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ORIGINAL ARTICLE

Characteristics of pregnant women with diabetes using injectable glucose-lowering drugs in the EVOLVE study

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ABSTRACT

Aims: To examine clinical parameters, glycemic control, folic acid supplementation, and the presence of other chronic diseases during early pregnancy in the EVOLVE study population (women with pre-existing diabetes treated with injectable glucose-lowering drugs).

Methods: Cross-sectional baseline evaluation of EVOLVE: an international, multicenter, non-interventional study investigating the safety of injectable glucose-lowering drugs in pregnant women with pre-existing type 1 (T1D) or type 2 diabetes (T2D). Data were collected at enrollment visit interviews before gestational week 16.

Results: In total, 2383 women from 17 mainly European countries were enrolled in the study: 2122 with T1D and 261 with T2D; mean age was 31 and 33 years, and duration of diabetes was 15 and 6 years, respectively. For women with T1D or T2D, 63% and 75%, respectively, received basal and rapid-acting insulin, 36% and 3% rapid-acting insulin only, 0.7% and 14.0% basal insulin only, 0.2% and 5.4% premix insulin, 0.0% and 1.2% injectable glucagon-like peptide-1 receptor agonist treatment without insulin. In women with T1D or T2D, respectively, during early pregnancy, 59% and 62% had HbA_{1c} <7.0% (53 mmol/mol); 16% and 36% reported not taking folic acid before or during early pregnancy. Overall, >40% of women had ≥1 chronic concomitant condition (predominantly thyroid disease or hypertension). Retinopathy was the most commonly reported diabetic complication. The most commonly reported previous pregnancy complication was miscarriage.

Conclusions: Baseline data from this large multinational population of women with pre-existing diabetes indicate that sub-optimal glycemic control, poor pregnancy planning, and chronic concomitant conditions were common in early pregnancy.

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KEYWORDS
Pregnancy; insulin; type 1 diabetes; type 2 diabetes; EVOLVE study

Introduction

Pregnancy in women with established diabetes is associated with an increased risk of adverse maternal and fetal outcomes, including perinatal and neonatal mortality and congenital malformations [1]. Three nationwide population-based studies demonstrated that the risks of stillbirth, perinatal mortality, infant death, and congenital malformations are approximately threefold higher in pregnant women with type 1 diabetes (T1D) than in those without diabetes [2–4]. The prevalence of pregnancy-related complications in women with type 2 diabetes (T2D)

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has been described at a similar or worse level compared with that of T1D [5,6].

The importance of optimal glycemic control in reducing the risk of complications and malformations in pregnant women with pre-existing diabetes is well established. Poorly controlled diabetes, as evidenced by elevated HbA_{1c}, before and during early pregnancy, increases the risk of pre-eclampsia [7,8], perinatal/neonatal death [9,10], congenital malformations [10,11], and childhood malignancy [12], and is a predictor of large-for-gestational-age neonates [13].

The aim of diabetes treatment, both pre-conception and during pregnancy, should be the attainment of near-normal glycemic control, thus pregnancy planning is central to achieving optimal clinical outcomes [14]. In women with diabetes who become pregnant, the American Diabetes Association (ADA) recommends a target HbA_{1c} of $<$6.0% (42 mmol/mol) in patients who are not susceptible to hypoglycemia or $<$7.0% (53 mmol/mol) in patients who are susceptible to hypoglycemia [15].

In addition to glycemic control, a number of other maternal factors, such as folic acid supplementation, diabetes-associated complications, chronic concomitant conditions, and maternal obesity, can influence pregnancy outcomes. Maternal obesity, independent of diabetes, is associated with congenital malformations [16] and an increased risk of perinatal mortality and delivering large- or small-for-gestational-age infants [17,18]. Folic acid prevents neural tube defects and may prevent other congenital malformations [19]. Women are therefore advised to supplement their diet with 0.4–5.0 mg folic acid before and during the first 12 weeks of pregnancy [20,21]. In terms of diabetes-associated complications, women with microalbuminuria or diabetic nephropathy before pregnancy are at increased risk of experiencing maternal and perinatal complications compared with women who have normal urinary albumin excretion at conception [22]. Other chronic diseases, such as hypertension [23], thyroid diseases [24], poor mental health [25], and asthma [26], may also have an adverse impact on pregnancy outcomes.

