Meta-analysis

Use of ondansetron during first trimester of pregnancy and risk of congenital anomalies

Abstract:

Introduction: Ondansetron is a 5-HT3 serotonin receptor antagonist indicated for the prevention of acute nausea and vomiting induced by cytotoxic chemotherapy in adults. The results of studies published in the scientific literature on use of ondansetron during pregnancy are inconsistent. The aim of this meta-analysis was to synthesize findings and increase statistical power for rare outcomes such as congenital anomalies.

Method: The literature references were provided by Novartis, the marketing authorization holder of ZOPHREN® (oral, rectal and IV forms), within the framework of a request for type II variation concerning 4.6 and 5.3 of SmPCs. The articles published after February 2018 (not taken into account by the laboratory) and those found after reading the literature references of each article were added. The meta-analysis was performed using RevMan 5.3.

Results: Ten studies were eligible. Compared to non-exposed (disease free, sick or not specified), first trimester exposure to ondansetron was significantly associated with an increased risk of cardiac malformations (OR= 1.45, 95% CI = 1.04-1.92, I^2 = 80%, n = 5 studies), cardiac septal defects (1.32, 95% CI = 1.12-1.56, I^2= 59% ; n = 4 studies), and oral clefts (1.30, 95% CI = 1.04-1.63, I^2 = 0%; 3 studies).
No statically significant association was found for major malformations (OR= 1.07, 95%CI = 0.95-1.20; I^2=20%; 5 studies), cleft lip with or without cleft palate (OR = 1.04, 95% CI = 0.84-1.21; I^2=0%; 7 studies) or cleft palate (OR = 1.23, 95% CI = 0.83-1.84; I^2 = 72%; 6 studies).

Conclusion: Ondansetron is associated with an increased risk of cardiac abnormalities, especially septal defects, and orofacial clefts. SmPC of ondansetron-based products need to be updated to take into account these risks.

Post european evaluation situation:

As part of the internal assessment of the signal procedure performed by the ANSM, a meta-analysis was conducted and shared as part of the comments from France on the Rapporteur's assessment report. The meta-analysis showed that ondansetron was associated with an increased risk of cardiac abnormalities, especially septal defects, and orofacial clefts. These conclusions were discussed by the State Member Rapporteur and PRAC (Pharmacovilance Risk Assessement Committee) members who highlighted that the methodological quality of the studies should also be considered, which was agreed by the ANSM. Based on literature and pharmacovigilance data, the PRAC concluded by consensus that the product information of ondansetron-containing products should be updated to provide information on the magnitude of the risk of orofacial malformations and recommendations on the use of ondansetron during pregnancy in its authorised indications.

I. Introduction

Ondansetron is a 5-HT3 serotonin receptor antagonist indicated for the prevention of acute nausea and vomiting induced by cytotoxic chemotherapy in adults.

Novartis sent a type II variation on 05/12/2018 concerning sections 4.6 and 5.3 of SmPC for its ondansetron-based products. The results published in the scientific literature on the use of ondansetron during pregnancy are inconsistent. The aim of this meta-analysis was to synthesize findings and increase statistical power for rare outcomes such as congenital anomalies.

II. Method

Research Strategy:

The literature references were provided by Novartis, the marketing authorization holder of ZOPHREN® (oral, rectal and IV forms), within the framework of a request for type II variation concerning 4.6 and 5.3 of SmPCs.
The research strategy used by Novartis was as follows:
The published literature including case series, epidemiological studies and pre-clinical studies concerning reproductive toxicity associated with the use of ondansetron in pregnancy was evaluated cumulatively in the last EU PSUR (01Mar2015-28Feb2018). The relevant epidemiological analysis, discussion and conclusions from the analysis are presented here. Embase was searched. Any relevant publications referred in the retrieved data and previously not identified in the Embase search were also reviewed.
18 articles were identified by Novartis, and 9 have been added by the ANSM (4 published after February 2018 and 5 found in literature references of studies).

Criteria for inclusion and exclusion:

Cohort studies, case-control or randomized trials on risks following *in utero* exposure to ondansetron were included.
Following informations were extracted: first author, year of publication, study design, data sources, sample size, potential confounding factors considered, as well as results (Odds Ratios and Hazard Ratios / Relative Risk) and their confidence intervals (95% CI).
Studies were excluded: if there was no control group, or if the control group was also exposed to ondansetron (n = 1), if the exposure was to a class of drugs (antiemetics) and not to ondansetron only (n = 1), or on a substance other than ondansetron of the same class (n = 1), if the available data did not allow the calculation of OR (n = 3). Systematic reviews and meta-analysis (n = 6) were also excluded (but were used to verify the completeness of the literature search), as were animal studies and case series (n = 1) and studies on efficacy or only describing use of ondansétron (n=3).

