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Investigating the efficacy and safety of metronidazole during pregnancy; A systematic review and meta-analysis

Priscilla Ajiji[a,b], Anil Uzunali[a], Emmanuelle Ripoche[a], Emilie Vittaz[a], Thierry Vial[c], Patrick Maison[a,b,*]

[a] Agence Nationale de Sécurité du Médicament et des Produits de santé (ANSM), France
[b] EA 7379, EpiDermE Faculté de Santé, Université Paris-Est Créteil, France
[c] Service Hospitalo-Universitaire de Pharmacotoxicologie, CHU-Lyon, Lyon, France

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ABSTRACT

Objective: We aimed to review and analyze studies focusing on the efficacy of metronidazole in reducing the risk of preterm birth and the safety of metronidazole taking into account the different doses, duration of treatment and routes of administration.

Study designs: Embase, Cochrane Library and PubMed were searched up to 29 July 2019 to identify studies assessing metronidazole exposure during pregnancy. Additional studies were identified from reference lists of retrieved papers. Measured outcomes were preterm births (<37 weeks of gestation) and associated delivery outcomes such as spontaneous abortions (≤ 20 weeks of gestation), stillbirths (≥20 weeks of gestation) and low birth weight (<2500 g) irrespective of the period of exposure and major malformations after first-trimester exposure. Overall effect estimates for RCTs and observational studies were calculated using the random-effects model and pooled using Risk Ratios (RR) and Odds Ratios (OR) respectively. ROB-2 and ROBINS-I tool were used to assess Risk of Bias for RCTs and observational studies, respectively.

Results: Twenty-four studies (17 observational studies and 7 RCTs) were selected. Pooled RR was 1.10 (95 % CI 0.78–1.55; n = 7; I^2 = 72 %) for preterm birth. Subgroup analysis found RR 1.67; 95 % CI 1.07–2.62; n = 3; I^2 = 32 %) for treatment duration of ≤3 days among women with a previous preterm delivery. Pooled OR for spontaneous abortion was 1.72 (95 % CI 1.40–2.12; n = 5; I^2 = 72 %) and 1.15 (95 % CI 0.98–1.34; n = 12; I^2 = 25 %) for major malformations. After exclusion of studies with critical risk of bias, pooled OR were 1.7 (1.42–2.04; n = 3; I^2 = 19 %) and 1.13 (0.93–1.36; n = 9; I^2 = 28 %) respectively. Among several specific malformations analyzed, only congenital hydrocephaly was significantly increased at 4.06 (95 % CI 1.75–9.42; n = 2; I^2 = 0%).

Conclusions: Data do not confirm the efficacy of metronidazole in reducing the risk of preterm birth and associated delivery outcomes. Further research is required to confirm the effect of high dose and short duration of metronidazole treatment on preterm birth among the high-risk group. Regarding the increased odds of spontaneous abortion, RCTs are required to assess the role of the underlying infection. The need for further studies to confirm the risk of congenital hydrocephaly is paramount.

Contents

* Corresponding author at: Agence Nationale de Sécurité du Médicament et des Produits de santé (ANSM), 143 Boulevard Anatole France, 93200 Saint Denis, France.
E-mail address: patrick.maison@ansm.sante.fr (P. Maison).

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1. Introduction

Metronidazole (MET) is an imidazole derivative acting both as an antiprotozoal and anti-bacterial agent [1]. It is commonly used to treat genitourinary tract infections in pregnant women [2]. A study conducted in 2010 found a prevalence of 7.1 % of bacterial vaginosis among 14,193 pregnant women in France [3]. In the United States (US), Koumans et al found that 21 million women suffered from bacterial vaginosis between 2001 and 2004 [4]. Accordingly, MET is used to prevent preterm birth [5] in pregnant women with bacterial vaginosis or trichomoniasis.

Inconsistent data regarding the efficacy of MET but also its safety for the mother and newborn has led to conflicting guidelines on its use during pregnancy [6,7]. Randomized Controlled Trials (RCTs) have evaluated the efficacy of MET in reducing the risk of preterm birth among pregnant women with either asymptomatic [8] or symptomatic vaginosis [5], which may be coupled with either a positive fetal fibronectin test [9,10] or a previous preterm birth [11,12]. The findings give conflicting information whereby, researchers have demonstrated both reduction [5,12] or increase [8,13] in the incidence of preterm birth. Others found the risk is increased among women with a history of preterm birth [11] which is cited as the most leading risk factor [14,16].

The safety of MET treatment during pregnancy has also been evaluated, whereby some studies found an association between MET and congenital malformations [17,18] or even spontaneous abortion [19]. Two meta-analyses conducted in 1995 [20] and 1997 [21] found no association between the risk of malformations and MET exposure. Since then, several studies have been published and some indicated an increased risk of major malformations [17], congenital hydrocephaly [22] and clubfoot [23]. Safety has also been discussed with regards to low birth weight [24,25] and stillbirth [26].