Few recent regional or national studies have examined the characteristics of pregnant women with diabetes, and there are no studies covering several countries. EVOLVE was a prospective, international, non-interventional study evaluating the safety of injectable glucose-lowering treatment regimens during pregnancy in a large cohort of women with pre-existing diabetes [27]. Accordingly, EVOLVE provides an opportunity to examine the aforementioned characteristics and their potential association with pregnancy outcomes. Here, we present the baseline characteristics (those reported at enrollment) of the EVOLVE cohort, with the aim of providing key insights into glycemic control, folic acid supplementation, and the presence of other chronic conditions during early pregnancy in women with pre-existing diabetes treated with injectable glucose-lowering drugs.

Methods

This analysis presents the characteristics of pregnant women (n = 2383) with either T1D (n = 2122) or T2D (n = 261) at the enrollment visit (conducted before gestational week 16) of the EVOLVE study (NCT01892319): an international, prospective, non-interventional, multicenter study to monitor and assess the safety of insulin detemir and other injectable glucose-lowering treatments in pregnant women with pre-existing diabetes. The EVOLVE study covered the gestational period and follow-up period of infants at 1 month and 1 year of age, with the frequency of standard routine visits determined by the individual study site. The full study design has been published previously [27]. The results presented herein are based on data extracted in June 2019, prior to study completion (September 2019).

EVOLVE recruitment

In EVOLVE, data were collected from 92 sites across 17 countries (Croatia, Denmark, Finland, France, Germany, Greece, Ireland, Israel, Italy, Malaysia, the Netherlands, Norway, Poland, Portugal, Romania, Spain, and the United Kingdom) from participants recruited between 30 September 2013 and 29 December 2017. Sites providing hospital care with relatively similar treatment procedures for women with diabetes during pregnancy, and with a relatively high prescription rate of insulin detemir, were mainly approached for inclusion in EVOLVE. All eligible women were invited to participate.

Written informed consent was required from all study participants. EVOLVE was conducted in accordance with Good Pharmacoepidemiology Practice and the Declaration of Helsinki, and was approved separately in each of the participating countries by national health authorities, local institutional review boards, or independent ethics committees.

Sample size

The original calculated sample size was revised during the recruitment phase, as the assumptions did not align with the actual recruitment outcome. Specifically, a greater proportion of women receiving insulin detemir were recruited than initially anticipated, which affected the proportions of women in the study treatment groups, requiring fewer women to be recruited than the originally calculated sample size [27].

EVOLVE inclusion/exclusion criteria

Pregnant women (confirmed by a positive pregnancy test according to local procedures) with T1D or T2D prior to conception, as assessed from maternal medical history, whose basal insulin and/or other injectable glucose-lowering drug therapy was unchanged from 4 weeks prior to conception up until the enrollment visit, were included. T1D or T2D diagnosis was assigned prior to pregnancy during routine clinical practice and early treatment with insulin (T1D), or lifestyle changes in combination with oral antidiabetic drugs or insulin as required before pregnancy (T2D), was commenced in accordance with current guidelines on pre-pregnancy management [15].

Women $\geq$16 weeks pregnant were excluded from the study. Women were initially excluded if they were $>$12 weeks pregnant at enrollment; however, this exclusion criterion was retrospectively changed (effective date 18 July 2016) given that some participants had first contact with the study site after 12 weeks. Women with singleton or multi-fetal pregnancies were included in the study.

Participant characteristics at enrollment

At the enrollment visit, clinical data were collected by interview or extracted from medical records. Information included aspects relating to maternal medical history (including the presence of hypertension, epilepsy, thyroid disorder, asthma, heart disease, psychiatric disorders, and inheritable diseases), obstetric history, diabetes history/diabetes complications (diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, and macroangiopathy), current pregnancy information, body measurements, vital signs, laboratory assessments, current glucose-lowering treatment, folic acid intake before and during first trimester, socioeconomic status, race, smoking, and alcohol intake.

At first visit, body mass index (BMI), blood pressure (systolic/diastolic, mmHg), pulse (beats/min), and HbA_{1c} (at maximum 16 weeks gestation) were recorded.

The type of injectable glucose-lowering treatment used by the participants was recorded and classified as follows: basal insulin only, rapid-acting insulin only, glucagon-like peptide-1 receptor agonist (GLP-1 RA) only, premix insulin (included premix insulin ± rapid-acting insulin), or basal-bolus (included basal and rapid-acting insulin ± GLP-1 RA). Data on insulin pump use were not systematically collected from all participants, but women with T1D receiving rapid-acting insulin-only treatment are likely to have been using an insulin pump.

Data on educational achievement were categorized as long (university or college degree), medium (technical school, high school, or A-levels), or short (intermediate or basic school leaving certificate or primary school).

