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Placenta-associated adverse pregnancy outcomes in women experiencing mild or severe hyperemesis gravidarum – a systematic review and meta-analysis

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Abstract

Background Nausea and vomiting in pregnancy (NVP) affects 50–80% of pregnant women and is correlated to the level of human chorionic gonadotropin (hCG). Hyperemesis gravidarum (HG) is a severe condition, with an incidence of 0.2–1.5%, characterized by consistent nausea, vomiting, weight loss and dehydration continuing after the second trimester.

Aim The aim of this systematic review was to investigate a potential correlation between NVP or HG with adverse pregnancy outcomes and hCG levels.

Method A systematic search in PubMed, Embase and CINAHL Complete was conducted. Studies on pregnant women with nausea in the first or second trimester, reporting either pregnancy outcomes or levels of hCG were included. The primary outcomes were preterm delivery (PTD), preeclampsia, miscarriage, and fetal growth restriction. Risk of bias was assessed using ROBINS-I. The overall certainty of evidence was assessed using GRADE.

Results The search resulted in 2023 potentially relevant studies; 23 were included. The evidence was uncertain for all outcomes, however women with HG had a tendency to have an increased risk for preeclampsia [odds ratio (OR) 1.18, 95% confidence of interval (CI) 1.03 to 1.35], PTD [OR 1.35, 95% CI 1.13 to 1.61], small for gestational age (SGA) [OR 1.24, 95% CI 1.13 to 1.35], and low birth weight (LBW) [OR 1.35, 95% CI 1.26 to 1.44]. Further, a higher fetal female/male ratio was observed [OR 1.36, 95% CI 1.15 to 1.60]. Meta-analyses were not performed for women with NVP; however, most of these studies indicated that women with NVP have a lower risk for PTD and LBW and a higher risk for SGA, and a higher fetal female/male ratio.

Conclusion There may be an increased risk in women with HG and a decreased risk in women with NVP for adverse placenta-associated pregnancy outcomes, however the evidence is very uncertain.

Trial registration PROSPERO: CRD42021281218.

Keywords Hyperemesis gravidarum, hCG, Placenta

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Introduction

Nausea and vomiting (NVP) in pregnancy affects about 50–80% of women. Usually, the nausea begins in the 4th week of pregnancy and resolves before the 20th week [1, 2]. The levels of hCG increase rapidly during the first weeks of pregnancy, typically peaking around 9 weeks, consistent with the peak of nausea and vomiting. The levels of hCG and the occurrence of nausea and vomiting are higher in molar- and multiple pregnancies, indicating that hCG correlates with these symptoms [3]. The levels of hCG have also been shown to be higher in hyperemesis gravidarum (HG) [4].

Hyperemesis gravidarum is a severe condition characterized by consistent vomiting and nausea, weight loss, dehydration, ketonuria and electrolyte imbalances, with an incidence of 0.2–1.5%. The cause of HG remains unknown [5–7]. It is classified as either mild or severe. Severe cases often require hospital care with intravenous fluids, antiemetics and sometimes parenteral nutrition. In fact, it is one of the common reasons for a pregnant woman to be admitted for hospital care [3, 8]. Research studies have shown that HG has an increased risk for placenta-associated complications, such as fetal growth restriction (FGR), preterm delivery (PTD), preeclampsia, placental abruption and small for gestational age (SGA), when compared to less severe nausea [3, 9–11]. Furthermore, it has been shown that there is an increased ratio between female and male fetuses in women admitted to the hospital due to HG [5, 8, 12, 13]. The mechanism for the correlation between fetal sex and HG is unclear, but it could be related to higher levels of hCG and different placental functions deriving from sexual dimorphism [12].

Women with NVP have been shown to have a 50–75% reduced risk for miscarriage, supporting the hypothesis that nausea is a sign of a well-functioning placenta [14, 15]. A dysfunctional placenta can result in a number of severe conditions including preeclampsia, intrauterine fetal death (IUFD), miscarriage, PTD, FGR and placental abruption [3, 9]. Preeclampsia affects 3–7% of pregnant women and causes 18% of maternal deaths worldwide, particularly in developing countries [16].

Many women suffer from nausea in pregnancy and there does not seem to be a consensus on any correlation between pregnancy induced nausea and adverse pregnancy outcomes. The aim of this systematic review was therefore to investigate if NVP or HG correlates with adverse pregnancy outcomes and if the levels of hCG differ between these groups.

Methods

The protocol of this systematic review was registered with the international prospective register of systematic reviews, PROSPERO (CRD42021281218), prior to screening studies for inclusion [17]. The protocol included relevant information including the review question, search strategy, eligibility criteria, primary and secondary outcomes, how to assess risk of bias, how to perform quality assessment, which data to extract and strategy for data synthesis.

Eligibility criteria

We included studies of pregnant women with NVP or HG in the first or second trimester; we excluded studies of women with pre-existing systemic diseases such as liver-, kidney- or thyroid disease, diabetes, and hyperemesis in the third trimester. We included randomised controlled trials, non-randomised controlled trials, case–control studies, and cohorts. We excluded conference abstracts, reviews, case reports and other study designs. A cohort study was defined as an observational study with one group only, in this review women with either NVP or HG. A case control study was defined as a study comparing two groups, in this review women with NVP or HG compared to women without these conditions. The primary pregnancy outcomes in this review were miscarriage (fetal death before week 20), preeclampsia, FGR (fetal estimated weight below the 10th percentile with a retardation in growth) and PTD (delivery before week 37). The secondary outcomes were SGA (weight below the 10th percentile), LBW (birth weight below 2500 g), IUFD (intrauterine death after week 28), placental abruption, fetal sex, rate of multiple pregnancies, congenital malformations, and admission to neonatal intensive care unit (NICU). Additionally, one included outcome not stated in the protocol was the level of hCG in the maternal blood. Studies that reported neither hCG levels nor any type of pregnancy outcome were excluded.

