Title: Perinatal outcomes of women with epilepsy compared to women without epilepsy

Subtitle: Systematic review and meta-analysis

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Short title: Perinatal outcomes of women with epilepsy

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KEY POINTS

Question: To synthesise available evidence from observational studies concerning the perinatal outcomes in women with epilepsy (WWE) compared to women without epilepsy (WWoE).

Findings: We provide updated effect estimates, and new data, showing that WWE are at increased odds of maternal death and that WWE are at increased odds of having offspring with congenital conditions, this is exacerbated by ASM exposure in-utero, and although not as high, the odds are still increased in the absence of ASM exposure in-utero.

Meaning: WWE should receive pre-pregnancy counselling at the time of epilepsy diagnosis and regularly during management from an epilepsy specialist. A complex care pathway could be most suitable for these individuals during pregnancy and childbirth.

ABSTRACT

Importance: Adequate engagement, information, pregnancy planning and management are essential to improve outcomes for pregnant women with epilepsy (WWE).

Objective: This systematic review and meta-analysis aimed to investigate perinatal outcomes in WWE compared to women without epilepsy (WWoE).

Data Sources: We searched MEDLINE, EMBASE, CINAHL, and PsycINFO, with no language or date restrictions (database inception-1st January 2021). We also searched on Open Grey and Google Scholar, and conducted hand-searching in journals and reference lists of included studies.

Study Selection: We included all observational studies comparing WWE and WWoE.

Data Extraction and Synthesis: We used the PRIMSA checklist for abstracting data and the Newcastle-Ottawa Scale for risk of bias assessment. Data extraction and risk of bias assessment was assessed independently by two authors with mediation conducted independently by a third author. We report the pooled unadjusted odds ratios (OR) or mean differences (MD) with 95% confidence intervals (CI) from random (I^2 heterogeneity statistic >50%) or fixed (I^2<50%) effects meta-analyses.

Main Outcome(s) and Measure(s): Outcomes of interest included Maternal and Foetal Complications as well as Neonatal Complications.

Results: Of 8,313 articles identified, we included 76 in meta-analyses. WWE had increased odds of miscarriage (12 articles, 25,478 pregnancies) [OR, 95% CI 1·62, 1·15-2·29], stillbirth (20 articles, 28,134,229 pregnancies) [1·37, 1·29-1·47], preterm birth (37 articles, 29,268,866 pregnancies) [1·41, 1·32-1·51] and maternal death (4 articles, 23,288,083 pregnancies) [5·00 (1·38-18·04]. Neonates born to WWE had increased odds of congenital conditions (29 articles, 24,238,334 pregnancies) [1·88, 1·66-2·12], NICU admission (8 articles, 1,204,428) [1·99, 1·58-2·51], and neonatal/infant death (13 articles, 1,426,692 pregnancies) [1·87, 1·56-2·24]. The increased odds of poor outcomes is higher with greater anti-seizure medication (ASM) load, but even pregnant WWE not on ASM have worse outcomes compared to WWoE.

Conclusions and Relevance: WWE have worse perinatal outcomes compared to WWoE. These require consideration during pregnancy counselling**.**

INTRODUCTION

Adequate pregnancy planning and management are essential to improve outcomes in Women with Epilepsy (WWE). Understanding their pregnancy risks helps shape treatment plans and contributes to reducing poor outcomes such as major congenital malformations in offspring [1].

Most research concerning maternal epilepsy and pregnancy outcomes focuses on anti-seizure medication (ASM) exposure and foetal complications. A systematic review and meta-analysis of observational studies [2] investigated the association between maternal epilepsy and reproductive outcomes (with or without ASM exposure) using data from studies between January 1, 1990, and January 21, 2015. However, that study did not investigate many outcomes of clinical interest, including likelihood for offspring congenital conditions or maternal death, and a number of important studies have been conducted since then [3-26]. One of these studies found an eleven fold increased adjusted odds of maternal death for pregnant WWE [15], and another, in contrast to findings of the previous review [2], that WWE had increased odds of preterm birth[7].

The current study aimed to:

1) Investigate perinatal (from the beginning of pregnancy up to 1-year post-delivery) outcomes in WWE compared to women without epilepsy (WWoE).
2) Assess the effect of ASM versus epilepsy itself by comparing outcomes of WWE not on ASM versus WWoE, WWE on ASM versus WWE not on ASM, and WWE on polytherapy compared to WWE on monotherapy.

