CERPO
Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Ondansetron y Embarazo: Riesgo de Malformaciones Congénitas.

Dra. Mª Francisca González.
Becada O&G HLTB Universidad de Chile

MAPA DE LA RUTA:

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- Introducción
- Ficha Farmacológica
- Epidemiología del fármaco en embarazo
- Estudios en relación a malformaciones congénitas
- Reacción de las sociedades
- Conclusiones

Introducción

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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04 July 2019
EMA/610728/2019
Pharmacovigilance Risk Assessment Committee (PRAC)

Updated Signal assessment report on birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications with ondansetron[1]
EPITT no: 19353

Agosto de 2019, la Agencia Europea de Medicamentos publicó el acta del Comité de Evaluación de Riesgos de Farmacovigilancia :

- Sospecha causa malformaciones orofaciales cuando se administra durante el primer trimestre del embarazo
- En relación a malformaciones cardíacas muestran resultados contradictorios
- Ondansetrón no debe usarse en el primer trimestre
- Si es una mujer en edad fértil, se le puede recomendar que use un método anticonceptivo eficaz.

3. Ondansetron – Signal of birth defects following in-utero exposure during the first trimester of pregnancy arising from recent publications (EPITT no 19353)

Summary of product characteristics

4.6. Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should consider the use of contraception.

Pregnancy

~~The safety of ondansetron for use in human pregnancy has not been established.~~ 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.
~~Evaluation of experimental~~ Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. ~~the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However, as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

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

Ficha Farmacológica: Ondansetrón

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- **Categoría farmacológica:** Antiemético; Antagonista selectivo del receptor 5-HT 3

- **Mecanismo de acción** : Actúa bloqueando la acción de la serotonina, una sustancia natural que puede causar náuseas y vómitos.

- **Indicaciones Oficiales:**
  - Náuseas y vómitos inducidos por la quimioterapia contra el cáncer: IV. Oral
  - Náuseas y / o vómitos postoperatorios: IV, IM, Oral
  - Náuseas y vómitos asociados con la radioterapia **:** Oral
- **RAM:** Prolongación QT: se han observado cambios en el ECG, incluida la prolongación del intervalo QT dependiente de la dosis, con el uso de ondansetrón, ya no se recomiendan dosis únicas> 16 mg de ondansetrón IV También se han informado casos de torsades de pointes.

Ondansetrón: información sobre medicamentos

Ficha Farmacológica: Ondansetrón

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- **Farmacocinética y Farmacodinamia:**
  - Inicio de acción: ~ 30 minutos
  - Absorción: Oral: 100%;
  - Unión a proteínas, plasma: 70% a 76%
  - Metabolismo: ampliamente hepático por hidroxilación, seguido de conjugación de glucurónido o sulfato; CYP1A2, CYP2D6 y sustrato CYP3A4; se produce algo de desmetilación
  - Biodisponibilidad: Oral: 50% a 70% debido a algún metabolismo de primer paso
  - Eliminación de semivida: Adultos de 3 a 6 horas
  - Tiempo de pick acción : oral: ~ 2 horas
  - Excreción: orina (44% a 60% como metabolitos, ~ 5% como fármaco inalterado); heces (~ 25%)

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Wolters Kluwer

Ondansetrón: información sobre medicamentos

Epidemiología del fármaco en embarazo

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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2017)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4185

BRIEF REPORT

Antiemetic use among pregnant women in the United States: the escalating use of ondansetron

Lockwood G. Taylor[1]*, Steven T. Bird[1], Leyla Sahin[1], Melissa S. Tassinari[1], Patty Greene[1], Marsha E. Reichman[1], Susan E. Andrade[2], Katherine Haffenreffer[3] and Sengwee Toh[3]

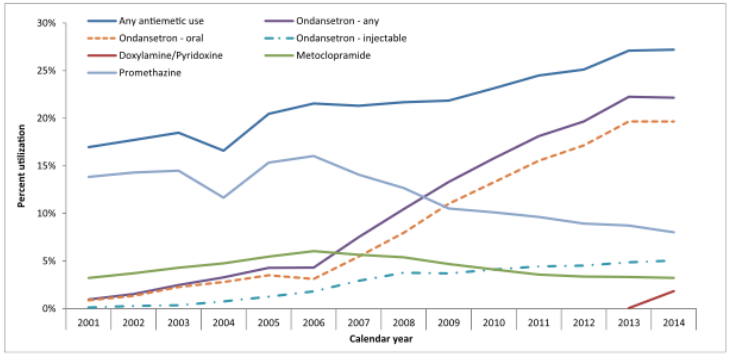

Figure 1. Utilization of antiemetic drugs among live birth pregnancies, by calendar year, in the Mini-Sentinel Distributed Database, 2001–2014[a,b] [Colour figure can be viewed at wileyonlinelibrary.com]

- Prevalencia 15.2 % (2.3 millones de embarazadas)
- Uso de Ondansetron a incrementado de <1% de los embarazos in 2001 a 22.2% in 2014, atribuible a la aparición de la presentación oral desde 2006.

