Untreated maternal syphilis and adverse outcomes of pregnancy: a systematic review and meta-analysis

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Objective To perform a systematic review and meta-analysis of reported estimates of adverse pregnancy outcomes among untreated women with syphilis and women without syphilis.

Methods PubMed, EMBASE and Cochrane Libraries were searched for literature assessing adverse pregnancy outcomes among untreated women with seroreactivity for *Treponema pallidum* infection and non-seroreactive women. Adverse pregnancy outcomes were fetal loss or stillbirth, neonatal death, prematurity or low birth weight, clinical evidence of syphilis and infant death. Random-effects meta-analyses were used to calculate pooled estimates of adverse pregnancy outcomes and, where appropriate, heterogeneity was explored in group-specific analyses.

Findings Of the 3258 citations identified, only six, all case-control studies, were included in the analysis. Pooled estimates showed that among untreated pregnant women with syphilis, fetal loss and stillbirth were 21% more frequent, neonatal deaths were 9.3% more frequent and prematurity or low birth weight were 5.8% more frequent than among women without syphilis. Of the infants of mothers with untreated syphilis, 15% had clinical evidence of congenital syphilis. The single study that estimated infant death showed a 10% higher frequency among infants of mothers with syphilis. Substantial heterogeneity was found across studies in the estimates of all adverse outcomes for both women with syphilis (66.5% [95% confidence interval, CI: 58.0–74.1]; $I^2 = 91.8\%$; $P < 0.001$) and women without syphilis (14.3% [95% CI: 11.8–17.2]; $I^2 = 95.9\%$; $P < 0.001$).

Conclusion Untreated maternal syphilis is associated with adverse pregnancy outcomes. These findings can inform policy decisions on resource allocation for the detection of syphilis and its timely treatment in pregnant women.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In 2008, the World Health Organization (WHO) estimated that 1.86 million cases of syphilis occur globally among pregnant women each year and that a large proportion of them are untreated or inadequately treated. Up to one third of the women attending antenatal care (ANC) clinics are not tested for syphilis.[1] If syphilis is left untreated during pregnancy, it can lead to fetal loss or stillbirth or, in a liveborn infant, neonatal death, prematurity, low birth weight or congenital syphilis. Programmes that include syphilis testing coupled with appropriate, prompt penicillin treatment for pregnant women who test positive for *Treponema pallidum* infection have been shown to be efficacious in reducing adverse pregnancy outcomes.[2–4] In addition, these interventions have been estimated to be highly cost-effective, even in settings where the burden of syphilis among pregnant women is moderate or low.[5–8]

Existing barriers to scaling up these programmes can only be overcome through active involvement from policy-makers. Evidence-based estimates of the burden of congenital syphilis at the global, national and subnational levels help make the case for allocating resources to these effective programmes, increasing access to interventions and making progress towards elimination. Calculating the burden relies on precise estimates of the local prevalence of syphilis and adverse pregnancy outcomes among untreated women with syphilis. Previous estimates of adverse pregnancy outcomes in women with syphilis have been based on point estimates from single studies. To improve the quality of these estimates in the context of WHO's global initiative for the elimination of congenital syphilis,[9,10] we performed a systematic review and meta-analysis of reported estimates of adverse pregnancy outcomes among women with untreated syphilis and women without syphilis.

Methods

We performed a systematic review and meta-analysis that accorded with MOOSE guidelines[11] and PRISMA requirements.[12]

Search strategy and inclusion criteria

We systematically searched the published literature without date or language restrictions to identify studies assessing pregnancy outcomes in the presence of maternal syphilis. We used combinations of the following terms to search PubMed, EMBASE and Cochrane Libraries: *syphilis*/*congenital syphilis*, *pregnancy*, *antenatal*/*prenatal*, *neonate*/*newborn*, *infant*, *birth*/*pregnancy outcome*, *mortality*, *death*, *stillbirth*/*fetal death*, *neonatal death*, *infant death*, *preterm*/*low birth weight* and *perinatal death*/*mortality*. The last search was performed in December 2011. We included literature published in any language and on any date. We reviewed references in seminal papers, review articles and medical textbooks. We canvassed experts in the field to identify additional studies, particularly older studies that may have been published before the avail-

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ability of online databases. The grey literature and conference abstracts were not searched.

Because our goal was to estimate the range of possible birth outcomes associated with untreated syphilis during pregnancy, our population of interest was pregnant women who had untreated syphilis. We included studies that described pregnancy outcomes among women presumed to have syphilis (i.e. women who were seroreactive for *T. pallidum* infection, irrespective of the test used), as well as uninfected (i.e. control) women. We focused on fetal, neonatal and infant outcomes because maternal outcomes of syphilis would not be expected for several years after disease onset and were unlikely to have been reported in the same studies. We included studies of at least 30 patients that described the sampling strategy used to recruit patients from the community, hospitals or ANC clinics. We excluded studies describing partially treated populations, unless adverse pregnancy outcomes were reported specifically among women who lacked syphilis testing or treatment (i.e. at least 2.4 million U of intramuscular penicillin). We considered a broad range of study designs, including clinical trials, observational studies, programme reviews and case series. We assessed potential studies to ensure that there was no duplication of case series.

The data extracted included study characteristics such as study year, geographical location, diagnostic test used, sample size for cases and controls, design, length of follow-up, type of outcome and frequency estimates for *T. pallidum*–associated seroreactivity in the study population or a comparable population from the same setting and period. Length of follow-up varied among the studies. The tests used to define seroreactivity varied across settings and over time, from the Wasserman and Kahn tests (for which sensitivity and specificity data are not available) in early studies, to the Venereal Disease Research Laboratory or rapid plasma reagin tests (sensitivity, 71–100%; specificity, 98%), the fluorescent treponemal antibody absorption test (sensitivity, 84–100%; specificity, 97%) and the microhaemagglutination assay for *T. pallidum* (sensitivity, 76–100%; specificity, 99%) in more recent studies.[13] The early literature did not always define birth outcomes (e.g. dates used to define stillbirth, fetal loss or prematurity) and in such cases we relied on the outcome terminology in the original papers.

