Pumps or Multiple Daily Injections in Pregnancy Involving Type 1 Diabetes: A Prespecified Analysis of the CONCEPTT Randomized Trial

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OBJECTIVE

To compare glycemic control, quality of life, and pregnancy outcomes of women using insulin pumps and multiple daily injection therapy (MDI) during the Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT).

RESEARCH DESIGN AND METHODS

This was a prespecified analysis of CONCEPTT involving 248 pregnant women from 31 centers. Randomization was stratified for pump versus MDI and HbA_{1c}. The primary outcome was change in HbA_{1c} from randomization to 34 weeks' gestation. Key secondary outcomes were continuous glucose monitoring (CGM) measures, maternal-infant health, and patient-reported outcomes.

RESULTS

At baseline, pump users were more often in stable relationships ($P = 0.003$), more likely to take preconception vitamins ($P = 0.03$), and less likely to smoke ($P = 0.02$). Pump and MDI users had comparable first-trimester glycemia: HbA_{1c} 6.84 ± 0.71 vs. 6.95 ± 0.58% (51 ± 7.8 vs. 52 ± 6.3 mmol/mol) ($P = 0.31$) and CGM time in target (51 ± 14 vs. 50 ± 13%) ($P = 0.40$). At 34 weeks, MDI users had a greater decrease in HbA_{1c} (−0.55 ± 0.59 vs. −0.32 ± 0.65%, $P = 0.001$). At 24 and 34 weeks, MDI users were more likely to achieve target HbA_{1c} ($P = 0.009$ and $P = 0.001$, respectively). Pump users had more hypertensive disorders ($P = 0.011$), mainly driven by increased gestational hypertension (14.4 vs. 5.2%; $P = 0.025$), and more neonatal hypoglycemia (31.8 vs. 19.1%, $P = 0.05$) and neonatal intensive care unit (NICU) admissions >24 h (44.5 vs. 29.6%; $P = 0.02$). Pump users had a larger reduction in hypoglycemia-related anxiety ($P = 0.05$) but greater decline in health/well-being ($P = 0.02$).

CONCLUSIONS

In CONCEPTT, MDI users were more likely to have better glycemic outcomes and less likely to have gestational hypertension, neonatal hypoglycemia, and NICU admissions than pump users. These data suggest that implementation of insulin pump therapy is potentially suboptimal during pregnancy.

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**A complete list of the members of the CONCEPTT Collaborative Group can be found in the Supplementary Data online.*

Insulin pumps or continuous subcutaneous insulin infusions (CSIIs) are increasingly used to optimize glucose control before and during pregnancy involving type 1 diabetes (T1D). Pump therapy has been shown to improve glycemic control, reduce severe hypoglycemic episodes, and improve quality of life in people with T1D outside of pregnancy (1). However, the effectiveness of insulin pump therapy during pregnancy is uncertain (2). Several randomized trials showed no differences in glycemic control or pregnancy outcomes (3–6). These studies were limited by small sample sizes, performed in the 1980s using outdated equipment, and lacked statistical power for evaluating obstetric and neonatal outcomes. More recent cohort studies have found conflicting results, with some but not all finding differences in glycemic control (7–14).

The largest observational study, including 113 pregnancies (>20 weeks' gestation), among insulin pump users reported clinically relevant differences in maternal HbA_{1c} levels, favoring pump users throughout pregnancy (10). Despite lower HbA_{1c} levels (0.7 and 0.3% in the first and third trimesters, respectively), pregnancy outcomes were not improved. Similar to an earlier Cochrane review reporting higher birth weight in infants of mothers who used insulin pumps in pregnancy (15), this Canadian study also described a higher proportion of infants who were large for gestational age (LGA): 55 vs. 39% for pump vs. multiple daily injection therapy (MDI). As with previous retrospective studies, these data were confounded by baseline differences, with pump users being older, of higher parity, better educated, and better prepared for pregnancy. However, pump users also had a longer duration of diabetes and more retinopathy, suggesting that they may have had a more severe glycemic disturbance.

The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) was a multicenter, open-label, randomized trial in 325 women with T1D, who were either planning pregnancy (n = 110) or in early pregnancy (n = 215), from 31 centers in Canada, England, Scotland, Spain, Italy, Ireland, and the U.S. (16). The primary objective was to evaluate the clinical effectiveness of real-time continuous glucose monitoring (CGM) (plus self-monitoring of blood glucose [SMBG]) compared with SMBG alone. The results demonstrated that use of CGM during pregnancy was associated with improved glycemic control with lower rates of neonatal complications in both insulin pump and MDI users (17).

The aim of this prespecified secondary analysis was to compare maternal glycemic control, obstetric and neonatal health outcomes, and patient-related outcome measures in CONCEPTT participants using pumps versus MDI.

