PROJECT: Treatment of Schistosomiasis Infections in Pregnancy on Fetal and Infant Outcomes: A Systematic Review and Meta-Analysis

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Introduction

Travelling to, or migrating from, equatorial regions of the world places individuals at risk for communicable infectious diseases, including parasitic and helminthic infections. Given the prevalence of international travel, as well as an appreciable burden of parasitic infections in ill-returned travellers, physicians caring for such populations will be required to treat intestinal protozoal and helminth infections in pregnancy, beyond the mass drug administration programming in place in endemic areas. Managing parasitic infections during pregnancy warrants a consideration of many factors including drug safety, efficacy, and potential impact on fetal and infant outcomes. However, a substantial knowledge gap exists in the treatment of parasitic infections during pregnancy. There are no definitive published and authoritative resources outlining specific management strategies for a number of parasitic infections in pregnancy. This project aims to fill this gap by mapping the available high-quality literature on the safety, efficacy, maternal and fetal outcomes of the use of anti-infectives, specifically praziquantel, in the treatment of schistosomiasis during pregnancy.

Methods

A literature search was conducted on Medline, Embase, CINAHL, Cochrane DbSR and Cochrane Central databases with the search terms "intestinal parasites," generic and organism specific; and "pregnant/pregnancy" from database inception to July 2021 without language restrictions irrespective of language, publication status or publication year to identify relevant papers. The search strategy was restricted to humans. Reference lists and cited bibliographies of topical reviews, trials, and systematic reviews were also hand searched. In addition, bibliographies in key papers were hand searched for relevant studies. The search terms for Medline are shown in Supplementary Table 1 and similar search terms were used for the other databases. We included all systematic reviews, randomized controlled trials, observational studies including cohort, cross-sectional and case-control studies, case series, and case reports assessing or reporting the use of anti-parasitic drugs in the management of schistosomiasis infections during any trimester of pregnancy. For randomized controlled trials, we included trials using a placebo or comparator anti-parasitic drug and those with "no treatment" arms. Titles and abstracts of all returned articles were reviewed, and if they did not explicitly mention both pregnancy and a parasitic infection, they were discarded. Full text articles were retrieved and assessed for eligibility. Inclusion criteria were:

1. Pregnant patient
2. Treated with praziquantel during pregnancy
3. Schistosomiasis infection (S. mansoni, S. japonicum, S. mekongi, S. haematobium)
4. Fetal, neonatal, infant or child outcomes reported after drug treatment

Selection of studies and reports identified by the search strategy and included in the review were independently assessed by two systematic review authors. Resolution of disagreement regarding inclusion was via discussion and arbitration by a third review author. Data was extracted from published studies with the following possible adverse, morbidity and development outcomes from the fetus stage to childhood:

- Stillbirth
- Preterm birth
- Birth weight (mean, low birth weight, very low birth weight)
- Neonatal deaths
- Congenital malformations
- Hemoglobin level
- Anemia
- Parasitic infection and other morbidities
- Immune response (cytokine responses, allergic events)
- Developmental markers
- Infant milestones

Means, standard deviations, and sample size were collected for continuous outcomes, such as birth weight and haemoglobin level. Dichotomous outcomes such as stillbirth and preterm birth were collected as frequencies and proportions (with 95% confidence intervals) from primary studies without a comparator arm. If a comparator arm was included in the primary study, we used a standardized measure of treatment difference for dichotomous outcomes (relative risk) and continuous outcomes (mean difference). Meta-analyses based on the same intervention, same outcome, similar study design and study population were conducted with random effects model, weighted by sample size and inversely by the variance of primary studies. Statistical analyses and meta-analysis were performed using GraphPad Prism 8 (GraphPad, USA) and RevMan5.3 (Cochrane, UK). Level of significance was set at a 5%-alpha level for summary estimates of outcomes measured against a comparator. We adhered to the GRADE approach for assessment of methodological quality, and assigned studies a quality grade of high, moderate, low, or very low (ref 12, 13 from previous paper).

Results

Literature Search

We searched and identified 3013 articles from the following literature databases: Medline (n= 1336), Embase (n= 1480), Cochrane Central (n= 92), Cochrane DbSR (n= 21), CINAHL (n= 84), grey literature and additional citations from general and systematic review papers (n=44). After deduplication, 2257 titles remained, of which 658 full-text publications were obtained and assessed for eligibility for inclusion in the review (Figure 1). Fifteen studies fulfilled inclusion criteria for qualitative synthesis: 12 randomized controlled trials (RCT) and 4 observational studies including a retrospective cohort, longitudinal study, case series and case report. Seven praziquantel RCT studies were included in meta-analysis (quantitative synthesis). The study characteristics were summarized in Table 1.

