Progestogens for the prevention of preterm birth and risk of developing gestational diabetes mellitus: a meta-analysis

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BACKGROUND: Several articles have implied that progestogen supplementation during pregnancy to reduce the risk of preterm birth may increase the risk for developing gestational diabetes mellitus.

OBJECTIVE: The purpose of the present meta-analysis was to accumulate existing evidence concerning this correlation.

DATA SOURCES: We searched Medline (1966–2019), Scopus (2004–2019), Clinicaltrials.gov (2008–2019), EMBASE (1980–2019), Cochrane Central Register of Controlled Trials CENTRAL (1999–2019), and Google Scholar (2004–2019) databases.

STUDY ELIGIBILITY CRITERIA: Randomized trials and observational studies were considered eligible for inclusion in the present meta-analysis. To minimize the possibility of article losses, we avoided language, country, and date restrictions.

STUDY APPRAISAL AND SYNTHESIS METHODS: The methodological quality of included studies was evaluated with the Cochrane risk of bias and the Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool. Meta-analysis was performed with the RevMan 5.3 and secondary analysis with the Open Meta-Analyst software. Trial sequential analysis was conducted with the trial sequential analysis program.

RESULTS: Overall, 11 studies were included in the present meta-analysis that recruited 8085 women. The meta-analysis revealed that women who received 17-alpha hydroxyprogesterone caproate had increased the risk of developing gestational diabetes mellitus (risk ratio, 1.73, 95% confidence interval, 1.32–2.28), whereas women who received vaginal progesterone had a decreased risk, although the effect did not reach statistical significance because of the unstable estimate of confidence intervals (risk ratio, 0.82, 95% confidence interval, 0.50–1.12). Meta-regression analysis indicated that neither the methodological rationale for investigating the prevalence of gestational diabetes mellitus (incidence investigated as primary or secondary outcome) (coefficient of covariance, −0.36, 95% confidence interval, −0.85 to 0.13, $P = .154$) nor the type of investigated study (randomized controlled trial/observational) (coefficient of covariance −0.361, 95% confidence interval, −1.049 to 0.327, $P = .304$) significantly altered the results of the primary analysis. Trial sequential analysis suggested that the meta-analysis concerning the correlation of 17-alpha hydroxyprogesterone caproate was of adequate power to reach firm conclusions, whereas this was not confirmed in the case of vaginal progesterone.

CONCLUSION: The results of the present meta-analysis clearly indicate that women who receive supplemental 17-alpha hydroxyprogesterone caproate for the prevention of preterm birth have an increased risk of developing gestational diabetes mellitus. On the other hand, evidence concerning women treated with vaginal progesterone remains inconclusive.

Key words: caproate, diabetes, meta-analysis, preterm birth, progesterone

Gestational diabetes mellitus (GDM) is a disease that affects approximately 10% of pregnancies worldwide.[1,2] Significant variation can be observed in an international level, ranging between <1% and 28%[3]; however, the International Diabetes Federation (an umbrella organization that represents approximately 230 national diabetes association) supports that approximately 1 in 7 pregnancies is affected by some form of hyperglycemia.[4]

Various risk factors have been implicated in the pathogenesis of the disease, including obesity, excessive weight gain during current pregnancy, history of previous GDM, advanced maternal age, gestational hypertension, a history of polycystic ovarian syndrome, etc.[5–8] Its maternal and neonatal implications are of extreme importance because they extend beyond the antenatal and early postnatal pregnancy course. Specifically, GDM has been implicated in the pathogenesis of gestational hypertension and preeclampsia, intrauterine growth restriction, fetal macrosomia and intrapartum complications, and preterm birth and seems to increase the risk of developing diabetes mellitus type 2 and metabolic syndrome.[9–12]

Preterm birth (PTB), on the other hand, is a major factor that is directly

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AJOG at a Glance

Why was this study conducted?

Several studies have implied an association between progestogen supplementation and risk of developing gestational diabetes; however, consensus is still lacking in this field.

Key findings

Our meta-analysis accumulated data that indicate an association between 17-alpha hydroxyprogesterone caproate for the prevention of preterm birth and risk of developing gestational diabetes mellitus.

What does this add to what is known?

Physicians should keep in mind this information during the antenatal management of women at risk of preterm birth and enhance their vigilance in detecting gestational diabetes mellitus when prescribing 17-alpha hydroxyprogesterone caproate.

related to neonatal deaths.[13,14] Several treatment strategies have been proposed for the prevention of PTB, including cervical cerclage and the use of Arabin pessary, 17-alpha hydroxyprogesterone caproate (17OHP-C), and vaginal progesterone.[15]

According to Romero and Stanczyk,[16] 17OHP-C has no obvious effect on myometrial activity and is suggested in women with a history of preterm birth who do not have a short cervical length. On the other hand, vaginal progesterone seems to protect against cervical shortening and may also prevent cervical ripening. A recent network meta-analysis suggested that vaginal progesterone is the only intervention that consistently reduces the risk of PTB, although recent reports suggest that this may not suffice in extremely shortened cervices (cervical length <15 mm).[17−19]

Although current clinical practice supports that supplemental natural progesterone, which is administered vaginally, do not seem to be accompanied by significant adverse effects,[20] and evidence concerning the potential safety profile of 17OHP-C seems to be inconclusive.[16] Specifically, in 2002 Picard et al[21] observed in an animal experimental model that progesterone receptor knockout mice had improved glucose homeostasis, which was attributed to beta-cell proliferation.

This led Branisteanu and Mathieu[22] to suggest in 2003 that progesterone might be a causative factor of GDM. In 2007 Rebarber et al were the first to report that prophylactic 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm delivery could increase the risk of developing GDM (odds ratio, 2.9 [95% confidence interval (CI), 2.1−4.1]).[23]

Since then, several articles have been published in this field; however, to date, firm consensus regarding the actual impact of progestogen therapy for the prevention of preterm birth is lacking; hence, it remains unknown whether these patients would actually require more thorough antenatal evaluation.

The purpose of the present meta-analysis is to accumulate existing evidence in the field and provide a summary of current evidence to provide directions for current clinical practice. Moreover, parameters of heterogeneity concerning the methodological characteristics of included studies and studied population will be summarized to help researchers design future trials which will help reach firm consensus concerning the optimal management of pregnant women at risk of delivering preterm.

