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REVIEW

Insulin Use During Gestational and Pre-existing Diabetes in Pregnancy: A Systematic Review of Study Design

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ABSTRACT

***Introduction*:** Insulin is the first-line pharmacologic therapy for women with diabetes in pregnancy. However, conducting well-designed randomized clinical trials (RCTs) and achieving recommended glycemic targets remains a challenge for this unique population. This systematic literature review (SLR) aimed to understand the evidence for insulin use in pregnancy and the outcome metrics most often used to characterize its effect on glycemic, maternal and fetal outcomes in gestational diabetes mellitus (GDM) and in pregnant women with diabetes.

***Methods*:** An SLR was conducted using electronic databases in Medline, EMBASE via Ovid platform, evidence-based medicine reviews (2010–2020) and conference proceedings (2018–2019). Studies were included if they assessed the effect of insulin treatment on glycemic, maternal or fetal outcomes in women with diabetes in pregnancy. Studies on any type of diabetes other than gestational or pre-existing diabetes as well as non-human studies were excluded.

***Results*:** In women diagnosed with GDM or pre-existing diabetes, most studies compared treatment of insulin with metformin ($n=35$) followed by diet along with lifestyle intervention ($n=24$) and glibenclamide ($n=12$). Most studies reporting on glycemic outcomes compared insulin with metformin ($n=22$) and glibenclamide ($n=4$). Fasting blood glucose was the most reported clinical outcome of interest. Among the studies reporting maternal outcomes, method of delivery and delivery complications were most commonly reported. Large for gestational age, stillbirth and perinatal mortality were the most common fetal outcomes reported.

***Conclusion*:** This SLR included a total of 108 clinical trials and observational studies with diverse populations and treatment arms. Outcomes varied across the studies, and a lack of consistent outcome measures to manage diabetes in pregnant women was observed. This

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elucidates a need for global consensus on study design and standardized clinical, maternal and fetal outcomes metrics.

Keywords: Gestational diabetes mellitus; Insulin use in pregnancy; Pregnancy; Systematic review; Type 1 diabetes mellitus; Type 2 diabetes mellitus

Key Summary Points

Why carry out this study?

The prevalence of diabetes during pregnancy has increased in recent years, and many women with this complication require insulin during their pregnancy. Despite this, there remains a paucity of well-designed clinical trials targeting insulin use in this unique population

This systematic literature review aimed to assess and summarize the current body of evidence for insulin use in pregnant women with gestational or pre-existing diabetes and its effects on clinical, maternal and fetal outcomes

What was learned from the study?

This SLR included a total of 108 unique studies, both clinical and observational, and the most commonly reported outcomes were fasting blood glucose, method of delivery and large for gestational age

Overall, the results of this review revealed that the outcomes evaluated in studies investigating the use of insulin as a treatment option for pregnant women with diabetes varied widely across the included studies, illustrating the need for standardization of study design and outcome metrics

INTRODUCTION

Diabetes is the most prevalent antenatal complication of pregnancy and can be subdivided into two types: pregestational and gestational diabetes mellitus (GDM) [1]. The prevalence of diabetes in pregnancy has been increasing in the USA [2]. About 1–2% of pregnant women have pre-existing diabetes, and approximately 1–14% of all pregnancies are affected by GDM [3, 4]. Women diagnosed with diabetes during pregnancy are at an increased risk to develop other maternal complications such as gestational hypertension, preeclampsia and hypoglycemia, which subsequently can lead to the development of type 2 diabetes (T2D) later in life [3]. They are also at a higher risk to undergo cesarean section or have premature delivery. In addition, diabetes in pregnancy is associated with a risk of developing fetal complications such as macrosomia and neonates with large for gestational age (LGA), small for gestational age, premature birth, neonatal respiratory distress, asphyxia, neonatal hypoglycemia and congenital anomalies [5, 6].

The recommendations from current standard of care of diabetes management in pregnant women are beyond regular blood glucose level monitoring, lifestyle behavioral changes, medical nutrition therapy (MNT), physical exercise and pharmacotherapy (metformin, glyburide or insulin) [7]. Insulin is considered the most efficacious pharmacotherapy for all types of diabetes in pregnancy, including GDM and pregestational diabetes [8]. The 2023 update of the the American Diabetes Association (ADA) guidelines, The American College of Obstetricians and Gynecologists-2018 (ACOG-2018) and International Diabetes Federation (IDF) guidelines recommend use of insulin as a first-line pharmacological therapy for management of pre-existing diabetes and GDM over other oral anti-diabetic agents [9–12].

Recent advances in insulin therapy are focused on improving the pharmacokinetics and pharmacodynamics of insulin. These goals enable prolonged profile of action, flexible dosing regimen and reduce the risk of hypoglycemia [13]. However, well-powered randomized clinical trials (RCTs) in pregnant women with diabetes are often conducted well after non-pregnant populations, if it is done at all, which leads to delayed implementation of evidence-based practices for insulin use in pregnancy. In addition, designing studies to demonstrate the

achievement of stringent glycemic targets as recommended by the guidelines remains challenging for this unique population [14]. A variety of insulins have been commercially available globally, many of which have limited data on their use in pregnancy. Real-world barriers such as access to insulin or newer insulins, access to glucose monitoring and delayed prenatal care can further make adhering to guidelines difficult, if not impossible. Considering the different insulin options available in the global market and understanding the use and effects of types of insulin and/or insulin regimens on glycemic, maternal and fetal outcomes may support clinical practice. This may as well aid in improving study designs for treatment of diabetes in pregnancy. Therefore, to assess and evaluate the current body of evidence including RCTs and real-world observational data, we performed a systematic literature review (SLR) to better understand and summarize the evidence for insulin use in pregnancy to harmonize future study design in this special population.

METHODS

Study Design

Search Strategy

A comprehensive search was conducted to identify relevant studies using electronic databases in Medline, EMBASE via Ovid platform and evidence-based medicine reviews from 1 January 2010 to 25 August 2020. In addition, manual (hand) searches were performed for relevant conference abstracts that were published from 2018 to 2019.

Inclusion and Exclusion Criteria

The eligibility for assessing the relevance of each article for data extraction was based on the population, intervention, comparison, outcomes and study design (PICOS) criteria (Supplementary Table 1). Inclusion criteria for the selection of articles consisted of studies that were RCTs, non-RCTs and observational studies (Supplementary Table 1). Studies were included with perinatal women diagnosed with either gestational, pre-existing diabetes (type 1 diabetes [T1D] or type 2 diabetes [T2D]) or mixed population (pregnant women with GDM, T1D or T2D). Specific glycemic (fasting blood glucose [FBG], post prandial glucose [PPG] and time in range), maternal (prevalence of hypoglycemia, cesarean section, preterm labor, hypertension, induced labor and preterm delivery) and fetal (fetal mortality, fetal morbidity and LGA) outcomes were included in this review (Supplementary Table 1). Studies on any type of diabetes other than gestational diabetes or pre-existing T1D or T2D as well as non-human studies were excluded.

Study Selection and Data Extraction

The DistillerSR tool, a cloud-based literature review software, was used to screen, compile and manage all the identified studies. Two independent reviewers screened the identified studies based on their titles and abstracts against the eligibility criteria. Subsequently, full-text articles were retrieved for full-text screening against eligibility criteria. A third, independent reviewer resolved any uncertainties/conflicts between the two reviewers. The reasons for exclusion are reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Fig. 1). DistillerSR was used to extract data from the included studies. Details of study characteristics, patient characteristics, interventions and outcomes of interest were extracted in the data extraction form. Studies with multiple publications were identified and linked to the primary study; all relevant data were extracted under the primary study. Identification and screening of the available literature was performed in accordance with PRISMA statement [15], the Centre for Reviews and Dissemination [16] and the Cochrane Collaboration [17].

Quality Assessment

The quality of the included RCTs was assessed using the quality assessment checklist, in accordance with the recommendations by the Centre for Reviews and Dissemination's

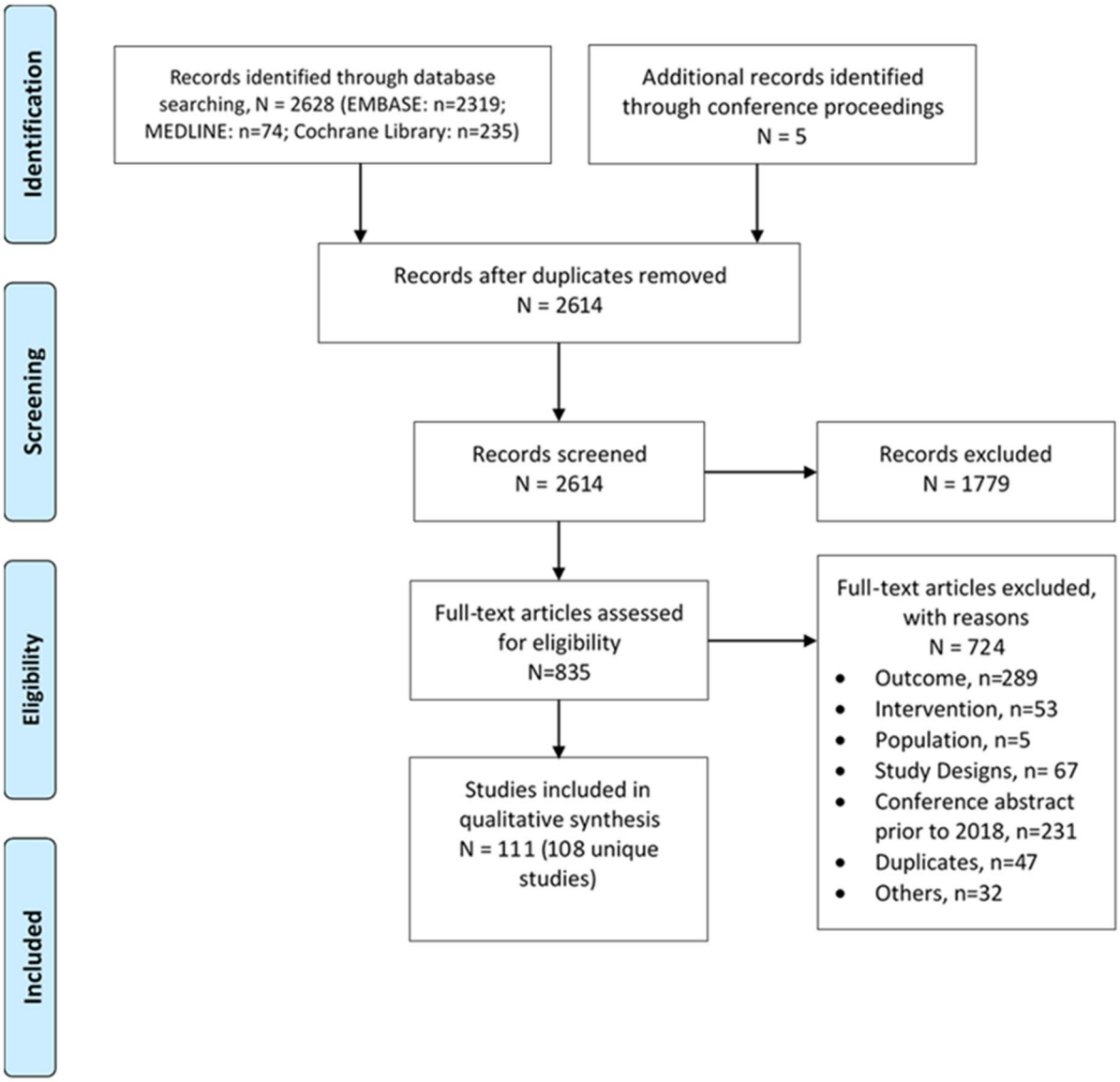

Fig. 1 PRISMA flow diagram presenting number of studies included and excluded at each stage of screening

Guidance for Undertaking Reviews in Health Care (NICE, 2019) [18]. The quality of observational studies was assessed using the Newcastle-Ottawa Scale, 2019 [19]. Three factors were considered to score the quality of included observational studies: selection, comparability and outcomes assessment.

Ethical Approval

This article is based on previously conducted studies and does not contain any studies with human participants or animals.

RESULTS

Study Selection

A total of 2628 citations were retrieved after initial search through electronic databases and conference proceedings (Fig. 1). After removing duplicates, 2614 articles were assessed for title-abstract screening. Subsequently, 835 articles were assessed for full-text screening. Overall, 724 records were excluded, and 111 publications, representing 108 unique studies were included in the SLR (Fig. 1).

Study and Patient Characteristics

Of the total 108 included studies, 30 were clinical trials, 74 were observational studies, and 1 was a quasi-experimental study. In three studies the study designs were not clear. The RCTs and observational studies included in this review covered perinatal women across different continents, like America, Europe, Asia, Oceania, Africa and/or multinational.

Details on patient characteristics including maternal age, gestational weight, gestational age at diagnosis and treatment initiation and relevant obstetrical history are given in Tables 1 and 2. Study characteristics are summarized in Supplementary Table 2 and 3, and treatment interventions along with types of insulin utilized by the women diagnosed with GDM or pre-existing diabetes are summarized in Supplementary Tables 4 and 5.

Glycemic Outcomes in People with GDM and Pre-existing Diabetes

Of the 108 included studies, 21 clinical trials and 20 observational studies reported the clinical outcomes of interest (FBG, PPG, glycemic range and glycemic variability) in women with GDM (Table 3). Six clinical trials and 12 observational studies reported the clinical outcomes of interest in women with pre-existing diabetes and mixed population (Table 4).

Evidence from Clinical Trials

In women diagnosed with GDM, majority of the trials compared an insulin regimen [basal only, basal/bolus, or bolus only] to metformin ($n=13$) (Table 3). In addition, few trials compared insulin to glibenclamide/glyburide ($n=3$), (Table 3). The difference in the glycemic outcomes in women treated with insulin versus other therapies varied across the trials and provided very low-quality of evidence for the outcomes. The study design varied widely across the trials.

FBG was the most reported clinical outcome ($n=22$). Some RCTs ($n=3$) reported a significantly better ($p\leq0.01$) FBG in the metformin-treated group compared to those with insulin [20–22]. Two RCTs by Zawiejska et al. and Khan et al. compared glycemic control in women diagnosed with GDM in response to insulin and metformin and reported significantly better FBG in the insulin-treated groups compared to other therapies ($p\leq0.01$) [23, 24]. Arshad et al. compared insulin with diet therapy and exercise and reported a significantly better FBG in the diet-treated group compared to those treated with insulin [25].

In an RCT by Somani et al. with no differences in glycemic outcomes between the metformin and insulin groups at baseline, higher PPG levels were reported in group treated with insulin compared to those treated with metformin ($p=0.005$) [26]. In an RCT by Ji et al. with mixed population, a significant improvement in PPG and time in range (TIR) was observed with insulin detemir compared to insulin neutral protamine Hagedorn (NPH) ($p<0.001$) [27].

Evidence from Observational Studies

In women with GDM, most observational studies that reported clinical outcomes of interest compared insulin to diet/MNT ($n=6$), metformin ($n=5$), combination of metformin and/or diet and/or lifestyle interventions ($n=4$). Additionally, other studies reported a comparison between different types of insulin ($n=3$), insulin versus no insulin ($n=1$) and insulin versus glyburide ($n=1$) (Table 3). Five studies showed significant improvement in FBG and PPG among

Table 1 Patient characteristics of randomized controlled trials in women with gestational diabetes mellitus and pre-existing diabetes

