Declining Insulin Requirement in the Late First Trimester of Diabetic Pregnancy

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OBJECTIVE — To investigate whether pregnancies complicated by type 1 diabetes are associated with a decrease in first-trimester insulin requirement.

RESEARCH DESIGN AND METHODS — We examined the weekly insulin requirement (as units per kilogram per day) during the first trimester of pregnancy in diabetic women in the Diabetes in Early Pregnancy Study (DIEP) with accurate gestational dating, regular glucose monitoring, daily insulin-dose recording, and monthly glycohemoglobin measurements.

RESULTS — In pregnancies that resulted in live-born full-term singleton infants, a significant 18% increase in mean weekly dosage was observed between weeks 3 and 7 ($P = 0.000$), followed by a significant 9% decline from week 7 through week 15 ($P = 0.000$). Further testing localized a significant change in insulin dose in the interval beginning weeks 7–8 and ending weeks 11–12 ($P = 0.014$). Within this interval, the maximum decrease was between weeks 9 and 10 (mean), 10 and 11 (median), and 8 and 9 (most frequent maximal decrease). To determine whether prior poor glucose control exaggerated these trends, we categorized the women based on their glycohemoglobin values: <2 SDs above the mean of a normal population (subgroup 1), 2–4 SDs (subgroup 2), and >4 SDs (subgroup 3) at baseline. Late first-trimester declines in dosage were statistically significant in subgroup 2 ($P = 0.002$) and subgroups 2 and 3 together ($P = 0.003$). Similarly, women with BMI >27.0 had a greater initial insulin rise and then fall compared with leaner women.

CONCLUSIONS — Observations in the DIEP cohort disclose a mid–first-trimester decline in insulin requirement in type 1 diabetic pregnant women. Possible explanations include overinsulinization of previously poorly controlled diabetes, a transient decline in progesterone secretion during the late first-trimester luteo-placental shift in progesterone secretion, or other hormonal shifts. Clinicians should anticipate a clinically meaningful reduction in insulin requirement in the 5-week interval between weeks 7 and 12 of gestation.

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Abbreviations: ASI, aggressive subcutaneous insulin; CSII, continuous subcutaneous insulin infusion; DIEP, Diabetes in Early Pregnancy Study; NICHD, National Institute of Child Health and Human Development.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

A consistent hallmark of the diabetic pregnancy is an increase in the insulin requirement in late gestation (1–5). The placenta-driven rise in anti-insulin hormones over the last two trimesters (2–9) is believed to be responsible. Conversely, if the placenta or pregnancy fails, as in threatened abortion or late gestation fetal demise, a decreasing or lower than expected insulin requirement is thought to be due to the decline in hormone secretion from the feto-placental unit.

A more subtle, transient decline in insulin requirement in the first trimester has been suggested mainly from clinical experience (10–12). The decrease can be sudden—even overnight—and can be preceded by a few days of normal or near-normal fasting and postprandial glucose levels. A majority of publications examining this possibility have observed such a fall (2,3,12–15), but two others show no change or a slight increase in insulin dosage, depending on type of diabetes and the manner of insulin administration (5,6).

An opportunity to examine in detail the pattern of change in the insulin requirement in the first trimester is afforded by the Diabetes in Early Pregnancy Study (DIEP) of the National Institute of Child Health and Human Development (NICHD). The DIEP is the largest prospective study of diabetes in early pregnancy and has reported on the relationships between plasma glucose levels and congenital malformations (16) and spontaneous abortion (17) in type 1 diabetic pregnancy. The DIEP collected information on daily insulin dosage for the first 15 weeks of pregnancy, allowing an analysis of the pattern of change of the insulin requirement in early diabetic pregnancy. A clearer description of the changes in insulin requirement in the first trimester would enable clinicians to anticipate these changes and make better treatment decisions in this vulnerable early time in gestation.

RESEARCH DESIGN AND METHODS

— The DIEP was a multicenter collaborative study. The DIEP included Cornell University, Harvard

University, Northwestern University, the University of Pittsburgh, and the University of Washington. The NICHD was the data and coordinating center. The study design has been described in detail elsewhere (18). Briefly, women with type 1 diabetes and normal control women were enrolled before conception (86%) or within 21 days of conception (14%) in cases in which conception could be dated on the basis of regular menstrual history. At the time the diagnosis of pregnancy was made (during the week of the missed menses), diabetic subjects were hospitalized for 2–5 days for monitoring of metabolic control and initial testing. Other than reinforcing the techniques of blood glucose self-monitoring, a standard approach to the management of diabetes was not imposed; nor were fixed goals for glycemic control mandated centrally.

