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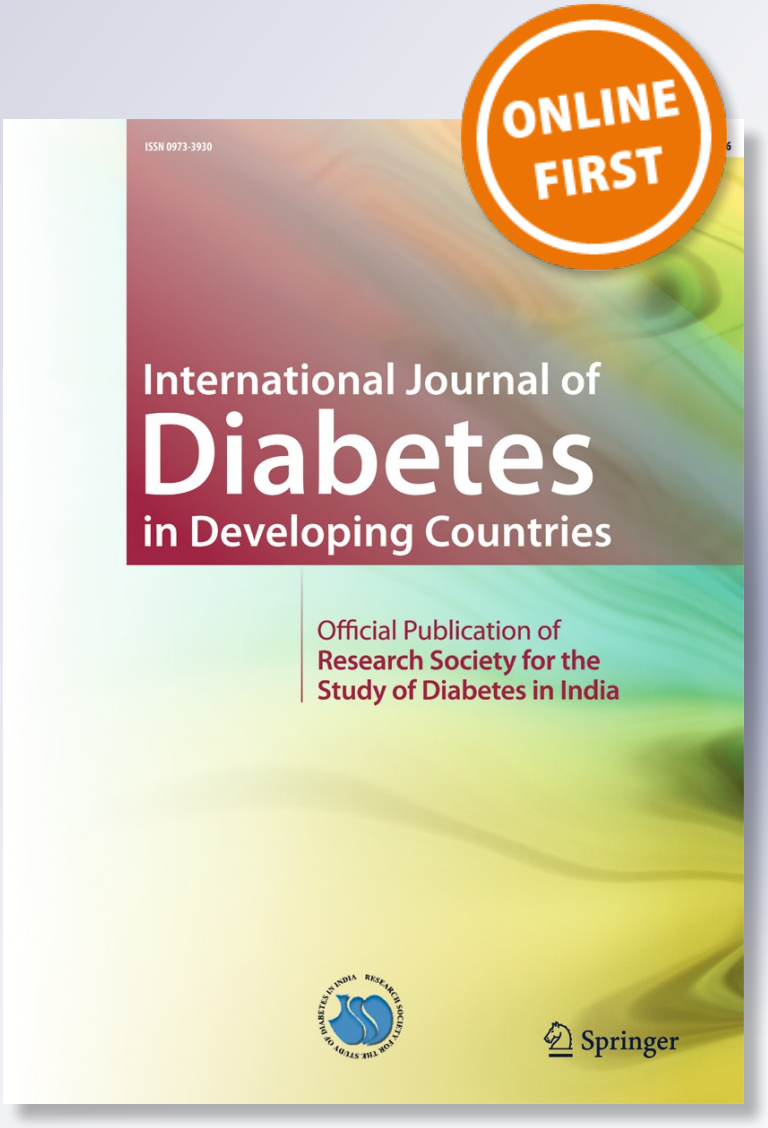
International Journal of Diabetes in Developing Countries
Incorporating Diabetes Bulletin

ISSN 0973-3930

Int J Diabetes Dev Ctries
DOI 10.1007/s13410-016-0541-2



Springer

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ORIGINAL ARTICLE

Insulin therapy in women with pregestational type 2 diabetes and its relevance to maternal and neonatal complications

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Received: 26 August 2016 / Accepted: 8 December 2016

Abstract The objective of this study is to assess the insulin requirement, its determinants, and its association with maternal complications and neonatal outcome in women with pregestational type 2 diabetes mellitus. One hundred two insulin treated pregnant women with pre-existing type 2 diabetes and those clinically diagnosed with type2 DM during pregnancy were selected. Insulin dose, distribution, relation with meal was assessed. Statistical analysis was done and insulin requirement was correlated with maternal factors and fetal outcome. Insulin dose at the 1st trimester was 32.65 ± 23.11 units/day, i.e., 0.52 U/kg/day of pre-pregnancy weight, which significantly increased to 47.62 ± 29.54 U/day at delivery i.e., 0.76 U/kg/day ($p < 0.0001$). Insulin dose was positively correlated to fasting and 2 h postprandial plasma glucose at diagnosis. Pre-dinner insulin requirement was significantly higher than pre-breakfast in the 3rd trimester (*P* value: 0.018). 19.6% neonates had a low birth weight, 5.8% had macrosomia, and 18.63% had neonatal hypoglycemia. Subjects on insulin analog showed a lower risk of low birth weight (17.4%) and macrosomia (Nil) versus those on conventional insulin with 21.6 and 8.1%, respectively. Insulin requirement in type 2 diabetes pregnancies progressively increases from the 1st trimester till delivery. Meal-related assessment needs attention in Indian population due to their varied dietary culture. Low birth weight is more frequent than macrosomia in our population. More studies are needed to ascertain the concept of a better neonatal outcome with insulin analog.

