



Congenital malformations among offspring of women with type 1 diabetes who use insulin pumps: a prospective cohort study

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Abstract

Aims/hypothesis Continuous subcutaneous insulin infusion by insulin pump is often superior in improving glycaemic control compared with conventional multiple daily insulin injection (MDI). However, whether pump treatment leads to improved pregnancy outcomes in terms of congenital malformations and perinatal death remains unknown. The present aim was to evaluate the risk of malformations and perinatal and neonatal death in pregnant women with type 1 diabetes treated with pump or MDI.

Methods We performed a secondary analysis of a prospective multinational cohort of 2088 pregnant women with type 1 diabetes in a real-world setting who were treated by pump ($n=750$) or MDI ($n=1338$). ORs for offspring with congenital malformations or perinatal or neonatal death were calculated using crude data and by logistic regression on propensity score-matched data.

Results At enrolment (gestational week 8; 95% CI 4, 14), pump users had a higher educational level (university degree: 37.3% vs 25.1%; $p<0.001$) and better glycaemic control (mean HbA_{1c}: 51±10 mmol/mol [6.8±0.9%] vs 54±14 mmol/mol [7.1±1.3%], $p<0.001$) compared with MDI users. Moreover, a greater proportion of pump users had an HbA_{1c} level below 75 mmol/mol (9%) (97.6% vs 91.9%, $p<0.001$), and more often reported taking folic acid supplementation (86.3% vs 74.8%; $p<0.001$) compared with MDI users. All clinically important potential confounders were balanced after propensity score matching, and HbA_{1c} remained lower in pump users. The proportion of fetuses with at least one malformation was 13.5% in pump users vs 11.2% in MDI users (crude OR 1.23; 95% CI 0.94, 1.61; $p=0.13$; propensity score-matched (adjusted) OR 1.11; 95% CI 0.81, 1.52; $p=0.52$). The proportion of fetuses with at least one major malformation was 2.8% in pump users vs 3.1% in MDI users (crude OR 0.89; 95% CI 0.52, 1.51; $p=0.66$; adjusted OR 0.78; 95% CI 0.42, 1.45; $p=0.43$), and the proportions of fetuses carrying one or more minor malformations (but no major malformations) were 10.7% vs 8.1% (crude OR 1.36; 95% CI 1.00, 1.84; $p=0.05$; adjusted OR 1.23; 95% CI 0.87, 1.75; $p=0.25$). The proportions of perinatal and neonatal death were 1.6% vs 1.3% (crude OR 1.23; 95% CI 0.57, 2.67; $p=0.59$; adjusted OR 2.02; 95% CI 0.69, 5.93; $p=0.20$) and 0.3% vs 0.3% ($n=2$ vs $n=4$, p =not applicable), respectively.

Conclusions/interpretations Insulin pump treatment was not associated with a lower risk of congenital malformations, despite better glycaemic control in early pregnancy compared with MDI. Further studies exploring the efficacy and safety of pump treatment during pregnancy are needed.

Keywords Congenital malformations · Continuous subcutaneous insulin infusion pump therapy · Perinatal death · Pregnancy outcomes · Type 1 diabetes mellitus

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Research in context

What is already known about this subject?

- Congenital malformations and perinatal mortality are two to four times more frequent in offspring of women with type 1 diabetes compared with the background population, and are strongly associated with poor glycaemic control during early pregnancy
- Continuous subcutaneous insulin infusion by insulin pump is often superior in improving glycaemic control compared with conventional multiple daily insulin injections (MDI) in non-pregnant people with type 1 diabetes. Pump treatment is increasingly used to optimise glycaemic control before and during pregnancy; however, the potential advantages in terms of congenital malformations and perinatal death remain unknown

What is the key question?

- Does insulin pump treatment reduce the risk of malformations and perinatal and neonatal death compared with MDI in pregnant women with type 1 diabetes?

What are the new findings?

- The prevalence of congenital malformations and perinatal and neonatal death was not improved with pump treatment, despite better glycaemic control at conception compared with MDI

How might this impact on clinical practice in the foreseeable future?

- Implementing a general change from MDI to pump treatment for pregnancy planning does not result in fewer malformations or perinatal deaths. However, pump treatment is probably useful in selected women to improve glycaemic control before and during pregnancy

Abbreviations

EVOLVE	EValuation Of LeVEmir in Pregnancy
MDI	Multiple daily injections

Introduction

Congenital malformations and perinatal mortality are serious complications for the offspring of women with type 1 diabetes mellitus, related to impaired glycaemic control, and are two to four times more frequent in the offspring of these women compared with the background population [1–4]. Poor preconceptional glycaemic control is strongly associated with the risk of congenital malformations in infants born to women with type 1 diabetes, and is the most important modifiable risk factor [3–5]. To a lesser extent, high maternal educational level [6] and folic acid supplementation [7] have been shown to be associated with a lower prevalence of malformations, whereas diabetic complications such as retinopathy and nephropathy are associated with a higher prevalence of malformations [5, 8]. Perinatal mortality risk in women with type 1 diabetes is multifactorial in origin, but poor glycaemic control appears to be a key modifiable factor in placing women at increased risk [9–12].

