

Increased risk of mood disorders associated with metoclopramide treatment for nausea and vomiting during pregnancy

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Background

- Metoclopramide is one of the most commonly used medicines to treat vomiting and nausea of pregnancy in the Netherlands.
- It is known that **metoclopramide may cause psychiatric adverse drug reactions** (ADR) including depression and anxiety in up to 10% of its users.
- Since pregnant women are more prone to the development or reoccurrence of mental health disorders, the **objective of this study was to determine whether pregnant women are at increased risk of mood-related ADR after metoclopramide use.**

Methods

- The database for spontaneous reports of the Netherlands Pharmacovigilance Centre Lareb was used.
- All spontaneous reports on ADRs after metoclopramide use by **women between the ages of 15 and 50 years** were selected. The case narratives were screened.
- Cases were defined as; **reports describing depression, depressed mood, suicidality and/or psychological restlessness.** Reports on other ADR were labelled as non-cases (Table 1).
- Cases and non-cases were subdivided into pregnant and non-pregnant women (Table 1). Pregnancy was identified by the coded indication, Preferred Term or by information in the case narrative.
- To correct for pregnancy and nausea, which on itself may negatively impact mood, **analyses were repeated with two other commonly prescribed anti-emetic drugs;**
 - ondansetron
 - meclozine/pyridoxine (also known as Emesafene®)
- **A Reporting odds Ratio (ROR)** was calculated to evaluate disproportionality in reports between pregnant and non-pregnant women & between anti-emetic drugs in the pregnancy.

Table 1. Definitions of cases and study population

Case	Non-case
Depression	All other ADR reports
Depressed mood	
Suicidality	
Psychological restlessness	
Pregnant	Non-pregnant
Coded indication (e.g. hyperemesis gravidarum, nausea of pregnancy)	All other reports of women between ages 15 – 50 years old
Preferred Term (e.g. maternal exposure during pregnancy)	
Other information in the case narrative	

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Results

- A total **372 spontaneous reports** of women between 15 and 50 years old were selected with an exposure to (**Table 2**);
 - Metoclopramide; N = 256
 - Ondansetron; N = 55
 - Meclozine with pyridoxine; N = 61
- After **metoclopramide** exposure, mood-related ADRs were **significantly more often reported** among pregnant women (**27.0%**) compared to non-pregnant women (**10.4%**) with a ROR of 3.2 (95% CI 1.6-6.6).
- For the metoclopramide cases reported during pregnancy; in four cases **suicidality** was reported with other mood-related ADR. In ten additional cases symptoms such as a **depressed mood, depression or mood changes** were reported. Three cases reported **inner restlessness**.
- Figure 1** (next slide) represents quotes of some case narratives.
- Cases of mood-related ADRs were also more often reported during pregnancy after exposure to **ondansetron (9.1% vs 3.0%)** and **meclozine with pyridoxine (8.9% vs 0.0%)** while not significantly different.
- During pregnancy**, mood-related ADRs were **significantly more often reported** after **metoclopramide** exposure compared to exposure to ondansetron and meclozine/pyridoxine **with an ROR of 3.8 (95% CI 1.4-9.7) (Table 3)**.

Table 2. Number of cases of mood disorders in the spontaneous reports database following metoclopramide exposure of pregnant and non-pregnant women

	Pregnant women		Non-pregnant women		ROR (95%CI) ^b
	Total	Cases ¹	Total	Cases ¹	
Metoclopramide	63	17 (27.0%)	193	20 (10.4%)	3.2 (1.6-6.6)
Ondansetron	22	2 (9.1%)	33	1 (3.0%)	3.2 (0.3-37.6)
Meclozine with pyridoxine	56	5 (8.9%)	5	0 (0.0%)	n.a. ²

Abbreviations; CI = confidence interval; n.a. = not applicable; ROR = reporting odds ratio

¹Cases are defined as reports describing a negative impact on mood (Table 1);

²ROR cannot be calculated due to the zero cases among the non-pregnant women, the p-value for this comparison with a Fisher's Exact Test= 1.00.

Table 3. Reporting Odds Ratio (ROR) for mood disorders following anti-emetic exposure of pregnant women

	Cases ¹ N = 24	Non-cases N = 117	ROR (95% CI)
Metoclopramide	17 (27.0%)	46 (73.0%)	3.8 (1.4-9.7)
Ondansetron	2 (9.1%)	20 (90.9%)	0.4 (0.1-2.0)
Meclozine with pyridoxine	5 (8.9%)	51 (91.1%)	0.3 (0.1-1.0)

Abbreviations; CI = confidence interval; ROR = reporting odds ratio

¹Cases are defined as reports describing a negative impact on mood (Table 1).

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Conclusion

- In the database of spontaneous reports, **mood disorders as an ADR of metoclopramide are significantly more frequently reported for pregnant women.**
- When compared to other drugs used for nausea and vomiting of pregnancy, the ROR for mood disorders after metoclopramide is significantly higher.
- This may indicate that **mood disorders as an ADR of metoclopramide are more common in pregnant women.**
- As this ADR may be severe and even include suicidality, **awareness** of this ADR and **the high vulnerability** of pregnant women for this ADR is essential.
- Metoclopramide should be **directly discontinued when mood changes occur during treatment** to prevent further psychological dysregulation.
- In most cases, **quick improvement** of the symptoms after discontinuation of metoclopramide occurred.
- Extra caution may be required in pregnant women with a **history of depression.**

*"I started metoclopramide in the first trimester until the 32nd week of pregnancy. **I was admitted to the hospital for 8 weeks because of suicidality.** The cause of my severe depression was unknown until I stopped taking metoclopramide and the symptoms disappeared"*

*"I was already feeling depressed due to all the vomiting, but the **metoclopramide made me feel worse. I would rather be vomiting than taking this medicine**"*

*"I was crying for hours after taking metoclopramide. **I had negative thoughts and needed help to end a panic attack multiple times**"*

Figure 1. Quotes of spontaneous ADR reports after metoclopramide exposure during pregnancy