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Meta-analysis

Ondansetron exposure during pregnancy is not associated with risk of congenital malformations: evidence from a meta-analysis

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ABSTRACT

Ondansetron is widely used drug for treatment of morning sickness and hyperemesis gravidarum. However, whether exposure to ondansetron during pregnancy is associated with risk of congenital malformations or not remains debatable. The present meta-analysis was performed for published cohort/registry-based studies which evaluated the association between ondansetron exposure and risk of congenital malformations. Major congenital malformations were considered as the primary outcome measure. Specific abnormalities like cardiac malformation, septal defect, cleft lip/palate, hypospadias, and genitourinary abnormalities were considered as secondary outcome measures along with spontaneous abortion/miscarriage, stillbirth, preterm delivery, and low birth weight babies. Pooled analysis was done using the Mantle-Hanzle method, random effect model and were expressed as odds ratio (OR) with 95% CI. Fourteen studies were included in systematic review. There was no significant difference for major congenital malformations [n=12; OR: 1.12 (95% CI: 0.93-1.36), I^2=96], septal defect [n=5; OR: 1.39 (95% CI: 1.01-1.91), I^2=48%], cleft lip/palate [n=3; OR: 1.11 (95% CI: 0.80-1.53), I^2=41%] between ondansetron exposed and control arms. However, a greater number of events were found in control arm than intervention arm for cardiac defect [n=7; OR: 1.26 (95% CI: 1.09-1.45), I^2=71%; p=0.002]. We also observed a greater number of events for stillbirth and pre-term labour in control arm than in intervention arm with OR: 1.57 (95% CI: 1.24-1.97); p=0.0001 and OR: 1.33 (95% CI: 1.05-1.69); p=0.02, respectively. This meta-analysis concludes that ondansetron exposure during pregnancy is not associated with any increased risk of major congenital malformations, septal /cardiac defect, cleft lip/palate, spontaneous abortion/miscarriage, stillbirth, pre-term labour and low birth weight babies.

Keywords: Antiemetic drugs, Ondansetron, Teratogenicity, Morning sickness, Pregnancy, Fetal outcome, Hyperemesis Gravidarum

INTRODUCTION

The most common medical condition during gestation is nausea and vomiting affecting up to 80% of all pregnancies. Severe nausea and vomiting (hyperemesis gravidarum) affect less than 1% of pregnant females which can be debilitating.[1] Ondansetron is 5-HT3 receptor antagonist that has been used widely to treat morning sickness and hyperemesis gravidarum. Ondansetron has been assigned category B1 in Australia and category B by

US FDA for its use in pregnancy.[2,3] The 2018 clinical guidelines from the American College of Gynecology (ACOG), recommended ondansetron, doxylamine and pyridoxine, metoclopramide, promethazine, and methylprednisolone, prochloroperazine, chlorpromazine, and trimethobenzamide for the treatment of NVP.[4] Due to heterogeneity in study populations, methodological limitations, and small sample sizes prior studies on the fetal safety of ondansetron have produced varied results. Studies done by Einarson et al, Asker et al, Colvin et al, Pasternak et al, and Parker et al found no increased risk of major birth defects, while Danielsson et al and Anderka et al found increased risks of cardiac defects and cleft palates, respectively.[1,2,5-10] Ondansetron was found superior to the combination of pyridoxine and doxylamine in morning sickness. It is similar to metoclopramide for hyperemesis gravidarum with better safety profile. However, there is concern regarding placental drug transfer and possible increase in risk of major congenital malformations in off springs.[11] Conflicting data leave clinicians unsure with respect to the appropriate risk-benefit for ondansetron use in pregnancy.[12] Thus, dilemma for use of ondansetron in pregnancy continues. This conflicting data formed the basis for conducting systematic review of available literature till date. The objective of this study was to check for the association between exposure of ondansetron during the pregnancy and risk of congenital malformations in off springs in comparison to the pregnancies not exposed to antiemetic drugs or other antiemetic drugs.

METHODS

Search strategy

MeSH terms like congenital abnormalities (birth defects, congenital defects, congenital deformities, fetal anomalies, fetal malformations) and ondansetron were used as search terms. PubMed and Google Scholar were searched for literature by two authors independently. Following search strategy was used, congenital malformations or birth defects or congenital deformities or fetal anomalies or fetal malformations or congenital defects and ondansetron. Relevant articles from bibliography of manuscript were also evaluated. The final search was run on 26th January, 2022. Two authors independently did the preliminary screening for eligible articles based on the title and abstract of articles. Final screening was done for full text articles by same authors and doubtful articles were included after discussion and consensus between the authors. Articles published in English at any time point was considered.

Selection of studies

Screened studies were included in the review based on the following criteria.

Inclusion criteria

Abstract or full-text articles reporting outcome of interest with following criteria were included.

Randomized controlled clinical trials (open labelled or blinded studies) which followed up pregnant females till delivery and outcome of interest have been noted. Comparative studies with ondansetron and any other interventions (no exposure or other anti-emetic drugs) which measure the association between exposure and risk of congenital malformations.

Exclusion criteria

Non-comparative studies, case-controlled studies, non-research articles (e.g., review articles, meta-analysis), duplicate publications and articles published in other than English language.