Data analysis:

In case of several studies focused on the same population, the study having the most important population was kept for the analysis.
In case of several control groups (i.e. first unexposed control group, second control group exposed to another antiemetic), the choice was made to keep the results compared to the most similar group to the exposed group, e.g sick and / or exposed to another antiemetic.
The meta-analysis were performed using Cochrane Collaboration Review Manager Software (RevMan, version 5.3). When available, the adjusted results reported in the articles were used. Otherwise, the odd ratio was estimated from the raw data. A random model was used.

III. Results: risks following exposure to ondansétron during first trimester of pregnancy

The 10 following studies have been included in the meta-analysis.

Table 1: studies included in meta-analysis

author	country	design	population	exposure	comparator groups	Period of exposure
Anderka et al. 2012	USA	case-control study	National Birth Defects Prevention Study (NBDPS)- 1997-2004	4524 cases, 5859 controls; 67.1% NVP and 15.4% (n=621) treated for NVP in T1 (all meds)	unexposed (not otherwise specified)	1st trimester
Andersen et al. 2013 (abstract)	Denmark	cohort study	Danish Nationwide Cohort Study 1997-2010 Data from Medical Birth Registry, National Hospital Register, National Prescription Register	n=897,018 births during study period n=1248 redeemed prescription for ondansetron in T1. 58 (4.7%) had baby with congenital malformation after T1 prescription compared to 31,357 (3.5%) in unexposed group.	1) unexposed 2) sick, exposed to other treatment	1st trimester
Colvin et al. 2013	Australia	cohort study	Data from Western Australian Data Linkage System (WADLS) 2002–2005 including WA Birth Defects Registry, Midwives Notification System and National Prescribing Data (PBS)	96,968 births 251 exposed to ondansetron (263 offspring), includig 211 in T1	unexposed (not otherwise specified)	1st trimester
Danielsson et al. 2014	Sweden	cohort study	Swedish Medical Birth Register + Swedish Register of Prescribed Drugs, 1998-2012	In total: 1 501 434 infants and 43 658 had malformations classified as a major, 2.9%. 1349 infants born of women who had taken ondansetron in early pregnancy	1) unexposed 2) sick, exposed to other treatment	1st trimester
Einarson et al. 2004	Canada	Prospective comparative cohort	Pregnant women who called Teratogen Information Services (TIS) within a two year period	n=176 exposed, n=176 exposed to other anti-emetics, n=176 nonteratogen controls	1) unexposed 2) sick, exposed to other treatment	1st trimester (most between 5-9 weeks of gestation)
Fejzo et al. 2016	USA	cohort study	Hyperemesis Education and Research Founda-tion Web between 2007 and 2014	771 pregnancies in womenwith a history of HG with no ondansetron exposure and 1555 pregnancies with neither a history ofHG nor ondansetron exposure.	1) unexposed 2) sick, exposed to other treatment	1st trimester (90%)
Huybrechts et al. 2018	USA	cohort study	1 502 895 women enrolled in Medicaid 2000-2013	14 577 of 1 727 947 unexposed and 835 of 88 467 exposed infants were diagnosed with a cardiac malformation	1) unexposed 2) sick, exposed to other treatment	1st trimester
Parker et al. 2018	USA	case-control study	National Birth Defects Prevention Study (1997–2011) and the Slone Birth Defects Study (1997–2014).	6,751 and 5,873 control mothersin NBDPS and 14,667 and 8,533 case mothers in SBDS who reported first-trimester nausea and vomiting of pregnancy	1) unexposed 2) sick, exposed to other treatment	1st trimester
Pasternak et al. 2013	Denmark	cohort study	Medical Birth Registry and the National, Patient Register from January 1, 2004, through March 31, 2011.	608,385 pregnancies spontaneous abortion (1849 exposed women vs. 7396 unexposed women), stillbirth (1915 vs. 7660), any major birth defect (1233 vs. 4932), preterm delivery (1792 vs. 7168), and birth of infants at low birth weight and small for gestational age (1784 vs. 7136).	unexposed (not otherwise specified)	1st trimester

