	Pregnancy (first trimester)	Lithium exposure in births with Ebstein's anomaly versus lithium exposure in births with neuroblastoma	One case of in utero lithium exposure in the 168 mother-child-pair control group with neuroblastoma, but no cases in mothers of 59 children with Ebstein's anomaly. The results can rule out (with 80% power and an alpha of 0.05) increased risk of more than 28-fold. This potential risk is much lower than the historically claimed 500-fold computed from the uncontrolled Danish registry (40).
Czeizel 1990 (41)	32,224	Hungarian Case-Control Surveillance of Congenital Anomalies	Pregnancy	Lithium exposure in births with versus without cardiac anomaly	No statistically significant association was found between the use of lithium and the appearance of any congenital anomaly.
Boyle 2017 (42)	114,832	15 congenital anomaly registries in the European Surveillance of Congenital Anomalies	Pregnancy (first trimester)	Lithium exposure in births with Ebstein's anomaly versus lithium exposure in births with another cardiac anomaly	Ebstein's anomaly was associated with maternal mental health problems generally rather than lithium or benzodiazepines specifically; therefore, changing or stopping medications may not be preventive.
Lisi 2010 (43)	18,131	International Clearinghouse of Birth Defects Surveillance and Research	Pregnancy (first trimester)	Lithium exposure in patients with versus without malformation	No statistically significant association was found between malformations and the use of lithium.
Safety: prospective cohort studies					
Schou 1976 (44)	120	Lithium Baby Register (Scandinavia)	Pregnancy (first trimester)	Physical and mental development of non-malformed babies exposed to lithium versus their unexposed siblings	This was is a questionnaire follow-up of the physical and mental development of lithium children who were not malformed at birth. Sixty lithium-exposed children were examined, and their unexposed siblings served as a control group. The data do not reveal any increased frequency of physical or mental anomalies among the lithium-exposed children.
Jacobson 1992 (26); included in the meta-analysis	286	Four teratogen information centers in the United States and Canada	Pregnancy (first trimester)	Malformations and perinatal complications in lithium exposure versus no exposure	No statistically significant difference was found between groups in total malformation rate (2.8% lithium group, 2.4% control group), and no difference was found in risk ratio for congenital malformation, cardiac malformation, or Ebstein's anomaly. Similar rates of spontaneous abortion were seen in the lithium and nonlithium groups (9% and 8%), as well as similar rates of premature delivery (4% and 5%).

continued

TABLE 1, *continued*

First Author, Year (Reference)	Sample Size (N)	Source	Lithium Exposure	Comparison	Main Safety or Tolerability Results (Systematic Qualitative Review)
Diav-Citrin 2014 (2); included in the meta-analysis	1,003	Israeli Teratology Information Service (Jerusalem)	Pregnancy (first trimester)	Malformations and perinatal complications in lithium exposure versus no exposure, and versus controls	There were significantly more miscarriages and elective terminations in pregnancies exposed to lithium (16.4% and 9.3%) and among mothers with bipolar disorder (8.3% and 8.3%) than in an unexposed group (5.7% and 2%). The rate of preterm deliveries was significantly higher in the lithium group (13.7%) and the bipolar disorder group unexposed to lithium (10.2%) compared with unexposed pregnancies (6.0%). The rate of major congenital anomalies after exclusion of genetic or cytogenetic anomalies was not significantly different among the three groups from the Israeli register. However, when data from Australia and Canada were also considered, babies exposed to lithium had significantly higher rates of major anomalies without chromosomal or genetic conditions (8.6% and 2.5%), cardiovascular anomalies (3.9% and 0.5%), cardiovascular anomalies excluding resolved cases (2.6% and 0.2%), and non-cardiovascular anomalies (5.9% and 2%).
Newport 2005 (34)	24	Women's Mental Health Program Delivery Information Sheet (USA)	Pregnancy and postpartum	Perinatal complications in high-lithium versus low-lithium exposure	The rate of all complications except gestational diabetes was consistently higher in the high lithium exposure group. In particular, the rates of CNS and neuromuscular complications were significantly higher, the duration of infant hospital stays was significantly longer, and 1-minute Apgar scores were significantly lower in the high lithium exposure group. The rates of preterm delivery, low birth weight, and infant respiratory complications were higher in the high lithium exposure group than in the low lithium exposure group, but the differences only approached significance.
Safety: retrospective cohort studies					
Schou 1973 (45)	118	Register of Lithium Babies (Scandinavia)	Pregnancy (first trimester)	Malformations in babies exposed to lithium	Of the 118 children exposed to lithium, five were stillborn and seven died within the first week of life; six of these twelve children had malformations. The total number of children with malformations was nine, of which two had Down's syndrome.
Weinstein 1975 (46)	143	Register of Lithium Babies (USA)	Pregnancy	Malformations in babies exposed to lithium	The 143 cases of lithium use during pregnancy recorded by the register showed that infants exposed to lithium appeared to have a higher than expected ratio of cardiovascular anomalies (7.7%) to all anomalies (9.1%) and may have an increased risk of congenital heart disease. The author believes that these findings justify a conservative policy on the use of lithium with fertile and pregnant women.