ANALYSIS OF ANTIEMETIC USE IN PREGNANCY

Table 1. Prevalence of antiemetic prescription among live birth pregnancies identified in the Mini-Sentinel Distributed Database, 2001–2015[1]

Generic name[2]	Use in the 90 days before pregnancy	Any use during pregnancy	Any use, first trimester	Any use, second trimester	Any use, third trimester	Use in first, second, and third trimester
No. pregnancies	n = 2,342,489	n = 2,342,489	n = 2,342,489	n = 2,342,489	n = 2,341,992[4]	n = 2,341,992[4]
Any antiemetic	78 770 (3.36%)	550 335 (23.49%)	390 217 (16.66%)	265 820 (11.35%)	157 217 (6.71%)	52 453 (2.24%)
Dolasetron	346 (0.01%)	3155 (0.13%)	2167 (0.09%)	1568 (0.07%)	578 (0.02%)	165 (0.01%)
Doxylamine/Pyridoxine[3]	30 (0.00%)	8735 (0.37%)	6812 (0.29%)	5943 (0.25%)	1903 (0.08%)	1006 (0.04%)
Granisetron	161 (0.01%)	352 (0.02%)	163 (0.01%)	133 (0.01%)	123 (0.01%)	10 (0.00%)
Metoclopramide	9797 (0.42%)	93 481 (3.99%)	57 433 (2.45%)	38 868 (1.66%)	21 615 (0.92%)	2250 (0.10%)
Ondansetron	39 775 (1.70%)	356 777 (15.23%)	255 825 (10.92%)	167 490 (7.15%)	90 549 (3.87%)	29 390 (1.25%)
Palonosetron	26 (0.00%)	101 (0.00%)	16 (0.00%)	55 (0.00%)	74 (0.00%)	2 (0.00%)
Prochlorperazine	3173 (0.14%)	16 500 (0.70%)	10 263 (0.44%)	6070 (0.26%)	2719 (0.12%)	185 (0.01%)
Promethazine	37 115 (1.58%)	240 748 (10.28%)	158 275 (6.76%)	92 380 (3.94%)	63 774 (2.72%)	13 266 (0.57%)

[1]Not all Mini-Sentinel data partners contributed data for the entire study period; 2015 represents partial year of data.
[2]All formulations included (injectable, oral, rectal).
[3]Approved in 2013.
[4]Total number of pregnancies is lower for third trimester exposure because some live births occurred in late the second trimester.

BJOG: an International Journal of Obstetrics and Gynaecology
September 2004, Vol. 111, pp. 940–943
DOI: 10.1111/j.1471-0528.2004.00236.x

Estudios

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The safety of ondansetron for nausea and vomiting of pregnancy: a prospective comparative study

Adrienne Einarson,[a] Caroline Maltepe,[a] Yvette Navioz,[a] Deborah Kennedy,[b] Michael Paul Tan,[a] Gideon Koren[a]

- **Diseño:** Estudio prospectivo observacional comparativo (2004 Canadá)
- **Objetivo:** Determinar si uso durante el embarazo esta asociado con aumento de riesgo de malformaciones mayores.
- **Método:** embarazadas de 5-9 semanas en 3 grupos expuestas a ondansetrón, responden Cuestionario de severidad de nauseas y vómitos, seguimiento 4-6 meses post parto para conocer resultados obstétricos.

Table 2. Comparison of pregnancy outcome among women exposed to ondansetron, other anti-emetic medications and non-teratogen drugs (n = 176 in each group). Values are given as mean [SD] or n (%).

Outcome	Ondansetron	Other anti-emetics	Non-teratogen	P
Live birth	169 (96.8)	160 (91)	162 (92)	0.68
Miscarriage	5 (2.9)	13 (7.5)	14 (8)	0.46
Stillbirth	0 (0)	1 (0.5)	0 (0)	0.70
Therapeutic abortion	2 (1.3)	2 (0.5)	0 (0)	0.89
Major malformation	6 (3.5)	3 (1.8)	3 (1.8)	0.52
Birthweight (grams)	3362 [525]	3372 [608]	3490 [606]	0.08
Gestational age at birth	38.7 [1.7]	38.7 [1.9]	39.4 [1.6]	0.57

- **Conclusión**: No hay aumento del riesgo de malformaciones.
- **Limitantes:** Muestra pequeña

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Use of ondansetron during pregnancy and the risk of major congenital malformations: A systematic review and meta-analysis

Yusuf Cem Kaplan[a,b], Jonathan Luke Richardson[c,*], Elif Keskin-Arslan[a,b], Hilal Erol-Coskun[a,b], Debra Kennedy[d,e]

- **Objetivo:** Investigar si el uso de ondansetrón durante el embarazo se asocia con mayores tasas de malformaciones mayores o subgrupos.

- **Métodos:** PubMed / MEDLINE, Cochrane y Reprotox Se incluyeron estudios de observación que comprendían un grupo expuesto y de control.

- **Resultados:** No se identificó un aumento significativo del riesgo de malformaciones mayores, defectos cardíacos, hendiduras orofaciales, malformaciones genitourinarias o hipospadias en nuestro análisis primario. Existía una heterogeneidad significativa para el paladar hendido aislado.

- **Conclusiones:** no se asoció con un aumento significativo en la tasa de malformaciones principales o subgrupos seleccionados Sin embargo, los resultados de los análisis secundarios justifican la necesidad de una vigilancia continua.
- Estos resultados pueden ser tranquilizadores para las mujeres embarazadas en quienes el uso de ondansetrón está clínicamente indicado, ya que los riesgos absolutos de posibles inquietudes parecen ser bajos.

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Table 1
Characteristics of the studies.

a. Cohort studies investigating major and organ-specific congenital malformation rates following ondansetron exposure during pregnancy