Outside pregnancy, several studies have suggested that continuous subcutaneous insulin infusion by insulin pump improves glycaemic control compared with conventional treatment by multiple daily injections (MDI) of insulin

[13–16]. Thus, insulin pump treatment is becoming increasingly used throughout Europe, Canada and the USA, with the aim of improving glycaemic control and quality of life [17]. Despite the expectation that insulin pump treatment will improve glycaemic control and reduce the prevalence of complications in pregnancy [18, 19], the anticipated benefit of using pump treatment during pregnancy has not yet been demonstrated, and papers evaluating the prevalence of congenital malformations and/or perinatal death in women who use pumps compared with MDI treatment are lacking.

The low incidence of malformations and perinatal death invoke the need for large cohort studies to evaluate the risk of congenital malformations and perinatal death in insulin pump users in a real-world setting, as randomised control trials are difficult to perform in this context. We recently established a large, multinational, prospective, non-interventional cohort – the so-called Diabetes Pregnancy Registry – that includes data from more than 2000 pregnant women with pre-existing type 1 diabetes, and assessed the impact of various long-acting insulin analogues on glycaemic control and pregnancy outcome in MDI-treated women in the EVOLVE study [20–22]. The Diabetes Pregnancy Registry includes 750 women who use pump treatment, which provides a unique opportunity to test our hypothesis that pump treatment in real-world conditions is associated with a reduced risk of congenital malformations and perinatal death.

The primary aim of this study was to evaluate the risk of having an offspring with congenital malformations or

perinatal or neonatal death in women with type 1 diabetes treated using a pump vs MDI before and during pregnancy.

Methods

The present study is an analysis of the participants in the Diabetes Pregnancy Registry including the Evaluation Of LeVEmir in Pregnancy (EVOLVE) study cohort [20]. Briefly, the study ([ClinicalTrials.gov](https://clinicaltrials.gov), number NCT01892319) was a multinational, prospective, non-interventional, multicentre cohort study designed to monitor and assess the safety of insulin detemir in pregnant women with pre-existing diabetes and their offspring. As part of the observational data collection, equivalent data were collected from pregnant women with pre-existing diabetes treated using other injectable glucose-lowering treatment regimens. This international Diabetes Pregnancy Registry is a unique opportunity for large-scale data collection that allows comparisons and analysis between various insulin treatment regimens in pregnant women with diabetes mellitus. The study covered the gestational period of women with pre-existing type 1 or type 2 diabetes, and a follow-up period for their infants to 1 year of age, with the frequency and mode of standard routine visits determined by the individual study site.

In the present analysis of this cohort, we investigated women with type 1 diabetes treated with pump therapy or MDI during pregnancy. Women treated with pump therapy or MDI followed the local routine care without a predefined schedule of study visits during pregnancy. Postpartum follow-up at 1 month and 1 year was performed using questionnaires and telephone interviews, and collected information on neonatal death (yes or no) and congenital malformations that were not detected at delivery or changes in major congenital malformations (see electronic supplementary material [ESM] Table 1).

Recruitment took place between September 2013 and September 2018. During the enrolment visit, signed informed consent was obtained after an eligibility check based on the inclusion criteria, which were: a positive pregnancy test and gestational age ≤ 16 weeks at enrolment, type 1 diabetes diagnosed prior to conception, and treatment for at least 1 month prior to conception with either pump therapy or MDI. Women were excluded if they withdrew consent or were lost to follow-up prior to the end of their pregnancy. All singleton offspring were investigated; for twin pregnancies, one of the offspring was randomly selected for investigation (Fig. 1).

At the enrolment visit, clinical data were collected by interview or extracted from medical records as previously described [21]. Information included aspects relating to maternal medical history (including the presence of hypertension), diabetes history and diabetes complications (diabetic retinopathy, diabetic neuropathy and diabetic nephropathy), current

glucose-lowering treatment, obstetric history, current pregnancy information, folic acid intake before and during the first trimester, socioeconomic status, race, smoking and alcohol intake. At the first visit, BMI, BP (systolic/diastolic) and HbA_{1c} (at maximum 16 weeks' gestation) were recorded.