After discharge, the diabetic women were monitored weekly for the first 12 weeks after the last menstrual period by a nurse during a clinic visit, including dietary assessment, blood pressure, and weight. HbA_1 was measured at every visit. The diabetic women recorded their daily insulin doses and self-determined fasting and three postprandial glucose measurements daily in a glucose diary, along with any measurements they chose to make before meals and at bedtime. They were also instructed to measure their blood glucose whenever they believed they were hypoglycemic or, if they were unable to measure their glucose, to note the episode in their glucose diary. The accuracy with which each woman took self-monitored blood glucose readings was checked by having her measure her blood glucose at each clinic visit while an aliquot of the same sample was assayed by the laboratory ($r = 0.83$, $P < 0.001$).

The thiobarbituric acid method was used for HbA_1 analysis (19). This method is not affected by fetal hemoglobin, which made it possible to perform all the tests on frozen washed erythrocytes in a single laboratory. The method relies on the formation of a color when the Amadori rearrangement product (1-deoxy-fructosyl adduct) is heated in the presence of 0.3 oxalic acid to form 5-hydroxymethylfurfuraldehyde.

The main cohort of subjects analyzed comprised 281 diabetic women who recorded daily insulin doses. The mean of each week's total insulin use was calculated and then divided by the patient's weight for that week to attain greater homogeneity of insulin dose among women of differing weights.

To test what the effects of different levels of glycemic control at baseline were, we examined insulin dose in three previously identified subgroups differing by initial HbA_1 level (20). Subgroup 1 comprised women who were in good metabolic control throughout the period of observation (i.e., preconception or early pregnancy through the first half of gestation [21 weeks]). Their initial glycohemoglobin was within 2 SDs of the mean for our normal control subjects (<46 nmol fructose), and the mean value throughout the first half of gestation remained within the normal range.

Subgroup 2 comprised women whose initial glycohemoglobin and/or the mean value for glycohemoglobin in the first 8 weeks of gestation was modestly above the normal range (>2 SDs but <4 SDs above the mean [> 46 – <56.21 nmol fructose]). They also showed improvement in their metabolic control from this initial level in that their glycohemoglobin reached the normal range (<46 nmol fructose) before mid-pregnancy (at 21 weeks).

Subgroup 3 comprised women who were in the poorest control at the outset, but they experienced significant improvement in control during the first half of gestation. First, their initial glycohemoglobin and/or the mean value through 8 weeks was >4 SDs above the mean normal value (≥56.21 nmol fructose). Second, the value declined >2 SDs by midgestation (21 weeks) and remained at least 2 SDs below the initial value for >4 weeks.

Statistical analysis

Examination of the distribution of insulin dosages at all weeks examined (3–15) disclosed marked upward skewness. For this reason, nonparametric statistical analyses were applied. A Friedman-type test was selected as a well-known distribution-free test for general alternatives in blocked data (21). The test was used to determine whether the insulin requirements did or did not change significantly over specific periods of weeks. With each individual, we ranked observed insulin requirement for each week of interest. The expected rank of each observation under the null hypothesis is $(k+1/2)$, where the number of weeks is k. Then, over individuals, we computed the adjusted sum of the deviation of actual rank from the expected value for each week of interest. We then squared the sum over the weeks and appropriately standardized the squared sum. The sum of squared deviations is tested by a χ^2 test with $(k-1)$ degrees of freedom.

The first application of the Friedman-type test was to test the significance of insulin dose differences at intervals forward from week 3 through week 15 and all intervals backward from week 15 to week 4. The next analyses examined the question of which week-by-week interval change was largest by different measures of central tendency; these analyses were then tested for significance by the Friedman-type test. Finally, the significance of changes in insulin dosage was tested over specific weekly intervals in diabetic control subgroups 1, 2, and 3, again using the Friedman-type test. The number of intervals examined was limited as was the number of questions posed, so as to minimize the multiple-testing artifact.

RESULTS — The subjects included in this report are those who had a consistent set of observations across the majority of the first trimester and in whom insulin doses were recorded. The characteristics of these subjects are shown in Table 1. The average age was 27.9 years in the cohort of 281 subjects. The mean age of the parent cohort of 347 subjects monitored for perinatal outcome was 27.8 years. The subset of 281 subjects comprising this analysis is representative of the whole for age, race, income, and education (Table 1). Subjects selected for a good, fair, or poor control at entry (subgroups 1, 2, and 3, respectively; RESEARCH DESIGN AND METHODS contains precise description) are also described in Table 1. Their characteristics as a whole are similar to the main cohort.

The mean and median insulin dosages by week in the entire cohort of diabetic subjects are presented in Table 2 and Fig. 1. A substantial increase in insulin dosage was observed from 0.679–0.800 $U \cdot kg^{-1} \cdot day^{-1}$ weeks 3–7 (18%, $P < 0.000$), followed by a fairly steady decline between weeks 7 and 15 to 0.720 $U \cdot kg^{-1} \cdot day^{-1}$ (9%, $P < 0.000$). In fact, using the Friedman-type test for all intervals between weeks 3 and 5, 3 and 15, and from weeks 15 to 10 and 15 to 4 tested highly significant ($P = 0.000$).