RESEARCH DESIGN AND METHODS

Full details of the clinical study protocol have previously been published (16). Women with T1D were eligible if they were aged 18–40 years, had >12 months' duration of diabetes, and were on an intensive insulin regimen using either a pump or multiple daily injections. Women planning pregnancy had to have an HbA_{1c} level between 7.0 and 10% (53–86 mmol/mol). Pregnant women had to have a live singleton fetus confirmed by ultrasound before 14 weeks' gestational age and an HbA_{1c} level between 6.5 and 10% (48–86 mmol/mol). After a run-in period where eligible women wore a masked CGM for at least 96 h (neither they nor their clinical teams could see the glucose values), women were randomized to the intervention, where they received a CGM, or to the control group, where they were instructed to continue with their usual SMBG at least seven times per day. The CGM group were asked to perform a glucose test prior to insulin dose adjustment to verify the accuracy of the CGM, as required by the regulatory labeling instructions of the CGM manufacturer.

In the main CONCEPTT trial, randomization was stratified by insulin delivery system (pump or MDI) and by baseline HbA_{1c} level (<7.5 vs. ≥7.5% or 58 mmol/mol during pregnancy and <8.0 vs. ≥8.0% or 64 mmol/mol while planning pregnancy). Women in the SMBG planning pregnancy and pregnant groups were asked to wear another masked CGM at 12 and 24 weeks and 24 and 34 weeks, respectively, for a minimum of 96 h. Visits occurred every 4 weeks. Women who conceived during the planning pregnancy trial continued in their original randomized group throughout pregnancy and are included in these analyses.

In the current analyses, the glycemic control, quality of life, and pregnancy outcomes of pregnant women using pump therapy were compared with those of pregnant women using MDI. The primary outcome was glycemic control as measured by a change in HbA_{1c} from baseline to 34 weeks' gestation. Severe hypoglycemia was defined as an episode requiring third-party assistance. Other secondary glycemic outcomes included CGM time in target range (63–140 mg/dL), time spent above and below the target range, episodes of hypoglycemia (defined as CGM glucose values <63 mg/dL for at least 20 min), and glucose coefficient of variation (CV) to reflect glycemic variability.

Patient-reported outcome measures included the following questionnaires completed at baseline and 34 weeks' gestation. These assessed satisfaction with their glucose monitoring system (Blood Glucose Monitoring System Rating Questionnaire) (18), fear of hypoglycemia (Hypoglycemia Fear Survey [HFS]-II]) (19), diabetes-related distress (Problem Areas in Diabetes scale) (20), and quality of life (12-Item Short-Form Survey [SF-12]) (21). All questionnaires had acceptable estimates of internal reliability calculated using Cronbach's α coefficient or the Spearman-Brown split-half reliability coefficient.

Obstetric outcomes included hypertensive disorders (worsening chronic hypertension, gestational hypertension with and without preeclampsia, and preeclampsia together and individually), cesarean section delivery, and gestational weight gain (22). Neonatal outcomes included pregnancy loss (miscarriage, stillbirth, neonatal death ≤28 days of life), preterm birth (<37 and <34 weeks' gestation), birth injury, shoulder dystocia, birth weight percentile, rates of LGA or small for gestational age (>90th or <10th percentile using Gestation Related Optimal Weight [GROW] software [23], which adjusts for infant sex and gestational age, maternal height, weight, parity, and ethnicity), neonatal hypoglycemia requiring intravenous glucose, hyperbilirubinemia, respiratory distress syndrome, neonatal intensive care unit (NICU) admission >24 h, cord blood C-peptide, and a prespecified composite outcome of pregnancy loss, birth injury, neonatal

hypoglycemia, hyperbilirubinemia, respiratory distress, and NICU admission >24 h (22).

Statistical Analysis

The primary analysis used ANCOVA to compare glycemic outcomes of insulin pump and MDI users at 34 weeks' gestation, controlling for baseline HbA_{1c} and stratifying by insulin delivery method. It was performed with and without adjustment for baseline differences in duration of diabetes, educational level, cigarette smoking, gestational age, and CGM compliance. For binary outcomes, the proportions between groups were compared using the Fisher exact test and, where applicable (n = 30 or more), using logistic regression with pump or MDI and baseline HbA_{1c} as covariates. For all continuous outcomes, the prespecified analysis is linear regression with pump or MDI and baseline HbA_{1c} as categorical variables. Repeated-measures ANCOVAs were used to determine the statistical significance of differences in scores on the patient-reported outcome measures as estimated by main effects for pump or MDI and for group-by-time interaction effects. A two-sided significance level of 5% was used without adjustment for multiple comparisons.