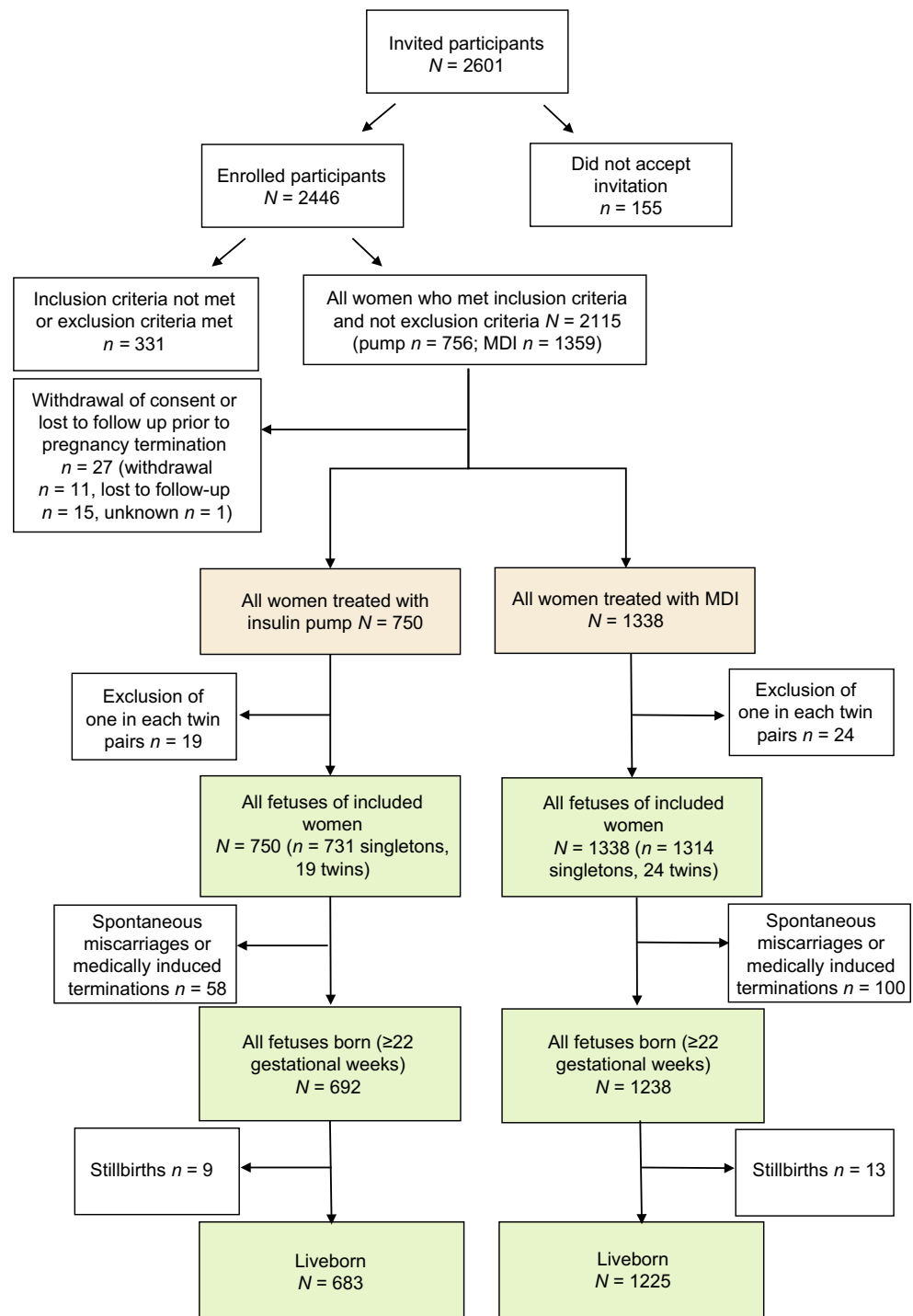
All pregnancies ending in spontaneous miscarriage or medically induced termination, or a liveborn or stillborn offspring, were recorded. Offspring were evaluated for any congenital malformations irrespective of whether liveborn or stillborn, as determined by the local practice, up to 1 month of age. Severe cases of malformations leading to medically induced termination of pregnancy were also registered.

All data were collected using electronic case report forms that were completed by physicians or their authorised staff. Major endpoints were verified by a physician.

Endpoints The primary endpoint was offspring with any congenital malformation (major and/or minor) (yes/no) diagnosed at birth or up to 1 year of age, including fetuses with major congenital malformation leading to medically induced termination of pregnancy. Fetuses with congenital malformations were divided into fetuses with one or more major congenital malformation and fetuses with one or more minor congenital malformation but no major malformation. A major congenital malformation was defined as a life-threatening structural malformation or an abnormality likely to cause significant impairment of health or functional capacity that requires medical or surgical treatment [23]. Minor malformations were defined as malformations that did not fulfil the criteria for a major malformation. The majority of the malformations were present at birth, and the medical records were used for documentation. In addition, any possible changes in the presence of malformations within the first year of life were determined from the medical record. Secondary outcomes included spontaneous miscarriages and medically induced termination of pregnancy before 22 weeks' gestation, stillbirth (from 22 weeks' gestation to delivery), perinatal death (from 22 weeks' gestation to 7 days after birth) or neonatal death (death of a liveborn infant 0–28 days after delivery).

Statistical methods Data management and statistical analyses were performed using SAS 9.4 M5 (SAS Institute, USA). A p value < 0.05 was used to indicate statistical significance. In the case of missing information for required variables, patients were excluded from the respective analysis.

Descriptive analyses were performed to summarise the characteristics of each treatment group at enrolment. For all binary endpoints (yes/no), total numbers and percentages are reported for pump therapy and MDI users. For continuous variables that followed a Gaussian distribution, means and SD are reported. For continuous variables that did not follow

Fig. 1 Flow chart of participant numbers

a Gaussian distribution, median and IQR are reported. Descriptive data were compared using χ^2 or Fisher's exact tests for categorical variables and Student's *t* test, the Wilcoxon test and the Welch–Satterthwaite test for continuous variables as applicable.