METHODS

SEARCH STRATEGY AND STUDY SELECTION

The study was registered on the International Register of Systematic Review Protocols (PROSPERO ID - CRD42020221100). We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guidelines [27] for reporting (**Supplemental material-Appendix 1**). The search strategies for each database are given in **Supplemental material-Appendix 2** and implemented (database inception-06/12/2022) on MEDLINE (Ovid), EMBASE (Ovid), CINAHL, and PsycINFO, with grey literature searches conducted on Google scholar and Open-Grey and hand-searching conducted on journal websites and reference lists of included studies. We placed no restrictions on language and included all observational studies

(prospective cohort, retrospective cohort, case-control, cross-sectional analysis) comparing WWE and WWoE. We excluded randomised-control trials, case series, case reports, in-vitro studies, books, editorials, comments and responses to comments, opinion pieces, studies without data, posters, abstracts, qualitative studies, animal studies, and studies where maternal epilepsy was not the primary exposure.

Search results were imported into Rayyan [28], and duplicates removed. One author (PM) screened titles and two authors (PM & KH) independently screened abstracts and full texts of all potentially eligible studies against inclusion and exclusion criteria. Disagreements were resolved by consensus or by third author (RC). Studies published across multiple reports were assessed as single units. We contacted authors for clarification if there was uncertainty surrounding study eligibility.

Two authors (PM and KH) independently collected data from 25% of eligible studies using a predetermined data extraction form. High (>80%) inter-rater agreement allowed for further data extraction by one reviewer (PM). Disagreements were resolved by consensus or by a third author arbitration (RC).

Risk of bias was independently assessed (eTable 2 in **Supplemental material**) initially in 20% of included samples by two of the authors (PM & RC) using the Newcastle-Ottawa scale (NOS) [29]. Interrater similarity of >80% justified subsequent assessment by one reviewer (PM). Studies were low risk if their score was ≥7 and high risk if <=6.

OUTCOMES OF INTEREST

We assessed maternal and foetal outcomes: caesarean section, preterm birth, induced labour, gestational diabetes (GDM), intrauterine growth restriction (IUGR), antepartum haemorrhage (APH), preeclampsia, miscarriage, stillbirth, gestational hypertension, any pregnancy loss, postpartum haemorrhage (PPH), placental abruption, foetal distress, maternal death, bleeding in pregnancy, premature rupture of membranes (PROMs), eclampsia, placenta praevia, induced abortion, assisted delivery (forceps or vacuum extraction).

We also assessed neonatal outcomes: neonatal intensive care unit (NICU) admission, small for gestational age (SGA), birthweight <2500 g, neonatal/infant death, 5-min APGAR <8, large for gestational age (LGA), 1-min APGAR <8, mean birth weight, mean body length, mean 1-min APGAR, mean 5-min APGAR, mean head circumference, mean gestational age. Congenital conditions were also investigated and comprised those with and without a known genetic condition resulting in major or minor structural and chromosomal anomalies such

as nervous system, eye, face and neck, congenital heart defects, oro-facial clefts, urinary, genital limb, skeletal dysplasia.

DATA ANALYSIS

Studies similar in study design, outcomes investigated, and comparison of WWE and WWoE were combined in Review Manager 5 (RevMan) [30] using the Mantel-Haenszel method of meta-analysis to estimate pooled unadjusted Odds Ratio (OR) with 95% confidence interval (CI) for each outcome. I^2 statistic was used to assess degree of inter-study statistical heterogeneity. We used a random-effects model for studies with an I^2 statistic o>= 50%; we used a fixed-effects model for those < 50%, with sensitivity analyses to determine model choice on effect estimates. Additional meta-analyses were performed comparing: WWE not on ASM to WWoE; WWE on ASM to WWE not on ASM; and WWE on ASM polytherapy to WWE on ASM monotherapy. Subgroup analyses investigated risk of bias on effect estimates. To aid interpretability, unadjusted pooled risk difference (RD) with 95% CI was reported for all binary outcomes, with fixed or random effects meta-analysis determined by the method employed in the corresponding relative effect analysis. We conducted ad-hoc sensitivity analyses to help interpret generalisability of our unadjusted pooled estimates by determining pooled adjusted OR (aOR) for each, comparing WWE vs WWoE only; only articles with aOR accounting for maternal factors were include in such analyses. We carried out sensitivity analyses to determined risk of bias on effect estimates.

ROLE OF FUNDING SOURCE

RESULT

Of 8,313 articles identified, 76 met inclusion criteria for synthesis with varying numbers applicable to each meta-analysis (**Figure 1**). Where articles used the same or overlapping time-points assessing an outcome, the article with largest total sample or largest sample of WWE spanning the longest time-period was included in the meta-analysis. For gestational hypertension where there was a 1-year overlap between two studies [6, 31], we included the study with the most recent sample (**eTable 1 in Supplemental material**).

