



Review

Pregnancy and Type 2 Diabetes: Unmet Goals

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Abstract: The increased frequency of type 2 diabetes worldwide has led to a concomitant increase in pregnancies complicated by type 2 diabetes for the past 20 years. This is mainly due to two factors: the earlier age of diabetes onset and the advanced age of pregnancy occurrence. Patients with type 2 diabetes in pregnancy show a high frequency of maternal and fetal complications, posing a series of problems in the follow-up of these women. In this narrative review, changes in epidemiology, maternal and fetal complications, and evidence of critical unmet needs before and during pregnancy complicated by type 2 diabetes are reported and discussed to review the possible approaches.

Keywords: diabetes; pregnancy; maternal complications; fetal complications

1. Introduction

Pregnancy complicated by diabetes, if not properly followed and treated, is associated with severe maternal and fetal complications [1]. In this context, the recent increase all over the world of type 2 diabetes and, consequently in pregnancy [2] highlighted new problems in terms of approach to medical care for these women. Recent publications evidence an increase in pregnancy in women affected by type 2 diabetes, which is often complicated by adverse maternal and fetal outcomes. Low attendance to pre-pregnancy care, non-optimal glycemic control during organogenesis, high utilization of harmful drugs during pregnancy, and low folic acid consumption contribute to adverse maternal and fetal outcomes. Furthermore, young women with type 2 diabetes in pregnancy experiencing these negative outcomes are often immigrants, minorities, and/or in low socioeconomic conditions that prevent adequate pre-pregnancy care and strict follow up during pregnancy.

In this narrative review, we aim to summarize the available evidence regarding the epidemiology, maternal and fetal outcomes, glycemic control, and other factors affecting pregnancy outcomes in pregnant women with type 2 diabetes. In addition, we investigate unmet goals in the management of these pregnancies in order to identify potential solutions.

2. Epidemiology

Over the last 20 years, the marked increase in the frequency of type 2 diabetes (T2D) worldwide has led to a concomitant increase in pregnancies in women affected by T2D, due to two main factors: the earlier age of diabetes onset and the advanced age of pregnancy occurrence [2]. In this context, many studies have evaluated the prevalence of T2D in pregnancy.

Utilizing data from the 1988 National Maternal and Infant Health Survey, Engelgau et al. estimated that in the U.S., diabetes was present in 154,000 (4%) pregnancies that resulted in live births, among which 8% were complicated by type 2 diabetes [3].

Albrecht et al. evaluated the prevalence of this condition in the United States between 1994 and 2004, reporting an increase of 367% [4]. From 1998 to 2012, the rate in Sweden rose from 0.003 to 0.1% [5]. Meanwhile, a report from Scotland evidenced a growth from 1998 to 2013 of 0.1 to 0.19% [6]. Using electronic health records of the United Kingdom (UK), Coton et al. showed that the prevalence of T2D increased from 1995 to 2008 from 2.34 per 1000 to 5.09 per 1000, with a more rapid increase in 2012 (10.2 per 1000) [7]. An



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observational retrospective study in Spain analyzed 2,481,479 deliveries between 2009 and 2015 [8]. The data showed that the incidence rate per 10,000 deliveries grew significantly in T2D pregnant women, from 14.56 in 2009 to 22.4 ($p < 0.001$) in 2015.

A national population-based pregnancy cohort was initiated in 2002 in the UK by a Confidential Enquiry into the Maternal and Child Health (CEMACH) program; it aimed to evaluate the quality of maternity care and pregnancy outcomes in women with diabetes. The first report (2002–2003) found a T2D percentage of 28%; subsequent studies in 2015 and 2020 reported 47% and 54%, respectively, double compared to the number observed in 2003 [9,10].

3. Pregnancy Outcomes

The summary of the studies on pregnancies complicated by type 2 diabetes are reported in Table 1.

Table 1. Summary of studies on pregnancies complicated by type 2 diabetes. PPC = pre-pregnancy counseling, FA = folic acid, NA = not available, CA = congenital anomaly, SB = stillbirth, PND = perinatal death, ND = neonatal death, LGA = large for gestational age, NM = neonatal mortality, SGA = small for gestational age, PTD = preterm delivery, NI = non indigenous, I = indigenous, IR = insulin resistance, Non IR = non-insulin resistance, CS = caesarean section.