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
GDM											
Galal_2019 [20]	Human insulin	50	32.82 ± 3.02	NR	30.52 ± 2.49	NR	NR	30.8 ± 2.22	NR	NR	NR
	Metformin	56	31.98 ± 3.49	NR	30.74 ± 2.41	NR	NR	30.64 ± 2.06	NR	NR	NR
Wasim_2019 [21]	Insulin-Humulin R and NPH	141	29.7 ± 4.8	NR	27.1 ± 5.3	NR	NR	28.6 ± 3.1	NR	NR	NR
	Metformin	137	29.5 ± 4.8	NR	26.5 ± 5.1	NR	NR	28.9 ± 2.9	NR	NR	NR
Das_2018 [66]	Insulin	41	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin	40	NR	NR	NR	NR	NR	NR	NR	NR	NR
Eid_2018 [34]	Insulin	116	30.4 ± 3.5	76.8 ± 11.2	30.5 ± 4.2	NR	NR	28.1 ± 3.1	NR	NR	NR
	Metformin	113	31.6 ± 3.6	75.9 ± 8.7	29.44 ± 4.53	NR	NR	27.4 ± 3.9	NR	NR	NR
Ghomian_2018 [33]	Levemir (insulin detemir) + aspart	143	28.41 ± 6.36	NR	24.0 ± 2.10	NR	NR	25.10 ± 1.05	History of GDM: 29 (20%)	NR	NR
	Metformin	143	28.30 ± 5.25, $p = 0.87$	NR	23.73 ± 1.87, $p = 0.25$	NR	NR	24.80 ± 1.45, $p = 0.39$	History of GDM: 34 (24%)	NR	NR
Huhtala_2018 [43]	NPH insulin and/or rapid-acting insulin lispro or insulin aspart	107	32.0 ± 5.47	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin	109	31.9 ± 5.01; $p = 0.89$ vs. insulin	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	103	30.6 ± 5.05	NR	NR	NR	NR	NR	NR	NR	NR
Senat_2018 [54]	Insulin	442	32.6 ± 5.3	NR	31.1 ± 5.4	NR	NR	Median (IQR): 26 + 3 (25 + 1 to 28 + 0)	Previous GDM: 88 (19.9%)	Median (IQR): 32 + 3 (30 + 3 to 34 + 1)	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Glyburide	367	32.5 ± 5.1	NR	30.7 ± 5.1	NR	NR	Median (IQR): 26 + 5 (25 + 3 to 28 + 0)	Previous GDM: 73 (20.0%)	Median (IQR): 32 + 6 (30 + 6 to 34 + 3)	NR
Hamadani_2017 [35]	Insulin NPH	30	29.63 ± 3.81	58.10 ± 5.01	23.43 ± 5.06	NR	NR	28.26 ± 2.46	NR	NR	NR
	Metformin	30	30.26 ± 3.97	58.90 ± 5.78	22.94 ± 5.86	NR	NR	28.13 ± 2.30	NR	NR	NR
Khan_2017 [24]	Insulin	385	28.01 ± 2.53	NR	23.82 ± 2.81	NR	NR	29.92 ± 2.27	NR	NR	NR
	Metformin	385	24.92 ± 2.57	NR	22.08 ± 2.98	NR	NR	27.94 ± 2.57	NR	NR	NR
Zawiejska_2017 [23]	Insulin	43	Median (IQR): 35 (30–38)	NR	32.0 ± 5.8	NR	NR	Median (IQR): 30 (28–31)	HTN: 4 (9.3%)	NR	NR
	Metformin and metformin + insulin	35	Median (IQR): 33 (29–39)	NR	32.2 ± 6.4	NR	NR	Median (IQR): 30 (28–32)	HTN: 7 (20%)	NR	NR
Ashoush_2016 [22]	Insulin (regular + NPH)- Group-1 control	48	32.1 ± 3.2	NR	31.4 ± 1.5	NR	NR	27.8 ± 1.4	NR	29.7 ± 1.9	NR
	Metformin and metformin + insulin-Group-II research	47	31.6 ± 2.8	NR	31.1 ± 1.3	NR	NR	28.2 ± 1.3	NR	29.8 ± 1.4	NR
Behrashi_2016 [67]	Regular insulin and NPH	129	29.98 ± 7.033	NR	22.59 ± 3.09	NR	NR	24.48 ± 4.51	NR	NR	NR
	Glibenclamide	120	30.69 ± 7.194	NR	21.94 ± 2.8	NR	NR	24.89 ± 3.90	NR	NR	NR
Somani_2016 [26]	Regular/NPH/both	33	26.3 ± 3.84	NR	NR	NR	NR	28.33 ± 2.57	Previous GDM: 7 (21.21%)	NR	NR
	Metformin	32	25.61 ± 4.72, $p = 0.52$	NR	NR	NR	NR	27.77 ± 2.49, $p = 0.38$	Previous GDM: 4 (12.5%), $p = 0.51$	NR	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Ainuddin_2015 [36]	Insulin (short + intermediate-acting)	75	31 ± 4	NR	NR	NR	NR	29.2 ± 1.5	NR	28.19 ± 1.5	NR
	Metformin	43	30.6 ± 2.9	NR	NR	NR	NR	29.9 ± 1.1	NR	NR	NR
	Insulin added-on to metformin	32	30 ± 3.3	NR	NR	NR	NR	29.7 ± 1.6	NR	31.78 ± 5.9	NR
Mirzamoradi_2015 [42]	Insulin	59	31.18 ± 5.01	NR	31.77 ± 5.11	NR	NR	193.59 ± 20.01	Previous GDM: 2 (3.38%)	211.89 ± 27.80 days	NR
	Glyburide	37	29.50 ± 4.06	NR	30.18 ± 5.35	NR	NR	194.89 ± 29.54	Previous GDM: 1 (2.07%)	209.24 ± 28.84	NR
Mukhopadhyay_2014 [58]	Insulin	30	26 ± 4.3	NR	23 ± 2.9	NR	NR	27.4 ± 2.7	NR	NR	NR
	Glibenclamide	30	26.3 ± 4.6	NR	23.7 ± 2.7	NR	NR	28.3 ± 2.2	NR	NR	NR
Ruholamin_2014 [37]	Insulin	50	23.4 ± 2.5	NR	25.1 ± 3.4	NR	NR	26.7 ± 3.5	NR	NR	NR
	Metformin	50	24.6 ± 6.3	NR	26.4 ± 2.8	NR	NR	27.6 ± 3.3	NR	NR	NR
Spaulonci_2013 [68]	Insulin	46	32.76 ± 4.66	NR	31.39 ± 5.71	NR	NR	30.63 ± 3.35	NR	NR	NR
	Metformin	46	31.93 ± 6.02	NR	31.96 ± 4.75	NR	NR	30.40 ± 3.71	NR	NR	NR
Balaji_2012 [69]	Premixed insulin aspart 30 (BIAsp 30)	163	29.15 ± 3.97	NR	26.01 ± 3.40	NR	NR	19.32 ± 6.34	NR	21.67 ± 9.27	NR
	Premixed human insulin (BHI 30)	157	29.64 ± 4.52	NR	25.83 ± 3.40	NR	NR	19.89 ± 7.12	NR	22.39 ± 10.14	NR
Hassan_2012 [40]	Regular and intermediate-acting Human insulin	75	30.88 ± 3.6	NR	28.74 ± 2.69	NR	NR	29.20 ± 1.48	NR	NR	NR
	Metformin	75	30.29 ± 3.06	NR	29.17 ± 1.94	NR	NR	29.53 ± 1.33	NR	NR	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Mesdaghinia_2012 [56]	NPH and regular	100	30.2 ± 5.9	NR	28.46	NR	NR	28.9 ± 3.8	NR	NR	NR
	Metformin	100	29.6 ± 5.3	NR	27.6	NR	NR	27.9 ± 3.22	NR	NR	NR
Niromanesh_2012 [39]	NPH and regular as needed	80	31.8 ± 5.1	NR	27.1 ± 2.1	NR	NR	26.0 ± 3.7	Previous GDM: 11 (13.8%), macrosomia: 5 (6.3%)	NR	NR
	Metformin	80	30.7 ± 5.5	NR	28.1 ± 4.0	NR	NR	26.0 ± 3.5	Previous GDM: 6 (7.55), macrosomia: 2 (2.5%)	NR	NR
	Diet	371	NR	NR	NR	NR	Other: European: 30%, Maori: 4.6%, Pacific: 7.6%, Indian: 13.5%, Other Asian: 39.4%, other: 5.1%	NR	NR	NR	NR
Tertti_2012 [38]	Insulin	107	32.1 ± 5.4	NR	28.9 ± 4.7	NR	NR	30.4 ± 1.8	NR	NR	NR
	Metformin	110	31.9 ± 5.0	NR	29.4 ± 5.9	NR	NR	30.4 ± 1.8	NR	NR	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Ijas_2011 [41]	Long- (Protaphane) and rapid-acting (Humalog) insulin	50	31.7 ± 6.1	NR	30.8 ± 5.4	NR	NR	30 ± 4.0	NR	NR	NR
	Metformin	47	32.3 ± 5.6	NR	31.5 ± 6.5	NR	NR	30 ± 4.9	NR	NR	NR
Preexisting diabetes											
Jing ji_2020 [27]	Insulin detemir + Novolin-R	120	31.67 ± 4.16	NR	24.82 ± 3.53	NR	NR	27.69 ± 6.05	NR	NR	NR
	Insulin NPH + Novolin-R	120	30.84 ± 5.24, $p = 0.178$	NR	24.39 ± 3.90, $p = 0.581$	NR	NR	27.70 ± 5.86, $p = 0.991$	NR	NR	NR
Ainuddin_2015 [44]	Insulin (short- + intermediate-acting)	NR	33.73 ± 2.95	NR	Early pregnancy: 32.96 ± 4.04, Late pregnancy: 38.01 ± 4.18	NR	NR	NR	NR	NR	NR
	Metformin	NR	31.75 ± 2.82, $p = 0.07$ vs. insulin	NR	Early pregnancy: 28.25 ± 1.98, $p < 0.01$ vs. insulin; Late pregnancy: 32.47 ± 2.19, $p < < 0.01$ vs. insulin	NR	NR	NR	NR	NR	NR
	Insulin added-on to metformin	NR	34.09 ± 3.51, $p = 0.956$ vs. insulin	NR	Early pregnancy: 33.59 ± 3.97, $p = 0.171$ vs. insulin; late pregnancy: 38.09 ± 4.26, $p = 0.714$ vs. insulin	NR	NR	NR	NR	NR	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Herrera_2015 [70]	Insulin detemir	42	Median (IQR): 35 (31–38)	NR	NR	NR	Black: 7 (17%), White: 11 (26%), other: Native American Alaskan: 12 (29%), Hispanic: 12 (29%)	Median (IQR): 26.1 (24.8–27.1)	Previous GDM: 8 (19%), PCOS: 5 (12%)	Median (IQR): 29.6 (27.5–31.4)	Chronic HTN: 5 (12%), renal disease: 1 (2%), thyroid disease: 6 (14%)
	Insulin NPH	45	Median (IQR): 35 (32–38)	NR	NR	NR	Black: 5 (11%), White: 17 (38%), other: Native American Alaskan: 6 (13%), others: 2 (4%), Hispanic: 15 (33%)	Median (IQR): 26.6 (25.4–28.2)	Previous GDM: 9 (20%), PCOS: 12 (27%)	Median (IQR): 30.0 (25.1–31.5)	Chronic HTN: 6 (13%), renal disease: 5 (11%), thyroid disease: 8 (18%)
Refuerzo_2015 [71]	Insulin	13	32.3 ± 4.3	NR	40.1 ± 8.4	NR	Black: 4 (30.8%), White: 6 (46.2%), other: Hispanic: 1 (7.7%), others: 2 (15.4%)	Median (range): 16 (6–18)	NR	NR	NR

Table 1 continued

First author_ Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/ Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Metformin	8	30.9 ± 5.5	NR	40.1 ± 8.4	NR	Black: 3 (37.5%), White: 4 (50%), other: 1 (12.5%)	Median (range): 16 (8–19)	NR	NR	NR
Hod_2014 [57]	Insulin detemir	152	29.7 ± 4.6	NR	24.3 ± 4.0	11.7 ± 8.1	NR	NR	NR	NR	Retinopathy: 43 (28.3)
	Insulin NPH	158	30.4 ± 4.2	NR	25.2 ± 4.2	12.8 ± 7.9	NR	NR	NR	NR	Retinopathy: 40 (25.3%)
Hickman_2013 [52]	Insulin	14	Median (IQR): 31 (26–33)	NR	NR	NR	Black: 2 (14%), White: 2 (14%), Hispanic: 10 (71%)	Median (IQR): 14 (13–19)	Previous GDM: 8 (67%), prior CS: 2 (17%)	NR	Chronic HTN: 4 (29%), hypothyroid: 1 (7%), depression: 3 (21%)
	Metformin	14	Median (IQR): 36 (35–37)	NR	NR	NR	Black: 2 (14%), Hispanic: 12 (86%)	Median (IQR): 17 (10–22)	Previous GDM: 8 (67%), prior CS: 6 (50%)	NR	Chronic HTN: 4 (29%), hypothyroid: 1 (7%), depression: 2 (14%), asthma: 2 (14%)

BHI biphasic premixed human insulin, *BMI* body mass index, *GA* gestational age, *GDM* gestational diabetes mellitus, *HTN* hypertension, *IQR* interquartile range, *n* sub-population size, *NPH* neutral protamine Hagedorn, *NR* not reported, *SD* standard deviation

Table 2 Patient characteristics of observational studies in women with gestational diabetes mellitus and pre-existing diabetes

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
GDM											
Han_2020 [72]	Insulin Lispro + metformin	62	27.63 ± 2.96	NR	25.51 ± 2.67	NR	NR	NR	Fibroid: 14 (22.58%)	NR	NR
	Insulin Lispro	55	27.41 ± 3.21	NR	25.12 ± 2.33	NR	NR	NR	Fibroid: 15 (27.27%)	NR	NR
Krishnakumar_2020 [73]	Insulin	37	26.05 ± 2.45	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin	44	26.05 ± 2.45	NR	NR	NR	NR	NR	NR	NR	NR
Osuagwu_2020 [74]	Insulin	103	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	146	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Overall population	255	30.7 ± 5.5	NR	33.2 ± 7.5	NR	Other: Itaukei Fijians: 49.4%, FIDs: 42%, Others: 8.6%	25.6 ± 7.8	Previous GDM: 4.3%	NR	NR
Rodrigues_2020 [50]	Insulin	41	NR	NR	Overall mean BMI NR but data provided in terms of BMI ranges	NR	Black: 12 (29.3), White: 27 (65.9), Asian: 2 (4.3)	18.6 ± 7.9	Previous GDM: 4 (9.8%); Previous macrosomia: 2 (4.9%); Previous abortions 12 (29.3%)	27.3 ± 7.0	Chronic hypertension: 11 (26.8)

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Metformin + insulin	94	NR	NR	Overall mean BMI NR but data provided in terms of BMI ranges	NR	Black: 27 (29.3), White: 61 (66.3), Asian: 4 (4.3); $p = 0.99$ vs. insulin	19.1 ± 8.2	Previous GDM: 14 (14.9%); $p = 0.42$, Previous macrosomia: 8 (8.5%); $p = 0.46$, Previous abortions 26 (27.7%); $p = 0.85$ vs. insulin	27.6 ± 7.1	Chronic hypertension: 10 (10.8); $p = 0.17$ vs. insulin
	Metformin only	77	NR	NR	Overall mean BMI NR but data provided in terms of BMI ranges	NR	Black: 20 (26.7%), White: 52 (69.3%), Asian: 3 (4%); $p = 0.92$ vs. insulin	19.5 ± 8.4	Previous GDM: 12 (15.6%)- $p = 0.38$ vs. insulin; Previous macrosomia: 6 (7.8%)- $p = 0.55$; Previous abortions 21 (27.2%)- $p = 0.82$	28.2 ± 7.3	Chronic hypertension: 6 (7.9); $p = 0.006$ vs. insulin
Zaharieva_2020 [75]	Insulin vs. non-insulins	Total-90; insulin: $n = 34$	31 ± 4	NR	NR	NR	NR	27 ± 1	NR	NR	NR
Cade_2019 [76]	Insulin	619	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Meghelli_2019 [77]	Insulin	63	31.6 ± 4.6	NR	44.0 ± 2.9	NR	NR	NR	History of C-section: 18 (28.6%), Hypertension: 11 (17.5%), GDM: 24 (38.1%)	NR	NR
	No insulin	56	29.0 ± 5.2	NR	43.6 ± 2.6	NR	NR	NR	C-section: 13 (23.2%), Hypertension: 4 (7.1%), GDM: 6 (10.7%)	NR	NR
Munn_2019 [78]	Glyburide	195,000	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin	195,000	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ng_2019 [79]	Insulin	576	31.93 ± 5.69	NR	31.20 ± 7.66	NR	NR	NR	NA	NR	NR
	No Insulin	1281	30.59 ± 5.55	NR	29.00 ± 7.42	NR	NR	NR	NA	NR	NR
Tang_2019 [31]	Insulin	180	32.5 ± 4.1	76.8 ± 12.8	NR	NR	NR	20.1 ± 8.6	PCOS: 2 (1.1%), previous adverse pregnancy outcome: 49 (27.2%)	NR	NR
	MNT	354	30.6 ± 3.9	71.0 ± 11.1	NR	NR	NR	22.3 ± 7.4	PCOS: 4 (1.1%), previous adverse pregnancy outcome: 72 (20.3%)	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Bogdanet_2018 [46]	Insulin detemir and insulin aspart	752	Median (IQR): 34 (31–37)	NR	Median (IQR): 32 (28–37)	NR	Other: Caucasian: 624 (84.7%), non-Caucasian: 113 (15.3%)	NR	NR	NR	NR
	MNT	567	Median (IQR): 33 (30–36)	NR	Median (IQR): 29.8 (26–34.3)	NR	Other: Caucasian: 465 (83.8%), non-Caucasian: 90 (16.2%)	NR	NR	NR	NR
	Normal glucose tolerance	2496	Median (IQR): 32 (28–35)	NR	Median (IQR): 26 (23–29)	NR	Other: Caucasian: 2335 (9.3%), non-Caucasian: 156 (6.3%)	NR	NR	NR	NR
Christian_2018 [80]	Insulin	17	Median (range): 34 (20–46)	NR	Median (range): 35 (23–53)	NR	Other: Middle eastern: 7 (41.2%), Rest of Asia: 6 (35.3%), Africa: 4 (23.5%)	Median (range): 29 (18–35)	NR	30.2 weeks	NR
	Metformin	58	Median (range): 32 (22–42)	NR	Median (range): 30 (23–41)	NR	Other: Middle eastern: 3 (5.2%), Rest of Asia: 45 (77.6%), Africa: 10 (17.2%)	Median (range): 31 (14–38)	NR	30.6 weeks	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Metformin + insulin	32	Median (range): 34 (25–45)	NR	Median (range): 32 (23–52)	NR	Other: Middle eastern: 6 (18.7%), Rest of Asia: 19 (59.4%), Africa: 7 (21.9%)	Median (range): 28 (15–35)	NR	27.8 (metformin)/30.7 (insulin) weeks	NR
Hedderson_2018 [60]	Insulin	401	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Glyburide	4622	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + glyburide	281	NR	NR	NR	NR	NR	NR	NR	NR	NR
Landi_2018 [49]	Insulin	3450	32.4	NR	Median (IQR): 28 (24–33)	NR	NR	30.1 ± 2.9	Prior GDM: 9.3%	31.6 ± 2.9	NR
	Metformin	3818	31.9	NR	Median (IQR): 28 (23–33)	NR	NR	30.5 ± 2.9	Prior GDM: 8.3%	32.0 ± 2.9	NR
Leung_2018 [81]	Insulin	223	NR	NR	31.89 ± 9.03	NR	NR	NR	NR	NR	NR
	glyburide	171	NR	NR	30.17 ± 7.43	NR	NR	NR	NR	NR	NR
McGrath_2018 [82]	Insulin	83	33.5 ± 4.3	NR	25.2 ± 6.3	NR	Asian: South Asian: 29 (34.9%), Asian: 20 (24.1%), SEA: 5 (6%), Caucasian: 25 (30.1%), Middle Eastern: 4 (4.8%)	24.0 ± 5.8	Previous GDM: 11 (13.3%)	28.0 ± 5.4	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Metformin	83	33.1 ± 4.8	NR	27.8 ± 8.0	NR	South Asian: 22 (26.5%), Asian: 18 (21.7%), SEA: 6 (7.2%), Caucasian: 34 (41%), Middle eastern: 2 (2.4%), Pacific Islander: 1 (1.2%)	23.6 ± 5.9	Previous GDM: 11 (13.3%)	27.1 ± 5.7	NR
	Diet + lifestyle	83	33.1 ± 4.3	NR	22.7 ± 2.9	NR	South Asian: 15 (18.1%), Asian: 27 (32.5%), SEA: 8 (9.6%), Caucasian: 34 (41%), Middle Eastern: 1 (1.2%), African: 1 (1.2%)	24.0 ± 5.7	Previous GDM: 11 (13.3%)	NA	NR
Meregaglia_2018 [83]	Insulin	1616	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	9924	NR	NR	NR	NR	NR	NR	NR	NR	NR
Patanjali_2018 [84]	Insulin	58 (20.1%)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Metformin	Only metformin: 23 (8%), Required insulin with metformin: 28 (9.7%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	179 (62.1%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rowan_2018 [85]	Insulin (Adelaide cohort)	51	33.9 ± 4.7	NR	34 ± 7.9	NR	Other: European/ Caucasians: 43 (84.3%), Indian: 4 (7.8%), Chinese and other Southeast Asian: 2 (3.9%), others/mixed: 2 (3.9%)	31.6 ± 2	Chronic HTN: 5 (9.8%)	NR	NR
	Metformin (Adelaide cohort)	58	33.6 ± 5.7	NR	34.2 ± 7.1	NR	Other: European/ Caucasians: 52 (89.7%), Chinese and other: 4 (6.9%), others/mixed: 2 (3.4%)	31.3 ± 2.8	Chronic HTN: 7 (12.1%)	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Insulin (Auckland cohort)	54	35.21 ± 4.72	NR	32.0 ± 6.3	NR	Other: European/ Caucasians: 21 (38.9%), Polynesian: 7 (13.0%), Indian: 16 (29.6%), Chinese and other South-east Asian: 7 (13.0%), others/ mixed: 3 (5.6%)	29.5 ± 3.4	Chronic HTN: 5 (9.3%)	NR	NR
	Metformin (Auckland cohort)	45	34.12 ± 5.12	NR	35.4 ± 11.3	NR	Other: European/ Caucasians: 25 (55.6%), Polynesian: 6 (13.3%), Indian: 7 (15.6%), Chinese and other: 6 (13.3%), Others/ mixed: 1 (2.2%)	29.9 ± 3.6	Chronic HTN: 7 (15.6%)	NR	NR
Simeonova-Krstevska_2018 [28]	Levemir (insulin detemir) + aspart	101	32.7 ± 5.7	NR	NR	NR	NR	24 ± 7.8	NR	NR	NR
	Metformin	48	32.2 ± 4.7	NR	NR	NR	NR	28.6 ± 5.6	NR	NR	NR
	Diet	200	31.5 ± 5.2	NR	NR	NR	NR	29.5 ± 5.8	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Vanlalhruaii_2018 [86]	Insulin	151	28.9 ± 4.03	NR	30.2 ± 6.6	NR	NR	23.67 + 7.65 weeks + days	Previous GDM: 34 (22.52%)	NR	NR
	Group A-metformin 1st trimesters	186	29.41 ± 4.64	NR	29.8 ± 5.6	NR	NR	10.04 ± 1.8 weeks + days	Previous GDM: 53 (28.5%)	NR	NR
	Group B-metformin 2nd trimesters	203	28.8 ± 5.12	NR	28.5 ± 7.1	NR	NR	22.45 ± 5.4	Previous GDM: 37 (18.23%)	NR	NR
Bowker_2017 [87]	Human insulin or insulin analogues	5057 (human insulin, *n* = 3724 or 73.6%)	33.2 ± 5.0	NR	NR	NR	Asian: Chinese: 320 (6.3%), South Asian: 385 (7.6%), other: general population: 4055 (80.2%), status aboriginal: 297 (5.9%)	NR	NR	NR	NR
	Metformin ± insulin	478 (human insulin or insulin analogues; *n* = 171 or 82.2%)	32.8 ± 5.0	NR	NR	NR	Chinese: 14 (2.9%), South Asian: 28 (5.9%), other: General population: 406 (84.9%), status aboriginal: 30 (6.3%)	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	No specific intervention	13,226	32.4 ± 5.2	NR	NR	NR	Asian: Chinese: 1052 (8.0%), South Asian: 770 (5.8%), other: General population: 10,575 (80.0%), Status aboriginal: 829 (6.3%)	NR	NR	NR	NR
Gibbons_2017 [88]	Insulin	315	33.2 ± 5.0	NR	Median (IQR): 28.6 (24.8–35.0)	NR	Asian: 49 (15.6%), other: Caucasian: 148 (47.0%), Indigenous: 13 (4.1%), Indian: 36 (11.4%), others: 69 (21.9%)	NR	HTN: 37 (11.7%), thyroid disease: 26 (8.3%)	NR	NR
	OHA (glyburide/ metformin)	211	32.5 ± 5.1	NR	Median (IQR): 26.1 (23.1–30.9)	NR	Asian: 45 (21.3%), other: Caucasian: 83 (39.3%), Indigenous: 2 (0.9%), Indian: 39 (18.5%), others: 42 (19.9%)	NR	HTN: 23 (10.9%), thyroid disease: 15 (7.1%)	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Diet	563	32.2 ± 5.3	NR	Median (IQR): 24.0 (20.9–28.5)	NR	Asian: 165 (29.3%), Other: Caucasian: 190 (33.7%), Indigenous: 10 (1.8%), Indian: 73 (13.0%), others: 125 (22.2%)	NR	HTN: 45 (8.0%), thyroid disease: 54 (9.6%)	NR	NR
Olmos_2017 [89]	BBIT	73	32.9 ± 5.2	NR	27.0 ± 5.0	NR	NR	24.6 ± 6.6	NR	NR	NR
	Without BBIT (diet/metformin)	58	32.5 ± 5.0	NR	24.5 ± 3.4	NR	NR	28.2 ± 7.7	NR	NR	NR
Xie_2017 [90]	Insulin aspart intensive treatment/ insulin pump (research arm)	45	30.8 ± 2.6 (range 23–36)	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin aspart + detemir (reference arm)	45	31.5 ± 2.4 (range 22–35)	NR	NR	NR	NR	NR	NR	NR	NR
Fazel-Sarjoui_2016 [91]	Short-acting insulin	70	30.1 ± 5.1	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	70	29.1 ± 4.6	NR	NR	NR	NR	NR	NR	NR	NR
Ito_2016 [92]	Insulin	32	33.3 ± 5.6	NR	24.6 ± 4.3	NR	NR	18.6 ± 8.4	Prior fetal macrosomia: 1 (3.1%)	23.1 ± 8.3	NR
	Diet	70	34.4 ± 5.6	NR	23.3 ± 3.6	NR	NR	20.8 ± 7.5	Prior fetal macrosomia: 0 (0%)	NA	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Koning_2016 [93]	Diet + additional insulin (aspart, NPH and aspart + NPH)	360 (43.9%)	32.6 ± 5.2	NR	NR	NR	Asian: 20 (5.6%), Other: Caucasian: 281 (78.1%), African-American: 17 (14.7%), Mediterranean: 35 (9.7%), unknown: 7 (1.9%)	Median (IQR): 27.1 (24.4–29.3)	History of PCOS: 16 (4.4%), previous GDM: 61 (16.9%), History of IUFD: 11 (3.1%), spontaneous abortion: 110 (30.6%), infant weighing ≥ 4500 g at birth: 55 (15.3%)	NR	Chronic hypertension: 22 (6.1%)
	Diet	460 (56.1%)	31.6 ± 4.9	NR	NR	NR	Asian: 35 (7.6%), Caucasian: 377 (82.0%), African-American: 22 (4.8%), Mediterranean: 35 (9.7%), unknown: 8 (1.7%)	Median (IQR): 28.4 (26.7–32.3)	History of PCOS: 24 (5.2%), previous GDM: 25 (5.4%), IUFD: 5 (1.1%), spontaneous abortion: 113 (24.6%), infant weighing ≥ 4500 g at birth: 35 (7.6%)	NR	Chronic hypertension: 15 (3.3%)