There were 45 retrospective [3, 5-10, 13-15, 19, 20, 22-25, 31-59] and 21 prospective [11, 16-18, 21, 26, 60-74] cohort studies, 9 case-control studies [4, 12, 75-81], and 1 cross-sectional [82]. 62 articles were low-risk [3-11, 13-16, 18-26, 31-40, 42, 45, 46, 48, 50-60, 62-71, 74-77, 79]and 14 high-risk of bias. [12, 17, 41, 43, 44, 47, 49, 61, 72, 73, 78, 80-82] (**eTable 2 in Supplemental material**).

WWE vs WWoE

WWE had increased odds of gestational hypertension, preeclampsia, IUGR, miscarriage, preterm birth, induced labour, stillbirth, caesarean section, and maternal death. Neonates born to WWE had increased odds of 1-min and 5-min APGAR <8, NICU admission, SGA, birthweight <2500 g, neonatal/infant death, and congenital conditions. Neonates born to WWE had reduced mean birth weight, mean body length, mean head circumference, and mean gestational age. For full details, see **Table 1**.

WWE not on ASM vs WWoE

WWE not on ASM had increased odds of caesarean section, induced labour, preterm birth, gestational diabetes mellitus, IUGR, pregnancy loss, preeclampsia, stillbirth, and placental abruption. Neonates born to WWE not on ASM had increased odds of NICU admission, SGA, birthweight <2500 g, and congenital conditions. Neonates born to WWE not on ASM had reduced mean body length. For full details, see **Table 2 and eTable 3 in the Supplemental material**.

WWE on ASM vs WWE not on ASM

WWE on ASM had increased odds of induced labour. Neonates of WWE on ASM had increased odds of NICU admission, SGA, birthweight <2500 g, neonatal/ infant death, and congenital conditions. They also had reduced mean birth weight. For full details, see **Table 2 and eTable 4 in the Supplemental material**.

WWE on ASM polytherapy vs monotherapy

WWE on ASM polytherapy had increased odds of caesarean section. Neonates of WWE on ASM polytherapy had increased odds of NICU admission, SGA, and congenital conditions. For full details, see **Table 2 and eTable 5 in the Supplemental material**.

Pooled adjusted meta-analysis

Although some adjusted odds ratios were lower for some outcomes and higher in others compared to the unadjusted estimates, universally the pooled adjusted meta-analysis continued to show that, in WWE compared to WWoE, there is increased odds of preeclampsia, preterm birth, APH, SGA, caesarean section, induced labour, maternal death, PPH and congenital conditions. For full details, see **Table 3 and eTables 7-16 in the Supplemental material**

Risk of Bias on Effect estimate

There were significant differences between low and high-risk articles for gestational hypertension, preeclampsia, induced abortion, any pregnancy loss, miscarriage, stillbirth, PPH, mean birthweight, mean 5-min APGAR, mean birthweight, and congenital conditions. For each, high-risk articles reported larger effect estimates with wider confidence intervals. Significant differences between effect estimates were not seen for GDM, IUGR, placenta praevia, APH, PROMs, placental abruption, foetal distress, induced labour, preterm birth, assisted delivery, maternal death, NICU admission, 1-min APGAR <8, birthweight <2500 g, neonatal/infant death, mean body length, mean 1-min APGAR, or mean head circumference. Due to all studies with relevant data being low-risk, intergroup comparison was not possible for bleeding in pregnancy, eclampsia, SGA, 5-min APGAR <8, LGA, or mean gestational age. For full details, see eTable 6 in the **Supplemental material.**

DISCUSSION

In this updated SR and meta-analysis of the perinatal outcomes for WWE compared to WWoE, more studies and outcomes are included, along with more up-to-date estimates compared to a previous review [2]. The main findings are: (1) WWE have higher odds compared to WWoE of a number of outcomes not reported in the earlier SR; this includes the finding that the odds of maternal death are over 5 times higher for WWE compared to WWoE and the odds of congenital conditions are over two times higher in offspring of WWE compared to WWoE; (2) WWE not on ASM are still at increased odds of worse outcomes compared with WWoE; (3) WWE on ASM have worse or similar outcomes to WWE not on ASM; (4) WWE on polytherapy have worse or similar outcomes to WWE on monotherapy.