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Keywords Pregestational diabetes mellitus · Insulin · Fetal outcome

Recent evidences show that over 415 million people worldwide have diabetes, which is expected to become 652 million by 2040. 78.3 million people with diabetes live in South East Asia. India has 68.1 million people with diabetes (appx. 8.8%), and half of them are undiagnosed. Globally, 199.5 million of women have diabetes, which is expected to increase to 313.3 million in 2035 [1]. Hyperglycemia is one of the most common medical conditions women encounter during pregnancy. The International Diabetes Federation (IDF) data says that one in six live births (16.8%) born of women with some form of hyperglycemia in pregnancy (20–49 years). FIGO (International Federation of Gynecology and Obstetrics) in their recently published guidelines [2] classified hyperglycemia in pregnancy into two categories: (a) gestational diabetes mellitus (GDM) and (b) diabetes in pregnancy (DIP) which is further subclassified as either pre-existing type 2 DM or type 1 diabetes with pregnancy or the hyperglycemia first detected at any time during the course of pregnancy, if meets the criteria for diagnosis of diabetes in the nonpregnant state. The stated criteria are fasting plasma glucose (FPG) ≥7.0 mmol/L or 126 mg/dL, and/or 2-h 75-g oral glucose tolerance test (OGTT) value ≥11.1 mmol/L or 200 mg/dL, or random plasma glucose (RPG) ≥11.1 mmol/L or 200 mg/dL associated with signs and symptoms of diabetes. In DIP, the susceptibility to complications is more because of the higher degree of hyperglycemia and the uncertainty as to whether the onset of hyperglycemia was prior to pregnancy or developed during early pregnancy. Though, diabetes detected for the first time in pregnancy might be type 1 or type 2

Published online: 19 December 2016

DM, a diagnosis of type 2DM is more likely. Compared with GDM, DIP is more likely to be detected as early as the 1st trimester (TM), provided appropriate testing is commenced. Although, 16% of hyperglycemia in pregnancy might be DIP, the majority (84%) is due to GDM. Furthermore, globally and more so in Asia, the age of onset of diabetes and pre-diabetes is declining, while the age of childbearing is increasing. Additionally, there is a rising prevalence of overweight and obese women of reproductive age; thus, women entering pregnancy have higher risk factors that make them susceptible to hyperglycemia during pregnancy [2]. Many recommendations define women with any type of diabetes, when attains pregnancy as pregestational diabetes mellitus (PGDM) [3] and those diagnosed to have hyperglycemia during pregnancy, though GDM, but is clinically pre-GDM or overt pre-GDM.

Pregnancy is a diabetogenic state that exacerbates pre-existing diabetes. Due to various counter-regulatory hormones, metabolism changes noticeably during pregnancy. Both basal and postprandial glucose metabolism gradually change during the course of pregnancy to meet the maternal and fetal nutritional demands. Optimal glycemic control is pivotal to the successful outcome of diabetes in pregnancy. It is imperative to achieve euglycemia during pregnancy with the goal of fasting blood glucose <90 mg, 2 h post meal as <120 mg% and HbA1c < 6%. While targeting these goals, we should also take care to avoid severe hypoglycemia. These goals are best obtained with diet, exercise, and insulin treatment, often a multiple-dose insulin regimen or insulin pump is required. Insulin therapy is the mainstay to achieve euglycemia during pregnancy complicated by any form of diabetes. Euglycemia for pregnancy can be best achieved through basal-bolus regimen of insulin therapy with judicious use of home monitoring of blood glucose (HMBG). Importantly, innovations in home blood glucose monitoring and insulin administration devices have provided the technology needed to not only allow women to successfully survive pregnancy but also to decrease the risks of diabetic fetopathy to those of the nondiabetic population [3, 4]. There is scanty data available on dose, frequency, and meal-related distribution of insulin therapy in type 2 women with diabetes during pregnancy.

In this retrospective noncontrolled observational study, we have tried to evaluate these parameters and their association with the maternal characteristics at diagnosis of pregnancy. Also, the change in the insulin requirement from the 1st to 3rd trimester and its effect on maternal and fetal complications was studied. This has been shown schematically in Fig. 1. Step I shows the assessment of baseline maternal characteristics at the diagnosis of pregnancy. These characteristics were correlated with the total insulin dose/day at the 1st trimester. Further, the dose requirement at the 1st trimester was compared with that of the 3rd trimester (step II) considering maternal and fetal complications as outcomes.