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Overall population	820	32.0 ± 5.1	NR	NR	NR	Asian: 55 (6.7%), Other: Caucasian: 658 (80.2%), African-American: 35 (4.3%), Mediterranean: 57 (7.0%), unknown: 15 (1.8%)	Median (IQR): 27.9 (25.9–30.7)	History of PCOS: 40 (4.9%), previous GDM: 86 (10.5%), IUFD: 16 (2.0%), spontaneous abortion: 223 (27.2%), infant weighing ≥ 4500 g at birth: 90 (11.0%)	NR	Chronic hypertension: 37 (4.5%)
Koren_2016 [55]	Insulin detemir	29	33.8 ± 4.7	NR	NR	NR	NR	NR	Previous GDM: 6 (20.7%), macrosomia: 4 (13.8%)	28.5 ± 8.1	HTN: 3 (10.3%)
	Glyburide	62	33.1 ± 4.0	NR	NR	NR	NR	NR	Previous GDM: 19 (30.5), macrosomia: 8 (12.9%)	29.4 ± 5.2	HTN: 3 (4.8%)
Ozgu-Erdinc_2016 [29]	Insulin	144	32.8 ± 5.6	NR	< 8th GW: Median: 32 (21–52)	NR	NR	NR	History of macrosomia: 22 (15.3%)	NR	NR
	Diet	115	31.9 ± 5.3	NR	< 8th GW: Median: 31.5 (21–50)	NR	NR	NR	History of macrosomia: 11 (9.6%)	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Saleem_2016 [94]	Insulin (BiD)	240	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin-QiD	240	NR	NR	NR	NR	NR	NR	NR	NR	NR
Watanabe_2016 [95]	Insulin	10	33.8 ± 7.0	NR	NR	NR	NR	18.9 ± 2.0	Previous GDM: 1 (10.0%)	26.1 ± 5.9	NR
	Diet	27	35.7 ± 3.6	NR	NR	NR	NR	21.6 ± 4.1	Previous GDM: 5 (18.5%)	NA	NR
Yanagisawa_2016 [30]	Insulin	36	34.2 ± 5.1	NR	NR	NR	NR	23.3 ± 6.4	Previous GDM: 3 (8%), macrosomia: 1 (3%)	NR	NR
	MNT	77	34.2 ± 4.2	NR	NR	NR	NR	27.0 ± 5.1	Previous GDM: 1 (1%), macrosomia: 2 (3%)	NR	NR
Benhalima_2015 [32]	Short-acting or long-acting insulin or both	145	32.5 ± 4.7	NR	29.1 ± 20.2	NR	NR	25.3 ± 4.9	Previous GDM: 31 (21.5%)	NR	NR
	Diet	456	31.8 ± 4.8	NR	26.8 ± 12.9	NR	NR	27.1 ± 3.7	Previous GDM: 47 (10.4%)	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Castillo_2015 [59]	Insulin	4191	34 ± 4.7	NR	NR	NR	NR	NR	NR	NR	Infertility treatment: 6.8%, hypothyroidism: 8.3%, PCOS: 4.1%, Hyperandrogenism: 1.6%, metabolic syndrome: 0.7%, Antihypertensive use: 7%
	Glyburide	4982	34 ± 4.7	NR	NR	NR	NR	NR	NR	NR	Infertility treatment: 5.6%, hypothyroidism: 7.1%, PCOS: 3.3%, hyperandrogenism: 2%, metabolic syndrome: 0.4%, antihypertensive use: 6.9%
Cosson_2015 [96]	Insulin	260	NR	NR	NR	NR	NR	NR	NR	NR	NR
Inocencio_2015 [97]	Insulin	460	–	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Koivunen_2015 [64]	Insulin-2006	1128	31.6 ± 5.6	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin-2010	887	32.1 ± 5.4	NR	NR	NR	NR	NR	NR	NR	NR
	Diet-2006	4057	30.9 ± 5.7	NR	NR	NR	NR	NR	NR	NR	NR
	Diet-2010	5796	30.9 ± 5.4	NR	NR	NR	NR	NR	NR	NR	NR
Kopec_2015 [98]	Insulin	205	30.9 ± 4.5	NR	NR	NR	NR	NR	Previous GDM: 18	NR	NR
	OHA	141	29.5 ± 4.1	NR	NR	NR	NR	NR	NR	NR	PIH: 18 (12%), Hypothyroidism: 2 (1.4%), $p = 0.003$ vs. OHA
You_2015 [99]	Regular insulin (NPH if required)	55	33.4 ± 3.8	NR	NR	NR	NR	NR	NR	NR	NR
	Fast-acting insulin analogues (NPH if required)-aspart or lispro	142	33.5 ± 3.9	NR	NR	NR	NR	NR	NR	NR	NR
Arshad_2014 [25]	Regular and NPH	25	31.60 ± 4.27	77.9 ± 9.03	NR	NR	NR	NR	NR	NR	NR
	Diet + exercise	25	30.08 ± 3.16	78.54 ± 6.93	NR	NR	NR	NR	NR	NR	NR
Deepaklal_2014 [100]	Insulin Lispro	201	Median (range): 29 (18–41)	NR	NR	NR	NR	Median (range): 21.75 (4–38)	Previous GDM: 26.6%, $N = 195$	NR	NR
Konig_2014 [101]	Insulin	40	32.26 ± 4.37	NR	27.71 ± 6.77	NR	NR	NR	NR	NR	NR
	No insulin	83	32.69 ± 4.9	NR	23.75 ± 3.84	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Marques_2014 [102]	NPH insulin	33	34.3 ± 5.3	NR	28.8 ± 6.3	NR	Other: Caucasian: 29 (87.9%), Africans: 4 (12.1%)	NR	NR	NR	NR
	Metformin	32	34.1 ± 5.2	NR	32.3 ± 7.7	NR	Other: Caucasian: 27 (84.4%), Africans: 4 (12.5%), Asian: 1 (3.1%)	NR	NR	NR	NR
Al_Rubeaan_2013 [103]	Regular insulin	674 (8.50%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	NPH	653 (8.58%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Premixed insulin	406 (3.41%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Glargine insulin analogues	58 (3.11%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Aspart insulin analog	80 (7.84%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Lispro insulin analog	3 (3.70%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Overall	1,878,386 (4.70%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hernandez-Rivas_2013 [104]	Insulin	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Latif_2013 [105]	Insulin	32	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin	68	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin + insulin	28	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Tempe_2013 [106]	Insulin	32	27.5 ± 3.04	NR	NR	NR	NR	NR	NR	27.3 ± 4.1	NR
	Glyburide	32	26.9 ± 3.06	NR	NR	NR	NR	NR	NR	25.9 ± 5.1	NR
Cheng_2012 [107]	Insulin	8609	NR	NR	NR	NR	Black: 77.7%, White: 82.7%, Asian: 75.1%, other: 83.2, Hispanic: 81.1%	NR	NR	NR	NR
	Glyburide	2073	NR	NR	NR	NR	Black: 22.3%, White: 18.1%, Asian: 24.9%, other: 16.8%, Hispanic: 18.9%	NR	NR	NR	NR
Donovan_2012 [47]	Insulin	359	NR	NR	NR	NR	NR	NR	Previous CS: 72 (20%)	NR	NR
	Lifestyle	505	NR	NR	NR	NR	NR	NR	Previous CS: 91 (18%)	NR	NR
Thomas_2012 [108]	Insulin	137	29.2 ± 4.1	NR	NR	NR	NR	NR	NR	NR	PIH: 18 (12%), Hypothyroidism: 10 (7%), $p = 0.003$ vs. OHA
	OHA	141	29.5 ± 4.1							NR	PIH: 18 (12%), Hypothyroidism: 2 (1.4%), $p = 0.003$ vs. OHA

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Varghese_2012 [45]	Regular/NPH/ both	186 (83.78%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Diet	36 (16.21%)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Goh_2011 [109]	Intermediate-acting isophane insulin and short-acting insulin analog	399	NR	NR	NR	NR	Other: European: 28.9%, Maori: 7%, Pacific: 21.3%, Indian: 19.6%, other Asian: 19.3%, other: 4%	NR	NR	NR	NR
	Metformin	465 (216 required insulin)	NR	NR	NR	NR	Other: European: 22%, Maori: 101%, Pacific: 20.9%, Indian: 19.1%, other Asian: 24.3%, other: 3.7%, $p < 0.001$ across ethnicity overall and treatment groups	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Diet	371	NR	NR	NR	NR	European: 30%, Maori: 4.6%, Pacific: 7.6%, Indian: 13.5%, Other Asian: 39.4%, other: 5.1%	NR	NR	NR	NR
Wong_2011 [110]	Insulin	323	31.9 ± 5.3	NR	29.9 ± 7.3	NR	Asian: SEA: 17.8%, SA: 19.4%, Middle eastern: 21.9%, Anglo-European: 30.8%. Other: 10%	NR	Previous GDM: 25.9%	NR	NR
	MNT	289	30.9 ± 5.4, $p = 0.140$	NR	26.5 ± 6.3, $p < 0.001$	NR	Asian: SEA: 28.4%, SA: 19.8%, Middle Eastern: 19.8%, Anglo-European: 23.8%, other: 8.2%; $p = 0.006$ for SEA	NR	Previous GDM: 16.7%	NR	NR
Flores-Le Roux_2010 [111]	Insulin	41	34.5 ± 5.9	NR	NR	NR	Caucasian: 17 (41.4%)	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Diet	70	32.4 ± 6.1	NR	NR	NR	Caucasian: 35 (50%)	NR	NR	NR	NR
	NEF-GDM	18	32.8 ± 4.7; $p = 0.21$ across groups	NR	NR	NR	Caucasian: 4 (22.2%), $p = 0.1$ across treatment groups	NR	NR	NR	NR
Preexisting diabetes/ mixed population											
Demasio_2020 [112]	Overall population	314	NR	NR	NR	NR	Black: 27%, White: 6%, Asian: 6%, Other: 27%, Hispanic: 38%	NR	NR	NR	NR
	Insulin Levemir-T2DM	96	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin Levemir-GDM	127	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin NPH-T2DM	41	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin NPH-GDM	50	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kong_2020 [113]	Insulin	4000	30.15 ± 5.37	NR	NR	NR	NR	NR	NR	NR	NR
Mathiesen_2020 [114]	Insulin detemir vs. other basal insulin (mainly insulin glargine)	1457	31	NR	26	NR	NR	NR	NR	NR	

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Sperling_2020 [115]	Metformin	2542	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin-GDM	729	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Glyburide-PGDM	9998	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Glyburide-GDM	1181	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + glyburide-PGDM	1113	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + glyburide-GDM	371	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + metformin-PGDM	1029	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + metformin-GDM	2036	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin-PGDM	6796	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin-GDM	5350	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin + glyburide-PGDM	960	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Metformin + glyburide-GDM	375	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + metformin + glyburide-PGDM	214	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Insulin + metformin + glyburide-GDM	423	NR	NR	NR	NR	NR	NR	NR	NR	NR
Alexander_2019 [116]	CSII	151	31.0 ± 5.5	NR	26.2 ± 5.8	15.4 ± 8.5	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Bartal_2019 [48]	Basal insulin analogues	114	NR	NR	NR	NR	Other: non-Hispanic White: 27 (23.7%), non-Hispanic Black: 34 (29.8%), non-Hispanic other: 2 (1.8%), unknown: 15 (13.2%), Hispanic: 36 (31.6%)	NR	NR	NR	Chronic hypertension: 49 (43.0%)
	Insulin NPH	119	NR	NR	NR	NR	Other: non-Hispanic White: 35 (29.4%), non-Hispanic Black: 52 (43.7%), non-Hispanic other: 1 (0.8%), unknown: 9 (7.6%), Hispanic: 22 (18.5%)	NR	NR	NR	Chronic hypertension: 49 (41.2%)
Christman_2019 [117]	CSII and MDI	154	31 ± 5.4	NR	42.9% obese at baseline	NR	White: 113/150 (73.4%)	NR	NR	NR	NR
Sleeman_2019 [118]	Insulin glargine or detemir	44	31.2 ± 6.5	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Insulin NPH	19	30.6 ± 6.6	NR	NR	NR	NR	NR	NR	NR	NR
Smrz_2019 [119]	CSII vs. MDI	117	NR	NR	NR	NR	NR	NR	NR	NR	
Vasquez_2019 [120]	Insulin (Humulin R U-500)	10	NR	NR	NR	NR	NR	NR	Pregnancies complicated by severe insulin resistance	Mean (range): 24 weeks (16.2–33.4)	Gestational age during conversion to U-500
Gupta_2018 [121]	Insulin	120	30.17 ± 4.2	NR	NR	NR	NR	NR	Previous GDM: 21 (20%)	NR	Hypothyroidism: 22 (21.57%)
Sunjaya_2018 [122]	Insulin	25	31.92 ± 4.3	71.88 ± 11.7	28.46 ± 4.0	NR	NR	NR	History of DM in previous pregnancy: 12%	NR	NR
	Oral antidiabetics	4	33.75 ± 4.5	73.33 ± 11.5	23.53 ± 0.97	NR	NR	NR	History of DM in previous pregnancy: 12%	NR	NR
	MNT	16	28.00 ± 2.8	66.21 ± 11.6	27.76 ± 3.83	NR	NR	NR	History of DM in previous pregnancy: 12%	NR	NR
Abell_2017 [62]	MDI-glargine/ detemir/NPH	127	Median (IQR): 29 (26–33)	NR	Median (IQR): 26.6 (24.4–30.0)	Median (IQR): 12 (8–20)	NR	NR	NR	NR	NR
	CSII-aspart	40	Median (IQR): 31 (28–34)	NR	Median (IQR): 25.1 (23.1–30.1)	Median (IQR): 20 (7–22)	NR	NR	NR	NR	NR
Billionnet_2017 [63]	Insulin-treated GDM	16,108	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Noninsulin-treated GDM	41,275	NR	NR	NR	NR	NR	NR	NR	NR	NR
	GDM-overall	57,383	NR	NR	NR	NR	NR	NR	NR	NR	NR
	No diabetes	7,29,105	NR	NR	NR	NA	NR	NA	NR	NA	NR
Stanirowski_2017 [123]	Insulin-treated GDM	6	Median (IQR): 34 (29–37)	NR	NR	NR	NR	Median (IQR): 39 (38–39)	NR	NR	NR
	Diet-treated GDM	16	Median (IQR): 33 (30–37)	NR	NR	NR	NR	Median (IQR): 39 (38–39)	NR	NR	NR
	Insulin-treated PGDM	6	Median (IQR): 35 (33–36)	NR	NR	NR	NR	Median (IQR): 37 (37–38)	NR	NR	NR
	Controls (no diabetes)	25	Median (IQR): 30 (28–32)	NR	NR	NR	NR	Median (IQR): 39 (39–39)	NR	NR	NR
Dalfra_2016 [124]	ILPS-GDM	572	34.6 ± 5.1	NR	NR	NR	NR	NR	NR	NR	NR
	NPH-GDM	242	34.1 ± 4.5	NR	NR	NR	NR	NR	NR	NR	NR
	ILPS-PGDM T1DM	58	NR	NR	NR	13.8 ± 9.0	NR	NR	NR	NR	NR
	NPH-PGDM T1DM	61	NR	NR	NR	13.4 ± 10.1	NR	NR	NR	NR	NR
Becquet_2015 [125]	Insulin	36	Median (IQR): 31.1 (29.4–36.4)	NR	NR	NR	NR	NR	NR	NR	NR
	No insulin	43	Median (IQR): 34.2 (30.8–37.2)	NR	NR	NR	NR	NR	NR	NR	NR
Neff_2014 [61]	CSII-aspart	40	35 ± 4	NR	NR	22 (5–33)	NR	NR	NR	NR	NR
	MDI-aspart + NPH	424	31 ± 5	NR	NR	13 (1–36)	NR	NR	NR	NR	NR

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
Colatrella_2013 [126]	Insulin lispro protamine suspension (ILPS)-T2DM	7	36.0 ± 4.3	NR	NR	8.0 ± 5.2	NR	15.4 ± 9.6	NR	NR	NR
	Insulin lispro protamine suspension (ILPS)-GDM	46	34.5 ± 6.0	NR	NR	NR	NR	23.3 ± 7.8	NR	NR	NR
	Insulin NPH-T2DM	18	33.4 ± 5.3	NR	NR	6.6 ± 4.7	NR	11.1 ± 7.1	NR	NR	NR
	Insulin NPH-GDM	18	34.9 ± 4.3	NR	NR	NR	NR	29.5 ± 4.9	NR	NR	NR
Fresa_2013 [127]	CSII-insulin lispro/aspart	47	30.5 ± 5	NR	NR	15 ± 8	White: 65 (100%)	NR	NR	NR	NR
	CSII (RT-CGM)	18	32 ± 6	NR	NR	17 ± 10	White: 18 (100%)	NR	NR	NR	NR
Bruttomesso_2011 [128]	CSII-rapid-acting insulin analog	100	32.0 ± 4.4	NR	23.52 ± 3.22	16.5 ± 7.3	NR	NR	Pre-pregnancy hypertension: 8 (8%)	NR	NR
	Glargine-MDI	44	31.4 ± 5.2	NR	23.63 ± 4.71	13.5 ± 7.9	NR	NR	3 (6.8%)	NR	NR
Garcia-Dominguez_2011 [53]	NPH and regular insulin	241	32 ± 3.9	NR	24.7 ± 4.2	12.2 ± 7.9	NR	19.7 ± 8.4	NR	NR	Chronic HTN: 24 (10%), Retinopathy: 50 (20.7%), Nephropathy: 12 (5%)

Table 2 continued

First author_Year	Treatment arms	Sample size	Maternal age (mean ± SD)	Gestational weight (mean ± SD) kg	BMI (mean ± SD kg/m^2)	Disease duration (years)	Race/Ethnicity; *n* (%)	GA (weeks) at diagnosis/ baseline (mean ± SD)	Obstetric history	GA (weeks) at treatment initiation (mean ± SD)	Comorbidities
	Insulin analogues (NPH and lispro/ aspart)	86	32.5 ± 3.8, $p = 0.467$ across treatment groups	NR	24 ± 3.9, $p = 0.127$ across treatment groups	11.9 ± 8.2, $p = 0.935$ across treatment groups	NR	20.5 ± 8.9, $p = 0.687$ across treatment groups	NR	NR	Chronic HTN: 9 (8.2%), Retinopathy: 16 (14.5%), Nephropathy: 4 (3.6%), $p = 0.544$ across treatment groups
Negrato_2010 [51]	Glargine + lispro-PGDM	18	30.4 ± 7.1	NR	NR	6.8 ± 6.3	NR	NR	NR	NR	NR
	NPH + lispro-PGDM	38	28.1 ± 7.2; $p > 0.05$ vs. glargine-PGDM	NR	NR	7.5 ± 5.2, $p > 0.05$ vs. glargine PGDM	NR	NR	NR	NR	NR
	Glargine + lispro-GDM	37	30.9 ± 4.2	NR	NR	NR	NR	NR	NR	NR	NR
	NPH + lispro-GDM	45	31.7 ± 6.8; $p > 0.05$ vs. glargine GDM	NR	NR	NR	NR	NR	NR	NR	NR