Available in oral, rectal, topical, vaginal and intravenous forms [1], MET is well absorbed, with an elimination half-life of six to eight hours in healthy subjects [27]. Whereas literature documents no difference in cure rates of different doses, durations of treatment [28] and routes of administration [29], the impact of these parameters on adverse pregnancy outcomes remains controversial. Therefore, this meta-analysis aims to review and analyze studies focusing on the efficacy and safety of MET taking into account the different doses, duration of treatment and routes of administration.

2. Methods

2.1. Data sources

We conducted a systematic review and meta-analysis on literature citing MET treatment during pregnancy. Electronic databases searched were Embase, Pubmed and Cochrane Central Register of Controlled Trials (CENTRAL) up to 29 July 2019 using the keywords “metronidazole”, “fetal or embryo or offspring”, “adverse or risk or side or toxicity or undesirable or complication or event or outcome”, and “congenital malformation or preterm or abortion or stillbirth or miscarriage or small for gestational age or growth retardation or birth weight or gestational age or birth defect or neonatal or teratogen or developmental disorders or child or neurodevelopment or cognitive or developmental disability or learning disorder or intelligence or cognition” without restrictions on language.

Other sources included: hand searching references from eligible studies, abstracts presented at conferences, communications with experts in the field of medicines and pregnancy, the International Prospective Register of Systematic Review Protocols (PROSPERO) and the Electronic Thesis Online Service (ETHOS). Corresponding authors were contacted to obtain data for publications without specific analysis when MET was studied along with other drugs.

2.2. Study selection

RCTs and observational studies i.e. case-control and retrospective or prospective cohort studies citing MET use during pregnancy were considered eligible. We included observational studies with control groups which included 1) unexposed with disease 2) unexposed, disease-free 3) exposed to other treatment with disease or 4) unexposed (unspecified). Case reports, systematic reviews, meta-analysis and letters to editors or commentaries were excluded, in addition to publications with insufficient data to reconstruct two by two contingency tables, even after having contacted corresponding authors.

Exposure was determined as randomized treatment with MET for RCTs, or prescription of MET for observational studies, whatever the route of administration, dose and duration of treatment or even period of exposure.

Selected outcomes were: Preterm births due to spontaneous or indicated preterm labour (<37 weeks) and associated delivery outcomes such as spontaneous abortions (death before 20 weeks of gestation), stillbirths (death after 20 weeks), low birth weight <2500 g and caesarian delivery irrespective of the period of exposure. We also explored the risk of preterm birth among women with a history of preterm birth, as a high-risk group.

Other outcomes were major malformations after first-trimester exposure, which were defined by using the Brighton Collaboration Congenital Anomalies Working Group [30] and classified by using the European Surveillance for Congenital Anomalies [31] (EUROCAT) criteria.

Two authors independently identified, screened and reviewed publications for eligibility thereby generating the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [32] flow diagram in Fig. 1. A data extraction form was developed and piloted to ensure its usefulness before data extraction commenced, which was equally conducted by two reviewers. Disagreements were resolved through consensus or discussion with a third-party.

Risk of Bias was assessed using the Revised Cochrane Risk-Of-Bias tool for randomized trials (ROB 2) [33] for RCTs and Risk Of Bias In Non-randomized Studies-of Interventions (ROBINS-I) [34] for observational studies.

Results were pooled using Risk Ratios (RR) for RCTs and Odds Ratios (OR) for observational studies with corresponding 95 % confidence interval (CI) calculated using the random-effects model, developed by DerSimonian and Laird in 1986 [35]. Heterogeneity was assessed utilizing Q and I-square statistics. The analysis was performed using R [36] with the packages meta [37] and metafor [38].

Subgroup analysis was conducted to explore differences in effect size between and across different groups. These include [1], indication for MET [2], period of exposure [3], dose [4], duration [5], route of administration and [6] study design. Sensitivity analysis was done to ascertain the robustness of our results, first by excluding studies with the critical risk of bias from the analysis and secondly, excluding studies whose overall effect was not adjusted.

3. Results

Twenty four studies published between 1965 and 2019 were selected for analysis i.e. 17 observational studies (5 case-control and 12 cohort studies) and 7 RCTs (Fig. 1). The total number of participants was 800,195 included at any time during pregnancy with 5044 MET-exposed cases and 158,060 unexposed cases. The systemic route of administration was cited in 13 studies and the local route in 2 studies. Whereas dose and duration were not mentioned in 10 studies, the administered doses under systemic administration were 250 mg (5 studies), 400 mg (3 studies), 200 mg (2 studies) and 2 g (2 studies) for 7 days (6 studies), 3 days (2 studies) or 2 days (2 studies). Indication of bacterial