To locate more precisely the interval of weeks during which the insulin dose

Table 1—*Characteristics of subjects studied for insulin requirement*

	Subjects with insulin data	Subjects with defined levels of glycemic control (subgroups 1, 2, or 3)
n	281	93
Age (years)	27.9 ± 4.0	28.1 ± 4.0
Duration of diabetes (years)	12.1 ± 6.6	11.6 ± 7.3
Insulin (years)	12.0 ± 7.0	11.9 ± 8.2
Age at diagnosis (years)	15.8 ± 7.1	16.5 ± 7.7
Race		
White	269 (95.7)	87 (93.5)
Nonwhite	12 (4.3)	6 (6.5)
Age (years)		
15–19	4 (1.4)	0
20–24	53 (18.9)	21 (22.6)
25–29	121 (43.1)	36 (38.7)
30–34	91 (32.4)	31 (33.3)
35–39	12 (4.3)	5 (5.4)
Income (dollars)		
<10,000	13 (4.9)	2 (2.3)
10,000–19,999	48 (18.0)	19 (21.8)
20,000–24,999	41 (15.4)	15 (17.2)
25,000–34,999	64 (24.0)	14 (16.1)
>35,000	101 (37.8)	37 (42.5)
Education		
High school graduate or less	52 (18.5)	19 (20.4)
Some college	89 (31.7)	28 (30.1)
College graduate	80 (28.5)	28 (30.1)
Some graduate school	23 (8.2)	10 (10.8)
Graduate degree	37 (13.2)	8 (8.6)
Cigarette smoking		
None	239 (85.1)	76 (81.7)
<1 pack/day	28 (10.0)	11 (11.8)
≥1 pack/day	13 (4.6)	6 (6.5)
Unknown	1 (0.4)	—
Alcohol consumption		
None	90 (32.0)	29 (31.2)
<1 drink/day	179 (63.7)	60 (64.5)
1–2 drinks/day	10 (3.6)	3 (3.2)
>2 drinks/day	2 (0.7)	1 (1.1)
History of retinopathy		
Yes	70 (24.9)	20 (21.5)
No	209 (74.4)	72 (77.4)
Unknown	2 (0.7)	1 (1.1)
History of proteinuria		
Yes	28 (10.0)	10 (10.8)

Data are *n*, means ± SD, or *n* (%).

decreased to the greatest extent, we examined narrower intervals. A statistically significant difference in the week-to-week change in insulin dose was seen between weeks 7 and 8 and 11 and 12 (Friedman-type test). Within this interval, the weekly decline in insulin dose was maximal between weeks 9 and 10 as a mean change (-0.019 U · kg^{-1} · day^{-1}), weeks 10 and 11 as a median change (-0.011 U · kg^{-1} · day^{-1}), weeks 8 and 9 as the percent of persons with the largest decreases (20.3%), and weeks 10 and 11 as the sum of rank scores of weekly decreases. When the Friedman-type test was used to statistically test the weeks when the values "stop changing," no significant change occurred between weeks 11 and 15. Thus, the majority of analyses localized the greatest reduction in insulin dose to between weeks 10 and 11 in a range of 8–12 weeks' gestation.

The next analyses were performed to examine possible mechanisms that might favor a reduction in insulin dose. For instance, the decrease in insulin requirement in mid-late first trimester could be caused in part by poor glycemic control at the beginning of pregnancy and the need to administer large doses of insulin to improve control rapidly. Once improved glucose control is achieved, it might be necessary to reduce the insulin dose to prevent hypoglycemia. This possible "overshoot" might obscure an otherwise level insulin requirement in diabetic pregnancy.

Table 3 and Fig. 2 show the mean and median values of the insulin requirement weeks 3–15 for the three diabetic subgroups in order of increasingly poor control (subgroups 1 through 3). In addition, the mean weekly insulin doses of subgroups 2 and 3 were combined, because both groups of women were not in ideal control at the start of pregnancy. No statistically significant decrease in insulin dosage was demonstrated in the well-controlled group (subgroup 1), although a downward trend is seen in median values between weeks 8 and 11. In the analysis of subgroup 2 separately, and subgroups 2 and 3 combined, a significant drop in insulin requirement was observed. In subgroup 2, significant drops were observed between weeks 8 and 10 ($P = 0.03$), weeks 9 and 11 ($P = 0.003$), and weeks 10 and 12 ($P = 0.02$), all by the Friedman test. When subgroup 3 was analyzed independently, no significant changes were observed in the first trimester, although a decreasing trend was seen from weeks 9 through 11. When the two groups of women who started their pregnancies in suboptimal control (subgroups 2 and 3) were combined (Table 3), a statistically significant fall was observed between weeks 8 and 10 ($P = 0.018$), weeks 9 and 11 ($P = 0.003$), and weeks 10 and 12 ($P = 0.029$). The three subgroups were not distinguishable on the basis of weight and body mass as the BMIs (kg/m^2) were 24.0, 23.8, and 23.9 in subgroups 1, 2, and 3, respectively.