Author (References)	N°	T2D Duration Years	AGE Years	HbA1c% 1st Trim.	BMI or % Obesity (O) (>30 kg/m ²)	Caucasian	PPC	Folic Acid	Pregnancy Outcomes	Country
Macintosh 2006 [11]	652	3(2–6)	33.5(30–37)	7.0(6.1–7.1)	O = 62%	50.8%	24.8%	29.4%	CA 4.3% SB 29.2% PND 32.3% ND 9.5% LGA 13.9%	UK CEMACH
Lapolla 2008 [12]	164	5.7(5.9)	33.2 (4.8)	6.6(1.7)	28.1(6.4)	NA	29.1%	NA	Miscarriage 10.7% ND 1.9% SB 1.9% CA 2.0% Macrosomia 11.8%	Italy
Owens 2015 [13]	108	4.3(3.8)	33.7(4.8)	6.9(1.7)	34.9(6.7)	70%	34%	55%	Miscarriage 8.3% SB 1.9% CA 2.8% LGA 20% SGA 5.6%	Ireland ATLANTIC DIP
Murphy 2017 [14]	1386	4.8(4.3)	33.6(5.2)	6.8	33.3(7.3)	46%	NA	22.5%	CA 34.6% ND 11.4% SB 10.5% PTD 21.7% LGA 23.9%	UK
Maple-Brown 2019 [15]	175 (NI 23 I 152)	NA	NI = 33.6(5.6) I = 31.1(5.6)	NI = 6.9(1.8) I = 7.8(2.0)	NI = 30.3(7.6) I = 31.3(5.7)	NA	NA	NA	CA NI = 4.2 vs. I = 4.6% LGA NI = 27.3 vs. I = 39.5% SGA NI = 18.2 vs. I = 6.9%	Australia PAN-DORA
Ali 2020 [16]	50	5.49(4.4)	35.5(3.8)	NA	32.6(8.1)	59%	46%	64%	Intrauterine fetal death 8.1% CA 2.7% Miscarriage 18.3% Macrosomia ≥ 4000 g 30%	Ireland
Lopez de Andres 2020 [8]	4391	NA	34.17(5.42)	NA	10.79%	NA	NA	NA	PTD 15.03%	Spain

Table 1. Cont.

Author (References)	N°	T2D Duration Years	AGE Years	HbA1c% 1st Trim.	BMI or % Obesity (O) (>30 kg/m ²)	Caucasian	PPC	Folic Acid	Pregnancy Outcomes	Country
Nadeau 2020 [17]	160	NA	IR 29.1(6.4) Non IR 30.6(5.5)	IR 8.4(2.0) Non IR 7.3(1.9)	IR 38.6(9.2) Non IR 36.6(8.2)	IR 28% Non IR 19%	NA	NA	PTD IR 23% NON-IR 25% SB IR 1% NON-IR 2% CA IR 6% NON-IR 6% LGA IR 20% NON-IR 32% SGA IR 3% NON-IR 4%	USA 2 groups according to insulin resistance
Murphy 2021 [18]	8685	3(0–10)	34 (22–37)	6.9	32.5 (24.8–43.0) ≥30 = 65%	43.2%	NA	22.3%	PTD 23.4% SB 13.5% ND 11.2% CA 40.5% LGA 26.2% SGA 14.1%	UK
Guarnotta 2021 [19]	62	4.11(3.1)	33.7(6.1)	NA	31.4(6.7)	NA	NA	NA	PTD 19.1% Miscarriage 12.9% LGA 25.8%	Italy
Gualdani 2021 [20]	606	NA	33.8(4.9)	NA	28.1(6.3)	78.3%	NA	NA	LGA 12.5% CA 0.9% PTD 25.6%	Italy
Newman 2021 [21]	244	6.8(6.3)	34.3(5.7)	6.7(3.5)	32.5(6.9)	61.1%	29.5%	49.6%	SB 0.4% PTD 22.4% CA 3.9%	Ireland
Newman 2022 [22]	374	5.6(3.2)	34.4(5.8)	6.7(3.5)	33.4 (7.6)	63.6%	25.9%	36.1%	SB 0.8% Miscarriage 15.6% PTD 20.7% CA 5.1%	Ireland
Pylypiuk C 2021 [23]	112	NA	22 (19–25.5)	9.3 (7.8–10.9)	27.5 (26.9–28.6) O = 39.6%	NA	NA	NA	Miscarriage 27.7% SB 11.6% NND 3.6% Shoulder distocia 13.1% CS 41% LGA 55.4% CA 19.6%	Canada
Today study 2022 [24]	141 (260 pregnancies)	8.1(3.2)	21.5(3.16)	8.7(2.78)	35.6 (7.16)	15%	20%	NA	Miscarriage 25.3% PTD 23.8% Fetal death 3.7% CA 10%	USA