BBIT basal-bolus insulin therapy, *BHI* biphasic premixed human insulin, *BiD* twice a day, *BMI* body mass index, *CGM* continuous glucose monitor, *CSII* continuous subcutaneous insulin infusion, *FID* Fijians of Indian descent, *GA* gestational age, *GDM* gestational diabetes mellitus, *GW* gestational week, *HTN* hypertension, *ILPS* insulin lispro protamine suspension, *IQR* interquartile range, *IUFD* intrauterine fetal demise, *MDI* multiple daily injection, *MNT* medical nutrition therapy, *n* sub-population size, *NA* not applicable, *NEF* no endocrinologic follow-up, *NPH* neutral protamine Hagedorn, *NR* not reported, *OHA* oral hypoglycemic agents, *PCOS* polycystic ovarian syndrome, *PGDM* pregestational diabetes *PIH* pregnancy-induced hypertension, *RT* real-time, *SA* South-Asian, *SEA* Sount-east Asian, *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *QiD* four times a day

Table 3 Clinical outcomes in women with gestational diabetes mellitus

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
RCT							
Wasim_2019 [21]	Insulin-Humulin R and NPH	141	Baseline	120 ± 22.4	NR	NR	NR
			Delivery	96.6 ± 6.2	NR	NR	NR
	Metformin	137	Baseline	117 ± 18.1; $p = 0.215$ vs. insulin	NR	NR	NR
			Delivery	92.1 ± 6.0; $p = 0.001$ vs. insulin	NR	NR	NR
Galal_2019 [20]	Human insulin	50	NA	92.42 ± 4.93	129.82 ± 7.88	NR	NR
	Metformin	56	NA;1 week	86.88 ± 5.02; $p = 0.0001$	117.30 ± 8.84; $p = 0.0001$	NR	NR
Eid_2018 [34]	Insulin (NPH + regular insulin)	116	Before treatment	116.83 ± 24.5	NR	NR	171.1 ± 41.8
			After treatment	84.1 ± 3.1	NR	NR	101.4 ± 4.8
	Metformin	113	Before treatment	114.38 ± 19.87; $p = 0.64$ insulin vs. metformin	NR	NR	168.9 ± 39.1; $p = 0.79$ insulin vs. metformin
			After treatment	81.7 ± 3.6, $p = 0.065$ insulin vs. metformin	NR	NR	95.9 ± 4.7, $p = 0.53$ insulin vs. metformin

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Huhtala_2018 [43]	NPH insulin and/or rapid-acting insulin lispro or insulin aspart	107	At enrolment	5.57 ± 0.42	NR	11.2 ± 1.24	7.91 ± 1.75
	Metformin	110	At enrolment	5.52 ± 0.55; $p = 0.44$ vs. insulin	NR	11.2 ± 1.49; $p = 0.61$ vs. insulin	8.33 ± 1.76; $p = 0.076$ vs. insulin
	Diet	103	At enrolment	5.38 ± 0.43	NR	10.9 ± 1.06	7.81 ± 1.91
Ghomian_2018 [33]	Levemir (insulin detemir) + aspart	143	At treatment onset	92.21 ± 4.41	NR	NR	152.58 ± 4.87
			Delivery	88.03 ± 5.00	NR	NR	118.99 ± 6.24
	Metformin	143	At treatment onset	91.22 ± 4.37; $p = 0.57$ vs. insulin	NR	NR	152.25 ± 5.11; $p = 0.69$ vs. insulin
			Delivery	89.16 ± 3.44; $p = 0.79$ vs. insulin	NR	NR	119.38 ± 4.03; $p = 0.33$ vs. insulin
Khan_2017 [24]	Insulin (mixed human suspension)	385	Before treatment	122.37 ± 9.94	NR	NR	174.46 ± 6.02
			After treatment	76.88 ± 7.75	NR	NR	112.34 ± 5.02
	Metformin	385	Before treatment	130.06 ± 10.34; $t = 10.53$; $p = 0.000$ vs. insulin	NR	NR	175.18 ± 7.89; $t = 1.42$; $p = 0.157$ vs. insulin

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			After treatment	82.28 ± 5.51; $t = 11.15$; $p = 0.000$ vs. insulin	NR	NR	111.94 ± 7.02; $t = -0.909$; $p = 0.364$ vs. insulin
Zawiejska_2016 [23]	Basal-bolus insulin (human recombined insulin)	43	At booking	5.5 ± 0.7	NR	NR	NR
			At term	4.7 ± 1; $p < 0.0001$ change from baseline	NR	NR	NR
	Metformin and metformin + insulin	35	At booking	5.8 ± 0.6	NR	NR	NR
			At term	5.2 ± 0.5; $p = 0.004$ change from baseline; p (booking) = 0.101; p (at term) = 0.008 vs. insulin	NR	NR	NR
Behrashi_2016 [67]	Regular insulin and NPH	129	NA	83.75 ± 6.77	NR	NR	107.14 ± 7.99
	Glibenclamide	120	NA	84.85 ± 5.26; $p = 0.38$ vs. insulin	NR	NR	114.38 ± 81.74; $p = 0.95$ vs. insulin
Ashoush_2016 [22]	Insulin-control (regular + NPH)	48	Baseline	106.4 ± 4.4	NR	208.3 ± 13.2	177.6 ± 8.8

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			1 week	93.5 ± 2.6	NR	NR	122.9 ± 7.2
			First 2 weeks	103.5 ± 3.5	NR	NR	170.5 ± 8.2
			Last week	79.9 ± 3.7	NR	NR	111.3 ± 4.2
			Last 2 weeks	80.8 ± 4.7	NR	NR	112.2 ± 6.8
	Metformin and metformin + insulin-research	36 + 11	Baseline	105.7 ± 4.7, $p = 0.417$ vs. insulin	NR	203.9 ± 9.9, $p = 0.075$ vs. insulin	175.7 ± 10.0, $p = 0.318$ vs. insulin
			1 week	92.8 ± 2.8, $p = 0.257$ vs. insulin	NR	NR	120.6 ± 7.8, $p = 0.142$ vs. insulin
			First 2 weeks	100.7 ± 3.3; $p = 0.014$ vs. insulin	NR	NR	166.9 ± 8.9, $p = 0.197$ vs. insulin
			Last week	78 ± 3.1; $p = 0.0008$ vs. insulin	NR	NR	109.9 ± 3.7; $p = 0.104$ vs. insulin
			Last 2 weeks	78.9 ± 3.5; $p = 0.029$ vs. insulin	NR	NR	111 ± 5.2; $p = 0.342$ vs. insulin
Somani_2016 [26]	Regular/NPH or both	33	Baseline	102.67 ± 9.61	NR	216.61 ± 22.39	179.0 ± 20.98
			Delivery	82.27 ± 5.57	NR	NR	113.06 ± 11.71
	Metformin	32	Baseline	100.03 ± 10.79; $p = 0.30$ vs. insulin	NR	215.22 ± 15.34; $p = 0.77$ vs. insulin	182.69 ± 17.33; $p = 0.44$ vs. insulin

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			Delivery	85.41 ± 5.96; $p = 0.32$ vs. insulin	NR	NR	121.28 ± 11.0; $p = 0.005$ vs. insulin
Mirzamoradi_2015 [42]	Insulin (regular + NPH)	59	At diagnosis	112.15 ± 19.39	NR	NR	NR
			At treatment to delivery	123.42 ± 14.71	120.15 ± 9.56	NR	NR
	Glyburide	37	At diagnosis	109.83 ± 68.99; $p = 0.72$ vs. glyburide	NR	NR	NR
			At treatment to delivery	114.02 ± 10.65; $p = 0.83$ vs. glyburide	115.46 ± 8.21; $p = 0.83$ vs. glyburide	NR	NR
Ainuddin_2015 [36]	Insulin (short- + intermediate-acting)-GDM	75	Treatment initiation	172 ± 21.5	NR	NR	NR
			Throughout pregnancy	97.4 ± 2.5	NR	NR	NR
	Metformin-GDM	43	Treatment initiation	138 ± 16	NR	NR	NR
			Throughout pregnancy	96.4 ± 5.7	NR	NR	NR
	Insulin + metformin-GDM	32	Treatment initiation	144 ± 23	NR	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			Throughout pregnancy	95.3 ± 6.3	NR	NR	NR
Arshad_2014 [25]	Regular and NPH	25	1 week of enrolment	117 ± 29.0	NR	NR	NR
	Diet + exercise	25	1 week of enrolment	90.96 ± 16.84; $p = 0.00$ vs. insulin	NR	NR	NR
Mukhopadhyay_2014 [58]	Insulin	30	At enrolment	109.3 ± 19.63	194.3 ± 18.47	NR	NR
			Before confinement	88.17 ± 8.44	128 ± 12.38	NR	NR
	Glibenclamide	30	At enrolment	103 ± 14.62; $p = 0.199$ vs. insulin	184.1 ± 20.46; $p = 0.048$ vs. insulin	NR	NR
			Before confinement	88.23 ± 6.55; $p = 0.97$ vs. insulin	122.7 ± 10.3; $p = 0.07$ vs. insulin	NR	NR
Mesdaghinia_2012 [56]	NPH and regular	100	Baseline	NR	NR	NR	NR
			Delivery	NR	NR	NR	NR
	Metformin	100	Baseline	NR	NR	NR	NR
Spaulonci_2013 [68]	NPH insulin	46	Before treatment	100.87 ± 15.05	Breakfast: 119.81 ± 21.59; lunch: 123.72 ± 19.4; dinner: 132.63 ± 23.82	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			After treatment	88.35 ± 7.45	Breakfast: 106.45 ± 11.75; lunch: 111.43 ± 8.84; dinner: 119.09 ± 16.47	NR	NR
	Metformin	46	Before treatment	102.15 ± 21.96	Breakfast: 120.67 ± 24.03; lunch: 120.61 ± 22.63; dinner: 131.22 ± 25.43	NR	NR
			After treatment	90.09 ± 16.29	Breakfast: 107.7 ± 16.69; lunch: 106.87 ± 11.16; dinner: 110.76 ± 11.57; $p = 0.020$	NR	NR
Tertti_2013 [38]	Insulin (NPH + lispro + aspart)	107	At randomisation	NR	NR	NR	NR
	Metformin (23 required additional insulin)	110	At randomisation	NR	NR	NR	NR
			Delivery	NR	NR	NR	NR
Niromanesh_2012 [39]	NPH and regular as needed	80	First 2 weeks after randomisation	91.2 ± 7.9	114.6 ± 12.1	NR	NR
			Second week after randomisation and until delivery	86.2 ± 8.7	107.6 ± 10.0	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			Randomisation-delivery	88.7 ± 6.3	111.1 ± 9.0	NR	NR
	Metformin	80	First 2 weeks after randomisation	90.3 ± 9.8; $p = 0.529$	112.2 ± 13.0; $p = 0.237$	NR	NR
			Second week after randomisation and until delivery	86.2 ± 8.6; $p = 0.985$	110.4 ± 11.9; $p = 0.106$	NR	NR
		80	Randomisation-delivery	88.3 ± 7.7; $p = 0.683$	111.3 ± 9.1; $p = 0.870$	NR	NR
Balaji_2012 [69]	BIAsp 30	163	At enrolment	103.77 ± 17.94	NR	NR	164.66 ± 38.71
			Delivery	92.97 ± 14.44	NR	NR	127.59 ± 28.99
	BHI 30	157	At enrolment	108.24 ± 24.88	NR	NR	163.83 ± 48.12
			Delivery	95.43 ± 18.96	NR	NR	126.98 ± 29.89
Hassan_2012 [40]	Regular and intermediate-acting human insulin	75	At enrolment	Median (range): 102.11 (89–110)	NR	NR	Median (range): 236.41 (180–309)
			Third trimester/delivery	NR	NR	NR	NR
	Metformin	75	At enrolment	Median (range): 100.89 (88–120); $p = 0.079$ vs. insulin	NR	NR	Median (range): 231.56 (188–280); $p = 0.058$ vs. insulin

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
			Third trimester/delivery	NR	NR	NR	NR
Ijas_2011 [41]	Long-(Protaphane) and rapid-(humalog) acting insulin	50	At randomisation	5.4 ± 0.6 mmol	NR	NR	8.1 ± 1.8
	Metformin	47	At randomisation	5.6 ± 0.9 mmol	NR	NR	8.2 ± 1.9
Observational							
Han_2020 [72]	Insulin lispro + metformin	62	Before treatment	8	NR	NR	Breakfast: 13; lunch: 11.8; dinner: 11.8
			After treatment	5.2	NR	NR	Breakfast: 7; lunch: 6; dinner: 6
	Insulin lispro	55	Before treatment	7.9	NR	NR	Breakfast: 12.8; lunch: 11.8; dinner: 11.8
			After treatment	7; $p < 0.05$ vs. insulin + metformin	NR	NR	Breakfast: 9.2, lunch: 8.8, dinner: 9; $p < 0.05$ vs. insulin + metformin
Krishnakumar_2020 [73]	Insulin	37	Baseline	103.81 ± 7.98	128.30 ± 7.26	NR	NR
			2 months	94.59 ± 5.77; $p < 0.0001$ vs. baseline	116.05 ± 6.01; $p < 0.0001$ vs. baseline	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
	Metformin	44	Baseline	105.16 ± 15.16	130.23 ± 16.83	NR	NR
			2 months	94.84 ± 6.18; $p < 0.0001$ vs. baseline	117.86 ± 6.54; $p < 0.0001$ vs. baseline	NR	NR
Rodrigues 2020 [50]	Insulin	41	3rd trimester	NR	NR	NR	NR
	Metformin + insulin	94	3rd trimester	NR	NR	NR	NR
	Metformin only (subgroup of metformin +)	77	3rd trimester	NR	NR	NR	NR
Zaharieva_2020 [75]	Insulin vs. no insulin	Total-90; insulin $n = 34$	NR	5.2 vs. 4.8; $p = 0.0004$	NR	NR	NR
Tang_2019 [31]	Insulin	180	NA	Median (IQR): 5.8 (5.5, 6.2)	NR	Median (IQR): 10.2 (9.0, 11.8)	Median (IQR): 8.6 (7.5, 9.3)
	MNT	354	NA	Median (IQR): 5.3 (5.1, 5.5); $p < 0.001$	NR	Median (IQR): 9.5 (8.3, 10.6); $p < 0.001$	Median (IQR): 8.3 (7.0, 9.4); $p < 0.292$
McGrath_2018 [82]	Insulin (NPH or Levemir and/or NovoRapid)	83	At diagnosis	4.8	NR	NR	NR
	Metformin	83	At diagnosis	4.9	NR	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
	Diet + lifestyle	83	At diagnosis	4.4; $p < 0.001$ across treatment arms	NR	NR	NR
Rowan_2018 [85]	Insulin (Adelaide cohort)	51	At enrolment	88 ± 13	NR	NR	NR
	Metformin (Adelaide cohort)	51	36 weeks	NR	NR	NR	NR
	Insulin (Auckland cohort)	58	At enrolment	88 ± 16	NR	NR	NR
	Metformin (Auckland cohort)	58	36 weeks	NR	NR	NR	NR
	Insulin (Adelaide cohort)	54	At enrolment	90 ± 11	NR	NR	NR
	Metformin (Adelaide cohort)	54	36 weeks	NR	NR	NR	NR
	Insulin (Auckland cohort)	45	At enrolment	95 ± 16	NR	NR	NR
			36 weeks	NR	NR	NR	NR
Simeonova-Krstevska_2018 [28]	Levemir (detemir) + aspart	101	NA	5.8 ± 1.4; $p < 0.05$ vs. metformin	7.9 ± 1.9; $p < 0.05$ vs. metformin	NR	NR
	Metformin	48	NA	5.3 ± 0.7; p = NS vs. diet	7.0 ± 1.2; p = NS vs. diet	NR	NR
	Diet	200	NA	5.1 ± 0.9; $p < 0.01$ vs. insulin	6.9 ± 1.6; $p < 0.05$ vs. insulin	NR	NR
Olmos_2017 [89]	Basal-bolus insulin therapy (BBIT)	73	NA	NR	NR	NR	NR

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
	Without BBIT (diet/metformin)	58	NA	NR	NR	NR	NR
Xie_2017 [90]	Research arm (insulin aspart intensive treatment/insulin pump)	45	NA	5.2 ± 0.6	NR	NR	7.3 ± 1.2
	Reference arm (insulin aspart + detemir)	45	NA	6.8 ± 0.6; $p < 0.05$ vs. research arm	NR	NR	8.8 ± 1.2; $p < 0.05$ vs. research arm
Ito_2016 [92]	RHI or rapid-acting insulin (insulin aspart or lispro) and NPH insulin)	32	At diagnosis	91.5 ± 7.9	NR	179.9 ± 34.9	150.5 ± 28.5
		32	Delivery	93.2 ± 9.4	NR	162.2 ± 41.2	124.2 ± 31.4
	Diet	70	At diagnosis	89.6 ± 8.7; $p = 0.313$ vs. insulin	NR	155.3 ± 33.6; $p = 0.001$ vs. insulin	135.3 ± 29.7; $p = 0.017$ vs. insulin
			Delivery	90.8 ± 7.7; $p = 0.251$ vs. insulin	NR	142.9 ± 40.7; $p = 0.064$ vs. insulin	118.0 ± 29.0; $p = 0.410$ vs. insulin
Koren_2016 [55]	Insulin detemir	29	NA	5.1 ± 0.5	NR	8 ± 1.3	7.78 ± 1.3
	Glyburide	62	NA	5.1 ± 1; $p = 0.91$	NR	7.8 ± 1.3; $p = 0.82$	7.12 ± 1.8; $p = 0.13$
Ozgu-Erdinc_2016 [29]	Insulin	144	NA	Median (range): 87 (56–275)	NR	Median (max–min): 144 (67–340)	Median (max–min): 132 (53–320)

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
	Diet	115	NA	Median (range): 80 (58–157); $p < 0.001$	NR	Median (max–min): 137.5 (72–212); $p = 0.002$	Median (max–min): 118.5 (72–207); $p < 0.001$
Yanagisawa_2016 [30]	Insulin	36	NA	OGTT: 88 ± 11 meal TT: 92 ± 16	NR	OGTT: 177 ± 29; meal TT: 147 ± 32	OGTT: 161 ± 22; Meal TT: 128 ± 32
	MNT	77	NA	OGTT: 83 ± 9; $p = 0.013$ vs. insulin, meal TT: 84 ± 7; $p = 0.014$	NR	OGTT: 173 ± 28; p = NS vs. insulin Meal TT: 121 ± 20 $p < 0.001$	OGTT: 157 ± 25; p = NS vs. insulin meal TT: 104 ± 18 $p < 0.001$
You_2016 [99]	Regular insulin (NPH if required)	55	Baseline	96.9 ± 15.4	NR	200.7 ± 33.9	195.9 ± 37.2
	Fast-acting insulin analogues (NPH if required)-aspart or lispro	142	Baseline	99.4 ± 20.5; $p = 0.494$	NR	208.0 ± 36.4; $p = 0.194$	188.8 ± 40.6; $p = 0.249$
Benhalima_2015 [32]	Short-acting or long-acting insulin or both	145	NA	97.6 ± 18.8	NR	194.7 ± 30.1	185.2 ± 28.5
	Diet	456	NA	87.7 ± 10.3; $p < 0.0001$ vs. insulin	NR	184.5 ± 25.8; $p < 0.0001$ vs. insulin	175.0 ± 22.8; $p < 0.0001$ vs. insulin

Table 3 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	1-h PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Deepaklal_2014 [100]	Insulin lispro	201	At enrolment/ first trimester	99.01	Post breakfast: 126.9 ± 44.2, post lunch: 125.5 ± 38.3, post dinner: 127.2 ± 38.6	NR	NR
			Delivery	NR	Post breakfast: 106.5 ± 18.8, post lunch: 111 ± 18.4, post dinner: 111.8 ± 19.5	NR	NR
Marques_2014 [102]	NPH insulin	33	NA	NR	NR	NR	NR
	Metformin	32	NA	NR	NR	NR	NR
Goh_2011 [109]	Intermediate-acting isophane insulin and short-acting insulin analog	399	NA	5.4 ± 1.1	NR	NR	9.9 ± 2.1
	Metformin	465	NA	5.3 ± 0.8	NR	NR	9.4 ± 1.6
	Diet	371	NA	4.5 ± 0.7, $p < 0.0001$ across treatment arms	NR	NR	9.5 ± 1.1, $p = 0.0008$ across treatment arms
Flores-Le Roux_2010 [111]	Insulin	41	3rd trimester	NR	NR	NR	NR
	Diet	70	3rd trimester	NR	NR	NR	NR
	NEF-GDM	18	3rd trimester	NR	NR	NR	NR

BBIT basal-bolus insulin therapy, *BHI* biphasic premixed human insulin, *BIAsp* biphasic insulin aspart, *FBG* fasting blood glucose, *GDM* gestational diabetes mellitus, *NA* not applicable, *NEF* no endocrinologic follow-up, *NPH* neutral protamine Hagedorn, *NR* not reported, *PPG* postprandial glucose, *RCT* randomized controlled trial, *RHI* regular human insulin, *SD* standard deviation

Table 4 Clinical outcomes in women with pre-existing diabetes and mixed population

