Insulin Requirements in Type 1 Diabetic Pregnancy

Do twin pregnant women require twice as much insulin as singleton pregnant women?

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OBJECTIVE—To evaluate the insulin requirements in women with type 1 diabetes during twin pregnancy compared with singleton pregnancy.

RESEARCH DESIGN AND METHODS—At 8, 14, 21, 27, and 33 gestational weeks, insulin requirements and HbA_{1c} were compared between 15 twin pregnant women from 2000 to 2011 and 108 singleton pregnant women from 2004 to 2006.

RESULTS—In twin pregnancies, the weekly increase in daily insulin dose between 14 and 27 weeks was higher than in singleton pregnancies (median 3.0 international units [IU] [range 0.9–4.9] versus 1.5 IU [−1.5 to 5.9]; $P = 0.008$) and remained stable from 27 to 33 weeks. The increment in total insulin requirement from before pregnancy until 33 weeks tended to be higher in twin pregnancies (103% [36–257%] versus 71% [−20 to 276%]; $P = 0.07$). Throughout pregnancy, HbA_{1c} was similar in twin and singleton pregnancies.

CONCLUSIONS—In twin pregnancies, the weekly increase in insulin dose between 14 and 27 weeks was doubled compared with singleton pregnancies.

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Based on clinical experience, some clinicians expect a doubling of insulin requirement in third trimester of twin pregnancies compared with singleton pregnancies in women with type 1 diabetes. As no studies have investigated the insulin requirement during twin pregnancy, we investigated this in women with type 1 diabetes during twin pregnancy compared with that in singleton pregnancies.

RESEARCH DESIGN AND METHODS

—A retrospective study including all twin pregnancies in women with type 1 diabetes referred to our center during 2000–2011. Data were available for 15 out of 16 twin pregnancies identified.

For comparison, 108 prospective singleton pregnant women with type 1 diabetes and previously studied relevant available clinical data from the same center during 2004–2006 were included (1).

At 8, 14, 21, 27, and 33 weeks weight, HbA_{1c}, insulin dose, and blood pressure were recorded, and a urine dipstick test was taken to screen for proteinuria. Total insulin doses are presented to focus on the usefulness of the data in the clinical setting. Data on insulin dose after 33 weeks were not available for the twin pregnancies due to high rate of preterm delivery.

The patients registered their self-monitored plasma glucose (SMPG) values in diabetes diaries, which were evaluated at each clinical visit. The values were not downloaded electronically from the glucose monitors. Patients were instructed to perform self-adjustments of insulin dose in between clinical visits based on the SMPG profiles of the previous 3 days to maintain preprandial SMPG of 4.0–6.0 mmol/L, 90 min postprandial SMPG of 4.0–8.0 mmol/L, and prebedtime SMPG of 6.0–8.0 mmol/L. Insulin dose was adjusted further at each visit after their caregiver reviewed their SMPG profiles. HbA_{1c} <5.6% in second part of pregnancy was recommended (1). Overall, patient management remained fairly unchanged during the study period.

Diabetic retinopathy was diagnosed with retinal photos at inclusion (2).

The study was approved by the Danish Data Protection Agency. According to Danish law, the regional committees for ethics and science did not have to be contacted.

Statistical analysis

Data are given as median (range) or number (%). Differences between groups were analyzed using χ^2 test or Fisher's exact test, as appropriate, for categorical variables and by Kruskal-Wallis or Mann-Whitney tests when appropriate for continuous variables.

The median increment in total insulin requirement during pregnancy was based on each patient's change in insulin dose from before pregnancy until 33 weeks.

Statistically significant differences were defined as $P < 0.05$.

RESULTS

—Patient characteristics are shown in Table 1. The changes in total insulin requirement during twin pregnancy were as follows: a small increase from before pregnancy until 8 weeks, a decrease from 8 to 14 weeks, a substantial increase from 14 to 27 weeks, and from 27 to 33 weeks, the insulin requirement was almost stable (Table 1).

Insulin requirements before pregnancy until 14 weeks were comparable in twin and singleton pregnancies. Between 14 and 27 weeks, the weekly increase in total insulin dose was higher in twin pregnancies compared with singleton pregnancies (3.0

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Table 1—*Patient characteristics in 15 twin pregnancies and 108 singleton pregnancies among women with type 1 diabetes*