The finding on increased risk of maternal death is mainly from data from one article [15], a regional study in the USA, but it is not the only source. Our unadjusted OR (95 CI) 5·00 (1·38-18·04) is smaller than both the

unadjusted 12·66 (9·68-16·56) and adjusted 11·46 (8·64-15·19) findings reported in the article. The authors accounted for maternal age, race and socioeconomic factors in their adjusted analyses, yet they could not account for ASM effects. Furthermore, this study used International Classification of Disease (ICD) 9 codes on hospital records only, and therefore, it is possible that women with symptomatic seizures and women with non-epileptic attack disorder were included in the study population. However, the authors conducted two sensitivity analyses to mitigate this potential bias. In the first sensitivity analysis, the authors removed women with a recorded hypertensive disorder and found that the measures of morbidity associated with epilepsy in the main analysis remained high. In the second analysis, the authors removed women with a recording of unclassified epilepsy finding little change in the effect of epilepsy on any outcomes. This suggests that misclassification did not solely drive the effect of epilepsy. The other three studies [4, 10, 12] provided data on the frequency of maternal death in their respective samples. However, only one of these studies [4] provided ORs and adjusted ORs (matched pregnancies on yearly income the year before the termination of the pregnancy, calendar year, parity, and maternal age) within their study analysis; reporting an OR (95 CI) of 6·19 (2·84–13·5). This OR is similar to what we reported in our meta-analysis, and our reported OR falls within the 95 CI reported in this study. Together, these data suggest there is a real increase in the odds of maternal death in WWE compared to WWoE; however, our analysis could not account for potentially confounding variables such as epilepsy severity or type, maternal age, deprivation, parity, smoker status, hypertensive disorder, alcohol use in pregnancy, or illicit drug use.

Although WWE are at increased odds of having children with a congenital condition, it would be reasonable to infer from our results that the increased odds for congenital conditions are largely driven by ASM load since WWE on ASM were at increased odds compared to WWE not on ASM, and those on polytherapy had higher odds than those on monotherapy. Our results support the current United Kingdom (UK) guidelines set out by the National Institute of Health and Care Excellence (NICE) [83] that WWE should receive pre-pregnancy counselling at the time of diagnosis and regularly during management; including pre-conceptual counselling on the risk of ASM use during pregnancy to offspring in terms of congenital conditions. We also found that the odds of congenital conditions are also greater in offspring of WWE not on ASM compared to offspring of WWoE; this suggests that other factors aside from ASM could contribute to the risk of congenital conditions, with NICE guidelines suggesting further advice to be given to WWE on the risks of smoking and alcohol use in pregnancy. However, we could not account for these potentially confounding variables, epilepsy severity or

type, maternal age, deprivation, parity, caffeine, or illicit drug use. We could also not account for whether those WWE not on ASM had been on or exposed to ASM, particularly sodium valproate, prior to pregnancy and how long before [84-87]; this is of particular importance, especially in light of emerging research suggesting a potential transgenerational impact of congenital conditions in offspring of mothers whom themselves suffered complications due to valproate exposure in-utero [86].

Findings in comparisons of WWE on ASM and WWE not on ASM of reduced odds of IUGR but increased odds of offspring SGA and reduced birthweight. This finding could, at least in part, be accounted for by the small number of studies included in the IUGR meta-analysis in this instance [13, 46, 66]. Furthermore, reduced odds of IUGR was not statistically significant, yet the odds of SGA and reduced birthweight were. Similarly in our analysis of WWE on polytherapy and WWE on monotherapy, there are some contradictory findings, such as offspring having increased odds of SGA, but increased mean birthweight in the polytherapy group, compared to monotherapy. This, again, could be explained by the small number of studies in these eta-analyses, and indeed the finding of reduced mean birthweight was not statistically significant, yet SGA was. These findings highlight the need for more research into the effect of ASM load on offspring outcomes.

Our meta-analyses also provide new pooled data on effect estimates comparing WWE and WWoE for induced abortion, any pregnancy loss, bleeding during pregnancy, placental abruption, placenta praevia, PROMS, premature labour, assisted delivery, foetal distress, LGA, 1-minute APGAR, 5-minute APGAR; and reduced mean head circumference, body length, gestational age, and birthweight. We have also expanded on the previous review [2] and provided more up-to-date effect estimates comparing WWE and WWoE for miscarriage, stillbirth, neonatal/infant death, gestational hypertension, gestational diabetes, preeclampsia, eclampsia, APH, PPH, induction of labour, caesarean section, preterm birth, IUGR, SGA, birthweight <2500g, and NICU admission.

As with our finding on an increased risk of congenital conditions, our finding that WWE not on ASM are still at increased odds of many adverse outcomes compared with WWoE suggests that other factors specific to WWE could be contributing. We acknowledge that care pathways for WWE may already consider the increased risk of worse perinatal outcomes and thus contribute to increased induced labour, caesarean section, and NICU admission. However, such pathways would not explain the increased odds of preeclampsia, gestational diabetes, preterm birth or having SGA children. Our findings support an approach/policy that WWE, even if not on ASM, require a complex care pathway during pregnancy.