continued

TABLE 1, *continued*

First Author, Year (Reference)	Sample Size (N)	Source	Lithium Exposure	Comparison	Main Safety or Tolerability Results (Systematic Qualitative Review)
Weinstein 1976 (47)	166	Register of Lithium Babies (USA)	Pregnancy	Malformations in babies exposed to lithium	The ratio of Ebstein's anomaly to all reported nontrivial anomalies was 1:4.5; the ratio of Ebstein's anomaly to all forms of congenital heart disease to all nontrivial malformations is 1:1.5. In the register, the ratio of malformations of the tricuspid valve and tricuspid atresia to all cardiac anomalies was about 1:2.4, and the ratio of tricuspid atresia to all congenital heart defects in the baseline studies was about 1:44. The maximum frequencies of congenital malformations reported to the register (10.8%) did not substantially exceed the expected incidence of such malformations in the general population.
Källén 1983 (25); included in the meta-analysis	287	Registry of congenital malformations, medical birth registry, discharge registry for inpatient psychiatric wards (Sweden)	Pregnancy (first trimester)	Malformations and perinatal outcomes babies exposed versus unexposed to lithium	There was no statistically significant difference between delivery outcome or malformations in women on lithium and women on other psychotropic drugs. None of the infants with heart disease had Ebstein's anomaly.
Van der Lugt 2012 (48)	30	Perinatal Center, Leiden University Medical Center (Netherlands)	Pregnancy	Cognition at follow-up (3–15 years) in babies exposed to lithium	This study reports the long-term outcome of 30 children who were exposed to lithium in utero and were breastfed. One child had signs of a minor neurological dysfunction but without further clinical implications. The results of the cognitive tests were within normal limits. Growth, behavior, and general development were within the normal range. Neurological screening and growth measurements did not show any significant abnormalities in the children; all were well within the normal range.
Forsberg 2018 (27); included in the meta-analysis	39	Karolinska University Hospital, Stockholm	Pregnancy	Cognition at 5 years, and perinatal complications in lithium exposure versus no exposure, and in mood disorder versus controls	The children's full-scale IQ, performance IQ, and verbal IQ results did not differ significantly between lithium-exposed and unexposed groups. The processing speed quotient was significantly lower in children exposed to mood disorders than control subjects. Similar rates of premature delivery and neonatal care and similar Apgar scores at 5 minutes are described across groups.
Patorno 2017 (11); included in the meta-analysis	1,325,563	U.S. Medicaid Analytic eXtract	Pregnancy (first trimester)	Cardiac malformations in babies exposed versus unexposed to lithium, and versus lamotrigine exposure	Cardiac malformations were present in 16 of the 663 infants exposed to lithium (2.41%), 15,251 of the 1,322,955 unexposed infants (1.15%), and 27 of the 1,945 infants exposed to lamotrigine (1.39%). The adjusted risk ratio for cardiac malformations among infants exposed to lithium compared with unexposed infants was 1.65 (95% CI=1.02–2.68). The risk ratio was 1.11 (95% CI=0.46–2.64) for a dosage ≤600 mg/day, 1.60 (95% CI=0.67–3.80) for 601–900 mg/day, and 3.22 (95% CI=1.47–7.02) for more >900 mg/day. The prevalence of right ventricular outflow tract obstruction defects was 0.60% among lithium-exposed infants and 0.18% among unexposed infants (adjusted risk ratio=2.66; 95% CI=1.00–7.06). Results were similar when lamotrigine-exposed infants were used as the reference group.