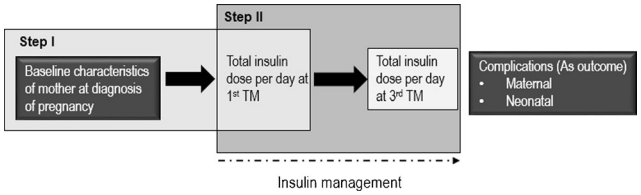


Fig. 1 Conceptual flow of the analysis

Materials and methods

A total of 120 pregnant women with DIP, as defined by FIGO [2], i.e., either pre-existing type 2 diabetes or those diagnosed to have diabetes for the first time during pregnancy (overt pre-GDM), attending a tertiary care diabetes center in Central India, during the period 2008 to 2015 were included in the study. Sample selection (through convenient sample method) has been depicted through Fig. 2. Out of these, 15 patients have opted to terminate pregnancy due to a high glycosylated hemoglobin A1c or other associated complications. There was one case with intrauterine death (IUD), one patient had an extremely high BMI, and one was on a diet therapy throughout the gestational period. This resulted into 102 cases for final evaluation. The study was approved by the institutional ethics committee, informed consent was obtained for using the data from the case file, and their privacy rights were maintained. Detailed history with pre-pregnancy weight and present 3 days dietary recall was taken for each case. Anthropometry measurements were taken. Biochemistry was done by fully automated Cobas c111 analyzer developed by Roche, glycosylated hemoglobin A1c was done by HPLC (high performance liquid chromatography) method with Bio-Rad D-10

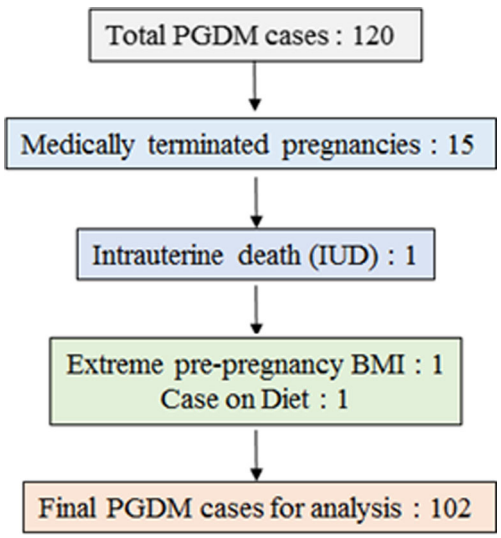


Fig. 2 Sample selection for the study

analyzer, thyroid function test was performed by electrochemiluminescence immunoassay (ECLIA), micro-angiopathy, and macro-angiopathy assessment were done through clinical examination and with resting ECG, micro-albuminuria was done by immunoturbidimetric assay and fundus examination through Zeiss direct system.

Subjects were initiated primarily on basal-bolus insulin regimen to achieve the goal of fasting blood glucose as less than 90 mg% and 2 h postprandial as less than 120 mg%. Few of them continued with premixed insulin. Their fasting, post-breakfast, pre-lunch, post-lunch, pre-dinner, post-dinner, and 3 am blood glucose were monitored regularly. Counseling for HMBG and self-adjustment of minor insulin doses was done. After achieving the glycemic targets, the insulin requirement was assessed from the diagnosis of pregnancy till delivery. Insulin dose requirement was calculated with respect to patient age, age of onset of diabetes, duration of diabetes, pre-pregnancy weight, pre-pregnancy BMI, fasting plasma glucose, postprandial plasma glucose and HbA1c at diagnosis of pregnancy, need of intermediate acting insulin, weight gain during pregnancy, and relation with meals, i.e., breakfast, lunch, and dinner. Eventually, maternal and fetal complications were assessed.

Statistical methods

The descriptive statistics like mean and standard deviation were obtained for continuous variables, while frequencies were obtained for variables defined on nominal scale. Relationship of different maternal characteristics with total insulin requirement at the 1st trimester was obtained using *Pearson's correlation coefficient* for continuous characteristics, and *t test for independent samples* for categorical characteristics. All the analysis was performed using SPSS 18.0 (SPSS Inc.) software, and statistical significance level was set at 5%.