	Einarson et al. 2004	Colvin et al. 2013	Pasternak et al. 2013	Andersen et al. 2013	Danielsson et al. 2014	Fejzo et al. 2016
Country	Canada and Australia	Australia	Denmark	Denmark	Sweden	United States
Study Period	–	2002-2005	2004-2011	1997-2010	1998–2012	2007-2014
Design/setting	Prospective Cohort	Registry-based Cohort	Registry-based Cohort	Registry-based Cohort	Registry-based Cohort	Retrospective Cohort
Data source	Nausea and Vomiting of Pregnancy Helpline or Teratogen Information Services (TIS) at The Motherisk Program in Toronto or The Mothersafe Program in Sydney	Australian Pharmaceutical Benefits Scheme, Western Australian Data Linkage System, Hospital Morbidity Data System, Midwives' Notification System, Registry of Births and Deaths, Western Australian Register of Developmental Anomalies	Danish Medical Birth Registry, Danish National Patient Register, Danish National Prescription Registry, Danish Central Person Register, Statistics Denmark	Danish Medical Birth Registry, National Hospital Register, Danish National Prescription Registry	Swedish Medical Birth Register, Swedish Prescription Register, Birth Defect Register, Midwife Interview	Hyperemesis Education and Research Founda-tion Web site (www.HelpHer.org)
Number of participants	528 pregnant women / 491 infants	96,698 pregnant women / 98,325 infants	608,385 pregnancies / 442,748 infants	897,018 births	1,501,434 infants	1335 pregnant women / 3396 pregnancies /2679 live birts
Number of events	Total birth: 169	Total: 211	Total: 1233	Total: 1234	Total: 1349	Total: 952
Ondansetron-exposed (First trimester):	MCM: 6 Heart defects: 1 Oral cleft: 0 Genitourinary: 4 Renal defects: 1 Hypospadias: 3	MCM: 10 Heart defects: [a] Oral cleft: [a] Genitourinary: 5 Renal defects: N/A Hypospadias: [a]	MCM: 36 Heart defects: 13 Oral cleft: 3 Genitourinary: 8 Renal defects: 4 Hypospadias: 4	CM: 58 Heart defects: N/A Oral cleft: N/A Genitourinary: N/A Renal defects: N/A Hypospadias: N/A	MCM: 38 Heart defects: 19 Oral cleft: 1 Genitourinary: 4 Renal defects: 0 Hypospadias: 3	MCM: 15 Heart defects: 5 Oral cleft: 1 Genitourinary: 2 Renal defects: 0 Hypospadias: 2
Unexposed:	Total birth: 162 MCM: 3 Heart defects: 2 Oral cleft: 0 Genitourinary: 1 Renal defects: 0 Hypospadias: 1	Total: 98,062 MCM: 3975 Heart defects: 641 Oral cleft: 215 Genitourinary: 1352 Renal defects: N/A Hypospadias: 361	Total: 4932 MCM: 141 Heart defects: 50 Oral cleft: 13 Genitourinary: 25 Renal defects: 11 Hypospadias: 12	Total: 895,914 CM: 31357 Heart defects: N/A Oral cleft: N/A Genitourinary: N/A Renal defects: N/A Hypospadias: N/A	Total: 1,458,697 MCM: 42,392 Heart defects: 14,412 Oral cleft: N/A Genitourinary: N/A Renal defects: N/A Hypospadias: N/A	Total: 1286 MCM: 16 Heart defects: 9 Oral cleft: 2 Genitourinary: 2 Renal defects: 1 Hypospadias: 1
NVP/HG control:	Total birth: 160 MCM: 3 Heart defects: 1 Oral cleft: 0 Genitourinary: 1 Renal defects: 1 Hypospadias: 0					Total: 441 MCM: 7 Heart defects: 1 Oral cleft: 0 Genitourinary: 1 Renal defects: 1 Hypospadias: 0
Inclusion criteria	exposure who were less than three months pregnant at the time of calling to the TIS within a two year period	Australian between 2002-2005	live birth or stillbirth or ended with any abortive outcome in Denmark between January 1, 2004 - March 31, 2011	in Denmark between 1997 and 2010	1998 and 2012 - Events with relatively severe congenital malformation	who recruited to website between 2007 and 2014 - Singleton pregnancy - Treatment with IV fluids and/or total parenteral nutrition/ nasogastric feeding tube

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able 1 (continued)

a. Cohort studies investigating major and organ-specific congenital malformation rates following ondansetron exposure during pregnancy

	Einarson et al. 2004	Colvin et al. 2013	Pasternak et al. 2013	Andersen et al. 2013	Danielsson et al. 2014	Fejzo et al. 2016
Covariates for adjustment	Age, smoking, alcohol status and gestational age at time of call	Maternal age, previous preterm birth, smoking during pregnancy, socioeconomic situation, parity, private health insurance, and multiple birth, caesarean delivery (The adjustment were done only for preterm birth, elective caesarean and postpartum haemorrhagia)	Age, place of birth, county of residence, married or living with partner, level of education, income, pregnancy history, smoking, pre-pregnancy BMI, medical history, health care utilization, use of other antiemetics (metoclopramide, antiemetic antihistamines, scopalamine, and domperidone)	Adjustment was reported but authors did not mention which covariates were included.	Year of birth, maternal age, parity, smoking in early pregnancy, and body mass index	Ethnicity, education, termination, miscarriage, age
Results relevant to this meta-analysis OR/RR (95%CI) or p value	**Use of ondansetron during first trimester** MCM: 6/169 vs 6/322 (p = 0.52) Hypospadias: 3/169 vs 1/322 (p = 0.25)	**Use of ondansetron any time during pregnancy** Any birth defect: OR: 1.3 (0.8-2.1) MCM: OR: 1.1 (0.6-2.0) **Use of ondansetron during first trimester** MCM: OR: 1.2 (0.6-2.2) Obstructive defects of renal pelvis and ureter: OR: 6.2 (2.0-19.5)	**Use of ondansetron during first trimester** MCM: aOR: 1.12 (0.69-1.82)	**Use of ondansetron during first trimester** MCM: aOR: 1.3 (1.0-1.7) Heart defect: aOR: 2.0 (1.3-3.1)	**Use of ondansetron during first trimester** Any malformation: OR: 0.95 (0.72-1.26) MCM: OR: 1.11 (0.81-1.53) Heart defect: OR: 1.62 (1.04-2.54)	**Use of ondansetron any time during pregnancy** Birth defects HG/Ondansetron group vs HG/No Ondansetron group 3.47% vs 3.40% (p = 1.0)
Quality assessment (Newcastle-Ottawa scale)	8	8	9	5	7	7

Colvin: No hay mayor reisgo de malformaciones, existe leve aumento de defectos mayores OR 1,2 (0,6-2,2) No es significativo.