Despite the comprehensive nature of the current study, there are other limitations besides those mentioned above. The meta-analysis has provided important information on how study risk of bias can influence effect estimates; studies with a high-risk of bias were more likely to offer more extreme ORs than low-risk of bias studies, and our analyses included both low-risk and high-risk of bias studies. Our analyses are unadjusted due to differences in study characteristics and adjustments made in statistical analyses in individual studies. Future research from primary data analysis, or indeed individual participant meta-analyses, should attempt to account for potentially confounding variables such as epilepsy severity or type, maternal age, deprivation, parity, smoker status, hypertensive disorder, alcohol use in pregnancy, or illicit drug use, as these are limitations for nearly all outcomes assessed. Furthermore, a significant proportion of included articles are retrospective cohort design, which provides inherent limitations such as missing data, which unless accounted for, can lead to reporting biases wherein outcomes that have occurred are not recorded. This is particularly pertinent when considering our findings for miscarriage. There are likely miscarriages that have gone undetected or unrecorded, particularly in retrospective studies, meaning that the reported rates of miscarriage could be dependent upon when pregnancy tracking started and how these were recorded. The findings of this review show that, for miscarriage, unadjusted pooled ORs were greater for WWE compared to WWoE which is contrast to the one study that tracked women prospectively from before pregnancy, through conception, and into the postnatal period [21]. This paper found similar rates of miscarriage in WWE compared to WWoE. However, this study is limited by a small sample size and the primary research objective was to determine differences in achieving pregnancy in WWE compared to WWoE. Therefore, miscarriage was not adjusted for potentially confounding variables such as hypertensive disorders. This is also a limitation of our meta-analysis, and a factor that should be considered in future research. It is also important to consider the accuracy of epilepsy diagnosis in included studies. Many studies provide data on WWE not on ASM, which could suggest that this group comprises, at least in part, women with a history of self-limited epilepsy, symptomatic seizures, or indeed those with inactive epilepsy. This highlights the need for future research, to try to account for epilepsy syndrome, seizure frequency and severity, and ASM exposure to try to unpick the role of epilepsy and ASM in outcomes. However, this is a difficult task, since those with a more severe epilepsy syndrome are likely to be administered an ASM regimen that has greater potential to increase odds of negative perinatal outcomes such offspring congenital conditions.

When counselling pregnant WWE and WWE of childbearing age, we submit that clinicians should consider the findings of this review. In addition, clinicians and WWE should bear in mind that there are increased odds of

negative adverse maternal and neonatal outcomes for WWE compared to WWoE. Still, such outcomes are uncommon, and most WWE will not experience worse outcomes. However, this has to be tempered by the effect sizes of the odds for some being large, with maternal death being the largest. Therefore, our results support the UK national guideline [83] that WWE should receive pre-pregnancy counselling at the time of epilepsy diagnosis and regularly during management, including pre-conceptual counselling on the risk of ASM use during pregnancy to offspring in terms of congenital conditions. In addition, we would support the view that advice on ASM use should come from an epilepsy specialist through counselling and pregnancy planning; and that a complex care pathway is most suitable for WWE during pregnancy and childbirth [83].

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 1. Pooled unadjusted meta-analyses of maternal and foetal, and neonatal outcomes in WWE compared to WWoE.

		WWE		WWoE					
Maternal and Foetal Outcomes	**Studies**	**Events**	**Pregnancies**	**Events**	**Pregnancies**	**Pooled OR (95 CI)**	**p-value**	**I^2 (%)**	**Pooled RD (95 CI)**
Caesarean section	37	44,045	119,289	14,030,246	44,464,028	1·54 [1·43, 1·65]	<0·001	91	0·08 [0·06, 0·09]
Preterm birth	37	13,146	125,574	2,086,248	29,143,292	1·41 [1·32, 1·51]	<0·001	69	0·02 [0·01, 0·03]
Induced labour	17	19,972	92,115	4,882,282	25,175,698	1·33 [1·22, 1·46]	<0·001	86	0·04 [0·03, 0·05]
GDM	15	5,005	90,207	1,403,241	25,032,261	1·11 [1·01, 1·23]	0·04	53	0·00 [-0·00, 0·00]
IUGR	11	2,901	76,363	799,595	39,455,420	1·89 [1·42, 2·52]	<0·001	81	0·03 [0·01, 0·04]
APH	6	1,641	74,724	329,830	20,924,813	1·38 [1·32, 1·45]	<0·001	0	0·00 [0·00, 0·01]
Preeclampsia	19	7,461	109,606	1,457,766	28,017,369	1·36 [1·05, 1·77]	<0.02	98	0·01 [-0·00, 0·03]
Miscarriage	12	229	2,582	688	22,896	1·62 [1·15, 2·29]	0·006	60	0·03 [0·01, 0·04]