Included Studies

All RCTs were conducted in low- or upper middle- income settings as defined by the World Bank in Africa and South America from 1995 to 2005. Praziquantel was the drug treatment employed in these intervention

studies. All studies from 11 RCTs were individual randomized trials. Most trials included pregnant women without severe anemia (defined as hemoglobin <11.2 g/dL) in their 2nd or 3rd trimester, while one was conducted specifically on pregnant women with severe anemia (defined as hemoglobin <7 g/dL) and one on pregnant women living with HIV. 23 All compared a drug treatment (praziquantel) with placebo in a 2-arm or 4- arm factorial design, and all reported outcomes following treatment of one or more of schistosomiasis infections that occurred at varying prevalence (depending on study site), and were typically confirmed by a single stool microscopic examination (where reported). Most of the observational studies also presented findings in the aforementioned country settings, while one was an observational cohort and another longitudinal study from Sudan, one case series from Africa and one case report from Somalia.

Discussion

Currently, quality evidence on treatment of schistosomiasis with praziquantel during pregnancy on the safety and developmental outcomes of the fetus, baby and child are limited. In this review, we have expanded our research by evaluating the effects of anti-helminthic drug treatment during pregnancy on fetal, neonatal, infant, and child outcomes.

Overall, we did not observe differences in adverse events (stillbirth, neonatal death, perinatal death, congenital malformations, preterm birth, infant mortality) to the fetus and baby of mothers who were treated with praziquantel from RCT data which are regarded to have higher quality of evidence. Our evaluations were concordant with the findings of two systematic reviews from Ndibazza and et al. and Honkpehedji et al.

With respect to data from cohort and care report/case series studies, there appeared to be no differences in outcomes as all reported healthy babies. There was no effect on rate of abortion, preterm deliveries, infant milestones and malformations, stillbirths, perinatal deaths or adverse events. Regardless, these types of studies generally do not have a comparable control study arm and findings can be subjected to other risk factors and various settings. Development outcomes of the infant and baby including mean birth weight, low (<2500g) and very low birth weight (<1500g), and hemoglobin levels at birth were evaluated. For praziquantel treatment overall, no negative nor beneficial effects were seen during growth and hemoglobin outcomes. While we were interested in the travelers population, most studies including higher quality evidence clinical trials were from endemic developing countries and hence the interpretation may not be generalized to the travelers population. Varying dosage from the different praziquantel studies should also be considered when interpreting the findings. In this systematic review and meta-analysis, we found praziquantel treatment in pregnant mothers is relatively safe for the fetus and infant and did not have any major effects on the development of the infant to early childhood.