Data recorded by CEMACH from 2002 and 2003 analyzed maternal and fetal outcomes of 652 T2D pregnant women. Type 2 pregnant women were more frequently from deprived areas and minority ethnicities. Perinatal mortality was 32.3/1000, four times higher than in the general population, and congenital malformations were 43.2/1000, two times higher than in the general population. No data on metabolic control were reported in the study [11].

A systematic review of pregnancy outcomes in women affected by pre-gestational diabetes was performed by Balsells et al., considering data published from 1987 to 2008 [25]. Thirty-three studies were included, showing that patients with T2D had mean glycated hemoglobin (HbA1c) levels of 7.2% at booking and 5.62% in the third trimester of pregnancy, as well as a high frequency of perinatal mortality (4%).

A prospective study of 33 centers in Italy (1999–2003) evaluated the pregnancy outcomes in 164 T2D women. The women had a mean age of 33.2 ± 4.8 year, mean body mass index (BMI) of 28.1 ± 6.4, mean disease duration of 5.7 ± 5.9 year, and mean HbA1c levels of 6.6 ± 1.7%. The congenital malformations, neonatal mortality, and stillbirth frequencies were higher in these women than the general population (2.0% vs. 0.86%, 1.9% vs. 0.32%, and 1.9% vs. 0.32%, respectively). Furthermore, neonatal mortality was positively associated with HbA1c values higher than 8% [12].

In a retrospective case-control study in 2015 at the Galway Diabetes Research Center (Ireland), pregnancy outcomes in 108 T2D pregnant women were compared to 660 normoglycemic patients [13]. The composite maternal negative outcome (gestational hypertension, preeclampsia, cesarean section) was slightly higher in T2D patients than in non-T2D pregnant women (38% vs. 29%). Meanwhile, the neonatal composite negative outcome (stillbirth, miscarriage, premature delivery polyhydramnios, hypoglycemia) was higher in T2D pregnancies than in non-diabetic pregnancies (32% vs. 10%, $p < 0.06$). Furthermore, a predictive factor for negative maternal outcomes was pregnancy BMI > 38 .

Murphy et al. compared the outcomes of T2D pregnant women who delivered in 2015 reported in the National Pregnancy in Diabetes Audit Report (NPID), to those reported in CEMACH in 2002–2003 [14]. In 2015, 3086 pregnant women followed by 155 National Health Services of the UK were taken into consideration and, in particular, 1386 type 2 T2D pregnant women were of advanced maternal age [26], had a high BMI, short disease duration, low frequency of folic acid use, and were socially deprived. Both HbA1c levels in early and late pregnancy were acceptable in these women (6.8% and 5.9%, respectively), and there was no difference compared to the CEMACH 2002–2003 report. However, more T2D women evaluated in 2015 were able to achieve HbA1c levels $< 7.0\%$ than the CEMACH cohort (85.9% vs. 75.4%, $p < 0.05$), with high variability between them. In 2015, the stillbirth rate was high in T2D pregnant women compared to the general population (10.5/1000 vs. 4.7/1000), as well as the neonatal death rate (11.4/1000) and congenital malformations (34.6/1000). Furthermore, the low rates of neonatal complications were found in pregnant women who achieved the target HbA1c ($< 6.5\%$). Comparing these data with CEMACH 2002–2003, in 2015, a reduction in the stillbirth rate per 1000 births was observed (10.4/1000 vs. 29.2/1000, $p < 0.009$). The neonatal death rate was unchanged in the two cohorts of the patients examined. Comparing congenital malformations was not possible because the 2015 data considered both minor and major malformations, while CEMACH considered only major congenital malformations [14].

In the observational retrospective study in Spain analyzing 2,481,479 deliveries between 2009 and 2015, the T2D pregnant women (4391) had a higher frequency of labor induction (30.4% vs. 29.58%), cesarean section (47.46% vs. 21.61%), severe maternal morbidity (2.05 vs. 1.4%), preterm birth (15.03% vs. 5.99%) and fetal overgrowth (7.33% vs. 1.21%) than non-diabetic pregnant women [7].