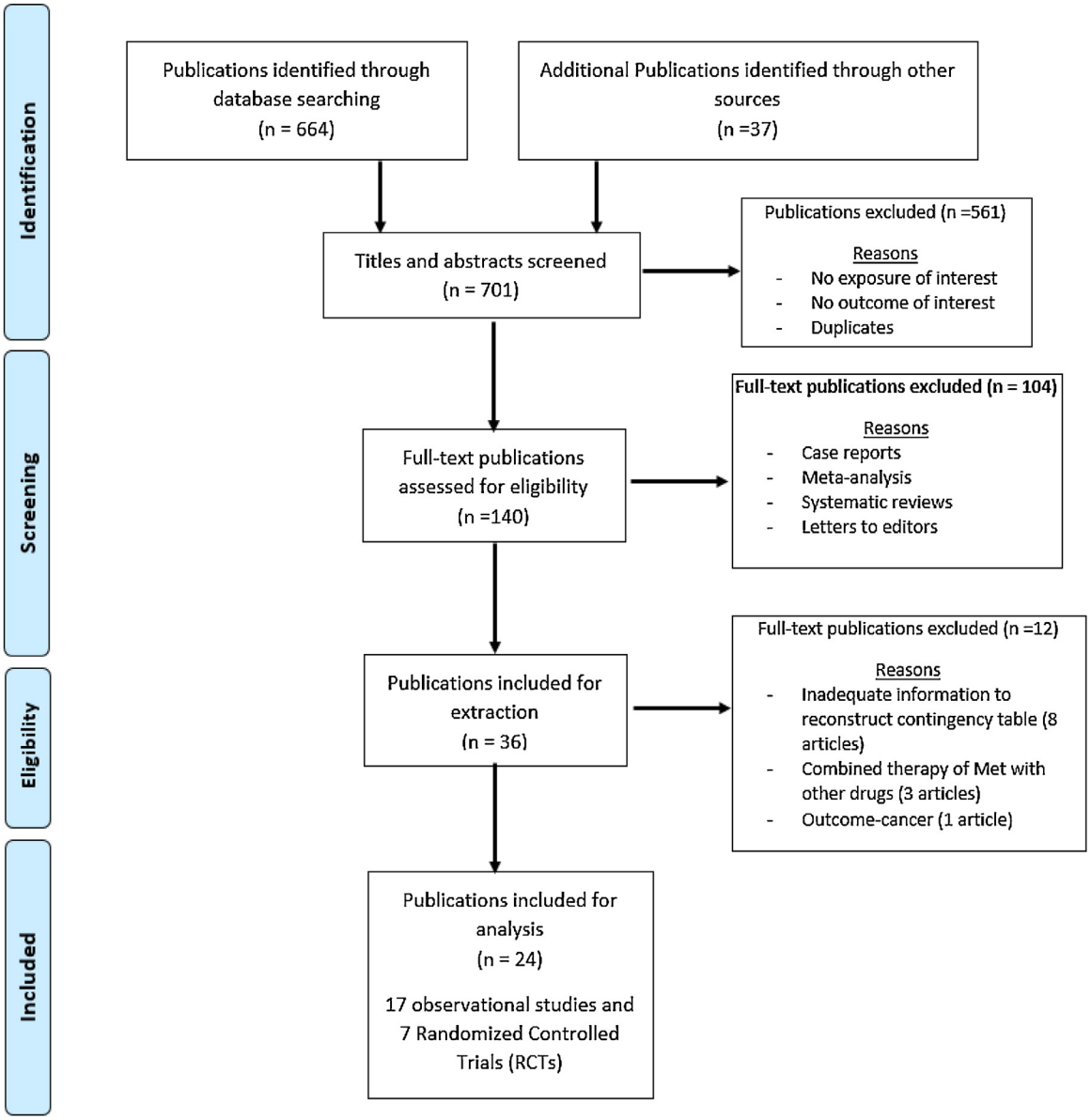

Fig. 1. PRISMA Flow diagram.

vaginosis/trichomoniasis was reported in 15 studies while others did not consider a specific indication as a criterion for participant inclusion. All RCTs used placebo in the control group while observational studies consisted of unexposed sick patients (2 studies), unexposed disease-free (8 studies), unexposed but not otherwise specified (5 studies) and exposed to other treatment (2 studies). Thirteen studies reported exposure in at least the first trimester while 9 reported exposure to MET outside the first-trimester (Table 1).

3.1. Risk of bias assessment

Four observational studies had a "critical" level of bias arising from bias in reporting, assessment of exposure and non-adjustment of confounding factors. Only one RCTs evaluated with ROB2 assessment had "some concerns" due to the selection of the reported result. A summary of ROB2 or ROBINS-I assessment is provided in Appendix B.