Search

A search strategy was developed in collaboration with an information specialist at the Lund University library to identify all studies on pregnant women with nausea, vomiting or HG, reporting pregnancy outcomes or levels of hCG in blood. The databases PubMed, Embase and CINAHL Complete were searched for eligible studies by using free text and Medical Subject Headings, described in Additional file 1. No restrictions regarding language, publication year or publication status were applied. The search was conducted on 28 September 2021.

Study selection and data extraction

The studies were screened by two independent researchers using Covidence, an online tool for screening and data extraction in systematic reviews [18]. Conflicts were solved by a third party or by reaching consensus between the researchers. Translators were contacted to translate

studies in languages other than English, if necessary. Title, author, year, country, study design, number of participants, trimester and outcomes were extracted and reported in a table. Odds Ratio (OR) were extracted for each outcome and reported in a table. If a study did not report OR, it was calculated using Review Manager 5.4 (RevMan) from the number of events and the total number of participants [19].

Risk of bias

Risk of bias was assessed for each study by two independent researchers using Risk Of Bias In Non-Randomized Studies—of Interventions (ROBINS-I) [20]. The eight domains assessed for risk of bias were: bias due to; I) confounding, II) selection of participants, III) classification of interventions, IV) deviation from intended interventions, V) missing data, VI) measurement of outcomes, VII) selection of the reported results and VIII) overall risk of bias. The risk could be low, moderate, serious, or critical. The overall risk of bias was set at the same level as the domain with the highest risk. The confounding factors considered were pre-gestational diseases (diabetes, hypertension, liver-, kidney-, thyroid- and autoimmune disease), preeclampsia, eclampsia, HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome, gestational trophoblastic disease, multiple pregnancy, and molar pregnancy.

Overall certainty of the evidence

The guidance for "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) was used to evaluate the overall certainty of evidence for the four primary outcomes: preeclampsia, PTD, miscarriage and FGR, and for the two secondary outcomes reported by most studies: SGA and LBW [21]. Women with NVP and women with HG were assessed together. Each outcome was assessed for risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Data analysis

Data was entered into RevMan, and OR with 95% confidence intervals (CI) were calculated for the dichotomous outcomes. Meta-analyses were performed for the outcomes with at least three studies, and forest plots were generated. For the outcomes reported in fewer than three studies, the study results were compared to each other and described in a narrative text. Women with NVP and with HG were analysed in different meta-analyses for the individual outcomes. Mild and severe HG were analysed together. Sensitivity analysis was performed for the studies with moderate or serious/critical risk of bias. Subgroups were created for each outcome, dividing the studies into women with NVP and women with HG. Heterogeneity was measured by I^2 and calculated in RevMan.

Results

Search results

The search resulted in 2023 studies; 109 duplicates were removed. The title and abstract screening resulted in 325 potentially relevant studies. A post hoc decision was made to only assess studies describing pregnant women with NVP or HG that reported either hCG levels or pregnancy outcomes. This resulted in 56 studies that were screened in full text. Seven of them had no full text available and were identified as "awaiting classification". Out of the 26 excluded studies, 15 did not report relevant outcomes, five were reviews, four did not study pregnant women with nausea, two were duplicates. This resulted in a total of 23 included studies [3–5, 8–11, 15, 22–36] (Fig. 1).

Flow chart of the study selection process.

Included studies

Of the 23 included studies, 20 were case control studies and three were cohort studies. Of the included studies, 12 were prospective and 11 were retrospective. Fourteen studies included women with HG, two studies included women with nausea, two studies included women with vomiting, two studies included women with nausea and vomiting, two studies included two variables: one with nausea and one with nausea and vomiting, and one study reported the use of antiemetics (Table 1). One study was translated from Persian, and one was translated from French. Most of the studies (13 studies) were considered to have an overall moderate risk of bias (Fig. 2).

Risk of bias assessment for all included studies. The risk of bias for each domain and the overall risk of bias are shown. The overall risk of bias was set at the same level as the domain with the highest risk of bias.

Data analysis

Odds ratios for each study and outcome are reported in Table 2. Most outcomes were not reported by a sufficient number of studies to be pooled in a meta-analysis and were therefore analysed individually. Sensitivity analysis did not reduce the heterogeneity remarkably and is not shown in the final analysis. The study by Weigel et al. [34], reporting PTD, miscarriage, SGA, low birth weight and congenital malformations, could not be included in the meta-analyses since the numbers for the control group was not reported. Outcome data for the secondary outcomes are reported in Table 2 and in Additional file 2.

Odds ratio with 95% confidence intervals, OR (CI), are shown for all the outcomes. *PTD* preterm delivery, *FGR* fetal growth restriction, *SGA* small for gestational

