Insulin Requirements in Insulin-Dependent and Insulin-Requiring GDM Women During Final Month of Pregnancy

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OBJECTIVE — To determine the significance of falling insulin requirements after the 36th wk of gestation in insulin-requiring pregnant women.

RESEARCH DESIGN AND METHODS — Insulin requirements of women with IDDM and IRGDM were assessed from the 36th wk of pregnancy, with evaluation of maternal characteristics and fetal outcomes.

RESULTS — In 32 pregnancies of women with IDDM, there was a 5 ± 2% decrease in insulin requirements, and in 19 pregnancies of women with IRGDM, there was a 28 ± 10% increase. Of the 62% of women whose insulin requirements declined, the decrement was 12 ± 2% and was associated with longer duration of diabetes (12 ± 2 vs. 6 ± 1 yr, $P < 0.05$) but not with age, prepregnancy BMI, weight gain, or maternal or fetal complications. Only 3 pregnancies in IRGDM women were associated with a decrease in insulin requirements. Although maternal parameters were no different from those with IDDM, infants born to women with IRGDM were smaller (3531 ± 123 vs. 3874 ± 94 g, $P < 0.005$).

CONCLUSIONS — Insulin requirements from the 36th wk of gestation commonly decreased in women with IDDM, associated with longer duration of diabetes but did not carry any adverse prognostic indication for the infants. Women with IRGDM experienced a continual increase in insulin requirements over the final weeks of pregnancy.

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IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; GDM, GESTATIONAL DIABETES MELLITUS; IRGDM, INSULIN-REQUIRING GESTATIONAL DIABETES MELLITUS; BMI, BODY MASS INDEX; hPL, HUMAN PLACENTAL LACTOGEN; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS.

It is common for an increase in insulin resistance to develop as pregnancy progresses (1–3). The onset of this resistance appears to be associated with rising levels of hPL, progesterone, cortisol, and prolactin (4–8). Therefore, as pregnancy advances in a woman with absolute insulin deficiency (as in IDDM) or significant β-cell insufficiency (as likely occurs in IRGDM), an increase in insulin dosage often is required to maintain euglycemia. Because hPL and progesterone are placental-dependent hormones, a drop in insulin requirements might be interpreted as indicating feto-placental compromise, and therefore a need for increased fetal surveillance or early delivery. However, some decline in insulin dosage during the last few weeks of gestation is not an unusual observation and has been noted in a previous clinical study (9). Therefore, we wanted to quantify weekly insulin requirements from the 36th wk of pregnancy in women with IDDM and IRGDM, with assessment of maternal characteristics and fetal outcomes.

RESEARCH DESIGN AND METHODS

— A 5-yr chart review at our diabetes clinic provided pre- and postpartum information on 51 pregnancies progressing past the 36th gestational wk in women with IDDM and IRGDM. There were too few individuals with pregestational NIDDM for evaluation.

IDDM was diagnosed by a history of diabetic ketoacidosis or young age of onset in a lean individual before pregnancy. GDM was diagnosed by National Diabetes Data Group criteria (10) with insulin being started when capillary blood glucose levels were >5 mM fasting or 6 mM 2 h after eating. All women performed capillary blood glucose monitoring at least four times/day and had a check of technical accuracy with each visit to the diabetes clinic. Insulin dosages were adjusted by the patients themselves or at the clinic visits. The pre-

Table 1—*Comparison of maternal and fetal characteristics in IDDM and IRGDM populations*

	IDDM WOMEN	IRGDM WOMEN
N	32	19
AGE (YR)	29.2 ± 0.8	30.9 ± 1.0
PREPREGNANCY BMI (KG/M^2)	24.7 ± 0.8	27.2 ± 1.2
WEIGHT GAIN TO DELIVERY (KG)	13.8 ± 0.8	12.9 ± 1.9
INSULIN DOSAGE:ABSOLUTE CHANGE (U)	−3.0 ± 2.2*	+3.8 ± 1.8
INSULIN DOSAGE:PERCENT CHANGE (%)	−5 ± 2†	+28.7 ± 10
MATERNAL HYPERTENSION (*N*)	5	6
MATERNAL PROTEINURIA (>200 MG/DAY) (*N*)	1	0
DELIVERY AGE (WK)	38.2 ± 0.1	38.7 ± 0.3
BIRTH WT (G)	3874 ± 94*	3531 ± 123
INFANTS >90TH PERCENTILE IN WEIGHT (%)	75*	42
INFANT OUTCOMES (*N*)		
NEONATAL INTENSIVE CARE UNIT ADMISSIONS	5	0
HYPERBILIRUBINEMIA	9	6
HYPOGLYCEMIA	0	0
HYPOCALCEMIA	0	0

Values are means ± SE, unless otherwise noted.
*$P < 0.05$.
†$P < 0.005$.