Statistical analysis

We calculated crude proportion estimates and standard errors (SEs) for all adverse pregnancy outcomes in women with untreated syphilis and women without syphilis. We then calculated crude proportion estimates and SEs for the following select adverse pregnancy outcomes: fetal loss or stillbirth (combined), neonatal death (defined as a death occurring from birth up to the age of 28 days), prematurity or low birth weight (combined) and clinical evidence of syphilis. We separately calculated crude proportion estimates of infant death (defined as a death occurring between ages 29 and 365 days) to allow for the differentiation between neonates and infants.

Proportions were transformed into logits. The SEs of the logits were calculated for the meta-analysis procedure. Both the logits and the SEs of the logits resulting from the meta-analysis routines were transformed back to percentages for the forest plots.[14,15] We used random-effects meta-analyses to pool estimates (with 95% confidence intervals [CIs]) and calculated measures of heterogeneity between studies (i.e. I^2 values and a P-value of < 0.05 was defined as indicative of a statistically significant difference in results).

We performed group-specific analyses for all adverse outcomes and for specific adverse outcomes to explore the sources of heterogeneity. We defined three groups of studies. Group 1 included studies calculating the frequency of an adverse pregnancy outcome involving women whose reproductive history was recorded before the existence of penicillin treatment. Group 2 comprised studies in which the frequency of an adverse pregnancy outcome was calculated for women attending an ANC clinic that offered no treatment or testing for syphilis. Group 3 comprised studies that examined the frequency of an adverse pregnancy outcome involving women attending an ANC clinic in which recruitment in the study was done at the time of delivery (and syphilis treatment was only available at that time). All data were prepared and analysed using Stata/SE version 11.0 (StataCorp. LP, College Station, United States of America).

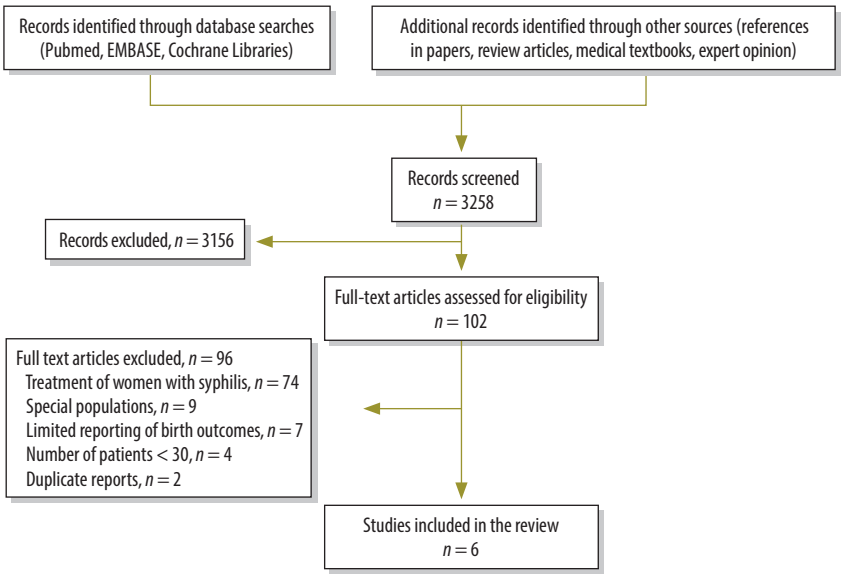
Results

Overall, 3258 citations were retrieved. Six articles[6,16–20] were considered eligible for the study (Fig. 1) and extracted data are shown in Table 1. All articles presented the findings of observational studies that included a "control" arm assessing adverse pregnancy outcomes among women without syphilis. Of these studies, Harman's investigation of family histories of infants with blindness predated the availability of syphilis treatment and was classified as a group 1 study.[16] Harman tabulated all pregnancy outcomes and child deaths from birth through the first year of life over the reproductive histories (as many as 18 pregnancies) of 150 mothers with syphilis and 150 "healthy" mothers living in the same impoverished London community. Wammock, Ingraham and McDermott et al. looked at pregnancy outcomes among women attending ANC clinics in which either screening or treatment was not available; all three investigations were classified as group 2 studies.[17–19] The studies by Ingraham and Wammock were conducted before the availability of penicillin treatment in the United States of America. The study by McDermott et al. had a primary goal of assessing malaria-associated adverse pregnancy outcomes in women attending a rural ANC clinic in Malawi. No antenatal syphilis testing programme existed at that time and seroreactivity was identified later on the basis of analysis of stored blood samples. The intervention study in Zambia, by Hira et al., and the retrospective study of women tested for syphilis at delivery in the United Republic of Tanzania, by Watson-Jones et al., were ANC evaluation studies conducted in the context of poorly implemented syphilis screening/treatment programmes; both investigations were considered to be group 3 studies.[6,20] All studies reported on stillbirth or fetal loss. Only three studies reported on neonatal death.[17–19] Five studies reported on clinical evidence of congenital syphilis in children[6,16–18,20] and four studies reported on prematurity or low birth weight.[6,17,18,20] Only McDermott et al. looked at infant death (i.e. deaths among subjects aged 29 days to one year).[19]

All adverse pregnancy outcomes

All studies consistently reported a higher proportion of adverse pregnancy

Fig. 1. **Flow diagram of study selection for a systematic review and meta-analysis of studies of adverse pregnancy outcomes among women without syphilis and women with untreated syphilis**



outcomes among untreated women with syphilis (range: 53.4–81.8%) than among women without syphilis (range: 10.2–20.8%). Fig. 2 shows the study-specific and summary estimates for all adverse pregnancy outcomes.