Pasternak: No hubo mayor riesgo de defectos mayores OR 1,12 (0,69- 1,82)

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Andersen: aumento riesgo de defecto cardíaco (OR 2)

Danielsson: aumento de riesgo defecto cardiaco (OR 1,62)

Feijzo: No hay aumento de riesgo de defectos.

Table 1 (*continued*)

a. Cohort studies investigating major and organ-specific congenital malformation rates following ondansetron exposure during pregnancy

	Einarson et al. 2004	Colvin et al. 2013	Pasternak et al. 2013	Andersen et al. 2013	Danielsson et al. 2014	Feijzo et al. 2016
Exclusion criteria	N/A	- Minor defects with no disfiguring or requirement of treatment - Less than five subjects in each defects subgroup were not mentioned	-Pregnancies with missing or implausible gestational age or birth weight (for birth weight analysis) - Multiple records on overlapping dates - The abortions which were occurred prior than 6th gestational weeks - Ondansetron prescriptions within 1 month before pregnancy onset -Infants with chromosomal aberrations (e.g., Down's syndrome) and those with known causes of birth defects (e.g., fetal alcohol syndrome) -Unpaired infants after propensity score analysis	N/A	- Relatively common and clinically less significant malformations with a variable registration such us preauricular tags, tonguetie, patent ductus in preterm infants, single umbilical artery,undescended testis, hip (sub)luxation, and nevus - Duplications in the prescription register and midwife interviews	-Under 18 years - Living outside the United States
Exposure	Ondansetron, Other antiemetics; diclectin, metoclopramide, phenothiazines and ginger	Ondansetron	Ondansetron	Ondansetron, metoclopramide	Ondansetron, meclozine	Ondansetron, metoclopramide, promethazine
Exposure time window	Exposure to ondansetron during first trimester Ondansetron exposures reported at the first prenatal visit	First trimester dispensing were included the analysis of major birth defect. -Ondansetron dispensing at any time during pregnancy for other outcomes (stillbirth, birth weight etc.)	Ondansetron dispensing to the women in first day of the last menstrual period through 12 gestational weeks for any major birth defect. -Ondansetron dispensing at any time during pregnancy for other outcomes (preterm birth, birth weight, stillbirth and spontaneous abortus)	Women redeemed ondansetron prescriptions during first trimester	Exposure to ondansetron after last menstruel period through 12 gestational weeks or ondansetron prescribed during first trimester	Exposure to ondansetron any time during pregnancy. For our analysis only first trimester exposures were extracted from unpublished data.
Control	Controls were enrolled in the same way with exposed group. Group 2 with NVP who were not exposed to ondansetron, they had used other anti-emetics Group 3 who were exposed ton on-teratogen drugs or had not used any medication	Women with no ondansetron dispensing in the same period with exposed group	Women with no ondansetron dispensing in the same period with exposed group, 1 exposed infant matched with 4 unexposed infants	Women with no ondansetron prescriptions	Women with no exposure to ondansetron and meclizine during first trimester	HG controls: Women who suffered from HG and not exposure ondansetron or exposed to other treatments for NVP and also had minimum 2 follow-up after 27 weeks. Healthy controls: Women with known history of normal nausea/vomiting or no nausea/vomiting at least in 2 pregnancies.
Method of congenital malformation diagnosis	Standardised interview with mothers and then for verification of baby's health were asked their physicians with letter	WARDA classification and 5-digit British Paediatric Association International Classification of Diseases, Ninth Revision (ICD-9) system	European Surveillance of Congenital Anomalies (EUROCAT) classification, International Classification of Diseases; the tenth revision (ICD-10)	EUROCAT classification	International Classification of Diseases code	Structured online surveys were done by mothers

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b. Case-control studies investigating the association between organ-specific malformations and ondansetron exposure during pregnancy

	Anderka et al. 2012	Van Bennekom et al. 2016		Anderka et al. 2012	Van Bennekom et al. 2016
Country	United States	United States	**Exposure**	Ondansetron	Ondansetron
Study Period	1997-2004	2005-2009		Other Antiemetics; promethazine, diphenhydramine, cetirizine, doxylamine plus pyridoxine, cetirizine, phenothiazines, prochlorperazine, metoclopramide, antacids, H_2 blockers, proton pump inhibitors, pyridoxine, steroids, emetrol/coke syrup, herbal/natural products, ginger	
Design/Setting	Multi-site Population-based Case-control Study	1997–2013 Population-based Case-control Study			
Data source	National Birth Defects Prevention Study (NBDPS)	National Birth Defects Prevention Study (NBDPS) (2005-2009) Slone Birth Defects Study (BDS) (1997–2013)	**Exposure time window**	First trimester use of ondansetron	First trimester use of ondansetron
Number of participants	22,381 pregnant women	N/A	**Control**	Control subjects without birth defects were randomly selected.	N/A
Case	4524			Hypospadias analysis done with only male controls.	
Control	5859				

Aderka : Destaca asociación con paladar hendido

Parker : En general no hubo mas riesgo. aumento moderado en riesgo de paladar hendido (OR: 1.6). Hallazgos se pueden atribuir al azar.

