Ondansetron: Concerns regarding birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications

Ondansetron is a 5HT-3 receptor antagonist licensed for prevention and treatment of nausea and vomiting caused by either abdominal surgery or cancer chemotherapy. It is not infrequently used to treat nausea and vomiting in early pregnancy, although it is not offically licensed for this purpose.

In July 2020, Swissmedic published a Healthcare Professional Communication [1] informing about ondansetron containing medicines, stating that [2]:

- Use of ondansetron containing medicines during pregnancy is not recommended
- Women of childbearing potential should be advised to use effective contraception during treatment and 2 days after treatment cessation
- Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy
- The available epidemiological studies on cardiac malformations show conflicting results

This Direct Healthcare Professional Communication was issued following the publication of four studies, which together included approximately 115,400 first trimester exposures to ondansetron [3, 4, 5, 6]. Two of them identified a small increase of the risk of cleft lip and/or palate [3, 4], while the third one described a small increase in cardiac malformations (ventricular septal defect risk ratio 1.7, 95% CI; 1.0 to 2.9) [6]. Although the findings of the first study identifying associations with cleft lip and/or palate appear robust, the absolute increase in risk of orofacial cleft following first trimester maternal ondansetron use was very small, corresponding to approximately 3 additional cases per 10,000 births, over a background rate of 11 per 10,000 unexposed pregnancies [3]. The same study found no statistically significant increase of the risk of cardiac defects, after adjusting the results for a large number of relevant co-variates (risk ratio 1.01, 95% CI; 0.92 to 1.12) [3]. In addition, the same authors separately published a subgroup analysis of 23,877 pregnant women with intravenous use of ondansetron during first trimesters of pregnancy, which was associated neither with an increased risk of cleft palate nor with an increased risk of heart defects [5].

Ondansetron use in the management of nausea and vomiting in pregnancy is rather common (up to 15% in some studies) [7-9] and has increased in

recent years [10]. This may be due to the improved efficacy and less problematic side effect profile of ondansetron in comparison with other antiemetic drugs like metoclopramide or H1 antagonists. There is also much more information available about safety during pregnancy for ondansetron than other antiemetic drugs, with data now available from over 200,000 women treated during the first trimester [3-18].

In our opinion, direct Healthcare Professional Communications, "contraindications" and "recommendations for contraceptive measures" should be restricted to those drugs, for which sizeable teratogenic or foetotoxic effects are evident [19]. Such warnings could indeed result in less effective control of maternal nausea and vomiting, increased maternal morbidity and hospitalisation, and an increased risk of termination of wanted pregnancies. Additionally, they could lead to disproportionate concerns for women who have received ondansetron in the first trimester.

In view of the most recently published data, ondansetron should be reserved as a second line agent for the treatment of severe nausea and vomiting in pregnancy, in particular persisting after the end of first trimester, once the risk of facial malformations is over. In case of earlier introduction, patients must be adequately counselled regarding the benefits of ondansetron together with the small increase in risk of orofacial cleft, which may exist. Ondansetron should still be considered as an option for patients with serious *hyperemesis gravidarum*, in whom first line treatments have failed.

References

[1] https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/health-professional-communication--hpc-/dhpc-veroeffentlichte-epidemiologische-studien.html

[2] Louise A Michie 1, Kenneth K Hodson. Ondansetron for nausea and vomiting in pregnancy: re-evaluating the teratogenic risk. Obstet Med. 2020 Mar;13(1):3-4.

[3] Huybrechts, K.F., S. Hernandez-Diaz, L. Straub, K.J. Gray, Y. Zhu, E. Patorno, R.J. Desai, H. Mogun, and B.T. Bateman, Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring. JAMA, 2018. 320(23): p. 2429-2437. PMID: 30561479.

[4] Parker, S.E., C. Van Bennekom, M. Anderka, and A.A. Mitchell, Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. Obstet Gynecol, 2018. 132(2): p. 385-394. PMID: 29995744.