continued

TABLE 1, *continued*

First Author, Year (Reference)	Sample Size (N)	Source	Lithium Exposure	Comparison	Main Safety or Tolerability Results (Systematic Qualitative Review)
Frayne 2018 (28); included in the meta-analysis	33	Childbirth and Mental Illness Clinic (Australia)	Pregnancy	Malformations and perinatal complications in babies exposed versus unexposed to lithium	In the cohort of women exposed to lithium during the first trimester of pregnancy, there were no recorded congenital abnormalities Women with lithium prescriptions, irrespective of whether they continued or discontinued the medication, represented a high-risk group obstetrically and in antenatal complications (88%).
Troyer 1993 (29); included in the meta-analysis	350	International Register of Lithium Babies (Scandinavia)	Pregnancy	Preterm birth in babies exposed versus unexposed to lithium	The lithium-exposed cohort had a 36% prevalence of preterm delivery. In a cohort of 350 women, significantly more infants in the lithium-exposed group were born at <38 weeks of gestation (33%), compared with infants born to mothers with manic-depressive illness who did not receive lithium (13%) or with mothers without a bipolar disorder diagnosis (12%). Thus, the relative risk of premature delivery for women taking lithium during pregnancy is 2.54 times that for women with or without manic-depressive illness who are not receiving lithium during pregnancy.
Munk-Olsen 2018 (8) (cumulative data from six cohorts); included in meta-analysis	22,124	Denmark register-based cohort (1997–2012); Sweden register-based cohort (2005–2013); Canada register-based cohort (2002–2013); Netherlands clinical cohort; UK clinical cohort (2007–2013); U.S. clinical cohort (2004–2015)	Pregnancy (first trimester or any time)	Lithium-exposed group versus mood disorder reference group	Primary data from pregnant women and their children from six international cohorts based in the community and clinics. Lithium exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. An increased risk for neonatal readmission within 28 days of birth was seen in the lithium-exposed group compared with the reference group (pooled prevalence, 27.5% [95% CI=15.8–39.1] compared with 14.3% [95% CI=10.4–18.2]; pooled adjusted odds ratio=1.62 [95% CI=1.12–2.33]). Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled prevalence, 7.4% [95% CI= 4.0–10.7] compared with 4.3% [95% CI= 3.7–4.8]; pooled adjusted odds ratio=1.71 [95% CI=1.07–2.72]), but for major cardiac malformations the difference was not significant (2.1% [95% CI=0.5–3.7] compared with 1.6% [95% CI=1.0–2.1]; pooled adjusted odds ratio=1.54 [95% CI=0.64–3.70]).
Efficacy: lithium versus nonlithium interventional studies					
Austin 1992 (36); included in the meta-analysis	17	Royal Edinburgh Hospital (Scotland)	Pregnancy and postpartum	Postpartum relapse in women using or not using lithium	Lower relapse rates for lithium-treated compared with non-lithium-treated women during postpartum (odds ratio=0.14, 95% CI=0–6.5). All relapsing women were admitted to hospital with moderate to severe episodes of mania, and all except two (in the untreated group) relapsed within 3 weeks of parturition. The average duration of inpatient stay was 7 weeks (range, 5–12 weeks), and four of six relapsing women from the untreated group were subsequently started on lithium prophylaxis.

continued

TABLE 1, *continued*

First Author, Year (Reference)	Sample Size (N)	Source	Lithium Exposure	Comparison	Main Safety or Tolerability Results (Systematic Qualitative Review)
Bergink 2012 (37); included in the meta-analysis	41	Peripartum Prevention Program, Department of Psychiatry, Erasmus Medical Center (Rotterdam, the Netherlands)	Pregnancy and postpartum	Relapse during pregnancy and postpartum in women using or not using lithium	Of the women with bipolar disorder (N=41), 24.4% relapsed during pregnancy, despite prophylaxis use by the majority throughout pregnancy. The postpartum relapse rate was highest in women with bipolar disorder who experienced mood episodes during pregnancy (60%). Patients with bipolar disorder require continuous prophylaxis throughout pregnancy and the postpartum period to reduce peripartum relapse risk.
Efficacy: lithium group only interventional study					
Rosso 2016 (49)	18	Psychiatric Unit of the Department of Neurosciences (University of Turin, Italy)	Pregnancy and postpartum	Rates of bipolar recurrence during pregnancy	Bipolar recurrences of any polarity during pregnancy occurred in 11.1% of the women. The results support the efficacy of lithium prophylaxis throughout pregnancy in lithium-responding women with bipolar I disorder. No serious side effects were noted for mother or baby.
Efficacy: retrospective cohort studies					
Viguera 2000 (7)	101	Perinatal and Reproductive Psychiatry Research Program, Massachusetts General Hospital, Boston, and Lucio Bini–Stanley Foundation Center for Mood Disorders Research, Cagliari, Sardinia	Pregnancy and postpartum	Recurrence rates in pregnant women versus nonpregnant women during rapid or gradual discontinuation of lithium, during pregnancy and postpartum	Rates of recurrence during the first 40 weeks after lithium discontinuation were similar for pregnant and nonpregnant women but then sharply increased postpartum. The risk was much lower with gradual discontinuation. Recurrence rates were similar for bipolar I and II disorders but were higher in patients with a history of four or more prior episodes of illness and for those who underwent rapid discontinuation of lithium.
Wesseloo 2017 (50)	114	Danish national registry	Pregnancy and postpartum	Postpartum recurrence of bipolar disorder in women using lithium versus women using lamotrigine	No difference was observed between lithium and lamotrigine in the prevention of severe postpartum episodes.

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).

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

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]