3.2. Preterm birth and associated delivery outcomes following MET exposure in utero

Fig. 2A presents results for the efficacy of MET in reducing the risk of preterm birth among pregnant women. The overall RR was 1.10 (95 % CI 0.78–1.55; n = 7; I^2 = 72 %). Subgroup analysis showed significant results for dose ≤250 mg (RR 0.41; 95 % CI 0.20−0.85; n = 1) and third-trimester exposure (RR 1.59; 95 % CI 1.05–2.41; n = 1). No significant effect on preterm birth was found after

Table 1
Characteristics of studies by study design, dose, duration, route of administration, indication and studied outcomes.

Ref.	Year	Study design	n	Dose (mg)	Duration (d)	Administration	Exposure (trimester)	Indication	Outcomes
[39]	Carey et al 2000	RCT	1953	2000	48 h apart	Systemic	2	Bacterial vaginosis	Preterm birth, low birth weight
[17]	Czeizel et al 1998	Case-control	47,963	2000 or 750	7	Systemic and local	1,3	Infectious disease of the respiratory system, urinary tract and genital organs	Malformations
[40]	Diav-Citrin et al 2001	Prospect. Cohort	765	973 (483)	7.9 (3.8)	Systemic and local	1	Helicobacter pylori, genital or urinary tract infection, giardiasis, trichomoniasis, amebiasis, and pelvic inflammatory disease.	Malformations and spontaneous abortion
[10]	Goldenberg et al 2001	RCT	89	2000	48 h apart	Systemic	2	Bacterial vaginosis or trichomonas vaginalis	Preterm birth
[41]	Heinonen et al 1977	Prospect. Cohort	50,282	–	–	Systemic	1	–	Malformations
[25]	Morgan et al 1978	Retrospec. Cohort	880	200	7 or 10	Systemic	–	Trichomoniasis	Stillbirth
[42]	Kazy et al 2004	Case-control	60,994	100	10	Local	–	Vulvovaginal candidosis or trichomoniasis	Preterm birth, low birth weight
[22]	Kazy et al 2005	Case-control	38,151	500	10	Local	1,2,3	Genitourinary tract infections	Malformations
[8]	Klebanoff et al 2001	RCT	617	2000	48 h apart	Systemic	2	Trichomonas vaginalis	Preterm birth, low birth weight
[24]	Koss et al 2012	Retrosp. Cohort	2829	250−500	7	Systemic	1	Bacterial vaginosis and trichomoniasis	Preterm birth, low birth weight, malformations
[43]	Zagorodnikova et al 2017	Retrospec. Cohort	901	–	–	–	1,2,3	Genitourinary tract infections	Malformations, spontaneous abortion
[44]	Leong et al 2019	Retrospec. Cohort	246,817	–	–	–	–	–	Spontaneous abortion
[45]	Mann et al 2009	Retrospe. cohort	3579	–	–	Systemic	3	Trichomoniasis	Preterm birth
[5]	McDonald et al 1997	RCT	857	400	2	Systemic	2	Gardnerella vaginalis	Preterm birth
[12]	Morales et al 1994	RCT	80	250	7	Systemic	2	Bacterial vaginosis	Preterm birth, spontaneous abortion, low birth weight
[18]	Muanda et al (a) 2017	Prospect. Cohort	124,881	–	–	–	1	Urinary or respiratory tract infections	Malformations
[19]	Muanda et al (b) 2017	Nested Case-control	95,722	–	–	–	1	Urinary or respiratory tract infections	Spontaneous abortion
[11]	Odendaal et al 2002	RCT	269	400	2	Systemic	2	Bacterial vaginosis	Preterm birth
[26]	Piper et al 1993	Retrospec. Cohort	2774	–	–	–	1	Unspecified indication	Malformations
[46]	Rosa et al 1987	Retrospec. Cohort	104,339	–	–	Systemic	1	Vaginitis	Spontaneous abortions, malformations
[47]	Scott-Gray et al 1964	Prospec. Cohort	183	200	7	Systemic	1 and 3	Trichomoniasis	Malformations
[9]	Shennan et al 2006	RCT	99	400	7	Systemic	2,3	Bacterial vaginosis	Preterm birth, low birth weight
[48]	Sorensen et al 1999	Retrospec. Cohort	13,451	–	–	–	1,2,3	–	Malformations, preterm birth
[23]	Werler et al 2014	Case-Control	2683	–	–	–	1	–	Malformations