RESULTS

Participants

The majority of the 248 participants entered the trial during early pregnancy (86%), with 34 (14%) recruited while planning for pregnancy. The U.K. and Canada had the largest numbers of participants (109 U.K., 103 Canada, 18 Spain, 12 Italy, 4 Ireland, and 2 U.S.). As randomization was stratified for method of insulin delivery, there was the same number of women using pump and MDI randomized to CGM (62 and 62). Although pump and MDI users were of similar age, pump users were more often married or in stable relationships, and more took preconception multivitamins. MDI users were more likely to smoke cigarettes at conception and were randomized ~1.5 weeks later than pump users (Table 1).

Table 1—Baseline characteristics of pregnant CONCEPTT participants (n = 248) using insulin pump and MDI therapy

	Insulin pump†	MDI	P
N	125	123	
Age (years)	31.9 ± 4.7	31.2 ± 4.5	0.23
European/Mediterranean origin	107 (85.6)	106 (86.2)	1.00
Married or common-law	**118 (94.4)**	**100 (81.3)**	**0.003**
College/university education€	103 (83.1)	90 (73.2)	0.08
Secondary school or less	21 (16.8)	33 (26.8)	
BMI (kg/m^2)	26.2 ± 4.6	25.4 ± 4.3	0.19
Gestational age at randomization (weeks)	**9.71 (7.29–12.00)**	**11.14 (9.50–12.71)**	**<0.001**
Primiparous	49 (39.2)	51 (41.5)	0.82
Duration of diabetes (years)	16.0 (11.0–23.0)	16.0 (10.0–22.5)	0.62
Smoking	**12 (9.6)**	**26 (21.1)**	**0.019**
Randomized to CGM	62 (49.6)	62 (50.4)	1.0
Preconception folic acid	74 (59.2)	58 (47.1)	0.08
Preconception multivitamin	**49 (39.2)**	**31 (25.2)**	**0.026**
Total insulin dose (units/kg/day)	0.72 ± 0.30	0.72 ± 0.24	0.89
Diabetes complications¥	30 (24.0)	36 (29.3)	0.43
Retinopathy	28	31	0.71
Nephropathy	4	4	1.00
Neuropathy	3	5	0.50
Hypertension	9 (7.2)	6 (4.9)	0.62
Severe hypoglycemia in past year*	8 (6.4)	10 (8.1)	0.78
Hypoglycemia awareness symptoms			0.16
Always aware	92 (73.6)	81 (65.8)	
Sometimes	32 (25.6)	37 (30.1)	
Never aware	1 (0.8)	5 (4.1)	

Data are counts (percentages) or means ± SD, except for gestational age at randomization and diabetes duration, which are median (interquartile range). †Twenty-five women (19 CGM and 6 capillary glucose monitoring) used insulin pumps with low glucose or threshold suspend features. €One missing from insulin pump group. ¥Diabetes complications are not mutually exclusive. *Represents severe hypoglycemia in up to 1.5 years prior to pregnancy in the women who were in the planning pregnancy group who became pregnant. Comparisons that are boldface type indicate significant differences ($P < 0.05$).

Glycemia Outcomes

At randomization, women on pump and MDI had similar mean HbA_{1c} (6.84 ± 0.71 vs. 6.95 ± 0.58%; P = 0.31). However, there was a larger decrease in HbA_{1c} from randomization to 34 weeks in the MDI group compared with the pump group (−0.55 ± 0.59 vs. −0.32 ± 0.65%; P = 0.01) (Table 2); with adjustment for covariates, the additional decrease in the MDI group was 0.28% (95% CI 0.12–0.44; P = 0.001). More MDI users achieved the target HbA_{1c} level of <6.5% (48 mmol/mol) at both 24 weeks (72.1 vs. 63.1%; P = 0.009) and 34 weeks (65.1 vs. 52.0%; P = 0.001). There were no differences in the numbers of women experiencing episodes of severe hypoglycemia or diabetic ketoacidosis, and the total daily insulin doses were comparable in pump and MDI users (Supplementary Table 2).

Compliance with CGM (defined as at least 60% use between randomization and 34 weeks' gestation) was comparable between pump (65.6%) and MDI (68.3%) users. The results of the adjusted analysis in compliant women only were similar to those in all women for the additional effect of MDI on the 34-week decrease in HbA_{1c} (0.31% [95% CI 0.10–0.51]; P = 0.003). The effect of pump versus MDI did not vary across countries (P = 0.97 [results not shown]).