Zambelli-Weiner et al. 2018	USA	case-control study	all live births from 2000 to 2014 who had 1 year follow up for the infant = 864,083 mother-child pairs	Early exposure to ondansetron occurred in 76,330 mother-child pairs (8.8%), and early exposure to medical administration of ondansetron occurred in 5557 mother-child pairs (0.64%). 802,253 infants with no birth defects, 32,100 infants were diagnosed with cardiovascular birth defects, and 1590 infants were diagnosed with orofacial cleft defects.	1) unexposed 2) sick, exposed to other treatment	1st trimester prescription for ondansetron or a claim for medical administration of ondansetron

A. Major malformations

Five studies investigated the risk of major congenital malformations related to ondansetron exposure during first trimester of pregnancy. The results did not show a significant increased risk in the overall risk of major malformation (OR = 1.07, 95% CI = 0.95-1.20; I^2= 20%).

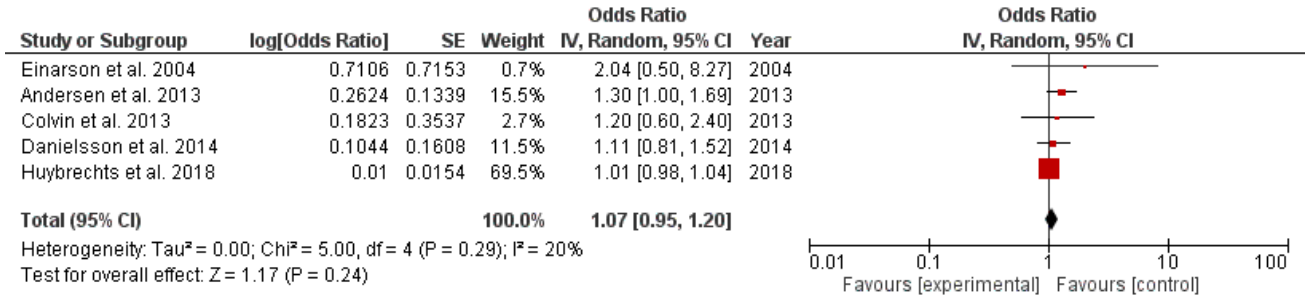


Figure 1: Ondansetron and risk of major congenital malformations

Pasternak et al. (2013) study was excluded because analysis were performed on the same Danish population than Andersen et al (2013) study but on a larger period and population. Including Pasternak et al study instead of Andersen did not change the results, except heterogeneity between studies (OR=1.0; IC95%=0.98-1.04; I^2=0%).

B. Cardiac anomalies

A meta-analysis of 5 studies showed an increased risk of global heart defects associated with ondansetron in first trimester of pregnancy (OR = 1.45, 95% CI = 1.04-2.03). Heterogeneity between studies is important (I^2= 80%).

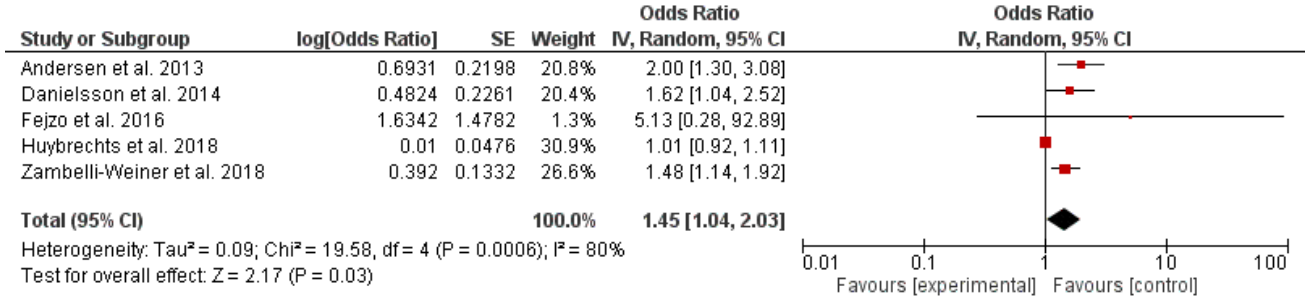


Figure 2: Ondansetron and risk of cardiac malformations

Pasternak et al. (2013) study was excluded because analysis were performed on the same Danish population than Andersen et al (2013) study but on a larger period and population. Moreover, OR from Andersen study were adjusted contrary to OR from Pasternak which were non-adjusted and were calculated from raw data.

Including Pasternak et al study instead of Andersen did not change the results (OR= 1.38 [1.03, 1.85]; I^2=75%).