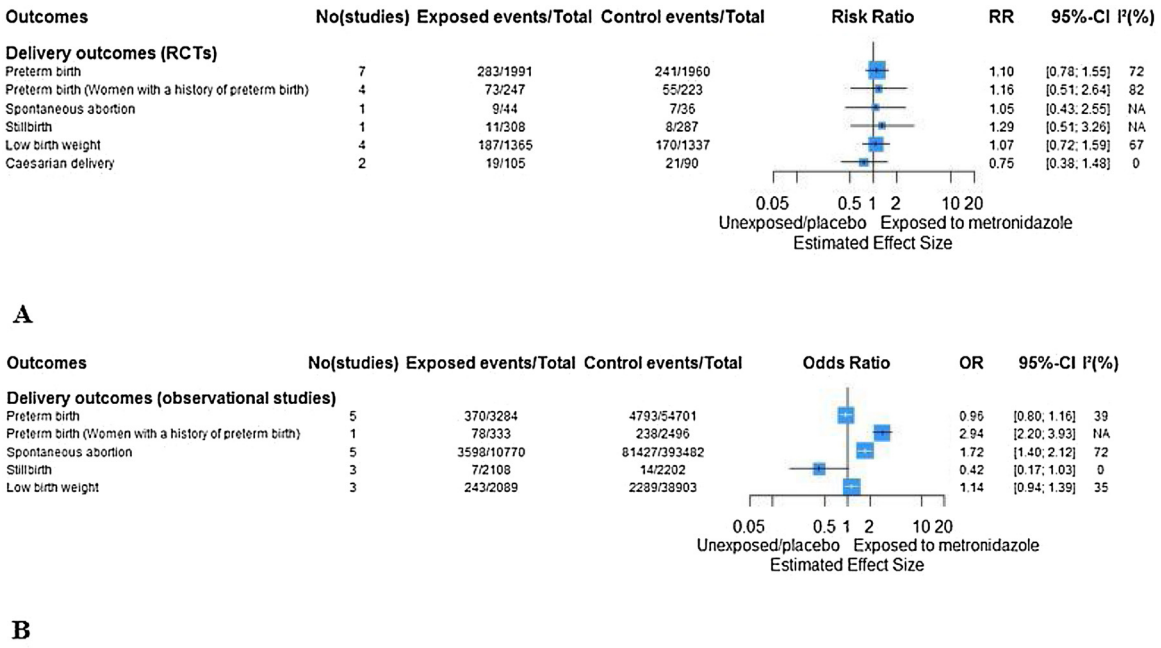

Fig. 2. Delivery outcomes after maternal metronidazole exposure.

subgroup analyses for the route of administration, treatment duration, effect estimates and the type of control group (Supplementary Fig. A1).

Conversely, 5 observational studies [24,40,42,45,48] evaluated the safety of MET exposure (OR 0.96; 95% CI 0.80- 1.16; $I^2 = 39\%$, Fig. 2B). Subgroup analysis showed significant results for third trimester exposure (OR 0.81; 95 % CI 0.66−0.98; n = 1) but not for study design, dose, route of administration, treatment duration, effect estimates and the type of control group (Supplementary Fig. A2).

3.3. Preterm birth among women with a history of preterm birth

We identified 4 RCTs [8,11,12,39] evaluating the use of MET in an attempt to reduce the risk of preterm birth among women with a preceding preterm birth (128 cases and 342 controls) (Fig. 2A). The control groups consisted of unexposed sick women with a history of preterm birth. Global results were not statistically significant however, an increased effect was found for the treatment duration of ≤3 days and dose of 400 mg-2 g