Stillbirth	20	948	109,931	167,599	28,024,298	1·37 [1·29, 1·47]	<0·001	30	0·00 [0·00, 0·00]
Gestational hypertension	14	3,669	80,707	2,413,026	39,930,919	1·32 [1·11, 1·58]	0·002	87	0·02 [0·01, 0·03]
Any pregnancy loss	27	906	85,352	140,807	22,962,914	1·38 [1·29, 1·48]	<0·001	37	0·00 [0·00, 0·00]
PPH	13	3,892	102,532	372,076	25,342,398	1.41 [0.85, 2.33]	0·18	99	0·01 [-0·00, 0·02]
Placental abruption	13	404	28,994	39,466	4,566,396	1·49 [1·35, 1·65]	<0·001	41	0·00 [0·00, 0·01]
Foetal distress	6	10,492	71,735	2,927,009	20,512,030	1·05 [1·03, 1·08]	<0·001	8	0·01 [0·00, 0·01]
Maternal death	4	68	88,052	1,969	23,200,031	5·00 [1·38, 18·04]	0·01	89	0·00 [-0·00, 0·00]
Bleeding in pregnancy	4	264	3,773	30,341	505,391	1·24 [0·93, 1·64]	0·14	54	0·02 [-0·01, 0·06]
PROMs	11	4,141	103,140	1,601,745	43,550,599	1·14 [1.00, 1·30]	0·04	79	0·00 [-0·00, 0·01]
Eclampsia	3	3	2,228	214	303,145	1·98 [0·72, 5·46]	0·19	0	0·00 [-0·00, 0·00]
Placenta praevia	9	20	2,103	2,143	273,237	1·03 [0·64, 1·65]	0·91	0	-0·00 [-0·00, 0·00]

Induced abortion	6	49	1,511	1,461	20,098	1·64 [0·52, 5·14]	0·39	80	0·01 [-0·03, 0·04]
Assisted delivery	7	463	5,390	31,668	480,698	1·28 [0·94, 1·74]	0·12	75	0·01 [0·00, 0·02]
Neonatal outcomes	**Studies**	**Events**	**Pregnancies**	**Events**	**Pregnancies**	**Pooled OR (95 CI)**	**p-value**	**I^2 (%)**	**Pooled RD (95 CI)**
Congenital conditions	29	3,091	94,670	422,992	24,143,664	1·88 [1·66, 2·12]	<0·001	65	0·02 [0·02, 0·03]
NICU admission	8	1,028	10,332	91,859	1,194,096	1·99 [1·58, 2·51]	<0·001	80	0·05 [0·01, 0·09]
SGA	14	1,813	23,634	139,537	3,026,766	1·38 [1·22, 1·55]	<0·001	55	0·02 [0·01, 0·03]
Birthweight <2500 g	23	1,304	19,720	95,189	1,859,089	1·35 [1·20, 1·53]	<0·001	51	0·02 [0·01, 0·03]
Neonatal/infant death	13	134	8,163	12,571	1,418,529	1·87 [1·56, 2·24]	<0·001	31	0·01 [0·00, 0·01]
5-min Apgar <8	10	221	15,529	33,304	3,139,407	1·29 [1·01, 1·63]	0·04	50	0·00 [-0·00, 0·01]
LGA	3	262	6,253	43,069	1,062,846	0·93 [0·67, 1·29]	0·65	79	-0·00 [-0·02, 0·01]
1-min Apgar <8	8	376	6,524	56,375	1,187,102	1·20 [1·08, 1·33]	0·008	47	0·01 [0·00, 0·01]

Neonatal outcomes	Studies	Events	Pregnancies	Events	Pregnancies	Pooled MD (95 CI)	p-value	I^2 (%)	Pooled RD (95 CI)
Mean birth weight	20	n/a	12,083	n/a	588,716	-71·57 [-88·82, -54·31]	<0·001	47	n/a
Mean body length	9	n/a	7,938	n/a	82,545	-0·31 [-0·56, -0·06]	0·02	75	n/a
Mean 1-min Apgar	7	n/a	862	n/a	82,919	-0·31 [-0·58, -0·05]	0·02	82	n/a
Mean 5-min Apgar	8	n/a	927	n/a	91,854	-0·16 [-0·26, -0·05]	0·005	63	n/a
Mean head circumference	8	n/a	1,229	n/a	82,040	-0·10 [-0·36, 0·16]	0·44	80	n/a
Mean gestational age	5	n/a	15,147	n/a	2,661,445	-1·72 [-3·52, 0·08]	0·06	78	n/a

Table 2. Pooled unadjusted effect estimates and p-values for all outcomes under each comparison from meta-analyses