Intervention and comparators

Ondansetron exposure amongst pregnant women irrespective of dose and duration was considered as an intervention arm. Pregnant women without any treatment, exposed to known non-teratogen or treated with antiemetics other than ondansetron was considered in control arm.

Risk of bias assessment of included studies

Quality of included studies were assessed independently by two authors using "Tool to Assess Risk of Bias in Cohort Studies".[13] Individual observations were discussed and any observed discrepancy was solved by discussion until consensus among the authors is achieved.

Data collection

The included studies were identified with the name of first author and year of publication. Data of study design, population covered, intervention and comparator (dose, frequency, duration of exposure), outcome measures (congenital malformations, specific defects, pregnancy related issues) were extracted from the literature and entered in Microsoft Excel sheet which was cross-checked by another author for accuracy of data. Any data discrepancy was resolved through a discussion and consensus amongst authors.

Outcome measures

Incidence of congenital malformations was considered as the primary outcome whereas, specific abnormalities like cardiac malformations, septal defect, cleft lip/palate, hypospadias, genitourinary abnormalities and pregnancy related complications like spontaneous abortion/miscarriage, stillbirth, pre-term labour and low

birth weight babies were considered as secondary outcomes.

Data synthesis

All outcome variables were the dichotomous variables mentioned as number of events and were summarized as odds ratio (OR) with 95% CI for pooled analysis. The pooled statistical analysis was performed using the Mantle-Hanzle method with random effect model to estimate the meta-analytic summary. The heterogeneity across the studies was assessed using I^2 test and interpreted as low, moderate and high when it was ≤25%, >25 to <75% and ≥75%, respectively. The funnel plot was plotted for primary outcome parameter and visually inspected for publication bias.

Sensitivity analysis was performed for major congenital malformations based on category of risk of bias assessment. Meta-analytic summary was re-checked after removing studies with high and moderate risk of bias. Review Manager Version 5.4 was used to perform meta-analysis.

RESULTS

Study characteristics

Based on search strategy, 153 articles were retrieved, of which 41 full text articles were assessed for possible inclusion. Fourteen comparative studies met the selection criteria and included in the analysis (Figure 1). In 14 included studies, in intervention arm, 2,87,223 pregnant women were exposed to ondansetron whereas, in control arm, 65,55,465 pregnant women were exposed to non-teratogenic drugs or antiemetic drugs other than ondansetron or were not exposed. Table 1 represents the general characteristics of all included studies in this review.