Both groups had increased time spent in the target range (63–140 mg/dL) and decreased time spent in the hyperglycemic range (>140 mg/dL) over the course of pregnancy, with no significant between-group differences (Fig. 1 and Supplementary Table 1). At 24 weeks' gestation, insulin pump users spent 5% less time in the target range and 6% more time in the hyperglycemic range, although these differences were no longer apparent by 34 weeks. Likewise, both groups spent less time in the hypoglycemic range (<63 mg/dL) and had less glycemic variability over the course of pregnancy, with slightly less time in the hypoglycemic range among insulin pump users throughout pregnancy (3 vs. 4%; P = 0.03). There was a nonsignificant

Table 2—Glycemic outcomes of CONCEPTT participants using pump and MDI during pregnancy (*n* = 248)

	Pump	MDI	Unadjusted *P*	Adjusted *P*
First trimester				
HbA_{1c} at randomization (%)‡	6.84 ± 0.71	6.95 ± 0.58	0.23	0.31
HbA_{1c} (mmol/mol)	51 ± 7.8	52 ± 6.3		
At target HbA_{1c} at randomization†	38/109 (34.9)	31/117 (26.5)	0.19	0.22
Second trimester				
HbA_{1c} at 24 weeks (%)‡	**6.37 ± 0.62**	**6.28 ± 0.62**	**0.26**	**0.014**
HbA_{1c} (mmol/mol)	46 ± 6.4	45 ± 6.4		
At target HbA_{1c} at 24 weeks	**65/103 (63.1)**	**80/111 (72.1)**	**0.19**	**0.009**
Third trimester				
HbA_{1c} at 34 weeks (%)‡	**6.54 ± 0.69**	**6.37 ± 0.58**	**0.07**	**0.001**
HbA_{1c} (mmol/mol)	**48 ± 7.7**	**46 ± 6.3**		
Change from randomization to 34 weeks (%)	**−0.32 ± 0.65**	**−0.55 ± 0.59**	**0.01**	**0.001**
At target HbA_{1c} at 34 weeks	**53/102 (52.0)**	**71/109 (65.1)**	**0.07**	**0.001**

Data are means ± SD or *n*/*N* (%). *P* values were adjusted for duration of diabetes, education level, cigarette smoking, and gestational age. ‡Follow-up assessments are at 34 weeks' gestation, except for maternal HbA_{1c}, for which data at 24 weeks' gestation are also provided. Maternal HbA_{1c} data were available for *N* = 109 and 117 at baseline, *N* = 103 and 109 at 24 weeks' gestation, and *N* = 102 and 109 at 34 weeks' gestation (minimum–maximum 32.6–35.9 weeks) for pump and MDI, respectively. †Target HbA_{1c} value was ≤6.5% (48 mmol/mol). Comparisons that are boldface type indicate significant differences ($P < 0.05$).

lower glucose CV in pump users. The nighttime CGM measures followed the same pattern as the combined day and night, with no differences between insulin pump and MDI users (Supplementary Table 1).

Patient-Reported Outcome Measures

There were no significant differences in mean scores on the Blood Glucose Monitoring System Rating Questionnaire or Problem Areas in Diabetes scale between pump and MDI users at 34 weeks (Supplementary Table 3). Mean scores for HFS-II showed a nonsignificant decrease in favor of pump users. There were no differences on the HFS behavior subscale, but the HFS worry subscale favored pump users, who had a larger reduction in hypoglycemia-related anxiety than MDI users (*P* = 0.05). However, pump users reported greater decline in self-rated health and well-being than MDI users on the SF-12 (*P* = 0.02).

Pregnancy Outcomes

There were 225 live births (93%), with 15 early pregnancy losses (6.2%), 1 termination of pregnancy after 20 weeks for congenital malformation (hypoplastic right heart), and 1 stillbirth. There were no neonatal deaths.

Obstetric Outcomes

More pump users had hypertensive disorders of pregnancy, defined as worsening chronic hypertension, gestational hypertension, or preeclampsia (pump 30.6% vs. MDI 15.5%; *P* = 0.011), and more gestational hypertension alone (14.4 vs. 5.2%, respectively; *P* = 0.025). There was no significant difference in gestational weight gain or total daily insulin doses between the groups (Table 3 and Supplementary Table 1). Rates of cesarean delivery were not statistically different between pump and MDI users (73.0 vs. 63.8%; *P* = 0.32).

Neonatal Outcomes

Significantly more infants of pump users had NICU admission for >24 h (44.5 vs. 29.6%; *P* = 0.02). More infants of pump users had neonatal hypoglycemia requiring intravenous dextrose (31.8 vs. 19.1%; *P* = 0.05). There were no between-group differences in birth weight, birth weight centile, birth weight SD scores, or rates of LGA or small for gestational age. There was no difference in hyperbilirubinemia or respiratory distress and no difference in the composite outcome between groups. There was no difference in cord C-peptide levels, infant length of hospital stay, or neonatal anthropometric measures.