To determine whether BMI at baseline influenced the first-trimester rise and fall in insulin dosage, we examined the dosage patterns for women with a BMI

Table 2—*Mean, median, and interquartile ranges of daily insulin doses by week of gestation in diabetic pregnant women in the first trimester*

		U · kg^{-1} · day^{-1}		
Week	*n**	Mean	Median	IQR
3	59	0.679	0.655	0.309
4	124	0.670	0.631	0.242
5	226	0.741	0.714	0.262
6	257	0.775	0.760	0.295
7	264	0.800	0.768	0.300
8	265	0.788	0.758	0.289
9	267	0.787	0.747	0.300
10	265	0.773	0.738	0.294
11	263	0.754	0.725	0.291
12	256	0.745	0.717	0.282
13	206	0.754	0.715	0.285
14	159	0.725	0.696	0.257
15	153	0.720	0.690	0.239

*Sample sizes vary, as all subjects did not record insulin doses every week. IQR (interquartile ranges) refers to the range including the central 50% of the observation around the median.

<24 (n = 153), 24–27 (n = 104), and >27 kg/m^2 (n = 28). As might be expected, the increments in mean insulin dose from week 3 to peak insulin dose were 0.08 U · kg^{-1} · day^{-1} in the BMI <24.0 group, 0.17 U · kg^{-1} · day^{-1} in the BMI 24–27 group, and 0.23 U · kg^{-1} · day^{-1} in the BMI >27.0 kg/m^2 group. Conversely, the insulin dose decrements from the peak dose to week 14 showed the same order: 0.14 U · kg^{-1} · day^{-1} in the >27 group, 0.09 U · kg^{-1} · day^{-1} in the 24–27 group, and 0.08 U · kg^{-1} · day^{-1} in the <24 kg/m^2 group. These results indicate that greater BMI predisposes to a greater insulin dose drop as does poorer diabetic control at baseline.

CONCLUSIONS — The DIEP was designed to discern the risk factors for congenital malformations (16) and spontaneous abortions (17) in type 1 diabetic pregnancy compared with nondiabetic control subjects. The protocol included documentation of the daily insulin requirement (18). In the present analysis, the DIEP examined the changes in insulin requirement from week to week in the first trimester of pregnancy and the influences of body weight and prior glycemic control. Insulin requirements were observed to drop in the last half of the first trimester, with the effect exaggerated by prior poor glycemic control and BMI >27.0 kg/m^2. These data are the first to describe fully the changes in insulin requirement over the entire first trimester and are based on the largest first-trimester cohort of type 1 diabetic women studies to date.

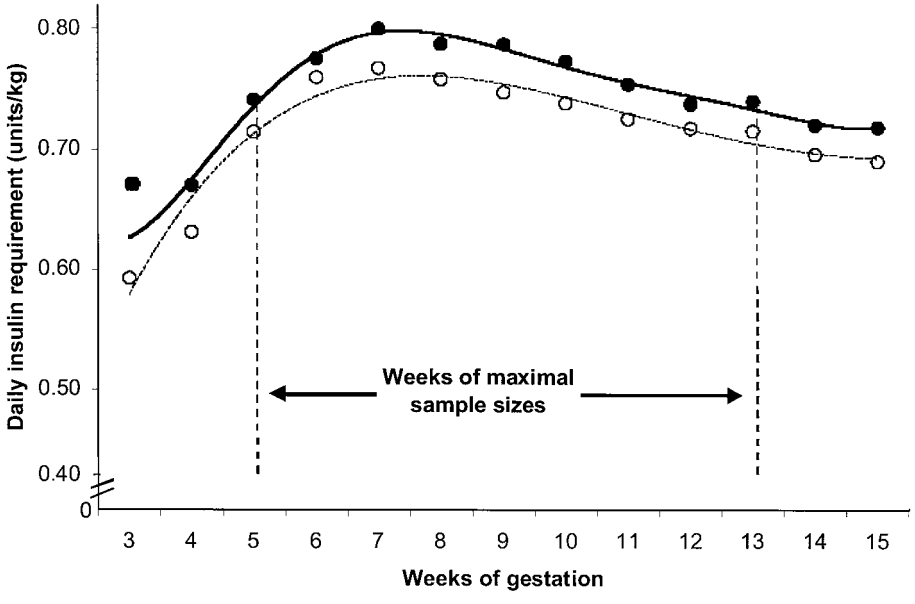

Figure 1—*Daily insulin dosage expressed as a weekly mean in units per kilogram from week 3 to week 15 among pregnant diabetic subjects participating in the DIEP. The number of subjects providing data at each week is at a maximum between weeks 5 and 13, as indicated by the vertical hatched lines. The numbers of subjects at each week are given in Table 1. ●, mean; ○, median.*

The initial observations of a decline in insulin requirement in late first trimester of diabetic pregnancy were clinical. In 1952, Pedersen (10,11) documented that first-trimester hypoglycemia was a symptom of pregnancy and that it was common knowledge among the physicians of the day. Pedersen wrote, "Those physicians who manage diabetic women should be particularly alert for hypoglycemia in women who have recently become pregnant. About the 10th week of gestation, there is an improvement in glucose tolerance manifesting itself as insulin coma, milder insulin reaction, or an improvement in the degree of compensation. When a reduction in insulin dosage is called for, it amounts to an average of 34%." He also observed that "once in a while, pregnancy may be diagnosed on account of inexplicable hypoglycemic attacks." In 26 cases of insulin coma observed in the early 1950s, all occurred in the first to fourth month, with the majority occurring at in the second and third months (weeks 6–12) (10,11).