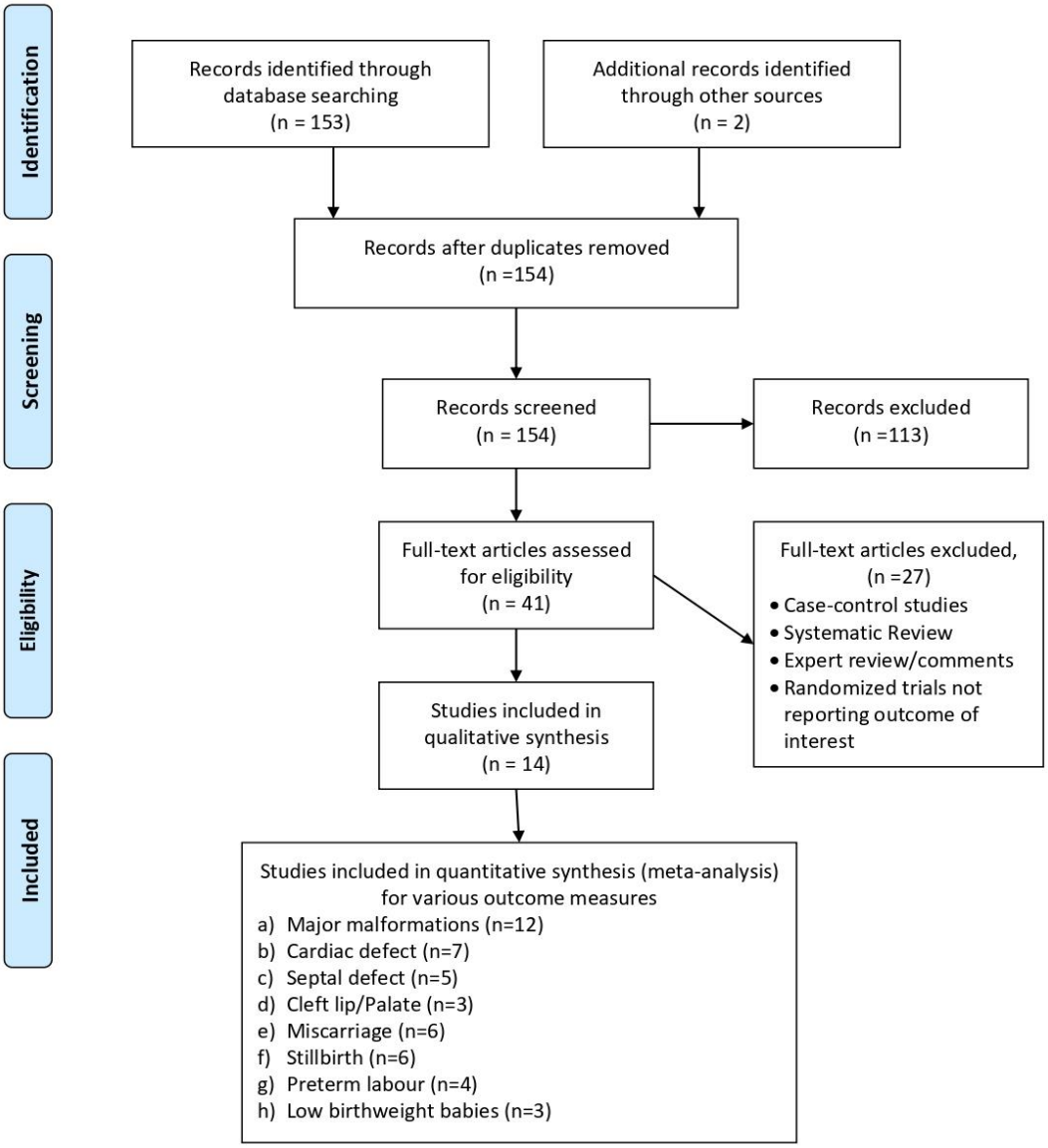


Figure 1: PRISMA flow in present systematic review.

Table 1: General characteristics of the included studies.

Study	Design	Country	Confirmation method of exposure	Exposure Period	Baseline characteristics considered in study	Outcome of interest studied	Confirmation of outcome	Exposure of comparator group (disease status)	Sample size exposed/ unexposed
Adrienne Einarson, 2004	Prospective comparative observational study	Canada Australia	Teratogen Information Services	5-9 weeks First trimester	More smokers in non-teratogen group	Major malformations, Cardiac defect, Hypospadias, Genitourinary, Abortion, Stillbirth	Verification of information through participant's physician	Other anti-emetics, Nonteratogen group	176/ 352
Andersen, 2013*	Cohort study	Denmark 1997-2010	National Prescription Register	First trimester	Not available	Major congenital malformations, Heart defect*, Septal defect* *number of events not given	National Hospital Register	Unexposed	1248/ 31357
Anick Berard, 2019	Quebec Pregnancy Cohort	Canada 1998-2015	Validation of prescription	First trimester	More tobacco and alcohol dependence in antiemetic exposed along with comorbidities	Major congenital malformations	Confirmation with database	Unexposed, Other anti-emetics (Doxylamine-pyridoxine, metoclopramide)	31/46581
Björn Pasternak, 2013	Cohort study	Denmark 2004-2008	National Prescription Registry	First trimester	Comparable	Major birth defects, abortion, stillbirth, pre-term labor, Low birth weight	Medical Birth Registry.	Unexposed to Ondansetron	Variable for different outcome as per propensity matching
Colin Dormuth, 2021	Multicenter cohort study	Canada province April 2002 and March 2016	Database	First trimester	Comparable	Major congenital malformations, Septal defect, heart defect, abortion, stillbirth	CPRD's pregnancy register	Unexposed, other anti-emetics (doxylamine with pyridoxine, metoclopramide, or promethazine)	163 810/ 306 766
Danielsson Bengt, 2014	Register based study	Sweden 1998-2012	Midwife interviews, Swedish	First trimester	Not available	Major congenital malformations, Septal defect, Heart defect	Medical Birth Register, Birth Defect Register, discharge	Unexposed, other anti-emetics (Meclozine)	1349/ 1500085

Continued.

Study	Design	Country	Confirmation method of exposure	Exposure Period	Baseline characteristics considered in study	Outcome of interest studied	Confirmation of outcome	Exposure of comparator group (disease status)	Sample size exposed/ unexposed
			Prescription Register				diagnoses from hospitalizations		
Elizabeth Suarez, 2021	Cohort study	April 2014 November 2017	Electronic health record data (Prescription)	First 20 weeks of pregnancy	More smoker and co-morbidities in Ondansetron group,	Miscarriage	Medical records	Other anti-emetics (Promethazine, or metoclopramide)	1712/ 908
Krista FH 2018	Retrospective cohort study	USA 2000-2013	Prescription record evaluation	First trimester	More smoker, in exposed group	Major congenital malformations, Heart defect, Cleft lip/palate	Medical records	Unexposed, Other anti-emetics (Metoclopramide, promethazine, pyridoxine)	88 467/ 1727947
Krista FH 2020	Population-based cohort study	Brigham 2000-2014	Records of Prescription	First trimester Exposed with intra-venous ondan-setron	Comparable	Major congenital malformations, Heart defect, Cleft lip/palate	Medical records	Unexposed	23866/ 1762018
Lara Lemon, 2020	Cohort study	PittsburghPA (2006–2014)	Inpatient electronic medical record, insurance claims	First trimester	Comparable	ventricular septal defect	Echocardiogram	Unexposed	3733/ 29944
Lyn Colvin, 2013	Retrospective cohort study	Western Australia 2002-2005	WA Data Linkage System	First trimester	More smoker in non-exposed group	Major birth defect, abortion, stillbirth, pre-term labor, Low birth weight	WA Register of Developmental Anomalies (WARDA), Hospital Morbidity Data System (HMDS), Midwives' Notification System (MNS), Registry of Births and Deaths	Unexposed	251/ 96447
Marlena Fejzo, 2016	Retrospective cohort study	2007-2014	Online survey	First trimester with hype-	Not comparable	Major congenital malformations,	Online survey	Unexposed, other antiemetics	1070/ 2326

Continued.