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b. Case-control studies investigating the association between organ-specific malformations and ondansetron exposure during pregnancy

	Anderka et al. 2012	Van Bennekom et al. 2016		Anderka et al. 2012	Van Bennekom et al. 2016
Number of ondansetron exposures in case vs control group OR/RR (95% CI)	**Cleft lip with or without palate** 7/933 vs 44/4,009 aOR: 0.88 (0.38–2.00) **Cleft palate** 11/525 vs 44/4009 aOR: 2.37 (1.18–4.76) **Neural tube defects (NTDs)** 4/711 vs 44/4,016 aOR: 0.60 (0.21–1.68) **Hypospadias** 5/655 vs 18/1956 aOR: 0.57 (0.20–1.60)	**Cleft palate** *NBDPS* aOR: 1.5 (0.9-2.5) *BDS* aOR: 0.4 (0.2-0.8) **Renal agenesis/dysplasia** *BDS* aOR: 2.3 (1.3-4.0) **Hypoplastic left heart syndrome** *NBDPS* aOR: 1.5 (0.7-3.1) **Diaphragmatic hernia** *NBDPS* aOR: 1.7 (0.9-3.5)	**Method of congenital malformation diagnosis**	Maternal interviews in the birth defects surveillance systems Clinical geneticists reviewed information of cases from medical and confirmed the cases	N/A
Inclusion criteria	-Infants whose follow-up interviews were available and expected dates of delivery were between September 24, 1997 and December 31, 2004. -All infants who reside in the study areas - Anencephaly, craniorachischisis, spina bifida, or encephalocele were included for NTDs - Only infants with severe hypospadias	N/A	**Covariates for adjustment**	Maternal age, race/ethnicity and education, parity, plurality, previous miscarriage, any smoking in the month before conception through the first trimester, body mass index, infant sex, any folic acid use in the month before conception through the first trimester, use of unknown antiemetic, site, and expected year of delivery	Adjustment was reported but authors did not mentioned which covariates were included.
Exclusion criteria	-Cases with recognized or strongly suspected chromosome abnormalities or single-gene conditions -Infants with clefts secondary to another defect (e.g., holoprosencephaly or amniotic band sequence) -Unconfirmed orofacial clefts after birth -First-degree hypospadias (urethral opening on the glans or corona) -For evaluation family history, cases with same birth defects with a parent, sibling or half sibling were excluded - Women with pre-existing diabetes and infants with more than one major birth defect	N/A	**Quality assessment (Newcastle–Ottawa scale)**	****/**/-** 8	****/*-/-*- 6

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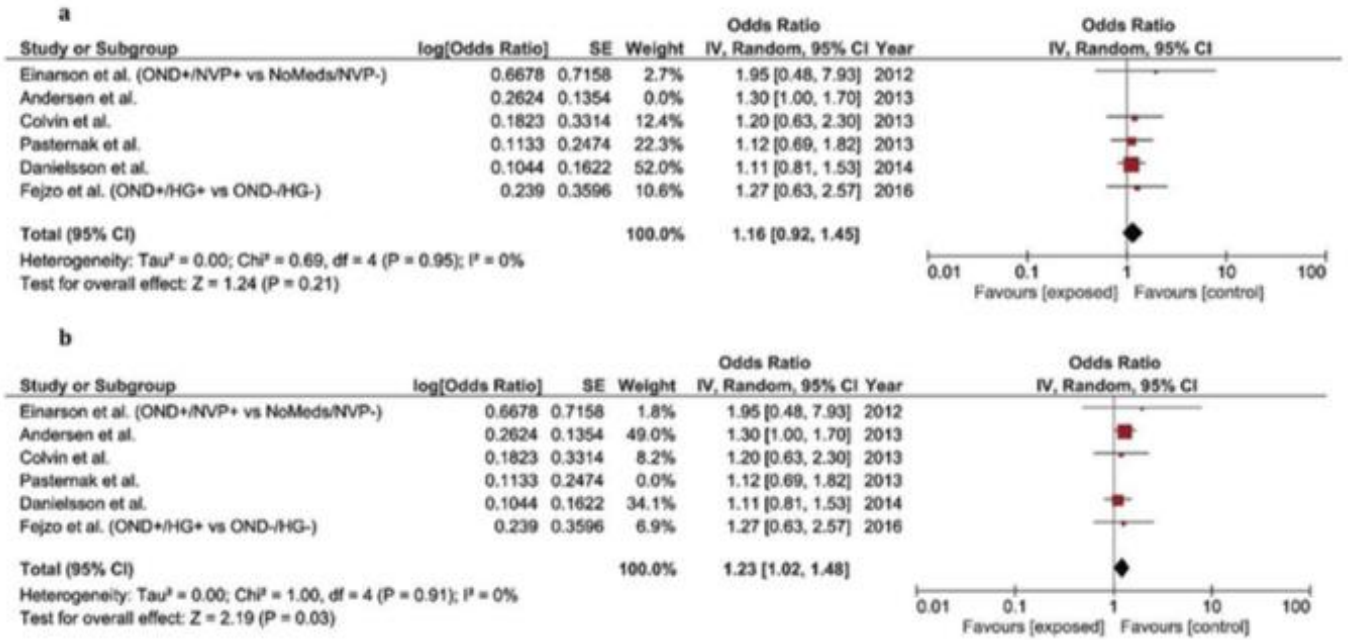

Fig. 2. Meta-analysis of overall major congenital malformation rates in ondansetron-exposed vs healthy controls Fig. 2**a.** Forest plot of the primary analysis including Pasternak et al. Fig. 2**b.** Forest plot of the sensitivity analysis substituting Pasternak et al. with Andersen et al.