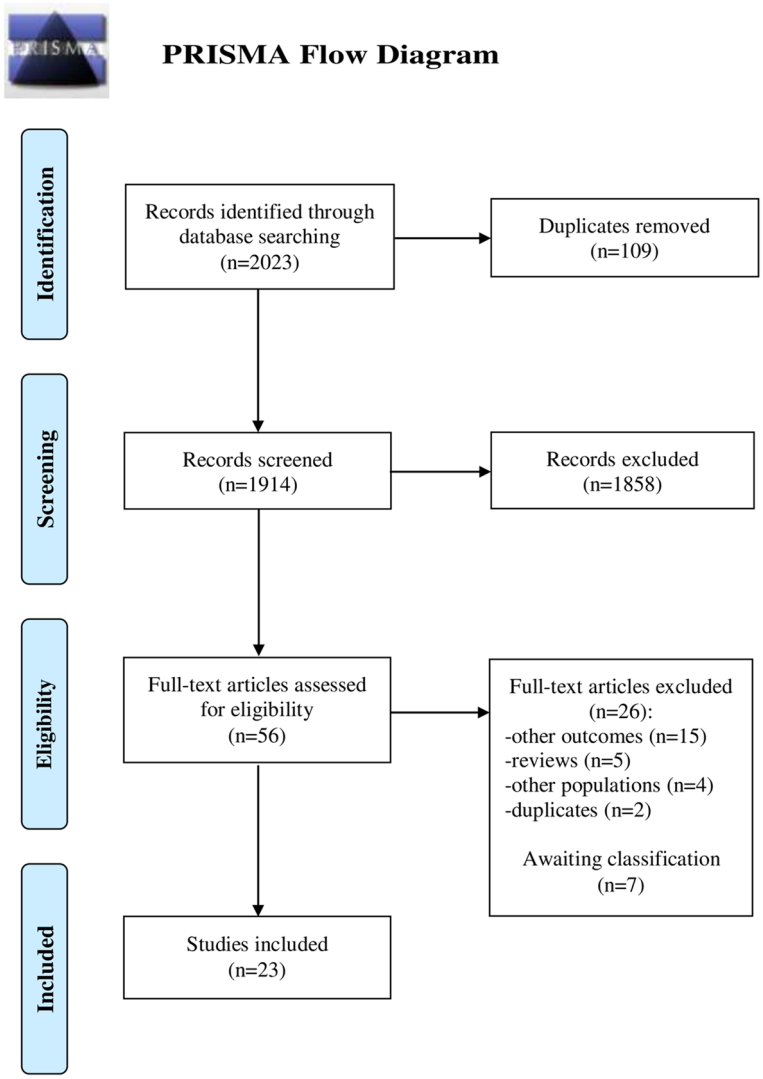

Fig. 1 Flow chart

age, *LBW* low birth weight, *IUFD* intrauterine fetal death, *OR* odds ratio, *aOR* adjusted OR, *CI* confidence interval, *HG* hyperemesis gravidarum, *NP* nausea during pregnancy, *NVP* nausea and vomiting during pregnancy. (I) Adjustments were made for maternal age, parity, body mass index (BMI), height, smoking, cohabitation with infant's father, infant's sex, mother's country of birth and years of formal education, presence of hyperthyreosis, pregestational diabetes, chronic hypertension, and year of birth of infant. (II) Preeclampsia: Adjusted for age, BMI, smoking, parity, education, and gender. SGA: Adjusted for age, BMI, smoking, education, and gender. LBW: Adjusted for age, BMI, smoking, parity, education, gender, gestational length, and energy intake. Fetal sex: Adjusted for age, BMI, smoking, parity, and education. (III) Mild HG: Weight gain ≥ 7 kg. Severe HG: Weight gain < 7 kg. (IV) Unclear what is adjusted for. (V) A: Adjusted for maternal age, parity and smoking. B: Adjusted for smoking, BMI and maternal blood pressure. C: Adjusted for smoking and BMI. Mild HG: weight gain ≥ 7 kg. Severe HG: weight gain < 7 kg. (VI) Adjusted model: adjusted for socio-economic status (as reflected by income), smoking status, gravidity, maternal age and pre-pregnancy BMI. Mild HG: weight loss ≥ 5% of pre-pregnancy weight. Severe HG: weight loss < 5% of pre-pregnancy weight. (VII) Adjusted for maternal age, neighborhood altitude, periconceptual use of prenatal tobacco, alcohol, antiemetic drugs, and vitamin-mineral supplements. SGA and low birth weight are in addition adjusted for gestational age. (VIII) Adjusted for maternal age, chronic illnesses, and paternal smoking. D: Adjusted for gravidity primae, maternal age > 30 years, chronic hypertension, chronic liver disease, congenital or rheumatic heart diseases, chronic renal illness, paternal smoking.