In the American experience, from the same era, the Joslin Clinic physicians, Drs. Priscilla White and Luke Gulispie, expressed the same view. Hypoglycemia was an early symptom of pregnancy in the diabetic woman (Luke Gulispie, personal communication).

Subsequent publications have supported these early clinical observations. Rayburn et al. (2) studied 58 pregnancies in 50 type 1 diabetic women who were followed for at least 26 weeks before delivery. In late gestation, average daily insulin requirements increased twofold from earlier in pregnancy, as expected. However, they noted that "following ini-

Table 3—*Mean and median daily insulin doses in three subgroups of pregnant diabetic subjects ranging from good (subgroup 1) to poor (subgroup 3) glycemic control at entry*

	U · kg^{-1} · day^{-1}											
	Subgroup 1			Subgroup 2			Subgroup 3			Subgroups 2 and 3		
Week	*n*	Mean ± SD	Median	*n*	Mean ± SD	Median	*n*	Mean ± SD	Median	*n*	Mean ± SD	Median
3	7	0.57 ± 0.24	0.46	6	0.85 ± 0.31	0.79	4	0.76 ± 0.25	0.70	10	0.81 ± 0.28	0.76
4	14	0.58 ± 0.24	0.50	15	0.74 ± 0.25	0.66	12	0.67 ± 0.22	0.61	27	0.71 ± 0.24	0.63
5	24	0.62 ± 0.20	0.61	20	0.77 ± 0.26	0.72	31	0.77 ± 0.24	0.76	51	0.77 ± 0.25	0.76
6	23	0.67 ± 0.21	0.70	26	0.79 ± 0.27	0.73	36	0.80 ± 0.25	0.81	62	0.79 ± 0.26	0.79
7	22	0.70 ± 0.21	0.76	27	0.83 ± 0.26	0.85	37	0.85 ± 0.27	0.81	64	0.84 ± 0.26	0.82
8	21	0.69 ± 0.21	0.7	27	0.83 ± 0.24	0.83	37	0.84 ± 0.26	0.82	64	0.84 ± 0.25	0.82
9	22	0.69 ± 0.23	0.64	27	0.82 ± 0.24	0.80	38	0.85 ± 0.28	0.82	65	0.84 ± 0.27	0.82
10	22	0.68 ± 0.24	0.61	27	0.79 ± 0.25	0.81	40	0.82 ± 0.28	0.80	67	0.81 ± 0.26	0.80
11	22	0.67 ± 0.21	0.61	26	0.77 ± 0.23	0.74	40	0.80 ± 0.28	0.76	66	0.79 ± 0.26	0.75
12	23	0.66 ± 0.21	0.63	27	0.75 ± 0.24	0.72	37	0.82 ± 0.31	0.76	64	0.79 ± 0.28	0.73
13	18	0.67 ± 0.24	0.62	23	0.74 ± 0.24	0.70	28	0.82 ± 0.29	0.76	51	0.79 ± 0.27	0.73
14	16	0.66 ± 0.25	0.64	18	0.66 ± 0.17	0.62	18	0.83 ± 0.27	0.75	36	0.74 ± 0.24	0.67
15	14	0.58 ± 0.16	0.57	16	0.70 ± 0.18	0.65	14	0.82 ± 0.25	0.73	30	0.76 ± 0.22	0.69

Insulin dose is expressed as units per kilogram per day.

tial hospitalization, insulin requirements often decreased before increasing almost linearly between the first and last trimester." In 33 well-controlled pregnant diabetic patients (White Classification B-R), Weiss and Hofmann (13) reported significantly decreased insulin requirements between the 10th and 16th weeks of gestation (−12%, $P < 0.001$). Thereafter, the expected increase in insulin requirement was seen, slightly from the 17th to the 28th week and then rapidly from the 28th to the 36th week (62%), and then declining. Plovie et al. (12) found a 26.6 ± 1.6% (mean ± SEM) decrease in insulin requirement at 10.5 ± 0.5 weeks of gestation in 9 of 11 consecutive subjects followed in one of the DIEP centers. This clinical experience indicated that the decrease in insulin requirement could develop quite suddenly, even overnight. Two recent abstracts to the European Association for the Study of Diabetes have made similar observations in groups of 36 and 132 patients, respectively (14,15).