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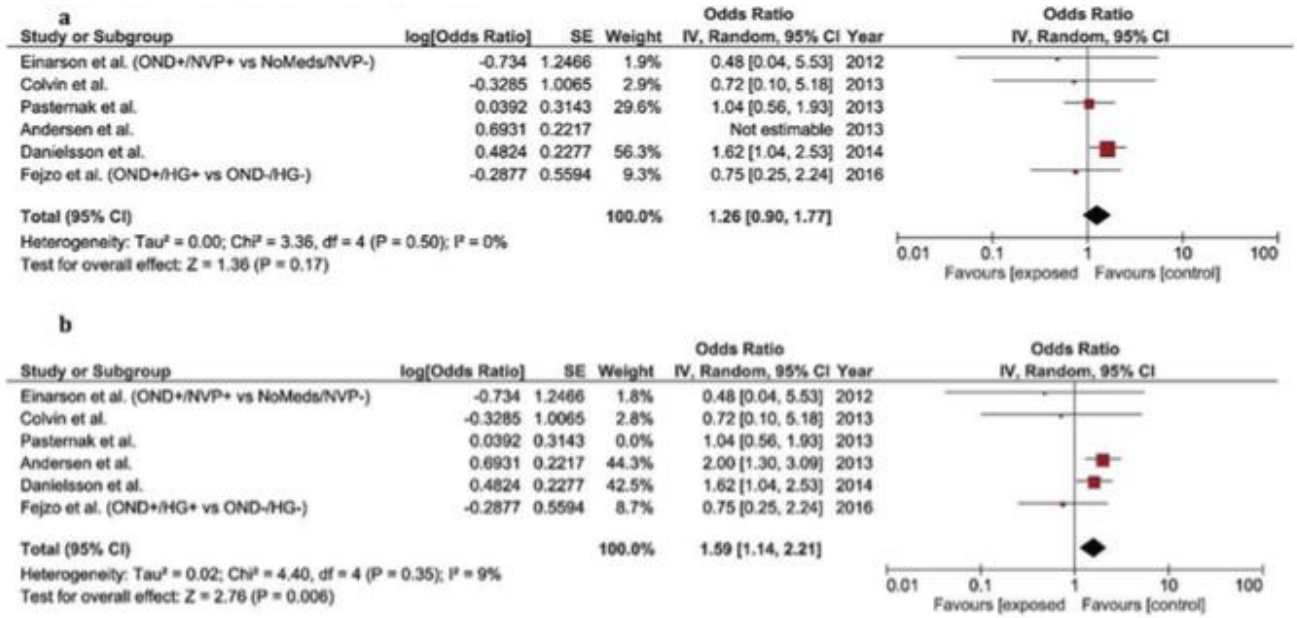

Fig. 3. Meta-analysis of heart defects in ondansetron-exposed vs healthy controls Fig. 3**a.** Forest plot of the primary analysis including Pasternak et al. Fig. 3**b.** Forest plot of the sensitivity analysis substituting Pasternak et al. with Andersen et al.

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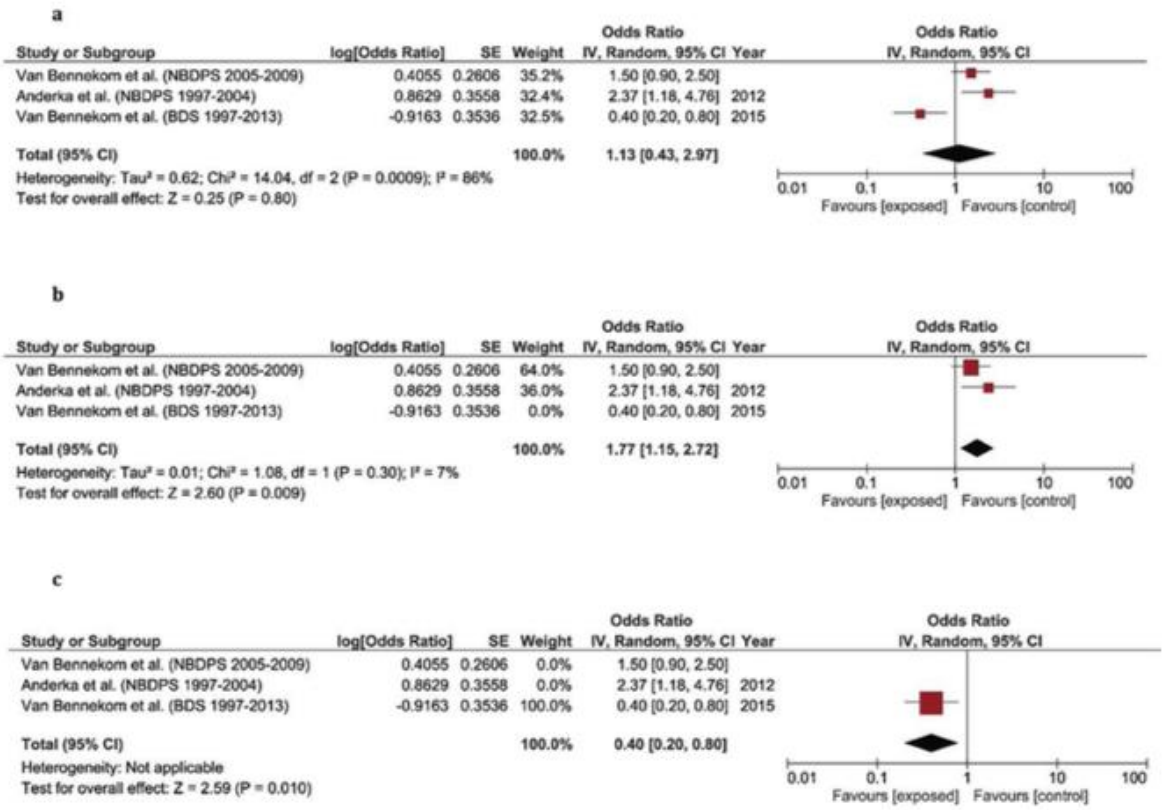

Fig. 4. Meta-analysis of isolated cleft palate in ondansetron-exposed vs healthy controls. Fig. 4**a.** Forest plot of the primary analysis with significant heterogeneity. Fig. 4**b.** Forest plot of the sensitivity analysis using National Birth Defects Prevention Study dataset (NBDPS 1997–2009). Fig. 4**c.** Forest plot of the sensitivity analysis using Slone Birth Defects Study dataset (BDS 1997–2013).