Selected adverse pregnancy outcomes

Fig. 3 and Fig. 4 show study-specific estimates for select adverse pregnancy outcomes and their summary statistics in women with and without syphilis, respectively. The pooled estimates of neonatal death were 12.3% (95% CI: 9.3–16.2) among women with syphilis and 3.0% (95% CI: 2.1–4.3) among women without syphilis, for an absolute difference of 9.3%.

Only the study by McDermott et al. reported data that allowed calculation of the proportion of infants who died.[19] An absolute difference of 11.2% in the frequency of infant death was observed among infants of women with and without syphilis: 21.3% (16 of 75 infants; 95% CI: 13.6–31.9) versus 10.1% (256 of 2530 infants; 95% CI: 9.0–11.4), respectively. Harman reported an absolute difference of 11.5% in the frequency of infant death between infants born to women with and without syphilis: 22.9% (229 of 1001 births; 95% CI: 20.3–25.5]) versus 11.4% (94 of 826 births; 95% CI: 9.2–13.6), respectively. However, these data could not be subclassified into neonatal and infant deaths because Harman reported deaths during the period from birth to one year of age.[16]

Pooled estimates and heterogeneity

Meta-analysis of the estimates of all adverse outcomes across the six studies revealed substantial heterogeneity for both women with syphilis (I^2 = 91.8%; P < 0.001) and women without syphilis (I^2 = 95.9%; P < 0.001; Fig. 2). A group-specific analysis of all adverse outcomes revealed a marked difference between estimates for women with syphilis, with the highest summary statistic observed for group 2 and the lowest observed for group 3 (Appendix A, available at: www.who.int/reproductivehealth/publications/rtis/syphilis_in_pregnancy/en/m). Heterogeneity was acceptable only for group 3 (56.4% [95% CI: 50.8–61.9]; I^2 = 0.0%; P = 0.547). Among women without syphilis, the summary statistic was highest for group 1 and lowest for group 3 (Appendix A). Again, heterogeneity was acceptable only for group 3 (10.3% [95% CI: 9.2–1.5]; I^2 = 0.0%; P = 0.658).

We also analysed summary estimates of selected adverse pregnancy outcomes by study group in women with and without syphilis (Appendix B and Appendix C, both available at: www.who.int/reproductivehealth/publications/rtis/syphilis_in_pregnancy/en/m). In pregnant women with syphilis, the summary statistic for stillbirth and fetal loss was highest for group 2 and lowest for group 1. Heterogeneity was acceptable only for group 3 (22.5% [95% CI: 18.1–27.5]; I^2 = 0.0%; P = 0.609). The summary statistic for clinical evidence of syphilis was highest for group 2 and lowest for group 3; heterogeneity was acceptable for group 2 (39.5% [95% CI: 34.0–45.4]; I^2 = 0.0%; P = 0.343) and group 3 (2.8% [95% CI: 1.4–5.4]; 0.0%; P = 0.508). For prematurity or low birth weight, heterogeneity was acceptable for group 2 (30.2% [95% CI: 22.4–39.3]; I^2 = 26.4%; P = 0.244) and group 3 (3.8% [95% CI: 1.3–10.4]; I^2 = 55.3%; P = 0.135).

In women without syphilis, the summary statistic for stillbirth and fetal loss was highest for group 1 and comparably low for groups 2 and 3, but heterogeneity was unacceptable for the latter groups (Appendix C). The frequency of prematurity or low birth weight was comparable for groups B and C but heterogeneity was acceptable only for group 3 (7.6% [95% CI: 4.8–11.7]; I^2 = 68.6%; P = 0.074).

Discussion

In this article, we quantified the proportion of all adverse pregnancy outcomes and specific adverse pregnancy outcomes among untreated women with syphilis and women without syphilis using data from six articles that met eligibility criteria for inclusion in our systematic review and meta-analysis. On average, pooled estimates of fetal loss or stillbirth, neonatal death and prematurity or low birth weight showed significantly higher rates among the offspring of women with syphilis than among the offspring of women without syphilis. The absolute differences were 21% for fetal loss or stillbirth, 9% for neonatal death and 6% for prematurity or low birth weight. Signs and symptoms of syphilis were found in 15% of the infants born to untreated women with syphilis. The frequency of any adverse pregnancy outcomes was 52% higher among women with syphilis than among women without syphilis.

Our estimates are consistent with previously published data. Holder[23] quoted a 1949 review by Thomas et al. in which 70% of women with syphilis reported adverse pregnancy outcomes and Rutgers et al.[24] reported adverse outcomes in 53% of women with syphilis. Both estimates are consistent with our summary estimate of 66.5%. Similar

Table 1. **Characteristics of studies included in a systematic review and meta-analysis to determine the frequency of adverse pregnancy outcomes (APOs) among untreated women with syphilis and women without syphilis**