CONCLUSIONS

In this observational study of pregnant women who participated in CONCEPTT, we found that when pump and MDI users started pregnancy with similar glycemic control, MDI users had a larger decrease in HbA_{1c} throughout pregnancy, and more MDI users reached the target HbA_{1c} level of <6.5% (48 mmol/mol) at both 24 and 34 weeks' gestation. Pump users spent slightly less time hypoglycemic throughout gestation. We also found that pump users had more gestational hypertension and that their infants had more neonatal hypoglycemia and more NICU admissions >24 h. There were no differences in neonatal birth outcomes. Unlike previous studies (8,10,11,13), diabetes duration, maternal age, and baseline rates of microvascular complications were comparable.

Although we made every effort to adjust for baseline differences in maternal demographic and diabetes characteristics, women and their caregivers choose their method of insulin delivery, and the reasons for their preferences may underlie the observed differences in obstetric and neonatal outcomes. Another possible explanation for the seemingly disappointing impact of pump therapy on maternal glycemia is that pumps may have been offered to women with more challenging diabetes. Real-world data suggest that insulin pump users have higher HbA_{1c} levels when starting pump therapy compared with non–pump users and are more likely to be female and aged 20–30 years (24). Although glycemic control measured both by HbA_{1c} and CGM (time in target, time above target, and glucose variability measures) were similar between the groups at the time of enrollment into CONCEPTT, this does not preclude previous differences at the time of pump therapy initiation.

It is also possible that insulin dose adjustment may be more challenging for pump users during the second half of pregnancy. Pharmacokinetic studies suggest that it takes ~20–30 min longer

