Pregnancy outcomes in type 2 diabetes: a systematic review and meta-analysis

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OBJECTIVE: Type 2 diabetes (T2D) now accounts for the majority of pre-existing diabetes affecting pregnancy in the UK. Our aim was to determine its impact on pregnancy outcomes compared to type 1 diabetes (T1D), gestational diabetes (GDM), and non-diabetes pregnancies.

DATA SOURCES: PubMed was searched 1 January 2009 to 2024.

STUDY ELIGIBILITY CRITERIA: Cohort observational studies reporting original data on at least one of the primary outcomes in ten or more T2D pregnancies were eligible for inclusion. Comparative diabetes and nondiabetes pregnancies were also collected.

METHODS: Primary outcomes included congenital anomalies, stillbirths, neonatal and perinatal mortality, birthweight, rates of large for gestational age (LGA), small for gestational age (SGA), and macrosomia. PROSPERO ID CRD42023411057.

RESULTS: Forty seven studies were analyzed. The number of pregnancies in each analysis varied depending on the available data from the outcome being analyzed but ranged from 723 to 4,469,053 pregnancies. When compared with T1D pregnancies, T2D were more likely to have SGA babies as well as greater neonatal and perinatal mortality (OR 2.29, 95% CI 1.12—4.67; OR 1.53 95% CI 1.20—1.94, and OR 1.31 95% CI 1.07—1.61, respectively). When compared with GDM, T2D were more likely to have babies with congenital anomalies (OR 1.91, 95% CI 1.04—3.50), LGA (OR 3.49, 95% CI 2.49—4.89), neonatal mortality (OR 3.96, 95% CI 3.38—4.64), and stillbirth (OR 16.55, 95% CI 5.69—48.11). In comparison to nondiabetic pregnancy, T2D were more likely to have babies with congenital anomalies (OR 1.76, 95% CI 1.11—2.79), LGA (OR 2.79, 95% CI 1.93—4.04), perinatal mortality (OR 4.18, 95% CI 2.91—6.01), and stillbirth (OR 7.27, 95% CI 3.01—17.53).

CONCLUSION: T2D pregnancies are associated with a greater perinatal mortality than other forms of diabetes in pregnancy. Given its increasing prevenance, greater awareness of the adverse pregnancy outcomes associated with T2D is needed, by both healthcare providers and policy makers, to improve care.

Key words: congenital malformations, diabetes in pregnancy, perinatal mortality, pregnancy outcomes, stillbirth, type 2 diabetes

Introduction

Early onset type 2 diabetes (T2D — generally diagnosed prior to the age of 40) is of major concern as its prevalence is increasing rapidly.[1] It is associated with a more aggressive phenotype than older onset T2D, with rapid deterioration in glycaemic control, a more severe cardiovascular risk factor profile, and higher rates of diabetes-related complications.[2] It disproportionately affects females, those of non-White ethnicity, and those living in the most deprived communities,[2] meaning it is affecting an increasing proportion of women in their childbearing years. Its prevalence in the reproductive population has more than doubled in the past 15 years, overtaking type 1 diabetes mellitus (T1D) as the leading cause of preexisting diabetes in pregnancy in the UK.[1] In 2022, 55% of pregnancies complicated by pregestational diabetes were due to T2D, compared to 27% in 2003.[1,3]

In 2009, Balsells et al published a systematic review and meta-analysis of 33 studies exploring the pregnancy outcomes of women with T2D.[4] This suggested that although they had a milder glycaemic disturbance at booking and during pregnancy, women with T2D experienced higher rates of perinatal mortality than T1D pregnancies.[4] However, data on other adverse outcomes is conflicting. Some data suggests an increase in the rates of stillbirth,[1,5] major congenital malformations,[5] and perinatal deaths[1] in T2D and some demonstrate no difference in these outcomes compared to T1D.[6]

Objectives

Given the increasing prevalence of T2D in pregnancy[1] and increasing awareness of its aggressive cardiometabolic phenotype, our aim was to perform a contemporary systematic review and meta-analysis to quantify the impact of

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Received Aug. 7, 2024; revised Nov. 13, 2024; accepted Nov. 28, 2024.

The authors declare no competing interests.

There was no funding for this study.

All views presented in this article are the authors own and do not represent an official position of the institution.

PROSPERO Registration: ID CRD42023411057; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=411057.

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0002-9378/$36.00

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https://doi.org/10.1016/j.ajog.2024.11.026

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AJOG at a Glance

Why this study was conducted?

- Type 2 diabetes is becoming increasing more common in pregnancy, overtaking type 1 diabetes as the leading cause of pre-existing diabetes in pregnancy in the UK.
- There is little awareness of its more severe phenotype in women in their childbearing years, and therefore its serious impact on pregnancy outcomes.

Key findings

- We assessed the impact of having type 2 diabetes on a comprehensive range of pregnancy outcomes and quantified this risk compared to pregnancies with and without diabetes.
- Type 2 diabetes increases the risk of small for gestational age babies, congenital abnormalities, stillbirth and infant mortality.

What does this add to what is known?

- Pregnancies complicated by type 2 diabetes are therefore extremely high-risk.
- Greater awareness of these serious adverse pregnancy outcomes is needed, by health care providers and policy makers, to improve care and outcomes.

T2D on pregnancy outcomes, demonstrating the high risk of T2D in pregnancy. To place this data into context, we compared outcomes to other pre-existing diabetes in pregnancy (T1D) as well as diabetes diagnosed during pregnancy (gestational diabetes mellitus - GDM) which shares a similar pathophysiology to T2D.[7] To contextualize this data in comparison to the background population, we also compared outcomes of pregnancies without diabetes (control pregnancies).