All data were collected by electronic case report forms, which were completed by physicians or their authorized staff.

Statistical methods

Enrollment characteristics were stratified by type of diabetes and by country. Characteristics were summarized descriptively: numbers of participants (*n*), percentages of participants with non-missing values for each of the individual variables (%), and mean/median values with SD. The proportion of pregnant women (percentage of total participants) with baseline HbA_{1c} were sub-grouped by 0.5% increments and reported according to type of diabetes and treatment group.

Results

Participant demographics and enrollment characteristics

In total, 2446 women provided informed consent to participate in the EVOLVE study, of whom 63 were excluded (exclusion details provided in Figure S1). Among the 2383 enrolled women, 2122 (89.0%) had T1D and 261 (11.0%) had T2D (Figure S1). The majority of enrolled women were White (96.3% and 78.5% for T1D or T2D, respectively), with small proportions of Asian (0.7% and 13.6%), Black/African-American (0.7% and 2.4%), and other races (2.2% and 5.6%). The majority of participants were from Denmark, Croatia, or the United Kingdom (Table S1).

Table 1. Demographic, socioeconomic, and clinical characteristics at enrollment.

	T1D (*n*= 2122)		T2D (*n*= 261)	
Parameter	*n*	% of total	*n*	% of total
Gestational age at enrolment				
<7 weeks	464	22.0	42	16.2
7–12 weeks	1366	64.7	170	65.4
12–16 weeks	282	13.4	48	18.5
Education				
Medium/long education	1611	85.1	195	84.1
Short/other/no education	283	14.9	37	15.9
Smoking status				
Current smoker	157	7.6	36	14.0
Never smoked	1568	76.1	189	73.3
Previous smoker	335	16.3	33	12.8
Alcohol consumption				
Alcohol drinker	23	1.1	2	0.8
Antidiabetic medication				
Basal and rapid-acting insulin	1336	63.2	194	75.2
Basal insulin only	15	0.7	36	14.0
Rapid-acting insulin only[a]	754	35.7	8	3.1
Premix insulin	4	0.2	14	5.4
GLP-1 RA (without insulin)	0	0.0	3	1.2
Insulin, uncertain type	4	0.2	3	1.2
Previous pregnancies and complications				
Number of previous pregnancies				
0	792	37.3	48	18.4
1	682	32.1	92	35.2
2	355	16.7	50	19.2
≥3	292	13.8	71	27.2
Number of previous live births[b]				
0	265	20.1	41	19.3
1	777	58.9	110	51.6
2	226	17.1	33	15.5
≥3	52	3.9	29	13.6
History of pregnancy complications[b]				
Miscarriage	453	34.1	84	39.4
Cesarean section	433	32.6	63	29.6
Pre-term delivery	141	10.6	19	8.9
Pre-eclampsia	99	7.5	12	5.6
Perinatal death	29	2.2	8	3.8
Major malformations	31	2.3	7	3.3
Chronic conditions[c]				
Thyroid disorders	602	28.4	39	15.0
Psychiatric disorders	182	8.6	18	6.9
Hypertension	139	6.6	47	18.0
Asthma	108	5.1	17	6.5
Inheritable conditions	65	3.1	11	4.2
Epilepsy	32	1.5	7	2.7
Heart conditions	20	1.0	2	0.8
Diabetic complications				
Retinopathy	604	28.5	15	5.8
Nephropathy	95	4.5	8	3.1
Neuropathy	60	2.8	8	3.1
Macroangiopathy	6	0.3	1	0.4
Unstable angina	1	0.1	0	0.0
Acute myocardial infarction	2	0.1	0	0.0

	T1D (*n*= 2122)			T2D (*n*= 261)		
Clinical parameters	Mean	Median	SD	Mean	Median	SD
Age, years	30.6	31.0	5.1	32.9	33.0	4.9
Body weight, kg	71.2	68.9	14.2	86.2	84.5	21.6
BMI, kg/m^2	25.7	24.7	4.8	31.7	31.2	7.3
Systolic blood pressure, mmHg	118.2	119.0	13.5	120.7	120.0	14.1
Diastolic blood pressure, mmHg	72.3	71.0	9.5	74.3	74.0	9.7
HbA_{1c}, %	7.0	6.8	1.2	7.0	6.5	1.6
HbA_{1c}, mmol/mol	53.0	50.8	13.1	53.0	47.5	17.5
Duration of diabetes, years	14.8	15.0	8.3	5.9	5.0	4.9

%: percentage of population in each diabetes group with non-missing values for that parameter; BMI: body mass index; GLP-1 RA: glucagon-like peptide-1 receptor agonist; *n*: number of participants; SD: standard deviation; T1D: type 1 diabetes; T2D: type 2 diabetes.

