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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

How safe is metformin when initiated in early pregnancy? A retrospective 5-year study of pregnant women with gestational diabetes mellitus from India

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ARTICLE INFO

Article history:
Received 13 September 2017
Received in revised form
29 November 2017
Accepted 2 January 2018
Available online 8 January 2018

ABSTRACT

Background: The initiation of metformin in early pregnancy in Gestational Diabetes mellitus (GDM) remains controversial. The aim of our study was to assess the influence of Metformin on maternal and fetal outcomes when initiated within the first trimester of pregnancy in GDM.

Methods and materials: A retrospective analysis of 540 women with diabetes complicating pregnancy (IADPSG criteria) over five years (January 2011 to May 2016) was done. The study population comprised of patients initiated on (a) metformin within the first trimester (Group A:n = 186), (b) metformin after the first trimester (Group B:n = 203) and (c) insulin at any time during their pregnancy (Group C:n = 151). The primary outcomes compared were prematurity, respiratory distress, birth trauma, 5-min APGAR score, neonatal hypoglycaemia and need for phototherapy, while secondary outcomes compared were neonatal anthropometric measurements, maternal glycemic control, maternal hypertensive complications, postpartum glucose tolerance.

Results: Individual and composite primary or secondary outcomes in group A were similar to Groups B and C, though numerically higher premature births were seen in Group A. There was a 1.3% overall incidence of stillbirths/IUD, while 1.11% congenital anomalies were noted of which 2.15% were in group A and 1.32% were in Group C (p = .16).

Conclusions: The initiation of metformin within the first trimester of pregnancy has no significant adverse maternal or fetal outcomes. However, vigilance for premature births is recommended in women exposed to metformin in early pregnancy.

Abbreviation: SMD, standard mean differences

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https://doi.org/10.1016/j.diabres.2018.01.002
0168-8227/

1. Introduction

Gestational diabetes mellitus (GDM) has been defined as, "Glucose intolerance of varying severity with onset or first recognition during pregnancy" [1]. The relationship between maternal glucose levels and fetal growth and fetal outcome is a basic biological phenomenon [2], yet it is associated with several adverse maternal and fetal outcomes along with a long term risk of developing subsequent impaired glucose tolerance. Diagnosed early and treated intensively, the risk of intrauterine fetal death and the overall frequency and severity of perinatal morbidities in GDM is not in excess of the general obstetric population [1].

The treatment options for GDM include mainly medical nutritional therapy and insulin. Among the oral antidiabetic agents, glibenclamide has been approved for use during pregnancy while the use of metformin during the early period of gestation remains controversial. Though metformin has also been shown to facilitate conception and prevent early pregnancy loss in patients with polycystic ovarian syndrome [3,4], a maternal to fetal transfer rate of 10–16%, has led to concerns with the use of metformin in early gestation. Even standard guidelines like those of the Endocrine society's Clinical practice guidelines advocate metformin therapy after the first trimester [5]. A number of studies including a randomised controlled trial from our centre, have reported that the composite of neonatal complications including neonatal hypoglycaemia, were significantly less in neonates of women treated with metformin than those treated with glibenclamide [6]. Given the lack of consensus on the use of metformin in the first trimester of pregnancy in GDM, we conducted this study with the objective of comparing the maternal and fetal outcomes in women with gestational diabetes mellitus who were initiated on metformin within the first trimester to those initiated on metformin after the first trimester or those initiated on insulin during their pregnancy.

2. Research design

2.1. Study design

This was a retrospective study carried out at Christian Medical College, Vellore. The outpatient and inpatient charts of consecutive patients with Diabetes Mellitus complicating pregnancy attending the Gestational Diabetes Clinic of the Department of Endocrinology and the Department of Obstetrics & Gynaecology were analyzed for data on maternal outcomes. The birth and neonatal records obtained from the Department of Neonatology were analyzed for data on the neonatal outcomes. The analysis of this five year data from January 2011 to May 2016 was done after obtaining approval from the institutional review board (IRB No: 10044).

2.2. Study subjects

All pregnant women diagnosed with GDM or overt diabetes during pregnancy and treated with metformin or insulin were included in the study. Those patients treated with medical nutritional therapy (MNT) alone were excluded. Patients with pre-gestational diabetes (defined as diabetes that was detected before conception), pre-gestational hypertension (hypertension present prior to conception) or pregnancies conceived through artificial reproductive techniques were also excluded from this study. No direct contact was made with the subjects and their names and hospital numbers were coded to maintain anonymity.