Materials and Methods

Study design

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and has been registered in PROSPERO (registration number CRD42019129296).[24] Eligibility criteria were predetermined by the authors.

Study selection

The electronic search was performed without applying language, country, or date restrictions to minimize the possibility of potential article losses. Retrieved studies were evaluated in 3 consecutive stages. In the first stage, we screened the titles and abstracts of deduplicated articles to evaluate their eligibility. Those that were presumed to meet the criteria for selection were retrieved as full texts. In the final stage, all observational (both prospective and retrospective) studies and randomized controlled trials (including quasi-randomized trials) that reported outcomes concerning the prevalence of gestational diabetes mellitus among women receiving 17OHP-C or vaginal progesterone for the prevention of preterm birth and compared those with women who did not receive progesterone or received placebo were selected for inclusion.

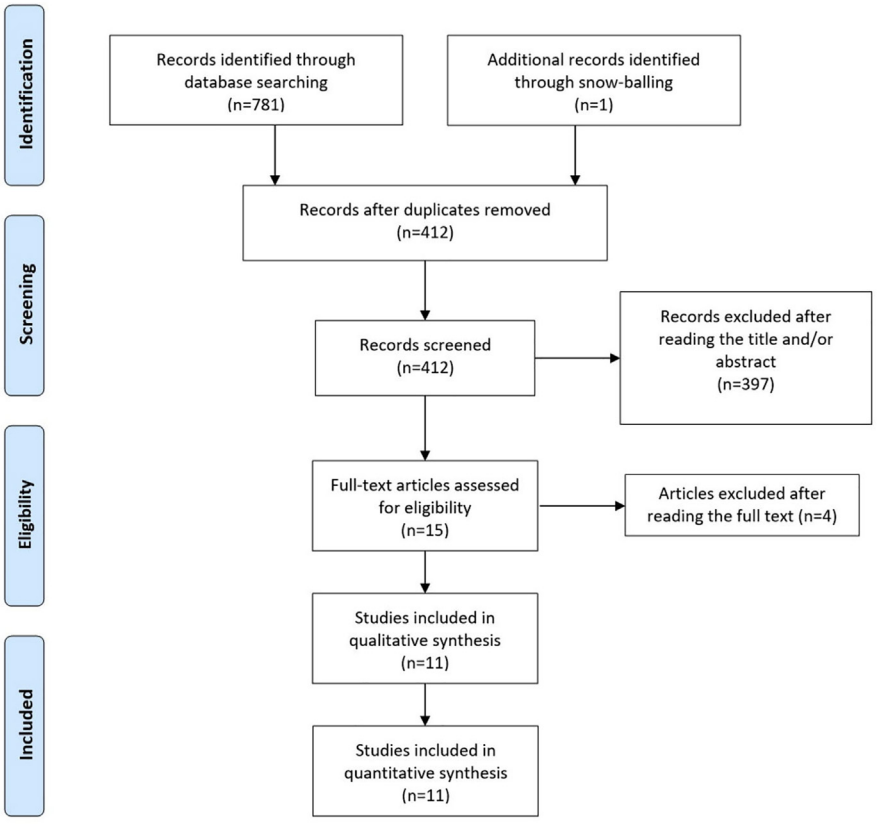
Despite the fact that some form of heterogeneity was anticipated in terms of duration of progestogen treatment prior to the diagnosis of GDM, we chose not to include a cutoff interval during the selection of studies. Conference proceedings and abstracts were also considered to be eligible, provided that the outcome of interest was available within their context. Animal studies, case reports, case series, and review articles were excluded from the present meta-analysis. When discrepancies arose between the 2 authors concerning article eligibility, assessment of the risk of bias, and selection of statistical analysis, they were resolved by the consensus of all authors.

Literature search and data extraction

We used the Medline (1966−2019), Scopus (2004−2019), Clinicaltrials.gov (2008−2019), EMBASE (1980-2019), Cochrane Central Register of Controlled Trials CENTRAL (1999−2019), and Google Scholar (2004−2019) databases in our primary search along with the reference lists of electronically retrieved full-text papers (snowballing). The date of last search was set at March 10, 2019.

The search strategy included the words progesterone, progestin, progestogen, preterm birth, short cervix, and diabetes mellitus and is schematically presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (Figure 1).

FIGURE 1
Search flow diagram



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Definitions

The definitions of the outcomes reported in the present meta-analysis varied significantly (whenever reported) and are summarized in Supplemental Tables 1 and 2.

Assessment of risk of bias

The methodological quality of included randomized controlled trials (RCTs) was evaluated by using the Cochrane risk of bias tool.[25] Two researchers independently evaluated the included studies based on the presence of possible selection (random sequence generation), detection (blinding of outcome assessment), performance (blinding of participants and personnel), attrition (incomplete outcome data), and reporting bias (selective reporting).

The quality of nonrandomized controlled studies was assessed using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[26] evaluating the possibility of bias because of confounding, selection, classification, deviation from intended intervention, missing data, measurement, and reporting of the outcomes.

Primary statistical analysis

Meta-analysis of risk ratios (RRs) among cases that received progesterone (17OHP-C or vaginal and those who did not receive treatment or received placebo) was performed with the RevMan 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011; Copenhagen, Denmark). Confidence intervals were set at 95%.

The DerSimonian-Laird random-effect model was selected to calculate the reported RRs as well as 95% CIs because of the significant heterogeneity of the methodological characteristics of included studies.[27] Subgroup analysis was conducted based on the type of administered progesterone (17-OHPC or vaginal), and substratification was also applied taking in mind the protocol for patient enrollment (prospective/retrospective).

Publication bias was evaluated for the sum of studies included in our primary analysis using funnel plots constructed with the Review manager software and the Begg and Mazumdar rank correlation as well as the Egger`s regression intercept were calculated using the regtest function in R.[28]

Secondary statistical analysis

Meta-regression analysis, sensitivity analysis and trial sequential analysis were performed to control for potential confounders that could affect the results of the primary analysis.

Meta-regression analysis

Univariate meta-regression was performed with Open Meta-Analyst statistical software.[29] We investigated the impact of the criteria used for the definition of GDM and the methodological characteristics of included studies (RCTs vs non-RCTs) (GDM as primary or secondary outcome).