Study	Country	Study group,[a] design and follow-up	*n*	Syphilis prevalence among mothers (%)	Syphilis diagnostic test	Comment
Harman, 1917[16]	United Kingdom	Group 1: Study of historical data to assess the frequency of APOs among women whose reproductive history was recorded before the existence of syphilis treatment. The follow-up period was birth to several years after delivery (but was not defined).	Cases: 1001; controls: 826	4.5[b]	Wasserman test (assumed)	This study assessed all pregnancy outcomes (over a lifetime) in a group of 150 women with syphilis and a group of 150 "healthy" women from a similar neighbourhood. Women had 1–18 pregnancies. The average was 7 pregnancies among women with syphilis. Timing of syphilis was not reported: some APOs may have preceded *T. pallidum* infection and some may have occurred many years after infection. The study did not differentiate between stages of syphilis.
Wammock, 1945–48[17]	United States of America	Group 2: Retrospective study to assess the frequency of APOs among women attending an ANC clinic in which syphilis treatment was not available. The follow-up period was birth to ≥ 28 days after delivery.	Cases: 61; controls: 5596	1.5[c]	Kahn test	This study assessed best practices in providing penicillin to pregnant women to prevent congenital syphilis and was done shortly after penicillin became available. Background data on APOs among untreated women who were seroreactive for *T. pallidum* infection were reported; uninfected women (historical controls) were used as a comparison group. Of 61 cases of early syphilis, 7 were "symptomatic" (which seems to correspond to primary or secondary infection) and resulted in no "normal living infants" (i.e. 2 stillbirths, 1 neonatal death and 4 infants with congenital syphilis). The remaining 54 cases had "early latent" syphilis (defined as "symptomless" seropositivity for *T. pallidum* infection of < 4 years' duration): these cases are combined with the 61 early cases in the meta-analysis. There were 14 cases with "late latent syphilis" (defined as symptomless infection of > 4 years' duration). Of these, 1 had a stillbirth and 13 had "normal living infants".
Ingraham, 1940–49[18]	United States of America	Group 2: Study to assess the frequency of APOs among women attending an ANC clinic in which treatment was not available. The follow-up period was birth to ≥ 60 days after delivery and, for at least 70% of the cohort, lasted for 6 months after delivery.	Cases: 220; controls: 10 323	1.5[c]	Kahn test (assumed)	This study described pregnancy outcomes among asymptomatic women with and without syphilis at two public hospitals in Philadelphia, United States of America. Asymptomatic women consisted of subjects who were seroreactive for *T. pallidum* infection and either untreated, treated with arsenicals or treated with various doses of penicillin. Subjects were followed for at least 60 days after delivery (77% were followed for 6 months). On the basis of clinical history, 220 of 302 women had "early" syphilis (defined as untreated syphilis of < 4 years' duration) and 82 had "late" syphilis (defined as untreated syphilis of > 4 years' duration). APOs were stillbirths for 10, neonatal deaths for 7, prematurity for 2 and congenital syphilis for 2; 61 women had "normal full-term infants".
Hira et al., 1990[6]	Zambia	Group 3: Study to assess the frequency of APOs among women attending an ANC clinic in which recruitment was at the time of delivery. There was no follow-up after delivery.	Cases: 230; controls: 2647	6.5[d]	RPR, with FTA-Ab confirmation	This study tested the effectiveness of an intervention to reduce APOs due to syphilis. The intervention was implemented in the context of an existing screening and treatment programme for syphilis and involved new health education methods and prenatal screening for syphilis. Overall, 8.0% of women were confirmed to be seroreactive for *T. pallidum* infection and there was no difference in seroprevalence between the intervention centres and the non-intervention centres. Uptake of screening and treatment at the intervention centres was suboptimal.

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Study	Country	Study group,[a] design and follow-up	*n*	Syphilis prevalence among mothers (%)	Syphilis diagnostic test	Comment
McDermott et al., 1987–90[19]	Malawi	Group 2: Study to assess the frequency of APOs among women attending an ANC clinic in which treatment was not available because routine syphilis screening was not performed. The follow-up period was birth to ≥ 1 year after delivery.	Cases: 130; controls: 2890	3.6	VDRL or RPR, with MHA-TP confirmation	In a study of APOs due to malaria, women were enrolled prospectively from four rural ANC clinics. All subjects received "routine ANC care", including monthly visits, tetanus toxoid vaccination, iron supplementation and malaria chemoprophylaxis, but routine syphilis screening was not provided through the ANC clinic system. Women were followed monthly and had blood drawn for later analysis of malaria outcome.
Watson-Jones et al., 1998–2000[20]	United Republic of Tanzania	Group 3: Retrospective study of data from antenatal health cards in which recruitment was at the time of delivery. There was no follow-up after delivery.	Cases: 73; controls: 233	8.0	RPR, with FTA-Ab or TPHA confirmation	"Relatively representative" pregnant women in urban and rural settings were recruited at delivery and tested for syphilis. Unscreened women, defined as those who had no ANC care or who did not have records of syphilis screening on their ANC card (17%), were invited to participate in screening at delivery (participation rate, 51%). Two consecutive women with an unreactive *T. pallidum* serologic test were selected as controls for each case, defined as a woman with high- or low-titre *T. pallidum* infection. The study assessed APOs in 73 women with high-titre *T. pallidum* infection (defined as an RPR titre of ≥ 1:8 and a positive result of a confirmatory test), 27 women with low-titre *T. pallidum* infection (defined as an RPR titre of < 1:8 and a positive result of a confirmatory test), 9 women with past or currently treated syphilis (defined as a negative result of an RPR test and a positive result of a treponemal test) and 233 women who were seronegative for *T. pallidum* infection. As soon as possible after delivery, treatment was administered to women with high- or low-titre *T. pallidum* infection and their infants. Study authors defined "stillbirth" (i.e. dead fetus > 22 weeks' gestation), "intrauterine fetal death" (i.e. fetal death ≤ 22 weeks' gestation) and "low birth weight" (i.e, < 2500 g). There were no intrauterine fetal deaths. Among unscreened women, the population attributable fraction of APOs due to high-titre *T. pallidum* infection was 51% for stillbirth, 24% for prematurity, 5% for intrauterine growth retardation and 12% for low birth weight. Overall, 17% of all APOs among unscreened women were attributable to syphilis.

ANC, antenatal care; ; FTA-Ab, fluorescent treponemal antibody absorption test; MHA-TP, microhaemagglutination assay for *Treponema pallidum*; ; RPR, rapid plasma reagin test; SB: stillbirth; *T. pallidum, Treponema pallidum*; TPHA, *T. pallidum* haemagglutination test; VDRL, Venereal Disease Research Laboratory test.