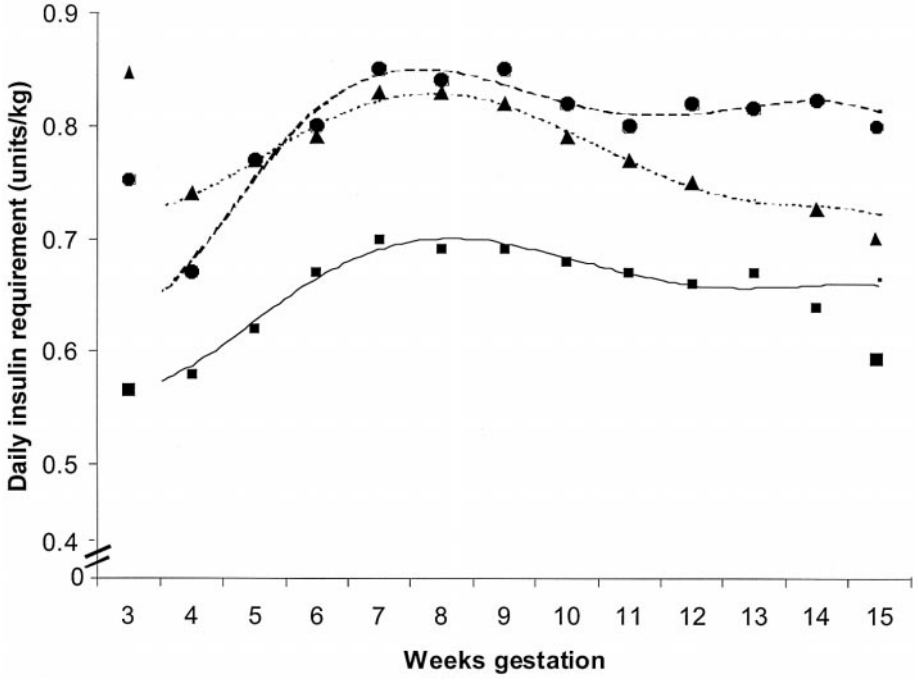

Figure 2—*Daily insulin dosage among pregnant diabetic subjects in subgroups 1, 2, and 3, representing good, fair, and poorer glycemic control at baseline.* ■, *Subgroup 1;* ▲, *subgroup 2;* ●, *subgroup 3.*

Other authors reporting changes in insulin requirement during diabetic pregnancy appear to have focused primarily on the gestational rise in insulin dosage and do not describe first-trimester insulin dosages in any detail (3,4). However, one patient history illustrated in the report of Steel et al. (3) does provide an instructive example. In this case, the insulin dose rose from 56 to 68 U between weeks 9 and 11 and then decreased to 50 U at week 13 on a background of an otherwise stable insulin dose in the first trimester (3).

Two other studies report stable or slight increases in insulin dosage in the first trimester. On the basis of data presented in illustrations, Carta et al. (6) showed a 1- or 2-U increase in daily insulin dose between weeks 8 and 12 and a 0- or 2-U increase between weeks 12 and 16 in 15 type 1 diabetic women treated with continuous subcutaneous insulin infusion (CSII) therapy or aggressive subcutaneous insulin (ASI), respectively. Insulin doses were not reported before 8 weeks. In 14 type 2 diabetic women, the insulin dose was not recorded before 12 weeks

and did not increase at 16 weeks in CSII-treated subjects, but did increase ~6 U in ASI-treated subjects. Langer et al. (5), also in an illustration, indicated no increase in insulin dose in 40 type 2 diabetic women in the 5-week interval between weeks 8 and 11 and 16 and 19. Insulin doses in 63 type 1 diabetic women increased from 50 U daily at 0- to 3- and 4- to 7-week intervals to 53 U at 8–11 weeks and 64 U at 12–15 weeks, then decreasing slightly to ~62 U at 16–19 weeks. Average gestational age at entry was 9 and 11 weeks in type 1 and 2 diabetic subjects, respectively. In summary, these two reports found no or only small increases in insulin requirement in the first trimester. Data before 8–12 weeks' gestation are very limited in these reports.

Several factors may be responsible for the decline in the first-trimester insulin requirement when it occurs. One possible mechanism is an increase in insulin sensitivity. Schmitz et al. (22) documented that the mean glucose disposal rate early in pregnancies complicated by type 1 diabetes (before the 13th week of gestation) is significantly increased compared with the last trimester (5.6 ± 0.0 vs. 3.4 ± 0.5 $mg \cdot kg^{-1} \cdot min^{-1}$, $P < 0.02$). They also reported an inverse relationship between serum human placental lactogen level and glucose disposal rate, but they found no relationship with serum estradiol, progesterone, or cortisol levels. Similarly, in a series of glucose tolerance tests in pregnancy, Lind et al. (23) found a lower rise in plasma glucose in the first trimester compared with observations in the nonpregnant state or later in gestation.

