Increased Insulin Requirements in Twin Pregnancy in Type 1 Diabetes

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During pregnancy in type 1 diabetes, insulin requirements increase from the second trimester onward, reaching maximum in the third trimester. In twin pregnancies, the larger placental mass leads to elevated circulating levels of placental hormones, many of which have been attributed to the insulin resistance of pregnancy (1,2). Hence, higher insulin requirements are anticipated in twin pregnant women with type 1 diabetes. Only one study has reported longitudinal insulin requirements during twin pregnancy; the research showed larger increments in insulin doses until mid-gestation among twin pregnant women but no differences in absolute insulin requirements (3).

A retrospective case-control study was undertaken in all identifiable twin pregnant women at Aarhus University Hospital between 2000 and 2018 ($n = 27$) and 81 singleton pregnant women with type 1 diabetes, matched 1:3 on maternal age and year of delivery. Nine women had repeat pregnancies with twin and singleton pregnancies.

Clinical data, insulin doses, and hemoglobin A_{1c} (HbA_{1c}) values were recorded. During the study period, guidelines for handling pregnant women with type 1 diabetes remained essentially unchanged. Data collection was approved by the regional health data authorities and the Danish Health Authority.

Twin and singleton pregnant women were comparable with regard to age, parity, prepregnancy BMI, smoking, duration of diabetes, and route of insulin administration (pen/pump) (Table 1). Gestational age at delivery was lower in twin pregnancies ($P < 0.001$). A total of 12 and 22 out of 27 twin pregnancies ended before gestational weeks 34^{+0} and 37^{+0}, respectively, compared with 4 and 23 out of the 81 singleton pregnancies.

The increments in insulin requirements between weeks 12 and 28 were significantly larger in twin pregnancies (31.0 IU [range: −28 to 96] vs. 17.5 IU [range: −16 to 91]; $P = 0.002$). Significantly higher insulin requirements were observed in second and early third trimester pregnancy in twin pregnant women compared with singleton pregnant women (two-way repeated measures [RM] ANOVA: $P = 0.039$) and were most pronounced around gestational week 28 (twins vs. singletons: $P = 0.003$). Thus, around gestational week 28, insulin requirements were ∼40–45% higher in the twin group compared with the singleton group, with a less pronounced difference of 15–20% in week 32. Insulin requirements converged in late third trimester pregnancy. No differences in HbA_{1c} levels were observed between groups. In confirmation of these findings, we observed that women with repeat pregnancies had higher insulin requirements during the second and third trimesters in twin pregnancy compared with their singleton pregnancies (two-way RM ANOVA; $P = 0.019$ for twins vs. singletons; $P < 0.001$ for gestational age; week 28 twins vs. singletons: $P = 0.007$) at similar HbA_{1c} levels.

In essence, analysis of changes in insulin requirements expressed as percent of first trimester levels and as IU insulin per kilogram pregestational body weight gave similar results.

During twin pregnancy, we observed a substantial increase in insulin requirements from the second trimester onward until a maximum was reached around gestational weeks 28–32. We confirm the near-double increase in insulin requirements from the second to the third trimester (3), and we further extend these findings, as statistically and clinically significant higher third trimester insulin requirements are observed in twin pregnancy in women with type 1 diabetes. Intriguingly, the largest differences in insulin requirements between twin and singleton pregnancies were observed in mid- to late gestation, whereupon converging insulin requirements were observed. Stable insulin requirements in third trimester twin pregnancy as observed here have been reported previously (3). The last trimester of pregnancy is dominated by fetal growth, whereas enlargement of maternal tissues occurs beginning in early trimesters (4). Furthermore, fetal

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Table 1—Clinical characteristics of twin and singleton pregnant women with type 1 diabetes