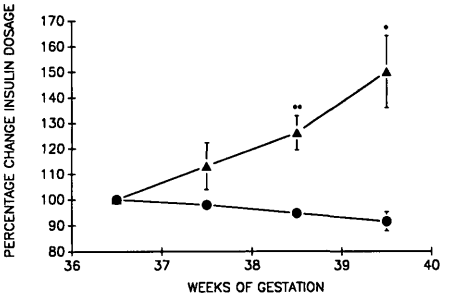

Figure 1—*Percentage change in insulin dosage from 36 wk of gestation to delivery. A progressive increase in insulin requirements in women with IRGDM (▲) was seen compared with a decline in women with IDDM (●). *$P < 0.05$; **$P < 0.005$.*

scribed diets provided 25–35 kcal/kg prepregnancy ideal body weight, with the lower caloric intake recommended for overweight individuals. Expected date of delivery was calculated from the last menstrual period, or ultrasound data, if clinically necessary. Women were seen weekly in the last 3 mo of pregnancy.

The women with IDDM had a mean ± SE HbA_{1c} of 0.052 ± 0.001 (normal ≤0.062) during the 3rd trimester. Women with IRGDM were well controlled with capillary blood glucoses ≤5 mM fasting and ≤6 mM 2 h postmeal. Maternal age, prepregnancy BMI, weight gain during pregnancy, weeks of insulin use (in IRGDM population), or years of diabetes (in IDDM population), and the presence of retinopathy, proteinuria, or hypertension were evaluated. Two women with IDDM were unaware of their hypoglycemia before conceiving, which then persisted throughout gestation. Fetal parameters of gestational age, weight, admission to the neonatal intensive care unit, presence of hypoglycemia (blood glucose <1.9 mM persisting after 24 h postpartum), hyperbilirubinemia (bilirubin >120 μM on 2nd day or >103 μM on 3rd day), and hypocalcemia (calcium <1.75 mM) were also recorded. The absolute change in insulin requirements was calculated. Dosages were expressed as U/kg actual body weight for each week before delivery, with determination of percentage change in comparison with the dosage at 36 wk gestation.

Statistics were analyzed by a nonparametric Kruskal-Wallis test and performed with SAS statistical software (SAS Institute, Cary, NC) on an IBM PC/AT. Categorical data were analyzed by χ^2 testing at $P = 0.05$. Results were expressed as means ± SE.

RESULTS— There were 32 singleton pregnancies in 23 women with IDDM and 19 singleton pregnancies in the 17 IRGDM women. Characteristics of the two populations are shown in Table 1.

IDDM population

The individuals with IDDM experienced an overall mean fall in insulin requirements of 3.0 ± 2.2 U (5 ± 2%) from the 36th wk of pregnancy until delivery (Fig. 1), a decline that was not significant. Within this group, ~33% of women had a rise in insulin needs of 6 ± 2% until the end of pregnancy, but most (62%) experienced a decline. When this latter population was selected, there was an overall mean decrease of 10.5 ± 2.0 U ($P < 0.05$ [12 ± 2%, $P < 0.005$]) by delivery with a range of 1–28% (Fig. 2).

The use of multivariate regression

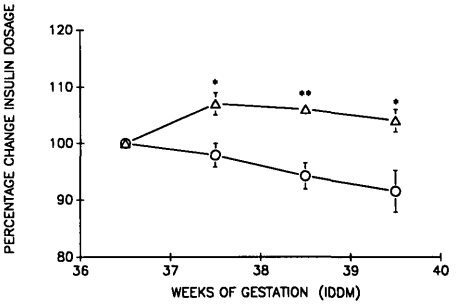

Figure 2—*Percentage changes in insulin requirements within IDDM population. △, Women with increase in insulin requirements; ○, women with decrease in insulin needs. *$P < 0.05$; **$P < 0.005$.*

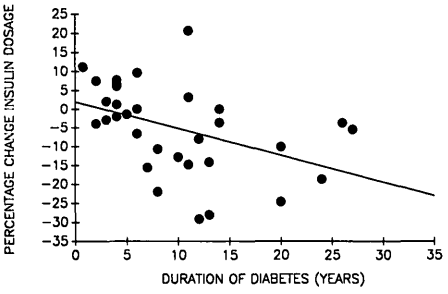

Figure 3—*Percentage change in insulin dosage from 36 wk gestation for all IDDM population (n = 32) correlated with duration of diabetes (r = −43, P < 0.02).*

analysis indicated that the only significant correlation with a decrease in insulin dosage was duration of diabetes (12 ± 2 yr vs. 6 ± 1 yr, $P < 0.05$). When diabetes duration was plotted against percentage change in insulin dosage, a moderate association became apparent with a correlation coefficient of −0.43 ($P < 0.02$) (Fig. 3).