Results

The sample selection in the study has been shown pictorially in Fig. 2. There were a total of 120 patients of DIP during the observation period; however, the analyses were performed on 102 eligible cases. Among these, 45 (44%) had known diabetes, while 57 (56%) cases were overt pre-GDM. Out of 45 known diabetics, 43 were type 2 DM cases, while 2 were known IGT (impaired glucose tolerance). The descriptive statistics for different patient characteristics are given in Table 1. The mean age of onset of DM in patients with known pre-existing T2DM was 29.00 ± 4.79 years, while the overall mean age of patients was 30.17 ± 4.25 years. There were 21 (20%) cases with a past history of GDM, 51 (50%) cases with bad obstetric history, and 75 (73.53%) cases with a family

Table 1 Descriptive statistics for different patient characteristics (n = 102)

Characteristics	Descriptive statistics
Age at onset of diabetes (yrs.) [M ± SD]†	29.00 ± 4.79
Age at gestation (yrs.) [M ± SD]	30.17 ± 4.25
Duration of DM before gestation (yrs.) [no. (%)] (n = 43)†	
≤1	19 (44.18)
>1	24 (55.81)
Past history of GDM (yes) [no. (%)]	21 (20)
Obstetric history—Gravida [no. (%)]	
1	29 (28.43)
>1	73 (71.57)
BOH (yes) [no. (%)]	51 (50)
Family history of diabetes (yes) [no. (%)]	75 (73.53)
Pre-pregnancy weight (Kg) [M ± SD]	62.59 ± 13.62
Pre-pregnancy BMI (Kg/m^2) [M ± SD]	26.32 ± 5.02
HbA_1c% at diagnosis of pregnancy [M ± SD]	7.39 ± 1.40
Fasting blood sugar (mg/dl) [M ± SD]	121.50 ± 44.03
Post-meal blood sugar (mg/dl) [M ± SD]	196.50 ± 71.18
Hypothyroidism (yes) [no. (%)]	22 (21.57)
Total insulin—1st trimester (units/day) [M ± SD]	32.65 ± 23.11
Before breakfast	9.15 ± 7.02
Before lunch	9.63 ± 7.38
Before dinner	10.02 ± 6.93
Bed time	5.31 ± 4.73
Total insulin—3rd trimester (units/day) [M ± SD]	47.62 ± 29.54
Before breakfast	12.74 ± 9.28
Before lunch	15.10 ± 9.73
Before dinner	15.89 ± 9.85
Bed time	8.00 ± 6.90
Total calorie intake (cal.)	
At breakfast	270.45 ± 127.95
At lunch	427.11 ± 123.08
At supper	463.86 ± 118.59
Weight gain in pregnancy (Kg) [M ± SD]	8.08 ± 3.53
Gender (baby): male [no. (%)]	53 (51.96)
Baby birth weight (Kg) [M ± SD]	2.76 ± 0.54
Neonatal complications [no. (%)]	
Requiring PBU admission	12 (11.76)
Macrosomia (>3.5 kg)	6 (5.88)
Low birth weight (<2.5 kg)	20 (19.61)
Neonatal hypoglycemia	19 (18.63)
Neonatal hyperbilirubinemia	4 (3.92)
Neosepsis	1 (0.98)
Maternal complication [no. (%)]	
PIH	14 (13.73)

†Only cases with known type 2 DM before pregnancy

history of diabetes. The mean pre-pregnancy weight of patients was 62.59 ± 13.62 kg, and pre-pregnancy BMI was 26.32 ± 5.02 kg/m^2. Other baseline features at diagnosis like HbA_1c was 7.39 ± 1.40, fasting plasma glucose (FPG) was 121.50 ± 44.03 mg/dl, and postprandial plasma glucose (PMPG) was 196.50 ± 71.18 mg/dl. Of them, 22 (21.57%) subjects had hypothyroidism. Pregnancy-induced hypertension (PIH) was observed in 14 (13.73%) mothers. The total per day insulin requirement at the 1st trimester was 32.65 ± 23.11 units, while per kg pre-pregnancy body weight requirement was 0.522 units/kg. The requirement increased to 47.62 ± 29.54 mg/dl at the time of delivery, and per kg pre-pregnancy body weight requirement was 0.76 units/kg. The day wise insulin requirement revealed that it was the highest at dinnertime both at the 1st and 3rd trimester as compared to morning and afternoon. The average weight gain in pregnancy was 8.08 ± 3.53 kg, and the average baby birth weight was 2.76 ± 0.54 kg. As regards neonatal complications, 20 (19.61%) babies had a low birth weight, while 19 (18.63%) had a neonatal hypoglycemia. There were 6 (5.8%) babies with macrosomia. There was no case of congenital malformation.