Study	Design	Country	Confirmation method of exposure	Exposure Period	Baseline characteristics considered in study	Outcome of interest studied	Confirmation of outcome	Exposure of comparator group (disease status)	Sample size exposed/ unexposed
				remesis gravi-darum		Heart defect, Septal defect, Cleft lip/palate		(Metoclopramide, promethazine)	
Razan Sakran, 2020	Prospective comparative observational study	Israel 2010-2014	Israeli TIS database	First trimester	More smokers in control group	Major congenital malformations, Septal defect, heart defect, abortion, stillbirth, pre-term labor	Follow up by telephonic interview, medical records	Non-teratogen exposure, Other antiemetics (metoclopramide)	200/840
Şafak Özdemirci, 2014	Retrospective study	Turkey 2006-2011	Computerized database	First trimester with hype-remesis gravi-darum	Comparable	Major congenital malformations, stillbirth, pre-term labor, Low birth weight	Not mentioned	Chlorpromazine	100/ 85

*only abstract was available.

Table 2: Risk of bias assessment as per "risk of bias in cohort studies tool.

Study	Exposed and Not exposed cohort drawn from same population?	Confidence in assessment of exposure	Outcome of interest not present at the start of the study	Matching during analysis	Assessment of prognostic factors#	Assessment of Outcome	Adequate follow up?	Similarity of co-interventions between groups
Adrienne Einarson, 2004	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Andersen, 2013*	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Anick Berard, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Moderate risk
Björn Pasternak, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Colin Dormuth, 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Danielsson Bengt, 2014	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Low risk	Moderate risk
Elizabeth Suarez, 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krista FH 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Krista FH 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lara Lemon, 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lyn Colvin, 2013	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	High risk
Marlena Fejzo, 2016	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Moderate risk
Razan Sakran, 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Şafak Özdemirci, 2014	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Moderate risk

*considered as high risk due to lack of information (only abstract was available); #considered as low risk as it was not applicable.

Einarson et al conducted prospective comparative observational study with pregnant women from Canada and Australia exposed to ondansetron (n=176), other antiemetic agents (diclectin, metoclopramide, phenothiazines and ginger; n=176) and non-teratogenic drug or not exposed (n=176) with measuring outcomes of miscarriages, therapeutic abortions, stillbirths, major malformations, gestational age at birth and mean birthweight. Pregnant women other than having ondansetron exposure were merged in control arm (n=352). Maternal characteristics were comparable in both intervention and control groups except for smoking habit which was found more in control arm.[1]

Andersen et al conducted a birth register-based cohort study in Denmark to find out congenital malformations associated with ondansetron exposure (n=1248) and non-exposed (n=895770).[14]

Berad et al conducted a study using Quebec pregnancy cohort in canada. Of 2,24,876 pregnant women, 31 were exposed to ondansetron, 45,623 exposed to doxylamine-pyridoxine, 958 to metoclopramide and 1,79,106 were not exposed. The mean exposed duration in the first trimester was lower in women exposed to ondansetron (12.8 days) as compared to doxylamine-pyridoxine (27.4 days) and metoclopramide (17.7 days).[11]

Pasternak et al conducted a historical cohort study from medical birth registry in Denmark with 608,385 pregnancies, of which 1,970 pregnant women were exposed to the ondansetron.[9] Propensity matched analysis was performed by the authors which was considered for the present study.

Dormuth et al conducted cohort study in 3 countries (Canada, USA and UK) with a meta-analysis. There were 1,63,810 pregnant women from all three databases exposed to the ondansetron of cohort of 4,56,963. Pregnant women exposed to ondansetron were little older than comparator arm. They measured congenital malformations as secondary parameter.

Danielsson et al identified ondansetron exposure through midwife interviews at the first antenatal care visit of the pregnant woman and through a Swedish Prescription Register. Outcome was assessed from various registers. There were 1,349 pregnant women exposed to ondansetron, 41,388 women exposed to meclizine of 15,01,434 total pregnant women. Major malformations, cardiac and septal defects were the outcome measures in the study.[6]

Elizabeth et al conducted a cohort study in USA with focus on miscarriage associated with ondansetron exposure. Of 2,620 pregnant women, 1,712 were exposed to ondansetron and 908 were exposed to other antiemetics (metoclopramide or promethazine). Both the groups were comparable for baseline characteristics and this study did not report any other outcome.[16]

Krista et al did the retrospective cohort study with 1,816,414 pregnancies, of which 88,467 were exposed with ondansetron. Adjusted data were considered for the analysis. They measured congenital malformation with specific malformations like cardiac defects and oral malformations as outcome measures.[12]

Krista et al did the retrospective cohort study with 1,880,594 pregnancies, of which 23,877 were exposed with intravenous ondansetron. Adjusted data were considered for the analysis. They measured congenital malformation with specific malformations like cardiac defects and oral malformations as outcome measures.[17]

Lemon et al evaluated the risk of ventricular septal defect associated with oral or intravenous ondansetron exposure during pregnancy through a retrospective cohort study. Of 3,733 pregnant women exposed to ondansetron, 24 developed ventricular septal defects. Both groups were comparable for baseline characteristics.[18]