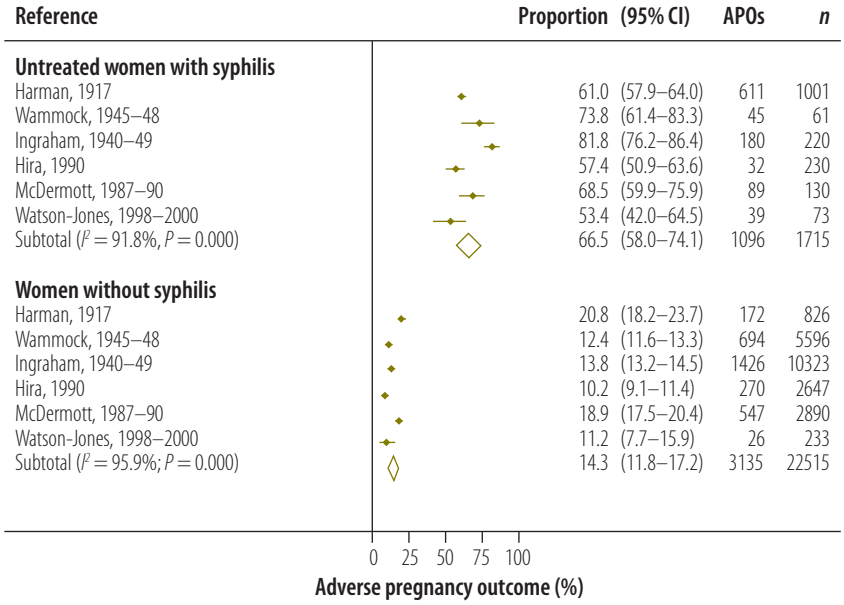
[a] Study groups were defined on the basis of study design, as follows: group 1, studies calculating the frequency of APOs among women whose reproductive history was recorded before the existence of penicillin treatment; group 2, studies in which the frequency of APOs was calculated for women attending an ANC clinic in which screening and treatment for syphilis were unavailable; and group 3, studies of the frequency of APOs among women attending ANC in which study recruitment was done at the time of delivery (and syphilis treatment was only available at that time).

[b] In Glasgow's Royal Maternity & Women's Hospital in 1922, 4.5% of umbilical cord samples had positive results on Wasserman tests.

[c] The rate of APOs was not directly reported in these papers but was 3.4% in Philadelphia's largest delivery hospital during the same period.[21]

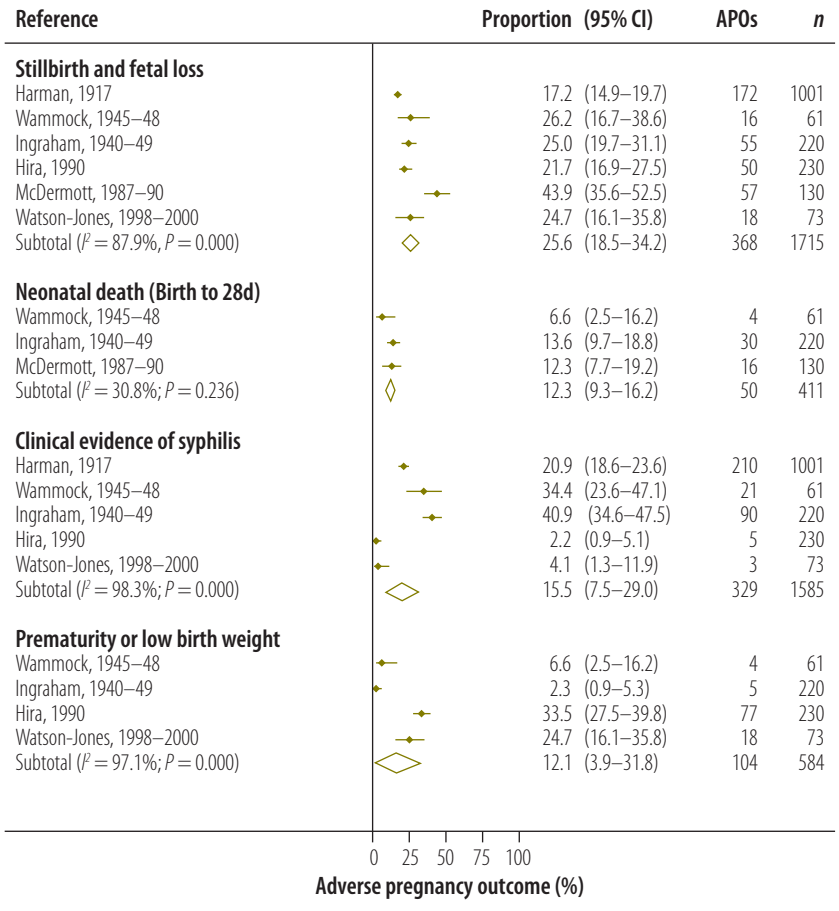
[d] Data are from the report by Powell et al.[22]

Fig. 2. **Study-specific and summary estimates of the proportion (%) of all adverse pregnancy outcomes (APOs) among women with untreated syphilis and women without syphilis**



CI, confidence interval.

Fig. 3. **Study-specific and summary estimates of the proportion (%) of selected adverse outcomes among women with untreated syphilis**



APO, adverse pregnancy outcome; CI, confidence interval; d, days.

