Use of medication for gastroesophageal reflux during pregnancy and adverse birth outcomes

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Disclosures

- Project funded by ZonMw (project number 848018010)
- No conflicts of interest

Background

- Symptoms of gastroesophageal reflux disease (GERD): 40-85% of pregnancies
- Negative impact of quality of life
- Management:
  - Lifestyle adjustments
  - Antacids
  - Proton pump inhibitors (PPIs) or H_2 antagonists } OTC medication
- Data on safety of GERD medication is scarce

Objective

To determine whether calcium-based antacid and PPI use during pregnancy is associated with selected adverse birth outcomes, focusing on dosage and timing of use

Study population

PRIDE Study

moeders van morgen

2012 – 2019: N = 9,054

2014 – 2019: N = 3,911

Exclusion criteria:

Participation in both cohorts

Multifetal gestation

Non-live birth

Incomplete exposure data

Van Gelder MMHJ, et al. *Paediatr Perinat Epidemiol* 2020;34:484-494.
Vorstenbosch S, et al. *Drug Saf* 2019;42:1-12.

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Exposure assessment

- Indication-oriented Web-based questionnaires (SE 0.89 (95% CI 0.86-0.93))[a]
- Calcium-containing antacids: ATC code A02A
  - Calcium carbonate per unit (in mg) * units taken per day
- PPIs: ATC code A02BC
  - Defined Daily Dose (DDD) per day
- Time-varying approaches for modeling exposure[b]

[a] Van Gelder MMHJ, et al. *Am J Epidemiol* 2018;187:326-336.
[b] Wood ME, et al. *Epidemiol Rev* 2021;43:130-146.

Outcome assessment

- Selected outcomes:
  - Preterm birth (<37 weeks of gestation)
  - Low birth weight (<2,500 grams)
  - Small-for-gestational age (SGA; <10th percentile)
  - Low Ponderal Index (<2.2)

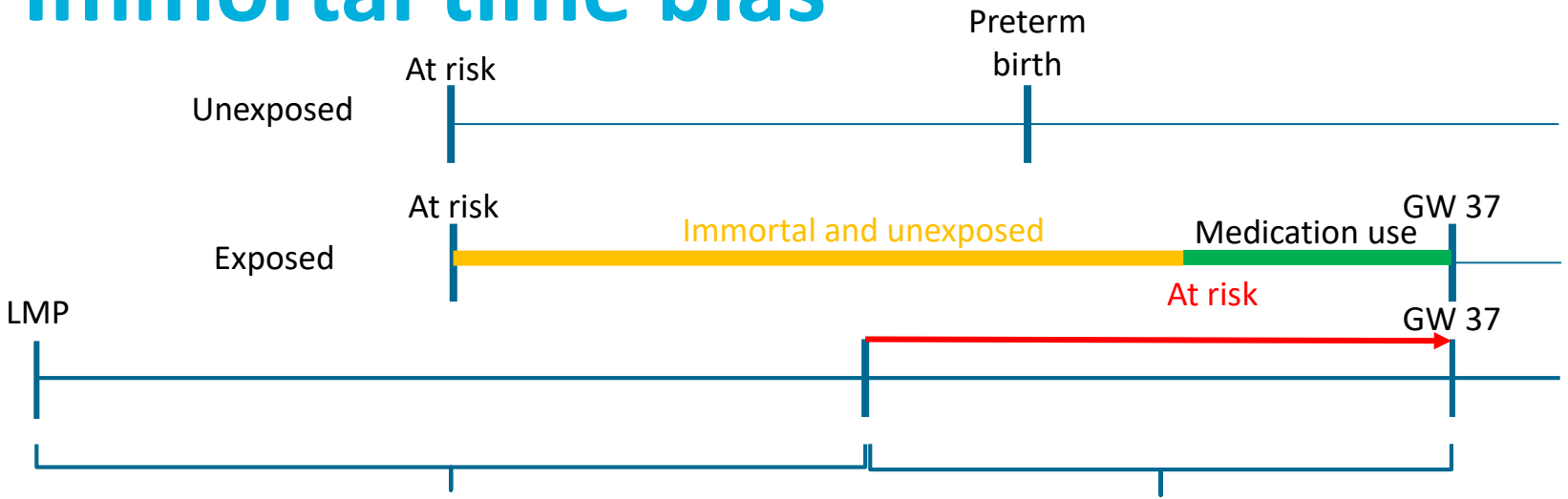
- Self-reported through validated questionnaire[a]
- PRIDE Study: obstetric records in case of loss-to-follow-up

[a] Van Gelder MMHJ, et al. *J Clin Epidemiol* 2017;90:136-143

Statistical analysis

- Minimally sufficient set of confounders identified through outcomes-specific Directed Acyclic Graphs (DAGs)
  (age, country of birth, asthma, chronic hypertension, depression, epilepsy, diabetes, BMI, parity, history of preterm birth, smoking, alcohol, depressive symptoms)
- Multiple imputation (40 iterations) for missing covariate data
- Time-varying approach to avoid immortal time bias
  - GW 0-22: Modified Poisson regression with inverse probability of treatment weighting
  - GW 23+: Cox proportional hazard models with time since day 161