	Twin pregnancies (n = 15)	Singleton pregnancies (n = 108)	P value
Maternal age (years)	31 (21–39)	30.5 (21–42)	0.83
Duration of diabetes (years)	11 (1–20)	16 (1–36)	0.03
Gestational age at inclusion (days)	58 (45–85)	61 (37–94)	0.55
BMI before pregnancy (kg/m^2)	23.0 (18.8–27.3)	24.3 (17.3–43.8)	0.01
HbA$_{1c}$ at first visit (%)	6.7 (5.5–7.5)	6.6 (4.9–10.5)	0.90
HbA$_{1c}$ at 33 weeks (%)	6.0 (5.5–6.9)	5.9 (4.8–7.3)	0.55
Insulin type (human insulin/insulin analogs)	6 (40)/9 (60)	60 (56)/48 (44)	0.26
Multiple injections/CSII	14 (93)/1 (7)	103 (95)/5 (5)	0.55
Microalbuminuria/diabetic nephropathy*	0/0	10 (9)/6 (6)	0.56
Antihypertensive treatment at inclusion	1 (7)	15 (14)	0.69
Diabetic retinopathy	8 (53)	60 (59)†	0.66
Chorionicity (dichorionic/monochorionic)	14 (93)/1 (7)	—	—
Conception (spontaneous/insemination/stimulation, IVF, ICSI)	7 (47)/2 (13)/6 (40)	—	—
Insulin dose before pregnancy (IU/day)	45 (21–79)	50 (22–102)	0.14
Insulin dose at 8 weeks (IU/day)	50 (13–72)	54 (25–114)	0.25
Insulin dose at 14 weeks (IU/day)	42 (18–72)	50 (22–110)	0.07
Insulin dose at 21 weeks (IU/day)	64 (20–80)	58 (27–111)	0.51
Insulin dose at 27 weeks (IU/day)	86 (42–126)	72 (29–148)	0.10
Insulin dose at 33 weeks (IU/day)	92 (60–157)	90 (43–198)	0.60
Preterm delivery (before 37 weeks)	11 (73)	23 (21)	<0.0001
Pre-eclampsia‡	3 (20)	9 (8)	0.16
Birth weight (g)	2,540 (548–3,455)	3,504 (2,040–5,620)	<0.0001
Total placental weight (g)	1,220 (682–1,550)	700 (400–1,030)§	<0.0001

Data are median (range) or n (%). CSII, continuous subcutaneous insulin infusions; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization. *Microalbuminuria: urine albumin excretions ≥30 mg/24 h; diabetic nephropathy: urine albumin excretions ≥300 mg/24 h based on two 24-h urine albumin excretions at inclusion. †n = 101. ‡Pre-eclampsia: either systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, and urinary albumin excretion >300 mg/24 h or ≥1+ on a sterile midstream urine dipstick after 20 weeks of gestation. §n = 43.

international units [IU] [0.9–4.9] versus 1.5 IU [−1.5 to 5.9]; P = 0.008).

The median increment in total insulin requirement during pregnancy tended to be higher in twin pregnancies compared with singleton pregnancies (a median increase of 103% [36–257%] versus 71% [−20 to 276%]), giving a 45% higher increase in the twin pregnancies (P = 0.07).

If insulin requirement was expressed in IU per kilogram and not as total insulin dose, a similar pattern of changes was seen for both groups (data not shown).

HbA$_{1c}$ was comparable throughout pregnancy in the two groups (Table 1).

The total placental weight was 74% higher in twin pregnancies ($P < 0.0001$). The total birth weight of twin pairs was 45% higher than that of singletons (Table 1).

CONCLUSIONS—This study documented a doubling of the weekly increase in total insulin requirement between 14 and 27 gestational weeks in twin pregnancies as compared with singleton pregnancies in women with type 1 diabetes.

The strength of this study is that the overall strategy of the insulin therapy in the patients was the same over the 11-year period and that a control group of singleton pregnancies with all clinical data including placental weight from the same large center was available. Despite a long inclusion period, a limited number of 15 cases of twin pregnancies were found. However, these data provide useful information for clinicians who are caring for these high-risk pregnancies, and a large prospective study on insulin therapy in twin pregnancies in diabetic women will probably not be performed.

At 14–27 weeks, a weekly increase in daily insulin dose of 3 IU was seen in the twin pregnancies. For singletons, the increase in this period was 1.5 IU in our study, which is comparable with previous findings of García-Patterson (3). These findings are certainly of clinical importance and probably associated with the growth of the larger total fetal and placental mass. From 27 to 33 weeks, the insulin requirement seemed rather stable compared with the continuous steady increase usually seen in singleton diabetic pregnancies (3–5). This may be due to restricted placental and fetal growth often seen in twin pregnancies in late pregnancy and therefore a possible stagnation in the hormonal production. In twin pregnancies in healthy women, the individual twin grows at the same rate as a healthy singleton up until ~30–32 weeks (6,7). In the remaining part of pregnancy, a restricted growth rate is seen, probably because of reduced physical intrauterine space or uteroplacental insufficiency (8).

The total increment of insulin dose was 45% higher in twin pregnancies compared with singleton pregnancies and not twice as much, corresponding well to the 45% higher fetal mass and 74% higher placental mass in these pregnancies.

In clinical use, pregnant women with type 1 diabetes expecting twins and their caregivers should be prepared for a possible decrease in insulin requirement in late first trimester, a weekly increase from 14 weeks, which is double as much as that seen in singleton pregnancies,

followed by a stable period from ~27 weeks.

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