Outcome (Reference)	Articles (N)	k	Cases Among Lithium-Exposed Women	Lithium-Exposed Women, Overall	Cases Among Lithium-Unexposed Women	Lithium-Unexposed Women, Overall	Odds Ratio[b]	95% CI	I^2 (%)	p	NNH[c]	95% CI	I^2 (%)	p
Overall exposure to lithium at any time during pregnancy compared with unexposed women (either with bipolar disorder or general-population controls)														
Spontaneous abortion (2, 26)	2	3	43	321	6	968	3.77	1.15–12.39	86.55	0.03	15	8–111	56.17	0.03
Preterm birth (2, 8, 26–29)	6	13	144	1,084	2,047	22,611	1.42	0.98–2.06	60.61	0.07	23	11–100	53.82	0.05
Low birth weight (2, 8, 26)	3	9	NA	980	NA	22,258	0.99	0.84–1.19	0	0.99	143[d]	38 –83	NA[d]	0.48
Any congenital anomaly (2, 8, 25, 26)	4	11	69	1,195	889	22,105	1.75	1.23–2.48	25.96	<0.01	33	22–77	6.61	<0.01
Cardiac anomaly (2, 8, 11, 25)	4	12	43	1,508	15,604	1,346,967	1.86	1.16–2.96	40.16	<0.01	71	48–167	4.62	<0.01
Exposure to lithium at any time during pregnancy compared with unexposed general population														
Preterm birth (2, 27)	2	2	19	151	42	694	2.22	0.99–4.97	6.68	0.05	18	7–29	22.27	0.22
Any congenital anomaly (2, 25)	2	2	15	182	24	821	2.03	1.03–3.99	0	0.04	22	12–200	0	0.03
Cardiac anomaly (2, 11, 25)	3	2	26	815	15,256	1,323,776	3.99	1.19–13.43	63.17	0.03	37	19–1000	46.36	0.04
Exposure to lithium at any time during pregnancy compared with unexposed patients with bipolar disorder[e]														
Spontaneous abortion (2, 26)	2	2	43	321	18	220	2.46	0.56–10.77	82.09	0.23	24	9–42	35.61	0.21
Preterm birth (2, 8, 26–29)	6	11	144	1,084	2005	21,917	1.34	0.89–2.01	62.85	0.16	26	11–62	61.46	0.16
Low birth weight (2, 8, 26)	3	8	NA	980	NA	21,547	1.07	0.85–1.34	0	0.56	143[d]	38–83	NA[d]	0.48
Any congenital anomaly (2, 8, 25, 26)	4	9	69	1,013	865	21,284	1.75	1.21–2.52	15.35	<0.01	38	20–333	29.31	0.03
Cardiac anomaly (2, 8, 11, 25)	4	9	42	1,508	348	23,191	1.59	0.91–2.77	35.44	0.10	91	50–500	0	0.01
Efficacy associated with lithium exposure during pregnancy/peripartum														
Relapse, postpartum, any mood episode (36, 37)	2	2	4	35	7	13	0.16	0.03–0.89	55.81	0.04	—[f]	1–12	52.76	0.12

[a] Egger's test p values were all nonsignificant (>0.05). NA=not applicable; NNH=number needed to harm; k=number of comparisons.
[b] Odds ratio was computed on the basis of the adjusted odds ratios in individual studies, where available.
[c] NNH was computed on the basis of unadjusted events frequencies in the two groups (lithium versus no lithium) and pooled data (not from individual cohorts) from Munk-Olsen et al. (8).
[d] NNH was computed from pooled data from Munk-Olsen et al. only (8).
[e] In one study (8), control subjects included patients with major depressive disorder in addition to those with bipolar disorder (exact figures undisclosed).
[f] The number needed to treat (NNT) is 3.

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).

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;

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

Outcome	k	Cases Among Lithium-Exposed Women	Lithium-Exposed Women, Overall	Cases Among Lithium-Unexposed Women	Lithium-Unexposed Women, Overall	Odds Ratio[b]	95% CI	I^2 (%)	p	NNH[c]	95% CI	I^2 (%)	p
Overall exposure to lithium during the first trimester compared with unexposed women (either bipolar disorder or general-population controls)													
Spontaneous abortion (2, 26)	3	43	321	61	968	3.77	1.15–12.39	86.55	0.03	15	8–111	56.17	0.03
Preterm birth (2, 26)	3	24	269	54	890	1.72	0.96–3.08	60.61	0.07	29	11–48	51.97	0.12
Low birth weight (2, 26)	3	NA	269	NA	890	1.01	0.80–1.28	9.13	0.99	NA		NA	NA
Any congenital anomaly (2, 8, 25, 26)	10	65	1123	889	22,105	1.81	1.35–2.41	0	<0.001	32	21–77	8.80	0.001
Cardiac anomaly (2, 8, 11, 25)	11	42	1,436	15,604	1,346,967	1.96	1.28–3.00	29.92	<0.01	71	48–143	11.8	<0.001
Exposure to lithium during the first trimester compared with the unexposed general population													
Any congenital anomaly (2, 25)	2	15	182	24	821	2.03	1.03–3.99	0	0.04	22	12–200	0	0.03
Cardiac anomaly (2, 11, 25)	3	26	815	15,256	1,323,776	3.99	1.19–13.43	63.17	0.03	37	19–1000	46.36	0.04
Exposure to lithium during the first trimester compared with unexposed patients with bipolar disorder[d]													
Spontaneous abortion (2, 26)	2	43	321	18	220	2.46	0.56–10.77	82.09	0.23	24	9–42	35.61	0.21
Preterm birth (2, 26)	2	24	269	13	207	1.17	0.56–2.44	0	0.68	25	23–31	0	0.86
Low birth weight (2, 26)	2	NA	269	NA	207	1.17	0.85–1.61	0	0.34	NA		NA	NA
Any congenital anomaly (2, 8, 25, 26)	8	65	941	865	21,284	1.75	1.21–2.98	15.35	<0.01	37	19–333	32.41	0.03
Cardiac anomaly (2, 8, 11, 25)	8	41	1,436	348	23,191	1.75	1.08–2.84	19.99	0.02	83	48–333	0	0.01