Table 1 Table of characteristics

Title	Study id	Year of enrolment	Country	Ethnicity	Participants	Trimester	Pregnancy outcome / hCG
Hormone profile of Kuwaiti women with hyperemesis gravidarum	Al-Yatama 2002	2000	Kuwait	Kuwaitis, Arabs, Asians, Other	50 women with vomiting and 50 women without vomiting	1st & 2nd	hCG
Use of antiemetic drugs during pregnancy in Sweden	Asker 2005	1995-2002	Sweden	Unclear	29,804 women using antiemetics, 635 768 not using antiemetics	1st, 2nd & 3rd	PTD, SGA, LBW, congenital malformations, fetal sex, rate of multiple pregnancies
Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study	Bolin 2013	1997-2009	Sweden	Not reported	1,156,050 women with HG	1st & 2nd	Preeclampsia, PTD, SGA, IUFD, placental abruption
Pregnancy complications and birth outcomes among women experiencing nausea only or nausea and vomiting during pregnancy in the Norwegian Mother and Child Cohort Study	Chortatos 2015	1999-2008	Norway	Not reported	20,371 with nausea, 17,070 with nausea and vomiting and 14,234 without nausea or vomiting	1st & 2nd	Preeclampsia, PTD, SGA, LBW, congenital malformations, fetal sex
Association between severe nausea and vomiting in pregnancy and lower rate of preterm births	Czeizel 2004	1980-1996	Hungary	European	3,869 women with nausea and vomiting and 34,282 women without nausea and vomiting	1st & 2nd	PTD, LBW, fetal sex
Hormonal and psychological factors in nausea and vomiting during pregnancy	Dekkers 2020	Not reported	Netherlands	Not reported	1,682 women with nausea	1st	hCG
Outcomes of Pregnancies Complicated by Hyperemesis Gravidarum	Dodds 2006	1988-2002	Canada	Not reported	1,270 women with HG and 154,821 women without HG	1st & 2nd	PTD, SGA, LBW
Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum	Fejzo 2013	2007-2011	USA	Caucasian	254 women with HG and 308 women without HG	1st	PTD, SGA, congenital malformations, fetal sex
Adverse Maternal and Birth Outcomes in Women Admitted to Hospital for Hyperemesis Gravidarum: a Population-Based Cohort Study	Fiaschi 2018	1997-2012	England	White, Black and white, Asian, Black, Chinese, Other	118,197 women with HG and 8,093,653 women without HG	1st & 2nd	Preeclampsia, PTD, SGA, LBW, IUFD, placental abruption, NICU admission
Pregnancy nausea related to women's obstetric and personal histories	Gadsby 1997	Not reported	UK	Unclear	363 women with nausea	Unclear	Fetal sex
Increased concentration of the free beta-subunit of human chorionic gonadotropin in hyperemesis gravidarum	Goodwin 1994	Not reported	USA	Not reported	39 women with HG and 23 women without HG	1st & 2nd	hCG
The role of chorionic gonadotropin in transient hyperthyroidism of hyperemesis gravidarum	Goodwin 1992	1990	USA	Not reported	57 women with HG and 57 women without HG	1st	hCG
[Hyperemesis gravidarum and pregnancy outcomes]	Hastoy 2015	2006-2009	France	Not reported	197 women with HG and 392 women without HG	1st & 2nd	FGR, PTD, SGA, LBW, fetal sex
Hyperemesis gravidarum: is an ultrasound scan necessary?	Kirk 2006	2001-2006	UK	Not reported	286 women with HG and 286 women without HG	1st	Miscarriage, rate of multiple pregnancies
Hyperemesis gravidarum and placental dysfunction disorders	Koudijs 2016	2012-2014	Indonesia	Not reported	400 women with HG and 1,833 women without HG	1st & 2nd	Miscarriage, preeclampsia, SGA, LBW, IUFD
Outcomes of pregnancies complicated by hyperemesis gravidarum	Kuru 2012	2003-2011	Turkey	Not reported	72 women with HG and 89 women without HG	1st & 2nd	PTD, SGA, IUFD, fetal sex
Immunologic and biochemical factors in hyperemesis gravidarum with or without hyperthyroxinemia	Leylek 1999	Not reported	Turkey	Not reported	30 women with HG and 15 women without HG	1st	hCG
Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum	Roseboom 2011	2000-2006	Netherlands	Non-Western and Western	5,207 women with nausea and vomiting and 76,279 women without nausea and vomiting	Unclear	PTD, SGA, IUFD, fetal sex, NICU admission
Pregnancy outcome in hyperemesis gravidarum and the effect of laboratory clinical indicators of hyperemesis severity	Tan 2007	2004-2005	Kuala Lumpur	Malay, Chinese, Indian, Others	166 women with HG and 498 women without HG	1st & 2nd	Miscarriage, PTD, LBW, IUFD
Adverse pregnancy outcomes in women with nausea and vomiting of pregnancy	Temming 2014	2004-2011	USA	African-American, American	5,207 women with nausea and vomiting and 76,279 women without nausea and vomiting	Not reported	PTD, SGA, LBW, IUFD, fetal sex
Is the nausea and vomiting of early pregnancy really feto-protective?	Weigel 2006	Not reported	Ecuador	Unclear	129 women with nausea, 373 women with nausea and vomiting and 131 women without nausea and vomiting	1st & 2nd	Miscarriage, PTD, SGA, LBW, congenital malformations
Evaluating complications of pregnancy in patients with hyperemesis gravidarum	Yazdani 2010	Not reported	Iran	Not reported	70 women with HG and 100 women without HG	1st & 2nd	Preeclampsia, PTD
Severe vomiting during pregnancy: antenatal correlates and fetal outcomes	Zhang 1991	1986-1987	China	Not reported	201 women with vomiting and 1,666 women without vomiting	Not reported	Preeclampsia, PTD, SGA, LBW, fetal sex

Characteristics of the included studies

HG hyperemesis gravidarum, *PTD* preterm delivery, *SGA* small for gestational age, *LBW* low birth weight, *IUFD* intrauterine fetal death, *NICU* neonatal intensive care unit, *FGR* fetal growth restriction