[5] Huybrechts, K.F., S. Hernandez-Diaz, L. Straub, K.J. Gray, Y. Zhu, H. Mogun, and B.T. Bateman, Intravenous ondansetron in pregnancy and risk of congenital malformations. JAMA (IF51.273) Pub Date: 2020-01-28,DOI: 10.1001/jama.2019.18587

[6] Lemon LS et al: Ondansetron use in the first trimester of pregnancy and the risk of neonatal ventricular septal defect. International Journal of Epidemiology, 2019, 1–9; doi: 10.1093/ije/dyz255

[7] Fiaschi, L., G. Housley, C. Nelson-Piercy, J. Gibson, A. Raji, S. Deb, and L.J. Tata, Assessment of discharge treatment prescribed to women admitted to hospital for hyperemesis gravidarum. Int J Clin Pract, 2019. 73(1): p. e13261. PMID: 30239072.

[8] Fiaschi, L., C. Nelson-Piercy, S. Deb, R. King, and L.J. Tata, Clinical management of nausea and vomiting in pregnancy and hyperemesis gravidarum across primary and secondary care: a population-based study. BJOG, 2019. 126(10): p. 1201-1211. PMID: 30786126.

[9] Taylor, L.G., S.T. Bird, L. Sahin, M.S. Tassinari, P. Greene, M.E. Reichman, S.E. Andrade, K. Haffenreffer, and S. Toh, Antiemetic use among pregnant women in the United States: the escalating use of ondansetron. Pharmacoepidemiol Drug Saf, 2017. 26(5): p. 592-596. PMID: 28220993.

[10] Anderka, M., A.A. Mitchell, C. Louik, M.M. Werler, S. Hernandez-Diaz, and S.A. Rasmussen, Medications used to treat nausea and vomiting of pregnancy and the risk of selected birth defects. Birth Defects Res A Clin Mol Teratol, 2012. 94(1): p. 22-30. PMID: 22102545.

[11] Berard, A., O. Sheehy, J. Gorgui, J.P. Zhao, C. Soares de Moura, and S. Bernatsky, Medications for nausea and vomiting of pregnancy and the risk of birth defects. J Clin Epidemiol, 2019. PMID: 31352006.

[12] Colvin, L., A.W. Gill, L. Slack-Smith, F.J. Stanley, and C. Bower, Off-label use of ondansetron in pregnancy in Western Australia. Biomed Res Int, 2013. 2013: p. 909860. PMID: 24396830.

[13] Danielsson, B., B.N. Wikner, and B. Kallen, Use of ondansetron during pregnancy and congenital malformations in the infant. Reprod Toxicol, 2014. 50: p. 134-7. PMID: 25450422.

[14] Einarson, A., C. Maltepe, Y. Navioz, D. Kennedy, M.P. Tan, and G. Koren, The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study. Bjog, 2004. 111(9): p. 940-3. PMID: 15327608.

[15] Fejzo, M.S., K.W. MacGibbon, and P.M. Mullin, Ondansetron in pregnancy and risk of adverse fetal outcomes in the United States. Reprod Toxicol, 2016. 62: p. 87-91. PMID: 27151373.

[16] Parker, S.E., C. Van Bennekom, M. Anderka, and A.A. Mitchell, Ondansetron for Treatment of Nausea and Vomiting of Pregnancy and the Risk of Specific Birth Defects. Obstet Gynecol, 2018. 132(2): p. 385-394. PMID: 29995744.

[17] Pasternak, B., H. Svanstrom, and A. Hviid, Ondansetron in pregnancy and risk of adverse fetal outcomes. N Engl J Med, 2013. 368(9): p. 814-23. PMID: 23445092.

[18] Van Bennekom, C., S.E. Parker, M. Anderka, C. Louik, and A.A. Mitchell, Ondansetron for the treatment of nausea and vomiting of pregnancy and the risk of birth defects [Abstract]. Pharmacoepidemiology and Drug Safety, 2015. 1(587): p. 401. PMID: NA

[19] C. Schaefer. Ondansetron und die Krux der Risikokommunikation zu Arzneimitteln bei Schwangeren. Arzneiverordnung in der Praxis vorab online 24. Februar 2020.

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