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
RCT						
Jing ji_2020 [27]	IDET + Novolin-R	120	Before treatment	6.84 ± 1.31	NR	9.40 ± 1.62
		120	7 days after treatment	5.33 ± 0.72	NR	6.73 ± 0.79
		120	3 months after treatment	NR	NR	NR
	Insulin NPH + Novolin-R	120	Before treatment	6.86 ± 1; $p = 0.918$ vs. IDET + Novolin-R	NR	9.55 ± 1.54; $p = 0.549$ vs. IDET + Novolin-R
		120	7 days after treatment	5.71 ± 0.87, $p < 0.001$ vs. IDET + Novolin-R	NR	7.38 ± 0.80; $p < 0.001$ vs. IDET + Novolin-R
		120	3 months after treatment	NR	NR	NR
Ainuddin_2015 [44]	Insulin (short- + intermediate-acting) T2DM	100	Treatment initiation	139.85 ± 29.43	NR	NR
		100	Throughout pregnancy	97.55 ± 3.29	NR	NR
	Metformin-T2DM	16	Treatment initiation	138.06 ± 45.58	NR	NR
		16	Throughout pregnancy	97.87 ± 3.83	NR	NR
	Insulin added-on to metformin-T2GDM	90	Treatment initiation	144.14 ± 29.64	NR	NR
		90	Throughout pregnancy	97.50 ± 3.35	NR	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Herrera_2015 [70]	IDET	42	NA	Per protocol: 100.7 ± 10.1; ITT: 101.2 ± 9.2	Per protocol: 115.2 ± 10.2 ITT: 115.2 ± 9.6	NR
	Insulin NPH	45	NA	Per protocol: 97.3 ± 7.4; $p = 0.1093$; ITT: 99.3 ± 8.8; $p = 0.3347$	Per protocol: 112.9 ± 8.9; $p = 0.3204$. ITT: 113.4 ± 9.0; $p = 0.3879$	NR
Refuerzo_2015 [71]	Regular + NPH	13	At enrolment/1st trimester	NR	NR	NR
			Mid-trimester	NR	NR	NR
			3rd trimester	NR	NR	NR
			Delivery	NR	NR	NR
			3rd trimester/delivery	NR	NR	NR
	Metformin	8	At enrolment/1st trimester	NR	NR	NR
			Mid-trimester	NR	NR	NR
			3rd trimester	NR	NR	NR
			Delivery	NR	NR	NR
			3rd trimester/delivery	NR	NR	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Hod_2014 [57]	IDET + aspart	152	Before treatment	106.0 ± 59.2	NR	NR
		152	24 weeks	96.8 mg/dl ± 5.4 mmol/l	NR	NR
		152	36 weeks	85.7 mg/dl ± 4.8 mmol/l	NR	NR
	Insulin NPH + aspart	158	Before Treatment	107.8 ± 58.1	NR	NR
		158	24 weeks	113.8 mg/dl ± 6.3 mmol/l; $p = 0.012$ vs. IDET	NR	NR
		158	36 weeks	97.4 mg/dl ± 5.4 mmol/l; $p = 0.017$ vs. IDET	NR	NR
Hickman_2013 [52]	Regular + NPH	14	At enrolment	Median (IQR): 95.04 (86–115)	Median (IQR): 128.62 (115–143)	NR
		14	18–20 weeks	Median (IQR): 92.38 (89–116)	Median (IQR): 120.46 (113, 142)	NR
		14	28–30 weeks	Median (IQR): 90.64 (84–106)	Median (IQR): 126.45 (115–137)	NR
		14	36–38 weeks	Median (IQR): 85.18 (80–107)	Median (IQR): 125.25 (112–138)	NR
	Metformin	14	At enrolment	Median (IQR): 97.38 (92–101); $p = 0.4$	Median (IQR): 120.40 (115–129); $p = 0.31$	NR
		14	18–20 weeks	Median (IQR): 97.00 (93–100); $p = 0.69$	Median (IQR): 118.40 (107–122); $p = 0.5$	NR
		14	28–30 weeks	Median (IQR): 92.43 (90–98); $p = 0.44$	Median (IQR): 119.00 (114–125); $p = 0.35$	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
		14	36–38 weeks	Median (IQR): 89.49 (82–96); $p = 0.93$	Median (IQR): 122.59 (118–130); $p = 0.63$	NR
Observational						
Christman 2019 [117]	IDET	154	Hospital stay duration	109.2 ± 22.6	NR	NR
Sleeman_2019 [118]	Insulin glargine or IDET	44	Baseline	NR	NR	NR
			Delivery	NR	NR	NR
	Insulin NPH	19	Baseline	NR	NR	NR
			Delivery	NR	NR	NR
Smrz_2019 [119]	CSII vs. MDI	117	NR	NR	NR	NR
Sunjaya_2018 [122]	Insulin (long-acting, intermediate-acting, short-acting, rapid-acting and human premixed)	25	Before treatment	157.12 ± 40.24	NR	234.88 ± 52.58
			After treatment	124.88 ± 34.14	NR	NR
	Oral antidiabetics (metformin and pioglitazone)	4	Before treatment	153.50 ± 21.64	NR	199.75 ± 14.43
			After treatment	175.75 ± 71.94	NR	NR
	MNT	16	Before treatment	134.33 ± 41.43	NR	207.31 ± 60.66
			After treatment	113.81 ± 34.20; $p = 0.021$ across treatment arms	NR	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Abell_2017 [62]	MDI-glargine/detemir/NPH	127	1st trimester	NR	NR	NR
		127	2nd trimester	NR	NR	NR
		127	3rd trimester/delivery	NR	NR	NR
	CSII-Aspart	40	1st trimester	NR	NR	NR
		40	2nd trimester	NR	NR	NR
		40	3rd trimester/delivery	NR	NR	NR
Stanirowski_2017 [123]	Insulin-treated GDM	6	NA	Median (IQR): 98 (96–112)	NR	Median (IQR): 153 (143–158)
	Diet-treated GDM	16	NA	Median (IQR): 86 (80–97)	NR	Median (IQR): 156 (138–163)
	Insulin-treated PGDM	6	NA	NR	NR	NR
	No diabetes	25	NA	Median (IQR): 79 (74–83); $p < 0.05$	NR	Median (IQR): 103.5 (85.5–116.5); $p < 0.01$
Dalfra_2016 [124]	ILPS-GDM	572	NA	4.9 ± 0.7	NR	NR
	NPH-GDM	242	NA	6.3 ± 1.5; $p < 0.001$ vs. ILPS-GDM	NR	NR
	ILPS-Pregestational T1DM	58	NA	6.0 ± 1.4	NR	NR
	NPH-Pregestational T1DM	61	NA	7.7 ± 2.2; $p = 0.001$ vs. ILPS-T1DM	NR	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Neff_2014 [61]	CSII-Aspart	40	At booking	NR	NR	NR
			Delivery	NR	NR	NR
	MDI-aspart + NPH	424	At booking	NR	NR	NR
			Delivery	NR	NR	NR
Colatrella_2013 [126]	ILPS-T2DM	7	Baseline	110.0 ± 7.8	NR	NR
			After treatment	89.2 ± 12.7	NR	NR
	ILPS-GDM	46	Baseline	98.6 ± 15.8	NR	NR
			After treatment	94.3 ± 13.5	NR	NR
	Insulin NPH-T2DM	18	Baseline	109.8 ± 15.8	NR	NR
			After treatment	95.5 ± 8.2	NR	NR
	Insulin NPH-GDM	18	Baseline	92.2 ± 14.5	NR	NR
			After treatment	95.8 ± 12.8	NR	NR
Bruttomesso_2011 [128]	CSII-rapid-acting insulin analog	100	1st trimester	NR	NR	NR
			2nd trimester	NR	NR	NR
			End of pregnancy	NR	NR	NR
	Glargine-MDI	44	1st trimester	NR	NR	NR
			2nd trimester	NR	NR	NR
			End of pregnancy	NR	NR	NR

Table 4 continued

First author_Year	Treatment arms	Sample size	Time points	FBG (mean ± SD) mg/dl or mmol/l	PPG (mean ± SD) mg/dl or mmol/l	2-h PPG (mean ± SD) mg/dl or mmol/l
Garcia-Dominguez_2011 [53]	Human insulin	241	1st trimester	NR	NR	NR
			2nd trimester	NR	NR	NR
			Delivery	NR	NR	NR
	Insulin analog	86	1st trimester	NR	NR	NR
			2nd trimester	NR	NR	NR
			Delivery	NR	NR	NR
Negrato_2010 [51]	Glargine + lispro-PGDM	18	36 weeks	107.9 ± 27.4	NR	NR
	NPH + lispro-PGDM	38	36 weeks	109.5 ± 37.1; $p > 0.05$ vs. glargine-PGDM group	NR	NR
	Glargine + lispro-GDM	37	36 weeks	82.8 ± 14.5	NR	NR
	NPH + lispro-GDM	45	36 weeks	91.6 ± 21.5; $p = 0.03$ vs. glargine-GDM group	NR	NR

FBG fasting blood glucose, *GDM* gestational diabetes mellitus, *IDET* insulin detemir, *ILPS* insulin lispro protamine suspension, *IQR* interquartile range, *MDI* multiple daily injection, *MNT* medical nutrition therapy, *NPH* neutral protamine Hagedorn, *NR* not reported, *OGTT* oral glucose tolerance test, *OHA* oral hypoglycemic agents, *PGDM* pregestational diabetes mellitus, *PPG* postprandial glucose, *SD* standard deviation, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

Table 5 Maternal outcomes in women with gestational diabetes mellitus

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
RCT												
Galal_2019 [20]	Human insulin (intermediate-acting and short-acting)	50	1 week	NR	NR	4 (7.4%)	NR	44 (81.5%)	NR	NR	NR	NR
	Metformin	56	1 week	NR	NR	7 (13.5%); $p=0.056$	NR	30 (57.7%); $p=0.031$	NR	NR	NR	NR
Ghomian_2019 [33]	Levemir (IDET) + aspart	143	Delivery	NR	NR	19 (13.2%)	NR	68 (48%)	NR	NR	NR	NR
	Metformin	143	Delivery	NR	NR	20 (13.9%);	NR	56 (39%)	NR	NR	NR	NR
Wasim_2019 [21]	Insulin-humulin R and NPH	141	Delivery	NR	NR	20 (14.5%)	NR	93 (65.9%)	NR	28 (19.8%)	NR	19 (13.4%)
	Metformin	137	Delivery	NR	NR	13 (9.2%); $p=0.226$	NR	76 (55.4%); $p=0.073$	NR	17 (12.4%); $p=0.092$ vs. insulin	NR	06 (4.3%)
Eid_2018 [34]	Insulin (NPH + regular)	116	After treatment	43 (37.1%)	NR	7 (6%)	NR	49 (42.2%)	NR	6 (5.2%)	NR	3 (2.9%)
	Metformin	113	After treatment	39 (34.5%); $p=0.29$	NR	8 (7.3%); $p=0.93$	NR	42 (37.2%); $p=0.81$	NR	5 (4.4%); $p=0.71$	NR	0

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Huhtala_2018 [43]	NPH insulin and/or rapid-acting insulin lispro or insulin aspart	107	Delivery	58 (54.2%)	NR	NR	NR	18 (16.8%)	NR	GHTN: 4 (3.7%) PE: 10 (9.3%)	NR	NR
	Metformin	110	Delivery	41 (37.6%); $p = 0.014$ vs. insulin	NR	NR	NR	15 (13.8%); $p = 0.53$ vs. insulin	NR	GHTN: 2 (1.8%); $p = 0.44$; PE: 5 (4.6%); $p = 0.17$ vs. insulin	NR	NR
	Diet	103	Delivery	31 (30.1)	NR	NR	NR	16 (15.5)	NR	GHTN: 4 (3.9%), PE: 2 (1.9%)	NR	NR
Senat_2018 [54]	Insulin (rapid analogues/basal or intermediate)	442	NA	NR	NR	18 (4.1%)	NR	Elective CS: 66 (14.9%), emergency CS: 58 (13.1%)	NA	NR	NR	13 (3.5%)

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Glyburide	367	NA	NR	NR	25 (6.8%)	RD: 2.7 (− 1.0 to 6.4); $p = 0.09$	Elective CS: 36 (9.8%), emergency CS: 63 (17.2%)	Elective CS RD: − 5.1 (− 9.6 to − 0.6), emergency CS RD: 4.0 (− 0.9 to 9.0); $p = 0.08$	NR	NR	93 (28.8%) $p < 0.001$
Hamadani_2017 [35]	Insulin NPH	30	NA	NR	NR	NR	NR	11 (36.7%)	NR	NR	NR	NR
	Metformin	30	NA	NR	NR	NR	NR	13 (43.3%); $p = 0.59$ vs. insulin	NR	NR	NR	NR
Khan_2017 [24]	Insulin (mixed human suspension)	385	After treatment	NR	NR	48 (12.5%)	NR	139 (36.1%)	NR	60 (15.6%)	NR	NR
	Metformin	385	After treatment	NR	NR	10 (2.6%), $\chi^2 = 26.93$; $p = 0.000$	NR	157 (40.8%), $\chi^2 = 1.778$; $p = 0.182$	NR	17 (4.4%), $\chi^2 = 26.68$; $p = 0.000$ vs. insulin	NR	NR
Somani_2016 [26]	Human insulin (regular, NPH or both)	33	Delivery	8 (24.24%)	NR	NR	NR	23 (69.7%)	NR	NR	NR	3 (9.09%)

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Metformin	32	Delivery	12 (37.5%); $p=0.29$ vs. insulin	NR	NR	NR	24 (75%); $p=0.64$ vs. insulin	NR	NR	NR	1 (3.1%); $p=0.57$ vs. insulin
Ainuddin_2015 [36]	Insulin (short- + intermediate-acting)-GDM	75	Throughout pregnancy	14 (18.7%)	NR	NR	NR	38 (50.7%)	NR	PIH: 18 (24%); PE: 6 (8%)	NR	NR
	Metformin-GDM	43	Throughout pregnancy	10 (23.3%)	NR	NR	NR	18 (41.9%)	NR	PIH: 8 (18.6); PE: 0%	NR	NR
	Insulin added on to metformin-GDM	32	Throughout pregnancy	10 (31.3%)	NR	NR	NR	18 (56.3%)	NR	PIH: 3 (9.4%); PE: 1 (3.1%)	NR	NR
Mirzamoradi_2015 [42]	Insulin (regular + NPH)	59	At treatment to delivery	NR	NR	NR	NR	42 (71.20%)	NR	13.6%	NR	NR
	Glyburide	37	At treatment to delivery	NR	NR	NR	NR	28 (75.7%); $p=0.63$	NR	8.1%; $p=0.41$	NR	NR
Ruholamin_2014 [37]	Insulin	50	NA	NR	NR	NR	NR	35 (70%)	NR	NR	NR	NR
	Metformin	50	NA	NR	NR	NR	NR	37 (74%) $p=0.66$	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Tertti_2013 [38]	Insulin (NPH + lispro + aspart)	107	Delivery	58 (54.2%)		NR	NR	18 (16.8%)		PIH: 4 (3.7%); PE: 10 (9.4%)	NR	NR
	Metformin	110	Delivery	42 (38.2%)	RR: 0.7 (0.5–1.0); $p = 0.08$	NR	NR	15 (13.6%)	RR: 0.8 (0.4–1.6); $p = 0.55$	PIH: 2 (1.8%); PE: 5 (4.6%)	RR (95% CI)- PIH: 0.5 (0.1–2.7); $p = 0.41$; PE: 0.5 (0.2–1.4); $p = 0.19$	NR
Balaji_2012 [69]	BIAsp 30	163	Delivery	NR	NR	1 (1.63%)	NR	144 (88.3%)	NR			NR
	BHI 30	157	Delivery	NR	NR	2 (3.26%); $p > 0.05$	NR	141 (89.8%); $p > 0.05$	NR			NR
Hassan_2012 [40]	Regular- and intermediate-acting human insulin	75	Delivery	14 (18.7%)	NR	NR	NR	42 (56%)	NR			NR
	Metformin	75	Delivery	20 (26.7%); $p = 0.001$ vs. insulin	NR	NR	NR	25 (33.3%); $p = 0.004$ vs. insulin	NR			NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Mesdaghinia_2012 [56]	NPH and regular	100	NA	NR	NR	8 (8)	NR	NR	NR			NR
	Metformin	100	NA	NR	NR	0 (0)	NR	NR	NR			NR
Niromanesh_2012 [39]	NPH and regular as needed	80	Randomisation-delivery	NR	NR	4 (5.0%)		Overall CS: 37 (46.3%), emergency CS: 16 (20.0%)	NR	PE: 7 (8.8%); PIH: 11 (13.8%)	NR	NR
	Metformin	80	Randomisation-delivery	NR	NR	9 (11.3%)	RR: 2.2 (0.7–7.0); $p = 0.148$	Overall CS: 34 (42.5%), emergency CS: 25 (31.3%)	RR-Overall CS: 0.7 (0.2–2.2); $p = 0.633$; emergency CS: 1.6 (0.9–2.7); $p = 0.102$	PE: 5 (6.3%); PIH: 4 (5%)	RR (95% CI)- PE: 0.7 (0.2–2.2), $p = 0.548$; PIH: 0.4 (0.1–1.1), $p = 0.058$	NR
Ijas_2011 [41]	Long- (Protaphane) and rapid- (Humalog) acting insulin	50	NA	26 (52.0%)	NA	NR	NR	10 (20.0%)	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Metformin	47	NA	24 (51.0%)	RR: 1.0 (0.67–1.45), *p* = 0.960 vs. insulin	NR	NR	18 (38.3%)	RR: 1.9 (0.99–3.31), *p* = 0.047 vs. insulin	NR	NR	NR
Observational												
Han_2020 [72]	Insulin lispro + metformin	62	After treatment	NR	NR	NR	NR	21 (33.87%)	NR	NR	NR	NR
	Insulin lispro	55	After treatment	NR	NR	NR	NR	34 (61.82%); *p* = 0.003 vs. lispro	NR	NR	NR	NR
Meghelli_2020 [77]	Insulin	63	NA	25 (39.7%)	NR	6 (9.5%)	NR	22 (34.9%)	NR	1 (1.6%)	NR	NR
	No Insulin	56	NA	18 (32.7%); *p* = 0.43 vs. insulin	NR	7 (12.7%)	NR	21 (37.5%)	NR	2 (3.6%)	NR	NR
Rodrigues_2020 [50]	Insulin	41	NA	22/40 (55)	NR	NR	NR	17/40 (42.5)	NR	1 (2.4)	NR	NR
	Metformin + insulin	94	NA	48/87 (55.2); *p* = 0.986 vs. insulin	NR	NR	NR	25/93 (26.9)	NR	1 (1.1); *p* = 0.52 vs. insulin	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Metformin only	77	NA	38/73 (52.1); $p = 0.076$ vs. insulin	NR	NR	NR	19/76 (25)	NR	0	NR	NR
Landi_2019 [49]	Insulin	3450	NA	1884 (54.6%)		311 (9.0%)		Elective CS: 808 (23.4%), emergency CS: 650 (17.0%)		116 (3.5%)		NR
	Metformin	3818	NA	1965 (51.5%)	RR (95% CI): 0.94 (0.90–0.98)	269 (7.1%)	RR (95% CI): 0.78 (0.67-0.92)	Elective CS: 720 (18.9%), emergency CS: 640 (18.6%)	RR (95% CI)- Elective CS: 0.81 (0.74-0.88), Emergency CS: 0.92 (0.83-1.01)	139 (3.6%)	RR (95% CI): 1.08 (0.85-1.38)	NR
Munn_2019 [78]	Glyburide	195,000	NA	NR	NR	NR	NR	64,368 (33%)	NR	NR	NR	NR
	Insulin	195,000	NA	NR	NR	NR	NR	63,982 (33%)	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Ng_2019 [79]	Insulin	576	NA	NR	NR	NR	NR	Emergency CS: 106 (18.40%), elective CS: 162 (28.13%)	NR	42 (7.29%)	NR	NR
	No insulin	1281	NA	NR	NR	NR	NR	Emergency CS: 215 (16.78%), elective CS: 287 (22.40%)	NR	52 (4.06%)	NR	NR
Bogdanet_2018 [46]	IDET and insulin aspart	752	NA	NR	NR	NR	NR	353/742 (47.6%)		PE: 41/718 (5.7%) PIH: 96/719 (13.4%)	NR	NR
	MNT	567	NA	NR	NR	NR	NR	172/567 (30.3%)	Adjusted: 1.67 (1.25–2.23)	PE: 24/567 (4.2%) PIH: 66/567 (11.6%)	Adjuster OR; PE: 0.81 (0.40–1.62), $p = 0.55$. PIH: 0.87 (0.57–1.33); $p = 0.53$ vs. insulin	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Normal glucose tolerance	2496	NA	NR	NR	NR	NR	608/2468 (24.63%)	Adjusted: 1.44 (1.11–1.87); $p < 0.01$ vs. insulin	PE: 94/2496 (3.76%); PIH: 190/2420 (7.85%)	Adjusted OR; PE: 0.64 (0.34–1.12); $p = 0.17$. PIH: 1.11 (0.74–1.66); $p = 0.60$ vs. insulin	NR
Christian_2018 [80]	IDET (with/without aspart)	17	NA	NR	NR	NR	NR	9 (53%)	NR	2 (12%)	NR	NR
	Metformin	58	NA	NR	NR	NR	NR	24 (41.3%)	NR	2 (3.4%)	NR	NR
	Metformin + insulin	32	NA	NR	NR	NR	NR	23 (71.8%)	NR	1 (3.1%)	NR	NR
Leung_2018 [81]	Insulin	223	NA	NR	NR	17 (7.6%)	NR	47 (21%)	NR	19 (8.5%)	NR	NR
	Glyburide	171	NA	NR	NR	11 (6.4%); $p = 0.871$	NR	23 (13.4%); $p = 0.950$	NR	8 (5.6%)	NR	NR
McGrath_2018 [82]	Insulin (NPH or Levemir and/or NovoRapid)	83	38.4 weeks	NR	NR	NR	NR	25 (30.1%)	NR	NR	NR	NR
	Metformin	83	38.6 weeks	NR	NR	NR	NR	35 (42.2%)	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Diet + lifestyle	82	38.9 weeks	NR	NR	NR	NR	27 (32.9%)	NR	NR	NR	NR
Patanjali_2018 [84]	Insulin	58 (20.1%)	NA	NR	NR	37.9%; $p = 0.04$ vs. other group	NR	0.66	NR	NR	NR	NR
	Metformin	Only metformin: 23 (8%), required insulin with metformin: 28 (9.7%)	NA	NR	NR	NR	NR	0.57	NR	NR	NR	NR
	Diet	179	NA	NR	NR	NR	NR	0.4	NR	NR	NR	NR
Rowan_2018 [85]	Insulin (Adelaide cohort)	51	NR	NR	NR	NR	NR	18 (35.3%)	NR	2 (3.9%)	NR	NR
	Metformin (Adelaide cohort)	58	NR	NR	NR	NR	NR	25 (43.1%)	NR	3 (5.1%)	NR	NR
	Insulin (Auckland cohort)	54	NR	NR	NR	NR	NR	20 (37.0%)	NR	0	NR	NR
	Metformin (Auckland cohort)	45	NR	NR	NR	NR	NR	15 (33.3%)	NR	2 (4.4%)	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Simeonova-Krstevska_2018 [28]	Levemir (IDET) + aspart	101	NA	NR	NR	20 (19.8%)	NR	66/100 (66%)	NR	6 (6%); p = NS vs. metformin	NR	NR
	Metformin	48	NA	NR	NR	2 (4.2%); p = NS vs. diet; $p < 0.01$ vs. insulin	NR	24/46 (52.2%); p = NS vs. insulin; $p < 0.05$ vs. diet	NR	4 (8.3%); $p < 0.01$ vs. diet	NR	NR
	Diet	200	NA	NR	NR	13 (6.5%); $p < 0.01$ vs. insulin	NR	41/130 (31.5%); $p < 0.05$ vs. insulin	NR	1 (0.5%); $p < 0.01$ vs. insulin	NR	NR
Vanlalhruaii_2018 [86]	Insulin	151	NA	NR	NR	Insulin throughout: 9 (6.27%), insulin 1st trimester: 5 (8.77%)	NR	NR	NR	PE: 3%; GHTN: 10.5%	NR	6.30%
	Metformin-1st trimesters	186	NA	NR	NR	23 (12.37%)	NR	NR	NR	PE: 5%; p = 0.44 vs. insulin; GHTN: 15.1%	NR	3.70%; p = 0.06 vs. insulin