Colvin et al evaluated risk of major birth defect in ondansetron exposed pregnancies in western Australia. There were 96,968 pregnancies resulted in birth in which 251 pregnancies (263 child birth) were exposed to ondansetron. Percentage of smoking in pregnant ladies were more in ondansetron exposed group.[2]

Fejzo et al conducted a retrospective cohort study conducted with pregnant women having hyperemesis gravidarum (HG). There were 1,070 pregnancies with HG exposed to ondansetron, whereas 771 pregnancies with HG exposed to other anti-emetic drugs (metoclopramide/ promethazine and 1,555 pregnancies without HG and any exposure.[3]

Sakran et al conducted a prospective observational study on pregnant women counselled by Israeli Teratology Information Services who were exposed to ondansetron (n=195), metoclopramide (n=110) and non-teratogenic exposure (n=778). All these groups were comparable at baseline for maternal characteristics.[19]

Özdemirci et al performed a retrospective study on pregnant female suffering from HG who did not respond to oral meclizine-pyridoxine and prescribed the ondansetron (n=100) and chlorpromazine (n=85). Both groups were comparable for baseline characteristics.[20]

Risk of bias in included studies

Table 2 shows the risk of bias assessment of individual study included in the present review.

Outcome measures

Major congenital malformations

Twelve studies were included in analysis of congenital malformations with 281778 pregnant women exposed to ondasetron and 6524613 pregnant women either not exposed, exposed to non-teratogens or other antiemetics. The pooled odds ratio for major congenital malformations (MCM) was found 1.12 (95% CI: 0.93-1.36) indicating no significant difference between intervention and control arms (Figure 2). Population was highly heterogeneous based on I^2 value of 96%. The funnel plot was asymmetrical on visual inspection which indicated publication bias (Figure 3).

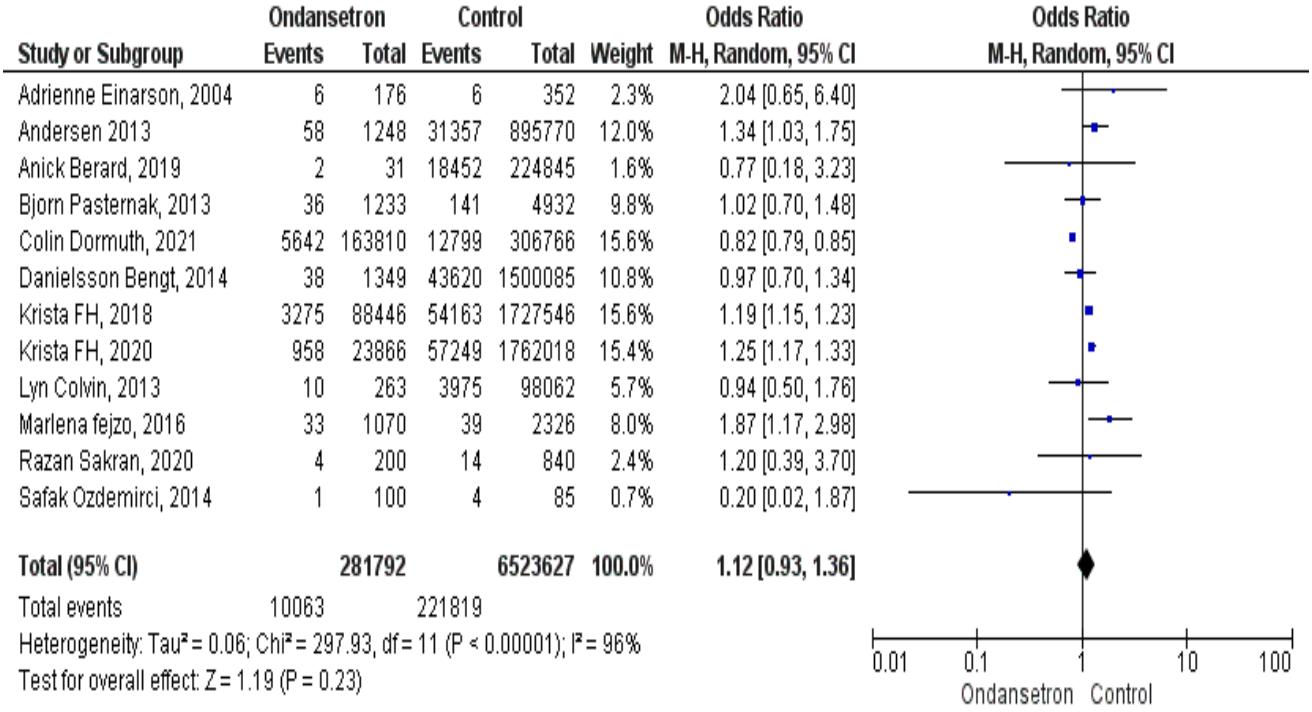


Figure 2: Meta-analytic summary of Major congenital malformations.