Pre-term delivery: delivery before 37 completed gestational weeks. Data were missing for the following numbers of women with T1D/T2D for each parameter: education, 228/29; smoking status, 62/3; alcohol consumption, 109/3; HbA_{1c}, 123/12; BMI, 127/4; systolic and diastolic blood pressure, 235/19; gestational age at enrollment, 10/1; antidiabetes medication, 9/3. Data for the number of previous pregnancies and previous live births were missing for one woman and nine women with T1D, respectively.

[a]Women with T1D receiving rapid-acting insulin-only treatment are likely to have been using an insulin pump (pump data not systematically collected during the study).

[b]Among women with ≥1 previous pregnancy (*n*= 1329 in the T1D group and *n*= 213 in the T2D group).

[c]Chronic conditions were pre-existing before pregnancy.

At enrollment, >70% of women with T1D or T2D were categorized as having a medium and/or long education (Table 1). A small proportion of women with T1D (7.6%) or T2D (14.0%) were smoking at the time of enrollment, and the consumption of alcohol was rare across groups (Table 1).

Clinical parameters

At enrollment, mean age was 30.6 and 32.9 years in women with T1D and T2D, respectively. Duration of diabetes was 14.8 and 5.9 years, respectively, and mean BMI was 25.7 and 31.7 kg/m^2, respectively (Table 1). The proportion of women with obesity (BMI ≥30 kg/m^2, as defined by the World Health Organization (WHO)), was 16.0% in women with T1D and 54.1% in women with T2D.

At enrollment, 63.2% of women with T1D administered basal and rapid-acting insulin while 35.7% administered rapid-acting insulin (Table 1). For women with T2D, 75.2% administered basal and rapid-acting insulin, 14.0% administered basal insulin only, and 3.1% administered rapid-acting insulin. A small proportion of women in each group administered alternative injectable therapies (Table 1). In addition, 1.8% of women with T1D and 15.3% with T2D were administering one oral hypoglycemic drug at the time of enrollment.

Overall, mean HbA_{1c} was 7.0% (53.0 mmol/mol) in women with T1D or T2D (Table 1), and mean HbA_{1c} ranged from 6.7% (49.7 mmol/mol) to 8.9% (73.8 mmol/mol) across countries (Table S2). The HbA_{1c} distribution according to type of diabetes is shown in Figure 1. Figure S2 shows the HbA_{1c} distributions in women with T1D among those receiving a combination of rapid-acting and basal insulin, and those receiving rapid-acting insulin alone: 55.2% and 64.4% had an HbA_{1c} <7.0%, respectively. At the enrollment visit, 58.6% and 34.2% of women with T1D, and 62.3% and 48.6% of women with T2D, had HbA_{1c} <7.0% (53 mmol/mol) and <6.5% (48 mmol/mol), respectively (Figure 1). The proportions of women achieving HbA_{1c} targets across countries are presented in Table S2.

Mean blood pressure measurements were 118/72 mmHg and 121/74 mmHg for women with T1D or T2D, respectively (Table 1).

Folic acid supplementation before and during early pregnancy

Overall, 16% of women with T1D and 36% of women with T2D reported not taking folic acid before and during early pregnancy. Across countries, the proportion of women reporting not using folic acid before and during early pregnancy ranged from 76% in Croatia to 2% in Spain (Table S3).