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Metformin-2nd trimesters	203	NA	NR	NR	20 (9.85%)	NR	NR	NR	PE: 4%; $p = 0.35$ vs. metformin 1st trimesters; GHTN: 10.5%	NR	3.10%; $p = 0.40$ vs. metformin 1st trimesters
Bowker_2017 [87]	Insulin	5057 (27.0%)	NA	NR	NR	583 (11.5%)	NR	NR	NR	NR	NR	NR
	Metformin ± insulin	478 (2.5%)	NA	NR	NR	91 (19.0%)	NR	NR	NR	NR	NR	NR
	No specific intervention	13,226 (70.5%)	NA	NR	NR	1553 (11.7%), $p < 0.001$ across treatment arms	NR	NR	NR	NR	NR	NR
Gibbons_2017 [88]	Insulin	315	NA	NR	NR	116 (36.8%)	1.82 (1.37–2.41); $p < 0.001$ vs. OHA and diet	151 (47.9%); $p < 0.001$ vs. OHA and diet	NR	NR	NR	NR
	OHA (glyburide/metformin)	211	NA	NR	NR	46 (21.8%)		89 (42.2%)	NR	NR	NR	NR
	Diet	563	NA	NR	NR	142 (25.2%)		187 (33.2%)	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Ito_2016 [92]	Insulin	32	Delivery	NR	NR	NR	NR	11 (34.4%)		NR	NR	NR
	Diet	70	Delivery	NR	NR	NR	NR	19 (27.1%)	Adjusted: 1.24 (0.47–3.16), $p = 0.656$ vs. insulin	NR	NR	NR
Koning_2016 [93]	Diet + additional insulin (aspart, NPH and aspart + NPH)	360 (43.9%)	NA	262 (72.8%)	NR	24 (6.7%)	NR	CS: 39 (10.8%), planned CS: 56 (15.6%)	NR	PE: 12 (3.3%) GHTN: 32 (8.9%)	NR	NR
	Diet	460 (56.1%)	NA	271 (58.9%)	NR	28 (6%)	NR	CS: 60 (13.0%), p = NS vs. insulin; planned CS: 37 (8.0%), $p = 0.0001$ vs. insulin	NR	PE: 16 (3.5%); p = NS vs. insulin GHTN: 43 (9.3%); p = NS vs. insulin	NR	NR
Koren_2016 [55]	IDET	29	NA	NR	NR	3 (10.3%)	NR	10 (34.5%)	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Glyburide	62	NA	NR	NR	6 (9.7%); *p* = 1 vs. insulin	NR	26 (41.9%); *p* = 0.64 vs. insulin	NR	NR	NR	Hypoglycaemia (< 3.3 mmol/L): 12 (19.4%); *p* = 0.01 Severe hypoglycaemia: 1 (1.6%); *p* = 1
Ozgu-Erdinc_2016 [29]	Insulin	144	NA	NR	NR	24 (16.7%)	NR	99 (68.8%)	NR	15 (10.4%)	NR	NR
	Diet	115	NA	NR	NR	14 (12.2%); *p* = 0.952 vs. insulin	NR	74 (64.3%); *p* = 0.507 vs. insulin	NR	10 (8.7%); *p* = 0.678 vs. insulin	NR	NR
Saleem_2016 [94]	Insulin BiD	240	NA	NR	NR	NR	NR	120 (50%)	NR	NR	NR	80 (33.3%)
	Insulin QiD	240	NA	NR	NR	NR	NR	72 (30%); *p* = 0.001 vs. BiD	NR	NR	NR	NR
Watanabe_2016 [95]	Insulin	10	NA	NR	NR	3 (30.0%)	NR	7 (70.0%)	NR	PIH: 3 (30.0%)	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Diet	27	NA	NR	NR	5 (18.5%); *p* = 0.451 vs. insulin	NR	10 (37.0%); *p* = 0.074 vs. insulin	NR	PIH: 2 (7.4%); *p* = 0.074 vs. insulin	NR	NR
Yanagisawa_2016 [30]	Insulin	36	NA	NR	NR	2 (6%)	NR	17 (47%)	NR	PIH: 3 (8%)	NR	NR
	MNT	77	NA	NR	NR	2 (3%); *p* = NS vs. insulin	NR	23 (30%); *p* = NS vs. insulin	NR	PIH: 6 (8%); *p* = NS vs. insulin	NR	NR
You_2016 [99]	Regular insulin (NPH, if required)	55	Delivery	NR	NR	9 (16.4%)	NR	Elective: 25 (45.5%), Emergency: 5/30 (16.7%)	NR	PE: 6 (10.9%)	NR	NR
	Fast-acting insulin analogues (NPH if required)-aspart or lispro	142	Delivery	NR	NR	29 (20.4%); *p* = 0.554	NR	Elective: 57 (40.1%), *p* = 0.522, Emergency: 21/85 (24.7%), *p* = 0.452 vs. regular insulin	NR	PE: 11 (7.7%); *p* = 0.572	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Benhalima_2015 [32]	Short-acting or long-acting insulin or both	145	NA	NR	NR	20 (13.9%)	NR	64 (44.1%)	NR	GHTN: 6 (4.2%); PE: 11 (7.6%)	NR	NR
	Diet	456	NA	NR	NR	58 (12.8%); $p = 0.743$	NR	122 (27.0%); $p < 0.0001$	NR	GHTN: 35 (7.7%); $p = 0.140$; PE: 18 (4.0%); $p = 0.076$	NR	NR
Castillo_2015 [59]	Insulin	4191	NA	NR	NR	371 (8.9%)		2201 (52.5%)	NR	NR	NR	NR
	Glyburide	4982	NA	NR	NR	472 (9.5%)	ARR: 1.06 (0.93–1.21)	2522 (50.6%)	ARR: 0.97 (0.93–1.00)	NR	NR	NR
Inocencio_2015 [97]	Insulin	167	NA	NR	NR	NR	NR	39.5% ($n = 87$)	NR	NR	NR	NR
Koivunen_2015 [64]	Insulin-cohort 2006	1128	NA	373 (33.1%)	NR	NR	NR	229 (20.4%)	NR	79 (7.0%)	NR	NR
	Insulin-cohort 2010	887	NA	398 (44.9%)	NR	NR	NR	245 (27.8%)	NR	105 (11.8%); $p < 0.0001$ vs. insulin-cohort 2006	NR	NR
	Diet-cohort 2006	4057	NA	961 (23.7%)	NR	NR	NR	847 (21.0%)	NR	343 (8.5%)	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Diet-cohort 2010	5796	NA	1495 (25.8%); $p < 0.0001$ vs. insulin across the cohort	NR	NR	NR	1224 (21.2%); $p = 0.012$ vs. insulin across the cohort	NR	503 (8.7%); $p = 0.696$ vs. diet-cohort 2006	NR	NR
Arshad_2014 [25]	Regular and NPH	25	NA	NR	NR	NR	NR	17 (68%)	NR	NR	NR	NR
	Diet + exercise	25	NA	NR	NR	NR	NR	10 (40%)	NR	NR	NR	NR
Deepaklal_2014 [100]	Insulin lispro	201	Delivery	NR	NR	NR	NR	50.6%, $n = 174$	NR	NR	NR	NR
Konig_2014 [101]	Insulin	40	Delivery	NR	NR	NR	NR	18/39 (46.15%)		NR	NR	NR
	No insulin	83	Delivery	NR	NR	NR	NR	26/81 (32.1%)	1.81 (0.83–3.97); $p = 0.14$	NR	NR	NR
Marques_2014 [102]	NPH insulin	33	NA	NR	NR	5 (15.2%)		10 (30.3%)		PE: 2 (6.1%)	NR	NR
	Metformin	32	NA	NR	NR	3 (9.4%)	0.58 (0.13–2.66); $p = 0.48$	12 (37.5%)	1.38 (0.49–3.87); $p = 0.54$	PE: 2 (6.3%)	1.03 (0.14–7.81); $p = 0.98$	NR
Tempe_2013 [106]	Insulin	32	NA	NR	NR	2 (5.9%)	NR	NR	NR	PE: 4 (11.7%)	NR	NR
	Glyburide	32	NA	NR	NR	1 (3.3%); $p = 1$	NR	NR	NR	PE: 6 (20%); $p =$ NS	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Cheng_2012 [107]	Insulin	8609	NA	NR	NR	< 37 weeks: 11.5%, < 34 weeks: 1.95%	NR	Overall CS: 44.9%, primary CS: 22.7%	NR	NR	NR	NR
	Glyburide	2073	NA	NR	NR	< 37 weeks: 12.2%, < 34 weeks: 2.56%	Adjusted < 37 weeks: 0.97 (0.75–1.24), < 34 weeks: 1.26 0.72–2.22	Overall CS: 38.8%, primary CS: 22.6%	Adjusted overall CS: 0.77 (0.65–0.91), primary CS: 0.84 (0.67–1.03)	NR	NR	NR
Donovan_2012 [47]	Insulin	359	NA	172 (47.9%)	NR	36 (10%)	NR	150 (41.8%)		PIH: 27 (7.5%)	NR	NR
	Lifestyle	505	NA	164 (32.5%)	NR	44 (9.1%)	NR	169 (33.5%)		PIH: 41 (8.1%)	NR	NR
	No diabetes	18,520	NA	5415 (29.2%); $p < 0.001$ across treatment arms	NR	1325 (7.1%); $p = 0.028$	NR	4567 (24.7%); $p < 0.0001$	Adjusted: 1.94 (1.54–2.44); $p < 0.001$	PIH: 1029 (5.6%); $p = 0.015$ across treatment arms	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Thomas_2012 [108]	Insulin	137	Delivery	NR	NR	26 (18.7%)	NR	52 (38.8%)	NR	NR	NR	NR
	OHA	141	Delivery	NR	NR	18 (12.9%); $p = 0.24$ vs. insulin	NR	67 (46.7%); $p = 0.22$ vs. insulin	NR	NR	NR	NR
Varghese_2012 [45]	Insulin	186		NR	NR	93 (50%)	NR	176 (94.6%)	NR	PIH: 26 (13.9%)	NR	NR
	Diet	36	NA	NR	NR	14 (38.8%); $p = 0.114$ vs. insulin	NR	30 (83.3%); $p = 0.013$ vs. insulin	NR	PIH: 6 (16.6%); $p = 0.675$ vs. insulin	NR	NR
Goh_2011 [109]	Bedtime intermediate-acting isophane insulin and premeal short-acting insulin	399	NA	NR	NR	19.2% (< 37 weeks), 3% (< 32 weeks)	NR	0.456	NR	Chronic HTN: 6.5%, GHTN: 5.3%, PE: 4%	NR	NR
	Metformin	465	NA	NR	NR	12.5% (< 37 weeks), 0.4% (< 32 weeks)	NR	0.37	NR	Chronic HTN: 5.4%, GHTN: 8%, PE: 3.4%	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
	Diet	371	NA	NR	NR	12.1% (< 37 weeks); *p* = 0.005 across treatment arms, 2.9% (< 32 weeks); *p* = 0.009 across treatment arms	NR	0.34	NR	Chronic HTN: 3.5%, GHTN: 5.7%, PE: 3.8%; *p* = 0.3 across treatment arms	NR	NR
Wong_2011 [110]	Insulin	323	NA	NR	NR	NR	NR	CS: 31%, emergency CS: 15.2%	NR	NR	NR	NR
	MNT	289	NA	NR	NR	NR	NR	CS: 24.8%; *p* = 0.082 vs. insulin emergency CS: 10.7%; *p* = 0.092 vs. insulin	NR	NR	NR	NR

Table 5 continued

First Author_ Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor, OR (95% CI), *p* value	Preterm labor/delivery *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/eclampsia: OR (95% CI), *p* value	Prevalence/rate of maternal hypoglycemia, *n* (%)
Flores-Le Roux_2010 [111]	Insulin	41	NA	19 (46.3%)	NR	2 (4.9%)	NR	16 (39%)	NR	NR	NR	NR
	Diet	70	NA	23 (32.9%)	NR	3 (4.3%)	NR	21 (30%)	NR	NR	NR	NR
	NEF-GDM	18	NA	5 (27.8%); $p = 0.37$ across treatment arms	NR	2 (11.1%); $p = 0.47$ across treatment arms	NR	6 (35.3%); $p = 0.86$ across treatment arms	NR	NR	NR	NR

ARR adjusted relative risk, *BiD* twice a day, *CI* confidence interval, *CS* cesarean section, *GDM* gestational diabetes mellitus, *GHTN* gestational hypertension, *IDET* insulin detemir, *MNT* medical nutritional therapy, *NA* not applicable, *NEF* no endocrinologic follow-up, *NPH* neutral protamine Hagedorn, *NR* not reported, *NS* not significant, *OHA* oral hypoglycemic agents, *OR* odds ratio, *PE* preeclampsia, *PIH* pregnancy-induced hypertension, *RCT* randomized controlled trial, *RR* relative risk, *QiD* four times a day

Table 6 Maternal outcomes in women with pre-existing diabetes and mixed population

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
RCT													
Jing ji_2020 [27]	IDET + Novolin-R	120	Delivery	NR	NR	15 (12.50%)	NR	78 (65%)	NR	HTN: 14 (11.67%)	NR	14 (11.67%)	NR
	Insulin NPH + Novolin-R	120	Delivery	NR	NR	18 (15%); $p = 0.574$ vs. IDET	NR	74 (61.67%); $p = 0.592$ vs. IDET	NR	HTN: 23 (19.17%); $p = 0.107$ vs. IDET	NR	28 (23.33%); $p = 0.017$ vs. IDET	NR
Ainuddin_2015 [44]	Insulin (short- + intermediate-acting)-T2DM	100	Delivery	NR	NR	NR	NR	82 (82.0%)	NR	PIH: 36 (36.0%); PE: 17 (17%)	NR	NR	NR
	Metformin-T2DM	16	Delivery	NR	NR	NR	NR	13 (81.2%)	NR	PIH: 1 (6.2%); PE: 4 (25%)	NR	NR	NR
	Insulin added-on to metformin-T2GDM	90	Delivery	NR	NR	NR	NR	47 (52.2%); $p < 0.01$	NR	PIH: 21 (23.3%); $p = 0.020$; PE: 9 (10%); $p = 0.184$	NR	NR	NR
Refuerzo_2015 [71]	Regular + NPH	13	Delivery	5 (38.5%)	NR	3 (23.1%)	NR	6 (46.2%)	NR	4 (30.8%)	NR	NR	NR
	Metformin	8	Delivery	5 (62.5); $p = 0.387$	NR	1 (12.5%); $p = 0.549$	NR	4 (50%); $p = 0.864$	NR	0; $p = 0.131$	NR	NR	NR
Hod_2014 [57]	IDET + aspart	152	Delivery	NR	NR	26 (20.3%)	NA	NR	NR	NR	NR	144 (95%)	

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
	Insulin NPH + aspart	158	Delivery	NR	NR	36 (26.5%)	0.71 (0.40–1.26); *p* = 0.238 vs. IDET	NR	NR	NR	NR	146 (92%)	RR: 1.11 (0.89–1.38); *p* = 0.365 vs. IDET
Herrera_2015 [70]	IDET	42	NA	NR	NR	NR	NR	NR	NR	NR	NR	11 (26%)	NR
	Insulin NPH	45	NA	NR	NR	NR	NR	NR	NR	NR	NR	16 (36%); *p* = 0.3454	NR
Hickman_2012 [52]	Regular + NPH	14	36–38 weeks	NR	NR	NR	NR	NR	NR	NR	NR	7 (50%)	NR
	Metformin	14	36–38 weeks	NR	NR	NR	NR	NR	NR	NR	NR	1 (7%); *p* = 0.03	NR
Observational													
Demasio_2020 [112]	Insulin Levemir-T2DM	96	NA	NR	NR	23 (23.96%)	NR	Unscheduled: 43.75%; scheduled: 23.96%	NR	6 (6.3%)	NR	NR	NR
	Insulin Levemir-GDM	127	NA	NR	NR	16 (12.6%)	NR	Unscheduled: 24.41%, scheduled: 27.56%	NR	9 (7.1%)	NR	NR	NR
	Insulin NPH-T2DM	41	NA	NR	NR	10 (24.4%)	NR	Unscheduled: 46.34%; scheduled: 21.95%	NR	PE: 4 (9.8%), eclampsia: 1 (2.4%)	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
	Insulin NPH-GDM	50	NA	NR	NR	5 (10%)	NR	Unscheduled: 30%; scheduled: 26%	NR	3 (6.0%)	NR	NR	NR
Kong_2020 [113]	Insulin	4000	NA	NR	NR	1483 (37.1%)	NR	NR	NR	NR	NR	NR	NR
Sperling_2020 [115]	Metformin-GDM	2542	NA	NR	NR	0.088	NR	0.5	NR	NR	NR	NR	NR
	Metformin-PGDM	729	NA	NR	NR	0.104	NR	0.583	NR	NR	NR	NR	NR
	Glyburide-GDM	9998	NA	NR	NR	0.072	NR	0.491	NR	NR	NR	NR	NR
	Glyburide-PGDM	1181	NA	NR	NR	0.11	NR	0.558	NR	NR	NR	NR	NR
	Insulin + glyburide-GDM	1113	NA	NR	NR	0.097	NR	0.56	NR	NR	NR	NR	NR
	Insulin + glyburide-PGDM	371	NA	NR	NR	0.162	NR	0.72	NR	NR	NR	NR	NR
	Insulin + metformin-GDM	1029	NA	NR	NR	0.088	NR	0.595	NR	NR	NR	NR	NR
	Insulin + metformin-PGDM	2036	NA	NR	NR	0.143	NR	0.713	NR	NR	NR	NR	NR
	Insulin-GDM	6796	NA	NR	NR	0.074	NR	NR	0.501	NR	NR	NR	NR
	Insulin-PGDM	5350	NA	NR	NR	0.164	NR	0.692	NR	NR	NR	NR	NR
	Metformin + glyburide-GDM	960	NA	NR	NR	0.09	NR	0.563	NR	NR	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
	Metformin + glyburide-PGDM	375	NA	NR	NR	0.128	NR	0.68	NR	NR	NR	NR	NR
	Insulin + metformin + glyburide-GDM	214	NA	NR	NR	0.075	NR	0.636	NR	NR	NR	NR	NR
	Insulin + metformin + glyburide-PGDM	423	NA	NR	NR	0.123	NR	0.723	NR	NR	NR	NR	NR
Bartal_2019 [48]	Basal insulin analogues	114	NA	44 (38.6%)	NA	63 (55.3%)	NA	CS: 76 (66.7%), primary CS: 24 (21.1%)	NA	GHTN: 2 (1.8%), PE: 6 (5.3%), PE with severe features: 31 (27.2%)	NR	15 (13.2%)	NR
	Insulin NPH	119	NA	42 (35.3%)	ARR: 0.89 (0.57–1.37); $p = 0.60$ vs. BIA	59 (49.6%)	ARR: 0.93 (0.68–1.26); $p = 0.39$	CS: 86 (72.9%), primary CS: 43 (36.4%)	ARR-CS: 0.93 (0.75–1.15); $p = 0.30$ vs. BIA, ARR-Primary CS: 0.44 (0.25–0.78); $p = 0.01$	GHTN: 5 (4.2%), PE: 5 (4.2%), PE with severe features: 34 (28.6%)	NR	24 (20.2%)	ARR: 0.72 (0.35–1.45); $p = 0.15$