Research design and methods

This meta-analysis was conducted according to the recommendations of Cochrane Systematic Reviews[8] and our findings reported in accordance with PRISMA and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Supplemental Figures 1 and 2).[9,10] The study was prospectively registered in the international database of prospectively registered systematic reviews (PROSPERO CRD42023411057). Due to this study only including previously published, anonymized data, ethical approval was not required.

Eligibility criteria, information sources, and search strategy

A systematic PubMed search was performed using the following search terms: "pregnancy AND type 2 diabetes mellitus" with results being uploaded to Rayyan.[11] Duplicate results were electronically detected by the Rayyan automation tool and reviewed manually prior to exclusion. Published, human studies written in English were included with a publication date of between January 1, 2009 and January 1, 2024 to update a previous systematic review and meta-analysis covering data published prior to 2009.[4] As the authors were aware of the National Pregnancy in Diabetes Audit (NPID) 2021 to 2022 data published online but not in a peer-reviewed manuscript form, this was also included via hand searches.[12] Previous NPID data (2014−2020) was available in published form[13] so was included via the systematic search described above.

Study selection

Two independent investigators assessed titles and abstracts for potential inclusion with discrepancies solved with discussion between the two investigators and a third investigator involved if discrepancies remained. If an abstract suggested potential suitability, the corresponding full text was acquired and assessed. Study author names, study locations, dates, and duration were checked to examine for duplicate publication. If uncertainty arose, study authors were contacted for clarification. If abstracts were identified with no corresponding full texts, study authors were contacted for full study information and results. We included published observational studies which provided original data of pregnancies in women with diabetes diagnoses prior to pregnancy. References of included studies were also examined for potentially eligible studies.

Data extraction

Summary estimates or raw numbers as reported in the papers were extracted and inputted into a predesigned form including country of study, year of publication, maternal background characteristics, and outcomes of interests. This was performed by two independent authors before results were compared. If there was any conflict, a third author was consulted to adjudicate.

All reports were compared for dates and location of data collection with duplicates removed. Studies which presented the largest numbers of pregnancies were included in the final analysis to prevent duplicate pregnancies being included in the final analysis. Studies which presented data on T1D, GDM, and control pregnancies were also extracted and used as the comparison pregnancies.

Inclusion and exclusion criteria

Studies which provided original data of pregnancies in women with known T2D, diagnosed prior to pregnancy, were included. Studies were required to have reported on a minimum of 10 pregnancies for T2D and include data on at least one primary outcome. Papers which had a population bias were excluded (eg, only including multiple pregnancies, only including pregnancies ending in a stillbirth, only including T2D who were on insulin or conceived only via in-vitro fertilization as well as those which reported women who were first diagnosed with T2D during pregnancy).

Outcomes

Maternal characteristics

Summary estimates of ethnicity, maternal age, weight, body mass index

(BMI), weight gain in pregnancy, duration of diabetes, HbA1c at booking and in the third trimester, gestational age at delivery, alcohol consumption, and socioeconomic status were collected when reported in two or more studies. Proportional characteristics were collected for number of primiparous, smokers, treatment with insulin, treatment with metformin, nephropathy, retinopathy, and chronic hypertension.

Primary outcomes

Number of events for congenital malformations, stillbirths, neonatal mortality, perinatal mortality, LGA (≥90th centile), macrosomia (≥4 kg), and SGA (≤10th centile) were collected as well as summary data for birthweight. Stillbirth was defined as death of a baby occurring before or during birth once a pregnancy reached 28 weeks' gestation. Neonatal mortality was defined as a baby who died within 4 weeks of being born alive and perinatal mortality was defined as a stillbirth or death within 7 days of birth. These were in keeping with World Health Organization definitions.[14,15]

Secondary outcomes

The number of events for diabetic ketoacidosis, hypoglycaemic coma, pregnancy-induced hypertension, preeclampsia, caesarean section, miscarriage, termination of pregnancy, preterm birth (both<37 weeks' gestation and<32 weeks' gestation), shoulder dystocia, neonatal glycaemia, respiratory distress syndrome, neonatal hyperbilirubinemia, neonatal hypocalcaemia, neonatal intensive care (NICU) admission, and APGAR scores<7 at 5 minutes of age were collected where this data was available.

Assessment of risk of bias

PRISMA and MOOSE guidelines were followed throughout the study.[9,10,16] The Newcastle-Ottawa Scale was utilized to assess quality based on the selection of groups, comparability, and the ascertainment of the outcomes of interest in all studies, including examining for adequacy of follow up.[17] Studies which were classified as poor quality by two independent authors were excluded from the final analysis.