The PANDORA study was performed in Australia between 2011 and 2017, and included 900 pregnant women (175 T2D, Europid, Aboriginal, and other ethnicities). Indigenous women were younger and had a higher frequency of diabetes and a poorer birth outcome than the non-indigenous. Furthermore, in a multivariate analysis, T2D was independently associated with adverse pregnancy outcomes. [15].

In a small study in Ireland on 50 T2D women (2015–2017), the clinical and metabolic characteristics of the women were similar to those reported by Murphy et al. [14]. In these patients, intrauterine fetal death was 8.1%, congenital malformation was 2.7%, and neonatal intensive care unit admission (NICU) was 32%; no comparison with the general population was made [16].

A large population cohort study was conducted by Murphy et al., involving 15,290 pregnant women, 50% of who had T2D. Data were collected from 172 maternity clinics in England, Wales, and the Isle of Mann from 2014 to 2018. In this cohort, T2D pregnant women were of advanced maternal age [26] with a high BMI, short disease duration, low frequency of use of folic acid, and were commonly socially deprived. Furthermore, both HbA1c levels in early and late pregnancy were acceptable (6.9% and 6.0%, respectively), and target HbA1c levels ($< 6.5\%$) were obtained in late pregnancy in 73.7%. It is noteworthy that these women had high frequencies of congenital malformations (40.5/1000), neonatal death (11.2%), stillbirths (13.5/1000), small-for-gestational-age babies (SGA), and large-for-gestational-age babies (LGA) (14.1% and 12.5%, respectively). Independent risk factors for perinatal death (stillbirth and/or neonatal death) were HbA1c levels in the third trimester higher than 6.5%, diagnosis of T2D, and being deprived [18].

The University Endocrinological Clinic in Palermo followed a cohort of 135 women with pre-gestational diabetes: 62 were affected by T2D. All women were treated with intensive insulin therapy and had a high frequency of cesarean section (81.2%), miscarriage (12.9%), gestational hypertension (21%), and LGA babies (25.8%). A multivariate analysis found that pre-gestational BMI and insulin requirement in the first trimester were independently associated with miscarriages in these women [19].

Galdani et al. analyzed singleton live births in Tuscany from 2011 to 2018; pre-gestational and gestational diabetes were identified utilizing regional administrative data. Considering 206,917 births, 606 were from T2D pregnant women. Looking at the maternal and fetal outcomes of these women with respect to non-diabetic pregnant women showed a high frequency of spontaneous abortions (19.8% vs. 4.8%, $p < 0.001$), cesarean sections (48.2% vs. 25.8%, $p < 0.001$), and preterm births (25.6% vs. 10.5%, $p < 0.001$) [20].

Newman et al. retrospectively analyzed the outcomes of pregnancies between 2015 and 2020 in 18 Antenatal Centers in Ireland. These women had an induction of labor frequency in 28.9%, elective cesarean section in 35.3–36.3%, emergency cesarean section in 23.3–23.6%, NICU admissions in 32.8–35.3%, preterm delivery 20.7–22.4%, congenital malformations 3.9–5.1%, stillbirth 0.4–0.8%, macrosomia in 12.4–13.9%, and LGA in 38.3–41.7% [21,22].

More recently, the results of pregnancy in young women with T2D enrolled in the TODAY study were reported [24]. TODAY is a multicenter intervention study aiming to evaluate the effectiveness of different therapeutic approaches (metformin, metformin and rosiglitazone, metformin and lifestyle intervention) on the metabolic control of young T2D patients (age 10–17 years, duration of diabetes <2 years, obese). Over 15 years, 260 pregnancies occurred in 142 women (age 21.5 ± 3 year, duration of diabetes 8.1 ± 3.2 year, BMI 35.6 ± 7.2 kg/m²). The mean HbA1c was $8.7 \pm 2.8\%$, indicating non-optimal metabolic control. Furthermore, 35% of the women were affected by chronic hypertension, 25% by nephropathy, and preeclampsia developed in 20% of women. Moreover, pregnancy loss occurred in 25.3%, preterm birth in 32.6%, congenital malformations in 10%, LGA babies in 26.8%, SGA in 7.8%, hypoglycemia in 29.4%, and respiratory distress in 18.6% of cases. The levels of HbA1c higher than 8% were significantly associated with miscarriage, preterm delivery, congenital malformations, neonatal hypoglycemia, respiratory distress, LGA, and SGA.