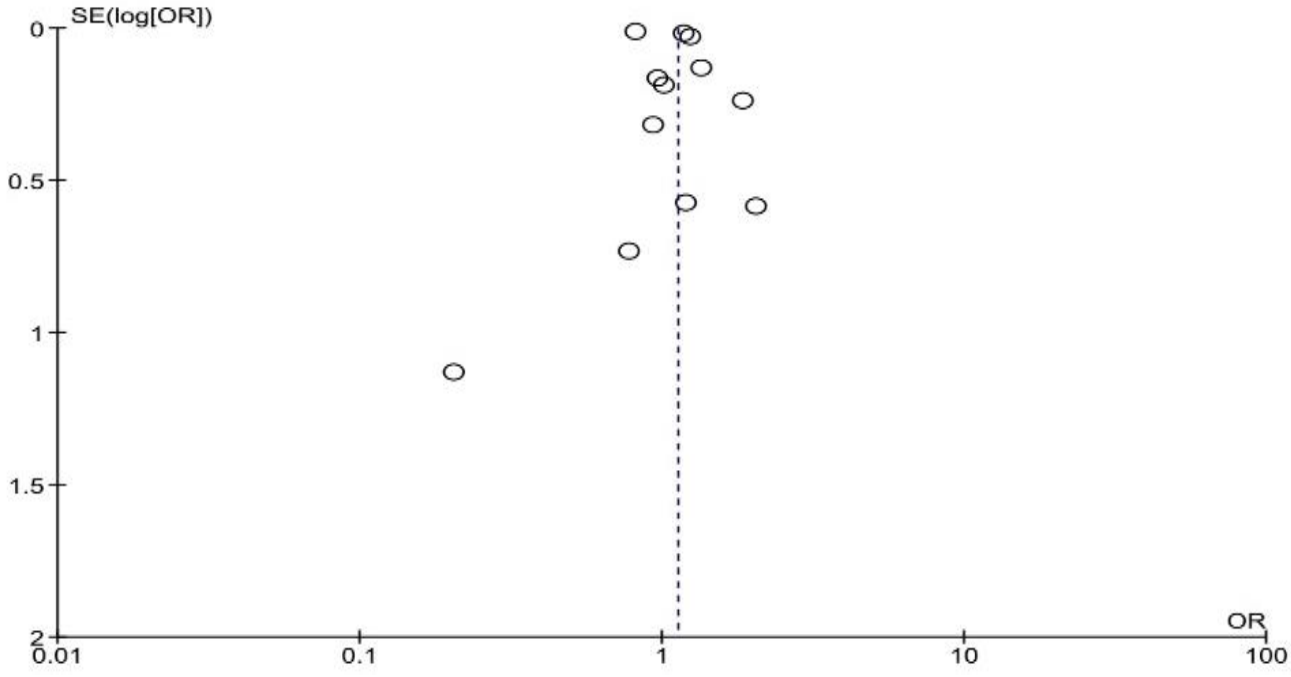
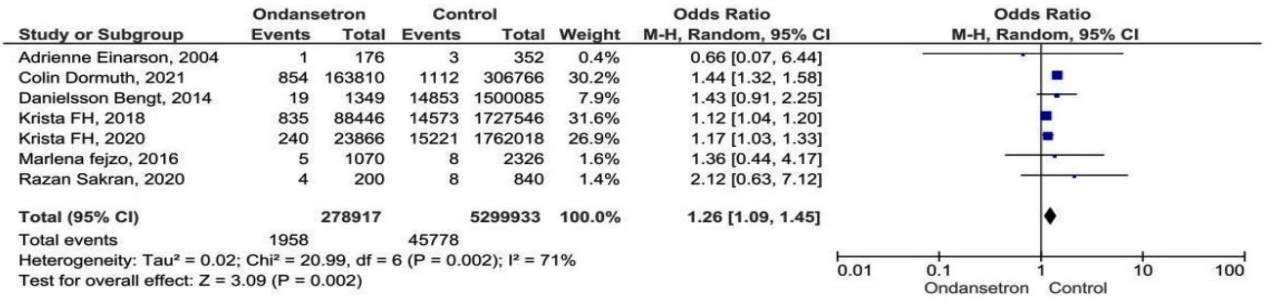
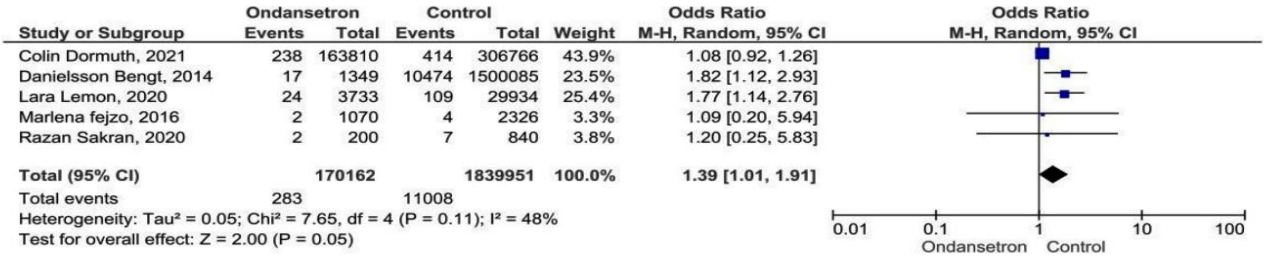


Figure 3: Funnel plot of publication bias for primary outcome measure.