[a] Egger's test p values were all nonsignificant (>0.05). NA=not applicable; NNH=number needed to harm; k=number of comparisons.
[b] Odds ratio was computed on the basis of the adjusted odds ratio in individual studies, where available.
[c] NNH was computed on the basis of unadjusted event frequencies in the two groups (lithium compared with no lithium) and from pooled data (not from individual cohorts) from Munk-Olsen et al. (8).
[d] In one study (8), control subjects included patients with major depressive disorder in addition to those with bipolar disorder (exact figures undisclosed).

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

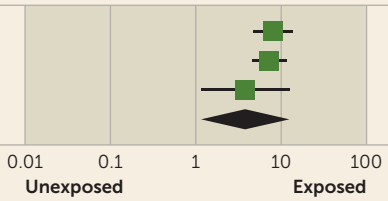
Our aim in this systematic review was to summarize the evidence on the safety and efficacy of lithium use during pregnancy and the postpartum period. The quantitative synthesis showed that lithium exposure at any time during pregnancy was associated with a significantly increased risk of spontaneous 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

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

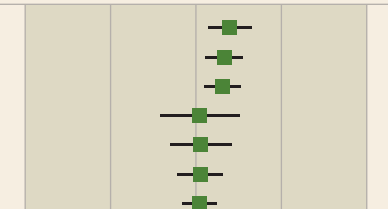
Spontaneous Abortion

Study First Author (Reference)	Point	Lower Limit	Upper Limit	Z	p	Relative Weight
Diav-Citrin (2)	8.06	4.72	13.76	7.65	0.00	36.01
Diav-Citrin (2)	7.28	4.58	11.60	8.37	0.00	67.24
Jacobson (26)	3.77	1.15	12.39	2.18	0.03	100.00
	3.77	1.15	12.39	2.18	0.03	



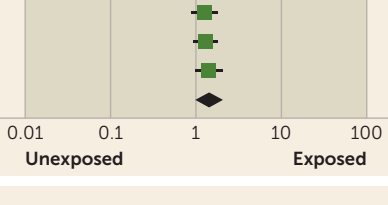
Preterm Birth

Study First Author (Reference)	Point	Lower Limit	Upper Limit	Z	p	Relative Weight
Diav-Citrin (2)	2.49	1.38	4.50	3.04	0.05	11.45
Diav-Citrin (2)	2.14	1.29	3.55	2.96	0.03	19.04
Forsberg (27)	2.05	1.25	3.38	2.84	0.05	20.56
Forsberg (27)	1.11	0.38	3.25	0.19	0.85	22.51
Jacobson (26)	1.13	0.49	2.60	0.30	0.76	29.08
Munk-Olsen (Canada) (8)	1.12	0.60	2.07	0.36	0.72	42.29
Munk-Olsen (Denmark) (8)	1.11	0.69	1.79	0.45	0.65	53.65
Munk-Olsen (Sweden) (8)	1.24	0.83	1.84	1.07	0.29	67.40
Munk-Olsen (Netherlands) (8)	1.32	0.91	1.93	1.45	0.15	74.40
Munk-Olsen (USA) (8)	1.24	0.84	1.82	1.10	0.27	78.62
Munk-Olsen (UK) (8)	1.27	0.89	1.81	1.31	0.19	85.14
Frayne (28)	1.28	0.91	1.80	1.44	0.15	88.35
Troyer (29)	1.42	0.98	2.06	1.85	0.06	100.00
	1.42	0.98	2.06	1.85	0.06	



Low Birth Weight

Study First Author (Reference)	Point	Lower Limit	Upper Limit	Z	p	Relative Weight
Jacobson (26)	1.31	0.86	2.01	1.25	0.21	17.89
Diav-Citrin (2)	1.05	0.72	1.53	0.24	0.81	54.88
Diav-Citrin (2)	1.01	0.80	1.27	0.11	0.93	67.90
Munk-Olsen (Canada) (8)	0.96	0.75	1.22	0.34	0.73	77.66
Munk-Olsen (Denmark) (8)	0.95	0.78	1.15	0.54	0.59	84.28
Munk-Olsen (Sweden) (8)	0.99	0.81	1.22	0.02	0.98	96.43
Munk-Olsen (Netherlands) (8)	0.99	0.83	1.19	0.07	0.94	97.41
Munk-Olsen (USA) (8)	0.99	0.83	1.19	0.06	0.95	98.39
Munk-Olsen (UK) (8)	0.99	0.83	1.19	0.01	0.99	100.00
	0.99	0.84	1.19	0.01	0.99	