The Next Generation Study, a longitudinal cohort study in Canada, enrolled mothers with T2D diagnosed before 18 years, between 2005 and 2015. The mean age was 22 years, and 60% were multiparous with a high frequency of previous pregnancy complications. As for clinical characteristics, the mean pre-pregnancy BMI was 27.5 kg/m² (26.9–28.6), and mean HbA1c was 9.3% (7.8–10.9%) in the first trimester and 6.9% (6.2–7.5%) in the third trimester. The mean gestational weeks of delivery (gw) was 37 weeks, of which 41% were cesarean sections, and 34.8% were emergency cesarean sections due to fetal distress. Macrosomia accounted for 55.4%, and 19.6% of babies had congenital malformations. Noticeably, seven neonates with congenital malformations went undiagnosed with ultrasound during pregnancy, mainly due to poor visualization because of the obesity of the mother [23].

Scarce data are present on the outcomes of pregnant women with T2D diagnosed in pregnancy. Lee et al. examined pregnancy outcomes in women with undiagnosed T2D in Canada (2002–2015) [27]. Pregnant women with undiagnosed diabetes had previous GDM and a T2D diagnosis one year after delivery. Overall, 995,990 women were enrolled: 1772 had undiagnosed T2D, were older, had a low socioeconomic status, and were more obese than the normoglycemic ones. The neonates had a higher frequency of preterm birth (OR 2.5 [2.3–2.9]), neonatal intensive care admission (NICU) (OR 3.1 [2.8–3.5]), congenital malformations (OR 2.1 [1.7–2.5]), and neonatal hypoglycemia (OR 406 [357–461]) than normoglycemic women. Furthermore, early GDM diagnosis, previous GDM, and chronic hypertension predicted undiagnosed T2D.

It is worth noticing that the studies taken into considerations are mostly retrospective and only few have compared T2D pregnancy outcomes with the background population.

4. Metabolic Control during Pregnancy

To clarify the behavior of glycemic profiles in T2D pregnant women, a prospective study was conducted by seven-day continuous glucose monitoring in 40 T2Ds in the first, second, and third trimesters of pregnancy. All patients were treated with insulin during pregnancy. The data show that the percentage of time spent in a state of hyperglycemia (>140 mg/dL per 24 h) was reduced during pregnancy (32.8% in the first, 19.5% in the second, and 11.6% in the third trimester, $p < 0.001$). However, the frequency of nocturnal hypoglycemia was not significantly different during pregnancy (14.8% in the first, 16.5% in the second, and 18.4% in the third trimester, $p > 0.05$) considering glucose values <70 mg/dL and <50 mg/dL [28].

However, new systems for glucose evaluation (continuous glucose monitoring systems) and new therapeutic strategies (continuous insulin infusion systems; insulin analogs) are not routinely used in T2D mothers.

Even if T2D pregnant women show low levels of HbA1c during pregnancy, only half of these pregnancies meet the recommended levels of HbA1c and glycemia [16,29,30]. The physiologic insulin resistance of pregnancy is amplified by obesity, which often characterizes T2D patients [31,32]. To evaluate the frequency of insulin resistance and its possible correlation with glycemic control and pregnancy outcomes in T2D pregnant women, self-monitoring blood glucose levels, insulin dosage, and pregnancy outcomes were recorded in 160 T2D pregnant women (all insulin treated). Severe insulin resistance was defined as insulin dosage ≥ 2 units/kg at delivery. Seventy-two patients experienced severe insulin resistance (45%), HbA1c levels ($7.2 \pm 1.1\%$ vs. $6.6 \pm 1.3\%$, $p = 0.003$), fasting (104 ± 17.4 vs. 95.2 ± 11.7 mg/dL, $p < 0.001$), post-prandial (132.4 ± 17.2 mg/dL vs. 121.9 ± 16.9 mg/dL, $p < 0.001$), and high plasma glucose. HbA1c levels $\geq 6.5\%$ and insulin use before pregnancy were associated with a higher frequency of insulin resistance. No differences in pregnancy outcomes between the two groups were reported, possibly due to good metabolic control during pregnancy [17].

How effective is adherence to treatment in pregnant women with diabetes? To answer this question, Wernimont et al. performed a prospective study of 103 women, 40 T2D at <29 sg, between December 2015 and June 2019. All patients were educated on a cellular glucometer that uploaded the glucose values to a cloud-based system. The overall adherence to glucose testing was low in these patients (51%). Interestingly, for every 10% increase in adherence, the odds for cesarean section, LGA babies, and neonatal hypoglycemia decreased by 15–20% [33].