For all primary and secondary endpoints, both crude and propensity score-matched (adjusted) analyses were performed to compare the risk between treatment groups. We calculated OR as odds in the pump therapy group/odds in the MDI group

using logistic regression. However, linear regression was used for HbA_{1c}, and the results are given as the relative difference as a percentage between the pump therapy group and the MDI group, as HbA_{1c} values were log-transformed before analysis. Because there were relatively few events for several of the outcomes, we used propensity score matching to adjust the estimated OR between groups for potential confounding. Propensity scores were based on the following potential confounders: maternal age, duration of diabetes, history of at

least one long-term diabetes complication (diabetic retinopathy, diabetic nephropathy and diabetic neuropathy), folic acid taken before and during the first trimester, history of spontaneous miscarriage, history of major malformations, BMI and education (proportion receiving a university degree). The nearest neighbour pair-matching without replacement, with a calliper width of 0.2 of the standard deviation of the logit of the propensity scores (predicted values), was used. Pump therapy users were matched with MDI users 1:1. For outcomes with fewer than ten events in each treatment group, data were not statistically tested and are summarised descriptively.

A sensitivity analysis was also performed, restricted to offspring of women from countries that contributed at least 30 participants to each treatment group.

Ethics statement All participants gave written informed consent to participate in the observational cohort study. The study was performed in accordance with the Declaration of Helsinki and the International Society for Pharmaceutical Engineering Guidelines for Good Pharmacoepidemiology Practice, and was approved separately in each of the participating countries by national health authorities, local institutional review boards or independent ethics committees.

Results

Participants Overall, 2601 women were invited to participate in the study, of whom 155 did not accept the invitation. Of the 2446 possible participants, 331 did not meet the inclusion criteria for the present study. Therefore, 2115 pregnant women with type 1 diabetes were enrolled in early pregnancy, of whom 27 (1%) either withdrew consent or were lost to follow-up prior to the end of pregnancy, resulting in 2088 women being included in this study (Fig. 1). Of these, 750 women were treated with a pump and 1338 women with MDI (Fig. 1). In total, there were 2045 singleton pregnancies (pump 731, MDI 1314) and 43 twin pregnancies (pump 19; MDI 24). A total of 158 pregnancies were lost before 22 weeks' gestation (pump 58, MDI 100), of which 104 were due to spontaneous miscarriage (pump 31, MDI 73), with the remaining 54 being reported as medically induced termination of pregnancy (pump 27, MDI 27). Of the 54 medically induced terminations of pregnancy, 14 (pump 6, MDI 8) were due to severe malformations present in the fetus. Of the 1930 offspring included in the study, 1908 were liveborn (>22 gestational weeks) and 22 were stillborn (Fig. 1).

The majority of the women were included during early pregnancy (median 8 gestational weeks; IQR 4–14). The participants originated from 15 countries in Europe, Israel and Malaysia. Denmark ($n=551$), the UK ($n=268$) and Croatia ($n=226$) contributed the most participants (ESM

Table 2). The baseline characteristics of the women included in the study were comparable between the two treatment groups with a few exceptions (Table 1). Pump users were better educated, i.e. more likely to have a university degree (pump 37.3% vs MDI 25.1%, $p<0.001$) and had a higher BMI (median [IQR] 25.5 [23.1–28.3] vs 24.3 [22.1–27.6] kg/m², $p<0.001$). Pump users also had a longer diabetes duration (mean±SD 18.3±7.8 vs 14.5±8.3 years, $p<0.001$), with a higher prevalence of retinopathy (35.8% vs 25.0%, $p<0.001$) but not nephropathy (4.7% vs 4.6%, $p=0.93$) or neuropathy (3.1% vs 2.9%, $p=0.78$). A higher proportion of pump users reported having taken folic acid supplementation before and/or during the first trimester of pregnancy (86.3% vs 74.8%, $p<0.001$) and to be less likely to smoke (4.9% vs 9.0%, $p<0.001$). Pump-treated women had a lower HbA_{1c} level at enrolment compared with MDI-treated (mean±SD 51±10 mmol/mol [6.8±0.9%] vs 54±14 mmol/mol [7.1±1.3%], $p<0.001$). Moreover, a greater proportion of pump users had HbA_{1c} level below 75 mmol/mol (9%) (97.6% vs 91.9%, $p<0.001$). All clinically important potential confounders were balanced after matching, with all standard mean differences less than 0.2 (Table 2). However, the significantly lower HbA_{1c} level in pump users remained at a similar magnitude (51±10 mmol/mol [6.8±0.9%] vs 54±14 mmol/mol [7.1±1.2%], $p<0.001$) (difference between pump and MDI: 3.2 percentage points; 95% CI 1.6%, 4.8%; $p<0.0001$). Moreover, the HbA_{1c} levels at enrolment for the subpopulation of 1564 pregnant women from countries contributing with more than 30 women to both treatment groups (ESM Table 3) did not demonstrate any differences from the entire study population, and mean HbA_{1c} levels at enrolment were not different from those of the full cohort (pump 51±10 mmol/mol [6.8±0.9%] vs MDI 54±13.9 mmol/mol [7.1±1.3%], $p<0.001$).