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

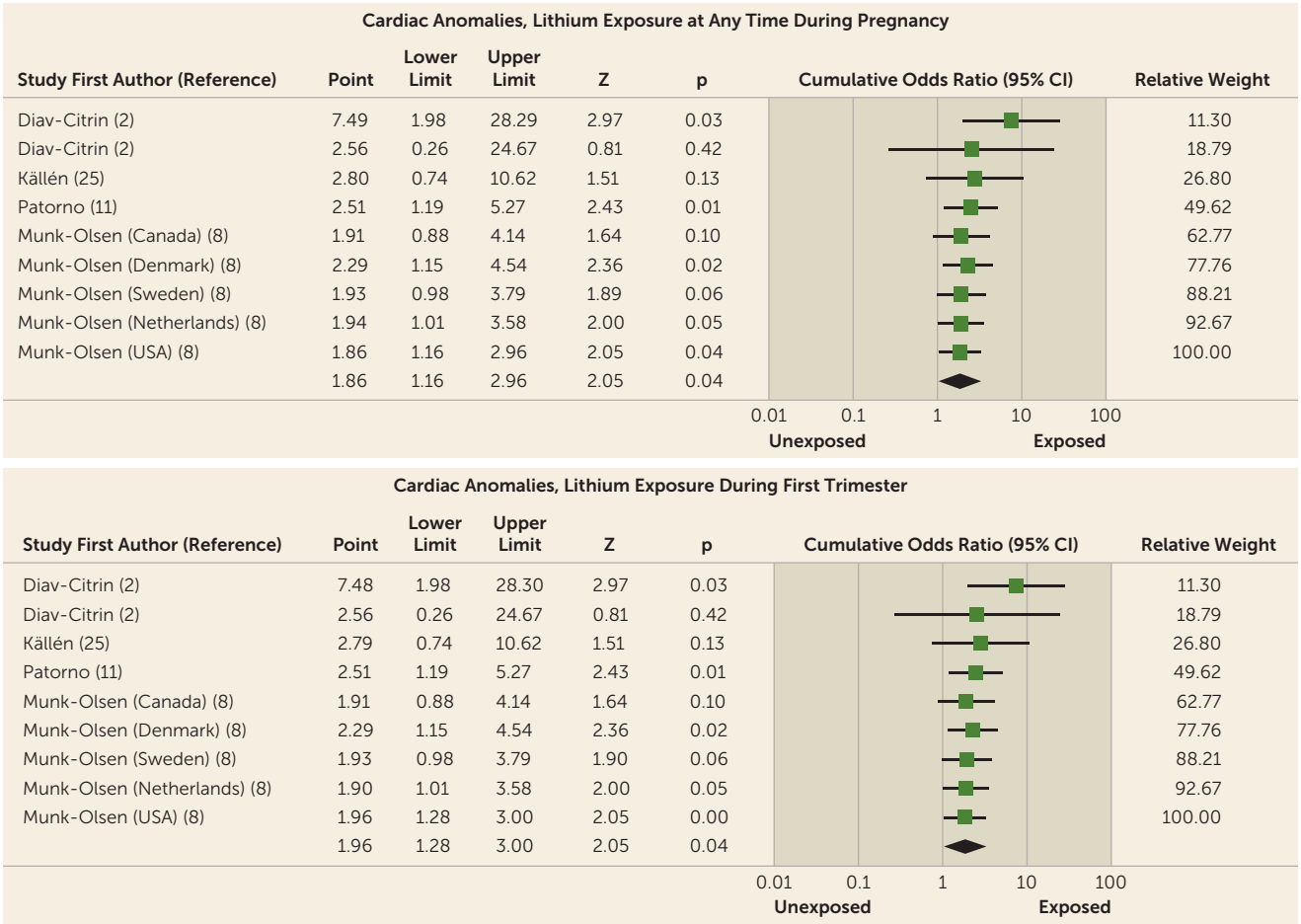
FIGURE 3. Risk of any congenital anomaly associated with lithium exposure at any time during pregnancy and during the first trimester compared with unexposed women (either bipolar disorder or general-population controls)

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

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)



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."

AUTHOR AND ARTICLE INFORMATION

Departments of Neuroscience, Reproductive Science, and Dental Science and Section of Psychiatry, University School of Medicine "Federico II," Naples (Fornaro); Department of Neurosciences, University of Padua, Padua, Italy (Maritan, Miola, Solmi); Department of Mental Health, Local Health Unit 6 "Euganea," Padua (Ferranti, Zaninotto); National Social Security Institute, Latina, Italy (Anastasia); Department of Psychiatry and Psychology, Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain (Murru, Solé, Vieta); Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London (Stubbs); Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, and South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Beckenham, U.K. (Stubbs, Young); Centre for Addiction and Mental Health, Toronto (Carvalho); Department of Psychiatry, University of Bologna, Bologna, Italy (Serretti); Early Psychosis: Interventions and Clinical Detection (EPIC) Lab, Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London (Fusar-Poli, McGuire, Dazzan, Solmi); OASIS service, South London and Maudsley NHS Foundation Trust, London (Fusar-Poli); Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy (Fusar-Poli); Women's College Research Institute and Department of Psychiatry, Women's College Hospital, Toronto, and Department of Psychiatry, Faculty of Medicine and Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto (Vigod); Department of Psychiatry, Zucker Hillside Hospital, Northwell Health, Glen Oaks, N.Y. (Correll); Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of

Medicine, Hempstead, N.Y. (Correll); Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin (Correll); Padova Neuroscience Center, University of Padua, Padua (Solmi).