Sensitivity analysis

The potential impact of individual studies on the overall outcome of the primary analysis was investigated with a leave-one-out analysis; 1 study was sequentially omitted at a time to evaluate its effect in the outcome of the meta-analysis using the Open Meta-Analyst software.

Trial sequential analysis

To evaluate the information size, we performed trial sequential analysis (TSA), which permits the investigation of the type I error in the aggregated result of meta-analyses. Repeated significance

testing increases the risk of type I error in meta-analyses, and TSA has the ability to readjust the desired significance level by using the O'Brien-Flemming a-spending function. Therefore, during TSA sequential interim analyses are performed that permit investigation of the impact of each study in the overall findings of the meta-analysis.

The risk for type I errors was set at 5% and for type II errors at 20%. The cumulative Z-curve of the meta-analysis was plotted to define sequential boundaries to assess type I and type II errors as well as the need for further trials in the field. During the analysis we also checked whether the total sample size of enrolled women reached the required information size that was needed to ensure adequate power. The TSA analysis was performed using the TSA version 0.9.5.10 Beta software (http://www.ctu.dk/tsa/).

Prediction intervals

Furthermore, prediction intervals were calculated because they provide an estimation of the effects to be expected by future studies in the field. More specifically, prediction intervals take into account the interstudy variation of the results and express the existing heterogeneity at the same scale as the examined outcome.

As proposed by IntHout et al,[30] prediction intervals are calculated in the logarithmic scale as $logRR \pm t \times SD_{PI}$, where RR represents the meta-analytic risk ratio, t the 2-sided critical t-value, and SD_{PI} the standard deviation of the prediction interval. It should be noted that t is estimated at k-1 degrees of freedom, with k indicating the number of studies included in the meta-analysis.

Calculation of SD_{PI} is performed according to the following formula: $SD_{PI} = \sqrt{\tau^2 + SE^2}$, where τ^2 represents the existing heterogeneity and SE the standard error of logRR. Exponentiation of the limits provides the prediction intervals at the RR scale. Moreover, the probability that the true effect would be on the other side of the null was estimated using the 1-tail cumulative t distribution with k-1 degrees of freedom.

Results

Overall, 11 studies were included in the present systematic review that recruited 8085 women.[23,31–40] Among them 5126 women did not receive progesterone in any form, whereas 2068 women received 17OHP-C and 891 women received vaginal progesterone. The methodological characteristics of included studies are summarized in Supplemental Table 1 and patient characteristics in Supplemental Table 2.

Four published randomized trials were identified among the included studies, and following their assessment with the Cochrane risk of bias tool, we observed that they suffered from multiple forms of bias with attrition bias being the most severe (Figure 2). The assessment of included observational studies revealed that they suffered from moderate risk of bias, which was mainly attributed to reasons of confounding (Table).

The majority of observational studies investigated the incidence of gestational diabetes as a primary outcome, whereas all but 1 randomized trial included reported it as a secondary outcome. Power analysis or sample size calculation was not provided in their methodology; thus, the adequacy of their findings is put into question.

The meta-analysis revealed that women who received 17OHP-C had an increased risk of developing gestational diabetes mellitus (RR, 1.73, 95% CI, 1.32–2.28, Figure 3), whereas the risk decreased in women who received vaginal progesterone, although the effect did not reach statistical significance because of the unstable estimate of CIs (RR, 0.82, 95% CI, 0.50–1.12, Figure 3).

We also stratified studies according to their protocol of patient enrollment (prospective [observational and randomized trials] or retrospective). In the case of 17OHP-C, the relative risk of gestational diabetes remained statistically significant both in prospective (outcome based on 4258 pregnancies, RR, 1.73, 95% CI, 1.18–2.53, $P = .005$[31,33,34,36,38]) and retrospective studies (outcome based on 1780 pregnancies, RR, 1.68, 95% CI, 1.06–2.65, $P = .03$[23,32,35]).

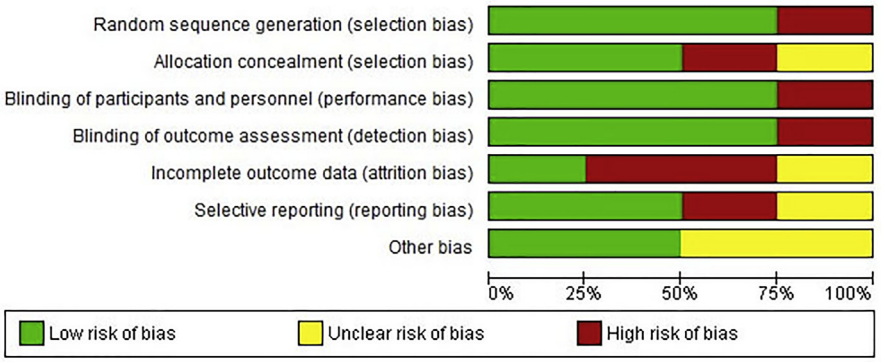
Similarly, the significance of the effect of vaginal progesterone that was observed in our primary analysis did not differentiate during the assessment of prospective (outcome based in OPPTIMUM study, RR, 0.73, 95% CI, 0.45–1.18, $P = .19$[37]) and retrospective studies (outcome based on 864 pregnancies, RR, 0.89, 95% CI, 0.59–1.36, $P = .60$[39,40]).

After evaluating the funnel plot, we observed that it was symmetrical (when accounting for the sum of studies included in the present meta-analysis) (Supplemental Figure 1). The results of the Egger`s ($t = -1.015$, $P = .337$) and Begg and Mazumdar`s test (tau $= -0.236$, $P = .359$) also supported this observation.

Leave-one-out meta-analysis revealed that individual studies included in the present meta-analysis did not influence the outcomes of the primary analysis (Supplemental Figures 2 and 3). The results of the meta-regression analysis indicated that neither the methodological rationale for investigating the prevalence of GDM (incidence investigated as primary or secondary outcome) (coefficient of covariance, −0.36, 95% CI, −0.85 to 0.13, $P = .154$) nor the type of investigated study (RCT/observational) (coefficient of covariance, −0.361, 95% CI, −1.049 to 0.327, $P = .304$) significantly altered the results of the primary analysis. The criteria used for the definition of GDM were not evaluated in the meta-regression analysis because there were no significant discrepancies among included studies (Supplemental Table 1).