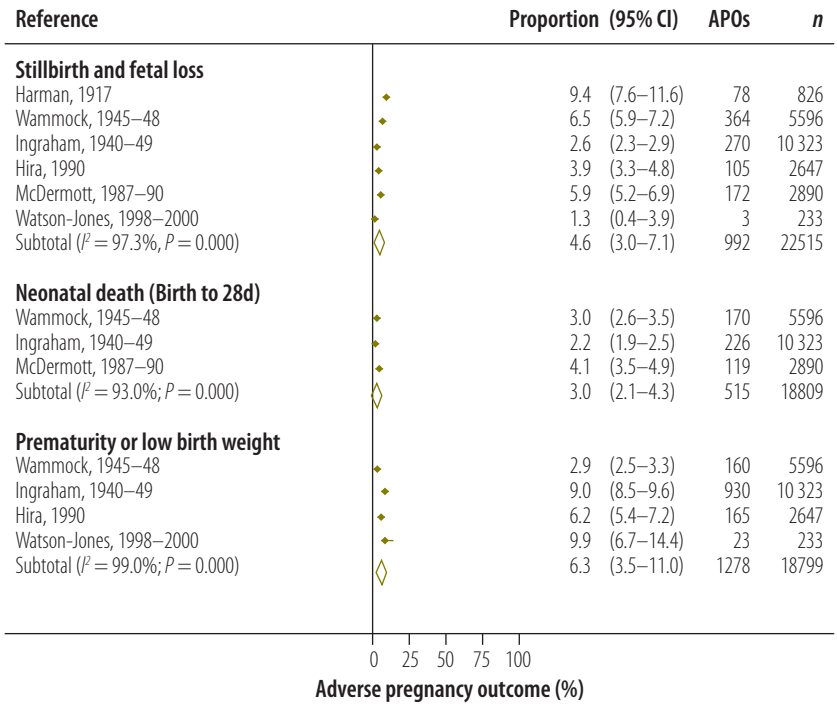
estimates have also been reported for specific pregnancy outcomes in women with syphilis. Thomas et al. estimated that 25–30% of pregnancies in women with syphilis resulted in neonatal death and Rabut et al.[25] reported that 39% resulted in perinatal death (although the latter outcome was not defined, it probably included neonatal deaths, stillbirths and fetal losses). Rutgers et al.[24] reported that 27% of infants were "admitted" because they were born before term (2.2%), had a low birth weight (13.5%) or presented with symptoms of congenital syphilis (11.3%).

Only one study evaluated in this report estimated death during the first year of life. It showed that infants delivered by untreated mothers with syphilis had 10% more deaths than those delivered by mothers without syphilis. This suggests that a considerable mortality burden is currently overlooked because of short follow-up periods in most cohort studies.

Early investigations evaluating syphilis testing and treatment preceded the use of experimental study designs; later studies have been limited by moral restrictions on the use of randomized controlled designs that withhold an effective intervention from a control group. Therefore, all studies included in our analysis had an observational design. Nevertheless, one strength of this review is that each study included a comparison group to assess adverse pregnancy outcomes among mothers without syphilis. This gave us the opportunity to estimate the excess adverse outcomes in the presence of maternal syphilis and give a broad idea of the risk of some of the adverse pregnancy outcomes in women with untreated syphilis.

Owing to the inherent differences between experimental and observational study designs and to biases commonly seen in observational data,[11] appropriate caution should be taken in interpreting our results. We relied on the outcome definitions used in the original papers, many of which were published before a consensus definition was available. There were also unacceptable heterogeneity in estimates across studies, variations in diagnostic tests across settings and periods, and a lack of control for potential confounders. Several potential sources of bias are present as well. Reporting bias is possible because infants born to moth-

Fig. 4. **Study-specific and summary estimates of the proportion (%) of selected adverse outcomes among women without syphilis I^2**



APO, adverse pregnancy outcome; CI, confidence interval.

ers known to have syphilis are more likely than infants born to mothers not known to have syphilis to be diagnosed with congenital syphilis. Group 2 studies included only asymptomatic women and therefore may have underestimated adverse pregnancy outcomes in women with untreated primary or secondary syphilis, both of which make transmission to offspring more likely and are associated with a fatality rate of nearly 100% (as noted among seven cases included in the Wammock cohort). Primary and secondary syphilis during pregnancy are not estimated to be common, so this potential bias is unlikely to change the magnitude of the findings. Another limitation associated with group 2 is that, although each study followed infants for at least a short period, the length of follow-up varied. Therefore, the burden of congenital syphilis might have been underestimated because congenital syphilis may have been missed in some infants. The lack of a search for grey literature sources could have introduced a reporting bias, but because of the nature of the research assessed we expect this to be minimal.

In the group 1 study, which assessed the lifetime reproductive histories of women infected with *T. pallidum* before the availability of anti-syphilis treatment, the timing of infection was not reported. This study probably underestimated the proportion of adverse pregnancy outcomes: some pregnancies included in the study may have occurred before women were infected and others may have occurred years after exposure, when syphilis was inactive and less likely to be transmitted to the fetus. Indeed, the risk of adverse pregnancy outcomes is recognized to be directly related to higher maternal antibody titres and such titres decrease over time in untreated women with syphilis.[26]

Finally, group 3 studies occurred in settings in which pregnant women might not have attended an ANC clinic, might have attended an ANC clinic but not been tested for syphilis, or were tested for syphilis but did not receive treatment before delivery. These studies probably underestimated the frequency of adverse pregnancy outcomes for several reasons. First, women with stillbirths and fetal losses who did not seek care would not have enrolled in a study. For example, the group 3 study by Watson-Jones et al. showed no fetal losses among 73 seroreactive women with rapid plasma reagin titres of ≥ 1:8. This is surprising given the large number of fetal losses in group 2 studies. Second, because penicillin is a highly effective intervention, treating neonates born to seroreactive mothers at birth probably prevented clinical infection or further progression of disease in the infants of infected mothers whose infections were not identified earlier.[2] This bias was important since congenital syphilis in live born infants represented a small fraction of pregnancy outcomes in group 3 studies, compared with group 1 and 2 studies. Third, women in group 3 who partially or fully completed a regimen of syphilis treatment during pregnancy might not have had this information reflected on their maternity card. This would have resulted in the misclassification of some women with syphilis as untreated. Finally, because group 3 studies did not follow up study subjects after delivery, neonatal deaths, infant deaths and clinical manifestations that occurred after this period would have been missed.

Our study suggests that, unless testing and treatment of syphilis in pregnancy are universally available, over half of pregnancies in women with syphilis will result in an adverse outcome. This is a preventable burden on mothers, families and health systems that highlights the need to prioritize global efforts to eliminate the mother-to-child transmission of syphilis. This paper also reminds policy-makers charged with resource allocation that the elimination of congenital syphilis is a public health priority that will enable immediate progress towards Millennium Development Goal 4: reducing the mortality rate among children younger than 5 years by two thirds. ■

Competing interests: None declared.