	Twin pregnancy (n = 27)	Singleton pregnancy (n = 81)	P value
Age (years)	31.0 ± 4.9	30.9 ± 5.0	0.86
Parity	0 (0–3)	1 (0–3)	0.11
BMI (kg/m^2)	26.7 (19.7–42.2)	25.0 (17.4–35)	0.14
ART* (yes/no)	14 (54)/12 (46)	5 (6)/75 (94)	$P < 0.001$
Chorionicity (MC/DC)	5 (23)/22 (77)		
Duration of type 1 diabetes (years)	15.1 ± 7.8	14.7 ± 8.9	0.70
Hypothyroidism (yes/no)	2 (7)/25 (93)	5 (6)/76 (94)	1.00
HbA_{1c}, week 12			
mmol/mol	53 (38–79)	50 (30–82)	0.39
%	7.0 (5.6–9.4)	6.7 (4.9–9.7)	
HbA_{1c}, week 32			
mmol/mol	47 (37–65)	45 (33–72)	0.21
%	6.5 (5.5–8.1)	6.3 (5.2–8.7)	
Insulin dose, week 12 (IU)	50 (22–115)	46 (12–123)	0.62
Insulin dose, week 20 (IU)	60 (21–137)	49 (14–137)	0.17
Insulin dose, week 28 (IU)	91 (41–196)	63 (21–186)	0.003
Insulin dose, week 32 (IU)	91 (24–265)	76 (27–226)	0.008
Insulin dose, week 34 (IU)	84 (40–223)	79 (20–260)	0.23
Preeclampsia*	6 (22)/21 (78)	9 (11)/70 (89)	0.20
Gestational age at delivery (days)	237 ± 21	265 ± 12	$P < 0.001$
Gestational age at delivery (weeks)	$33^{+6} \pm 3^{+0}$	$37^{+6} \pm 1^{+5}$	
Total birth weight at delivery (g)	4,612 ± 1,334	3,653 ± 619	$P < 0.001$
Birth weight z score vs. singleton	4.02 (0.24–9.74)	1.01 (−0.97 to 3.62)	$P < 0.001$
Placental weight (g)†	1,050 ± 217	752 ± 174	$P < 0.001$

Data are given as mean ± SD, median (range), or number (%). Birth weight z scores were calculated from a contemporary background population of approximately 22,900 singleton and 1,400 twin deliveries in women without diabetes. ART, assisted reproductive techniques; DC, dichorionic twins; MC, monochorionic twins. *Information on ART and preeclampsia was missing for one and two patients, respectively, in each group. †Placental weights were available for 26 and 74 deliveries, respectively.

growth rates in twin pregnancy level off after week 32 (5). Thus, both a shift from an anabolic to a more catabolic maternal metabolism and third trimester twin growth trajectories would be coherent with less increments in maternal insulin requirements in late twin pregnancy compared with singleton pregnancy.

A major strength in the current study is the inclusion of women with repeat pregnancies for the study of twin and singleton gestation. A weakness is that despite being the largest study on twin pregnancies in women with type 1 diabetes to date, only a modest number of twin pregnancies are included. A high prevalence of preterm deliveries in the twin group should be taken into account.

In conclusion, increased insulin requirements in twin pregnancy in type 1 diabetes is observed in the second trimester and the early but not late third trimester. Caregivers should recognize this observation to optimize glycemic control during twin pregnancy in type 1 diabetes. The differentiated trajectories of insulin requirements between twin and singleton pregnancy remains to be explained.

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References

1. Spellacy WN, Buhi WC, Birk SA. Human placental lactogen levels in multiple pregnancies. Obstet Gynecol 1978;52:210–212

2. McIntyre HD, Chang AM, Callaway LK, et al.; Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group. Hormonal and metabolic factors associated with variations in insulin sensitivity in human pregnancy. Diabetes Care 2010;33:356–360

3. Callesen NF, Ringholm L, Stage E, Damm P, Mathiesen ER. Insulin requirements in type 1 diabetic pregnancy: do twin pregnant women require twice as much insulin as singleton pregnant women? Diabetes Care 2012;35:1246–1248

4. Butte NF, Ellis KJ, Wong WW, Hopkinson JM, Smith EO. Composition of gestational weight gain impacts maternal fat retention and infant birth weight. Am J Obstet Gynecol 2003;189:1423–1432

5. Ong S, Lim MN, Fitzmaurice A, Campbell D, Smith AP, Smith N. The creation of twin centile curves for size. BJOG 2002;109:753–758