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
Christman_2019 [117]	IDET	154	NR	NR	NR	NR	NR	79 (51.3%)	NR	NR	NR	NR	NR
Sleeman_2019 [118]	Insulin glargine or IDET	38	Delivery	NR	NR	18 (47.4%)	NR	26 (68.4%)	NR	3 (7.9%)	NR	NR	NR
	Insulin NPH	14	Delivery	NR	NR	7 (50%); $p=0.866$ vs. glargine/detemir	NR	10 (71.4%); $p=0.835$ vs. glargine/detemir	NR	3 (21.4%); $p=0.324$	NR	NR	NR
Sunjaya_2018 [122]	Insulin (long-acting, intermediate-acting, short-acting, rapid-acting and human premixed)	25	After treatment	NR	NR	NR	NR	0.76	NR	NR	NR	NR	NR
	Oral antidiabetics (metformin and pioglitazone)	4	After treatment	NR	NR	NR	NR	0.5	NR	NR	NR	NR	NR
	MNT	16	After treatment	NR	NR	NR	NR	0.75	NR	NR	NR	NR	NR
Abell_2017 [62]	MDI-glargine/detemir/NPH	127	Delivery	37 (35.9%)	NR	45 (35.4%)	NR	80 (63.0%)	NR	8 (6.3%)	NR	NR	NR
	CSII-aspart	40	Delivery	17 (54.8%); $p=0.060$	NR	19 (47.5%); $p=0.171$	NR	25 (62.5%); $p=0.955$	NR	3 (7.5%); $p=0.726$	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
Billionnet_2017 [63]	Insulin-treated GDM	16,108	Delivery after 28 weeks	NR	NR	9.20% (< 37 weeks)	1.5 (1.4; 1.6)	0.34	1.7 (1.7; 1.8)	0.024	1.6 (1.4; 1.7)	NR	NR
		14,633	Delivery after 37 weeks	NR	NR	NR	NR	0.327	1.8 (1.7; 1.9)	0.016	1.6 (1.4; 1.8)	NR	NR
	Noninsulin-treated GDM	41,275	Delivery after 28 weeks	NR	NR	0.076	1.2 (1.2; 1.3)	0.253	1.3 (1.2; 1.3)	0.026	1.7 (1.6; 1.8)	NR	NR
		38,147	Delivery after 37 weeks	NR	NR	NR	NR	0.238	1.3 (1.2; 1.3)	0.017	1.7 (1.6; 1.9)	NR	NR
	GDM-overall	57,383	Delivery after 28 weeks	NR	NR	0.08	1.3 (1.3; 1.4)	0.278	1.4 (1.4; 1.4)	0.025	1.7 (1.6; 1.7)	NR	NR
		52,780	Delivery after 37 weeks	NR	NR	NR	NR	0.262	1.4 (1.4; 1.4)	0.017	1.7 (1.6; 1.8)	NR	NR
	No diabetes	729,105	Delivery after 28 weeks	NR	NR	0.061	NR	0.195	NR	0.015	NR	NR	NR
		684,398	Delivery after 37 weeks	NR	NR	NR	NR	0.183	NR	0.01	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
Stanirowski_2017 [123]	Insulin-treated GDM	6	NA	NR	NR	NR	NR	6 (100%)	NR	NR	NR	NR	NR
	Diet-treated GDM	16	NA	NR	NR	NR	NR	10 (62.5%)	NR	NR	NR	NR	NR
	Insulin-treated PGDM	6	NA	NR	NR	NR	NR	6 (100%)	NR	NR	NR	NR	NR
	No diabetes	25	NA	NR	NR	NR	NR	16 (64.0%)	NR	NR	NR	NR	NR
Dalfra_2016 [124]	ILPS-GDM	572	NA	NR	NR	0.086	NR	0.312	NR	NR	NR	0.003	NR
	NPH-GDM	242	NA	NR	NR	14.9%; $p = 0.01$	NR	46.2%; $p = 0.01$	NR	NR	NR	2.1%; p = NS vs. ILPS-GDM	NR
	ILPS-pregestational T1DM	58	NA	NR	NR	0.155	NR	0.482	NR	NR	NR	0.052	NR
	NPH-pregestational T1DM	61	NA	NR	NR	32.8%; $p = 0.05$	NR	63.9%; $p = 0.001$	NR	NR	NR	13.1%; p = NS vs. ILPS-T1DM	NR
Becquet_2015 [125]	Insulin	36	NA	NR	NR	NR	NR	CS: 8 (22%), elective CS: 16 (45%)	NR	GHTN: 2 (6%), PE: 2 (6%)	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
	No insulin	43	NA	NR	NR	NR	NR	CS: 12 (28%), elective CS: 4 (9%)	NR	GHTN: 1 (2%); $p = 0.33$; PE: 1 (2%); $p = 0.74$ vs. insulin	NR	NR	NR
Neff_2014 [61]	CSII-aspart	40	Delivery	NR	NR	0.1	NR	0.8	NR	NR	NR	NR	NR
	MDI-aspart + NPH	424	Delivery	NR	NR	16%; $p = 0.17$	NR	54%; $p = 0.001$	NR	NR	NR	NR	NR
Colatrella_2013 [126]	ILPS-T2DM	7	After treatment	NR	NR	0	NR	1	NR	GHTN: 42.8%	NR	NR	NR
	ILPS-GDM	46	After treatment	NR	NR	0.087	NR	0.652	NR	GHTN: 17.4%	NR	NR	NR
	Insulin NPH-T2DM	18	After treatment	NR	NR	0	NR	1	NR	GHTN: 44.4%	NR	NR	NR
	Insulin NPH-GDM	18	After treatment	NR	NR	0.055	NR	0.611	NR	GHTN: 33.3%	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
Fresa_2013 [127]	Insulin lispro/aspart-CSII	47	NA	NR	NR	13 (27.6%)	NR	41 (87%)	NR	NR	NR	NR	NR
	Insulin lispro/aspart-CSII (RT-CGM)	18	NA	NR	NR	3 (16.6%)	NR	15 (83%)	NR	NR	NR	NR	NR
Garcia-Dominguez_2011 [53]	Human insulin	241	Delivery	NR	NR	NR	NR	154 (64.7%)	NR	GHTN: 66 (27.4%), PE: 18 (7.5%)	NR	24 (10%)	NR
	Insulin analog	86	Delivery	NR	NR	NR	NR	47 (54.7%); $p = 0.1$ vs. human insulin	NR	GHTN: 17 (19.8%); $p = 0.163$, PE: 12 (14%); $p = 0.074$ vs. human insulin	NR	2 (2.3%); $p = 0.025$ vs. human insulin	NR
Negrato_2010 [51]	Glargine + lispro-PGDM	18	NA	NR	NR	NR	NR	0.945	NR	0	NR	NR	NR
	NPH + lispro-PGDM	38	NA	NR	NR	NR	NR	94%, $p > 0.05$ vs. glargine-PGDM	NR	PE: 7 (19%); $p < 0.0001$ vs. glargine-PGDM group	NR	NR	NR
	Glargine + lispro-GDM	37	NA	NR	NR	NR	NR	0.95	NR	1 (2.5%)	NR	NR	NR

Table 6 continued

First Author_Year	Treatment arms	Sample size	Time-points	Proportion of induced labor, *n* (%)	Induced labor: OR (95% CI), *p* value	Preterm labor/delivery, *n* (%)	Preterm labor/delivery OR (95% CI), *p* value	Proportion of CS, *n* (%)	CS: OR (95% CI), *p* value	Prevalence/rate of preeclampsia/eclampsia, *n* (%)	Preeclampsia/ECLAMPSIA: OR (95% CI), *p*-value	Prevalence/rate of maternal hypoglycaemia, *n* (%)	Maternal hypoglycemia: OR (95% CI), *p* value
	NPH + lispro-GDM	45	NA	NR	NR	NR	NR	96%, $p > 0.05$ vs. glargine-GDM	NR	PE: 4 (9%)	RR: 0.35 (0.09–1.2), $p > 0.05$ vs. glargine-GDM	NR	NR
Bruttomesso_2011 [128]	CSII-rapid-acting insulin analog	100	Delivery	NR	NR	NR	NR	NR	NR	PIH: 14 (15.1%), PE: 9 (9.7%)		NR	NR
	Glargine-MDI	44	Delivery	NR	NR	NR	NR	NR	NR	PIH: 3 (7%), PE: 1 (2.3%); p = NS for both		NR	NR
Gupta_2018 [121]	Insulin	102	NA	NR	NR	NR	NR	NR	NR	PIH: 14 (13.73%)	NR	NR	NR

ARR adjusted relative risk, *CGM* continuous glucose monitor, *CS* cesarean section, *CSII* continuous subcutaneous insulin infusion, *GDM* gestational diabetes mellitus, *GHTN* gestational hypertension, *IDET* insulin detemir, *ILPS* insulin lispro protamine suspension, *MDI* multiple daily injection, *MNT* medical nutritional therapy, *NA* not applicable, *NPH* neutral protamine Hagedorn, *NR* not reported, *OR* odds ratio, *PE* preeclampsia, *PGDM* pregestational diabetes mellitus, *PIH* pregnancy-induced hypertension, *RCT* randomized controlled trial, *RR* relative risk, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

Table 7 Fetal outcomes in women with gestational diabetes mellitus

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
RCT									
Wasim_2019 [21]	Insulin-Humulin R and NPH	141	Delivery	NR	NR	NR	NR	3 (2.1%)	NR
	Metformin	137	Delivery	NR	NR	NR	NR	1 (0.7%)	NR
Eid_2018 [34]	Insulin (NPH regular)	116	After treatment	18 (15.5%)	NR	NR	NR	NR	NR
	Metformin	113	After treatment	13 (11.5%); $p = 0.001$	NR	NR	NR	NR	NR
Somani_2016 [26]	Regular/NPH or both	33	Delivery	NR	NR	1 (3.03%)	NR	NR	NR
	Metformin	32	Delivery	NR	NR	0%; $p = 0.32$ vs. insulin	NR	NR	NR
Ainuddin_2015 [36]	Insulin (short- + intermediate-acting)-GDM	75	Throughout pregnancy	28 (37.3%)	NR	NR	NR	NR	NR
	Metformin-GDM	43	Throughout pregnancy	10 (23.3%)	NR	NR	NR	NR	NR
	Insulin added on to metformin-GDM	32	Throughout pregnancy	9 (28.1%)	NR	NR	NR	NR	NR
Mukhopadhyay_2014 [58]	Insulin	30	Before confinement	2 (6.7%)	NR	NR	NR	NR	NR
	Glibenclamide	30	Before confinement	4 (13.3%)	NR	NR	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Mesdaghinia_2012 [56]	NPH and regular	100	NA	24 (24%)	NR	NR	NR	0 (0)	NR
	Metformin	100	NA	16 (16%); *p* = NS	NR	NR	NR	0 (0)	NR
Ijas_2011 [41]	Long- (Protaphane) and rapid-acting (Humalog) insulin	50	NA	5 (10.0%)	NA	NR	NR	NR	NR
	Metformin	47	NA	4 (8.5%)	RR: 0.9 (0.24–2.98); *p* = 0.801 vs. insulin	NR	NR	NR	NR
Observational									
Meghelli_2020 [77]	Insulin	63	NA	LGA > 90th Percentile: 18 (29.5%); LGA > 97th Percentile: 18 (29.5%)	NR	0	NR	NR	NR
	No insulin	56	NA	LGA > 90th Percentile: 19 (35.2%), *p* = 0.52; LGA > 97th Percentile: 12 (22.2%), *p* = 0.37	NR	0	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Rodrigues_2020 [50]	Insulin	39	NA	NR	NR	NR	NR	0	NR
	Metformin + insulin	93	NA	NR	NR	NR	NR	0	NR
	Metformin only	76	NA	NR	NR	NR	NR	0	NR
Landi_2019 [49]	Insulin	3450	NA	653 (19.1%)	NA	NR	NR	NR	NR
	Metformin	3818	NA	549 (14.5%)	RR (95% CI): 0.77 (0.69-0.85)	NR	NR	NR	NR
Bogdanet_2018 [46]	IDET and insulin aspart	752	NA	143/727 (19.7%)	NA	NR	NR	NR	NR
	MNT	567	NA	71/566 (12.5%)	Adjusted: 1.67 (1.15–2.41); $p < 0.01$ vs. insulin	NR	NR	NR	NR
	NGT	2496	NA	388/2476 (15.67%)	Adjusted: 1.07 (0.77–1.47); $p = 0.67$ vs. insulin	NR	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Hedderson_2018 [60]	Insulin	401	NA	20.50%	NA	NR	NR	NR	NR
	Glyburide	4622	NA	17.90%	RR (95% CI): 1.12 (0.90–1.39) vs. insulin	NR	NR	NR	NR
	Insulin + glyburide	281	NA	NR	RR (95% CI): 1.49 (1.21-1.83) vs. glyburide only	NR	NR	NR	NR
McGrath_2018 [82]	Insulin (NPH or Levemir and/or NovoRapid)	83	38.6 ± 1.2	12 (14.5%)	NR	NR	NR	0	NR
	Metformin	83	38.6 ± 1.2	18 (21.7%)	NR	NR	NR	0	NR
	Diet + lifestyle	82	38.6 ± 1.2	7 (8.5%), $p = 0.059$ across treatment arms	NR	NR	NR	1 (1.2%)	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Rowan_2018 [85]	Insulin (Adelaide cohort)	51	36 weeks	3 (5.9%)	NR	NR	NR	NR	NR
	Metformin (Adelaide cohort)	58	36 weeks	12 (20.7%); $p = 0.029$ vs. insulin Adelaide	NR	NR	NR	NR	NR
	Insulin (Auckland cohort)	54	36 weeks	6 (11.1%)	NR	NR	NR	NR	NR
	Metformin (Auckland cohort)	45	36 weeks	5 (11.1%); $p = 1$ vs. insulin Auckland	NR	NR	NR	NR	NR
Simeonova-Krstevska_2018 [28]	Levemir (IDET) + aspart	101	NA	22 (21.7%)	NR	NR	NR	NR	NR
	Metformin	48	NA	6 (12.5%); $p < 0.05$ vs. insulin and diet	NR	NR	NR	NR	NR
	Diet	200	NA	59 (29.5%); $p =$ NS vs. insulin	NR	NR	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Bowker_2017 [87]	Insulin	5057 (27.0%)	NA	862 (17.0%)	1.40 (1.28; 1.54); $p < 0.001$ vs. no pharmacologic intervention	NR	NR	NR	NR
	Metformin ± insulin	478 (2.5%)	NA	79 (16.5%)	1.27 (0.99; 1.62); $p < 0.056$ vs. no intervention	NR	NR	NR	NR
	No pharmacologic intervention	13,226 (70.5%)	NA	1694 (12.8%)	NR	NR	NR	NR	NR
Gibbons_2017 [88]	Insulin	315	NA	41 (13.0%)	NA	NR	NR	2 (0.6%)	1.64 (0.27–9.87), $p = 0.54$ across treatment arms
	OHA (glyburide/metformin)	211	NA	14 (6.6%)	NA	NR	NR	0	NA
	Diet	563	NA	54 (9.6%); $p = 0.051$ vs. OHA and diet	1.55 (1.03–2.34); $p = 0.036$ vs. OHA and diet	NR	NR	3 (0.5%)	NA

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Olmos_2017 [89]	BBIT	73	NA	8 (10.9%)	NR	NR	NR	NR	NR
	Without BBIT (diet/metformin)	58	NA	5 (8.6%); $p = 0.772$	NR	NR	NR	NR	NR
Fazel-Sarjoui_2016 [91]	Short-acting Insulin	70	NA	NR	NR	NR	NR	1 (1.4%)	NR
	Diet	70	NA	NR	NR	NR	NR	0%; $p < 0.05$ vs. insulin	NR
Ito_2016 [92]	Insulin	32	Delivery	1 (3.1%)	NA	NR	NR	NR	NR
	Diet	70	Delivery	9 (12.8%)	Adjusted: 0.22 (0.01–1.26); $p = 0.096$ vs. insulin	NR	NR	NR	NR
Koning_2016 [93]	Diet + additional insulin (aspart, NPH and aspart + NPH)	360	NA	65 (18.1%)	NR	2 (0.6%)	NR	NR	NR
	Diet	460	NA	98 (21.3%); $p =$ NS vs. insulin	NR	0%; $p =$ NS vs. insulin	NR	NR	NR
	Overall Population	820	NA	163 (19.9%)	NR	2 (0.2%)	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Koren_2016 [55]	IDET	29	NA	4 (13.8%)	NR	NR	NR	NR	NR
	Glyburide	62	NA	16 (25.8%); $p = 0.28$	NR	NR	NR	NR	NR
Benhalima_2015 [32]	Short-acting or long-acting insulin or both	145	NA	41 (28.5%)	NR	NR	NR	NR	NR
	Diet	456	NA	59 (13.1%); $p < 0.0001$	NR	NR	NR	NR	NR
Castillo_2015 [59]	Insulin	4191	NA	134 (3.2%)	NA	NR	NR	NR	NR
	Glyburide	4982	NA	234 (4.7%)	ARR: 1.43 (1.16–1.76)	NR	NR	NR	NR
Cosson_2015 [96]	Insulin	260	-	50 (19.2%)	NR	NR	NR	NR	NR
Marques_2014 [102]	NPH insulin	33	NA	3 (9.1%)	NA	NR	NR	NR	NR
	Metformin	32	NA	1 (3.1%)	0.32 (0.03–3.28); $p = 0.34$	NR	NR	NR	NR
Hernandez-Rivas_2013 [104]	Insulin	161	NA	NR	Adjusted: 2.29 (1.09–4.82)	NR	NR	NR	NR
Tempe_2013 [106]	Insulin	32	NA	NR	NR	0%	NR	NR	NR
	Glyburide	32	NA	NR	NR	1 (3.3%); $p = 0.47$	NR	NR	NR

Table 7 continued

First author_ Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Thomas_2013 [108]	Insulin	137	Delivery	51 (36.7%)	NR	NR	NR	NR	NR
	OHA	141	Delivery	46 (33%); $p = 0.61$	NR	NR	NR	NR	NR
Donovan_2012 [47]	Insulin	359	NA	NR	NR	1 (0.3%)	NR	NR	NR
	Lifestyle	505	NA	NR	NR	1 (0.2%)	NR	NR	NR
	No diabetes	18,520	NA	NR	NR	64 (0.3%)	NR	NR	NR
Varghese_2012 [45]	Insulin	186		15 (10.6%)	NR	NR	NR	NR	NR
	Diet	36	NA	4 (11.11%); $p = 0.5498$ vs. insulin	NR	NR	NR	NR	NR
Goh_2011 [109]	Intermediate-acting isophane insulin and short-acting insulin analog	399	NA	18.50%	NR	NR	NR	NR	NR
	Metformin	465	NA	12.50%	NR	NR	NR	NR	NR
	Diet	371	NA	12.4%; $p = 0.02$ across treatment arms	NR	NR	NR	NR	NR

ARR adjusted relative risk, *BBIT* basal-bolus insulin therapy, *CI* confidence interval, *GDM* gestational diabetes mellitus, *IDET* insulin detemir, *LGA* large for gestational age, *MNT* medical nutritional therapy, *NA* not applicable, *NPH* neutral protamine Hagedorn, *NR* not reported, *OHA* oral hypoglycemic agents, *OR* odds ratio, *RCT* randomized clinical trial, *RR* relative risk