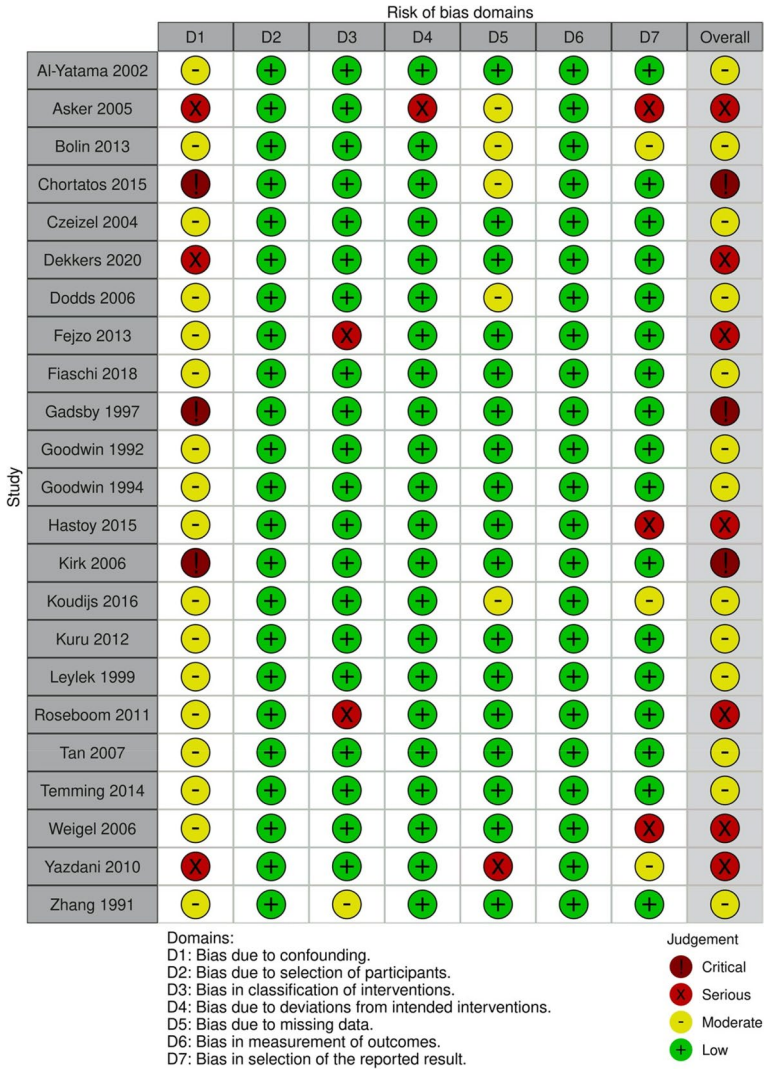

Fig. 2 Risk of bias assessment

Preterm delivery (PTD) was reported in 14 studies with a total of 9,054,950 participants, of whom Fiaschi et al. [11], contributed 6,835,060. The meta-analysis for HG resulted in OR 1.35, 95% CI 1.13 to 1.61, indicating that women with HG have a higher risk for PTD (Fig. 3). Due to the high heterogeneity, the studies on women with NVP could not be pooled in a meta-analysis. Three of these five studies showed a significantly lower risk for PTD in women with NVP, although the certainty of evidence is very low. One study showed a significant higher risk for PTD in women with NVP, and one study showed no difference. The study by Weigel et al. [34] was excluded due to missing data.

Forest plot showing the meta-analysis for preterm delivery in women with HG. Odds ratios with 95% confidence intervals (CI) are reported. The heterogeneity is showed as the value of I^2.

Preeclampsia was reported in six studies with a total of 9,421,054 participants. Four of these studies reported women with HG and the meta-analysis resulted in OR 1.18, 95% CI 1.03 to 1.35, suggesting that HG is a risk factor for preeclampsia (Fig. 4). Since only two studies reported on women with NVP, a meta-analysis was not performed. One of the studies showed a significant higher risk for preeclampsia in women with NVP. The other study showed no difference.

Forest plot showing the meta-analysis for preeclampsia in women with HG. Odds ratios with 95% confidence intervals (CI) are reported. The heterogeneity is showed as the value of I^2.

Miscarriage was reported in three studies including 3,438 women. A meta-analysis was not performed due to high heterogeneity and missing data. The study by Weigel et al. [34] did not report the numbers for