Factors and their relatedness with insulin dose (step I)

As per the conceptual flow (Fig. 1), the statistical relevance of baseline features with total insulin dose required during the 1st trimester was established, with the results are shown in Table 2. Age at onset of DM in patient subgroup with known T2DM was insignificantly correlated with the total insulin dose at the 1st trimester with a coefficient of −0.243 (*P* value: 0.124). In the same subgroup, the duration of DM showed insignificant difference of mean total insulin requirement per day as indicated by a *P* value of 0.282. The mean dose required for patients with the past history of GDM (30.95 ± 29.52 units/day) was insignificantly different from those without history (33.10 ± 21.32 units/day) as indicated by a *P* value of 0.757. Patients with and without bad obstetric history also did not show statistically significant difference in the mean dose requirements (*P* value: 0.922). The dose requirement was uninfluenced by the family history of diabetes, pre-pregnancy BMI, and HbA_1c at the diagnosis of pregnancy in patients as revealed by *P* values 0.147, 0.977, and 0.129, respectively. However, fasting blood sugar at diagnosis showed a significant positive correlation (0.219) with insulin dose requirement in the 1st trimester with an associated *P* value of 0.03. At the 3rd TM, the correlation was slight negative (−0.013) and statistically insignificant (*P* value: 0.898) with insulin dose. Moreover, post-meal blood sugar was significantly correlated (0.179) with dose requirement (*P* value: 0.073), which was significant at 10% level of confidence; while at the 3rd TM, the correlation was 0.019 (*P* value: 0.852).

Change in the insulin dose requirement (step II)

The insulin requirement of the 1st trimester was 32.65 ± 32.11/day while the total insulin dose requirement at the 3rd trimester showed a mean of 47.62 ± 29.54 U/day (Table 1). This increase in the mean dose requirement from the 1st to the 3rd trimester was statistically highly significant with $P < 0.0001$. The overall requirement at the 3rd trimester was nearly 1.46 times more than that of the 1st trimester.

Moreover, the split of insulin requirement at different times during the day at the 1st trimester revealed a linear increase in dose with the day progression. The insulin requirement was higher at supper (10.02 ± 6.93 U/day) than at breakfast (9.15 ± 7.02 U/day). The mean change in the dose requirement between breakfast and supper was 0.87 units, which was statistically insignificant (*P* value: 0.408). At the 3rd trimester, the mean insulin requirement at supper (15.89 ± 9.85 U/day) was higher than at breakfast (12.74 ± 9.28 U/day). The mean difference of doses between these time points was 3.15 units, which was statistically significant with a *P* value of 0.018. Further, the mean change in the insulin requirement at breakfast between the 1st and 3rd trimester (3.59 U) was significant with a *P* value of 0.0042, while at supper, the mean change (5.87 U) was highly significant with $P < 0.0001$. The change in bedtime insulin NPH/detemir from diagnosis of pregnancy till delivery (2.97 U) was significant with a *P* value of 0.0005.

The increase in the insulin dose requirement from breakfast to dinner at diagnosis of pregnancy as well as at delivery corroborates with a high total calorie intake of the population at supper (463.86 ± 118.59 cal.) as against breakfast (270.45 ± 127.95 cal.).

Insulin dose requirement and its relation with maternal and neonatal complications as outcome

Maternal complications like hypothyroidism and pregnancy-induced hypertension (PIH) were observed in the study sample. Table 3 reveals that in patients with hypothyroidism, the mean total per day dose requirement at the 1st trimester was 30.59 ± 18.57 units; while at delivery, it was 54.23 ± 39.96 units. The change in the dose was statistically significant (*P* value: 0.017). Also, in patients without hypothyroidism, the change in the insulin dose was significant with $P = 0.002$. Overall, the mean increase in hypothyroidism group (~24 units) was higher as compared to that of nonhypothyroidism group (~13 units). However, this difference was statistically insignificant with a *P* value of 0.1616. Further, in mothers who developed PIH, the mean total per day insulin requirement at the 1st trimester was 22.92 ± 9.46 units, while at the time of delivery, it was 43.86 ± 30.03 units. The increase was statistically significant

Table 2 Relationship of different maternal characteristics with total insulin requirement per day during the 1st and the 3rd trimester (n = 102)