Table 8 Fetal outcomes in women with pre-existing diabetes and mixed population

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
RCT									
Ainuddin_2015 [44]	Insulin (short- + intermediate-acting)-T2DM	100	Throughout pregnancy	27 (27.0%)	NR	NR	NR	NR	0
	Metformin – T2DM	16	Throughout pregnancy	2 (12.5%)	NR	NR	NR	NR	0
	Insulin added on to metformin-T2GDM	90	Throughout pregnancy	30 (33.3%), $p = 0.208$	NR	NR	NR	NR	0
Hod_2014 [57]	IDET + aspart	152	Delivery	59 (46.1%)		NR	NR	2 (1.4%)	NR
	Insulin NPH + aspart	158	Delivery	73 (53.7%)	74 (0.46–1.21); $p = 0.228$ vs. IDET	NR	NR	1 (0.7%)	NR
Observational									
Kong_2020 [113]	Insulin	4000	NA	1585 (39.6%)	NR	NR	NR	NR	NR
Mathiesen 2020 [114]	IDET vs. other basal insulins	IDET-727, Other basal-730	NR	NR	NR	NR	NR	IDET-6/741 (0.8%); Other basal-13/740 (1.8%)	Adjusted risk diff (95% CI): 0.002 (– 0.015, 0.02)

Table 8 continued

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Alexander_2019 [116]	CSII	151	NA	38/73 (52%)	Association LGA and CSII: 2.08 (0.94–4.61); $p = 0.07$	NR	NR	NR	NR
Bartal_2020 [48]	Basal insulin analogues	114	NA	30 (26.5%)	NA	NR	NR	5 (4.4%)	NA
	Insulin NPH	119	NA	29 (24.4%)	ARR: 1.56 (0.89–2.73); $p = 0.70$	NR	NR	2 (1.7%)	ARR: 1.89 (0.27–13.32); $p = 0.37$
Smrz_2019 [119]	CSII vs. MDI	117	NR	CSII vs. MDI-57% vs. 49%; $p = 0.370$ vs. MDI	NR	NR	NR	NR	NR
Abell_2017 [62]	MDI-glargine/detemir/NPH	127	Delivery	52 (40.9%)	NR	NR	NR	6 (6.9%)	NR
	CSII-aspart	40	Delivery	21 (52.5%); $p = 0.199$	NR	NR	NR	1 (5.0%); $p = 1.000$	NR

Table 8 continued

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Billionnet_2017 [63]	Insulin-treated GDM	16,108	Delivery after 28 weeks	NR	NR	NR	NR	0.35%	1.0 (0.8; 1.4)
		14,633	Delivery after 37 weeks	NR	NR	NR	NR	0.21%	1.3 (0.9; 1.9)
	Noninsulin-treated GDM	41,275	Delivery after 28 weeks	NR	NR	NR	NR	0.36%	1.1 (0.9; 1.3)
		38,147	Delivery after 37 weeks	NR	NR	NR	NR	0.21%	1.3 (1.1; 1.7)
	GDM-overall	57,383	Delivery after 28 weeks	NR	NR	NR	NR	0.36%	1.1 (0.9; 1.3)
		52,780	Delivery after 37 weeks	NR	NR	NR	NR	0.21%	1.3 (1.1; 1.6)
	No diabetes	7,29,105	Delivery after 28 weeks	NR	NR	NR	NR	0.32%	NR
		6,84,398	Delivery after 37 weeks	NR	NR	NR	NR	0.15%	NR

Table 8 continued

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Dalfra_2016 [124]	ILPS-GDM	572	NA	16.60%	NR	0.50%	NR	NR	NR
	NPH-GDM	242	NA	19.4%; p = ns vs. ILPS-GDM	NR	0.4%; p = ns vs. ILPS-GDM	NR	NR	NR
	ILPS-pregestational T1DM	58	NA	43.10%	NR	3.40%	NR	NR	NR
	NPH-pregestational T1DM	61	NA	37.7%; p = ns vs. pregestational T1DM	NR	1.6%; p = ns vs. pregestational T1DM	NR	NR	NR
Neff_2014 [61]	CSII-aspart	40	Delivery	36%	NR	NR	NR	NR	NR
	MDI-aspart + NPH	424	Delivery	20%; p = 0.03	NR	NR	NR	NR	NR
Colatrella_2013 [126]	ILPS-T2DM	7	After treatment	14.30%	NR	NR	NR	NR	NR
	ILPS-GDM	46	After treatment	15.20%	NR	NR	NR	NR	NR
	Insulin NPH-	18	After treatment	22.20%	NR	NR	NR	NR	NR
	Insulin NPH-GDM	18	After treatment	22.20%	NR	NR	NR	NR	NR

Table 8 continued

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Fresa_2013 [127]	Insulin lispro/aspart-CSII	47	NA	20 (42.5%)	NR	NR	NR	NR	NR
	Insulin lispro/aspart-CSII (RT-CGM)	18	NA	8 (44%)	NR	NR	NR	NR	NR
Bruttomesso_2011 [128]	CSII-rapid-acting insulin analog	100	Delivery	46 (46%)	NR	NR	NR	NR	NR
	Glargine-MDI	44	Delivery	20 (45.5%)	NR	NR	NR	NR	NR
Garcia-Dominguez_2011 [53]	Human insulin	241	Delivery	91 (38.4%)	NR	4 (1.7%)	NR	NR	NR
	Insulin analog	86	Delivery	43 (50.0%); $p = 0.061$ vs. human insulin	NR	1 (1.2%); $p = 0.747$ vs. human insulin	NR	NR	NR

Table 8 continued

First author_Year	Treatment arms	Sample size	Time points	Proportion of LGA neonates, *n* (%)	LGA: OR (95% CI), *p* value	Proportion of stillborn, *n* (%)	Stillborn: OR (95% CI), *p* value	Perinatal mortality rate, *n* (%)	Perinatal mortality: OR (95% CI), *p* value
Negrato_2010 [51]	Glargine + lispro-PGDM	18	NA	9 (50%)	NA	NR	NR	0	NR
	NPH + lispro-PGDM	38	NA	14 (37%)	RR: 1.35 (1.02–1.77); $p > 0.05$ vs. glargine-PGDM	NR	NR	2 (6%); $p = 0.028$ vs. glargine-PGDM	NR
	Glargine + lispro-GDM	37	NA	13 (34%)	NA	NR	NR	0	NR
	NPH + lispro-GDM	45	NA	18 (40%)	RR: 0.87 (0.65–1.18); $p > 0.05$ vs. glargine-GDM	NR	NR	0	NR

ARR adjusted relative risk, *CGM* continuous glucose monitor, *CI* confidence interval, *CSII* continuous subcutaneous insulin infusion, *IDET* insulin detemir, *ILPS* insulin lispro protamine suspension, *LGA* large for gestational age, *MDI* multiple daily injection, *NA* not applicable, *NPH* neutral protamine Hagedorn, *NR* not reported, *OR* odds ratio, *PGDM* pregestational diabetes mellitus, *RCT* randomized clinical trial, *RR* relative risk, *RT* real time, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus

those managed with other therapies compared to the insulin-treated group [28–32] ($p<0.05$). These observational studies provide an insight into the real-world use of insulin within this specific population, highlighting that potential barriers of insulin use may be limiting its full benefits in optimizing glycemic control.

Maternal Outcomes in People with GDM and Pre-existing Diabetes

Of the 108 included studies, 18 clinical trials and 44 observational studies reported the maternal outcomes of interest (prevalence of hypoglycemia, cesarean section, preterm labor, hypertension, induced labor and preterm delivery) in women with GDM (Table 5). Maternal outcomes in women with diabetes prior to pregnancy and mixed population were reported in 6 trials and 18 observational studies (Table 6).

Evidence from Clinical Trials

Most trials included in this study had small numbers of participants and no prolonged follow-up after the treatment. Some of the included trials had unclear risk of bias due to lack of blinding, unclear methods of randomization and selective reporting of outcomes. The primary outcomes of interest were different across the included studies.

Most included trials reported no difference in the proportion of cesarean sections among women treated with metformin versus insulin [21, 24, 26, 33–39]. However, two RCTs by Galal et al. and Hassan et al. reported a significantly higher rate ($p\leq0.05$) of cesarean sections in the insulin-treated group [20, 40], while an RCT by Ijas et al. reported a lower rate of cesarean section in the insulin-treated group versus metformin ($p=0.047$) [41]. In three RCTs by Khan et al., Mirzamoradi et al. and Huhtala et al., numerically higher rates of preterm delivery, preeclampsia and induced labor were observed in the insulin-treated group relative to comparator group using oral anti-diabetic agents [24, 42, 43]. Other RCTs by Galal et al., Niromanesh et al. and Hassan et al. reported a numerically higher incidence of preterm delivery and induced labor in the group treated with metformin versus insulin [20, 39, 40]. In women with pre-existing diabetes, an open-label, randomized study by Ainuddin et al. reported a significantly high rate of incidence of pregnancy-induced hypertension in the insulin-treated group compared to only metformin group and metformin and insulin-treated group [44], while an RCT by Ji et al. demonstrated a numerically higher incidence of gestational hypertension in the insulin NPH-treated group compared to the insulin detemir-treated-group [27].

Evidence from Observational Studies

Among women diagnosed with GDM, across different interventions, retrospective analyses revealed that cases of cesarean section and preterm delivery were higher in women managed with insulin than in those managed with other interventions such as diet/MNT, metformin and metformin + insulin [28, 32, 45, 46]. Compared with other interventions, insulin did not show a significant difference in the rate of gestational hypertension and induced labor in women treated with insulin and those managed with lifestyle modification [47, 48] or metformin [49, 50]. In the mixed population, a prospective cohort study by Negrato et al. compared insulin glargine with NPH and reported a significantly higher rate of preeclampsia in the NPH-treated group compared to the glargine-treated group ($p<0.0001$) in women diagnosed with diabetes prior to pregnancy [51].

Maternal Hypoglycemia in Clinical Trials and Observational Studies

The overall rate of hypoglycemia in women with GDM and a mixed population was significantly higher in the insulin-treated group compared to metformin and metformin with additional insulin therapy [27, 52, 53]. Contrarily, a significantly lower incidence of hypoglycemia was reported with insulin ($p<0.001$) compared to glyburide [54, 55].

Fetal Outcomes in Women with GDM and Pre-existing Diabetes or Mixed Population

Of the 108 included studies, 7 RCTs and 24 observational studies reported fetal outcomes of interest in women with GDM, and 2 trials and 14 observational studies reported fetal outcomes of interest in women diagnosed with diabetes prior to pregnancy and a mixed population (Tables 7, 8). Most of the included studies scored low to moderate on the Newcastle-Ottawa Scale and quality assessment checklist; they had limited power, relatively small sample size, long individual study period and a high drop-out rate.

Evidence from Clinical Trials

A number of studies on women with GDM and pre-existing diabetes reported a numerically higher proportion of LGA in women treated with insulin compared to women treated with metformin [34, 36, 41, 56], with a significant difference ($p=0.001$) reported by Eid et al. [34]. In an RCT, Hod et al. compared insulin detemir with NPH in pregnant women diagnosed with diabetes and reported a significantly higher rate of LGA in the group treated with insulin NPH compared to the group treated with insulin detemir [57]. Other RCTs by Ainuddin et al. and Mukopadhyay et al. reported a lower proportion of LGA in women treated with basal/bolus insulin compared to metformin + insulin and glibenclamide, respectively [44, 58]. In another RCT, Somani et al. compared stillbirth in women treated with insulin (regular or NPH or both) versus metformin. This trial reported one case of stillbirth in the insulin-treated group compared to no stillbirth in the metformin group ($p=0.32$) [26].

Evidence from Observational Studies

In women diagnosed with GDM, three retrospective cohort studies by Koren et al., Castillo et al. and Hedderson et al. compared insulin versus glyburide and reported no substantial differences in the proportion of LGA in between the treatment groups [55, 59, 60]. However, other retrospective analyses by Simeonova-Krstevska et al., Benhalima et al. and Bogdanet et al. reported a significantly higher proportion of LGA in the insulin-treated group compared to diet/MNT and metformin ($p<0.0001$–$p<0.05$) [28, 32, 46]. In women diagnosed with diabetes prior to pregnancy, one retrospective database review by Neff et al. reported a significantly higher rate of delivery of LGA in mothers treated with CSII-aspart and NPH compared to those treated using MDI-aspart and NPH ($p=0.03$) [61]. Most of the studies did not report stillbirth, with only five studies reporting this outcome. Perinatal mortality among women with pre-existing diabetes was reported in retrospective studies by Bartal et al., Abell et al. and Billionnet et al., and no differences across the treatment arms were observed [48, 62, 63]. However, in a prospective cohort study by Negrato et al., a significantly higher rate of perinatal mortality ($p=0.028$) in pregnant women diagnosed with diabetes prior to pregnancy was reported among NPH-treated women compared to those treated with glargine [51].

DISCUSSION

We conducted an SLR that assessed the paradigm of reported insulin use in pregnant women with diabetes, as well as the outcomes, including recommended clinical parameters related to glycemic control as part of their treatment goals and maternal and fetal outcomes. The wide variety in outcomes of interest when comparing insulin use with other anti-diabetic agents across the included studies makes it extremely difficult and potentially misleading to summarize findings and make management recommendations, illustrating the need for standardization of study design with consistent glycemic and maternal/fetal efficacy outcomes to evaluate the use of glucose-lowering medications in pregnancy.

Glycemic outcomes of interest were reported in 27 clinical trials and 32 observational studies. Notably, while 1-h and 2-h PPGs are the recommended treatment goals in patients with GDM, many of the studies captured in this

review focused on HbA_{1c} as a primary outcome measure. Furthermore, compared to the non-pregnant population, there are very few well-powered RCTs evaluating insulin use in pregnancy. Ji et al. published a well-designed RCT in 2020 showing that in pregnant women diagnosed with diabetes prior to pregnancy, a significant improvement in PPG and TIR was observed among those treated with detemir compared with insulin NPH as basal insulin. Both groups received the short-acting human insulin three times a day before the meals [27]. These results increase the options for women requiring basal insulin therapy for diabetes management in pregnancy [27]. Use of continuous glucose monitoring (CGM) was also observed to be effective in improving glycemic range metrics in women treated with insulin. However, at the time of this SLR there was limited evidence to draw a conclusive statement on the impact of CGM role in improving glycemic outcomes for diabetes in pregnancy. Overall, there was no clear consensus between the study outcomes and use of various intervention types and regimens. The quality of the included studies was assessed, and they were found to be low on evidence with high risk of bias. Therefore, we could not conclude which intervention type or regimen was best for pregnant women with diabetes.

Maternal outcomes such as hypoglycemia, preeclampsia, cesarean delivery, preterm delivery and induced labor were reported in 18 RCTs, which may be due to the difficulty in collecting these outcome measures. They were reported more frequently in studies designed to compare an insulin regimen to another regimen such as in women treated with insulin versus those treated with metformin, diet/MNT and other anti-diabetic agents [20, 28, 32, 40, 45, 46, 64]. Most of the studies included in this review used insulin therapy as the last option of treatment, after the failure of nutritional therapy or in association with other drug interventions such as metformin and/or sulfonylureas. This suggests that these patients could have had more severe insulin resistance and/or deficiency than the other patients, and this would likely confound glycemic, maternal and fetal outcomes. Heterogeneity was observed across maternal outcomes among the studies, including rates of cesarean delivery, gestational age at delivery and induction of labor. The plausible reason for heterogeneity could be due to various ethnic groups, study designs, treatment requirements and selection criteria.

The most common fetal complication reported across the included studies for any type of diabetes during pregnancy was LGA, confirming that these patients were mostly in hyperglycemic state, a common cause of LGA. Other common neonatal outcomes observed, commonly associated with LGA and the mother's hyperglycemia, included the rate of complications such as preterm birth and neonatal hypoglycemia. Across studies covered in this review, insulin was associated with fewer cases of LGA only compared with glibenclamide, as observed in a study by Mukopadhyay et al. that compared insulin and glibenclamide for treatment of GDM [58]. In accordance with another meta-analysis, women treated with glibenclamide reported the highest incidence of LGA, preeclampsia, neonatal hypoglycemia and preterm birth; metformin (plus insulin when required) had the lowest risk of macrosomia, pregnancy hypertension, LGA, preterm birth and low birth weight [65]. Overall, there was no clear evidence of the risk of delivery of LGA in those born of mothers with diabetes treated with insulin versus other oral antidiabetic agents. Based on the current results, it is difficult to make a conclusive affirmation of the most effective form of treatment to reduce incidence of neonatal complications in pregnant women with diabetes.

Across the included studies, treatments with metformin and diet/MNT were associated with better clinical, maternal and fetal outcomes than those treated with insulin therapy. However, the studies did not provide enough evidence on whether insulin can help achieve improved outcomes compared with other therapies. Overall, the quality of the evidence of RCTs ranged from low to moderate, whereas for observational studies the quality ranged from low to good. A variety of methods was used to diagnose GDM in the included studies. Furthermore, it is difficult to draw conclusions about the optimal approach to treatment of diabetes in pregnancy because of inconsistencies in the criteria for management of glucose targets, patient adherence to treatment,

clinical outcome measures across studies and lack of long-term safety data.

The current SLR included clinical trials and observational studies with diverse populations and treatment arms. Some studies lacked appropriate sample size, and many studies utilized a variety of methods for diagnosis of GDM. Data on pregnant women diagnosed with diabetes prior to pregnancy were very limited. Furthermore, high-quality studies are needed to identify the optimal treatment regimens for women with diabetes in pregnancy who are treated with insulin.

There were clear limitations to the current SLR. With limited evidence and meta-analyses, the included studies did not provide sufficient evidence to identify clear differences between the various insulin types and regimens. Most of the included studies did not adjust for other potential confounding factors such as maternal age, educational status, income, ethnicity and other factors that might influence the results; therefore, findings should be interpreted with caution. This SLR included clinical trials and observational studies with varied populations and treatment arms. For some studies, sample size was small, and many studies did not report statistical tests for significance. In the included studies, there was no consensus on the types of outcome measures reported in pregnant women with diabetes. Most of the studies reported that there was no evidence of clear-cut benefit of one intervention type or regimen over the other. Hence, no firm conclusions or management recommendations could be made about different insulin types and regimens in pregnant women with diabetes. Future trials are required that are multi-centered, randomized, well-powered and of improved methodological quality with standardization of glycemic and maternal/fetal efficacy outcome measures. Furthermore, more research is warranted with larger groups of pregnant women, with transparent reporting of how the trials were conducted, and that reports clinical, maternal and fetal outcomes.

CONCLUSION

In summary, the findings of this review were comparable to the existing reviews evaluating treatment of diabetes in pregnancy. There is a tremendous paucity of well-designed RCTs and no consensus for the study design and definition of diabetes in pregnancy in the existing literature. We identified a variety of definitions being used that did not always overlap. We observed that the lack of standard diagnosis also results in a diversity of outcomes that are used in clinical practice to evaluate optimal medical management in pregnant women with diabetes. It would be helpful for the practitioners and patient populations if the outcomes were consistently defined and reported globally. According to the ADA Management of Diabetes in Pregnancy guidelines, the standard treatment goals for pregnant women with diabetes are aimed at maintaining target blood glucose levels (fasting glucose 70–95 mg/dl [3.9–5.3 mmol/l], 1-h postprandial glucose 110–140 mg/dl [6.1–7.8 mmol/l] and/or 2-h postprandial glucose 100–120 mg/dl [5.6–6.7 mmol/l]) to prevent maternal and fetal complications, achieved through stringent glucose monitoring and insulin therapy [11]. However, the universal adoption of these recommendations in the real-world is limited, as we identified in the observational studies analyzed, and some misalignment still exists in randomized clinical trials as well. This makes identifying any real-world association of the effectiveness of insulin in maternal and fetal outcomes difficult. With the increased access to CGM, the collection of glycemic values will increase, and more glycemic outcome data will be generated. However, this will require a more standardized approach, especially without a clear consensus on clinically relevant CGM metrics for GDM and T2D.

Conducting well-designed RCTs to evaluate the efficacy of various insulins or insulin regimens in this unique population remains an area that requires specialized attention. There is a need to be better aligned on clinical endpoints to study pregnant populations to delineate what treatment or therapies unequivocally demonstrate improvement in maternal and neonatal outcomes, especially with introduction of innovative insulin formulations and improved technologies that evaluate glucose management.

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Declarations

Conflict of Interest. Beatrice Osumili, Kushal Kumar Banerjee, Andrea Goldyn, and Carolina Piras De Oliveira are full-time employees and shareholders of Eli Lilly and Company. Theophilus Lakiang was an employee of Eli Lilly and Company at the time this research was conducted and is currently an employee of GE Healthcare. Kristin Castorino receives research support provided to her institution from Dexcom, Abbott, Medtronic, Novonordisk, Ely Lilly, and Insulet and consulting fees from Dexcom. Theophilus Lakiang: Author affiliation has changed since the time this research was conducted. Assigned affiliation is the institution of employment at the time this research was conducted.

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