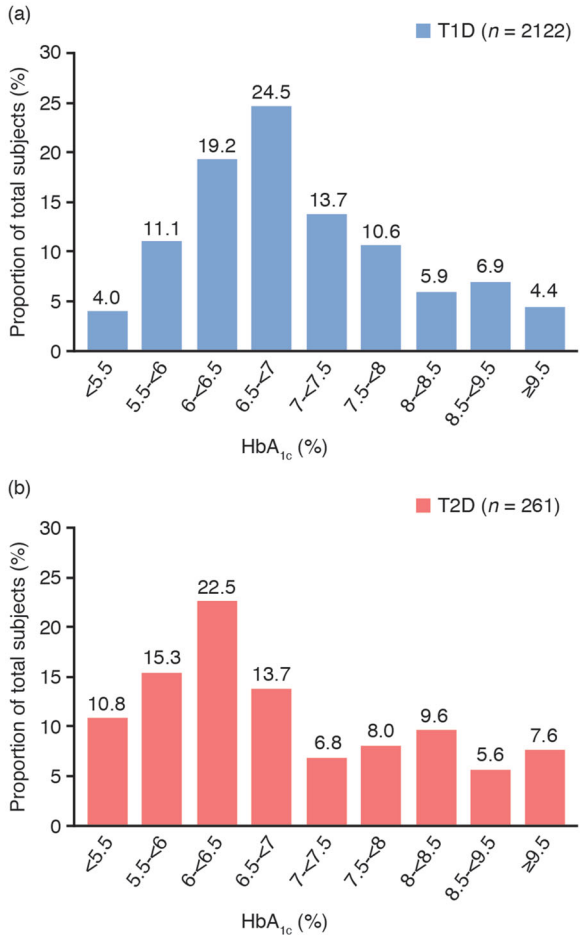

Figure 1. HbA_{1c} distribution according to type of diabetes. Data were missing for 123 and 12 women in the T1D and T2D groups, respectively. T1D: type 1 diabetes; T2D: type 2 diabetes.

Diabetic complications

Retinopathy was the most commonly reported diabetic complication at enrollment, present in 28.5% of women with T1D and 5.8% of those with T2D. Overall and across countries, a minority of women experienced nephropathy, neuropathy, macroangiopathy, unstable angina, or acute myocardial infarction (Table 1, Table S4).

Medical history and concomitant chronic conditions

Concomitant chronic conditions before pregnancy are described in Table 1. In T1D and T2D, 42.9% and 40.6% of women reported having at least one pre-existing chronic condition. Overall and across

countries, the most commonly reported conditions were thyroid disorders, psychiatric disorders, and hypertension (Table 1, Table S5). Relevant concomitant medication use is shown in Table S6.

Previous pregnancies and pregnancy complications

At the enrollment visit, 37.3% of women with T1D and 18.4% with T2D were pregnant for the first time, while 32.1% and 35.2%, respectively, had only been pregnant once before (Table 1). Pregnancy complications are described in Table 1. The most commonly reported pregnancy complication across both diabetes groups was miscarriage (range: 34–39%). Among women with ≥1 previous pregnancy, perinatal mortality and major malformations were reported in 2.2% and 2.3% of women with T1D, respectively, and 3.8% and 3.3% of women with T2D, respectively (Table 1).

Discussion

EVOLVE was a prospective, real-world study conducted in 15 European countries, Israel and Malaysia, aimed at assessing the impact of injectable glucose-lowering drugs on pregnancy outcomes in women with pre-existing diabetes. However, it is also the largest study of its kind to provide data on glycemic control, folic acid intake, and the presence of chronic concomitant conditions during early pregnancy in women who predominantly administer insulin. Here, we explore the significance of the latter characteristics, while the results pertaining to the primary objective of EVOLVE will be published separately.

A substantial proportion of the women in the study had a suboptimal HbA_{1c} (≥7.0% (53 mmol/mol)) during early pregnancy. This is concerning, as the risk of congenital malformations, other pregnancy complications, and neonatal morbidity, such as respiratory distress syndrome [28], increases with increasing HbA_{1c} [7–11]. Therapeutic compliance is difficult to quantify and was not captured in this study. It is possible that high HbA_{1c} values may be a result of poor compliance with dietary measures and/or insufficient insulin dose.

To prevent congenital malformations, such as neural tube defects, women are advised to start folic acid supplementation prior to pregnancy to cover conception and early pregnancy [20,21]. Here, the majority of women were reported to have received folic acid supplementation before and during the first trimester, although the proportion of women who initiated supplementation before as opposed to after conception is unknown. Folic acid supplementation varied across participating countries; this variation is likely to be due to differences in local guidelines [29,30]. The lowest intake reported was in Croatia, this possibly being associated with the generally low awareness of folic acid benefits reported previously in Croatian women [31]. Our results also indicate that women with T2D were less likely than those with T1D to take the recommended supplementation, which is in alignment with other studies [10,32]. This highlights the importance of improving folic acid prophylaxis in women with diabetes in order to prevent congenital malformations.

