Parity Increases Insulin Requirements in Pregnant Women With Type 1 Diabetes

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Context: Tight glycemic control throughout pregnancy in women with type 1 diabetes is crucial, and knowledge about which factors that affect insulin sensitivity could improve the outcome for both mother and offspring.

Objective: To evaluate insulin requirements in women with type 1 diabetes during pregnancy and test whether parity affects insulin requirements.

Design: Observational cohort study consisting of women with type 1 diabetes who gave birth at Aarhus University Hospital, Denmark, from 2004 to 2014.

Main Outcome Measure: Daily insulin requirement (the hypothesis that parity could affect insulin resistance was formulated before data collection).

Results: A total of 380 women with a total of 536 pregnancies were included in the study. Mean age was 31.1 years, and prepregnancy hemoglobin A1c was 60 mmol/mol. Parity was as follows: P0, 43%; P1, 40%; P2, 14%; and P3+4, 3%. Insulin requirements from weeks 11 to 16 decreased significantly by 4% ($P = 0.0004$) and rose from week 19 to delivery with a peak of 70% ($P < 0.0005$) at weeks 33 to 36. Overall, insulin requirements increased significantly with parity. The unadjusted differences between P0 and P1, P2, and P3+4 were 9% ($P < 0.0005$), 12% ($P < 0.0005$), and 23% ($P < 0.0011$), respectively. After adjustment for confounders, differences were 13% ($P < 0.0005$), 20% ($P < 0.0005$), and 36% ($P < 0.0005$). We also observed an adjusted difference between P1 and P3+4 of 20% ($P < 0.0012$).

Conclusions: The data show changes in insulin requirements from week to week in pregnancy and indicate that insulin requirements increase with parity. This suggests that the patient's parity probably should be considered in choosing insulin dosages for pregnant women with type 1 diabetes. (***J Clin Endocrinol Metab*** **103: 2302–2308, 2018)**

Alterations in insulin requirements and insulin resistance during pregnancies complicated by diabetes constitute a challenge for both patients and clinicians. Pregnancies in women with type 1 diabetes are associated with an increased risk for congenital malformations, obstetric complications, and neonatal morbidity—a risk that is directly correlated to glycemic control immediately before and during pregnancy (1, 2). Thus, tight glycemic control throughout pregnancy is crucial and can be achieved only if a successful collaboration between patients and clinicians is established.

To allow patients and clinicians to act preventively, knowledge about alterations in insulin requirements over time during pregnancy is essential to enable implementation of appropriate insulin dosage preemptively. During normal pregnancy, high levels of diabetogenic placental hormones lead to a physiological decrease in peripheral insulin sensitivity as pregnancy proceeds (3).

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Abbreviations: BMI, body mass index; CI, confidence interval; HbA1c, hemoglobin 1Ac.

Another factor that could be affecting insulin requirement is parity. Some studies have reported an increase in the incidence of type 2 diabetes with increasing parity (4–6), whereas others have found no such association (7–10). Several of these studies have included a limited number of patients, and the influence of parity on insulin requirement during pregnancy in women with type 1 diabetes remains uncertain.

In type 2 diabetes and gestational diabetes, increasing parity may increase insulin requirement because of exhaustion of the pancreatic β cells due to the high insulin need during pregnancy. In type 1 diabetes, however, there is essentially no insulin production in the β cells. Any increase in insulin requirements with increasing parity would be determined by insulin resistance in target tissues probably related to such factors as age, increasing body mass index (BMI), or altered hormone secretion from the placenta.

The progressions in insulin requirements during pregnancy vary considerably between individuals. Some women experience subtle changes, whereas others have to triple or quadruple insulin doses late in pregnancy.

We and others (11–13) have studied insulin resistance during pregnancy. Insulin resistance can be estimated in different ways; analyzing insulin requirements during pregnancy is one approach. This has previously been done only in relatively small cohorts of patients with type 1 diabetes (11–14).

In the current study, we evaluated insulin requirements during 536 pregnancies in 380 patients with type 1 diabetes. Using the same dataset, we examined whether parity affects insulin requirements.

Patients and Methods

A retrospective observational cohort study was conducted. The cohort consisted of women with type 1 diabetes who gave birth at Aarhus University Hospital, Denmark, between January 2004 and December 2014. All pregnant women with type 1 diabetes residing in Central Denmark Region are treated at Aarhus University Hospital, which is a tertiary center with highly specialized service. The Central Denmark Region has 1.3 million residents and is very diverse in terms of socioeconomic status covering both rural and urban areas. The ethnicity of the cohort was predominantly white (15), but the ethnicity of each participant was not recorded.

