Ondansetron in pregnancy revisited: Assessment and pregnancy labelling by the European Medicines Agency (EMA) & Pharmacovigilance Risk Assessment Committee (PRAC).

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Ondansetron in pregnancy

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Ondansetron is an effective antiemetic that is being widely used as a second-line treatment option for severe Nausea and Vomiting of Pregnancy (NVP) in accordance with clinical guidelines (1–4).

In July 2019, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) released updated comprehensive assessment report on the use of ondansetron in first trimester (5). This report is a detailed assessment of the available published data on the subject, including responses to supplementary questions posed to the Marking Authorization Holder (MAH), and the authors to the two central publications discussed below. The ensuing Summary of product Characteristics (SmPC) was updated in November 2019 with important changes to section 4.6 "Fertility, pregnancy and lactation" (6), which now state that ondansetron should not be used in first trimester of pregnancy.

We acknowledge that the EMA SmPC in principal only frames the way that the MAH are legally allowed to market their product within the EU. It does not bind the physician as such; they must act and adhere with reference to the legal framework of their respective countries. We also acknowledge that EMA operates within a given formalized set of options on SmPC phrasings. In everyday practice however, the wording of the SmPC has consequences for treatment options and decision support beyond those formal to the legal ramifications of the SmPC.

We applaud the EMA for the following nuanced phrasings in the SmPC:

- *Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.*
- *In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).*
- *The available epidemiological studies on cardiac malformations show conflicting results.*

We believe that data from animal studies are of less relevance in these and analogue situations with an abundance of human data available:

"Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity."

We do not believe that the most important sentence therein is appropriately substantiated or justified:

"Ondansetron should not be used during the first trimester of pregnancy."

The latter statement comes with very clear and immediate consequences to clinical practice and pregnant women suffering from NVP. Previous somewhat contradictory data notwithstanding (7), the core of the discussion is down to the interpretation of two extraordinarily large sets of data. These are recent publications each comprising 80.000+ first-trimester exposed liveborn children. Previous studies with somewhat contradictory results comprise cumulated first trimester exposures less than 10% of these new data.

Huybrechts et al., a well-established research group within studies of adverse pregnancy outcome following drug exposure during pregnancy with an elite publication track-record, published their large study in December 2018 (8). In this meticulously designed, conducted and reported study comprising 88.000 liveborn children exposed to ondansetron in first trimester, they reported no increased overall risk of malformations and null associations for any or cardiac malformations and a small increased risk for oral cleft. Compared to 1,727.000 unexposed liveborn, propensity score adjusted relative risks were 1.01 (95% CI 0.98-1.05), 0.99 (95% CI 0.93-1.06) and 1.24 (95% CI 1.03-1.48) for any, cardiac and oral cleft malformations, respectively. The increased risk of oral clefts corresponds to about 3 additional cases for every 10.000-liveborn children exposed to ondansetron in first trimester.

Zambelli-Weiner et al. published their findings from a large study in January 2019 (9). This triggered controversy and extensive discussions among clinicians and researchers within the field.

They reported data on 82.000 liveborn children exposed to ondansetron in first trimester. Compared to about 780.000 unexposed liveborn, their overall analysis identified a weak but no clinically meaningful association with cardiac effects, aOR 1.04 (95% CI 1.00-1.08) and a weak association to orofacial clefts, aOR 1.12 (95% CI: 0.95-1.33). A*de facto* subgroup analysis – defined by the authors as "primary analysis" - restricted exposure to 5.500 women who were administered ondansetron in hospitals ("medical administration"). The inferential analysis substantially reinforced the overall weak signal for cardiac effects (aOR 1.43; 95% CI 1.28-1.61) but not orofacial clefts, (aOR 1.30; 95% CI: 0.75-2.25). The technical analysis appears suboptimal as adjustments were made as by a crude approach; i.e. the selection of confounder variables was based on these resulting in at least 10% change in effect estimates rather than simply including all selected confounders in the model.

It appears plausible that this subpopulation of pregnant women in whom hospital treatment was deemed necessary, suffered from a more severe presentation of NVP, a confounder that they did not accounted for. The sensitivity analysis performed in patients assigned a diagnosis of NVP or hyperemesis gravidarum does not satisfactorily account for this. In almost all exposed cases, the exposure comprised a single intravenous dose of ondansetron. It is biologically counterintuitive that a causal relation to cardiac malformations be present based on such exposure. The paper reports extraordinarily high rates of congenital cardiac malformations be it among unexposed (3.7%) or exposed (5.5 and 4.1% for intravenous and any exposure, respectively) liveborn children. These observations are incompatible with all other reported data on the rate of congenital cardiac malformations. The external validity of the study findings is therefore less convincing and compromises comparisons to other findings.

The authors did not provide satisfactory responses to additional questions poses by PRAC during the assessment process. Five specific questions were posed, and the authors did not address any of these. They provided a short narrative statement that did not serve to clarify or advance understanding of their findings (5). Not least, this paper is severely compromised by an initially undisclosed serious conflict of interest. The formal COI disclosure in the paper state: *"As an organization, TTi reports receiving funds from plaintiff law firms involved in ondansetron litigation..."* The extent of this COI was only revealed during a litigation process. The specific study received substantial funding ($ 210.000) from plaintiffs' representation who was pursuing litigative damage by claiming malformations from ondansetron use in pregnancy (10). It is the position of the undersigned and ENTIS Scientific Committee that this study is methodologically and ethically compromised to an extent that the results thereof *cannot be considered* when assessing the totality of evidence on the safety of ondansetron in pregnancy.