a) Cardiac defect



b) Septal defect



c) Cleft lip/palate

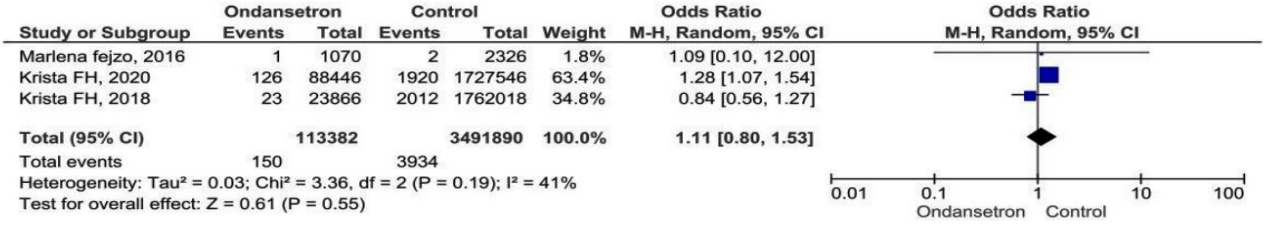


Figure 4: Meta-analytic summary for cardiac defect, septal defect and cleft/lip palate for pregnant woman exposed to ondansetron and control group.

The sensitivity analyses performed after removing data of studies with moderate to high risk did not show any deviation from primary pooled analysis.

3.3.2. Cardiac defect

Seven studies mentioning specifically about cardiac defect contributed in final analyses. As shown in Figure 4a, there were significantly more events amongst control arm as compared to intervention arm [OR: 1.26 (95% CI: 1.09-1.45); p=0.002]. There was moderate level of heterogeneity across the included studies with I^2 value 71%.

Septal defect

Five studies showed that septal defect was high in control arm than in intervention arm however, the difference was not statistically significant [Figure 4b; OR: 1.39 (95% CI: 1.01-1.91); p=0.05]. An I^2 of 48% suggested a moderate degree of heterogeneity amongst the included studies.

Cleft lip/palate

Three studies were considered for analyses. There is no significant difference for cleft lip/palate between control arm and intervention arm [Figure 4c; OR: 1.11 (95% CI: 0.80-1.53); p=0.55]. An I^2 of 41% suggested a moderate degree of heterogeneity *amongst* the included studies.

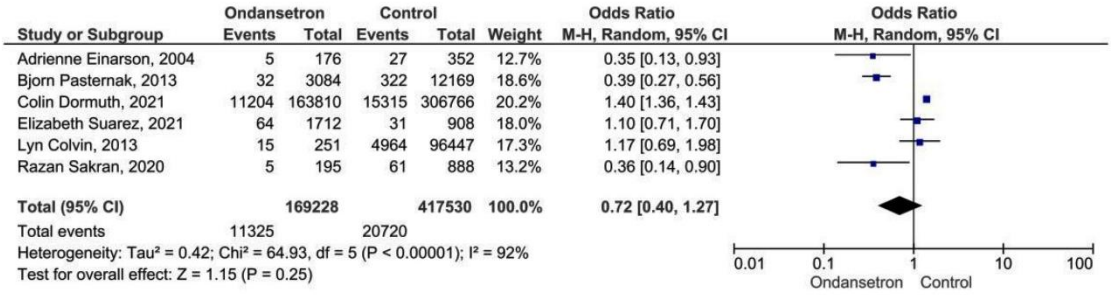
There was only one study specifically measured hypospadias and genitourinary abnormalities hence, meta-analysis was not possible for these two outcomes.

Other pregnancy related outcomes

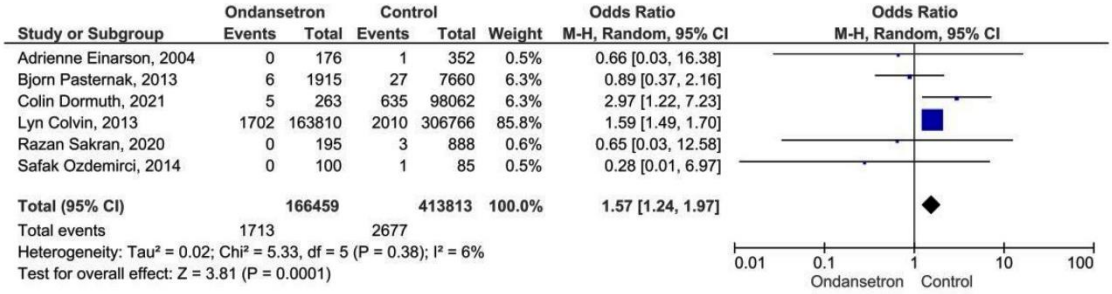
There was no significant difference found for spontaneous abortion/miscarriage and low birth weight

babies as shown in Figure 5a and 5d. Number of events for stillbirth and pre-term labour was significantly high in control arm than in intervention arm with OR: 1.57 (95% CI: 1.24-1.97); p=0.0001 and OR: 1.33 (95% CI: 1.05-1.69); p=0.02, respectively (Figure 5b and 5c).