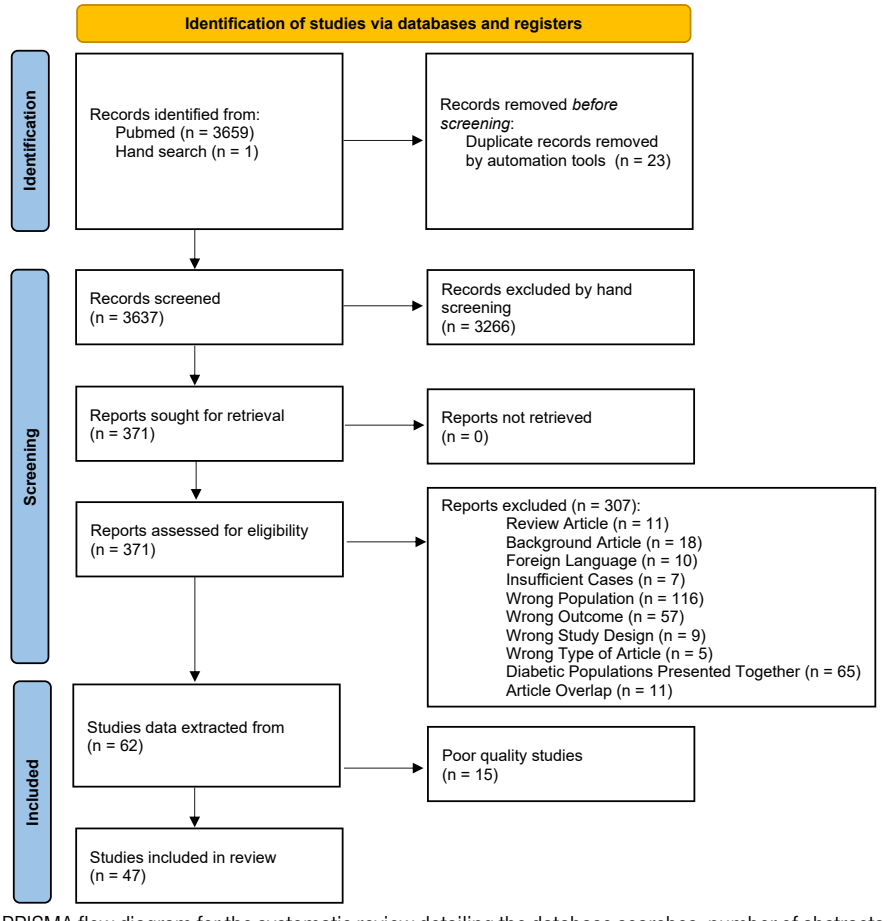
Data synthesis and analysis

Background characteristics were summarized for each patient group and expressed using descriptive statistics.

Outcome measures were analyzed with metanalyses using Review Manager Software (version 5.4.1).[18] Numbers of events from the original studies for each outcome were pooled and Mantel-Haenszel odds ratios (OR) were calculated, along with 95% confidence intervals, or mean differences and 95% confidence intervals, using a random effect model in order to reduce the effect of any heterogeneity. Outcome measures were calculated when presented in three or more studies.

To determine the proportion of variation between studies attributable to heterogenicity, I^2 was calculated. An I^2 value of greater than 75% was considered to indicate substantial heterogeneity.[19] Random effects analysis was used during analysis to minimize the effects of any heterogeneity present although the level of heterogeneity was taken into account when analyzing the results of the meta-analysis. Sensitivity analysis was undertaken on primary outcomes when ten or more studies were included in the analysis to ensure results were robust and one, large study was not influencing results. 95% prediction intervals were also calculated for the primary outcomes, where five or more studies were included in the analysis, in order to demonstrate the expected interval within which the effect of a future study will lie.[8] This was done in Stata Version 18.[20]

FIGURE 1
PRISMA flow diagram



PRISMA flow diagram for the systematic review detailing the database searches, number of abstracts screened, the full texts retrieved, reports assessed for eligibility, and reason for exclusion.

TABLE 1
Studies included in final analysis including year published, country data collected in, dates data collected, quality score of data presented following the Newcastle-Ottawa Scale[18] and numbers of pregnancies included in the studies

					n			
Author	Year published	Country	Dates collected	Quality score	T2D	T1D	GDM	Control
J Seah	2021	Australia	2004–2014	Good	106	92	0	119
H Jang	2018	Korea	2003–2010	Good	100	100	0	0
M Sidell	2021	USA	2008–2015	Good	7836	537	19,558	190,296
L A Owens	2015	Republic of Ireland	Not Reported	Fair	108	215	0	213
D Kothari	2014	Australia	2006–2011	Fair	19	34	288	0
R Starikov	2014	USA	2003–2011	Good	176	117	0	0
S A Wernimont	2019	USA	2015–2018	Good	39	0	63	0
C C Beauharnais	2012	USA	2001–2009	Fair	45	53	0	0
K Cyganek	2011	Poland	1999–2009	Good	70	345	0	0
N Holman	2011	England	2007–2008	Good	556	812	0	0
A J Allen	2018	USA	1997–2006	Good	34,587	0	0	0
F Hauffe	2020	Germany	2010–2017	Good	118	218	0	0
M B Fischer	2020	Denmark	2015–2018	Good	86	118	0	0
I Diboun	2020	Qatar	Not Reported	Fair	14	0	32	21
J A Rowan	2009	New Zealand	1998–2003	Good	212	0	0	0
M Persson	2014	Sweden	Not Reported	Fair	412	4092	8602	905,565
A Handisurya	2011	Austria	1995–2006	Good	66	75	0	0
E M Strøm-Roum	2021	Norway	2009–2017	Good	704	1360	11,840	304,758
S T Mackin	2018	Scotland	1998–2013	Good	1452	3229	0	808,953
J M Yamamoto	2020	Canada	2007–2014	Good	350	182	6208	0
J Alessi	2018	Brazil	2005–1015	Good	135	85	0	0
F Bánhidy	2010	Hungary	1980–1996	Fair	216	164	347	59,792
H R Murphy	2021	England, Wales & Isle of Man	2014–2018	Good	8685	8690	0	0
H van Zyl	2018	South Africa	2010–2011	Good	194	35	192	0
K M Knight	2012	USA	2000–2008	Good	213	0	0	213
T Sato	2014	Japan	2003–2009	Good	579	369	0	0
T Joshi	2017	Australia	2009–2014	Good	88	159	0	0
J L Racine	2021	USA	2009–2019	Good	254	0	0	0
I-L Lee	2020	Australia	2011–2017	Good	97	0	419	0
S S Delaney	2015	USA	2009–2011	Good	24	37	24	0
J Immanuel	2021	New Zealand	2011–2017	Fair	493	0	1425	0
S K Abell	2017	Australia	2010–2013	Good	138	0	0	27,075
C B Parellada	2014	Denmark	2008–2013	Good	142	0	0	0
M N Feghali	2017	USA	2009–2012	Good	198	0	0	0
M F Higgins	2013	Republic of Ireland	2006–2008	Good	10	40	0	30
A Metcalfe	2017	Canada	2004–2015	Good	11,028	7362	149,780	2,688,231
C Newman	2022	Republic of Ireland	2015–2020	Good	374	696	0	0