Exclusion criteria were multiple pregnancy, stillbirth, termination of pregnancy, and spontaneous abortion.

The women were seen at the outpatient clinic for pregnant women with diabetes at Aarhus University Hospital or contacted by telephone every 2 to 4 weeks from gestational week 4 to week 28 and every 1 to 2 weeks from week 28 to delivery. A diabetologist adjusted insulin dose according to current hemoglobin 1Ac (HbA1c) and the patient's own daily recordings of fasting and postprandial glucose measurements. The target HbA1c values for pregnant women with type 1 diabetes were according to the Danish National Guidelines: 48 mmol/mol (6.5%) before gestational week 20 and 37 mmol/mol (5.6%) after gestational week 20 (16). Diabetes regulation was managed by self-monitoring of glucose and insulin adjustments, aiming at capillary plasma glucose levels of 4 to 6 mmol/L preprandial and 4 to 8 mmol/L 1.5 hours postprandial. An obstetrician or a sonographer obtained serial ultrasound scans to monitor fetal growth, and a dietitian gave nutritional advice.

From the patients' medical records, we obtained the following data at every visit: daily insulin requirements, current HbA1c, and weight. We also extracted the following prepregnancy data: weight, height, parity, last known daily insulin dosage before pregnancy, last known HbA1c (not older than 6 months), and number of years since diabetes onset (duration of diabetes). Relevant data on the offspring, such as gestational age at delivery, sex, and birth weight, were also obtained.

Daily insulin requirement was calculated by adding long-acting and short-acting insulin. The mean daily insulin requirement was determined at the following time intervals: prepregnancy, weeks 5 to 10, weeks 11 to 14, weeks 15 to 18, weeks 19 to 22, weeks 23 to 28, weeks 29 to 32, weeks 33 to 36, and weeks 37 to 40.

Our primary outcome was mean daily insulin requirement (IU) at the above-mentioned time intervals. Secondary outcomes were (1) percentage change from prepregnancy insulin requirement at the above-mentioned time intervals, (2) the effect of parity on mean daily insulin requirement for the whole pregnancy, and (3) the effect of fetal sex on insulin requirement.

The Danish Health Authority (no. 3-3013-625/1) and the Danish Data Protection Agency (no. 1-16-02-347-14) approved our study.

Statistics

The Biostatistical Advisory Service at the Faculty of Health, Aarhus University, helped perform all statistical analyses by using the statistical software Stata 13 (Stata Corp., College Station, TX). Continuous data are expressed as mean with standard deviation and categorical variables as percentages. Repeated-measurement analysis of variance was used to compare the paired data between the groups. Both the repeated measurements in every pregnancy and the repeated measurements for each of the woman's pregnancies were taken into account by using nested random effects in a mixed model. Measurements were analyzed on log scale, and results were back-transformed to obtain relative comparisons.

Model validation was performed by visual inspection of residuals, fitted values, and random effect estimates, which did not give cause to reject the model. For the subgroup analyses, paired t test was used. Statistical significance was defined as $P < 0.05$.

Five different models were made to adjust for factors that could affect insulin requirement: (1) unadjusted; (2) adjusted for prepregnancy BMI; (3) adjusted for prepregnancy BMI and age; (4) adjusted for prepregnancy BMI, age, and prepregnancy HbA1c; and (5) adjusted for prepregnancy BMI, age, prepregnancy HbA1c, and duration of diabetes.

Results

We reviewed 583 pregnancies. Exclusion criteria were multiple pregnancy (n = 34), stillbirth (n = 3), termination

of pregnancy (n = 5), spontaneous abortion (n = 2), and missing data (n = 3). Thus, 380 women with a total 536 pregnancies were included in the study. Several of the women gave birth more than once within the time period. Two hundred thirty-six women (62%) gave birth once, 132 women (35%) gave birth twice, and 12 women (3%) gave birth three or four times. Table 1 presents the clinical features of each pregnancy in the cohort. When we divided the cohort into parity groups (P0, P1, P2, and P3+4), we found no statistical difference in prepregnancy BMI or prepregnancy HbA1c between the groups.