Trial sequential analysis revealed that the sample size that was achieved to support the hypothesis of increased risk of gestational diabetes among women that received 17OHP-C was enough to exclude the possibility of type 1 and type 2 errors, using the cutoffs that were described in the methodology section (Supplemental Figure 4). On the other hand, the available data were not sufficient to reach definitive conclusions in

FIGURE 2
Methodological quality of randomized controlled trials



The methodological quality of randomized controlled trials according to the Cochrane risk of bias tool is shown.

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the field of vaginally administered progesterone (Supplemental Figure 5).

Prediction intervals ranged from 0.90 to 3.35 for the 17OHP-C outcome and from 0.41 to 1.61 for vaginal progesterone. Moreover, regarding 17OHP-C, the probability that the true RR in a new study would be less than or equal to 1 was calculated to be 4.6%, while in the case of vaginal progesterone, the probability that the true RR would be ≤ 1 was equal to 83%. The latter finding suggests that future studies might designate vaginal progesterone as a protective factor against GDM.

Comment

Principal findings and pathophysiological background

The findings of this meta-analysis suggest that treatment with 17OHP-C is a factor that nearly doubles the risk of developing GDM. The result is mainly attributed to the findings of the larger studies included in our analysis,[23,32,35,38] whereas differences among treated women and controls were vague in smaller studies.[31,33,34,36] Nevertheless, this finding is of adequate power according to the results of the sequential analysis that we performed and can thus

TABLE
Methodological quality of nonrandomized trials according to the ROBINS-I tool

Author, year	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Rosta and Ott, 2018[39]	a	a	b	b	b	b	b	b
Zipori et al, 2018[40]	a	a	b	b	b	b	b	b
Nelson et al, 2017[38]	a	a	b	b	a	b	b	a
Egerman et al, 2014[35]	Obesity[c]	a	b	b	b	b	b	a
Wolfe et al, 2011[33]	PreGDM[c]	a	b	b	b	b	b	a
Waters et al, 2009[32]	PreGDM[c]	a	b	b	b	b	b	a
Rebarber et al, 2007[23]	PreGDM[c]	a	b	b	b	b	b	a

Serious possibility of bias was recorded when the following were present: preGDM, patient history of gestational diabetes mellitus; obesity, population was unanimously obese. Bias in selection bias is unanimously recorded[a] because controls were not stated as a consecutive series of patients who were managed during the same period as patients receiving progesterone. ROBINS-I, Risk Of Bias In Nonrandomized Studies of Interventions tool.

[a] Indicates moderate possibility of bias; [b] Indicates low possibility of bias; [c] Indicates serious possibility of bias.

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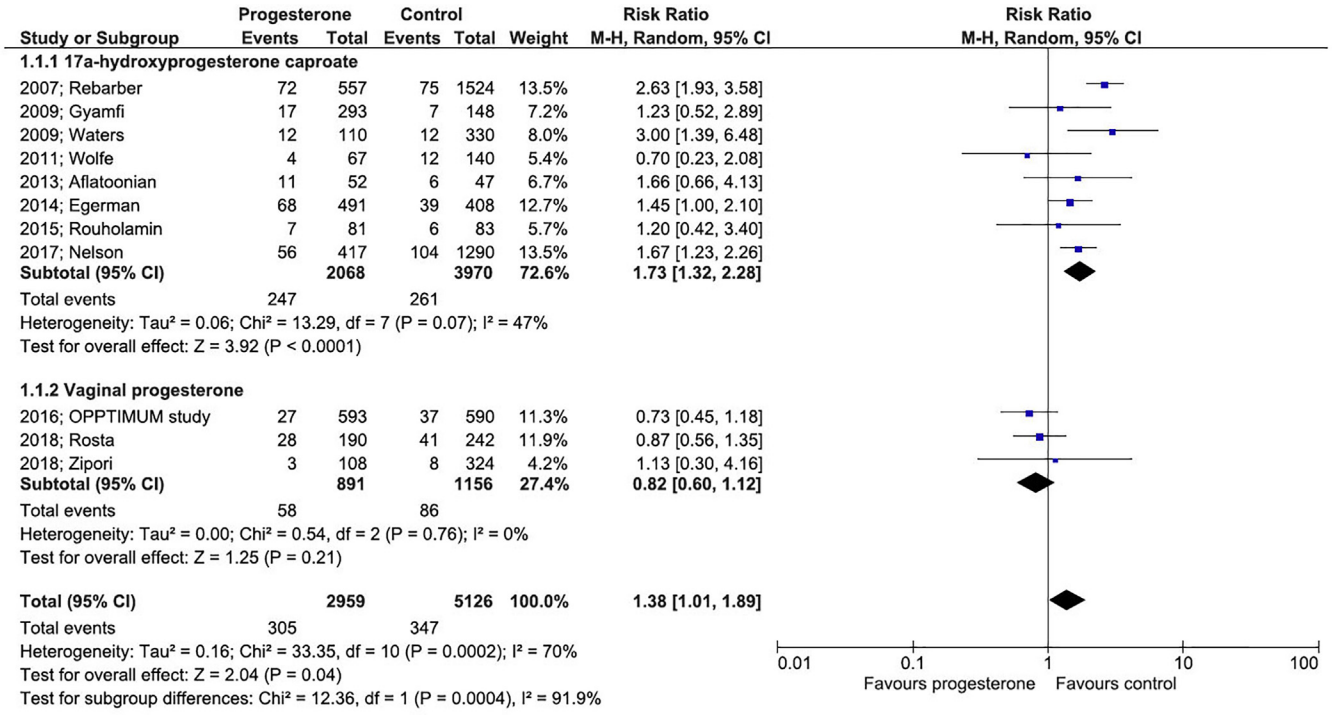
FIGURE 3
Forest plot diagram of primary analysis



Odds ratio was significantly increased among patients receiving 17-alpha hydroxyprogesterone caproate.

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be used for guidance in current clinical practice.

On the other hand, evidence in the field of vaginal progesterone does not suffice to reach firm conclusions because the number of included studies and enrolled patients has not reached the required sample size (an effect that explains the unstable estimate of CIs). The result, however, is of particular interest because it indicates that women treated with vaginal progesterone may have a decreased risk of developing GDM. Predictive interval analysis concerning this latter observation is, after all, very promising. Nevertheless, the actual pathophysiology behind this observation remains, to date, unknown.