In EVOLVE, more than 40% of participating women reported having at least one concomitant chronic condition. A strength of the study is that the collection of such data was prospectively planned and included all disease categories independent of known impact on the risk of pregnancy complications. The most common chronic condition was thyroid disease and, although a higher prevalence of thyroid disease in T1D was expected (compared with T2D), the relatively high prevalence of thyroid disease in women with T2D was surprising. Poor pregnancy outcomes, and increased risk of cesarean section and pre-eclampsia, have been described with both hyper- and hypothyroidism [33–35]. As might be expected, women with T2D had a higher BMI than those with T1D, with one in two women with T2D classified as obese compared with approximately one in six women with T1D [10,32,36]. Weight control should be carefully monitored in pregnant women given the association between obesity and pregnancy complications [16].

Hypertension was present in 6.6% of women with T1D and 18% of women with T2D at enrollment, consistent with data in non-pregnant women [37], but higher than the prevalence of hypertension in women without diabetes (1–5%) [38]. Pre-existing chronic hypertension significantly increases the risk of perinatal mortality, pre-eclampsia, pre-term birth, and impaired fetal growth [38]. Some categories of antihypertensive treatment (beta-blockers, alpha-beta-blockers, or centrally acting adrenergic agents) have been associated with an increased risk of congenital malformations [39]. Furthermore, use of antidepressants, asthma medication, or epilepsy medication in early pregnancy might also increase the risk of congenital malformations [40–42].

Overall, retinopathy was the most common microvascular diabetic complication, which is consistent with the literature [22,43]. The low

prevalence of diabetic nephropathy is reassuring, as diabetic nephropathy has been associated with congenital malformations [22]. In the EVOLVE study population, miscarriage and cesarean sections were the most common complications experienced by women with previous pregnancies.

The relatively low number of women with T2D in this study is expected given the typically later onset of T2D and, therefore, the lower proportion of women with T2D relative to T1D who are of reproductive age. Additionally, it is likely that many women with T2D of reproductive age would have been treated with diet and/or oral hypoglycemic drugs, rather than injectable drugs, and therefore would not have met the eligibility criteria for EVOLVE. As treatment reimbursement varies across countries, it is also possible that some women with T2D were not receiving any treatment, and thus would not have been eligible for the study.

EVOLVE includes a large population size with broad inclusion/exclusion criteria and includes data from many countries, so is reflective of a real-world population divided across a mix of different healthcare systems. However, as the study sites may not be representative of their respective countries, and some countries (e.g. Greece, Germany, and Portugal) had relatively small numbers of women enrolled in the study, care is needed when interpreting the country-stratified data. Despite the large overall sample size, additional data from a larger population of patients with T2D would be beneficial. Other limitations include: missing data in regard to the percentage of available women who did not participate in the study, lack of random selection of study centers, the absence of a standardized method for HbA_{1c} measurement, the lack of data collection on insulin pump use, potential for incomplete medical records across sites, and the imprecise recording of the time that folic acid was started in some women, thus making it difficult to determine whether the women were receiving folic acid prior to pregnancy, as recommended.

Conclusions

These baseline data of the EVOLVE study highlight the need to improve glycemic control, pregnancy planning, and care management of chronic conditions during early pregnancy in women with pre-existing diabetes. Many women were not achieving glycemic targets at enrollment or taking appropriate folic acid supplementation during early pregnancy. Furthermore, a large proportion of the women reported having at least one or more additional chronic conditions, further increasing the risk of congenital malformations and other pregnancy complications.

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EM has received speakers' fees from Novo Nordisk, Lilly, and Sanofi Aventis; and has participated in steering committee tasks and guidance involving writing protocols for Novo Nordisk. KC has received speaker honoraria from or has participated in advisory boards for Novo Nordisk, Lilly, Sanofi, AstraZeneca, Boehringer Ingelheim, and Servier. JMD has received speaker honoraria from or has participated in advisory boards for Novo Nordisk, Lilly, Sanofi, Amgen, Abbott, AstraZeneca, Boehringer Ingelheim, Mundipharma, and MSD. ME and LLNH are employees of, and hold shares in, Novo Nordisk. RKN is an employee of Novo Nordisk. SDG is a consultant for Sanofi-Aventis, Eli Lilly and Co., Novo Nordisk, Takeda, MSD, Servier, and Theracos. HH has received lecturer and scientific advisor fees from Abbott, Eli Lilly, Lifescan, and Novo Nordisk; and research grants from Abbott, Lifescan, and Novo Nordisk. HPK has received speaker honoraria from, or has participated in advisory boards for, Novo Nordisk, Lilly, Sanofi-Aventis, AstraZeneca, and Servier. DRM has received speaker honoraria from, or has participated in advisory boards for, Novo Nordisk. NA, EA, HWdV, FD, and MI have no conflicts of interest to declare.

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Data availability statement

The subject-level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

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