We compared duration of diabetes among the groups and, as expected, found that the P0 group had statistically significantly shorter diabetes duration, at 14.4 years, than the P1 group, at 15.6 years, and P2 group, at 16.7 years. The P3+4 group, however (n = 16), had an even shorter duration, at 12.8 years, probably due to the small number of included individuals and the influence of a few extremes affecting the average.

Mean age overall was 31.1 years, and age increased, also as expected, with parity: P0, 29.1 years; P1, 32.0 years; P2, 33.6 years; and P3+4, 36.7 years. Mean HbA1c was 55.0 mmol/L [95% confidence interval (CI), 54.7 to 55.4 mmol/L], 48.3 mmol/L (95% CI, 48.1 to 48.6 mmol/L), and 48.3 mmol/L (95% CI, 48.0 to 48.5 mmol/L) for first, second, and third trimesters, respectively.

Mean daily insulin requirements at the different time intervals for all included pregnancies (n = 536) are shown in Fig.1. Figure 1 also shows the mean daily insulin requirements in percentages relative to prepregnancy levels. Insulin requirements at weeks 11 to 16 decreased significantly by 4% (95% CI, 2% to 6%; $P = 0.004$) and rose significantly from week 19 to delivery, with a peak at weeks 33 to 36 at 70% (95% CI, 65% to 75%; $P < 0.0005$), relative to prepregnancy levels. After week 37, the insulin requirement decreased and terminated at 66% (95% CI, 59% to 72%) relative to prepregnancy levels.

Table 1. Demographic Characteristics of Patients With Type 1 Diabetes Included in Study

	Parity				
Variable	**P0**	**P1**	**P2**	**P3+4**	**All**
Patients, n (%)	229 (43)	216 (40)	75 (14)	16 (3)	536 (100)
Age, y	29.1	32.0	33.6	36.7	31.1
Duration of diabetes, y	14.4	15.6	16.7	12.8	15.2
Prepregnancy HbA1c					
In mmol	60	59	62	65	60
In %	7.6	7.5	7.8	8.1	7.6

A total of 380 women gave birth 536 times. Two hundred thirty-six women (62%) gave birth one time, 132 women (35%) gave birth two times, and 12 women (3%) gave birth three times.

When comparing mean daily insulin requirements for the entire pregnancy, we found that insulin requirements increased with parity. Figure 2 shows how mean daily insulin requirement developed during pregnancy for P0, P1, and P2.

The unadjusted differences between P0 and P1, P2, and P3+4 were 9% (95% CI, 4% to 14%; $P < 0.0005$,), 12% (95% CI, 4% to 20%; $P < 0.0005$), and 23% (95% CI, 5% to 44%; $P = 0.011$), respectively. To avoid any confounding, we adjusted for age, prepregnancy BMI, prepregnancy HbA1c, and duration of diabetes. After adjustment for all four variables, the differences between P0 and P1, P2, and P3+4 were 13% (95% CI, 8% to 18%; $P < 0.0005$), 20% (95% CI, 12% to 30%; $P < 0.0005$), and 36% (95% CI, 17% to 38%; $P < 0.0005$), respectively. An additional significant difference between P1 and P3+4 in mean daily insulin requirements of 20% (95% CI, 4% to 39%; $P = 0.012$) was found. Table 2 presents all estimates, both unadjusted and adjusted.

To confirm our results, we performed a subgroup analysis that included only women who were in the cohort more than once (n = 147). We compared mean daily insulin requirements in the woman's first pregnancy in the cohort with her subsequent pregnancies. We found a significant difference in insulin requirement between the pregnancies of 11% (95% CI, 9% to 13%; $P < 0.0005$). This was across all parities. Table 3 shows all estimates and 95% CIs for comparisons of the parities.

The sex ratio at birth (live male newborns/total live newborns) in our study was 0.496, and we found no difference in mean daily insulin requirements when comparing women with male offspring and female offspring (data not shown).

Discussion

The fall and rise in insulin requirements during pregnancy are well known. The S-shaped curve has been reported before (11, 14), but here we have clearly confirmed it with a large number of participants. The decrease in insulin requirements around weeks 10 to 14 is important to acknowledge in order to avoid hypoglycemia in early pregnancy. With our results, we have attained a more detailed estimate of this decrease, and we hope this will help lower the incidence of potentially dangerous hypoglycemia in early pregnancy (17, 18). We have also identified the time span within which the rapid increase in insulin requirements occurs, thereby allowing clinicians to reduce hyperglycemia and maintain steady and tight glycemic control during the last part of the pregnancy.