Table 2 Table of outcomes

Outcome	Asker 2005 (I)	Bolin 2013 (II)	Chortatos 2015	Cereid 2004	Diddis 2006 (III)	Fejzo 2013 (IV)	Fiaschi 2018	Hastoy 2015 (V)	Kirk 2006	Kostlijn 2016 (VI)	Kuru 2012	Rosebboom 2011	Tan 2007	Temming 2014	Weigel 2006 (VII)	Yazdani 2010	Zhang 1991 (VIII)
PTD	OR 0.93 (0.88-0.98)		NP: OR 0.81 (0.74-0.90), NVP: OR 0.87 (0.78-0.96)	OR 0.66 (0.58-0.75)	Severe HG: OR 0.84 (0.60-1.18), Mild HG: OR 3.20 (1.99-5.14)	OR 4.12 (2.20-8.19) aOR 4.05 (2.08-8.30)	OR 1.29 (1.25-1.33)	Mild HG: OR 1.20 (0.67-2.15), Severe HG: OR 1.78 (0.86-3.67) **A**			OR 0.80 (0.31-2.08)	OR 1.37 (1.17-1.60)	OR 0.65 (0.30-1.43)	OR 1.42 (1.30-1.56)	NP: OR 1.05 (0.47-2.30), aOR 1.03 (0.46-2.29) NVP: OR 1.32 (0.67-2.57), aOR 1.14 (0.82-1.59)	OR 10.14 (1.19-86.32)	OR 1.0 (0.5-2.2) aOR 1.0 (0.5-2.1)
Preeclampsia		All preeclampsia: aOR 1.19 (1.05–1.34), Preterm preeclampsia: aOR 1.36 (1.09–1.70), Term preeclampsia: aOR 1.13 (0.98–1.30)	NP: OR 0.83 (0.74–0.94) aOR 1.13 (1.01–1.27), NVP: OR 1.13 (1.01–1.27) aOR 1.13 (1.01–1.27)				OR 1.27 (1.23-1.32)			Mild HG: OR 0.97 (0.55-1.72), aOR 0.91 (0.47-1.76) Severe HG: OR 0.90 (0.21-3.81), aOR 0.99 (0.23-4.34)						OR 0.51 (0.02-12.69)	OR 1.6 (1.0-2.5) aOR 1.5(1.0-2.4)
Miscarriage									OR 0.09 (0.01–0.04)	Mild HG: OR 1.07 (0.70-1.64), aOR 1.17 (0.60-2.70), Severe HG: OR 0.57 (0.13-2.37)					NP: OR 0.41 (0.20-0.85), aOR 0.45 (0.22-0.94), NVP: OR 0.40 (0.19-0.84), aOR 0.66 (0.46-0.96)*		
FGR								Mild HG: OR 1.10 (0.69-1.75), Severe HG: OR 1.81 (1.00-3.25) **B**									
SGA	OR 0.9 (0.82-0.99)*	Total aOR 1.18 (1.04–1.33) First aOR 1.13 (0.99–1.30), Second aOR 1.39 (1.06–1.83)	NP: OR 0.78 (0.73–0.84) aOR 0.78 (0.73–0.84), NVP: OR 0.84 (0.78–0.90) aOR 0.87 (0.81–0.93)		Mild HG: OR 0.93 (0.74-1.16). Severe HG: OR 1.57 (0.99-2.49)	OR 2.88 (0.79-13.47), aOR 2.05 (0.50-10.23)	OR 1.38 (1.35-1.41)			Mild HG: OR 1.24 (0.89-1.73), aOR 1.29 (0.87- 1.91), Severe HG: OR 1.08 (0.44-2.64), aOR 1.74 (0.68- 4.44)	OR 0.48 (0.16-1.43)	OR 1.12 (0.98-1.28)		OR 1.26 (1.14-1.38)	NP: OR 0.59 (0.26-1.32), aOR 0.60 (0.27-1.35), NVP: OR 0.77 (0.37-1.61), aOR 0.89 (0.61-1.29)		OR 1.4 (0.9-2.2) aOR 1.4 (0.9-2.3)
LBW	OR 0.89 (0.83-0.96)		NP: OR 0.66 (0.57–0.77) aOR 0.73 (0.60–0.88), NVP: OR 0.74 (0.64–0.87) aOR 0.72 (0.60–0.88)	OR 0.85 (0.73-0.99)	Mild HG: OR 0.81 (0.56-1.16). Severe HG: OR 3.29 (2.00-5.39)		OR 1.38 (1.34-1.41)	Mild HG: OR 0.88 (0.47-1.65) Severe HG: OR 1.93 (0.95-3.90) **C**		Mild HG: OR 1.03 (0.63-1.67), aOR 1.36 (0.74- 2.51), Severe HG: OR 0.74 (0.18-3.13), aOR 1.44 (0.33- 6.33)			OR 1.25 (0.70-2.24)	OR 1.93 (1.80-2.06)	NP: OR 0.60 (0.33-1.10), aOR 0.61 (0.33-1.11), NVP: OR 0.78 (0.45-1.32), aOR 0.88 (0.67-1.16)		OR 1.5 (0.7-3.0) aOR 1.6 (0.8-3.0)
Fetal sex (female)			NP: OR 1.18 (1.13–1.23) aOR 1.18 (1.13–1.23), NVP: OR 1.33 (1.27–1.39) aOR 1.34 (1.28–1.40)	OR 1.24 (1.16-1.32)		OR 1.54 (1.10-2.16)		OR 1.62 (1.15-2.30)			OR 1.54 (0.82-2.89)	OR 1.22 (1.12-1.32)		OR 1.15 (1.09-1.21)			OR 1.2 (0.9-1.7) aOR 1.3 (0.9-1.7) **D**
IUFD		Total aOR 0.99 (0.68–1.44), First aOR 0.95 (0.62–1.44), Second aOR 1.18 (0.53–2.64).					OR 0.93 (0.86-1.01)			Mild HG: OR 1.24 (0.35-4.43), aOR 1.41 (0.37-5.40), Severe HG OR 3.26 (0.41-25.72), aOR 4.18 (0.50-35.10)	OR 0.41 (0.02-10.14)	OR 0.36 (0.14-0.97)	OR 1.45 (0.15-14.06)	OR 1.40 (0.71-2.78)			
Congenital malformations	OR 0.90 (0.84-0.96)		NP: OR 1.06 (0.96–1.17) aOR 1.10 (1.00–1.22), NVP: OR 0.98 (0.88–1.09) aOR 1.03 (0.93–1.15)			OR 1.72 (0.54-5.48)									NP: OR 0.79 (0.21-2.95), aOR 0.90 (0.24-3.40), NVP: OR 0.98 (0.31-3.13), aOR 1.06 (0.59-1.90)		
Placental abruption		Total aOR 1.47 (1.10–1.95), First aOR 1.13 (0.80–1.61), Second aOR 3.07 (1.88–5.00)					OR 1.13 (1.03-1.23)										
Rate of multiple pregnancies	OR 1.51 (1.40–1.64)								OR 1.00 (0.39-2.56)								
Need for admission to NICU							OR 1.19 (1.13-1.25)					OR 0.12 (0.08-0.18)					

the control group, hence no OR, anticipated absolute effect or event rates could be calculated. One study showed a significant decreased risk for miscarriage in women with HG, and the other study reported no difference. The study by Tan et al. [32] reported two cases of miscarriage but excluded them from their analysis.

Fetal growth restriction (FGR) was only reported in one study, Hastoy et al. [8]. Its definition was translated to SGA in the English abstract but was then described as FGR in the rest of the French article. The total number of participants in this study was 589 and the results indicated an increased risk for FGR in women with HG.

Secondary outcomes

Results for secondary outcomes are reported in Additional file 2, including meta-analysis for SGA (Figure S1), LBW (Figure S2), fetal sex (Figure S3) and IUFD (Figure S4).

Human choriogonadotropin (hCG) levels

The five studies that reported levels of hCG in women with NVP or HG are described in Table 3. Four of them were case control studies and one was a cohort study. Since the cohort study did not have a control group, only the levels of hCG in hyperaemic patients are reported in Table 3. The studies measured hCG with different