	WWE vs WWoE			WWE not on ASM vs WWoE			WWE on ASM vs WWE not on ASM			WWE polytherapy vs monotherapy		
Maternal and Foetal Outcomes	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**
Caesarean section	1·54 [1·43, 1·65]	<0·001	38,909,282	1·37 [1·21, 1·55]	<0·001	5,401435	1·02 [0·97, 1·08]	0·40	30,590	1·64 [1·33, 2·02]	<0·001	3,402
Induced labour	1·41 [1·32, 1·51]	<0·001	22,569,594	1·33 [1·01, 1·75]	0·04	1,934,922	1·37 [1·05, 1·78]	0·02	7,153	no data	no data	no data
Preterm birth	1·33 [1·22, 1·46]	<0·001	23,578,181	1·65 [1·58, 1·73]	<0·001	5,479,992	0·90 [0·74, 1·09]	0·27	32,324	1·29 [0·97, 1·73]	0·08	4,530
GDM	1·11 [1·01, 1·23]	0·04	22,424,835	1·51 [1·04, 2·18]	0·03	1,426,639	1·13 [0·66, 1·92]	0·65	3,385	no data	no data	no data
IUGR	1·89 [1·42, 2·52]	<0·001	39,531,783	1·74 [1·26, 2·41]	0·008	47,960	0·79 [0·49, 1·29]	0·34	1,004	no data	no data	no data
Any pregnancy loss	1·38 [1·32, 1·45]	<0·001	22,804,584	1·43 [1·05, 1·95]	0·02	1,952,954	1.35 [0.91, 2.02]	0·14	9,933	1·01 [0·58, 1·76]	0·98	2,455
APH	1·36 [1·05, 1·77]	<0.02	20,999,537	0·96 [0·57, 1·61]	0·88	365,666	2·00 [0·97, 4·13]	0·06	2,953	no data	no data	no data
Preeclampsia	1·62 [1·15, 2·29]	0·006	22,709,748	1·59 [1·17, 2·17]	0·003	4,659,751	0·84 [0·52, 1·38]	0·50	26,091	no data	no data	no data

Miscarriage	1·37 [1·29, 1·47]	<0·001	24,565	1·01 [0·51, 2·01]	0·98	18,960	1·28 [0·66, 2·49]	0·46	1,392	0·75 [0·36, 1·57]	0·44	757
Stillbirth	1·32 [1·11, 1·58]	0·002	22,717,002	1·46 [1·26, 1·69]	<0·001	4,669,509	0·92 [0·71, 1·20]	0·53	26,059	1·55 [0·47, 5·13]	0·47	1,366
Gestational hypertension	1·38 [1·29, 1·48]	<0·001	40,011,626	1·23 [0·70, 2·17]	0·47	322,921	1·22 [0·75, 1·98]	0·43	2,179	0·91 [0·55, 1·52]	0·72	1,611
PPH	1.41 [0.85, 2.33]	0·18	22,666,370	1·17 [1·08, 1·28]	<0·001	4,595,560	1·09 [0·70, 1·71]	0·69	24,927	no data	no data	no data
Placental abruption	1·49 [1·35, 1·65]	<0·001	1,783,804	1·64 [1·43, 1·87]	<0·001	4,169,404	0·84 [0·65, 1·07]	0·16	21,959	no data	no data	no data
Foetal distress	1·05 [1·03, 1·08]	<0·001	20,550,739	no data	no data	no data	no data	no data	no data	no data	no data	no data
Maternal death	5·00 [1·38, 18·04]	0·01	#VALUE!	no data	no data	no data	no data	no data	no data	no data	no data	no data
Bleeding in pregnancy	1·24 [0·93, 1·64]	0·14	509,164	1·16 [0·96, 1·40]	0·12	509,164	0·94 [0·70, 1·26]	0·68	3,478	no data	no data	no data
PROMs	1·14 [1.00, 1·30]	0·04	40,875,179	1·00 [0·92, 1·08]	0·95	4,169,706	1·03 [0·90, 1·17]	0·69	21,959	no data	no data	no data
Eclampsia	1·98 [0·72, 5·46]	0·19	305,373	no data	no data	no data	no data	no data	no data	no data	no data	no data