C. Cardiac septal defects

Among cardiac malformations, meta-analysis on 4 articles showed an increased risk of cardiac septal defects associated with ondansetron at first trimester (OR = 1.32, 95% CI = 1.12-1.56, I^2 = 59%).

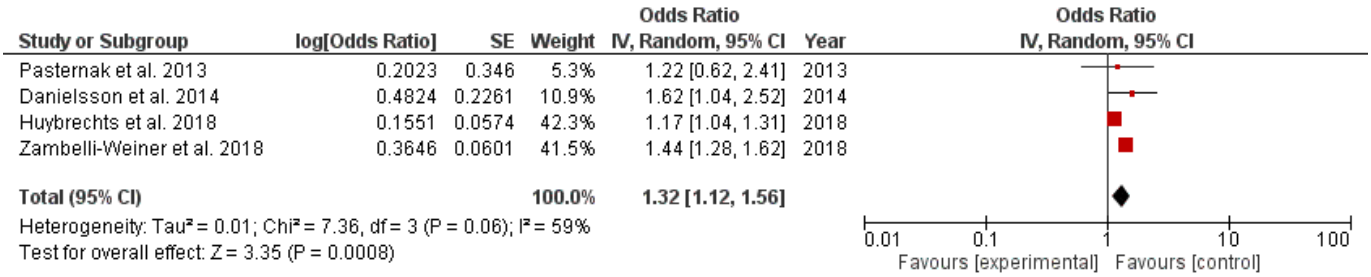


Figure 3: Ondansetron and risk of cardiac septal defects

D. Oral clefts

Based on 3 studies, first-trimester exposure to ondansetron is associated with an increased risk of oral cleft (OR = 1.30, 95% CI = 1.04-1.63, I^2 = 0%).

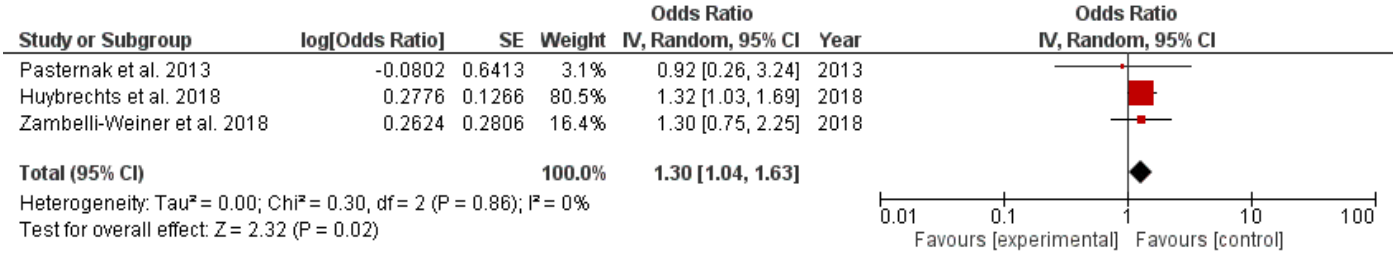


Figure 4: Ondansetron and risk of orofacial cleft

E. Clefts palate

Six studies evaluated the risk of cleft palates. The meta-analysis did not show an increased risk associated with ondansetron in early pregnancy (OR = 1.23, 95% CI = 0.83-1.84; I^2 = 72%).