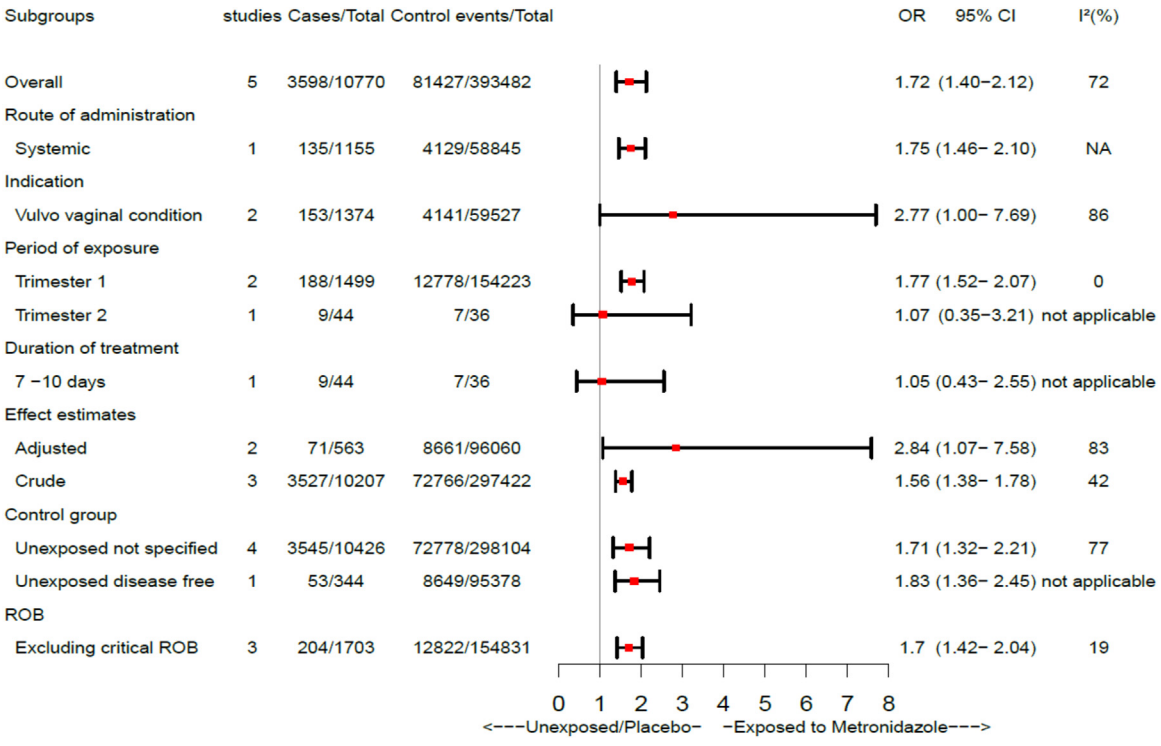

Fig. 3. Subgroup analysis of spontaneous abortion after maternal metronidazole exposure.

(RR 1.67; 95 % CI 1.07–2.62; n = 3; I^2 = 32 %) compared to a duration of 7 days and dose ≤250 mg (RR 0.26; 95 % CI 0.10−0.63; n = 1), Supplementary Fig. A3.

Regarding the safety of MET, only 1 study [24] was identified. Women with a history of preterm birth exposed to MET were 2.94 times more likely to have a preterm birth compared to their unexposed counterparts (Fig. 2B).

3.4. Spontaneous abortions

One RCT [12] documented spontaneous abortion as an outcome when MET was used in an attempt to reduce the risk of preterm birth (Fig. 2A).

Five observational studies [19,40,43,44,46] evaluated the association of spontaneous abortion and MET exposure (Fig. 2B). Subgroup analysis showed a statistically significant effect for women exposed in the first trimester (Fig. 3). The results of sensitivity analysis remained similar to the original result after the exclusion of two studies with a "critical" risk of bias (OR 1.7; 95 % CI 1.42–2.04; n = 3; I^2 = 19 %).

3.5. Stillbirths

Only 1 RCT [8] documented stillbirth as an outcome when MET was used in an attempt to reduce the risk of preterm birth (Fig. 2A). Regarding safety, we included 2108 exposed and 2202 unexposed pregnant women from 3 observational studies [25,26,40]. No statistically significant association was found between stillbirth and MET exposure at any point during pregnancy (Fig. 2B). Subgroup analysis was not conducted due to the limited number of studies.

3.6. Low birth weight

We included 4 RCTs [8,9,12,39] documenting low birth weight as an outcome when MET was used to reduce the incidence of preterm birth. No statistically significant association was found between low birth weight and MET exposure during pregnancy, even after subgroup analysis. (Supplementary Fig. A4).

Based on three observational studies [24,25,42] (2532 cases and 38,460 controls), no statistically significant association was found between low birth weight and MET exposure during pregnancy (Fig. 2B). Subgroup analysis was not conducted due to the limited number of studies.

3.7. Caesarian delivery

Based on two RCTs [8,9], 195 pregnant patients were included in the analysis. The risk of caesarian delivery was not significantly decreased after exposure to MET at any point during pregnancy (Fig. 2A).

3.8. Major congenital malformations

Twelve (10 cohort, 2 case-control) studies [17,22–24,40,41,25,43,26,46–48,18] were included in the analysis. Out of 411,380 pregnant women, 57,718 were cases in which 440 were exposed at least in the first-trimester (OR 1.15: 95 % CI 0.98–1.34; I^2 = 25 %, Fig. 4). The odds of major malformations were increased for case-control studies (OR 1.32; 95 % CI 1.02–1.70; n = 3, I^2 = 35 %) but not with studies with a higher level of evidence (prospective and retrospective cohort studies). No difference was found between the systemic and local route of administration. After the exclusion