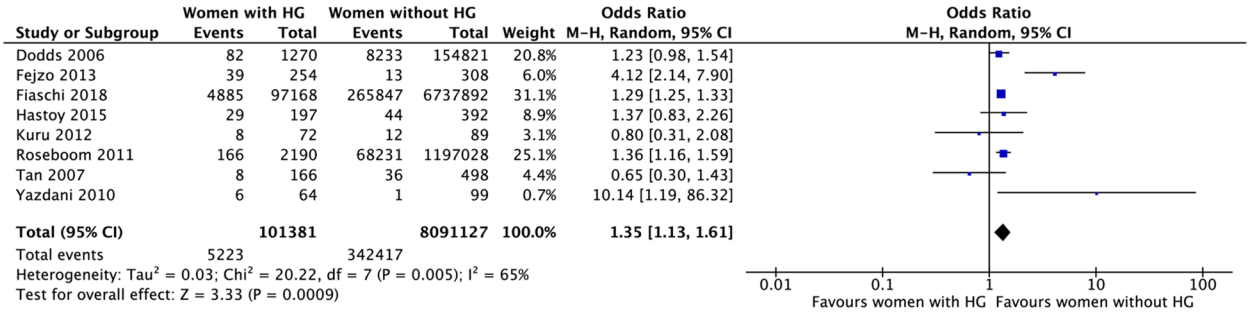

Fig. 3 Meta-analysis for preterm delivery

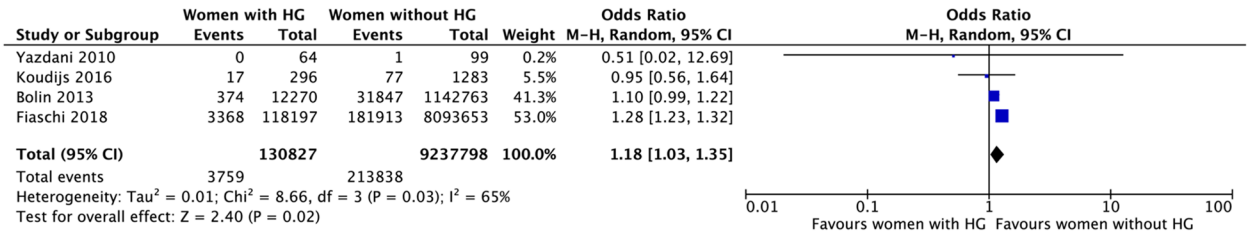

Fig. 4 Meta-analysis for preeclampsia

Table 3 Levels of hCG

Study id	Sample size	Participants	Method	Gestational week	hCG levels in controls (mean ± SD)	hCG levels in cases (mean ± SD)	P-value
Al-Yatama 2002	50 cases and 50 controls	Women with vomiting in the first 14 weeks of pregnancy	β-hCG in plasma. Analysed using MPIA (micro particle enzyme immunoassay)	Week 5-16	**β-hCG:** 61,845±53,080 **mIU/ml**	**β-hCG:** 133,439±59,486 **mIU/ml**	p<0.0001
Goodwin 1994	39 cases and 23 controls	Women with HG, symptoms before week 16	hCG, β-hCG and *α*-hCG in blood. Method of analysis not reported	Week 8-16	**hCG:** 5,543±2,290 **ng/ml** **β-hCG:** 31±31**ng/ml** ***α*-hCG:** 377±214 **ng/ml**	**hCG:** 9,237±3,613 **ng/ml** **β-hCG:** 101±70 **ng/ml** ***α*-hCG:** 399±231 **ng/ ml**	p<0.01
Goodwin 1992	57 cases and 57 controls	Women with HG, symptoms before week 16	hCG in serum. Analysed using RIA (radioimmunoassay)	Week 10	**hCG**: 29,000±2,000 m**IU/ml***	**hCG:** 97,000±8,000 m**IU/ml***	p<0.001
Leylek 1999	30 cases and 15 controls	Women with HG	ß-hCG in serum. Analysed using RIA (radioimmunoassay)	Week 12	**ß-hCG**: 179±60 **mIU/ml**	**ß-hCG:** 269±85 **mIU/ml**	p<0.01
Dekkers 2020	1,682 cases	Women with nausea in first trimester	hCG in plasma. Analysed using electrochemiluminescence assays	Week 10-12		**hCG:** 65,447.50±35,184.59 **mIU/ml**	

methods, at different gestational ages and reported the results in different units. Free ß-hCG was reported in three studies, intact hCG in three studies, and α-hCG in one study.

Comparison of hCG levels, reported in five studies. *HG* hyperemesis gravidarum, *hCG* human chorionic gonadotropin, *IU* international unit. *Originaly in IU/ml

GRADE assessment

Certainty of evidence for the four primary outcomes and for SGA and LBW was very low (see Table 4). All outcomes were downgraded for imprecision of the estimates. Miscarriage and FGR were downgraded also for serious risk of bias. Preeclampsia, PTD, SGA and LBW were downgraded for inconsistency. Study event rates and anticipated absolute effect are reported in the summary of findings table (Table 4).

Summary of findings and certainty of evidence assessment (GRADE). Both women with NVP and with HG are included. (a) due to serious risk of bias, high heterogeneity and wide CI; (b) due to high heterogeneity and wide CI; (c) due to serious risk of bias and wide CI.

Discussion

The aim of this systematic review was to explore if there are any correlations between NVP or HG and adverse placenta-associated outcomes. We found that there might be an association between HG and an increased risk for PTD, preeclampsia, SGA, and LBW, however the certainty of evidence was very low. Most studies indicated that women with NVP have a lower risk for PTD and LBW, but a higher risk for SGA. The fetal female/male ratio was in general higher in both women with NVP and HG.

Limitations of this review include the post hoc decision to not include the studies on hCG in correlation to adverse pregnancy outcomes, as specified in the review protocol [17]. By including studies in all languages, not applying restrictions for publishing year and by performing an extensive search in three different large databases, the risk of missing potentially relevant studies was minimised. To reduce the risk of confounders, studies on women with intercurrent diseases were excluded. Several intercurrent diseases have been associated with an increased risk for HG, e.g., pre-gestational diabetes and thyroid diseases [5, 37]. The confounding factors existing for nausea are difficult to adjust for in observational studies. Therefore, none of the studies were individually considered to have an overall low risk of bias due to confounding factors. One of the cohort studies reported the use of antiemetics in pregnant women, i.e., indirectly reporting on the symptom nausea. The study included women with prescriptions for antiemetics as cases and all other women as controls. Women buying antiemetics over the counter were not registered as cases, generating a higher risk of bias due to misclassifications of the interventions. Some of the studies did not report a clear