5. Factors Affecting Pregnancy Outcomes in Women with Type 2 Diabetes

Confident that T2D in pregnancy is often associated with adverse pregnancy outcomes, which factors are involved?

One answer comes from Gaudio et al., who evaluated the outcome of T2D pregnancy in women of childbearing age (16–45 yr), taking into consideration women that delivered in 2004 (3218), compared with those who delivered in 2017 (6.657) [34]. Of the patients examined, 61.5% were affected by T2D in 2004 and 65% in 2017. The glycemic control improved in T2D women in 2017 compared to 2004; in particular, the proportion of women with HbA1c $< 6.5\%$ increased from 27.2% to 35.4%. Furthermore, more were treated with antihypertensive and statin drugs at preconception. However, there were unfavorable factors (e.g., smoking, obesity) in 70.7% of these pregnancies, and only 23% received counseling on the necessity of utilizing appropriate contraception when metabolic control is not optimal.

Using statistical data linked to birth certificates for a cohort of T2D patients (38,324) who delivered in California (US) between 1997 and 2006, it was found that 33,502 attended prenatal care in the first, 3723 in the second, and 810 in the third trimester of pregnancy, and 275 in the 36th gestational week. The frequency of intrauterine fetal demise was higher in women attending prenatal care at the time of delivery than those attending in the first trimester (11.3% vs. 0.9%, $p < 0.001$). The same true is for the rate of preterm delivery (29.4%

vs. 21.0%, $p < 0.004$). After adjusting for possible confounding variables, the significant differences were confirmed [35].

The in-depth analysis of the aforementioned works shows that most cohorts evaluated had many factors of adverse pregnancy outcomes in T2D pregnancy.

The rate of pre-pregnancy counseling was 29.1% in the Italian survey [12]. In a UK report, only 36.2% of T2D pregnant women attended maternity units before 8 gw, and 22.5% took folic acid before conception [14]. In the retrospective case-control study performed at the Galway Diabetes Research Center (Ireland), 34% of T2D women attended pre-pregnancy care, and 55% were taking folic acid at booking [13]. In the Ireland survey, only 29.5% of T2D pregnant women were followed by specialized centers in the first week of pregnancy, and folic acid use was observed in 49.6% [21]. In an update of the retrospective cohort study of Ireland that considered a high number of patients (374 T2D) from 2015 to 2020, the attendance to pre-pregnancy clinics was 25.9%, and folic acid was used in 36.1%. The elevated pre- and early-pregnancy HbA1c values, smoking, and non-attendance at pre-pregnancy clinics were significantly related to an increased frequency of NICU admission of neonates [22]. In the TODAY study, preconception counseling occurred in only 20% of T2D pregnant women, despite 35% having hypertension and 25% having nephropathy. Furthermore, most cases had sub-optimal glycemic control (14.9%) and only 13.3% of the cases utilized contraception methods [24]. A high smoking frequency was reported in the Next Generation Study (53%) [23].

The NPID Audit (2020) underlines that in preconception care, only 40% of T2D patients showed HbA1c levels $< 6.5\%$, only 20% took folic acid, and 2% took drugs potentially harmful to the fetus (e.g., ACE inhibitors, ARBs, statins) [9]. The frequency of congenital malformations rose from 2.0% with HbA1c levels of 6.3–6.5% to 6.2% with HbA1c levels of 8.6–9.5%. Finally, other neonatal complications increased with HbA1c levels in late pregnancy; in particular, with HbA1c of 6.3–6.5%, the frequency of preterm births was 20%, LGA infants 30%, NICU admission 30%, and perinatal death 2.0%. These frequencies dramatically increased with HbA1c levels of 8.6% to 9.5% (45%, 45%, 60%, 9.0%, respectively) [9].

The frequency of obesity complicating T2D pregnancy was high in most studies examined. Obesity worsens the physiological insulin resistance characteristic of pregnancy and the insulin resistance typical of T2D [31,32,36,37]. This amplifies low-grade inflammation of the adipose tissue and the secretion of inflammatory cytokines. Elevated cytokine levels alter normal placental development and contribute to complications in T2D pregnancy [38].