Several factors may influence the association between 17OHP-C treatment and risk of developing GDM including maternal obesity, excessive weight gain during pregnancy, a family history of diabetes mellitus, a personal history of polycystic ovarian syndrome, etc.

To date, however, the actual impact of these confounders in the examined correlation of antenatal 17OHP-C supplementation with GDM remains relatively unexplored. Only Egerman et al[35] evaluated some of these parameters and observed that the risk increases the earlier the initiation of 17OHP-C is established (odds ratio, 1.59 when administered before the 21st week of gestation). In the same study, the authors reported that advanced maternal age (>35 years) was an independent factor that doubled the odds (odds ratio, 2.11).

Pathophysiologically, several articles have implicated progesterone to the development of insulin resistance during the antenatal period.[41] Specifically, progesterone seems to enhance appetite during pregnancy by increasing the hypothalamic expression of neuropeptide Y and agouti-related peptide.[42] Moreover, it is implicated in induced apoptosis of insulin-secreting cells and in altered signaling in 3T3-L1 adipocytes.[43,44]

This effect is evident after midgestation when growth hormone, free cortisol, and tumore necrosis factor−alpha levels increase and serum adiponectin decreases.[42] On the contrary, during early pregnancy, growth hormone levels are relatively low, thus increasing insulin sensitivity and promoting fat storage, which is essential for the growing fetus.[42] Therefore, progesterone supplementation is expected to alter the glycemic profile only when pregnancy has advanced beyond the first trimester.

Differences observed between 17OHP-C and vaginal progesterone in the present meta-analysis were anticipated, given their chemical, biological, and pharmacological differences, which have been already summarized by Romero et al in 2013.[16] Specifically, following 17OHP-C supplementation, its plasma levels rise and this effect becomes more evident as pregnancy advances (possibly because of increased inhibition of CYP3A4).[45] On the other

hand, vaginal progesterone results in a rapid and increased endometrial tissue concentration, which is combined with decreased systemic exposure when it is compared with intramuscularly administered regimens.[46]

Strengths and limitations

The present meta-analysis is based on a meticulous review of a wide range of databases. The search strategy was not restricted by language and date criteria; hence, limiting the possibility of potential article losses that could significantly alter our findings. Given the differences in methodological characteristics of included studies and studied population, several factors could have influenced the meta-analysis results. However, we tried to overcome these barriers by implementing several secondary analyses that partially diminish the possibility of heterogeneity bias. Lastly, although most of the studies that were included in the present meta-analysis based their findings on the 100 g, 3-hour oral glucose tolerance test to define GDM,[47] the criteria were not accurately stated in 4 studies.[23,34,35,37]

Clinical implications

Professional bodies recommend 17OHP-C as a preventive measure of spontaneous preterm birth in women with a prior history of preterm birth of a singleton pregnancy.[48] The findings of our meta-analysis indicate that clinicians should consider increasing their vigilance in detecting GDM when prescribing 17OHP-C. Moreover, it would be prudent to reconsider 17OHP-C as an option in specific populations such as obese women, women who gained excessive weight during the antenatal period, women with a family history of diabetes, and women with a history of polycystic ovarian syndrome.

Implications for future research

The results of this study suggest that further studies are needed to elucidate whether vaginal progesterone could contribute to the development of GDM. However, we believe that this is highly unlikely, given the existing evidence concerning its pharmacokinetics in nonpregnant women.[46] Moreover, it remains unclear whether 17OHP-C actually alters insulin levels; hence, it would be prudent to evaluate them during the oral glucose tolerance test and compare them with those of women who did not receive treatment.

An interesting finding of our review is the actual prevalence of GDM among studies included, which seems to be lower compared with that suggested by the International Diabetes Federation.[4] This might be explained by regional differences in the prevalence of hyperglycemia in pregnancy, and future studies should evaluate the impact of 17OHP-C in the various populations.

Taking this information into consideration, it seems prudent to evaluate in future studies the parameters that could potentially influence insulin resistance among women receiving 17OHP-C, which should, at least, include prepregnancy body mass index, pregnancy weight gain, a family history of diabetes mellitus, a personal history of polycystic ovarian syndrome, country of origin, and smoking habits.

Another factor that requires further investigation is to evaluate whether the incidence of GDM varies substantially among patients receiving progesterone supplementation when implementing the 1-step, 75 g, 2-hour oral glucose tolerance test as a screening tool.[47]

Conclusion

The results of the present meta-analysis clearly indicate that women who receive supplemental 17OHP-C for the prevention of preterm birth have an increased risk of developing gestational diabetes mellitus. On the other hand, evidence concerning women treated with vaginal progesterone is still inconclusive. Physicians should keep in mind this information during the antenatal management of women at risk of preterm birth, and if they decide to treat them with 17OHP-C, they should enhance their vigilance in detecting GDM. Further studies are needed to evaluate which factors enhance this correlation and thus help determine which women should be discouraged to undergo treatment with 17OHP-C.

Ethics statement

The present systematic review is based on outcomes already published from previous trials in the field. The study is based on aggregated patient data and no institutional review board approval was required. ■

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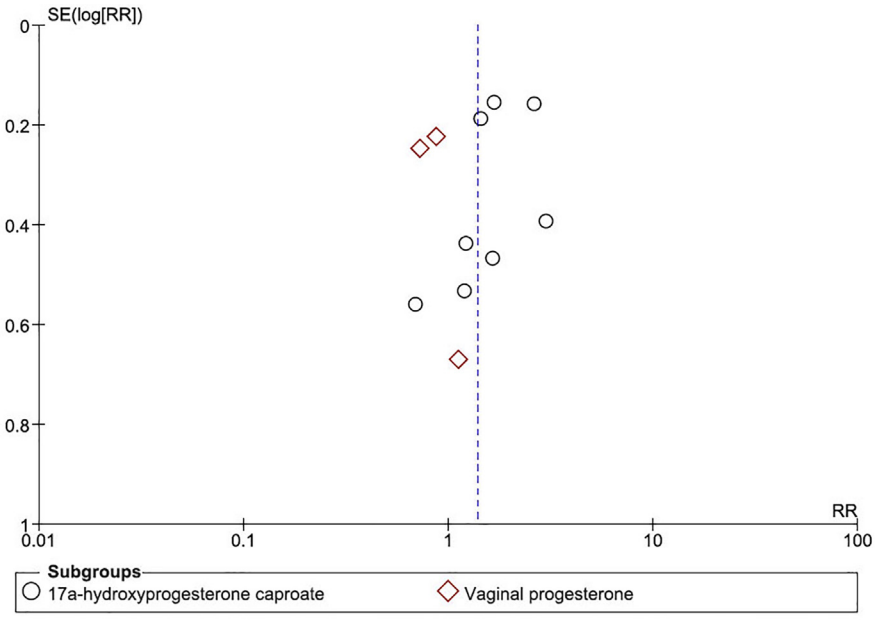
SUPPLEMENTARY FIGURE 1
Funnel plot of the primary analysis



Black circles refer to 17OHPC studies, and *red diamonds* refer to vaginal progesterone studies.