Reproductive Toxicology 83 (2019) 14–20

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First trimester ondansetron exposure and risk of structural birth defects

April Zambelli-Weiner[a,*], Christina Via[a], Matt Yuen[a], Daniel J. Weiner[a], Russell S. Kirby[b]

[a] TTi Health Research & Economics, 1231 Tech Ct, Suite 201, Westminster, MD 21157, USA

[b] Department of Community and Family Health, College of Public Health, University of South Florida, 13201 Bruce B Downs Blvd, Tampa, FL 33612, USA

- **Diseño:** estudio caso control (Octubre 2018)
- **Objetivo:** Determinar si uso durante el embarazo esta asociado con aumento de riesgo de malformaciones mayores.
- **Método:** Base de dato Truven Health Marketscan Commercial, 864.083 madre hijo de 2000-2004.
- **Resultado**: aumenta el riesgo de malformación cardíaca (OR: 1.52) Y hendiduras orofaciales (OR : 1.32)

- **Conclusión**: Hay aumento del riesgo de malformaciones.
- **Limitantes:** Muestra pequeña, Clasificación de exposición errada, error de indicación por diagnostico, falta información demográfica y factores de riesgo.

Table 2
Association of Ondansetron Exposure with Structural Birth Defects.

Outcome (no. %)	Unexposed During Pregnancy n = 787,753	Exposed in First Trimester (Med Only) n = 5557	Exposed in First Trimester (Rx or Med) n = 76,330	Prevalence Odds Ratio (95% CI) Medical Administration Only Unadjusted	Prevalence Odds Ratio (95% CI) Medical Administration Only Adjusted[a]	Prevalence Odds Ratio (95% CI) Prescription or Medical Administration Unadjusted	Prevalence Odds Ratio (95% CI) Prescription or Medical Administration Adjusted[a]
Primary Analysis							
Cardiac defects	29,001 (3.67)	303 (5.45)	3099 (4.06)	1.52 (1.35-1.70)	1.43 (1.28-1.61)	1.11 (1.07-1.16)	1.04 (1.00-1.08)
Orofacial clefting	1,433 (0.18)	13 (0.23)	157 (0.21)	1.32 (0.76-2.28)	1.30 (0.75-2.25)	1.14 (0.97-1.35)	1.12 (0.95-1.33)
Secondary Analysis							
Septal defects	28,666 (3.63)	301 (5.42)	3069 (4.02)	1.53 (1.36-1.71)	1.44 (1.28-1.62)	1.12 (1.08-1.16)	1.04 (1.00-1.08)
Ventricular septal defect	9,058 (1.15)	81 (1.46)	883 (1.16)	1.30 (1.04-1.62)	1.29 (1.03-1.61)	1.02 (0.95-1.09)	1.00 (0.93-1.07)
Atrial septal defect	23,903 (3.03)	267 (4.81)	2633 (3.45)	1.62 (1.43-1.84)	1.49 (1.32-1.69)	1.15 (1.10-1.20)	1.04 (0.99-1.08)
Atrioventricular septal defect	813 (0.10)	15 (0.27)	97 (0.13)	2.68 (1.61-4.47)	2.71 (1.62-4.52)	1.24 (1.01-1.54)	1.24 (1.00-1.53)
Hypoplastic Left Heart Syndrome	343 (0.04)	5 (0.09)	43 (0.06)	2.12 (0.88-5.12)	2.12 (0.87-5.13)	1.31 (0.95-1.80)	1.31 (0.95-1.81)
Other circulatory defects	6,044 (0.77)	76 (1.37)	678 (0.89)	1.83 (1.45-2.29)	1.75 (1.39-2.20)	1.17 (1.08-1.27)	1.11 (1.02-1.20)
Cleft palate	1,068 (0.14)	11 (0.20)	112 (0.15)	1.49 (0.83-2.71)	1.46 (0.81-2.65)	1.09 (0.90-1.33)	1.06 (0.87-1.30)
Cleft lip	638 (0.08)	5 (0.09)	74 (0.10)	1.14 (0.47-2.74)	1.16 (0.48-2.81)	1.21 (0.95-1.54)	1.22 (0.96-1.56)
Cleft lip with or without palate	696 (0.09)	8 (0.14)	71 (0.09)	1.67 (0.83-3.35)	1.69 (0.84-3.40)	1.06 (0.83-1.36)	1.07 (0.84-1.38)
Laryngeal cleft	6,295 (0.80)	56 (1.01)	808 (1.06)	1.29 (0.99-1.68)	1.16 (0.89-1.51)	1.34 (1.24-1.44)	1.18 (1.09-1.27)
Craniosynostosis	11,759 (1.49)	94 (1.69)	1329 (1.74)	1.16 (0.95-1.43)	1.11 (0.90-1.36)	1.18 (1.11-1.25)	1.12 (1.05-1.18)
Diaphragmatic hernia	409 (0.05)	7 (0.13)	55 (0.07)	2.49 (1.18-5.25)	2.51 (1.19-5.31)	1.40 (1.06-1.86)	1.40 (1.05-1.87)
Renal collecting system anomalies	7,803 (0.99)	69 (1.24)	835 (1.09)	1.28 (1.01-1.63)	1.24 (0.98-1.58)	1.34 (1.24-1.44)	1.07 (1.00-1.16)
Limb reduction defects	557 (0.07)	4 (0.07)	49 (0.06)	1.04 (0.39-2.79)	1.03 (0.38-2.75)	0.92 (0.69-1.23)	0.91 (0.67-1.22)
Other defects (negative control)	113,106 (0.14)	878 (0.16)	12,216 (0.16)	1.10 (1.03-1.18)	1.02 (0.95-1.10)	1.12 (1.09-1.14)	1.02 (1.00-1.04)

[a] Odds ratios are adjusted for: mother's age, infant year of birth, and infant gender.