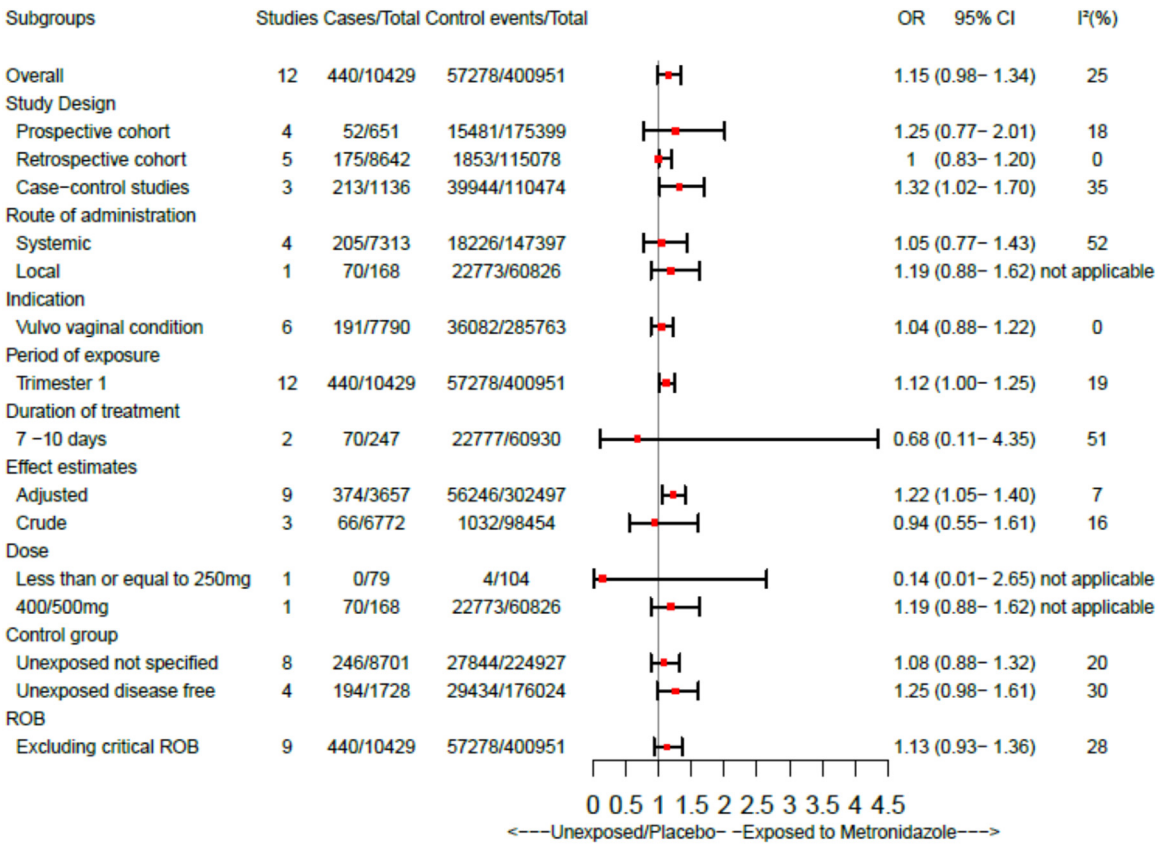

Fig. 4. Major malformations and subgroup analysis after maternal metronidazole exposure.

of 3 studies with a "critical" level of bias, the results remained similar to the original result. Further sensitivity analysis based on adjusted effect estimates (after excluding 3 studies with crude effect estimates showed an increased result of 1.22 (95 % CI 1.05–1.40; n = 9; I^2 = 7%).

3.9. Specific malformations

Results of specific malformations were grouped for visualization purposes. Among 10 types of malformations, only the odds of congenital hydrocephaly were significantly increased (OR 4.06, 95 %CI 1.75–9.42, n = 2; I^2 = 0 %) after first-trimester exposure to MET (Fig. 5).

4. Discussion

This systematic review and meta-analysis of 24 studies on MET exposure during pregnancy including 163,104 cases and 637,091 controls did not confirm the efficacy of MET in reducing the risk of preterm birth. Regarding other adverse pregnancy outcomes, a significant effect was observed between spontaneous abortion and MET exposure.

4.1. Preterm birth and associated delivery outcomes

No relationship was found between MET treatment during pregnancy and preterm birth, stillbirth, low birth weight and caesarian delivery. There are conflicting views on the use of MET in averting or increasing the risk of preterm birth and associated outcomes [13,49–51]. Recent guidelines for clinical practise and reviews stated insufficiency of data on the efficacy of MET to recommend its use (or non-use) [6,50]. Based on the analysis, we cannot confirm the efficacy of MET in reducing the risk of preterm birth.

Contrary to previous studies [11,24], the overall risk of preterm birth was not significantly decreased among women with previous preterm birth. Subgroup analysis suggested pregnant women who were administered MET for ≤3 days may have an increased risk of preterm birth. The recommended guidelines for the treatment of trichmoniasis and or bacterial vaginosis among pregnant women include the single dose of 2 g or 400 mg–500 mg for up to 7 days [52,7,53]. In our meta-analysis, the duration of treatment of <3 days is related to two doses of 2 g administered 48 h apart (Klebanhoff et al., Carey et al.) [8,39] and 400 mg for 2 days (Odendaal et al.) [11]. Further studies are required to assess the hypothesis that a high dose for a short duration may increase the risk of preterm birth among women with a previous preterm birth, compared to a lower dose for a longer duration. In observational studies, pregnant women with preterm birth in the preceding pregnancy had a higher likelihood of preterm birth compared to their unexposed counterparts. Unfortunately, the results are based on one study.