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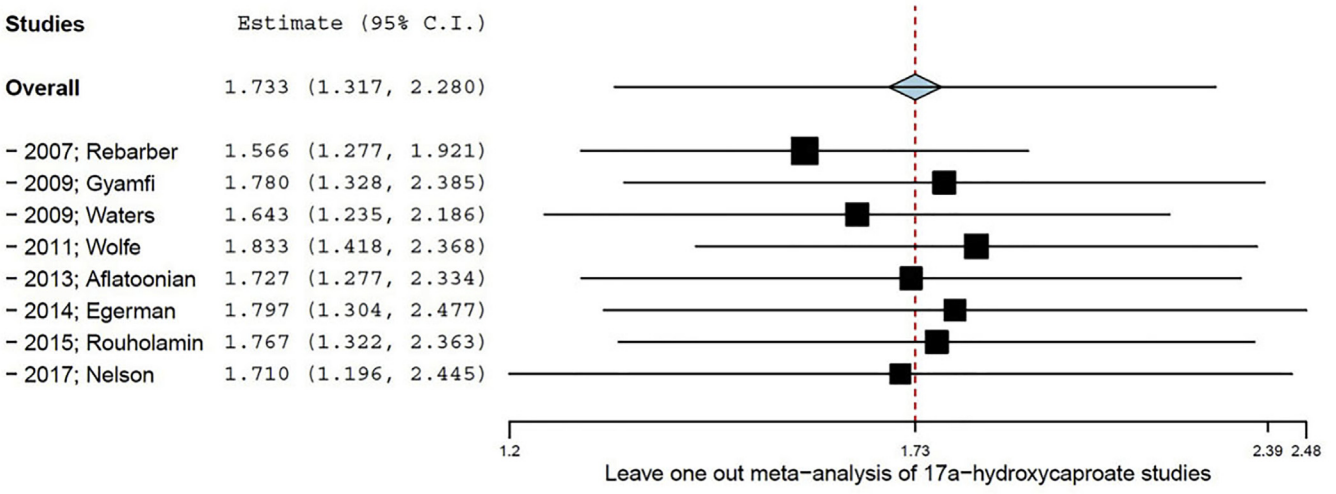
SUPPLEMENTARY FIGURE 2
Leave one out meta-analysis for 17OHPC studies



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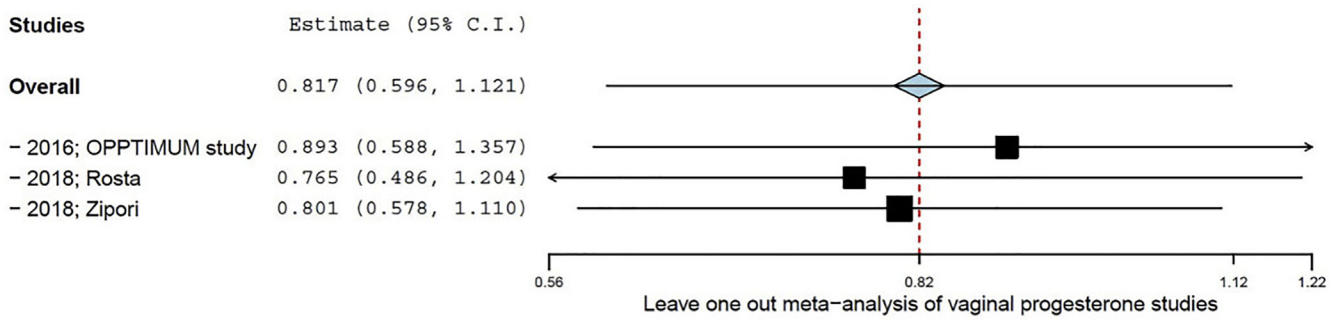
SUPPLEMENTARY FIGURE 3
Leave one out meta-analysis for vaginal progesterone studies