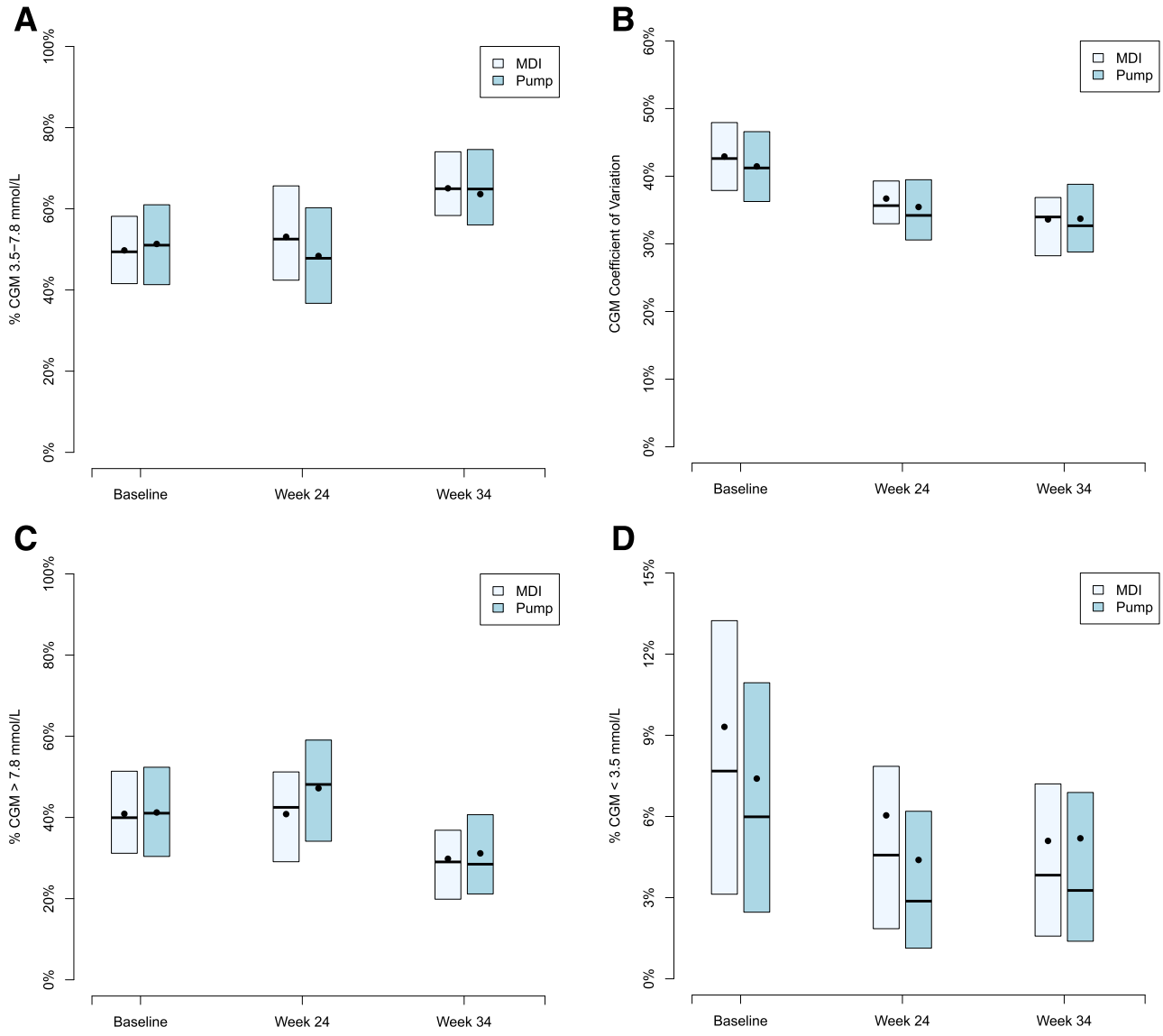

Figure 1—*A*: Percentage of time in target range (63–140 mg/dL). The percentage of time in target mean ± SD increased during pregnancy, with no between-group differences for insulin modality ($P = 0.40$). *B*: CGM glucose CV. Glycemic variability as measured by CV median (interquartile range) decreased during pregnancy, with a nonsignificant trend favoring less variability in insulin pump users ($P = 0.07$). *C*: Percentage time above target (>140 mg/dL). The percentage time spent above target median (interquartile range) decreased during pregnancy, with no between-group differences ($P = 0.86$). *D*: Percentage time below target (<63 mg/dL). The percentage time spent below target median (interquartile range) decreased during pregnancy and was lower throughout pregnancy in insulin pump users ($P = 0.03$).

for prandial insulin administered by pump to reach maximal plasma concentrations at 28 weeks' compared with 12 weeks' gestation (25). Furthermore, the day-to-day variability in prandial insulin pharmacokinetics increases during the second and third trimesters (26). It is unclear to what extent these physiological and pharmacokinetic differences also affect MDI users. The marked variability in prandial insulin pharmacokinetics may be most apparent among pump users who require substantial intensification of insulin-to-carbohydrate ratios to optimize prandial insulin doses in late gestation (7,25). In CONCEPTT, insulin pump users spent an additional 1.4 h/day in the hyperglycemic range at 24 weeks' gestation, suggesting that patients and clinicians may not have been sufficiently proactive at increasing the prandial doses and/or encouraging earlier premeal bolusing.

A key advantage of pump therapy is the bolus calculator and the ability to tailor prandial insulin doses according to the macronutrient content of each meal. Additional advantages of using a pump are the ability to tailor basal insulin requirements, i.e., at dawn or at dusk, and to suspend insulin delivery when in or approaching hypoglycemia. On the other hand, MDI users are increasingly counting carbohydrates and using bolus calculators and "smart-pens" to optimize insulin doses. Prandial pump settings are more complicated, and users (and their clinical teams) may struggle with the complexity of bolus delivery patterns (super boluses vs. dual or square wave patterns) to match the systemic absorption of postmeal glucose. While insulin pump settings allow small, precise dose increments, MDI users may be more aggressive

Table 3—Obstetric and neonatal outcomes of CONCEPTT participants using pump and MDI

	Pump	MDI	Unadjusted *P**	Adjusted *P*
Maternal outcomes	***N* = 111**	***N* = 116**		
Hypertensive disorders‡	**34 (30.6)**	**18 (15.5)**	**0.007**	**0.011**
Worsening chronic hypertension	5 (4.5)	1 (0.9)	0.11	N/A
Gestational hypertension	**16 (14.4)**	**6 (5.2)**	**0.02**	**0.025**
Preeclampsia	16 (14.4)	12 (10.3)	0.42	0.31
Cesarean section	81 (73.0)	74 (63.8)	0.15	0.32
Maternal weight gain (kg)				
Entry to 34 weeks	13.5 ± 5.4	13.5 ± 5.7	0.76	0.48
From 16 to 34 weeks	9.3 ± 3.3	9.9 ± 4.0	0.46	0.68
Maternal length of stay (days)	4.2 (2.4–5.3)	3.9 (2.9–6.1)	0.78	0.92
Neonatal outcomes	***N* = 120**	***N* = 122**		
Pregnancy loss <20 weeks	9 (7.5)	6 (4.9)	1.0	N/A
Stillbirth	1	0		
Termination	0	1		
Congenital anomaly§	3	2		
Composite neonatal outcomeΨ	68 (56.7)	56 (45.9)	0.10	0.45
	***N* = 111**	***N* = 116**		
Preterm <37 weeks	48 (43.2)	42 (36.2)	0.34	0.10
Early preterm, <34 weeks	9 (8.1)	7 (6.0)	0.61	N/A
Late preterm, 34–37 weeks	39 (35.1)	35 (30.2)	0.48	0.46
Gestational age at delivery (weeks)	37.3 (36.2–38.0)	37.4 (36.4–38.1)	0.53	0.26
	***N* = 110**	***N* = 115**		
Birth weight (g)◇	3,600 ± 729	3,568 ± 684	0.68	0.91
Z score >1 SD	73 (66.4)	78 (67.8)	0.89	0.75
Z score >2 SD	49 (44.5)	43 (37.4)	0.28	0.34
Mean birth weight percentile	81.5 ± 27.0	83.5 ± 23.7	0.66	0.56
Median birth weight percentile	95.8 (72.0–99.7)	94.4 (79.1–99.6)		
SGA <10th centile	3	1		
LGA >90th centile	70 (63.6)	69 (60.0)	0.59	0.55
Extreme LGA: >97.7th centile	50 (45.5)	43 (37.4)	0.23	0.30
Macrosomia: ≥4,000 g	30 (27.3)	29 (25.2)	0.76	0.89
	N = 110	*N* = 115		
High-level neonatal care (NICU)	**49 (44.5)**	**34 (29.6)**	**0.03**	**0.02**
Neonatal hypoglycemia	**35 (31.8)**	**22 (19.1)**	**0.03**	**0.05**
Hyperbilirubinemia	31 (28.2)	31 (27.0)	0.88	0.94
Respiratory distress	11 (10.0)	8 (7.0)	0.48	N/A
Birth injury	1	0		
Shoulder dystocia	0	1		
Infant length of hospital stay	3.8 (2.2–7.0)	3.3 (2.2–6.6)	0.66	0.44
	***N* = 66**	***N* = 74**		
Cord blood C-peptide (pmol/L)	797.5 (501.5–1,438.2)	729.5 (493.0–1,367.5)	0.79	0.40
Cord blood C-peptide >566 pmol/L (90th centile [HAPO])	41 (62.1)	51 (68.9)	0.48	0.59

