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E-Poster 27

Association between in utero exposure to acetaminophen and external genital tract malformations in boys and girls: a systematic review and meta-analysis.

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Introduction

- Acetaminophen is widely used by pregnant women
- Findings are conflicting regarding a possible increased risk of genital malformations
- The aim of this study was to investigate the association between *in utero* exposure to acetaminophen and external genital tract malformations in the offspring in both sexes.

Methods

- This **systematic review and meta-analysis** followed the recommendations of the Cochrane handbook and PRISMA and MOOSE reporting guidelines.
- We searched MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, International Clinical Trials Registry Platform, ClinicalTrials.gov on April 18, 2024, for **randomized controlled trials and observational studies**.
- The two primary outcomes were a **composite endpoint including cryptorchidism, hypospadias, and penile hypoplasia in boys**, and a **composite outcome including clitoral enlargement, labial fusion, vulvar malformations, and rectovaginal fistula in girls.** Secondary outcomes included individual genital malformations and differences in anogenital distance (AGD).
- Two reviewers independently screened studies, extracted data and assessed risk of bias using Robins-I.
- Metanalysis was performed using OR. Fixed and random-effects models were performed.
- GRADE was used to evaluate the level of certainty.

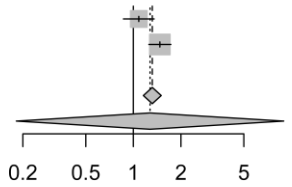
Results

- **Ten observational studies** were included, most of them followed a retrospective design.
- Regarding boys, meta-analysis of the primary outcome could not be performed, due to lack of data for penile hypoplasia.
- **Another composite endpoint** including **cryptorchidism and/or hypospadias** was reconstructed. **No statistically significant association was found**.
- **No statistically significant association** was found **for cryptorchidism or hypospadias separately** based on adjusted estimates.
- **The level of certainty was low to very low.**
- No statistically significant difference was found for short AGD.
- It was **not possible to perform meta-analysis for the outcomes in girls due to lack of data.**

Meta-analysis of the composite outcome

Study	Exposed (events/total)	Unexposed (events/total)	Risk of Bias	Odds ratio(crude)	OR	95%-CI	Weight (fixed)	Weight(random)
Rebordosa, 2008	113 / 26424	244 / 61718	Serious		1.08	[0.87; 1.35]	39.5%	46.6%
Zafeiri, 2022	203 / 12354	616 / 54866	Serious		1.47	[1.25; 1.73]	60.5%	53.4%
Fixed effect model					**1.32**	**[1.16; 1.50]**	**100.0%**	.
Random effects model					**1.27**	**[0.18; 8.94]**	.	**100.0%**

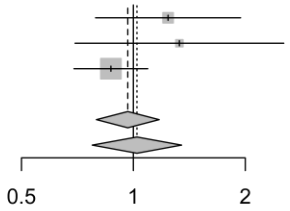
Heterogeneity: I^2 = 79%, τ^2 = 0.0374, p = 0.03



Meta-analysis for cryptorchidism

Study	Exposed (events/total)	Unexposed (events/total)	Risk of Bias	Odds ratio(adjusted)	OR	95%-CI	Weight (fixed)	Weight(random)
Rebordosa, 2008	33 / 26424	63 / 61718	Serious		1.24	[0.79; 1.94]	18.7%	27.1%
Kristensen, 2011	23 / 233	19 / 257	Critical		1.33	[0.70; 2.54]	9.0%	15.4%
Zafeiri, 2022	107 / 12354	357 / 54866	Serious		0.87	[0.69; 1.09]	72.2%	57.5%
Fixed effect model					**0.97**	**[0.80; 1.17]**	**100.0%**	.
Random effects model					**1.02**	**[0.78; 1.35]**	.	**100.0%**

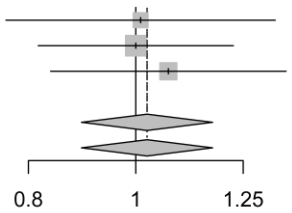
Heterogeneity: I^2 = 32%, τ^2 = 0.0211, p = 0.23



Meta-analysis for hypospadias

Study	Exposed (events/total)	Unexposed (events/total)	Risk of Bias	Odds ratio(adjusted)	OR	95%-CI	Weight (fixed)	Weight(random)
Rebordosa, 2008	80 / 26424	181 / 61718	Serious		1.01	[0.76; 1.34]	23.7%	23.7%
Interrante, 2017	783 / 2704	424 / 1506	Serious		1.00	[0.82; 1.22]	45.2%	45.2%
Zafeiri, 2022	96 / 12354	259 / 54866	Serious		1.07	[0.84; 1.37]	31.1%	31.1%
Fixed effect model					**1.02**	**[0.89; 1.17]**	**100.0%**	.
Random effects model					**1.02**	**[0.89; 1.17]**	.	**100.0%**

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.91



Discussion

Strength

- This is the first systematic review and meta-analysis investigating the association between *in utero* exposure to acetaminophen and external genital tract malformations.
- We performed an extensive search and followed Cochrane handbook
- The role of **confounding** and of the **timing** of acetaminophen exposure was investigated.

Limitations

- This SRMA relies on **a limited number of studies.**
- The included studies were assessed as having **serious or critical risks of bias due to the limited control of confounding factors.**
- There was significant heterogeneity in reporting of results and a lack of information in terms of acetaminophen exposure (duration, cumulative dose) or maternal characteristics.

Conclusion

This meta-analysis found **no link between *in utero* acetaminophen exposure and genital tract malformations in boys.**

Studies in girls are needed.

Studies were of low to very-low methodological quality and future studies should address this issue.