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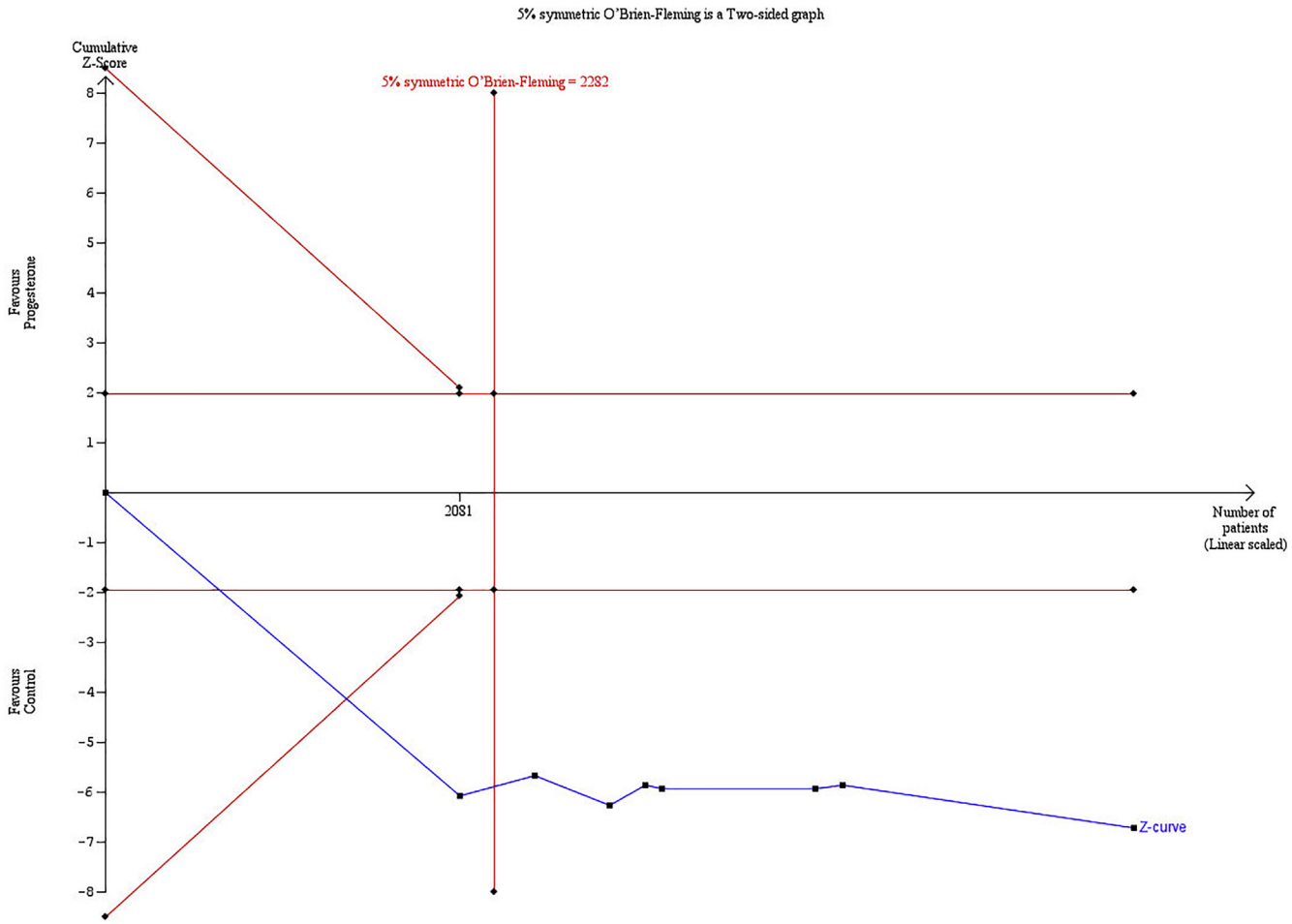
SUPPLEMENTARY FIGURE 4
Trial sequential analysis for 17OHPC studies



Vertical line refers to the 5% symmetric O'Brien-Flemming value that was expected to suffice for the meta-analysis to reach statistical significance.

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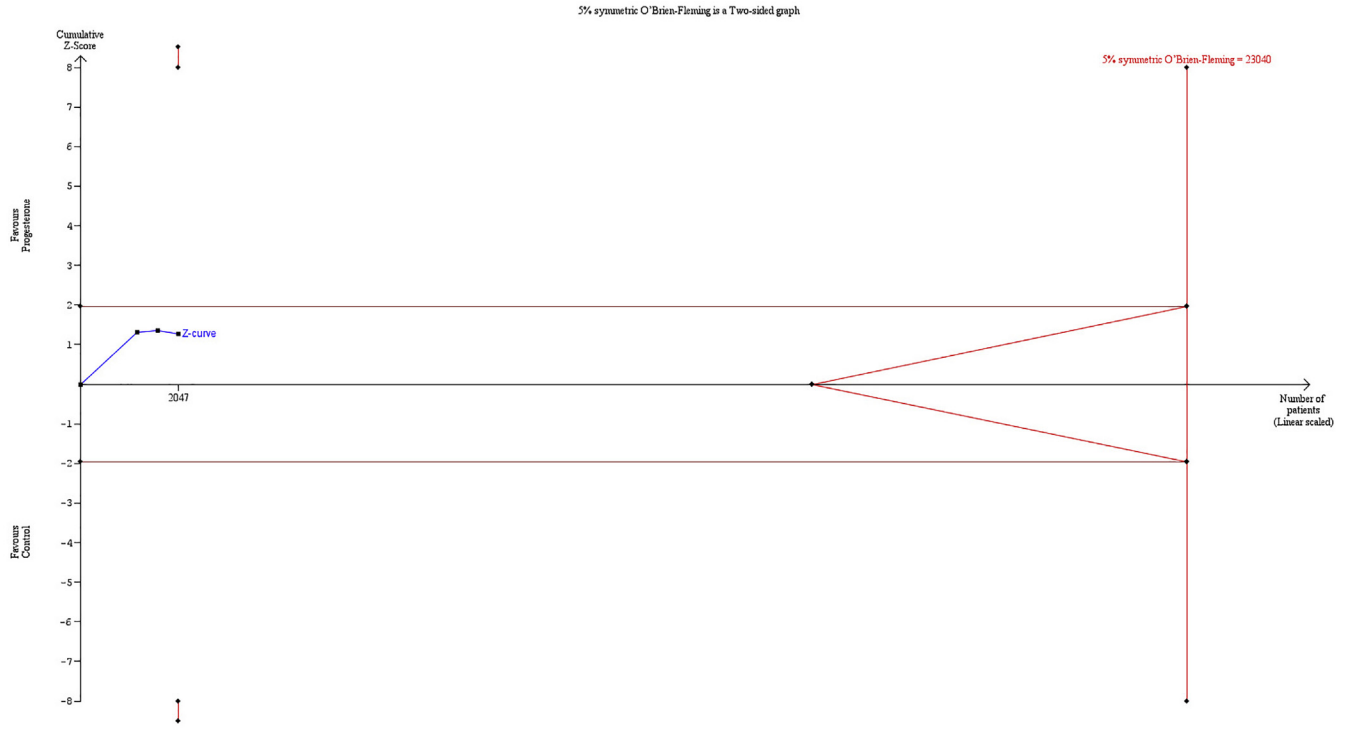
SUPPLEMENTARY FIGURE 5
Trial sequential analysis for vaginal progesterone studies



Vertical line refers to the 5% symmetric O'Brien-Flemming value that was expected to suffice for the meta-analysis to reach statistical significance.