The majority of the women used insulin aspart in both groups (pump 73.3%, MDI 78.8%), and the most commonly used basal insulins in the MDI group were insulin detemir (45.9%) and insulin glargine (45.4%) (Table 1 and ESM Table 4).

Malformations and mortality risk In total, 251 offspring with any malformations were identified, of whom 63 had a least one major congenital malformation. The proportions of offspring with at least one congenital malformation (major and/or minor) were 13.5% in pump users and 11.2% in MDI users (crude OR 1.23; 95% CI 0.94, 1.61; $p=0.13$; adjusted OR 1.11; 95% CI 0.81, 1.52; $p=0.52$) (Fig. 2). The proportion of offspring with a least one major congenital malformation was 2.8% vs 3.1% (crude OR 0.89; 95% CI 0.52, 1.51; $p=0.66$; adjusted OR 0.78; 95% CI 0.42, 1.45; $p=0.43$) (Fig. 2). A total of 12 offspring had more than one major malformation (0.5% in both groups).

Table 1 Baseline characteristics of pregnant women with pre-existing type 1 diabetes receiving insulin treatment through continuous subcutaneous insulin infusion by insulin pump or MDI at enrolment

	<i>n</i>	Pump (<i>N</i> = 750)	<i>n</i>	MDI (<i>N</i> = 1338)	<i>p</i> value
Age, years	750	31.0 ± 4.9	1338	30.4 ± 5.2	0.0118
White	680	629 (92.5)	1313	1237 (94.2)	<0.0001*
University degree	748	279 (37.3)	1337	335 (25.1)	<0.0001*
BMI, kg/m ²	694	25.5 (23.1–28.3)	1272	24.3 (22.1–27.6)	<0.0001*
Current smoker	737	36 (4.9)	1295	117 (9.0)	0.0009*
Alcohol consumption	719	6 (0.8)	1267	16 (1.3)	0.3809
Systolic BP, mmHg	638	119.0 (110.0–126.0)	1218	119 (110–127.0)	0.3227
Diastolic BP, mmHg	638	72.0 (67.0–79.0)	1218	71.0 (65–80)	0.7004
Hypertension	750	47 (6.3)	1337	90 (6.7)	0.6808
Diabetes duration, years	750	18.3 ± 7.8	1328	14.5 ± 8.3	<0.0001*
History of retinopathy	748	268 (35.8)	1330	332 (25.0)	<0.0001*
History of nephropathy	749	35 (4.7)	1331	61 (4.6)	0.9304
History of neuropathy	749	23 (3.1)	1330	38 (2.9)	0.7829
HbA _{1c} , mmol/mol	706	51 ± 10	1261	54 ± 14	<0.0001*
HbA _{1c} , %	706	6.8 ± 0.9	1261	7.1 ± 1.3	<0.0001*
Folic acid ^a	731	631 (86.3)	1324	991 (74.8)	<0.0001*
Bolus (fast-acting) insulin	750	750 (100)	1338	1338 (100)	
Insulin aspart		550 (73.3)		1055 (78.8)	
Basal insulin	750	0 (0)	1338	1338 (100)	
Insulin detemir		–		614 (45.9)	
Insulin glargine		–		608 (45.4)	
Metformin	750	0 (0)	1338	26 (1.9)	
Nulliparous	750	371 (49.5)	1338	668 (49.9)	0.7272
Previous major malformations	750	11 (1.5)	1337	20 (1.5)	0.9578
Previous spontaneous miscarriage	750	159 (21.2)	1338	293 (21.9)	0.7101

Values are median (IQR), mean (SD) or number of patients (%)

^a Taken before and/or during first trimester

Asterisks indicate statistically significant *p* values (*p*<0.05)

The major congenital malformations across the two groups were most commonly related to the cardiovascular system (*n*=21), the genitourinary system (*n*=9) or the nervous system (*n*=6). Individual details of the type of major malformations and the characteristics of the mothers are presented in ESM Table 5.

Pump users had more offspring with at least one minor malformation but no major malformation compared with MDI users (10.7% vs 8.1%), with a crude OR of 1.36 (95% CI 1.00, 1.84; *p*=0.05); the adjusted OR was of similar magnitude but was non-significant (OR 1.23; 95% CI 0.87, 1.75; *p*=0.25) (Fig. 2). The minor congenital malformations were mostly related to the cardiovascular system, followed by the genitourinary system.

Crude and propensity score-matched analyses of offspring malformations according to the type of maternal insulin treatment in the subpopulation of 1564 women from the seven countries contributing at least 30 participants to each treatment group are given in ESM Table 3. No obvious

differences from the total cohort were identified (ESM Table 3).

Figure 3 shows the prevalence of any congenital malformation (major and/or minor) by category of HbA_{1c} level at enrolment for each treatment group. In women with HbA_{1c} levels above 75 mmol/mol (9%), a numerically increased prevalence (not statistically tested owing to low numbers of participants) of any congenital malformations was observed in MDI-treated women compared to women with lower HbA_{1c} levels. At ‘close to target’ HbA_{1c} levels, pump users had a numerically higher prevalence (not statistically tested owing to low numbers of participants) of any congenital malformations compared to women treated with MDI (Fig. 3).