In addition, we have established that after the maximal insulin requirement levels are reached around week 37, a minor decline of 4% is observed. It is well known that a

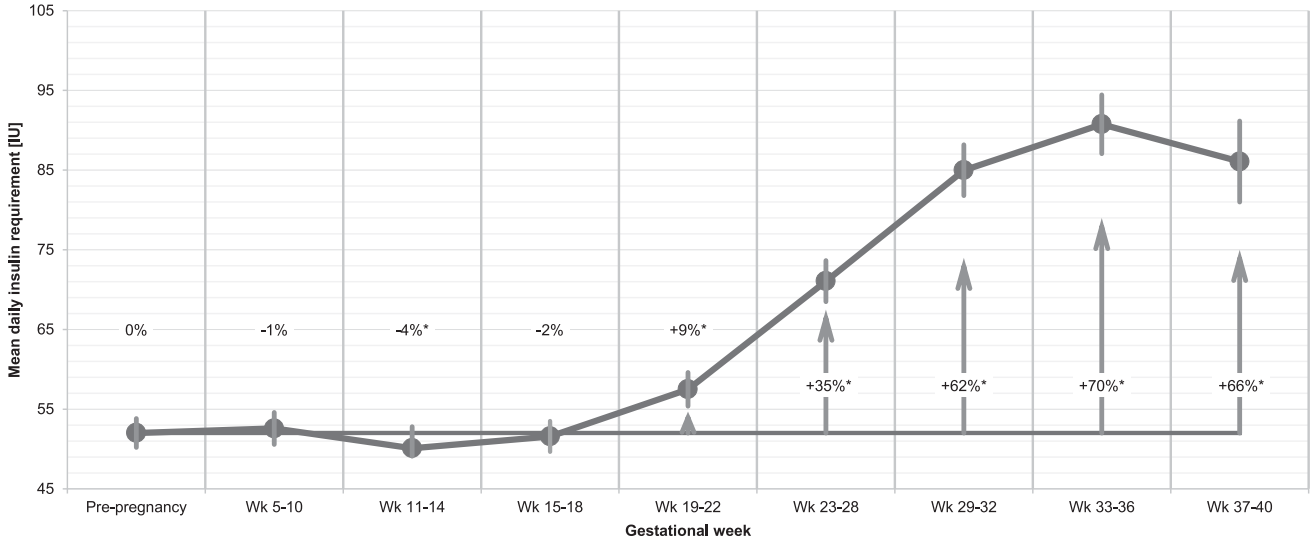

Figure 1. Mean daily insulin requirements at the different time intervals for all included pregnancies (with 95% CI error bars). The dashed line represents the prepregnancy insulin requirement, and numbers in percentages indicate the increase or decrease in percentage relative to prepregnancy levels. *Statistical significance ($P < 0.05$).

decline in insulin requirement of ≥15% in late pregnancy can be a sign of placental insufficiency (19). The observed 4% decline is probably a part of the normal type 1 diabetes pregnancy and should not by itself lead to induction of birth.

Finally, we established that parity is a factor that should be considered when treating pregnant women with type 1 diabetes. We have found a statistically and clinically significant difference in mean daily insulin requirement during pregnancy between the P0 group and P1, P2, and P3+4 groups at 9%, 12%, and 23% respectively. Because this difference could be due to a difference between the groups in BMI, age, or prepregnancy HbA1c, we also presented an adjusted model, which increased the differences to 13%, 20%, and 36%, respectively. In addition, after adjustment we found a significant difference between the P1 group and P3+4 group of 20%.

In our subgroup analysis, where we compared mean daily insulin requirement in the woman's first pregnancy in the cohort with the following pregnancy, we were able to confirm these findings, thereby diminishing the effect of variation between individuals. This further strengthens the concept that parity predicts increased insulin requirements as this clearly shows how women who had given birth several times in our cohort increased their individual total insulin requirement during pregnancy with each pregnancy. Furthermore, when we looked at