Finally, some considerations must be made regarding the hypoglycemic therapy utilized in T2D pregnant women. In most studies, metformin is the most common drug utilized (alone or in conjunction with insulin). In particular, Murphy et al. found that most T2D women were treated with metformin and only 18.5% received insulin, with a high frequency of SGA babies [18]. This is surprising, considering that T2D pregnant women often have a short duration of disease and no severe chronic diabetic complications. Although, vasculopathy can reduce uteroplacental flux with a consequent reduction in nutrients for the fetus. Similar results were reported by Feig et al. in a study on the effect of metformin + insulin in T2D pregnant women. In this case, patients treated with metformin showed a high rate of SGA babies [39]. Metformin crosses the placenta and can reduce the production of ATP, which is critical for embryo development [39]. Therefore, studies evaluating the long-term effects on the offspring of mothers treated with metformin are necessary to safely utilize this drug in pregnancy [40].

6. Physiopathology: New Trends

Despite the poor metabolic control in T2D pregnant women, a high rate of perinatal mortality and other negative maternal outcomes are experienced by these women.

The negative effect of obesity, often present in T2D pregnant women, is well known and can explain (in part) these outcomes [36–38]; however, other factors may play a role.

Kurana et al. evaluated the endothelial function, utilizing flow-mediated vasodilatation (FMD) in T2D pregnant women in the second and third trimesters during a

hyperinsulinemic–hyperglycemic clamp study [41]. The results showed that hyperinsulinemia did not affect FMD in both trimesters (second and third); this could be due to endothelium resistance to the vasodilatory effect of insulin. However, hyperglycemia significantly reduced FMD in late pregnancy and may contribute to increased negative pregnancy outcomes.

Gene expression and the function of endothelial cells in the human fetal umbilical vein were studied in 17 T2D pregnant women using flow cytometry and genome-wide microarray expression methods. High levels of mitochondrial superoxide anions, increased apoptosis, and reduced cell proliferation were found. Furthermore, 42 genes were down-regulated, and 90 genes were up-regulated. Up-regulated genes are important in endothelial dysfunction, which in turn, influences cellular movements and the inflammatory response; this can contribute to the maternal and fetal complications of these women [42].

In the last years, the importance of genetics and epigenetics has been emphasized in physiological and in pathological pregnancy [43].

In this context, Moreli et al. [44] studied the possible occurrence of DNA damage in the blood samples of pregnant women with different degrees of glycemia, comparing 23 T2D patients to normoglycemic women. In T2D pregnant women, higher levels of oxidative stress parameters, nuclear and mitochondrial DNA damage, and lower expression of mRNA and proteins involved in cellular repair (BER) have been found with respect to normoglycemic ones. Hyperglycemic levels were directly associated with apoptosis in *in vitro* experiments. In the babies of T2D mothers, an increased expression of BER mRNA was found compared to babies of normoglycemic women. The authors concluded that maternal blood cells are more susceptible to the modifications of glucose levels, while fetal cell seems to have a more adaptive response to hyperglycemia. However, further studies on more patients are needed to confirm the results.

In a more recent paper, the dimethylation of histones H3K4, H3K9, H3K27, H3K36, and H3K79 was assessed in the blood cells of T2D pregnant women compared to normal pregnancy at 30 gw and in the postpartum state [45]. In the third trimester of pregnancy, H3K4 and H3K27 were higher in T2D than in non-T2D pregnant women, while H3K36 and H3K79 were lower. At postpartum (8–10 weeks), H3K4, H3K9, and H3K27 were higher in type 2 than in non-T2D pregnant women, and H3K36 and H3K79 were lower. At 20 weeks postpartum, H3K4 and H3K27 were higher in T2D than non-T2D pregnant women, and H3K79 was lower in T2D pregnant women. The high glycemic levels of T2D pregnant women can explain the differences in histone methylation, as reported in previous studies [46]. Furthermore, the methylation of H3K36 and H3K79 has been associated with an increased expression of genes involved in the development of type 2 diabetes [47].

7. Strategies to Improve Pregnancy Outcomes in Women with TD2

In this context, the NPID 2019–2020 report identified crucial areas of intervention to reduce maternal and fetal complications, focusing attention on T2D pregnant women. It states that for T2D women, “access to structured education, management of weight, and diabetes prevention should be prioritized”. Then, “support for provision of contraception and pregnancy preparation to improve glycemic management, and 5 mg folic acid supplementation in women with T2D is recommended” [9]. This agrees with the conclusions of the audit meeting of the Diabetic Pregnancy Study Groups of the European Association of the Study of Diabetes [48] and the recommendations of the American Diabetes Association [49].