ملخص

الزهري غير المعالج لدى الأمهات وحصائل الحمل السلبية: استعراض منهجي وتحليل وصفي

الغرض إجراء استعراض منهجي وتحليل وصفي لتقديرات حصائل الحمل السلبية المبلغ عنها بين النساء المصابات بالزهري غير المعالج والنساء غير المصابات بالزهري.

الطريقة تم البحث في قاعدة بيانات PubMed و EMBASE ومحفوظات شبكة كوكرين عن الأبحاث المنشورة التي تقيّم حصائل الحمل السلبية بين النساء غير المعالجات باستخدام تفاعلية المصل للعدوى الناجمة عن اللولبية الشاحبة والنساء غير المصابات بتفاعلية المصل. وكانت حصائل الحمل السلبية فقدان الجنين أو ولادة جنين ميت أو وفاة المواليد أو الابتسار أو انخفاض وزن الطفل عند الميلاد أو البيّنات السريرية للزهري ووفاة الرضع. وتم استخدام التحليلات الوصفية للتأثيرات العشوائية لحساب التقديرات المجمعة لحصائل الحمل السلبية وتم، حسب الاقتضاء، استعراض التغايرية في التحليلات وفقاً للفئة.

النتائج من بين 3258 استشهاداً تم تحديدها، تضمن التحليل ست دراسات فقط، وجميعها من دراسات الحالة المقارنة. وتبين من التقديرات المجمعة زيادة معدل تكرار فقدان الجنين وولادة الجنين ميتاً بنسبة 21 ٪ ووفيات المواليد بنسبة 9.3 ٪ والابتسار أو انخفاض وزن الطفل عند الميلاد بنسبة 5.8 ٪ بين النساء الحوامل المصابات بالزهري غير المعالج عنه بين النساء غير المصابات بالزهري. وكان لدى 15 ٪ من رضع الأمهات المصابات بالزهري غير المعالج بيّنات سريرية للإصابة بالزهري الخلقي. وتبين من الدراسة الوحيدة التي قامت بتقدير وفاة الرضع زيادة معدل التكرار بنسبة 10 ٪ بين رضع الأمهات المصابات بالزهري. وتم التوصل إلى وجود تغايرية كبيرة بين الدراسات في تقديرات جميع الحصائل السلبية لكل من النساء المصابات بالزهري (66.5 ٪ [فاصل الثقة 95 ٪، فاصل الثقة: من 58.0 إلى 74.1]؛ قيمة I^2 = 91.8 ٪؛ الاحتمال <0.001) والنساء غير المصابات بالزهري (14.3 ٪ [فاصل الثقة 95 ٪: من 11.8 إلى 17.2]؛ قيمة I^2 = 95.9 ٪؛ الاحتمال <0.001).

الاستنتاج ارتبط الزهري غير المعالج لدى الأمهات بحصائل الحمل السلبية. ومن الممكن أن توفر هذه النتائج المعلومات اللازمة لاتخاذ قرارات السياسات بشأن تخصيص الموارد من أجل اكتشاف الزهري وعلاجه في الوقت المناسب لدى النساء الحوامل.

摘要

未经治疗的母体梅毒和妊娠的不良结果：系统回顾和元分析

目的 执行未经治疗的梅毒妇女和非梅毒妇女的不良妊娠结果估计报告的系统综述和元分析。

方法 在PubMed、EMBASE和Cochrane库中搜索评估未经治疗梅毒螺旋体感染血清反应妇女和无血清反应的妇女中不良妊娠结果的文献。不良妊娠结果是妊娠丢失或死胎、新生儿死亡、早产或低出生体重、梅毒临床证据和婴儿死亡。使用随机影响元分析计算汇聚的不良妊娠结果估计，并根据具体情况在针对特定人群的分析中探讨异质性。

结果 在确定的3258份引文中，仅六份纳入本分析，所有都是病例对照研究。汇集的估算值表明，在未经治疗的梅毒妇女妊娠中，较之非梅毒妇女，妊娠丢失和死胎率要高出21%，新生儿死亡率高出9.3%，早产或低出生体重高5.8%。未经治疗梅毒母亲的婴儿中，15%有临床证据表明其感染先天性梅毒。估计婴儿死亡率的单次研究显示梅毒母亲的婴儿死亡率高10%。在梅毒妇女（66.5% [95%置信区间，CI：58.0－74.1]；I^2=91.8%；P<0.001）和非梅毒妇女（14.3% [95% CI：11.8－17.2]；I^2=95.9%；P<0.001）的旨在估计所有不良结果的各个研究中均发现显著的异质性。

结论 未经治疗的母体梅毒与不良妊娠结果相关联。这些发现可以为检测梅毒的资源配置和孕妇及时治疗的政策决定提供信息。

Résumé

Syphilis maternelle non traitée et issues de grossesse défavorables: revue systématique et méta-analyse

Objectif Effectuer une revue systématique et une méta-analyse des estimations rapportées des issues de grossesse défavorables chez les femmes syphilitiques non traitées et les femmes non syphilitiques.

Méthodes Une recherche a été effectuée dans les bibliothèques PubMed, EMBASE et Cochrane pour trouver la documentation évaluant les issues de grossesse défavorables chez les femmes non traitées présentant une séroréactivité à l'infection à Treponema pallidum, ainsi que chez les femmes non séroactives. Les issues de grossesse défavorables étaient la perte du fœtus ou la mortinaissance, la mort néonatale, la prématurité ou le faible poids de naissance, des signes cliniques de la syphilis et la mortalité infantile. Les méta-analyses des effets aléatoires ont été utilisées pour calculer les estimations groupées des issues de grossesse défavorables et, le cas échéant, l'hétérogénéité a été étudiée dans les analyses de groupes spécifiques.