Within the IDDM population, there were no significant differences in the maternal characteristics of age, HbA_{1c}, prepregnancy BMI, weight gain, or associated complications of hypertension, retinopathy, or proteinuria. One woman unaware of her hypoglycemia experienced a fall in insulin requirements by delivery, whereas the other had an ongoing increase. Although there was a trend for the infants of the women with decreased insulin requirements to be heavier and in >90th percentile in weight, these results were not statistically significant. In addition, there were no significant adverse outcomes, with the infants having no differences in ages at delivery, admissions to the neonatal intensive care unit, or abnormalities of metabolic parameters (Table 2).

When the subset of women experiencing the largest drop in insulin dosages (>15%, representing a decline of 18.8 ± 4.0 U; n = 6) was selected, the previous observations held true: a nonsignificant trend toward heavier infants in the women with the largest decline but no adverse outcomes, and the only significant association to decline being the duration of diabetes (14 ± 3 vs. 6 ± 1 yr, $P < 0.05$) (Table 3).

Two twin pregnancies occurred within the IDDM population, although the outcomes were not included in the preceding calculations. Both occurred in the subgroup of women who experienced a fall in insulin requirements (2 and 28%, respectively). The duration of diabetes was also long in these women (23 and 28 yr, respectively), with maternal ages being 36 and 32 yr, respectively.

IRGDM population

The mean time of starting insulin in this population was 31 ± 1 wk gestation. The average increase in insulin needs after the 36th wk of gestation in the IRGDM population was 28 ± 10%, which represented a nonsignificant change of 3.8 ± 1.8 U. Only 3 of these pregnancies were associated with any drop in insulin dosage, with 2 occurring in the same individual at different gestations. Note that there were no statistically significant differences in maternal characteristics compared with the IDDM population other than an incidence of retinopathy in the latter (9/32 vs. 0/19, respectively; $P < 0.05$). The infants born to IRGDM mothers tended to be smaller than those in the IDDM population (3531 ± 123 vs. 3874 ± 94 g, respectively; $P < 0.05$), with 47% of infants in >90th percentile for weight compared with 75% of the offspring of women with IDDM. Mean age at delivery was not different. Again, there were no significant adverse fetal outcomes (Table 1).

CONCLUSIONS— All women experience an increase in insulin resistance as pregnancy progresses (1–3), and a pregnant woman with IDDM will require more insulin in the final two trimesters

Table 2—***Comparison of maternal and fetal parameters within IDDM populations with decreased or increased insulin requirements***

	Insulin dosage	
	Decreased	Increased
N	20	12
Age (yr)	30 ± 1	28 ± 1
Duration of diabetes (yr)	12 ± 2*	6 ± 1
HbA_{1c}	0.055 ± 0.002	0.051 ± 0.001
Prepregnancy BMI (kg/m^2)	25 ± 1	25 ± 1
Weight gain (kg)	13.8 ± 1.0	14.4 ± 1.4
Insulin dosage:absolute change (U)	−10.5 ± 2.0*	+6.8 ± 2.9
Insulin dosage:percentage change (%)	−12 ± 2†	6 ± 2
Delivery age (wk)	38.2 ± 0.2	38.1 ± 0.2
Maternal complications (hypertension, retinopathy, proteinuria) (*n*)	7	2
Birth wt (g)	3906 ± 98	3821 ± 196
Infants >90th percentile (%)	85	58
Infant outcomes (*n*)		
Neonatal intensive care unit admissions	1	4
Hyperbilirubinemia	6	3
Hypocalcemia	0	0
Hypoglycemia	0	0

Results are means ± SE, unless otherwise noted.
*$P < 0.05$.
†$P < 0.005$.