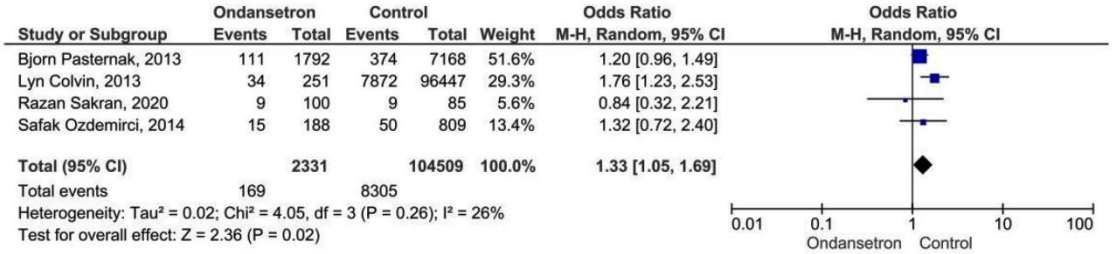
a) Spontaneous abortion/miscarriage



b) Stillbirth



c) Pre-term labour



d) Low birth weight babies

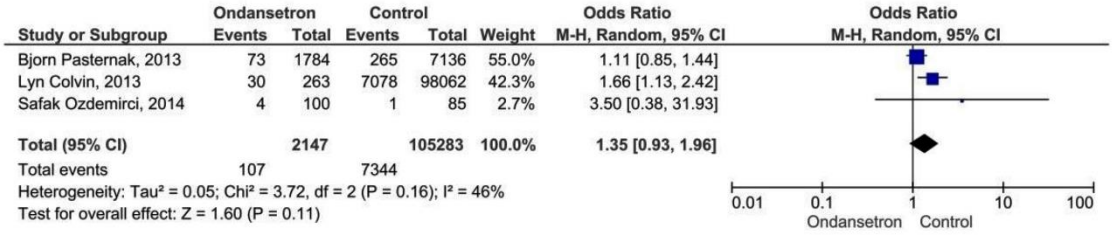


Figure 5: Meta-analytic summary for spontaneous abortion/miscarriage, stillbirth, pre-term labour, and low birth weight babies for pregnant women exposed to ondansetron and control group.

DISCUSSION

Nausea and vomiting during pregnancy are a common problem during first trimester and its early treatment is recommended to prevent progression into hyperemesis gravidarum (HG) by American College of Obstetricians and Gynecologists.[21] According to various clinical guidelines, ondansetron has been considered as a second-line treatment for severe NVP.[21-24] However, may be due to superior efficacy of ondansetron over pyridoxine-doxylamine and equivalent/superior efficacy as compared to metoclopramide, its utilization has been increased in last few years as a first line drug despite of its controversial safety profile in context to congenital malformations.[25-27] The present systematic review provide insight for

association between ondansetron exposure and congenital malformation. Ondansetron was not found to be associated with major congenital malformation, cardiac defect, septal defect, cleft lip/palate as compared to the control group. Cardiac defect was found significantly more in control group as compared to the ondansetron exposed group and this finding was in contrast to the study conducted by Dannielson et al.[6] Sensitivity analysis after removing moderate to high-risk studies did not affect the primary analysis findings of having no association of congenital malformation with ondansetron exposure. Thus, ondansetron is found to be safe in pregnancy. A study conducted by Parker et al using data from the National Birth Defects Prevention Study (1997-2011) and the Slone Birth Defects Study (1997-2014) showed no risk of birth defects with ondansetron whereas it warranted further investigations due to modest association of cleft palate and renal agenesis-dysgenesis.[5] In present study, we could not perform meta-analysis for hypospadias and genitourinary abnormality as it was mentioned only in study by Einarson et al.[1] In another case-control study conducted in USA, increased risk of cardiac and orofacial cleft defects with OR: 1.52 95% CI: 1.35-1.70 and OR: 1.32 95% CI: 0.76-2.28, respectively was found in offspring exposed to ondansetron as compared to women with no antiemetic exposure during pregnancy.[10] We did not include case control studies in present meta-analysis due to variability in study design as compared to cohort study. There were very few studies which consider cleft lip/palate hence, further investigation can be done to find out its robust association with ondansetron use. In present study, meta-analysis was also performed for various pregnancy related outcomes like spontaneous abortion/miscarriage, stillbirth, pre-term labour and low birth weight babies. There was high number of events of stillbirth and pre-term labour in control group as compared to ondansetron group. It may be due to effectiveness of treatment with ondansetron started for NVP and HG patients which might have helped in reducing the severity of disease.

United States Food Drug Administration (USFDA) does not restrict the use of ondansetron due to non-availability of reliable human epidemiological study data on association of ondansetron exposure and congenital malformation.[28] Whereas, in 2019, European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) assessment report based on same epidemiological data suggest not to use ondansetron during first trimester pregnancy.[29] The present review included the cohort and register based more recent studies from various countries in which exposure and occurrence of outcome were verified using records or interview. Few studies conducted matched or adjusted statistical analysis and we considered adjusted data whenever available to reduce the heterogeneity between the groups to increase the strength of the present systematic review. However, inclusion of population of different origin, lack of certainty about actual consumption of medication, and presence of other unadjusted confounding factors might have affected the outcome of interest. Hence, interpretation of present study finding should be taken into consideration after keeping these limitations in mind.

CONCLUSION

The present study concludes that there is no risk of major congenital malformations including septal/cardiac defects and cleft lip/palate with ondansetron exposure during first trimester pregnancy. However, special attention should be given to genitourinary abnormalities and hypospadias due to scarcity of data. Ondansetron exposure during pregnancy does not increase risk of spontaneous abortion/miscarriage, stillbirth, pre-term labour and low birth weight babies.

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