Tables and Figures

Figure 1: PRISMA Flow Design

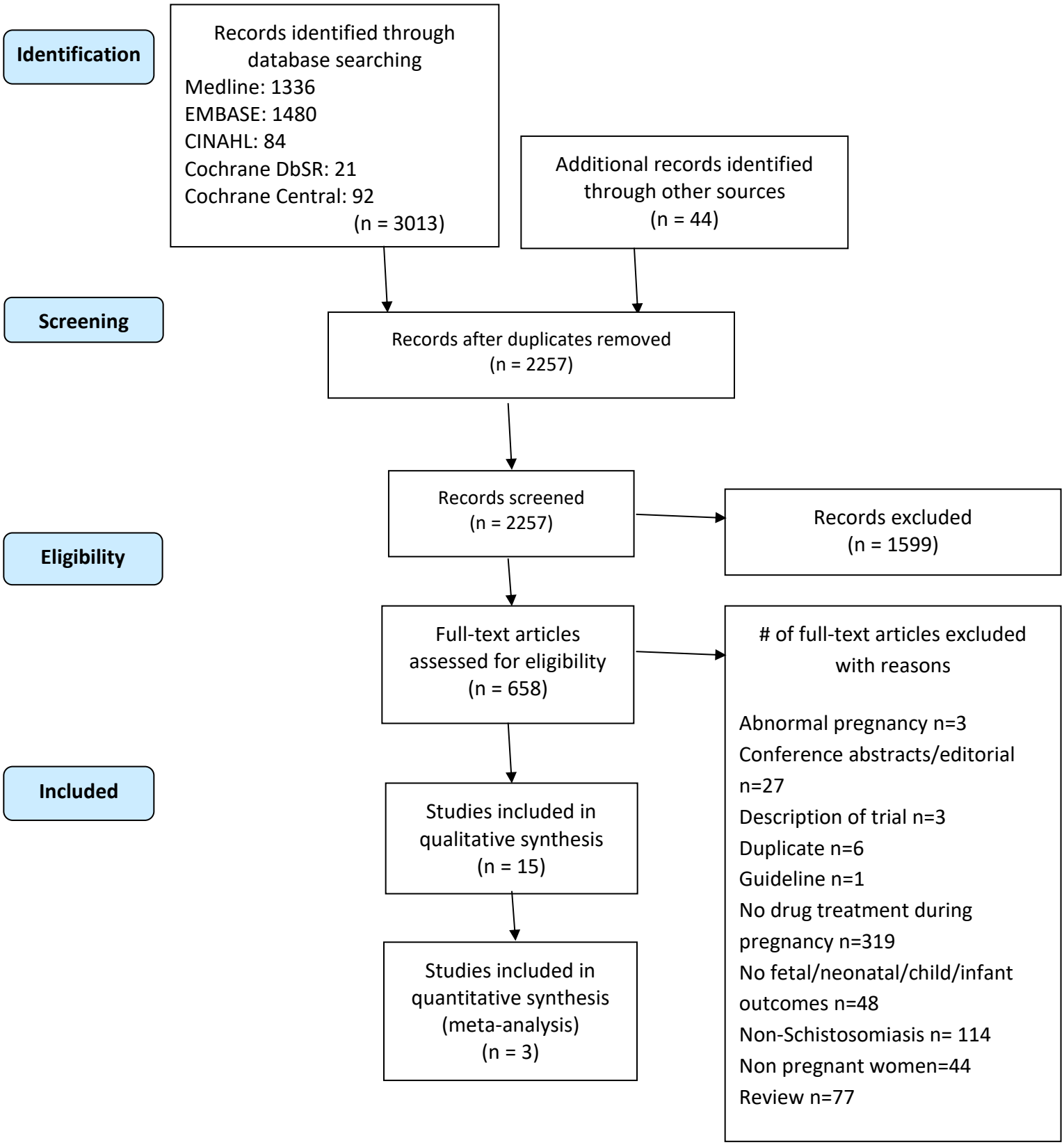

Table 1. Fetal and infant outcomes following praziquantel treatment in pregnant mothers with *S. mansoni* compared to placebo

Fetal and Infant Outcomes	Study Design and Sample Size	Effect of Maternal Praziquantel Treatment Compared to Placebo	Certainty of Evidence (GRADE)
Birth weight; low birth weight (<2.5kg); very low birth weight (<1.5kg)	1 RCT; n = 1953	No difference in birth weight, nor were there differences in incidence of low birth weight and very low birth weight babies.	⊕⊕⊕◯ **MODERATE** [b]
Height and weight at 15 months	1 RCT; n = 483	No difference in height and weight of infants measured at 15 months.	⊕⊕⊕◯ **MODERATE** [a]
Fetus small for gestational age	1 RCT; n = 370	No difference in incidence of fetus being small for gestational age.	⊕⊕⊕⊕ **HIGH**
Apgar score at 10 minutes	1 RCT; n = 483	No difference in Apgar score measured at 10 minutes.	⊕⊕⊕◯ **MODERATE** [a]
Live birth rate	1 RCT; n = 366	No difference in live birth rates.	⊕⊕⊕⊕ **HIGH**
Stillbirth at >20 weeks gestation	2 RCTs; n = 2759	No difference in incidence of stillbirths.	⊕⊕⊕◯ **MODERATE** [c]
Unhealthy newborn	1 RCT; n = 366	No difference in newborn health.	⊕⊕⊕◯ **MODERATE**
Congenital anomalies	2 RCT; n = 2726	No difference in incidence of congenital anomalies.	⊕⊕⊕◯ **MODERATE**
Serious infant adverse events	1 RCT; n = 362	No difference in incidence of serious infant adverse events.	⊕⊕⊕◯ **MODERATE**
Early neonatal death (<7 days)	1 RCT; n = 2345	No difference in incidence of early neonatal death.	⊕⊕⊕⊕ **HIGH**
Infant cytokine levels (IFN-γ; IL-1, 2, 4, 5, 6, 10, 12, 13; CXCL8, 9; TNF; sTNFRI; sTNFII; IFN-γ:IL-4 ratio)	1 RCT; n = 238	No difference in infant cytokine levels.	⊕⊕⊕⊕ **HIGH**
Hemoglobin levels (in newborn; in cord blood; in infant at 1 year)	1 RCT; n = 1342 1 RCT; n = 483	No difference in hemoglobin levels measured in newborns, in cord blood nor in infants at 1 year.	⊕⊕⊕⊕ **HIGH;** ⊕⊕◯◯ **LOW** [e]**;** ⊕⊕⊕◯ **MODERATE** [a]

Newborn serum transferrin receptor level; newborn serum ferritin levels; newborn transferrin receptor:ferritin ratio)	1 RCT; n = 361	No difference in serum transferrin receptor levels of newborns, serum ferritin levels nor transferrin receptor:ferritin ratio.	⊕⊕⊕⊕ **HIGH;** ⊕⊕⊕◯ **MODERATE** [d] ⊕⊕⊕⊕ **HIGH**
Non-anemic at 6 months; non-anemic at 12 months	1 RCT; n = 361 1 RCT; n = 303	No difference in incidence of non-anemic babies, measured at 6 months and 12 months.	⊕⊕⊕⊕ **HIGH**
Iron-deficiency anemia at 6 months; iron-deficiency anemia at 12 months	1 RCT; n = 320 1 RCT; n = 304	No difference in incidence of iron-deficiency anemia, measured at 6 months and at 12 months.	⊕⊕⊕⊕ **HIGH**
Non-iron-deficient anemic at 6 months; non-iron-deficient anemia at 12 months	1 RCT; n = 314 1 RCT; n = 310	No difference in incidence of non-iron-deficient anemia, measured at 6 months and at 12 months.	⊕⊕⊕⊕ **HIGH**