(continued)

TABLE 1
Studies included in final analysis including year published, country data collected in, dates data collected, quality score of data presented following the Newcastle-Ottawa Scale[18] and numbers of pregnancies included in the studies *(continued)*

Author	Year published	Country	Dates collected	Quality score	n			
					T2D	T1D	GDM	Control
H Yokomichi	2022	Japan	2011–2014	Good	102	67	2045	19,132
K F Shingu	2022	Japan	1982–2020	Good	407	214	0	0
J M Yamamoto	2022	Canada	2011–2017	Fair	1506	0	0	4301
G Capobianco	2022	Italy	2016–2020	Good	14	42	0	0
M Koyama	2023	Japan	2014–2022	Good	15	22	0	0
Y Ren	2023	China	2018–2020	Good	20	0	0	60
T Schiller	2023	Isreal	2014–2021	Good	86	0	0	0
A McLean	2023	Australia	2019–2021	Good	41	0	0	0
A H Xiang	2023	USA	1995–2015	Good	6636	680	42,420	389,854
NPID	2022	England & Wales	2021–2022	Good	5670	4510	0	0
				Total	84,421	34,751	243,243	5,398,613

GDM, gestational diabetes; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes.

Data and resource availability

The datasets generated during and analyzed in the current study are available from the corresponding author upon reasonable request.

Results

Literature search and study selection (including risk of bias of included studies)

The search strategy identified 3660 abstracts, 371 full-text articles were examined including one study (NPID 2021–2022) identified by hand-searching. Of these, 62 were selected for inclusion in the final analysis (Figure 1). Sixty five studies were excluded as they included aggregated T1D and T2D pregnancies and 11 studies were excluded due to overlapping data. In this scenario, the study describing the largest population was included. On assessing study quality, a further 15 studies were excluded due to poor quality data, leaving 47 for inclusion in the final analysis (Table 1). Studies excluded at the full text stage may be seen in Supplemental Table 1, including the reason for exclusion, and assessment of quality of all studies can be seen in Supplemental Table 2.

Included studies

Included studies (Table 1) originated from a wide range of countries, demonstrating an international population. Included were 84,421 T2D pregnancies, 34,751 T1D pregnancies, 243,243 GDM pregnancies, and 5,398,613 control pregnancies.

Background maternal characteristics

Generally, T2D mothers were older and heavier than T1D, GDM, and control mothers (Table 2). They had a shorter duration of diabetes (3.6 vs 13.4 years) and a lower first trimester HbA1c (53.1 vs 56.7 mmol/mol) and third trimester HbA1c (43.2 vs 47.5 mmol/mol) than T1D. A larger proportion had chronic hypertension (17.1%) than T1D (7.6%), GDM (2.7%), and controls (0.7%) and were on metformin (44%) but a smaller proportion had diabetes-related microvascular complications such as nephropathy and retinopathy than T1D. T1D and T2D were delivered at an earlier gestational age (37.4 and 37.8 weeks, respectively) when compared to GDM and controls (38.5 and 39.3 weeks, respectively). Data on alcohol consumption and socioeconomic status was limited, so these characteristics were not analyzed. Data on ethnicity was also presented in a limited number of studies and all using different categories so this was also unable to be analyzed.

Primary outcomes

T2D vs T1D

Compared to women with T1D, those with T2D had a lower risk of having an LGA baby (OR 0.51, 95% CI 0.40–0.64, $P<.00001$, $I^2=93\%$) but a higher risk of having a small for gestational age baby (OR 2.52, 95% CI 1.24–5.10, $P=.01$, $I^2=95\%$), neonatal mortality (OR 1.53, 95% CI 1.20–1.94, $P=.0005$, $I^2=0\%$, 95% PI 1.17–2.01) and perinatal mortality (OR 1.31, 95% CI 1.07–1.61, $P=.009$, $I^2=0\%$) (Table 3, A and Figure 2, A). On average, those with T2D had babies 80.20 g lighter than those with T1D (95% CI −136.61 to −23.78, $P=.005$, $I^2=67\%$).

Heterogeneity (I^2) was low or moderate for most of these outcomes but was high for LGA, macrosomia, and SGA.

T2D vs GDM

Compared to women with GDM, those with T2D had a higher risk of having a baby with congenital anomalies (OR 1.91, 95% CI 1.04–3.50, $P=.04$, $I^2=88\%$), an LGA baby (OR 3.49, 95% CI 2.49–4.89, $P<.00001$, $I^2=61\%$, 95% PI 1.01–13.21), perinatal mortality (OR

TABLE 2
Maternal characteristics in all groups

	N	T2D	T1D	GDM	Control
Age (y)	42	33.6	30.2	32.2	30.2
BMI (kg/m^2)	33	32.4	26.1	30.7	26.2
First trimester HbA1c (mmol/mol)	27	53.1	56.7	36.5	Not Reported
First trimester HbA1c (%)	27	7.0	7.3	5.5	Not Reported
Third trimester HbA1c (mmol/mol)	17	43.2	47.5	34.4	Not Reported
Third trimester HbA1c (%)	17	6.1	6.5	5.3	Not Reported
Gestational age at delivery (wk)	36	37.8	37.4	38.5	39.3
DM duration (y)	21	3.6	13.4	Not Reported	Not Reported
On insulin (%)	16	4.5	98.8	33.1	Not Reported
On metformin (%)	11	44.0	12.9	24.0	Not Reported
Primip (%)	19	30.9	51.5	32.2	37.8
Smoker (%)	21	18.9	12.2	14.9	17.1
Chronic hypertension (%)	20	17.1	7.6	2.7	0.7
Nephropathy (%)	7	8.2	12.2	Not Reported	Not Reported
Retinopathy (%)	9	4.8	14.9	Not Reported	Not Reported

GDM, gestational diabetes mellitus; *N*, number of studies contributing to data; *NR*, not reported; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes.