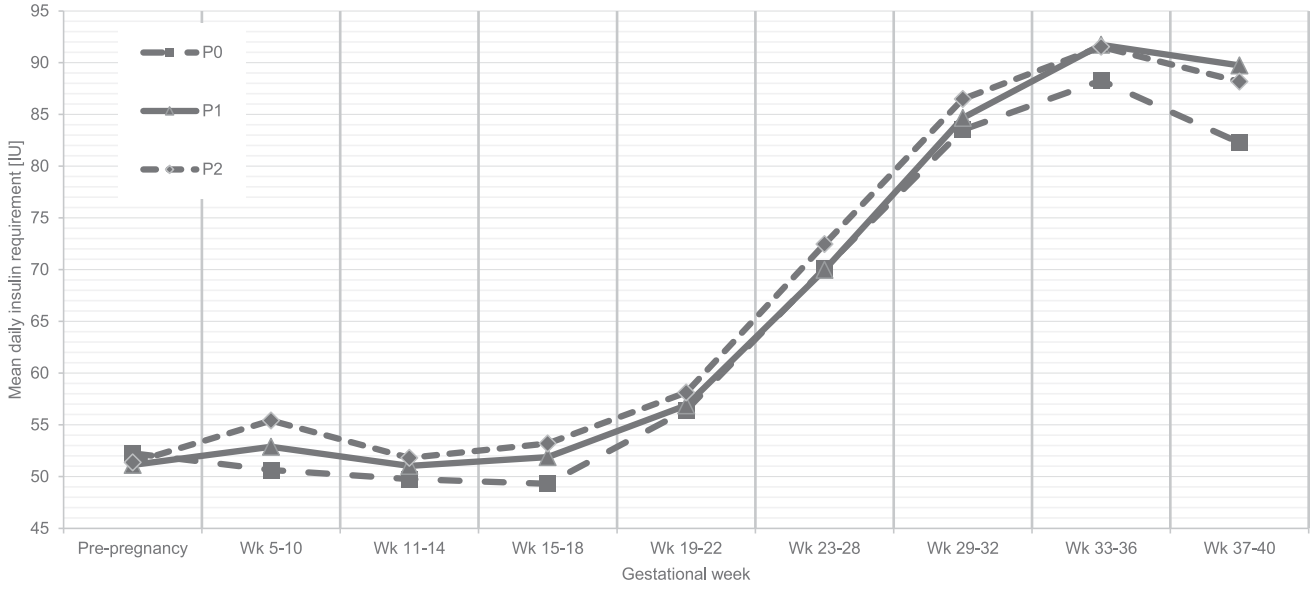

Figure 2. Difference in mean daily insulin requirement at the different time intervals between parity groups.

Table 2. Comparison of Total Insulin Requirement for Whole Pregnancy Between Parity Groups: Unadjusted and Adjusted

	Insulin Requirement per Parity Group (%)		
Model	**P1**	**P2**	**P3+4**
Unadjusted			
P0	9[a] (4.3–13.6)	12[a] (3.9 to 20.4)	23[a] (4.9 to 43.8)
P1		3 (−4.2 to 10.1)	13 (−3.6 to 32)
P2			10 (−5.8 to 28.1)
Adjusted for BMI			
P0	8[a] (3.4–12)	10[a] (3.2 to 18.3)	17[a] (1.5 to 35.6)
P1		3 (−3.7 to 9.5)	9 (−5.6 to 26)
P2			6 (−9.6 to 22.4)
Adjusted for BMI and Age			
P0	15[a] (9.9–20.3)	25[a] (15.2 to 34.6)	40[a] (20.0 to 64.6)
P1		8[a] (1.4 to 15.7)	22[a] (5.1 to 41.2)
P2			12 (−2.4 to 29.6)
Adjusted for BMI, age, prepregnancy HbA1c			
P0	13[a] (8.2–18.3)	21[a] (11.5 to 30.2)	34[a] (15.5 to 56.3)
P1		6 (−0.3 to 13.7)	19[a] (2.8 to 37.1)
P2			11 (−2.9 to 28.0)
Adjusted for BMI, age, prepregnancy HbA1c, and duration of diabetes			
P0	13[a] (8.1–18.2)	20[a] (11.5 to 30.1)	36[a] (16.8 to 58.1)
P1		7 (−0.2 to 13.8)	20[a] (4.1 to 38.9)
P2			13 (−1.7 to 29.6)

[a] Statistically significant ($P < 0.05$).

the insulin requirements before pregnancy, we found no difference between parity groups, indicating that the difference observed only concerns pregnancy.