Immortal time bias



Identical for complete study population:

- Exposure yes/no
- Week 0-22 (day 0-160)
- K-means clustering

Time-varying changes in use per day

Statistical analysis

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Results

Characteristics (N=9,153)

GW 0-22	Calcium-based antacids		PPIs	
	Yes (N=1,037)	No (N=7,683)	Yes (N=223)	No (N=8,405)
Age (year)	31.5 (3.6)	31.4 (3.7)	31.6 (3.9)	31.4 (3.7)
Education (high)	806 (77.7%)	5,839 (76.0%)	158 (70.9%)	6,439 (76.6%)
Asthma	97 (9.4%)	447 (5.8%)	26 (11.7%)	503 (6.0%)
Depression	19 (1.8%)	122 (1.6%)	9 (4.0%)	131 (1.6%)
BMI	24.6 (4.7)	23.6 (4.0)	26.1 (5.9)	23.6 (4.0)
Primiparous	594 (57.3%)	4,156 (54.1%)	107 (48.0%)	4,598 (54.7%)
Smoking	69 (6.7%)	372 (4.8%)	21 (9.4%)	414 (4.9%)

Use in GW 0-22 (adjusted RR with 95% CI)

Exposure	Preterm birth	Low birth weight	SGA	Low Ponderal Index
Calcium-based antacids				
Any use	1.1 (0.8-1.4)	0.7 (0.5-1.1)	0.9 (0.7-1.1)	1.0 (0.7-1.4)
Low dose (<1 g/day)	1.1 (0.7-1.6)	0.6 (0.3-1.2)	0.9 (0.7-1.2)	0.7 (0.4-1.2)
High dose (≥1 g/day)	1.1 (0.8-1.6)	0.9 (0.5-1.4)	1.0 (0.7-1.3)	1.2 (0.8-1.9)

Use in GW 0-22 (adjusted RR with 95% CI)

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Calcium-based antacids				
Any use	1.1 (0.8-1.4)	0.7 (0.5-1.1)	0.9 (0.7-1.1)	1.0 (0.7-1.4)
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High dose (≥1 g/day)	1.1 (0.8-1.6)	0.9 (0.5-1.4)	1.0 (0.7-1.3)	1.2 (0.8-1.9)
PPIs				
Any use	1.4 (0.8-2.4)	1.0 (0.5-2.3)	1.0 (0.6-1.7)	--
Low dose (≤1 DDD)	1.1 (0.5-2.5)	--	1.3 (0.7-2.2)	--
High dose (>1 DDD)	1.9 (0.9-4.1)	2.6 (1.1-6.2)	0.6 (0.2-1.5)	--

Use after GW 22 (adjusted HR with 95% CI)

Exposure	Preterm birth	Low birth weight	SGA	Low Ponderal Index
Calcium-based antacids				
Any use	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.9 (0.7-1.1)	0.7 (0.5-1.0)
Low dose (<1 g/day)	0.8 (0.5-1.2)	0.8 (0.5-1.4)	0.9 (0.7-1.2)	0.8 (0.5-1.4)
High dose (≥1 g/day)	0.6 (0.4-1.0)	0.6 (0.3-1.0)	0.8 (0.6-1.0)	0.6 (0.3-1.0)

Use after GW 22 (adjusted HR with 95% CI)

Exposure	Preterm birth	Low birth weight	SGA	Low Ponderal Index
Calcium-based antacids				
Any use	0.7 (0.5-1.0)	0.7 (0.5-1.0)	0.9 (0.7-1.1)	0.7 (0.5-1.0)
Low dose (<1 g/day)	0.8 (0.5-1.2)	0.8 (0.5-1.4)	0.9 (0.7-1.2)	0.8 (0.5-1.4)
High dose (≥1 g/day)	0.6 (0.4-1.0)	0.6 (0.3-1.0)	0.8 (0.6-1.0)	0.6 (0.3-1.0)
PPIs				
Any use	1.5 (0.9-2.5)	1.8 (1.0-3.1)	1.7 (1.2-2.4)	2.0 (1.2-3.5)
Low dose (≤1 DDD)	1.6 (1.0-2.7)	1.5 (0.7-2.9)	1.6 (1.1-2.5)	2.5 (1.4-4.4)
High dose (>1 DDD)	--	2.7 (1.1-6.8)	1.8 (0.8-3.8)	--

Discussion

- Results for PPIs seem to be in line with literature
  Microbiome as possible mechanism?
- Strengths and limitations:
  + Large study population with self-reported exposure
  + Assessment and analysis of time-varying exposures
  + Broad range of confounders
  – Confounding by indication / reverse causation
  – Generalizability?

Conclusion

- No indication for increased risks of adverse birth outcomes associated with use of calcium-based antacids during pregnancy
- PPI use, both in early and late pregnancy, was associated with increased risks of low birth weight, SGA, and low Ponderal Index
- Restrained policy with regard to PPI use (and prescriptions) during pregnancy might be considered

Thank you

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  - Yrea van Rijt-Weetink (Netherlands Pharmacovigilance Centre Lareb)
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