3.96, 95% CI 3.38−4.64, *P*<.00001, I^2=0%), and stillbirths (OR 16.55, 95% CI 5.69−48.11, *P*<.00001, I^2=0%) (Table 3, B and Figure 2, B). There was no significant difference in birthweight between T2D and GDM.

Heterogeneity (I^2) was low or moderate for all of these outcomes except for congenital anomalies and birthweight.

T2D vs controls

Compared to women with no diabetes, those with T2D had a higher risk of having a baby with congenital anomaly (OR 1.76, 95% CI 1.11−2.79, *P*=.02, I^2=90%), perinatal mortality (OR 4.18, 95% CI 2.91−6.01, *P*<.0001, I^2=64%), and stillbirth (OR 7.27, 95% CI 3.01−17.53, *P*<.00001, I^2=46%) (Table 3, C and Figure 2, C). T2D women on average had babies who were 27.91 g heavier then control pregnancies (95% CI 2.06−53.75, *P*=.03, I^2=27%)

On initial analysis, the difference in the rates of LGA between T2D and control pregnancies was not statistically significant (Figure 2, C, plot 3.1.2). However, upon sensitivity analysis, T2D had a higher risk of having an LGA baby (OR 2.79, 95% CI 1.93−4.04, *P*<.00001, I^2=76% - Figure 2, C, plot 3.1.3).

Heterogeneity (I^2) was low or moderate for the majority of these outcomes but was high for congenital anomalies, LGA, and macrosomia.

Sensitivity analysis

Sensitivity analysis was undertaken on all primary outcomes where 10 or more studies were included in the analysis in order to exclude studies with significant sample sizes and therefore impact on overall results. Other than differing rates of LGA between T2D and control, there was no change to the findings (Supplemental Figure 3).

Secondary outcomes

With regards to the secondary outcomes, there was no data for hypoglycaemic coma events and limited data on episodes of diabetic ketoacidosis (one study) so these outcomes were not able to be analyzed.

T2D vs T1D

There were no differences between T2D and T1D pregnancies for most secondary outcomes (Table 4, A). However, T1D pregnancies were more likely to result in preterm birth<37 weeks (OR 0.69, 95% CI 0.59−0.82, *P*<.00001), neonatal hypoglycaemia (OR 0.62, 95% CI 0.48−0.80, *P*=.0002), and NICU admission (OR 0.55, 95% CI 0.46−0.66, *P*<.00001).

T2D vs GDM

For comparison of secondary obstetric and neonatal outcomes between T2D and GDM, data was limited (Table 4, B). However, T2D were more likely to experience pregnancy-induced hypertension (OR 1.80, 95% CI 1.43−2.26, *P*<.00001), pre-eclampsia (OR 1.78, 95% CI 1.20−2.66, *P*=.004), caesarean section (OR 1.94, 95% CI 1.70−2.22, *P*<.00001), and preterm birth<37 weeks (OR 2.72, 95% CI 2.25−3.28, *P*<.00001).

T2D vs control

Compared to controls without diabetes, T2D pregnancies were more likely to result in pregnancy-induced hypertension (OR 2.62, 95% CI 1.52−4.52, *P*=.0005), preeclampsia (OR 3.40, 95% CI 2.30−5.03, *P*<.00001), caesarean section (OR 3.13, 95% CI 2.64−3.72, *P*<.00001), preterm birth<37 weeks (OR 4.36, 95% CI 3.73−5.11, *P*<.00001), preterm birth<32 weeks (OR 2.46, 95% CI 1.37−4.43, *P*=.03), shoulder dystocia (OR 2.96, 95% CI 1.53−5.73, *P*=.001), neonatal hypoglycaemia (OR 6.62, 95% CI 5.09−8.60, *P*<.00001), respiratory distress syndrome (OR 3.52, 95% CI 1.55−8.00, *P*=.003), fetal hyperbilirubinaemia (OR 2.66, 95% CI 2.01−3.54, *P*<.00001), fetal hypocalcaemia (OR 25.32, 95% CI 7.31−87.78, *P*<.00001), and NICU admission (OR 4.24, 95% CI 2.19−8.22, *P*<.00001) (Table 4, C).

Comment

Principle findings

We have shown that T2D pregnancies are associated with increased risk, both for the mother and for the fetus. Women with T2D were more likely to have an SGA baby than T1D and experience perinatal mortality compared to T1D, GDM and control pregnancies. They were also significantly more likely to experience stillbirth than GDM and control pregnancies. However, women with T1D were

TABLE 3
Primary outcome analysis

A: T2D vs T1D

		T2D			T1D							
	N	Events	Total	%	Events	Total	%	OR	95% CI	95% PI	I^2	*P* value
Congenital abnormalities	20	2174	23248	9.4	1008	19840	5.1	0.97	0.82—1.15	0.59—1.56	34%	NS
LGA	16	4640	17516	26.5	8963	18144	49.4	0.51	0.40—0.64	0.15—1.73	93%	<.00001
Macrosomia	9	280	2154	13.0	501	4594	10.9	0.98	0.62—1.55	0.19—4.98	81%	NS
SGA	14	2143	15160	14.1	405	14981	2.7	2.52	1.24—5.10	0.30—22.29	95%	.01
Neonatal mortality	12	178	15828	1.1	121	19018	0.6	1.53	1.20—1.94	1.17—2.01	0%	.0005
Perinatal mortality	4	244	13086	1.9	210	14718	1.4	1.31	1.07—1.61	Analysis not possible	0%	.009
Stillbirth	19	55	17271	0.3	45	18131	0.2	1.15	0.96—1.38	0.00—0.54	0%	NS
								Mean Difference	95% CI			
Birthweight	15		11950			7787		−80.20	−136.61 to −23.78		67%	.005