Baseline maternal characteristics	Insulin dose—1st TM		Insulin dose—3rd TM	
	Descriptive statistics	*P* value	Descriptive statistics	*P* value
Age at onset of diabetes (yrs.) [r]	−0.243	0.124†	−0.251	0.099†
Overt pre-GDM	29.95 ± 22.93	0.174*	40.75 ± 27.61	0.006*
Pre-GDM (T2DM)	36.30 ± 23.11		57.47 ± 30.36	
Duration of DM before gestation (yrs.) [M ± SD]				
(Among pre-GDM T2DM)				
≤1	31.23 ± 24.90	0.282*	46.89 ± 30.04	0.601*
>1	36.03 ± 18.13		50.21 ± 29.41	
Past history of GDM [M ± SD]				
Yes	30.95 ± 29.52	0.757*	51.94 ± 30.43	0.547*
No	33.10 ± 21.32		47.12 ± 29.68	
Obstetric history—Gravida [M ± SD]				
1	30.90 ± 19.77	0.764*	43.60 ± 25.57	0.296*
> 1	32.29 ± 23.42		49.91 ± 31.34	
Bad obstetric history [M ± SD]				
Yes	32.32 ± 19.52	0.922*	52.56 ± 32.88	0.142*
No	32.78 ± 24.47		43.70 ± 26.01	
Family history of DM [M ± SD]				
Yes	34.39 ± 24.72	0.147*	50.11 ± 29.08	0.258*
No	27.89 ± 17.51		42.07 ± 31.27	
Pre-pregnancy BMI [r]	0.002	0.977	0.067	0.509
HbA_1c at diagnosis of pregnancy [r]	0.151	0.129	0.016	0.868
Fasting blood sugar [r]	0.219	0.030	−0.013	0.898
Post-meal blood sugar [r]	0.179	0.073	0.019	0.852

r Pearson's correlation coefficient, *M* mean, *SD* standard deviation

†Only cases with known type 2 DM before pregnancy,

*Obtained using *t-test for independent samples*

with a *P* value of 0.025. In patients without PIH, the difference in the total daily dose requirement was also significant (*P* value: 0.001). Overall, the mean increase in PIH group (~21 units) was higher than that of non-PIH group (~14 units). However, this difference was statistically insignificant with a *P* value of 0.249. The occurrence of maternal complications like hypothyroidism and PIH in overt PGDM and type 2 DM groups was insignificantly different (Table 4). There was no case of maternal hypoglycemia reported.

As regards neonatal complications, 20 (19.61%) babies had a low birth weight (birth weight less than 2.5 kg), 6 (5.8%) had macrosomia (birth weight more than 3.5 kg), and 19 (18.63%) had neonatal hypoglycemia. Among the low birth weight cases, 1 (5%) had hypoglycemia, 5 (25%) required PBU (premature baby unit) admission, and the rest had no complications. In the normal birth weight category, 17 (22.4%) had hypoglycemia and 6 (7.9%) cases required PBU. Among babies with macrosomia, 1 (16.7%) had hypoglycemia, and 1 (16.7%) case required PBU admission. The proportion of neonatal cases with complications like macrosomia, low birth weight, neonatal hypoglycemia was insignificantly different between pre-existing type 2 DM and overt pre-GDM groups (Table 4).

The insulin requirement in cases with neonatal complications was also studied (Table 3). In low birth weight, the change in the requirement of insulin from the 1st to 3rd trimester (at delivery) was statistically insignificant, as indicated by a *P* value of 0.246. Similarly, in macrosomia cases, the change was statistically insignificant with a *P* value of 0.702. However, in normal babies, the change in the requirement was highly significant with a *P* value of 0.0001. In babies with hypoglycemia, the insulin requirement in the 3rd TM was significantly higher than that of the 1st TM (P = 0.047). Similar was the observation in babies without neonatal hypoglycemia (*P* value: 0.001).

The effect of the type of insulin was also studied in patients through Sankey chart (Fig. 3). There were 74 mothers with conventional insulin (Regular, Regular + NPH, premixed-50/50) treatment throughout gestation period, while 25 mothers were on insulin analogs (rapid acting insulin analog insulin

Table 3 Relevance of maternal and infant complications with insulin requirement (n = 102)

Complications	Total per day insulin requirement at		P value*
	1st TM	3rd TM	
Maternal complications			
Hypothyroidism			
Yes (n = 22)	30.59 ± 18.57	54.23 ± 39.96	0.017
No (n = 80)	33.23 ± 24.30	45.80 ± 26.00	0.002
PIH			
Yes (n = 14)	22.92 ± 9.46	43.86 ± 30.03	0.025
No (n = 88)	34.09 ± 24.19	48.22 ± 29.59	0.001
Neonatal complications			
Body weight			
Low birth weight (n = 20)	31.20 ± 19.04	38.85 ± 21.88	0.246
Normal (n = 76)	31.72 ± 22.77	49.17 ± 30.72	0.0001
Macrosomia (n = 6)	49.17 ± 35.80	57.17 ± 34.61	0.702
Hypoglycemia			
Yes (n = 19)	26.37 ± 19.16	44.47 ± 32.92	0.047
No (n = 83)	34.11 ± 23.80	48.34 ± 28.88	0.001

*Obtained using *paired t test*;