Data are means ± SD, *n*, or *n* (%), except for infant length of hospital stay and cord blood C-peptide, which are median (interquartile range). HAPO, Hyperglycemia and Adverse Pregnancy Outcome; N/A, too few events for adjustment by regression modeling; SGA, small for gestational age. **P* values are shown without adjustment/with adjustment for maternal baseline characteristics (diabetes duration, smoking, gestational age at randomization, and educational level). ‡For maternal hypertensive disorders, *N* = 111 pump and 116 MDI includes all women with a live birth, stillbirth, or termination. §Congenital anomalies were aortic stenosis, aberrant right subclavian artery, and hypospadias grade 1 in the pump group and hypoplastic right heart syndrome (termination of pregnancy after 20 weeks' gestation) and congenital bilateral hydronephrosis in the MDI group. ΨComposite outcome: pregnancy loss (miscarriage, stillbirth, neonatal death), birth injury, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress, and high-level neonatal care >24 h. *N* = 105 pump and *N* = 106 MDI. ◇Birth weight is calculated for live births with birth weight percentile using GROW software. Comparisons that are boldface type indicate significant differences ($P < 0.05$).

adjusting insulin doses in response to the increasing gestational insulin requirements. During CONCEPTT, both pump and MDI users were given written instructions to facilitate insulin dose adjustment according to SMBG and CGM glucose levels (17). Unfortunately, we do not have data on the bolus calculator settings or the day-to-day insulin dose adjustment decisions for pump or MDI users.

While differences in laboratory methodology limit between-studies HbA_{1c} comparisons, a key difference between ours and many previous studies is that the glucose levels of CONCEPTT pump and MDI users were both well controlled and comparable at baseline. Other nonrandomized studies, with some exceptions (11,12), included MDI users with suboptimal glucose control (8,10,13).

The Relative Effectiveness of Pumps Over MDI and Structured Education (REPOSE) trial found that among nonpregnant adults with poorly controlled T1D (HbA_{1c} >7.5% or 58 mmol/mol) and no preference for pumps or MDI, both groups had improved glycemic control following diabetes self-management education (27). The REPOSE trial also reported greater improvement in diabetes treatment satisfaction and some

quality of life measures, including increased dietary freedom and decreased daily hassles among pump users (28). Since CONCEPTT participants were not randomized to pump or MDI and had experienced these insulin delivery methods before enrollment, it is not surprising that overall change in patient-reported outcomes did not differ in CONCEPTT.

Hypoglycemia is a major barrier to safely optimizing maternal glycemia, and insulin pump users reported less worry about hypoglycemia, even though the objectively measured difference in time spent <63 mg/dL was quite small. The CONCEPTT MDI users reported less decline in self-rated health and well-being during pregnancy. This was unexpected, and we speculate that it may have been related to the finding that more pump users developed gestational hypertension.