Low attendance to pre-pregnancy care, low consumption of folic acid, low utilization of contraceptives in T2D women with bad glycemic control to avoid pregnancy, non-optimal metabolic control before and during pregnancy, and high utilization of harmful drugs during pregnancy are the unmet goals evidenced by the studies analyzed here (Figure 1). Hence, to answer these unmet problems and better individualize specific needs to prevent maternal and fetal complications of pregnancy complicated by type 2 diabetes, we recommend the implementation of pre-pregnancy counseling, addressing

health care inequalities, early diagnosis of T2D in women of childbearing age, treatment of obesity, correct utilization of contraceptives, folic acid use, therapeutic approaches in all pregnant women with type 2 diabetes of childbearing age to avoid medications that can negatively affect fetal health, and a follow-up by a multidisciplinary team (endocrinologist, diabetologist, gynecologist, specialized nurse, obstetric, dietician) (Table 2).

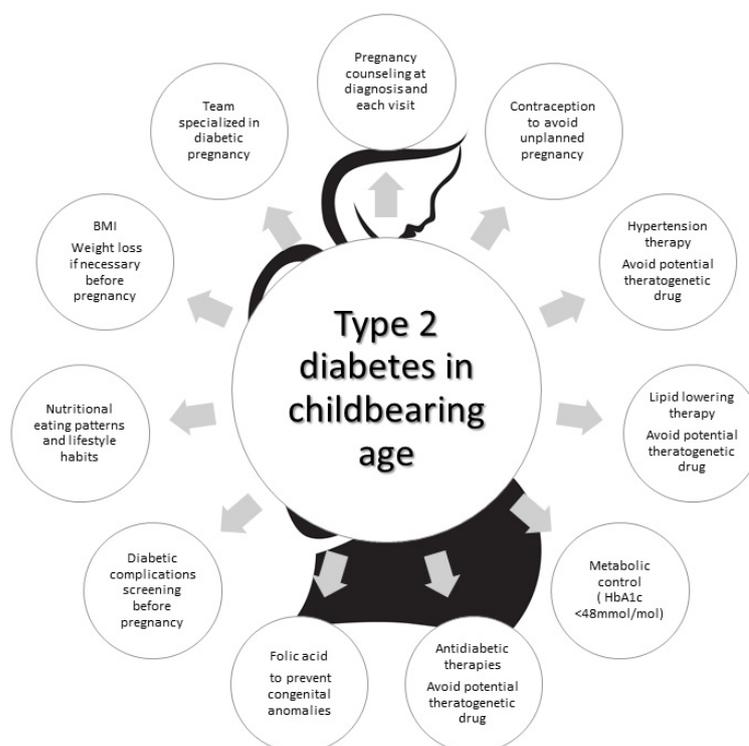


Figure 1. Strategies to be used to address the unmet goals in pregnant women with type 2 diabetes.

Table 2. Planning pregnancy in women with type 2 diabetes: action chart.

Identify type 2 diabetes as soon as possible in high risk women
Inform all type 2 diabetic women of childbearing age about the risk of an unplanned pregnancy at diagnosis and at each visit
Inform all type 2 diabetic women of childbearing age about the recommended HbA1c at conception in order to reduce congenital anomalies
Inform all type 2 diabetic women of childbearing age about the risks during pregnancy related to overweight and obesity
Screen diabetes complications before pregnancy
Modify diabetic therapy before conception
Stop statin if used
Modify antihypertensive therapy if used
Loss of 5–10% body weight if overweight or obese before pregnancy
Nutrition education
SBG monitoring education
Considering starting FGM or CGM
Agree with the women on the timing of conception
Start folic acid at least one month before conception
Use safe contraception until the best clinical-metabolic conditions for conception are achieved

8. Conclusions

This narrative review shows that epidemiological studies on large patient cohorts have found an increase in type 2 diabetes in pregnancy. Clinical studies from different countries show that women with T2D undergo adverse maternal and fetal outcomes, emphasizing factors that can contribute to adverse outcomes; this contradicts the Saint Vincent's Declaration in 1989 [50].

The implementation of pre-conception counseling by a multidisciplinary team that also includes a general practitioner who sees these patients before conception, careful management during pregnancy to obtain and maintain a good metabolic control, and strict obstetric surveillance during pregnancy are the strategies that must be implemented to reduce maternal and fetal complications.

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