Send correspondence to Dr. Fornaro (dott.fornaro@gmail.com).

The first two authors contributed equally to this study.

Dr. Murru has received CME-related honoraria from Asofarma, Otsuka, and Pfizer. Prof. Serretti has served as a consultant or speaker for Abbott, AbbVie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. Dr. Vieta has received grants and served as consultant, adviser, or CME speaker for AB-Biotics, Allergan, Angelini, AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, GlaxoSmithKline, Janssen, Lundbeck, Otsuka, Pfizer, Roche, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the Seventh European Framework Programme and Horizon 2020, and the Stanley Medical Research Institute. Prof. Young has served as paid lecturer and advisory board member for AstraZeneca, Eli Lilly, Janssen, Livanova, Lundbeck, Servier, and Sunovion and as a consultant for Johnson & Johnson; he has served as lead investigator for the Embolden Study (AstraZeneca), the BCI Neuroplasticity study, and the Aripiprazole Mania Study and as an investigator in investigator-initiated studies from AstraZeneca, Eli Lilly, Lundbeck, Wyeth, and Janssen; he has received grant funding from the British Medical Association, the CCS Depression Research Fund, the Canadian Institutes of Health Research, Janssen, the Medical Research Council (UK), NARSAD, the Michael Smith Foundation for Health Research, the National Institute for Health Research (UK), NIMH, the Stanley Medical Research Institute, the Royal College of Physicians (Edinburgh), the VGH & UBC Hospital Foundation (Canada), WEDC (Canada), and Wellcome Trust; and he is funded by the National Institute for Health Research Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. Dr. Vigod receives royalties from UpToDate for authorship of chapters. Dr. Correll has been a consultant and/or adviser to or has received honoraria from Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/Johnson & Johnson, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva; he has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka; he has served on data safety monitoring boards for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva; he has received royalties from UpToDate and grant support from Janssen and Takeda; and he is a shareholder of LB Pharma. The other authors report no financial relationships with commercial interests.

Received March 1, 2019; revision received May 26, 2019; accepted July 16, 2019.

REFERENCES

1. Snellen M, Malhi GS: Bipolar disorder, psychopharmacology, and pregnancy, in Psychopharmacology and Pregnancy: Treatment Efficacy, Risks, and Guidelines. Edited by Galbally M, Snellen M, Lewis A. Berlin, Springer, 2014, pp 103–117
2. Diav-Citrin O, Shechtman S, Tahover E, et al: Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. Am J Psychiatry 2014; 171:785–794
3. Bodén R, Lundgren M, Brandt L, et al: Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ 2012; 345:e7085
4. Barnes C, Mitchell P: Considerations in the management of bipolar disorder in women. Aust N Z J Psychiatry 2005; 39:662–673
5. Di Florio A, Forty L, Gordon-Smith K, et al: Perinatal episodes across the mood disorder spectrum. JAMA Psychiatry 2013; 70: 168–175
6. Baldessarini RJ, Tondo L, Hennen J: Effects of lithium treatment and its discontinuation on suicidal behavior in bipolar manic-depressive disorders. J Clin Psychiatry 1999; 60(suppl 2):77–84
7. Viguera AC, Nonacs R, Cohen LS, et al: Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000; 157:179–184
8. Munk-Olsen T, Liu X, Viktorin A, et al: Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry 2018; 5: 644–652
9. Yonkers KA, Wisner KL, Stowe Z, et al: Management of bipolar disorder during pregnancy and the postpartum period. Am J Psychiatry 2004; 161:608–620
10. Poels EMP, Schrijver L, Kamperman AM, et al: Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. Eur Child Adolesc Psychiatry 2018; 27:1209–1230
11. Patorno E, Huybrechts KF, Bateman BT, et al: Lithium use in pregnancy and the risk of cardiac malformations. N Engl J Med 2017; 376:2245–2254
12. US Food and Drug Administration: FDA Drug Safety Communication: Antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. February 22, 2011. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-antipsychotic-drug-labels-updated-use-during-pregnancy-and-risk
13. Gentile S: Lithium in pregnancy: the need to treat, the duty to ensure safety. Expert Opin Drug Saf 2012; 11:425–437
14. National Institute for Health and Care Excellence: Bipolar Disorder: Assessment and Management (Clinical Guideline 185). London, National Institute for Health and Care Excellence, September 24, 2014 (https://www.nice.org.uk/guidance/cg185)
15. Gentile S: Bipolar disorder in pregnancy: to treat or not to treat? BMJ 2012; 345:e7367
16. Moher D, Shamseer L, Clarke M, et al: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4:1
17. Stroup DF, Berlin JA, Morton SC, et al: Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283:2008–2012
18. Pacchiarotti I, León-Caballero J, Murru A, et al: Mood stabilizers and antipsychotics during breastfeeding: focus on bipolar disorder. Eur Neuropsychopharmacol 2016; 26:1562–1578
19. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013.
20. Higgins JP, Altman DG, Gøtzsche PC, et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928
21. Agency for Healthcare Research and Quality (AHRQ): AHRQ Comparative Effectiveness Reviews. https://www.ncbi.nlm.nih.gov/books/NBK42934/
22. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–188
23. Borenstein M, Rothstein D, Cohen J: Comprehensive Meta-Analysis: A Computer Program for Research Synthesis. Englewood, NJ, Biostat, 2005
24. Egger M, Davey Smith G, Schneider M, et al: Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315:629–634
25. Källén B, Tandberg A: Lithium and pregnancy: a cohort study on manic-depressive women. Acta Psychiatr Scand 1983; 68:134–139
26. Jacobson SJ, Jones K, Johnson K, et al: Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992; 339:530–533
27. Forsberg L, Adler M, Romer Ek I, et al: Maternal mood disorders and lithium exposure in utero were not associated with poor cognitive development during childhood. Acta Paediatr 2018; 107:1379–1388