Enhanced insulin sensitivity in the last half of the first trimester might be due to a decline in levels of anti-insulin hormones (1,7,8,24). Specifically, a fall in insulin requirements in the first trimester may be mediated through a decline in progesterone, an anti-insulin hormone (7,24). The nadir of progesterone is at 8 weeks and remains below the peak level seen at week 4 until at least 16 weeks' gestation, reflecting the shift in progesterone secretion from the corpus luteum to the placenta (luteo-placental shift) (25–27). Preliminary data point to a temporal association between the decrease in plasma progesterone and glucose levels (12). Other hormonal fluctuations could also be involved, including human chorionic gonadotropin and thyroid hormone levels (28).

Early first-trimester overinsulinization might also explain a late first-trimester drop in insulin requirement. One manifestation of this effect may be the significantly greater weight gain documented during the first trimester in diabetic women compared with nondiabetic control women in this study (9). Since the weight of the diabetic and the control women was the same at the beginning of gestation, the increased weight gain seen in type 1 diabetic women could be the result of the treatment program or an interaction between diabetes and pregnancy per se. An increased caloric intake to prevent hypoglycemia in the first trimester may have contributed to the first-trimester excessive weight gain in the diabetic women compared with the control subjects (9). The maternal weight gain in the first trimester is unlikely to be responsible for the decline in insulin regime since the percentage decline in insulin requirement in weeks 8–12 is 5.6%, more than twice the percentage weight gain of 2.3% over the same interval (9). What is clear from the present data is that women with poorer initial diabetic control have a greater decrease in insulin requirement, as do persons with BMI >27.0 kg/m^2 in the latter half of the first trimester.

A first-trimester decline in blood glucose levels is also seen in normal pregnancy. The study group for DIEP has recently reported (29) that maternal blood glucose levels decrease in the first trimester in their population of normal pregnant women, confirming many earlier studies (24). This reduction could be due to increased maternal insulin sensitivity and glucose clearance in the late first trimester as described above. Since the embryo/fetus is very small in early gestation, this putative enhanced sensitivity to insulin in the late first trimester is likely rooted in the maternal physiological adjustment to normal pregnancy rather than glucose demands of the embryo/fetus (24). Therefore, it is to be expected that a similar effect would be seen in early diabetic pregnancy as a decline in insulin requirement.

In conclusion, a decline in insulin dosage in type 1 diabetic subjects treated early in the first trimester of pregnancy has been demonstrated in the largest and most carefully studied cohort of pregnant diabetic subjects examined to date. The rise and fall in insulin requirement is most notable among initially poorly controlled diabetic subjects and in the heaviest subjects, but can also be seen in very well controlled, otherwise uncomplicated diabetic pregnant women. Particularly for women in good glycemic control, even a modest decrease in insulin requirement could place them at heightened risk for hypoglycemia. Thus, all insulin-dependent diabetic women and their caregivers should be taught to anticipate the possibility of a decrease in insulin requirement in mid-late first trimester. From the physiological point of view, these clinical observations are consistent with the underlying pattern of declining glucose in the first trimester of normal pregnancy. The decline in glucose appears to reflect a transient increase in insulin sensitivity in the latter half of the first trimester, which in turn is rooted in the underlying maternal endocrine adaptations to pregnancy. This trend is the opposite of the better-known late rise in insulin requirement, which reflects a rise in maternal contra-insulin hormones in late pregnancy. Taken together, these data provide a basis to anticipate a sometimes sudden and dramatic decrease in insulin requirement in mid-late first trimester of the diabetic pregnancy.

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References

1. Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD: Feasibility of maintaining normal glucose profiles in insulin-dependent pregnant diabetic women. *Am J Med* 68:105–112, 1980
2. Rayburn W, Piehl E, Lewis E, Schork A, Sereika S, Zabrensky K: Changes in insulin therapy during pregnancy. *Am J Perinatol* 2:271–275, 1985
3. Steel JM, Johnstone FD, Hume R, Mao JH: Insulin requirements during pregnancy in women with type I diabetes. *Obstet Gynecol* 83:253–258, 1994
4. McManus RM, Ryan EA: Insulin requirements in insulin-dependent and insulin-requiring GDM women during final month of pregnancy. *Diabetes Care* 15: 1323–1327, 1992
5. Langer O, Anyaegbunam A, Brustman L, Guidetti D, Levy J, Mazze R: Pregesta-