Whereas pregnant women infected with T.vaginalis are more likely to have a stillbirth [54], the literature does not confirm the impact of MET treatment on perinatal mortality [55]. Our study did not confirm the beneficial effect of MET on stillbirth (OR 0.42; 95 % CI 0.17–1.03; n = 3; I^2 = 0%).

MET exposure was associated with an increased risk of spontaneous abortion. The results from sensitivity analysis remained similar to the original result with a decreased level of heterogeneity (I^2 = 19 %). Findings from recent studies show a relationship between bacterial vaginosis and miscarriage in the first [56] and second trimester [57]. Because the analysis was based on observational studies, our results regarding spontaneous abortion may be subject to indication or protopathic bias.

4.2. Major congenital malformations

Our meta-analysis revealed no statistically significant association between major malformations and MET exposure during the first trimester of pregnancy. This is consistent with the meta-analyses conducted by Caro-Paton et al. [21] and Burtin [20] et al. Despite the increased odds after analyzing only adjusted effect estimates, we are unable to conclude on the risk of major malformations due to the quality of some studies included in the analysis, even after adjusting for confounding factors. Moreover, when studies with the critical risk of bias are excluded, the risk remains similar to the original result. Regarding specific malformations, MET exposure in the first trimester was associated with congenital hydrocephaly. The results are based on two case-control studies conducted by Kazy et al. [22] (70 cases exposed to vaginal MET treatment during the first trimester) and Czeizel et al. [17] (136 cases exposed to oral MET during the first trimester) who both used the same data source with malformed cases identified from the Hungarian Congenital Abnormality Registry, matched to controls and were subject to recall bias regarding drug exposure. The possible risk of overlap between the two studies should be noted.

4.3. Strengths and limitations

This is the first meta-analysis to highlight both the safety and efficacy of MET during pregnancy. Moreover, the robustness of our results was proved using sensitivity analyses that produced

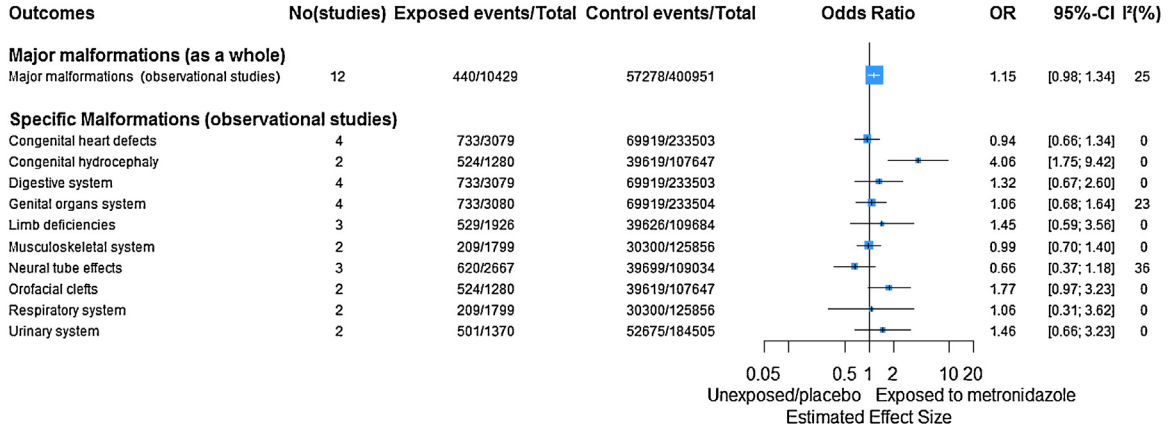

Fig. 5. Specific major malformations after maternal metronidazole exposure.

findings similar to the original analyses. Compared to two previous meta-analyses of 1995 [20] (7 studies) and 1997 [21] (5 studies) on malformations, our meta-analysis is an update of 12 studies with 411,380 participants. Furthermore, this is the first meta-analysis to consider the assessment of risks related to MET exposure in light of the dose, duration, route of administration, indication and the period of exposure of the treatment. Lastly, the symmetric funnel plot (Supplementary Fig. A5) does not suggest the presence of publication bias.

However, our analysis was dependent on the precision of authors regarding the dose, duration, route of administration, indication, the period of exposure of the treatment and the definition of outcomes such as stillbirth. This was not always the case. Finally, most of the observational studies included in our analysis use the prescription of MET as a proxy for exposure, which may bias the results.

4.4. Conclusion

In conclusion, data do not confirm the efficacy of MET in reducing the risk of preterm birth and associated delivery outcomes. Further research is required to confirm the effect of high dose and short duration of metronidazole treatment on preterm birth among the high-risk group. Regarding the increased odds of spontaneous abortion, RCTs are required to assess the role of the underlying infection. The need for further studies to confirm the risk of congenital hydrocephaly is paramount.

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Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2021.100128.

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