**Obtained using *t test for independent samples*;

‡ Obtained using *one-way ANOVA*

aspart and long acting insulin analog, insulin detemir) during the period. In subjects on conventional insulin group, 16 (21.62%) babies had a low birth weight (birth weight less than 2.5 kg.), followed by 14 (18.92%) with neonatal hypoglycemia (blood glucose less than 40 mg%), 9 (12.16%) required PBU (premature baby unit) admission, and 6 (8.11%) had macrosomia (birth weight more than 3.5 kg). In the insulin analog treated group, 4 (17.39%) had a low birth weight, 5 (21.74%) had neonatal hypoglycemia, while 3 (12%) babies required PBU, and there was no case of macrosomia. There were 2 cases with the change of treatment from conventional to analog, while 1 case with the change from analog to conventional, and thus they were not included in the analysis.

Discussion

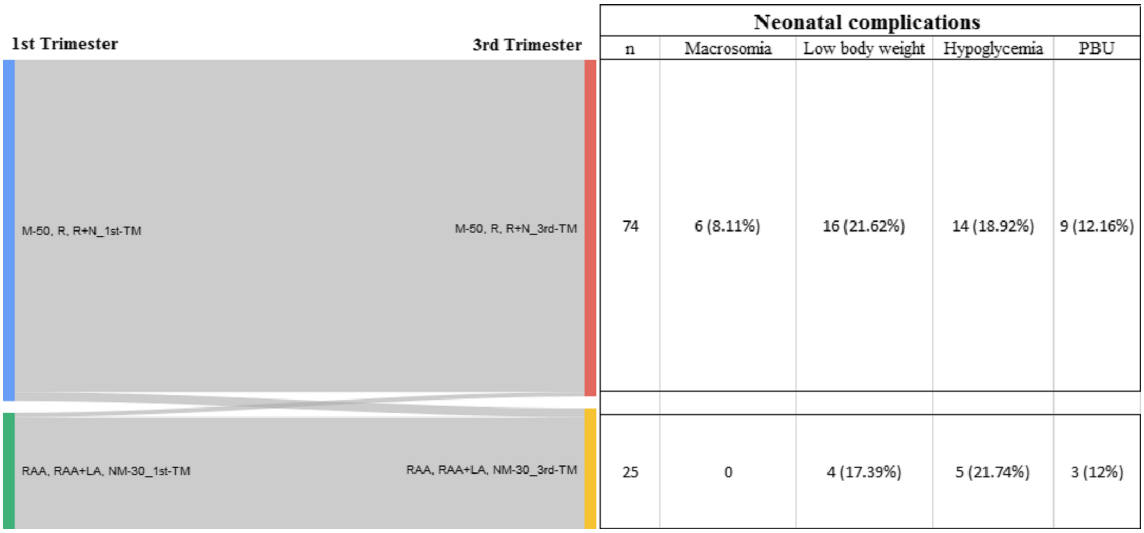
Subcutaneous insulin administration is the mainstay of intensified therapy for diabetes in pregnancy (DIP), i.e., pre-existing diabetes in pregnancy. Basal-prandial insulin delivery through a multiple-injection regimen or CSII is most effective [5]. Type 2 diabetes women on insulin therapy may require an initial total daily dose of 0.7–1.0 units/kg actual body weight, adjusted according to subsequent blood glucose concentrations. Obese women may require a higher insulin dosage, and insulin requirements may double or triple during the course of pregnancy [6]. In our study, all subjects were primarily treated with basal-bolus

Table 4 Complications according to type 2 DM and clinically PGDM mothers

Complications	Type 2 DM (n = 42)	Clinically PGDM (n = 60)	P value*
Maternal complication			
Hypothyroidism	10 (23.8%)	12 (20.0%)	0.8291 (NS)
PIH	9 (21.4%)	5 (8.30%)	0.1097 (NS)
Neonatal complications			
Requiring PBU admission	3 (7.14%)	9 (15.0%)	0.3682 (NS)
Macrosomia (>3.5 kg)	2 (4.76%)	4 (6.67%)	0.9999 (NS)
Low birth weight (<2.5 kg)	8 (19.5%)	12 (20.0%)	0.9999 (NS)
Neonatal hypoglycemia	8 (19.5%)	11 (18.3%)	0.9999 (NS)
Neonatal hyperbilirubinemia	2 (4.76%)	2 (3.33%)	0.9999 (NS)

NS nonsignificant

*Obtained using *chi-Square test*



	Neonatal complications			
n	Macrosomia	Low body weight	Hypoglycemia	PBU
74	6 (8.11%)	16 (21.62%)	14 (18.92%)	9 (12.16%)
25	0	4 (17.39%)	5 (21.74%)	3 (12%)