B: T2D vs GDM

		T2D			GDM							
	N	Events	Total	%	Events	Total	%	OR	95% CI	95% PI	I^2	*P* value
Congenital abnormalities	7	1541	8067	19.1	3982	55301	7.2	1.91	1.04—3.50	0.38—9.43	88%	.04
LGA	5	282	938	30.1	915	8283	11.0	3.49	2.49—4.89	1.01—13.21	61%	<.00001
Macrosomia	Analysis is not possible											
SGA	3	78	802	9.7	824	7836	10.5	0.96	0.59—1.57	Analysis not possible	58%	NS
Neonatal mortality	Analysis is not possible											
Perinatal mortality	3	205	11634	1.8	696	158574	0.4	3.96	3.38—4.64	Analysis not possible	0%	<.00001
Stillbirth	4	19	798	2.4	5	3932	0.1	16.55	5.69—48.11	Analysis not possible	0%	<.00001
								Mean Difference	95% CI			
Birthweight	11		9879			35162		−6.24	−68.95 to 56.46		82%	NS

C: T2D vs Control

		T2D			Control							
	N	Events	Total	%	Events	Total	%	OR	95% CI	95% PI	I^2	*P* value
Congenital abnormalities	10	1655	9539	17.3	71324	1406428	5.1	1.76	1.11—2.79	0.51—6.34	90%	.02
LGA	9	801	2292	34.9	2816	32296	8.7	2.79	1.93—4.04	0.75—10.30	76%	<.00001
Macrosomia	3	42	310	13.5	176	19430	0.9	2.88	0.52—16.02	Analysis not possible	93%	NS
SGA	7	148	2185	6.8	4392	32137	13.7	1.00	0.66—1.51	0.32—3.03	62%	NS
Neonatal mortality	Analysis is not possible											
Perinatal mortality	4	239	13030	1.8	18097	4429824	0.4	4.18	2.91—6.01	Analysis not possible	64%	<.00001

(continued)

TABLE 3
Primary outcome analysis *(continued)*

C: T2D vs Control

		T2D			Control							
	N	Events	Total	%	Events	Total	%	OR	95% CI	95% PI	I^2	*P* value
Stillbirth	5	48	1981	2.4	3991	828658	0.5	7.27	3.01–17.53	0.49–109.24	46%	<.00001
								Mean difference	95% CI			
Birthweight	9		10629			1383478		27.91	2.06–53.75		27%	.03

CI, confidence interval; *GDM*, gestational diabetes; I^2, statistical heterogeneity; *N*, studies included in analysis; *NS*, not significant; *OR*, odds ratio; *PI*, prediction interval; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes.

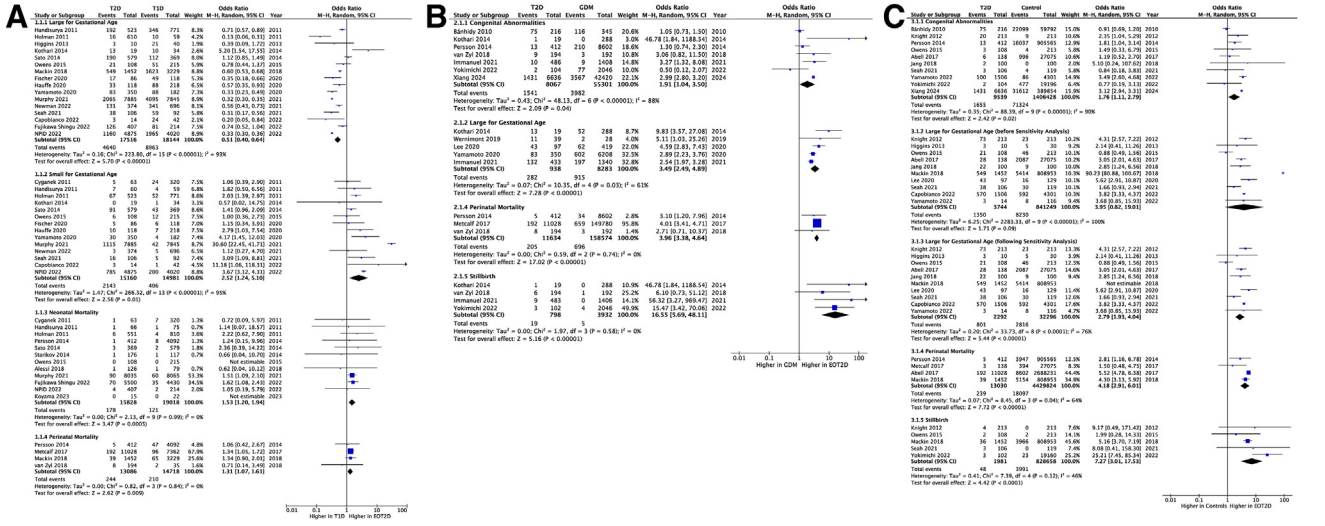
more likely to have preterm birth<37 weeks, an LGA baby, neonatal hypoglycaemia, and NICU admission. The finding that T2D is associated with increased perinatal morbidity and mortality is consistent with its severe metabolic phenotype outside of pregnancy.[21,22] This may reflect the underlying maternal cardiometabolic status, with increased rates of chronic hypertension in T2D, impacting on placental function and fetal growth. Women from ethnic minorities and socioeconomically deprived communities are also most impacted by T2D, with socioeconomic deprivation further contributing to perinatal mortality and widening healthcare disparities.[2] This suboptimal start in life may also have a lifelong impact on infant health, increasing the risks of type 2 diabetes, cardiovascular disease, and obesity in the future, with substantial economic burden.[23]

Comparison to existing literature

These findings align with previous studies with higher rates of perinatal mortality and SGA in T2D pregnancies than T1D.[1,4] The observation that several common, but less severe, secondary outcomes (preterm births; large birthweight; neonatal care admissions) are higher in T1D reflects the pathophysiology and current clinical practice; babies are more likely to be delivered prematurely due to more severe hyperglycaemia and concomitant clinicians concerns for safely delivering an LGA baby.