The limitations of HbA_{1c} for assessing glycemic control during pregnancy are well established (29). Our study is, to our knowledge, the first to report directly observed CGM measures of glucose control among pump and MDI users during pregnancy. Although both groups spent similar time in target range (65% or 15.6 h/day) and similar time above target (28% or 6.8 h/day) at 34 weeks' gestation, pump users spent less time in target and more time above target at 24 weeks' gestation, and this may have played a role in the outcomes. Differences in glycemic variability tended to slightly favor insulin pump users, but these were small and not statistically significant. The rates of severe hypoglycemia and diabetic ketoacidosis were low and did not differ between pump and MDI users.

Previous studies report conflicting results regarding insulin doses, gestational weight gain, and rates of LGA in pump and MDI users. An earlier Spanish study found that pump users had less gestational weight gain (8), while another from Poland found higher gestational weight gain presumed to be due to greater dietary flexibility (9). We found no differences in total daily insulin dose, maternal gestational weight gain, or any measure of infant birth weight. The rates of LGA (*Z* score >1 SD or birth weight >90th percentile) and extreme LGA (*Z* score >2 SD or birth weight >97.7th percentile) are high compared with recent Canadian and U.K. studies despite comparable or lower baseline HbA_{1c} and BMI levels (10,30,31). Maternal glycemic control in CONCEPTT compares favorably with that reported in a nationwide study from England and Wales (30); yet, the CONCEPTT babies had substantially higher rates of LGA (>60% LGA compared with 46% in England and Wales) using the same customized birth weight measures. The maternal gestational weight gain of 13.5 kg in CONCEPTT is lower than the 16.3 kg in the Canadian pump study (10). A recent Scottish study suggests that LGA rates are increasing in offspring with T1D (31), suggesting that more research is needed to better understand the detailed patterns of glycemia, dietary patterns, or other factors contributing to the persistently high LGA rates.

It is also hard to explain the high rates of hypertensive disorders and gestational hypertension in CONCEPTT pump users. There were more pump users with baseline hypertension, and this contributed to those with worsening chronic hypertension (although not significantly different). However, this does not explain the increased gestational hypertension. The higher rate of gestational hypertension among pump users could, in part, be explained by the higher rate of smoking in MDI users, which has been found to be protective against maternal hypertensive disorders (32). Interestingly, higher HbA_{1c} levels have been associated with higher rates of preeclampsia (33) but not with gestational hypertension (34). The maternal hypertensive disorders may have contributed to the higher-than-expected rates of NICU admissions in CONCEPTT pump users and to the lack of differences in birth weight–related variables in the two cohorts. Although there were slightly higher categorical rates of preterm delivery before 37 weeks' gestation in pump users (43 vs. 36%), the mean gestation at delivery (37.3 vs. 37.4 weeks) was very similar and probably does not explain the higher rates of NICU admission, which are more likely attributed to the higher rates of neonatal hypoglycemia (32 vs. 19%). The rates of neonatal hypoglycemia treated with intravenous dextrose are similar to most (10,14) but not all (12) previous studies.

Our study has many strengths. It includes a large, carefully characterized cohort of women who participated in a randomized trial; hence, the data were collected prospectively with detailed demographic data to adjust for potential confounders. It was conducted across 31 international sites, so the data are generalizable to current clinical practice. We had both HbA_{1c} and direct CGM measures to evaluate maternal glycemic control and detailed patient-reported outcomes to examine treatment satisfaction. Furthermore, glycemic control was comparable at baseline, with the exception of small differences in hypoglycemia. Both pump and MDI users received comparable diabetes self-management education with written instructions to optimize insulin dose adjustment.

However, there are also several important limitations. Firstly, the CONCEPTT participants were not randomized to insulin pumps or MDI. Although we adjusted for potential confounders, participants' and caregivers' preferences for pump or MDI may have confounded the results, as well as other unknown confounders, such as the clinical team's experience of implementing insulin pump therapy in pregnancy. Unfortunately, we have no record of the day-to-day insulin dose adjustments, the frequency of capillary glucose tests, insulin pump downloads, or use of bolus calculators and therefore cannot comment on the intensification of insulin dosing or whether pump and MDI were optimally implemented. Clinical registry data from three large transatlantic registries of pediatric patients suggest that clinics with higher rates of insulin pump use achieve lower HbA_{1c} (35). We do not have data on the frequency of insulin pump use during pregnancy in CONCEPTT sites. Twenty-five women (19 CGM and 6 control) used insulin pumps with low glucose or threshold suspend features. Unfortunately, data regarding the use or frequency of insulin suspension are not available.

Our study is the first to report detailed CGM and quality of life outcomes in contemporary insulin pump and MDI users. We found that MDI users had a larger decrease in HbA_{1c} and less decline in health and well-being throughout pregnancy. Insulin pump users had less hypoglycemia and less hypoglycemia worry but did not have better glycemic control or pregnancy outcomes. More research is needed to better understand which women benefit from insulin pumps and how clinical teams can implement

new technologies more effectively to optimize glycemic control during pregnancy involving T1D.

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