The mechanisms behind the parity-associated increase in insulin requirements are unknown. Studies have shown that anthropometric measures increase with parity and that this could influence insulin resistance (20, 21). Although we did not find any difference when we adjusted for BMI, other anthropometric measures (*e.g.,* subcutaneous fat or intra-abdominal fat) could increase with parity and thereby influence our findings (22).

Sex of the offspring could also potentially affect the insulin resistance. The sex ratio at birth in the general population is 0.515 (23), and in a cohort like ours, Garcia-Patterson *et al.* (24) found a sex ratio at birth at 0.509. Our sex ratio at birth at 0.496 was, as expected, not significantly different from any of the cohorts mentioned. Male fetuses are known to grow faster in the womb, be larger at birth, and have more efficient placentas (25–27). Moreover, women carrying a male fetus have a higher risk of developing gestational diabetes (28). We thus hypothesized that male fetuses for this reason could make the mother more insulin resistant during pregnancy, but our analysis did not show any difference in insulin requirement between mothers with male and female offspring.

A possible mechanism for the observed increase in insulin requirements with parity could be pregnancy-induced endogenous insulin secretion (29, 30). It could be speculated that during the first pregnancy, there is limited residual endogenous insulin secretion that is attenuated during the next pregnancies. Unfortunately, we have no measurements of C-peptide to support such a hypothesis.

Exercise and diet could also change with parity. It could be that mothers of more than one child have less time for exercise and healthy eating during pregnancy. This would negatively affect insulin sensitivity and thus increase insulin requirement. Because of the lack of available data on these possible confounders, we were not able to adjust for them.

We did not record the patients' ethnicity, and this could be a weakness in our study. We know that ethnicity affects insulin sensitivity, and this too could be a confounder. Our cohort consisting of Danish women is, however, almost exclusively white and thus highly ethnically homogeneous. Hence, the influence of ethnicity in this study must be inconsiderable.

Our study is to our knowledge the largest study on insulin requirements during pregnancy to date, which is an obvious strength and produces convincingly low *P* values and narrow CIs.

In conclusion, our data show that parity *per se* increases insulin requirements during pregnancy between 9% and 36% in type 1 diabetes and confirm that insulin dosages exhibit a characteristic pattern with a modest early decrease and a pronounced late increase during

Table 3. Subgroup Analysis: Comparison of Total Insulin Requirement for Whole Pregnancy Between Parity Groups: Unadjusted and Adjusted

	Insulin Requirement per Parity Group (%)		
Model	**P1**	**P2**	**P3+4**
Unadjusted			
P0	11[a] (5.7–16.0)	15[a] (5.4 to 25.3)	44[a] (20.2–73.3)
P1		4 (−4.2 to 12.5)	30[a] (8.7–56.3)
P2			26[a] (5.5–49.4)
Adjusted for BMI			
P0	8[a] (3.5–13.2)	12[a] (2.7 to 20.9)	31[a] (10.5–56.1)
P1		3 (−4.5 to 11.0)	21[a] (2.3–43.9)
P2			18[a] (0–38.8)
Adjusted for BMI and age			
P0	17[a] (10.9–24.2)	31[a] (18.0 to 46.0)	65[a] (35.8–101)
P1		12[a] (2.9 to 21.5)	41[a] (17.6–68.4)
P2			26[a] (6.7–48.4)
Adjusted for BMI, age, and prepregnancy HbA1c[a]			
P0	15[a] (8.5–21.3)	27[a] (13.9 to 40.6)	59[a] (30.9–91.8)
P1		10[a] (1.6 to 19.7)	38[a] (16.0–64.5)
P2			25[a] (6.7–47.1)
Adjusted for BMI, age, prepregnancy HbA1c, and duration of diabetes			
P0	15[a] (8.2–21.1)	26[a] (13.4 to 40.2)	59[a] (30.6–91.5)
P1		7[a] (1.5 to 19.6)	39[a] (16.0–64.6)
P2			25[a] (6.8–47.3)

[a]Statistically significant ($P < 0.05$).

pregnancy. Furthermore, the large number of participants in our study has yielded more accurate information on how parity affects insulin requirements in pregnant women with type 1 diabetes and shows that the more times a woman with type 1 diabetes gives birth, the more insulin she needs. The finding of increasing insulin requirements with increasing parity is not only a highly interesting physiological observation. Our findings also provide valuable information the clinician can use to achieve tight glycemic control throughout pregnancy. They indicate that adjustment of insulin doses should consider not only HbA1c values, blood glucose values, fetal size, and awareness but also the patient's parity.

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