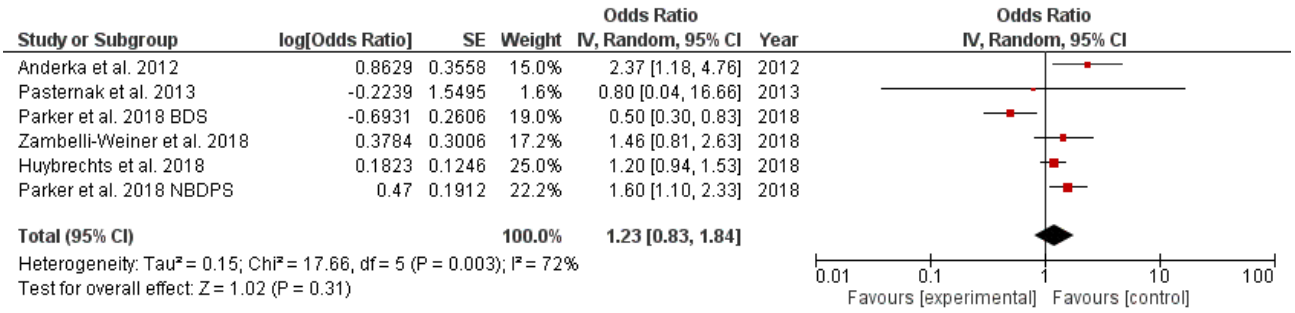


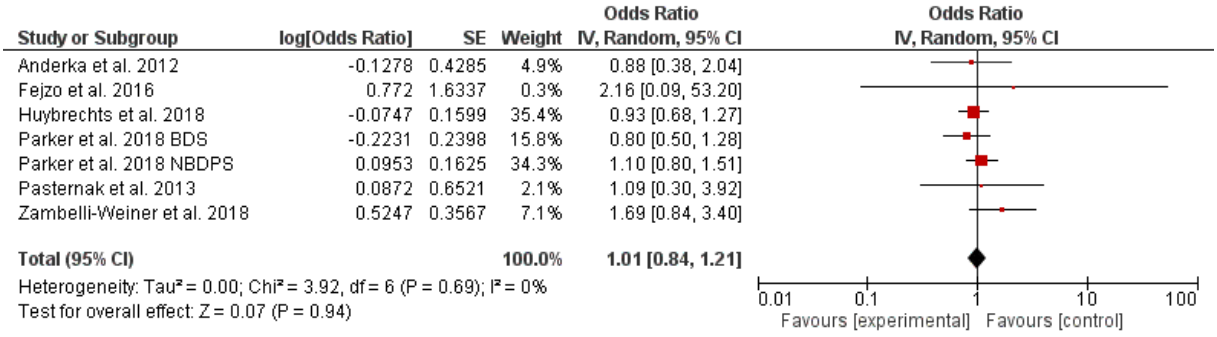
Figure 5 : Ondansetron and risk of cleft palate

It should be noted that a study (Pasker et al., based on the Birth Defect Study data) found a significantly *decreased* risk of cleft palate after in utero exposure to ondansetron in first trimester. The authors, who performed the same analysis based on another population (National Birth Defects Prevention Study), conducted several sensitivity analysis to explain this inconsistent result, but no explanation could be given. After removing this study (Pasker et al, BDS) from meta-analysis, the heterogeneity between studies became low and the association between ondansetron and cleft palate risk was then significantly increased (OR = 1.40, 95% CI = 1.14). 1.72, I^2 = 8%, 5 studies).

When considering the safety of ondansetron, the choice could have been made to be as conservative as possible using a fixed-effect model, even if there was considerable heterogeneity between analysis. In this case, the risk of cleft palate would have been statistically increased, even including Parker et al-BDS study (OR= 1.22, 95% CI = 1.03-1.46, I^2 = 72%).

F. Clefts lip with or without cleft palate

A meta-analysis on 7 studies showed no increased risk of cleft lip with or without cleft palate exposure to ondansetron in utero (OR = 1.01, 95% CI = 0.84-1.21; I^2=0%).



<u>Figure 6 :</u> Ondansetron and risk of cleft lip with / without cleft palate

G. Sensitive analysis

As Andersen's study is an abstract that has not resulted in a peer-reviewed publication, caution is warranted concerning its inclusion in meta-analysis. Moreover, reluctance to include Pasternak's study can be justified as in most cases only raw data were available to calculate an unadjusted OR. We conducted sensitive analysis to address these limitations. Results showed that pooled effect estimate are not significantly changed without Pasternak's or Andersen's studies for oro-facial clefts and septal defects. Take into consideration only adjusted OR provided by the authors does not substantially modified pooled estimates studies (see table below).

outcome	including all studies	exluding Pasternak* or Andersen's** study	excluding OR calculated based on raw data
major malformations	OR = 1.07, 95% CI = 0.95-1.20; I^2= 20%	1.01 [0.98, 1.04]; I^2= 0%**	1.07 [0.95, 1.20] ; I^2= 20% [1]
oro-facial clefts	**OR= 1.30, 95% CI = 1.04-1.63, I^2= 0%**	**1.32 [1.05, 1.65]. I^2= 0%***	**1.32 [1.05, 1.65]. I^2= 0% [1]**
cleft lip w/wo cleft palate	OR= 1.01, 95% CI = 0.84-1.21; I^2= 0%	1.00 [0.83, 1.21].i^2=0%*	1.05 [0.81, 1.36] ; I^2= 10% [3]
cleft palate	OR= 1.23, 95% CI = 0.83-1.84; I^2= 72%	1.24 [0.82, 1.88] ; I^2=77%*	1.24 [0.82, 1.88] ; I^2=77% [1]
cardiac malformation	**OR= 1.45, 95% CI = 1.04-2.03; I^2= 80%**	1.31 [0.94, 1.82] ; I^2=75%**	**1.43 [1.02, 2.00] ; I^2=84% [2]**
cardiac septal defects	**OR= 1.32, 95% CI = 1.12-1.56, I^2= 59%**	**1.43 [1.02, 2.00] ; I^2=73%***	**1.43 [1.02, 2.00] ; I^2=73% [1]**