The proportion of pregnancies resulting in stillbirth (*n*=9 (1.3%) vs *n*=13 (1.1%); *p*=not applicable), perinatal death (*n* = 11 (1.6%) vs *n*=16 (1.3%); crude OR 1.23; 95% CI 0.57, 2.67; *p*=0.59; adjusted OR 2.02; 95% CI 0.69, 5.93; *p*=0.20) or neonatal death (*n*=2 (0.3%) vs *n*=4 (0.3%); *p*=not applicable) was not different between the two treatment groups.

Table 2 Baseline characteristics (crude and propensity score-matched for potential confounders) in pregnant women with type 1 diabetes receiving insulin treatment with continuous subcutaneous insulin infusion by pump or MDI

	Crude data					Propensity score-matched data		
	<i>n</i>	Pump	<i>n</i>	MDI	SMD	Pump	MDI	SMD
Fetuses								
Age (years)	750	31 (28–34)	1338	30 (27–34)	0.10	31 (27–34)	31 (27–34)	0.03
University degree	748	279 (37.3)	1337	335 (25.1)	−0.26	251 (37.0)	234 (34.5)	−0.05
History								
Diabetes complications	750	287 (38.3)	1335	367 (27.5)	−0.25	267 (39.4)	255 (37.6)	−0.04
Major malformation	750	11 (1.5)	1337	20 (1.5)	−0.01	10 (1.5)	8 (1.2)	−0.02
Spontaneous miscarriage	750	159 (21.2)	1338	293 (21.9)	0.04	140 (20.6)	113 (16.7)	−0.10
BMI (kg/m ²)	694	26 (23–28)	1272	24 (22–28)	0.16	26 (23–28)	25 (23–29)	−0.04
Folic acid ^a	731	631 (86.3)	1324	991 (74.8)	−0.29	582 (85.8)	582 (85.8)	0.00
All fetuses born								
Age (years)	692	31 (27–34)	1238	30 (27–34)	0.09	31 (27–34)	31 (27–34)	0.06
University degree	692	258 (37.3)	1238	310 (25.0)	−0.27	236 (37.2)	227 (35.8)	−0.03
History of diabetes complications	692	260 (37.6)	1235	337 (27.3)	−0.24	245 (38.6)	231 (36.4)	−0.05
BMI (kg/m ²)	647	26 (23–28)	1182	24 (22–28)	0.14	26 (23–28)	26 (23–29)	−0.05
Folic acid ^a	677	583 (86.1)	1228	923 (75.2)	−0.28	544 (85.8)	543 (85.6)	−0.00
Liveborn fetuses								
Age (years)	683	31 (27–34)	1225	30 (27–34)	0.08	31 (27–34)	30 (27–34)	0.05
University degree	683	255 (37.3)	1225	309 (25.2)	−0.26	234 (37.4)	214 (34.2)	−0.07
History of diabetes complications	683	258 (37.8)	1222	332 (27.2)	−0.24	243 (38.8)	232 (37.1)	−0.04
BMI (kg/m ²)	639	26 (23–28)	1170	24 (22–28)	0.15	26 (23–28)	26 (23–29)	−0.08
Folic acid ^a	668	574 (85.9)	1215	911 (75.0)	−0.28	536 (85.6)	540 (86.3)	0.02

Values for continuous variables are median (IQR). Values for categorical variables are number of patients (%). For propensity score-matched data *n* in the different subpopulations are: Fetuses: *n*=678 in both treatment groups. All fetuses born: *n*=634 in both treatment groups. Liveborn fetuses: *n*=626 in both treatment groups

^a Taken before and/or during first trimester

SMD, standard mean difference

Discussion

This prospective study of a multinational cohort of 2088 pregnant women with type 1 diabetes revealed that the risks of having an offspring with a congenital malformation was not significantly different for pump treatment compared with MDI treatment. No advantage of pump treatment was demonstrated, either before or after propensity score matching, despite pump users exhibiting better glycaemic control, having a higher educational level, and more frequently reporting supplementation with folic acid.

In the present study, pump-treated women had better glycaemic control at enrolment than the MDI-treated women, in terms of both mean HbA_{1c} level and the percentage without high HbA_{1c} levels, both before and after propensity score matching. This could be anticipated to lead to reduced prevalence of malformations due to the tight relationship between glycaemic control and malformations described in other cohort studies [5, 24, 25]. Therefore, HbA_{1c} was considered

as a mediator variable between insulin treatment and prevalence of malformations in the present study.