Since the PRAC recommendation two additional studies have been published that should be considered in the overall assessment of the risk during pregnancy.

In January 2020, Huybrechts et al. published an additional study on intravenous administration of ondansetron in early pregnancy and risk of congenital malformations (11). In this study, the authors revisited the study population from their original paper, but restricted their analysis to those women who received intravenous ondansetron in first trimester (8). The resulting propensity-score adjusted inferential analysis of about 24.000 pregnancies exposed to intravenous ondansetron did not result in increased risk of cardiac malformations (RR 0.97; 95% CI 0.86-1.10), oral clefts (RR 0.95; 95% CI 0.63-1.43), or any congenital malformation(RR 1.02; 95% CI 0.96-1.08). Unadjusted analyses suggested a small increased risk for cardiac and any malformation (11). These data strongly mitigate the previous data on intravenous ondansetron (9).

Lemon and colleagues reported a small increased risk of ventricular septal defect (VSD) following first trimester exposure to intravenous or oral ondansetron in first trimester among 3700 pregnancies (12). Across various methodological approaches the adjusted risk ratio varied between 1.7 and 2.1 with 95% CI ranging between 1.0 and 4.0. In an overall analysis though there was no increased risk for any birth defect or any heart defect, illustrating the dilemma of splitting versus lumping in such analyses (13). In this study, there may be an issue of ascertainment bias. Women exposed to ondansetron likely suffered from more severe NVP and thus may have been be subject to more attention and their newborn babies to a greater extent are subject to an echocardiograph evaluation. VSDs may be clinically asymptomatic and "Up to 80% of small, muscular VSDs and 30%-50% of perimembranous defects will close spontaneously" (14).

In summary, we believe that the abundance of most methodologically convincing data on cardiovascular malformations is reasonably reassuring. Even if a small excess risk may still be present, ondansetron in first trimester should remain an option for pregnant women with severe NVP.

It is the opinion of ENTIS that the EMA decision to explicitly discourage first trimester treatment with ondansetron puts pregnant women with severe NVP, physicians and health care professionals between a rock and a hard place. We do not agree that the specific wording against the use of ondansetron in first trimester is justified and we do not support the conclusion of EMA/PRAC assessment report and this section of the SmPC.

We urge the EMA/PRAC to carefully consider everyday clinical consequences of formal regulatory decisions. In cases with likely widespread clinical consequences, we suggest that EMA/PRAC consult liberally with relevant patient organizations, clinicians and health care professionals before final adoption of a recommendation.

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Disclosure of interests

The author declares no conflict of interest.

Contribution to authorship

Per Damkier conceived and drafted the manuscript. The ENTIS Scientific Committee provided critical comments and approved the final version of the manuscript.

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References:

1. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69) [Internet]. Royal College of Obstetricians & Gynaecologists. [cited 2020 Feb 25]. Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

2. Fiaschi L, Nelson-Piercy C, Deb S, King R, Tata LJ. Clinical management of nausea and vomiting in pregnancy and hyperemesis gravidarum across primary and secondary care: a population-based study. BJOG Int J Obstet Gynaecol. 2019 Sep;126(10):1201–11.

3. Taylor LG, Bird ST, Sahin L, Tassinari MS, Greene P, Reichman ME, et al. Antiemetic use among pregnant women in the United States: the escalating use of ondansetron. Pharmacoepidemiol Drug Saf. 2017 May;26(5):592–6.

4. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 189: Nausea And Vomiting Of Pregnancy. Obstet Gynecol. 2018;131(1):e15–30.

5. Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron [Internet]. 2019 [cited 2020 Feb 25]. Available from: https://www.ema.europa.eu/en/documents/prac-recommendation/updated-signal-assessment-report-birth-defects-following-utero-exposure-during-first-trimester_en.pdf

6. Ondansetron 4 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc) [Internet]. [cited 2020 Feb 25]. Available from: https://www.medicines.org.uk/emc/product/5222/smpc#PREGNANCY

7. Kaplan YC, Richardson JL, Keskin-Arslan E, Erol-Coskun H, Kennedy D. Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis. Reprod Toxicol Elmsford N. 2019;86:1–13.

8. Huybrechts KF, Hernández-Díaz S, Straub L, Gray KJ, Zhu Y, Patorno E, et al. Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA. 2018 18;320(23):2429–37.

9. Zambelli-Weiner A, Via C, Yuen M, Weiner DJ, Kirby RS. First trimester ondansetron exposure and risk of structural birth defects. Reprod Toxicol Elmsford N. 2019;83:14–20.

10. Schachtman Law ¿¿ Litigation Science – In re Zambelli-Weiner [Internet]. [cited 2020 Feb 27]. Available from: http://schachtmanlaw.com/litigation-science-in-re-zambelli-weiner/

11. Huybrechts KF, Hernandez-Diaz S, Straub L, Gray KJ, Zhu Y, Mogun H, et al. Intravenous Ondansetron in Pregnancy and Risk of Congenital Malformations. JAMA. 2019 Nov 15;

12. Lemon LS, Bodnar LM, Garrard W, Venkataramanan R, Platt RW, Marroquin OC, et al. Ondansetron use in the first trimester of pregnancy and the risk of neonatal ventricular septal defect. Int J Epidemiol. 2019 Dec 20;

13. Kallen B. Lumping or Splitting? In: Drugs During Pregnancy: Methodological Aspects. Springer 2016. pp89-91.

14. Scholz T, Reinking B. Congenital Heart Disease. In: Gleason A, Juul SE (eds). Avery's Diseases of the Newborn. 10th edn. Philadelphia, PA: Elsevier, 2018.