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SUPPLEMENTAL TABLE 1

Methodological characteristics of included studies

Author, year	Study type	Patients, n	Type of progestin	GDM outcome (primary or secondary outcome)	Definition of GDM	Exclusion criteria
Rosta and Ott, 2018[39]	Case-control	190 vs 242	Vaginal progesterone (200 mg)	Primary	100 g, 3 h OGTT	Preexistent DM, multiple pregnancy; delivery <28 weeks, prepregnancy BMI >37 kg/m^2
Zipori et al, 2018[40]	Case-control	108 vs 324	Vaginal progesterone (200 mg)	Primary	50 g, 1 h GCT (>200 mg/dl) or 100 g, 3 h OGTT	Preexisting DM, multiple pregnancy, intramuscular 17OHP-C administration due to obstetric history, cervical cerclage, beta-blocker use, corticosteroid administration, any fetal malformation
Nelson et al, 2017[38]	Prospective cohort	417 vs 1290	Intramuscular 17OHP-C (250 mg)	Secondary	100 g, 3 h OGTT	Prior medically indicated preterm birth, delivery <20 weeks
Norman et al, 2016[37]	RCT	593 vs 590	Vaginal progesterone (200 mg)	Secondary	Not stated	Age <16 years, multiple pregnancy, any structural/chromosomal fetal malformation, rupture of fetal membranes at recruitment, any drug intake interacting with progesterone
Rouholamin et al, 2015[36]	RCT	81 vs 83	Intramuscular 17OHP-C (250 mg)	Primary	100 g, 3 h OGTT	Age <16 years, history of GDM/preeclampsia, family history of GDM, chronic hypertension, aspirin intake, BMI >30 kg/ m^2, delivery <28 weeks, abnormal OGTT at recruitment
Egerman et al, 2014[35]	Retrospective cohort	491 vs 408	Intramuscular 17OHP-C (250 mg)	Primary	Not stated[a]	Preexisting DM, multiple pregnancy, BMI <30 kg/ m^2, GDM at recruitment, delivery ≤28 weeks
Aflatoonian et al, 2014[34]	RCT	52 vs 47	Intramuscular 17OHP-C (250 mg)	Secondary	Not stated	Preexisting DM, multiple pregnancy, chronic hypertension, any thyroid disease, any uterine abnormality, history of preterm labor or previous abortion
Wolfe et al, 2011[33]	Prospective cohort	67 vs 140	Intramuscular 17OHP-C (250 mg)	Secondary	50 g, 1 h GCT (>200 mg/dL) or 100 g, 3 h OGTT	Age <18 or >50 years, preexisting DM, multiple pregnancy, any fetal malformation, any placental abnormality, prior medically indicated preterm birth
Waters et al, 2009[32]	Retrospective cohort	110 vs. 330	Intramuscular 17OHP-C (250 mg)	Primary	50 g, 1 h GCT (>200 mg/dL) or 100 g, 3 h OGTT	Preexisting DM, multiple pregnancy
Gyamfi et al, 2009[31]	RCT	293 vs. 148	Intramuscular 17OHP-C (250 mg)	Secondary	100 g, 3 h OGTT[b]	Preexisting DM, multiple pregnancy
Rebarber et al, 2007[23]	Retrospective cohort	557 vs. 1524	Intramuscular 17OHP-C (250 mg)	Primary	Not stated[a]	Preexisting DM, multiple pregnancy, recurrent preterm delivery <28 weeks in current pregnancy

BMI, body mass index; *DM*, diabetes mellitus; *GCT*, glucose challenge test; *GDM*, gestational diabetes mellitus; *OGTT*, oral glucose tolerance test, *17OHP-C*, 17α-hydroxyprogesterone caproate; *RCT*, randomized controlled trial.

[a] Screening method was not stated, but cases were included following a complete pregnancy outcome interview and documentation of GDM diagnosis recorded as a yes or no in the database; [b] Data were recorded as a yes or no in the database (results of the 100 g, 3 h OGTT were not reviewed for verification).

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SUPPLEMENTAL TABLE 2
Characteristics of enrolled patients

Author, year	Maternal age	Prepregnancy BMI	Start of management	Ultrasound/ history indicated	History of GDM	Smoking	Beta-mimetic tocolysis	Corticosteroid
Rosta and Ott, 2018[39]	31.46 ± 5.91 vs 31.22 ± 5.51	24.0 ± 4.72 vs 24.16 ± 4.28	16–24 weeks	Ultrasound or history indicated	24 vs 43	NR	NR	93 vs 57[a]
Zipori et al, 2018[40]	31.2 ± 5.5 vs 30.5 ± 4.7	28.9 ± 5.7 vs 28.0 ± 4.7	16–20 weeks	Ultrasound indicated	3 vs 8	NR	NR	—
Nelson et al, 2017[38]	NR	NR	16–20 weeks	History indicated	NR	NR	NR	NR
Norman et al, 2016[37]	31.5 ± 5.6 vs 31.4 ± 5.8	26.9 ± 6.4 vs 26.7 ± 6.1	22–24	Ultrasound or history indicated	NR	111 vs 125	NR	80 vs 71
Rouholamin et al, 2015[36]	26.4 ± 4.5 vs 27.2 ± 4.1	25.8 ± 4.4 vs 25.1 ± 3.3	16–20 weeks	History indicated	—	NR	NR	NR
Egerman et al, 2014[35]	NR	NR	16–24 weeks	NR	—	NR	88 vs 102[a]	NR
Aflatoonian et al, 2014[34]	30.32 ± 4.5 vs 29.06 ± 4.94	NR	16th week	ART	—	NR	NR	NR
Wolfe et al, 2011[33]	26.9 ± 6 vs 26.8 ± 5.0	28.6 ± 9.1 vs 28.8 ± 8.6	16–26 weeks	History indicated	2 vs 11	NR	NR	8 vs 27
Waters et al, 2009[32]	27.3 ± 5.6 vs 27.3 ± 5.6	28.8 ± 8.4 vs 28.6 ± 7.6	NR	History indicated	NR	NR	NR	NR
Gyamfi et al, 2009[31]	25.9 ± 5.6 vs 26.4 ± 5.4	26.7 ± 7.9 vs 25.8 ± 6.9	16–20 weeks	History indicated	NR	67 vs 28	NR	NR
Rebarber et al, 2007[23]	29 (16–44) vs 30 (16–45)	26.2 ± 6.6 vs 26.2 ± 6.7	16–20 weeks	History indicated	—	54 vs 87[a]	101 vs 375[a]	NR

ART, assisted reproductive technology; *BMI*, body mass index; *GDM*, gestational diabetes mellitus; *NR*, not reported.

[a] $P < .05$.

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