A recent Danish population-based register study found an adjusted OR of 2.9% for major malformations in women with type 1 diabetes, mainly driven by women with sub-optimal glycaemic control [3]. This is in line with our findings in the few women with HbA_{1c} levels above 75 mmol/mol (9%), with a numerically increased prevalence of any congenital malformations in MDI-treated women with higher HbA_{1c} levels compared to women with lower HbA_{1c} levels. However, in the Danish population study, the risk for major malformations was not significantly greater than for the background population when HbA_{1c} levels were below 48 mmol/mol (6.5%) in early pregnancy [3]. As we observed generally good glycaemic control in both treatment groups in the present study, with most women having an HbA_{1c} level below 75 mmol/mol (9%) and the mean HbA_{1c} being close to 48 mmol/mol (6.5%), we therefore cannot exclude the possibility that the level of glycaemic control in both groups did not leave much room for further reduction in the

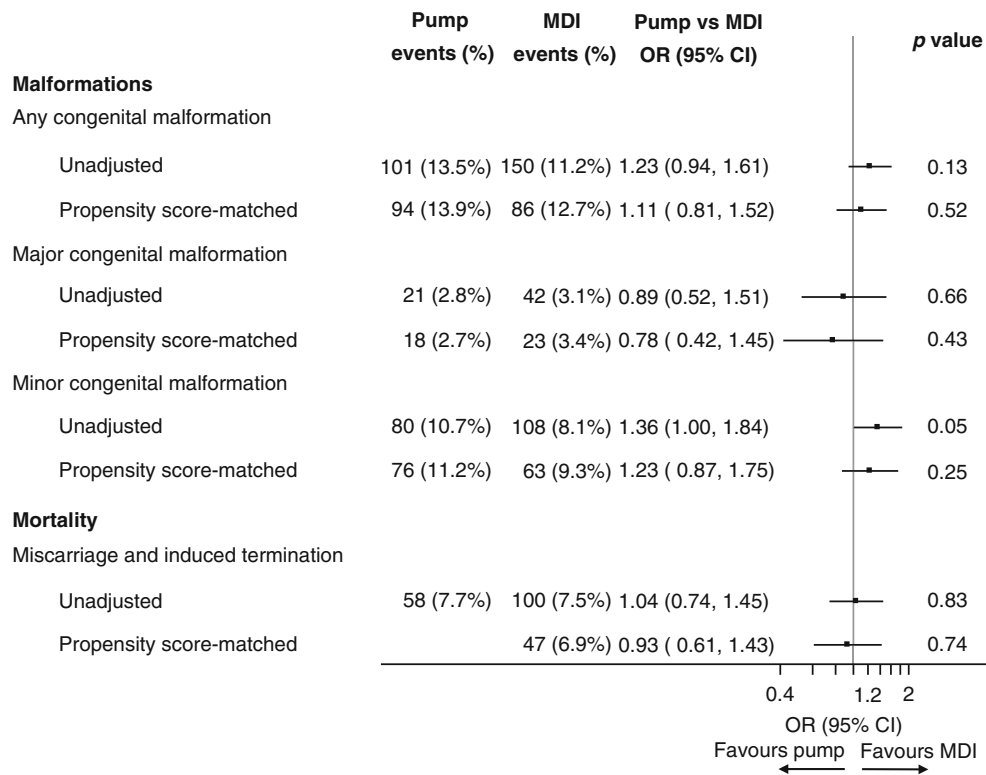


Fig. 2 Crude and propensity score-matched analyses of offspring malformations and mortality rate according to maternal type of insulin treatment (pump or MDI). Offspring with malformations and spontaneous miscarriage/medically induced termination were analysed for all fetuses of included women. Stillbirth and perinatal death were analysed for all fetuses born, and neonatal death was analysed for the liveborn population. Any congenital malformations comprise major and/or minor

malformations. Major congenital malformation indicates one or more major congenital malformations. Minor congenital malformation indicates one or more minor congenital malformations but no major malformation. Miscarriage and induced termination represent spontaneous miscarriage and medically induced termination of pregnancies that ended before 22 weeks’ gestation. The total numbers included in the analyses differ slightly due to missing information for some of the endpoints

prevalence of major malformations in the pump users. Baseline HbA_{1c} levels reflect the glycaemic control for the preceding approximately 8 weeks, during which organogenesis of the offspring organs, including the heart, mainly takes place. In this

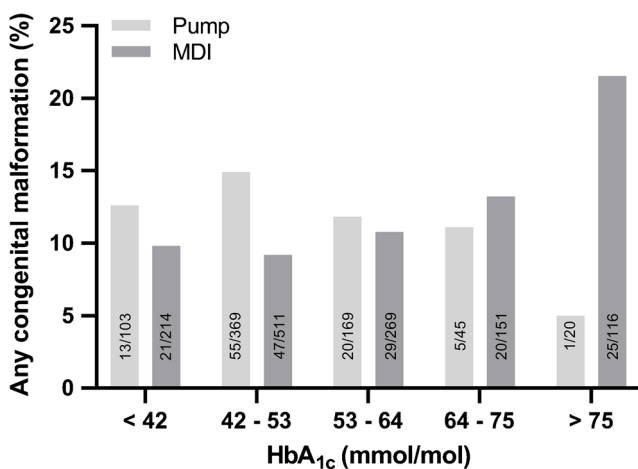


Fig. 3 Prevalence (%) of any congenital malformations (major and/or minor) according to level of maternal HbA_{1c} at enrolment among pregnant women with type 1 diabetes receiving insulin treatment by pump or MDI. The number of malformations/number of women in each HbA_{1c} interval are indicated

study, the HbA_{1c} levels at baseline, which mainly cover the time before the women recognise their pregnancy, show better glycaemic control in women using an insulin pump compared with MDI. In addition, pump treatment has been reported to reduce glucose fluctuations compared with MDI treatment [26]. Therefore, the numerically higher prevalence of any malformations in the pump users appears not to be related to less optimal glycaemic control. Other factors than glycaemic control are probably involved in the numerically higher prevalence of malformations in pump-treated women, but this remains speculative and needs to be confirmed in other studies.