28. Frayne J, Nguyen T, Mok T, et al: Lithium exposure during pregnancy: outcomes for women who attended a specialist antenatal clinic. J Psychosom Obstet Gynaecol 2018; 39:211–219
29. Troyer WA, Pereira GR, Lannon RA, et al: Association of maternal lithium exposure and premature delivery. J Perinatol 1993; 13: 123–127
30. EUROCAT: European Surveillance of Congenital Anomalies. http://www.eurocat-network.eu/
31. Malhi GS, Gessler D, Outhred T: The use of lithium for the treatment of bipolar disorder: recommendations from clinical practice guidelines. J Affect Disord 2017; 217:266–280
32. Wesseloo R, Wierdsma AI, van Kamp IL, et al: Lithium dosing strategies during pregnancy and the postpartum period. Br J Psychiatry 2017 ; 211:31–36
33. Freeman MP, Farchione T, Yao L, et al: Psychiatric medications and reproductive safety: scientific and clinical perspectives pertaining to the US FDA pregnancy and lactation labeling rule. J Clin Psychiatry 2018; 79:18ah38120
34. Newport DJ, Viguera AC, Beach AJ, et al: Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. Am J Psychiatry 2005; 162:2162–2170
35. Galbally M, Snellen M, Lewis A (ed): Psychopharmacology and Pregnancy: Treatment Efficacy, Risks, and Guidelines. Berlin, Springer, 2016
36. Austin MP: Puerperal affective psychosis: is there a case for lithium prophylaxis? Br J Psychiatry 1992; 161:692–694
37. Bergink V, Bouvy PF, Vervoort JS, et al: Prevention of postpartum psychosis and mania in women at high risk. Am J Psychiatry 2012; 169:609–615
38. Edmonds L, Oakley G: Ebstein's anomaly and maternal lithium exposure during pregnancy. Teratology 1990; 41:551–552
39. Zalzstein E, Koren G, Einarson T, et al: A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol 1990; 65:817–818
40. Park JM, Sridaromont S, Ledbetter EO, et al: Ebstein's anomaly of the tricuspid valve associated with prenatal exposure to lithium carbonate. Am J Dis Child 1980; 134:703–704
41. Czeizel A, Rácz J: Evaluation of drug intake during pregnancy in the Hungarian Case-Control Surveillance of Congenital Anomalies. Teratology 1990; 42:505–512
42. Boyle B, Garne E, Loane M, et al: The changing epidemiology of Ebstein's anomaly and its relationship with maternal mental health conditions: a European registry-based study. Cardiol Young 2017; 27:677–685
43. Lisi A, Botto LD, Robert-Gnansia E, et al: Surveillance of Adverse Fetal Effects of Medications (SAFE-Med): findings from the International Clearinghouse of Birth Defects Surveillance and Research. Reprod Toxicol 2010; 29:433–442
44. Schou M: What happened later to the lithium babies? A follow-up study of children born without malformations. Acta Psychiatr Scand 1976; 54:193–197
45. Schou M, Goldfield MD, Weinstein MR, et al: Lithium and pregnancy, I: report from the Register of Lithium Babies. BMJ 1973; 2: 135–136
46. Weinstein MR, Goldfield M: Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry 1975; 132:529–531
47. Weinstein MR: The International Register of Lithium Babies. Drug Inf J 1976; 10:94–100
48. van der Lugt NM, van de Maat JS, van Kamp IL, et al: Fetal, neonatal, and developmental outcomes of lithium-exposed pregnancies. Early Hum Dev 2012; 88:375–378
49. Rosso G, Albert U, Di Salvo G, et al: Lithium prophylaxis during pregnancy and the postpartum period in women with lithium-responsive bipolar I disorder. Arch Women Ment Health 2016; 19:429–432
50. Wesseloo R, Liu X, Clark CT, et al: Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: a population-based cohort study. J Affect Disord 2017; 218:394–397