Table 3—*Comparison between women with IDDM who had increased insulin requirements and those who had a >15% decrease in insulin needs*

	Insulin dosage	
	Decreased (≥15%)	Increased
N	6	12
Age (yr)	30 ± 2	28 ± 1
Duration of diabetes (yr)	14 ± 3*	6 ± 1
HBA_{1c}	0.050 ± 0.002	0.051 ± 0.001
Prepregnancy BMI (kg/m^2)	32 ± 2	25 ± 1
Weight gain to delivery (kg)	13.2 ± 2.3	14.4 ± 1.4
Insulin dosage:absolute change (U)	−18.8 ± 4.0†	+6.8 ± 2.9
Insulin dosage:percentage change (%)	−23 ± 2†	+6 ± 2
Maternal complications (hypertension, retinopathy, proteinuria) (*n*)	2	2
Delivery age (wk)	38.2 ± 0.3	38.1 ± 0.2
Birth wt (g)	4017 ± 154	3821 ± 180
Infants >90th percentile (%)	67	58

Results are means ± SE, unless otherwise noted.
*$P < 0.05$.
†$P < 0.005$.

of pregnancy. This may be the result of many factors: increasing caloric intake and weight gain and the hormonal effects associated with pregnancy (4–8). Although the level of the placental hormone hCG does not significantly increase after the 1st trimester (11), levels of two diabetogenic hormones, progesterone and hPL, increase along with placental size (5,8). The increased insulin resistance that is seen as pregnancy progresses appears related to the rising levels of these hormones and may be attributed partly to a defect induced distal to insulin-receptor binding (2,12,13). Although these changes are common to all pregnant women, hyperglycemia will result if pancreatic β-cell reserve is deficient, and exogenous insulin may be needed as glucose tolerance worsens in pregnancies complicated by GDM.

Because the principal diabetogenic hormones are placental in origin, a drop in insulin needs in late pregnancy may be interpreted as suggesting fetoplacental compromise. Therefore, the frequency of fetal monitoring may be increased or consideration given to early delivery if insulin requirements seem to be falling significantly near term. However, we found that it was not uncommon to have a decrease in total insulin dosage in the well-controlled IDDM population after the 36th wk of gestation. This situation was more frequent in women with a longer duration of diabetes but was not associated with an increased risk for maternal or fetal complications.

Of particular interest is the fact that even large reductions in insulin dosage (up to 28%) in the last few weeks of gestation were not associated with any adverse fetal outcome. Previous investigators have found continual increases in insulin dosages in women with IDDM throughout all three trimesters (14). However, mean insulin doses for the entire population were expressed on a monthly basis, which may have potentially obscured short-term changes in the individual. Our results are consistent with a trend noted by Weiss et al. (9), in which decreasing insulin needs occurred in some women with IDDM after the 36th wk. However, the magnitude of decline and its relationship to duration of diabetes had not been quantified previously. Note that our study examined women after the 36th wk of gestation, and therefore the results are not applicable to falling insulin requirements before the final month of pregnancy.

The pattern of insulin needs was different in IRGDM with an ongoing increase in insulin requirements throughout the last weeks of pregnancy. Although other authors (15) have found a plateau in insulin requirements in the IRGDM population after 30 wk of gestation, their subjects required insulin earlier than our patients (26 ± 1 vs. 31 ± 1 wk of gestation), suggesting a greater severity of β-cell impairment and allowing for a longer dosage stabilization period. Insulin dosages were small, and duration of insulin use was relatively short in our population so that minor changes were subsequently reflected in large percentage differences. The use of maximal insulin doses (sufficient to produce hypoglycemia) would have permitted a more exact assessment of insulin requirements in this population. However, this would not reflect our current practice, and we feel it would have posed unacceptable risks to the mother and fetus.

Although the IRGDM women tended to be heavier, we noted no significant differences in age, prepregnancy BMI, weight gain of pregnancy, or presence of hypertension and proteinuria. The infants of the mothers with IDDM tended to be heavier than the offspring of IRGDM women, perhaps in keeping with the shorter duration of abnormal glucose tolerance in the IRGDM population.

One of the striking findings of this study was the differing insulin requirements between women with IDDM and IRGDM in late pregnancy. Because the IRGDM women tended to be slightly heavier than the IDDM women, they may have experienced ongoing increases in insulin resistance, with resulting increased insulin requirements. Another explanation may be that the failing islet in GDM may continue to show further

deterioration of endogenous insulin production with resultant increased exogenous insulin needs. Also, as decreased insulin needs were associated with longer duration of IDDM, this may have reflected decrements in placental blood flow or functioning placental mass, which resulted in the lowering of insulin requirements but not in any adverse outcome.

In conclusion, we found that 62% of women with well-controlled IDDM had a mean fall in insulin requirements of 12% after the 36th wk of pregnancy, which was associated with longer duration of diabetes, but without evidence of significant adverse outcomes. Conversely, women with IRGDM who were not significantly different in maternal characteristics from the IDDM population experienced ongoing increases in insulin needs until delivery.

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