Placenta praevia	1·03 [0·64, 1·65]	0·91	242,314	no data	no data	no data	no data	no data	no data	no data	no data	no data
Induced abortion	1·64 [0·52, 5·14]	0·39	21,412	no data	no data	no data	no data	no data	no data	no data	no data	no data
Assisted delivery	1·28 [0·94, 1·74]	0·12	486,088	no data	no data	no data	no data	no data	no data	no data	no data	no data
Neonatal outcomes	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**	**Pooled OR (95 CI)**	**p-value**	**Sample size**
Congenital conditions	1·88 [1·66, 2·12]	<0·001	24,238,334	1·21 [1·06, 1·37]	0·005	1,874,789	1·32 [1·10, 1·58]	0·002	10,104	1·53 [1·17, 1·99]	0·002	3,477
NICU admission	1·99 [1·58, 2·51]	<0·001	1,184,116	1·27 [1·14, 1·41]	<0·001	1,092,384	1·53 [1·32, 1·78]	<0·001	7,110	1·64 [1·28, 2·08]	<0·001	3,564
SGA	1·38 [1·22, 1·55]	<0·001	2,806,718	1·18 [1·07, 1·31]	0·002	2,605,473	1·29 [1·09, 1·53]	0·003	12,767	1·87 [1·31, 2·67]	<0·001	4,127
Birthweight <2500 g	1·35 [1·20, 1·53]	<0·001	1,635,126	1·20 [1·04, 1·39]	0·02	403,794	1·49 [1·17, 1·90]	0·001	No data	No data	No data	No data
Neonatal/infant death	1·87 [1·56, 2·24]	<0·001	1,183,010	1.17 [0.69, 2.00]	0·56`	722,894	2·96 [1·23, 7·12]	0·02	5,328	1.39 [0.57, 3.40]	0·46	3,086
5-min Apgar <8	1·29 [1·01, 1·63]	0·04	2,911,254	1·11 [0·86, 1·43]	0·42	2,519,914	1·41 [0·97, 2·04]	0·07	7,761	no data	no data	no data

LGA	0·93 [0·67, 1·29]	0·65	825,417	no data	no data	no data	no data	no data	no data	no data	no data	no data
1-min Apgar <8	1·20 [1·08, 1·33]	0·008	949,944	no data	no data	no data	no data	no data	no data	no data	no data	no data
Neonatal outcomes	**Pooled MD (95 CI)**	**p-value**	**Sample size**	**Pooled MD (95 CI)**	**p-value**	**Sample size**	**Pooled MD (95 CI)**	**p-value**	**Sample size**	**Pooled MD (95 CI)**	**p-value**	**Sample size**
Mean birth weight	-71·57 [-88·82, -54·31]	<0·001	600,799	-70.95 [-155.08, 13.19]	0·10	106,156	-93.73 [-174.49, -12.97]	0·02	941	29·06 [-83·08, 141·21]	0·61	560
Mean body length	-0·31 [-0·56, -0·06]	0·02	90,483	-0·48 [-0·87, -0·09]	0·01	24,609	-0·08 [-0·72, 0·55]	0·79	325	no data	no data	no data
Mean 1-min Apgar	-0·31 [-0·58, -0·05]	0·02	83,781	no data	no data	no data	no data	no data	no data	no data	no data	no data
Mean 5-min Apgar	-0·16 [-0·26, -0·05]	0·005	92,781	no data	no data	no data	no data	no data	no data	no data	no data	no data
Mean head circumference	-0·10 [-0·36, 0·16]	0·44	83,269	-0·11 [-0·35, 0·14]	0·39	24,811	-0·33 [-1·11, 0·45]	0·41	398	no data	no data	no data
Mean gestational age	-1·72 [-3·52, 0·08]	0·06	8,149	no data	no data	no data	no data	no data	no data	no data	no data	no data

Table 3. Pooled unadjusted OR (95 CI) and pooled aOR (95 CI) of maternal and foetal, and neonatal outcomes in WWE compared to WWoE.

Maternal and Foetal Outcomes	**Pooled OR (95 CI)**	**Pooled aOR (95 CI)**
Caesarean section	1·50 [1·38, 1·63]	1.36 [1.23, 1.51]
Preterm birth	1·30 [1·17, 1·44]	1.34 [1.11, 1.61]
Induced labour	1·41 [1·25, 1·60]	1.14 [1.12, 1.16]
APH	1·38 [1·32, 1·45]	1.38 [1.31, 1.45]
Preeclampsia	1·62 [1·57, 1·66]	1.42 [1.08, 1.86]
Gestational hypertension	1·32 [1·11, 1·58]	0.96 [0.92, 1.00]
PPH	1.48 [0.85, 2.59]	1.37 [1.28, 1.48]
Maternal death	5·00 [1·38-18·04]	9.41 [5.36, 16.53]
Neonatal outcomes	**Pooled OR (95 CI)**	**Pooled aOR (95 CI)**
Congenital conditions	1·88 [1·66, 2·12]	1.69 [1.62, 1.78]
SGA	1·38 [1·22, 1·57]	1.17 [1.01, 1.36]

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