We also demonstrated that women with T2D were more likely than those with GDM to have congenital anomalies, perinatal mortality, and stillbirth, as well

FIGURE 2
Pregnancy outcomes of significance



Primary outcomes of significance between type 2 diabetes (T2D) and type 1 diabetes (T1D) pregnancies (**A**), gestational diabetes (GDM) pregnancies (**B**), and control pregnancies (**C**).

TABLE 4
Secondary outcome analysis

A: T2D vs T1D

		T2D			T1D						
	N	Events	Total	%	Events	Total	%	OR	95% CI	I^2	*P* value
Maternal outcomes											
Pregnancy-induced hypertension	9	1576	12515	12.6	1112	8500	13.1	1.03	0.83–1.28	38%	NS
Pre-eclampsia	11	803	12915	6.2	960	8909	10.8	0.87	0.56–1.35	85%	NS
Total caesarean section	20	10354	18683	55.4	12670	20653	61.3	0.90	0.77–1.07	85%	NS
Miscarriage	9	681	7126	9.6	515	6242	8.3	0.85	0.59–1.23	66%	NS
Termination of pregnancy	Analysis is not possible										
Fetal outcomes											
Preterm delivery<37 wk	20	6589	28613	23.0	10233	29998	34.1	0.69	0.59–0.82	90%	<.00001
Preterm delivery<32 wk	4	74	2627	2.8	271	9226	2.9	0.77	0.56–1.08	16%	NS
Shoulder dystocia	4	4	381	1.0	10	343	2.9	0.53	0.16–1.67	0%	NS
Neonatal hypoglycemia	8	272	1881	14.5	725	5390	13.5	0.62	0.48–0.80	44%	.0002
Respiratory distress syndrome	3	70	1005	7.0	130	4503	2.9	0.99	0.68–1.46	0%	NS
Fetal hyperbilirubinaemia	6	164	984	16.7	149	819	18.2	0.92	0.60–1.39	47%	NS
Fetal hypocalcaemia	3	26	761	3.4	35	685	5.1	1.39	0.65–2.97	0%	NS
NICU admission	14	4437	15476	28.7	6639	14990	44.3	0.55	0.46–0.66	83%	<.00001
APGAR<7 at 5 min	3	21	409	5.1	13	314	4.1	1.20	0.58–2.50	0%	NS

B: T2D vs GDM

		T2D			GDM						
	N	Events	Total	%	Events	Total	%	OR	95% CI	I^2	*P* value
Maternal outcomes											
Pregnancy-induced hypertension	3	1404	11482	12.2	12614	158034	8.0	1.80	1.43–2.26	56%	<.00001
Pre-eclampsia	5	673	11832	5.7	3692	151841	2.4	1.78	1.20–2.66	70%	.004
Total caesarean section	8	6541	12625	51.8	63213	168557	37.5	1.94	1.70–2.22	57%	<.00001
Miscarriage	Analysis is not possible										
Termination of pregnancy	Analysis is not possible										
Fetal outcomes											
Preterm delivery<37 wk	5	2818	11909	23.7	17464	166919	10.5	2.72	2.25–3.28	58%	<.00001
Preterm delivery<32 wk	Analysis is not possible										
Shoulder dystocia	Analysis is not possible										
Neonatal hypoglycemia	Analysis is not possible										
Respiratory distress syndrome	Analysis is not possible										
Fetal Hyperbilirubinaemia	Analysis is not possible										
Fetal hypocalcaemia	Analysis is not possible										
NICU admission	Analysis is not possible										
APGAR<7 at 5 min	Analysis is not possible										

(continued)

TABLE 4
Secondary outcome analysis *(continued)*

C: T2D vs Control

		T2D			Control						
	N	Events	Total	%	Events	Total	%	OR	95% CI	I^2	*P* value
Maternal outcomes											
Pregnancy-induced hypertension	6	1391	11697	11.9	108594	2735047	4.0	2.62	1.52–4.52	82%	.0005
Pre-eclampsia	6	651	11693	5.6	35231	2715951	1.3	3.40	2.30–5.03	56%	<.00001
Total caesarean section	11	7771	15088	51.5	1062058	4453807	23.8	3.13	2.64–3.72	88%	<.00001
Miscarriage	Analysis is not possible										
Termination of pregnancy	Analysis is not possible										
Fetal outcomes											
Preterm delivery<37 wk	10	3642	15163	24.0	277746	4453890	6.2	4.36	3.73–5.11	78%	<.00001
Preterm delivery<32 wk	3	65	1970	3.3	15350	1714637	0.9	2.46	1.37–4.43	63%	.003
Shoulder dystocia	3	21	385	5.5	505	20384	2.5	2.96	1.53–5.73	0%	.001
Neonatal hypoglycaemia	6	126	1077	11.7	12746	933285	1.4	6.62	5.09–8.60	0%	<.00001
Respiratory distress syndrome	5	73	877	8.3	5100	933069	0.5	3.52	1.55–8.00	64%	.003
Fetal hyperbilirubinaemia	6	164	677	24.2	3908	46913	8.3	2.66	2.01–3.54	26%	<.00001
Fetal hypocalcaemia	Analysis is not possible										
NICU admission	8	721	2192	32.9	1173	32106	3.7	4.24	2.19–8.22	89%	<.00001
APGAR<7 at 5 min	Analysis is not possible										