Fig. 3 Sankey chart displaying the number of patients according to the type of insulin administered during the 1st and 3rd trimester and the respective neonatal complications

regimen of insulin therapy, and it was observed that to achieve target fasting plasma glucose as less than 90 mg% and 2 h postprandial plasma glucose as less than 120 mg%; they require 0.52 U/kg of pre-pregnancy body weight/day of insulin in the 1st trimester, which gradually increases to 0.76 U/kg of pre-pregnancy body weight/day. The overall requirement at the 3rd trimester was nearly 1.46 times more than that of the 1st trimester. The increment in the dose requirement from the 1st trimester to the 3rd trimester was observed to be less in our population than shown in other studies [7, 8]. The dose requirement of insulin lispro (another rapid acting insulin analog) was observed by Durnwald [9], which is almost similar to our finding. He found 0.58 and 0.98 U/kg of pre-pregnancy body weight insulin lispro needed in the 1st and 3rd trimester, respectively. R Chaudry et al. [10] mentioned that many obese women may require as much as 1.5–2.0 U/kg initially to overcome the combined insulin resistance of obesity and pregnancy. Our data showed that insulin requirement is uninfluenced by pre-pregnancy BMI in these pre-GDM women.

Sapienza AD et al. [11] have shown in their study on gestational diabetes mellitus, a positive correlation between insulin therapy and pre-pregnancy BMI, family history of diabetes, hypertension, prior GDM, prior fetal macrosomia, and HbA1c in univariate analysis. Pre-pregnancy BMI, family history of diabetes, and HbA1c were statistically significant variables in the logistic regression model in this study. Our type 2 diabetes mellitus pre-GDM women did not show any statistically significant relationship of insulin dose requirement with the duration of DM, past history of GDM, bad obstetric history, positive family history of diabetes, pre-pregnancy BMI, and HbA_1c at diagnosis. Insulin requirement did show a statistically significant relation with fasting and postprandial plasma glucose at the diagnosis of pregnancy.

Our study is unique to show the statistically significant increase in insulin doses from pre-breakfast to pre-supper, especially at delivery. The increase in the insulin dose requirement from breakfast to dinner at diagnosis of pregnancy as well as at delivery corroborates with a high total calorie intake of the population at supper as against breakfast. The increase in the mean levels of insulin dose requirement was much higher in women with hypothyroidism and PIH as compared to those without hypothyroidism or without PIH. This might be due to a more insulin resistance in women with hypothyroidism and PIH. The increase in insulin requirement from the 1st trimester to the 3rd trimester was significantly higher in mothers who delivered normal babies (74.5%) as against mothers who delivered low birth weight (19.6%) or macrosomic babies (6%). This indicates that adequate insulin intensification might play an important role for a better fetal outcome, which could be attained through proper glucose monitoring at different times during the day. While comparing the use of conventional human insulin versus insulin analog, there was no significant difference found in neonatal hypoglycemia, low birth weight, or PBU admission. These results are consistent with Pettitt DJ et al. [12] who used insulin aspart and Seshiah et al. [13], Jovanovic et al. [14], and Meccaci et al. [15], when they have used insulin lispro. Deepakala MC et al. [16] have found 12.8% of macrosomia and 11% of babies with a low birth weight in women who were on insulin lispro. Our data has shown 8.11% babies to have macrosomia and all of them were on conventional human insulin. There was no case of macrosomia in women who were on insulin analogs (aspart and detemir). Our limitation was a small sample size of women on insulin analog and thus, further studies are needed to ascertain these observations.

Conclusion

Insulin is the first line therapy recommended for women with diabetes in pregnancy. Though the insulin requirement needs to be individualized, there is scanty data available for the factors affecting the insulin dose requirement, frequency, and relation with various meals during pregnancy. The insulin dose requirement progressively increases from the 1st trimester to the 3rd trimester. Monitoring of all pre and post-meal blood glucose helps to have a better glycemic control. Post-supper blood glucose monitoring needs emphasis. Careful intensification of insulin therapy and the use of insulin analog might help to have better feto-maternal outcomes.

Acknowledgements Dr. Dhananjay Raje for the statistical assistance.

Compliance with ethical standards

Funding None.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval This study is approved by the Institutional Ethics Committee, though it is retrospective noncontrolled observational study. There is no intervention as insulin was given to the women participants as part of the standard of care and not as part of any study; the authors only documented the dose, type, and duration of insulin that were administered to the participants.

Informed consent Informed consent from all the subjects was taken for using their personal data for research purposes.

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