Résultats Parmi les 3 258 citations identifiées, seules six, toutes des études de cas-témoins, ont été incluses dans l'analyse. Les estimations groupées ont montré que parmi les femmes enceintes syphilitiques non traitées, la perte fœtale et la mortinatalité étaient 21% plus fréquentes, les décès néonataux 9,3% plus fréquents et la prématurité ou le faible poids de naissance 5,8% plus fréquents que chez les femmes non syphilitiques. Chez les nourrissons nés de mères atteintes de syphilis non traitées, 15% présentaient des signes cliniques de syphilis congénitale. La seule étude qui estimait la mortalité infantile a montré une fréquence de 10% plus élevée chez les nourrissons de mères syphilitiques. Une hétérogénéité importante entre les études a été trouvée dans les estimations de tous les effets indésirables pour les femmes syphilitiques (66,5% [intervalle de confiance à 95%, IC: 58 à 74,1]; I2 = 91,8%; P < 0,001) et les femmes non syphilitiques (14,3% [IC à 95%: 11,8 à 7,2]; I2 = 95,9%; P < 0,001).

Conclusion La syphilis maternelle non traitée est associée à des issues de grossesse défavorables. Ces résultats peuvent informer les décisions politiques sur l'allocation des ressources pour le dépistage de la syphilis et son traitement en temps opportun chez les femmes enceintes.

Резюме

Нелеченный сифилис у матерей и неблагоприятные исходы беременности: систематический обзор и мета-анализ

Цель Выполнить систематический обзор и мета-анализ собранных данных по неблагоприятным исходам беременности среди женщин с нелеченным сифилисом и женщин без данного заболевания

Методы Используя такие библиотеки, как PubMed, EMBASE и Кокрановская база данных, был выполнен поиск литературы по вопросам оценки неблагоприятных исходов беременности среди нелеченных женщин с положительной серологической реакцией на бледную трепонему и среди женщин, не проявивших данную реакцию. Неблагоприятными исходами беременности считались выкидыш или мертворождение, неонатальная смертность, преждевременные роды или низкий вес при рождении, клинические признаки сифилиса и младенческая смертность. Для расчета общей оценки неблагоприятных исходов беременности были использованы методы мета-анализа на основе рандомизированных исследований и, при необходимости, неоднородности были дополнительно исследованы посредством анализа конкретных групп.

Результаты Из 3258 найденных цитат в анализ были включены только шесть исследований, использующих метод «случай-контроль». Обобщенная оценка показала, что среди беременных женщин с нелеченным сифилисом наблюдалась повышенная частота неблагоприятных исходов беременности: гибель плода и мертворождение встречались на 21% чаще, неонатальная смертность – на 9,3%, а преждевременные роды или низкий вес при рождении – на 5,8% чаще, чем у женщин без данного заболевания. Из числа младенцев, рожденных от матерей с нелеченным сифилисом, 15% имели клинические признаки врожденного сифилиса. Одно исследование, посвященное младенческой смертности, показало, что частота смертности младенцев, рожденных от матерей, больных сифилисом, была на 10% выше среднестатистической. В ходе исследований была обнаружена существенная неоднородность в оценках неблагоприятных исходов, как для женщин с сифилисом (66,5% [95% доверительный интервал, ДИ: 58,0–74,1]; $I^2 = 91.8\%$; $P < 0.001$), так и для женщин без этого заболевания (14,3% [95% ДИ: 11,8–17,2]; $I^2 = 95,9\%$; $P < 0,001$).

Вывод Нелеченный сифилис у матерей связан с повышенным риском неблагоприятного исхода беременности. Эти данные могут помочь лицам, ответственным за принятие решений, правильнее распределить ресурсы для своевременного обнаружения и лечения сифилиса у беременных женщин.

Resumen

La sífilis materna no tratada y los resultados adversos en el embarazo: revisión sistemática y metanálisis

Objetivo Realizar una revisión sistemática y un metanálisis de los cálculos presentados sobre los resultados adversos en los embarazos entre mujeres con sífilis no tratada y mujeres sin sífilis.

Métodos Se buscó literatura que evaluara los resultados adversos en el embarazo entre mujeres con sero-reactividad para la infección por Treponema pallidum no tratada y mujeres no sero-reactivas en las bibliotecas de PubMed, EMBASE y Cochrane. Los resultados adversos en el embarazo consistieron en la pérdida del feto, muerte prenatal, muerte neonatal o peso bajo al nacer, pruebas clínicas de sífilis y muerte infantil. Se emplearon metanálisis con efectos aleatorios para calcular los resultados adversos en bruto en los embarazos y, en caso necesario, se analizó la heterogeneidad en análisis de grupos concretos.

Resultados De las 3258 citaciones identificadas sólo se incluyeron seis en el análisis, todas ellas estudios de control de casos. Los cálculos brutos mostraron que, entre las mujeres con sífilis no tratada, la pérdida del feto y la muerte prenatal fueron un 21% más frecuentes, las muertes neonatales, un 9,3% más frecuentes y los casos de nacimientos prematuros o peso bajo al nacer, un 5,8% más frecuentes que entre las mujeres sin sífilis. Entre los recién nacidos de madres con sífilis no tratada, el 15% presentó pruebas clínicas de sífilis congénita. El estudio sencillo que calculó la muerte infantil mostró una frecuencia un 10% superior entre los niños de madres con sífilis. Se descubrió una heterogeneidad sustancial en los cálculos de todos los resultados adversos de los estudios, tanto para las mujeres con sífilis (66,5% [intervalo de confianza del 95%, IC: 58,0–74,1]; $I^2 = 91,8\%$; $P < 0,001$) como para las mujeres sin sífilis (14,3% [95% IC: 11,8–17,2]; $I^2 = 95,9\%$; $P < 0,001$).

Conclusión La sífilis materna no tratada está relacionada con resultados adversos en el embarazo. Estos hallazgos pueden servir de información a la hora de tomar decisiones sobre las políticas acerca de la asignación de recursos para detectar y tratar a tiempo la sífilis en mujeres embarazadas.

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