tional diabetes: insulin requirements throughout pregnancy. *Am J Obstet Gynecol* 159:616–621, 1988
6. Carta Q, Meriggi E, Trossarelli GF, Catella G, Dal Molin V, Menato G, Gagliardi L, Massobrio M, Vitelli A: Continuous subcutaneous insulin infusion versus intensive conventional insulin therapy in type I and type II diabetic pregnancy. *Diabet Metab* 12:121–129, 1986
7. Knopp R, Bonet B, Zhu X-D: *Lipid Metabolism in Pregnancy*. 2nd edition. Cowett R, Ed. New York, Springer-Verlag, 1998, p. 221–258
8. Catalano PM, Huston L, Amini SB, Kalhan SC: Longitudinal changes in glucose metabolism during pregnancy in obese women with normal glucose tolerance and gestational diabetes mellitus. *Am J Obstet Gynecol* 180:903–916, 1999
9. Peterson CM, Jovanovic-Peterson L, Mills JL, Conley MR, Knopp RH, Reed GF, Aarons JH, Holmes LB, Brown Z, Van Allen M, et al.: The Diabetes in Early Pregnancy Study: changes in cholesterol, triglycerides, body weight, and blood pressure. The National Institute of Child Health and Human Development—the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 166:513–518, 1992
10. Pedersen J: Course of diabetes during pregnancy. *Acta Endocrinol* 9:342–345, 1952
11. Pedersen J: *The Pregnant Diabetic and Her Newborn: Problems and Management*. Baltimore, Williams & Wilkins, 1977
12. Plovie B, Brown Z, Knopp R, Richter K: Hypoglycemia and falling progesterone levels during diabetic pregnancy. *Diabetes* (Suppl. 1) 31:59A, 1982
13. Weiss PA, Hofmann H: Intensified conventional insulin therapy for the pregnant diabetic patient. *Obstet Gynecol* 64:629–637, 1984
14. Garcia-Patterson A, Albareda M, Corcoy R: Transient increase of insulin requirements in early pregnancy of women with type 1 diabetes mellitus: program of the European Association for the Study of Diabetes. Barcelona, Spain, 1998
15. Aldridge V, Yaxley L, Durkan M, Kelly M, Temple R: Reduced insulin requirements in early pregnancy in IDDM: program of the 1998 European Association for the Study of Diabetes. Barcelona, Spain, 1998
16. Mills JL, Knopp RH, Simpson JL, Jovanovic-Peterson L, Metzger BE, Holmes LB, Aarons JH, Brown Z, Reed GF, Bieber FR, et al.: Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med* 318:671–676, 1988
17. Mills JL, Simpson JL, Driscoll SG, Jovanovic-Peterson L, Van Allen M, Aarons JH, Metzger B, Bieber FR, Knopp RH, Holmes LB, et al.: Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. *N Engl J Med* 319: 1617–1623, 1988
18. Mills JL, Fishl AR, Knopp RH, Ober CL, Jovanovic LG, Polk BF: Malformations in infants of diabetic mothers: problems in study design. *Prev Med* 12:274–286, 1983
19. Pecoraro RE, Graf RJ, Halter JB, Beiter H, Porte D Jr: Comparison of a colorimetric assay for glycosylated hemoglobin with ion-exchange chromatography. *Diabetes* 28:1120–1125, 1979
20. Chew EY, Mills JL, Metzger BE, Remaley NA, Jovanovic-Peterson L, Knopp RH, Conley M, Rand L, Simpson JL, Holmes LB, Aaron JH, National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study: Metabolic control and progression of retinopathy: the Diabetes in Early Pregnancy Study. *Diabetes Care* 18:631–637, 1995
21. Skillings J, Mack G: On the use of a Friedman-type statistic in balanced and unbalanced block design. *Technometrics* 23: 171–177, 1981
22. Schmitz O, Klebe J, Moller J, Arnfred J, Hermansen K, Orskov H, Beck-Nielsen H: In vivo insulin action in type 1 (insulin-dependent) diabetic pregnant women as assessed by the insulin clamp technique. *J Clin Endocrinol Metab* 61:877–881, 1985
23. Lind T, Billewicz WZ, Brown G: A serial study of changes occurring in the oral glucose tolerance test during pregnancy. *J Obstet Gynaecol Br Commonw* 80:1033–1039, 1973
24. Knopp RH: Hormone-mediated changes in nutrient metabolism in pregnancy: a physiological basis for normal fetal development. In *Adolescent Nutritional Disorders: Prevention and Treatment*. Jacobsen MS, Rees JM, Golden NH, Irwin CE, Eds. New York, NewYork Academy of Sciences, 1997, p. 251–271
25. Csapo AI, Pulkkinen M: Indispensability of the human corpus luteum in the maintenance of early pregnancy: luteectomy evidence. *Obstet Gynecol Surv* 33:69–81, 1978
26. Ellinwood WE, Stanczyk FZ, Lazur JJ, Novy MJ: Dynamics of steroid biosynthesis during the luteal-placental shift in rhesus monkeys. *J Clin Endocrinol Metab* 69: 348–355, 1989
27. Yoshimi T, Strott CA, Marshall JR, Lipsett MB: Corpus luteum function in early pregnancy. *J Clin Endocrinol Metab* 29: 225–230, 1969
28. Ballabio M, Poshychinda M, Ekins RP: Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. *J Clin Endocrinol Metab* 73:824–831, 1991
29. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, Lee YJ, Holmes L, Simpson JL, Metzger B: Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the Diabetes in Early Pregnancy Study. *Metabolism* 47:1140–1144, 1998