Table 4 Summary of findings

Outcomes	Number of participants (studies)	Overall certainty of evidence (GRADE)	Relative effekt OR (95% CI)	Anticipated absolute effects	
				Risk without nausea	Risk with nausea
Miscarriage	3438 (3)	Very low ⨁OOO (a)			
Preeclampsia	9421054 (6)	Very low ⨁OOO (b)	1.14 (0.97 to 1.33)	23 per 1000	8 more per 1000
Preterm delivery	9054950 (14)	Very low ⨁OOO (b)	1.13 (0.94 to 1.36)	43 per 1000	8 more per 1000
Fetal growth restriction	589 (1)	Very low ⨁OOO (c)	1.30 (0.87 to 1.93)	217 per 1000	47 more per 1000
Small for gestational age	7796711 (12)	Very low ⨁OOO (b)	1.28 (0.95 to 1.73)	75 per 1000	9 more per 1000
Low birth weight	7824780 (11)	Very low ⨁OOO (b)	1.04 (0.83 to 1.30)	45 per 1000	3 more per 1000

definition for HG, also increasing the risk of bias for classification of interventions. ROBINS-I was used since it is the most suitable tool for assessing risk of bias in non-randomised studies. For many of the outcomes, the heterogeneity was high due to different study characteristics and diverse results. The imprecision was also high due to few studies reporting the outcome, a small number of participants in the included studies and broad CIs. The certainty of evidence according to GRADE was therefore considered very low for all the assessed outcomes. The uncertain evidence entails the greatest limitation of this review.

Other systematic reviews by Veenendaal et al. [38] and Varela et al. [39] studying women with HG and adverse pregnancy outcomes including PTD, LBW and SGA, have shown results in line ours, namely, an increased risk for adverse pregnancy outcomes in women with HG. The increased risk for these outcomes in women with HG could be a consequence of the systemic and metabolic effects generated by HG, negatively affecting the woman and the fetus. When studying mild and severe HG separately, an increased risk for adverse pregnancy outcome is particularly associated with the severe form of HG [8, 10, 40]. Severe HG is associated with low caloric intake, weight loss, electrolyte imbalance and disturbances in glucose metabolism, reducing the availability of nutrients for the fetus as well. It is a state comparable to famine, where studies have shown that a reduction of intrauterine nutrition correlates to lower birth weight [41]. Only one review, Koren et al. [42], was found that reported adverse pregnancy outcomes in women with NVP. They showed a reduced risk for miscarriage, congenital malformations and PTD; results that are in line with this review.

This systematic review also intended to investigate if there are correlations between levels of hCG and NVP or HG. The studies reporting levels of hCG were heterogeneous and reported different types of hCG (alfa-, beta- and intact hCG), with different analysing methods, at different gestational ages and in different units. As there is a lack of consensus regarding equivalent units, a comparable unit could not be generated. However, this was not a major limitation in the aspect of this review, since the comparison between cases and controls was the most important, showing higher levels of hCG in the cases. On the other hand, only five studies were found and most of them were published over 20 years ago, indicating that there is limited amount of ongoing research in this area. Although the levels of hCG in pregnant women have not changed throughout the years, more studies are needed to be able to draw well-grounded conclusions about to which extent the levels differ in women with HG.

It could be argued that high levels of hCG originate from a well-functioning placenta producing adequate levels and thereby ensuring a decreased risk for adverse pregnancy outcomes. Nausea has shown to be protective against miscarriage, and the levels of hCG seem to be higher in women experiencing nausea in early pregnancy [4, 14, 15]. On the other hand, results from other studies have shown the opposite effect, indicating that too high levels of hCG are associated with adverse pregnancy outcomes. The levels of hCG have been shown to be higher in women with HG, in which the incidence of adverse pregnancy outcomes also is high, confirming the results in this review [43]. In addition, hCG in combination with other biomarkers, such as pregnancy-associated plasma protein A (PAPP-A), alpha fetoprotein (AFP), inhibin-A and unconjugated estriol (uE3) is used in prenatal screening tests for chromosome abnormality, where high levels of hCG are indicative for, such as Down syndrome. However, there seems to be an important difference between milder nausea and HG. As shown in this review, the rate of adverse pregnancy outcomes seems to be reduced in women with NVP but increased in women with HG. Women with nausea might have a light increase of hCG that could indicate a well-functioning placenta. To date, this has seemingly not been studied specifically in women with NVP.

No other systematic review was found that reported the correlations for both NVP and HG, levels of hCG and pregnancy outcomes. The results of this review are important to help our understanding of the risks for adverse pregnancy outcomes in women with NVP or HG, which could contribute to a decreased morbidity and mortality for both the mother and the child. This review also highlights the need for further research in this area. It is important that future research further decreases the risk of confounders to make the results more reliable. For instance, by reporting data in women with intercurrent diseases separately. Future studies should also focus on studying HG stratified by mild and severe HG, given the results of a higher incidence of adverse pregnancy outcomes in women with severe HG.

Conclusion

The evidence of this research, although uncertain, suggests that women with HG may have an increased risk for adverse placenta-associated outcomes whilst women with NVP may have a reduced risk. Both women with NVP and HG have a high female/male fetal ratio, suggesting an interesting sexual dimorphism. The levels of hCG were found to be higher in women with HG. Further research is needed to draw grounded conclusions about any correlations. Above all, studies with lower risk of bias are needed to improve the certainty of evidence.

Supplementary Information

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Additional file 1.

Additional file 2.

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Authors' contributions
TM, SH and MB contributed to conceptualization. TM, LV, SH and MP screened studies for inclusion. TM, LV and EP assesed risk of bias. TM and MB assessed certainty of evidence. SH and MB supervised. TM wrote the original draft of the article. LV, EP, SH and MB revised the manuscript. All authors approved the final version of this article.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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