Supplementation with folic acid [7], a good maternal socioeconomic level, [6] and avoiding smoking [27] are known factors related to a reduced risk of malformations in the healthy population [6, 7]. Interestingly, in the present study, pump users appeared to have higher socioeconomic status (evidenced by a higher maternal educational level) and were more likely to take the recommended folic acid supplementation and be non-smokers. Together, this suggests a healthier lifestyle in the pump users, which is expected to contribute to a lower prevalence of malformations. On the other hand, insulin pump treatment is often initiated in women with inappropriate glycaemic control,

and pump users may therefore represent women with more challenging diabetes. Unfortunately, we were only able to report HbA_{1c} levels, and have no data on fluctuation of plasma glucose. The observed higher prevalence of retinopathy in pump users in the present study may be indicative of a history of prolonged poor glycaemic control, which could increase the risk of malformations [5, 8]. However, our propensity score-matched data took these factors into account, and demonstrated that prevalence of malformations was not significantly different regardless of pump treatment or not. It is possible that, as women on pump therapy were better educated, they may have increased diabetes awareness and may adhere to the screening programme for retinopathy more carefully, leading to a higher prevalence of retinopathy being detected compared to women treated with MDI.

The prevalence of stillbirths and neonatal mortality was not numerically different between treatment modalities, but was not statistically tested due to the low number of events in the cohort. The prevalence of perinatal mortality was not significantly different between pump and MDI users. The perinatal mortality risk was mainly driven by stillbirth and is higher than the prevalence of perinatal mortality risk in the Danish background population (approximately 0.4%) [28]. We are not aware of any published data regarding perinatal mortality rate in pump-treated women, but an observational study found that offspring of pump users were more likely to be admitted to neonatal care units for more than 48 h than offspring of MDI users [18].

The present study has several strengths. Data were collected prospectively from early pregnancy, included many relevant clinical variables to adjust for potential confounders, and comprised real-world data from many nationalities and healthcare systems, thereby increasing the generalisability of the findings. One limitation is that the presence of microvascular complications was combined into one variable in the propensity score matching. However, the prevalence of retinopathy was 36% and 25%, respectively, in the pump and MDI groups, while the prevalence of nephropathy was below 5% in both groups. Despite including more than 2000 women, we observed few events for many of the outcomes, resulting in a relatively low statistical power, especially for perinatal death, and the number of offspring with malformations was too small to assess any differences in the various classes of malformations. Even though the presence of congenital malformations was identified through medical records and verified by a physician, it may be possible that the more highly educated pump users were more likely to identify malformations in their offspring and have them reported.

A further limitation is that the women were recruited from selected sites with routine care ensuring relatively good glycaemic control, which may affect the generalisability of the study. Also, that data were collected between 2013 and 2018. Since then, insulin pump technology has improved, and we cannot exclude the possibility that use of more modern

insulin pumps may have a different impact on congenital malformations. Studies including newer insulin pumps with closed-loop systems are warranted.

Our finding of no significant difference in the prevalence of malformations in the offspring of women with and without insulin pump treatment despite more appropriate HbA_{1c} level, and even a non-significant higher prevalence of minor malformations in pump users, was surprising, and suggests the need for further studies evaluating the impact of insulin pump use on development of malformations. Population-based studies are required to evaluate the impact of pump treatment on rare events such as malformations and perinatal death. Investigating possible independent predictors of malformations, including HbA_{1c} level, treatment modality, folic acid supplementation and late diabetes complications, is warranted. The prevalence of other poor pregnancy outcomes such as fetal overgrowth, pre-eclampsia and preterm delivery in pump-treated women will be analysed in a separate report based on this real-world cohort.

In conclusion, it was surprising that the risk of congenital malformations was not lower in offspring of women treated with insulin pumps despite better glycaemic control in early pregnancy, when compared with women receiving MDI treatment. Further studies exploring the efficacy and safety of using pump treatment during pregnancy are needed.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at <https://doi.org/10.1007/s00125-022-05864-6>.

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Data availability Source data are available from the corresponding author on written request.

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Authors' relationships and activities IHT, LLNH, RBN, ACA and M-AG are employers of, and hold shares in, Novo Nordisk. ERM has received speaker's fees from Novo Nordisk, and has participated in steering committee tasks and guidance involving writing protocols for Novo Nordisk. ERM is participating in several multinational clinical studies on the use of insulin in pregnant women with pre-existing diabetes, in collaboration with Novo Nordisk. ERM is a member of the editorial board of *Diabetologia*. The remaining author (JP) declares that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement IHT, LLNH, ACA, M-AG and ERM conceptualised and designed the study. IHT, LLNH, RBN and JP performed the statistical analyses. IHT and ERM drafted the manuscript. All authors were involved in the interpretation of results, edited the manuscript, and provided input, critical review and approval of the final version

of the manuscript. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. IHT and ERM accept responsibility for the overall conduction, integrity and accuracy of the work, had access to the data, and controlled the decision to publish.

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