CI, confidence interval; *GDM*, gestational diabetes; I^2, statistical heterogeneity; *N*, total number of studies included in analysis; *NS*, not significant; *OR*, odds ratio; *T1D*, type 1 diabetes; *T2D*, type 2 diabetes.

as LGA babies. T2D were more likely to experience pregnancy-induced hypertension, preeclampsia, caesarean section, and preterm birth<37 weeks. Rates of SGA babies were similar between the two groups, although the pathophysiology behind this is unclear given the differing rates of pregnancy-induced hypertension and preeclampsia. Previous work has shown that GDM pregnancies are significantly associated with poorer pregnancy complications;[24] however, this data suggests that T2D is of even higher risk than GDM.

Compared to pregnancies without diabetes, T2D were more likely to experience congenital anomalies, perinatal mortality, stillbirth, and LGA babies. SGA rates were similar between the two groups. Most secondary obstetric and neonatal outcomes were more likely in T2D pregnancies.

In developed populations, resources are focused on women with GDM or those at risk of GDM,[25] due to its high prevalence; however, as shown in this meta-analysis, those with T2D have higher rates of congenital anomalies, LGA, perinatal mortality, and stillbirth than those with GDM and control pregnancies. The National Pregnancy in Diabetes Audit 2020 identified glucose control as being the main modifiable risk factor for pregnancy outcomes in T2D. The *Saving Babies' Lives Care Bundle (version three)* recommends more stringent pregnancy glucose targets with HbA1c of less than 43 mmol/mol from 24 weeks gestation and increased antenatal surveillance to mitigate these risks.[1,26] Continuous glucose monitoring (CGM) is associated with improved glucose control (and therefore pregnancy outcomes) in T1D. Given the severity of pregnancy outcomes in T2D, the use of interventions such as CGM warrant further investigation.

It is well established that unplanned pregnancies in both T1D and T2D increase the risk of congenital anomalies and perinatal deaths.[27] Planning pregnancies in these groups allows optimization of blood glucose levels, folic acid supplementation, management of blood pressure and diabetes related complications, smoking cessation, and discontinuing potentially teratogenic medications.[28] The vast majority of T2D patients worldwide are managed in the community, where the focus on managing T2D has tended to be more on cardiovascular risk reduction and less so on providing preconception care.[29]

Women with T2D have a higher BMI than those with T1D, GDM, and controls. BMI is known to independently increase the risk of stillbirth, neonatal, and perinatal mortality.[30] Likewise for smoking[31] and of chronic hypertension,[32] both of which are more common in T2D as shown in this and previous

studies. Improved preconception care to effectively manage these factors pre-pregnancy may also improve outcomes. A higher proportion of T2D are on metformin preconception and during pregnancy. The data of the effect of metformin on fetal outcomes, however, is of poor quality so the impact this may have on pregnancies with diabetes is uncertain.[33]

Strengths and limitations

To the best of our knowledge, this is the largest, most contemporary meta-analysis to summarize pregnancy outcomes between T2D, T1D, GDM, and controls, including data from the last 30 years over a large range of ethnicities and nationalities. This systematic review and meta-analysis was done in accordance with PRISMA guidelines and was carried out systematically and structurally with the best evidence available (Supplemental Figures 1 and 2).

When examining the 95% prediction intervals, generally these were wider than the 95% confidence intervals. This is to be expected to some degree as prediction intervals focus on a single future observation rather than the likely location of the true population parameter, introducing natural population variation.[34] However, two outcomes did have PIs which suggested significant findings. It can be therefore concluded with confidence that the rates of neonatal mortality in T2DM compared to T1DM and rates of LGA in T2DM compared to GDM are significantly higher.

We acknowledge that the number of T2D pregnancies with data on the rates of neonatal mortality and macrosomia outcomes was less than the other patient groups, which limits the statistical power to detect differences. Additional limitations are high heterogeneity for some outcomes, particularly birthweight, and rates of congenital abnormalities and LGA. Furthermore, some studies did not define their measures for birth centiles, although studies of poor quality were excluded. Adjustment for confounders, most importantly maternal ethnicity and BMI, was not possible due to the design and variability between included studies. We included only English language studies as we did not have access to translation services which may have introduced publication bias. However, the background maternal characteristics of each of the groups are in keeping with expected values, implying that the data was generally representative of the relative populations.[1] A further potential source of publication bias was that the data for T1D, GDM, and control pregnancies was obtained from papers which coreported T2D data.

Conclusions and implications

In conclusion, T2D pregnancies are associated with greater perinatal mortality than other forms of diabetes in pregnancy. Congenital malformations and stillbirth are also higher than that seen in GDM and nondiabetes pregnancy. Further studies are needed to investigate the cause of these poorer pregnancy outcomes, as they are likely to be multifactorial and not just a reflection of hyperglycaemia, including exploration of the differences in BMI, hypertension, and smoking rates between these groups. The fact that T2D is increasingly common in women having children highlights that clinicians, researchers, and policy makers need to be aware of these increased risks and work collaboratively with patient groups to optimize pregnancy outcomes and reduce longer term health inequalities for both mothers and their children. Enhanced, supportive care for those with T2D both before and during pregnancy is urgently needed. ■

ACKNOWLEDGMENTS

The authors would like to thank Vinson Wai-Shun Chan for his help in the statistical analysis.

GLOSSARY

BMI body mass index
CGM continuous glucose monitoring
GDM gestational diabetes
LGA large for gestational age
NICU neonatal intensive care
OR odds ratio
SGA small for gestational age
T1D type 1 diabetes
T2D type 2 diabetes

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