[1] *excluding Pasternak's study only*
[2] *excluding Fejzo's study only*
[3] *excluding Pasternak's, Fejzo's and Huybrecht's studies*

II. Discussion

The results published in the scientific literature on the risks of exposure to ondansetron during pregnancy were inconsistent. This meta-analysis found an increased risk of cardiac abnormalities, especially septal defects, and oral clefts after first trimester exposure to ondansetron, compared to non-exposed (sick or not).

This literature review and meta-analysis has several limitations: the literature search was done by a laboratory and was not verified. However, the literature references of each study initially identified by the laboratory were checked to include additional studies. In addition, an abstract of a meta-analysis made by another French team on risks related to the use of ondansetron during pregnancy was published and used the same articles (authors have been contacted). Several biases may be mentioned in selected studies: some important confounders could not be taken into account (e.g known teratogenic drugs) and some results used for the meta-analysis were not adjusted. It is not known if miscarriages following malformations have been taken into account. Not taken into account these cases, would probably have led to increase the risk associated to in utero exposure to ondansetron.
Some studies have chosen a comparator group not exposed to ondansetron (sick or not, exposed to other drugs or not), not allowing to take into account the risk related to the pathology itself (although some studies have shown decreased risk of miscarriage in patients with vomiting in early pregnancy). In order to reduce bias associated with the pathology, when the studies permitted it, the comparator group "sick, exposed to another antiemetic" was chosen. It might have been interesting to make sensitivity analysis by type of comparator group.

We choose to include the effect estimates from the Zambelli-Weiner et al (2019) when “medical administration of ondansetron” occurred, to address classification bias found in other studies based on prescription data only (prescribed does not mean administrated and not necessarily the same day than the prescription, leading to misclassification in period of exposure too).

Another difficulty is related to conflicting results with data from the same origins, without explanations, for instance:

- Based on the same databases, with an overlapping study period, almost the same number of exposed pregnancies, Andersen 2013 retrieved a double risk of cardiac malformations after in utero exposure to ondansetron, whereas Pasternak 2013 did not. However, including Pasternak’s study instead of Andersen’s did not change the results;
- In their publication, Parker 2018 used data from two case–control studies, the National Birth Defects Prevention Study (1997–2011) and the Slone Birth Defects Study (1997–2014) to investigate the association between malformations and prenatal exposure to ondansetron. For cleft palate, the association with ondansetron was elevated in the National Birth Defects Prevention Study but not in the Birth Defects Study. To explore the discrepant findings for cleft palate in the two studies, the authors conducted several sensitivity analyses, but all failed to explain the differences observed in the main analysis.

We were informed after the finalization of this analysis that the estimate from Andersen et al (2013) selected for the meta-analysis was later revised by the authors and moved from 2.0 (CI95% 1.3-3.1) to 1.6 (CI95% 1.1-3.1) with increased number of exposures (Andersen et al 2014). However, taking into account this odd ratio, results remain in favor of an increased risk (OR= 1.37 [1.02, 1.84]; I^2=75%) of congenital anomalies.

Finally, we can note the small number of studies for some pregnancy outcomes that did not allow to make sensitivity analysis depending on the design study, divergent results (sometimes a significant heterogeneity, between studies), and potential publication bias.

Another French team worked on a meta-analysis on use of ondansetron during pregnancy. The study is not published yet but it has been presented during a congress in France in June 2019. The results are also in favor of an increased risk of oro-facial cleft and septal defect. The abstract is available at the following link https://onlinelibrary.wiley.com/doi/epdf/10.1111/fcp.12468 (réf.CO-054); this meta-analysis addresses some limitations of ANSM meta-analysis, in particular, authors assessed the risk of bias of each study included in their meta-analysis. The authors used a proprietary collaborative WEB-based meta-analysis platform. Main results and protocol are available online: http://metapreg.org/viewMA.aspx?exposition=281.

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