Estudios

Research

JAMA | Original Investigation

Association of Maternal First-Trimester Ondansetron Use With Cardiac Malformations and Oral Clefts in Offspring

Krista F. Huybrechts, MS, PhD; Sonia Hernández-Díaz, MD, DrPH; Loreen Straub, MD, MS; Kathryn J. Gray, MD, PhD; Yanmin Zhu, MS, PhD; Elisabetta Patorno, MD, DrPH; Rishi J. Desai, PhD; Helen Mogun, MS; Brian T. Bateman, MD, MS

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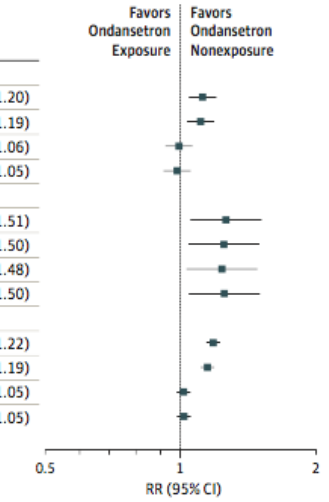
- **Diseño:** cohorte retrospectivo (Diciembre 2018)
- **Objetivo:** Evaluar la asociación entre la exposición a ondansetrón durante el embarazo y el riesgo de malformaciones congénitas.
- **Método:** Medicaid 2000-2013. 1.816.414 embarazos, inscritas desde 3 meses antes del último período menstrual hasta 1 mes o más después del parto.
- **Resultado:** El riesgo relativo ajustado (RR) para las malformaciones cardíacas fue de 0,99 (IC del 95%, 0,93 a 1. 06) y para las hendiduras orales, el RR ajustado fue 1.24 (IC 95%, 1.03 a 1.48)
- **Conclusión:** no se asoció con malformaciones cardíacas o malformaciones congénitas en general después de tener en cuenta los factores de confusión medidos, pero se asoció con un pequeño aumento del riesgo de hendiduras orales.
- **Limitantes:** consumo real (2 recetas), sin datos de pérdidas o interrupciones de embarazo.

Figure 1. Risk of Congenital Malformations in Infants Following Exposure to Ondansetron During the First Trimester: Main Analyses

Level of Adjustment	Exposed to Ondansetron: No. of Events	Exposed to Ondansetron: Total No. of Infants	Unexposed to Ondansetron: No. of Events	Unexposed to Ondansetron: Total No. of Infants	RR (95% CI)
Cardiac malformations (primary outcome)					
Unadjusted	835	88 467	14 577	1 727 947	1.12 (1.04-1.20)
Propensity score stratified (level 1)	835	88 467	14 577	1 727 947	1.11 (1.03-1.19)
Propensity score stratified (level 2)	835	88 446	14 573	1 727 546	0.99 (0.93-1.06)
High-dimensional propensity score stratified	835	88 467	14 577	1 727 925	0.98 (0.92-1.05)
Oral clefts (primary outcome)					
Unadjusted	124	88 467	1921	1 727 947	1.26 (1.05-1.51)
Propensity score stratified (level 1)	124	88 467	1921	1 727 947	1.25 (1.04-1.50)
Propensity score stratified (level 2)	124	88 446	1920	1 727 546	1.24 (1.03-1.48)
High-dimensional propensity score stratified	124	88 467	1921	1 727 925	1.25 (1.04-1.50)
Any congenital malformation (secondary outcome)					
Unadjusted	3277	88 467	54 174	1 727 947	1.18 (1.14-1.22)
Propensity score stratified (level 1)	3277	88 467	54 174	1 727 947	1.15 (1.11-1.19)
Propensity score stratified (level 2)	3275	88 446	54 163	1 727 546	1.01 (0.98-1.05)
High-dimensional propensity score stratified	3277	88 467	54 174	1 727 925	1.02 (0.98-1.05)



Respuestas de Sociedades

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

Agencia Española de Medicamentos y Productos Sanitarios
AEMPS

ONDANSETRÓN: RIESGO DE DEFECTOS DE CIERRE OROFACIALES (LABIO LEPORINO, PALADAR HENDIDO) TRAS SU USO DURANTE EL PRIMER TRIMESTRE DEL EMBARAZO

Información para profesionales sanitarios

Fecha de publicación: 12 de septiembre de 2019

Categoría: MEDICAMENTOS DE USO HUMANO, SEGURIDAD
Referencia: MUH (FV), 15 /2019

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- Los resultados del conjunto de estudios disponibles no son concluyentes sobre el riesgo de malformaciones cardiacas debido a la inconsistencia de los resultados y a la heterogeneidad de los diversos estudios.

- Ondansetrón no está indicado para tratar a mujeres embarazadas y este uso debe de evitarse especialmente durante el primer trimestre de la gestación.

- Es importante informar a todas las pacientes que estando en edad fértil requieran/se encuentren en tratamiento con ondansetrón, acerca del riesgo de defectos de cierre orofaciales en caso de administración durante el primer trimestre del embarazo, recomendándoles el uso de medidas anticonceptivas eficaces. SEP

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Respuestas de Sociedades

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- Warning genera aumento de la morbilidad materna y la hospitalización y mayor riesgo de interrupción de los embarazos deseados.

- Se minimizar la preocupación inevitable y desproporcionada generada por los cambios propuestos a la literatura del producto para las mujeres que han tomado ondansetrón en el primer trimestre.

- En vista de los datos publicados más recientemente Se recomienda reservar como agente de segunda línea para el tratamiento de las náuseas y los vómitos en el embarazo (según lo recomendado actualmente por la Guía RCOG Green-top del Reino Unido)

- Aconsejar sobre los beneficios junto con el pequeño aumento en el riesgo de hendidura orofacial que pueda existir.

- Aún debe considerarse como opción para pacientes con vómitos severos en el embarazo en quienes los tratamientos de primera línea han fallado.

Conclusiones

- Los resultados de estudios disponibles no son concluyentes por lo que se requiere utilizar el criterio médico valorando los beneficios vs eventuales riesgos del uso de este medicamento y explicar esto detalladamente a las pacientes para la toma de una decisión informada.

- Se requieren realizar nuevos estudios con menos limitaciones que puedan determinar la discusión.

CERPO
Centro de Referencia Perinatal Oriente
Facultad de Medicina, Universidad de Chile

Ondansetron y Embarazo: Riesgo de Malformaciones Congénitas.

Dra. Mª Francisca González.
Becada O&G HLTB Universidad de Chile