Data obtained included the age of the mother, history of co-morbidities, a past history of GDM, pre-eclampsia or pregnancy loss, a family history of diabetes mellitus, the gestational age at the time of diagnosis of GDM and at delivery in the pregnancy being studied, plasma glucose levels at the diagnosis of hyperglycaemia, anti-diabetic agents used and the gestational age at the time of initiating the agent. Patients with incomplete data with respect to their primary or secondary outcomes were excluded from this study.

After obtaining the necessary data from the data base, the patients were divided into three groups: Group A included patients treated with metformin from the first trimester of pregnancy, Group B included patients treated with metformin after the first trimester of pregnancy and Group C included patients treated with insulin initiated at any time during their pregnancy. The primary and secondary outcomes evaluated in our study were chosen based on the findings of the MiG Trial which is the largest study till date to have looked at maternal and fetal outcomes of metformin in pregnancy [7]. Our study was designed to measure the incidence of primary and secondary outcomes in Group A when compared to that in Group B and Group C respectively.

The primary outcomes that were assessed were prematurity (<37 weeks), respiratory distress, birth trauma, 5-min APGAR score [8], neonatal hypoglycaemia (defined as a plasma glucose value <40 mg/dL) and need for phototherapy for hyperbilirubinemia. The secondary outcomes that were assessed included neonatal anthropometric measurements, maternal glycemic control, maternal hypertensive complications (preeclampsia-blood pressure >140/90 mmHg with proteinuria >0.3 g/24 h) [9], postpartum glucose tolerance (as recorded in first post-natal visit within 6 months from delivery). The maternal glycemic control was categorized as 'adequate control' or 'inadequate control' on the basis of the documented SMBG readings and the clinicians notes in the out-patient charts during the follow up of the pregnancy. Macrosomia was defined as a birth weight >4 kg [10].

2.3. Diagnosis of glucose intolerance in pregnancy

The diagnosis of GDM and overt diabetes in pregnancy were made as per the IADPSG criteria [5]. All the patients who had presented within the first 24 weeks of gestation had an estimation of fasting and prandial sugars and an additional HbA1c estimation if the values were found to be deranged. A fasting sugar value (after an overnight fasting for 8 h) > 92 mg/dl or an HbA1c of 5.7–6.5% was diagnosed as GDM whereas a fasting sugar > 126 mg/dl or an HbA1c more than

6.5% was confirmed as overt diabetes. This was the institution protocol followed to diagnose GDM in first trimester.

All patients who had normal sugars initially or had presented after 24 weeks of gestation, had undergone a 75 g, 2-h Oral glucose tolerance test (OGTT) with plasma glucose measurement at 0, 1 and 2 h after the glucose load [2]. The diagnosis of GDM was confirmed if any one or more of the following thresholds were met or exceeded: a baseline (0 h) plasma glucose ≥92 mg/dl, one hour plasma glucose ≥180 mg/dl or a two hour plasma glucose ≥153 mg/dl. A diagnosis of overt diabetes in pregnancy was confirmed if the baseline plasma glucose was ≥126 mg% or 2 h plasma glucose was ≥200 mg% with or without an HbA1c ≥ 6.5% [5].

2.4. *Study population*

The sample size was calculated based on the composite outcome in infants of women treated with metformin as compared with those treated with insulin as reported in the MiG trial by Rowan et al. [7]. With a power of 80% and alpha error of 5%, the sample size for the study was determined as 540, with equal proportion (0.32%) in the treatment arms.

Of the 3160 charts with diabetes complicating pregnancy screened, within the time line of January 2011 to May 2016, 1368 patients who had a documented evidence of pre-gestational diabetes mellitus, 788 patients who did not meet the inclusion criteria and 464 patients who had an incomplete set of data were excluded. Out of the remaining 580 subjects, who fulfilled the study criteria, data of 540 subjects were included in the study as per the sample size calculated (Fig. 1).

Based on the antidiabetic treatment received, the 540 patients were divided into three groups with 186 (34.44%) patients in group A (metformin initiated during first trimester of pregnancy), 203 (37.59%) patients in group B (metformin initiated after the first trimester of pregnancy) and 151 (28%) patients in group C (insulin initiated at any time during the pregnancy).

2.5. *Statistical analysis*

An Independent-t Test was used to test the significance of the variables obtained. A Chi-square was performed in order to identify the differences in categorical variables between sub-groups.

3. Results

The 540 study subjects were grouped into three groups, i.e. Group A with 186 (34.44%) subjects on Metformin from the first trimester of pregnancy, Group B with 203 (37.59%) subjects on Metformin from the second or third trimester of pregnancy and Group C with 151 (28%) subjects on insulin only throughout their pregnancy. Out of the total 389 (72.03%) subjects taking metformin, 99 (53.22%) in Group A and 85 (41.87%) in Group B required insulin in addition to metformin and lifestyle modification on follow up.

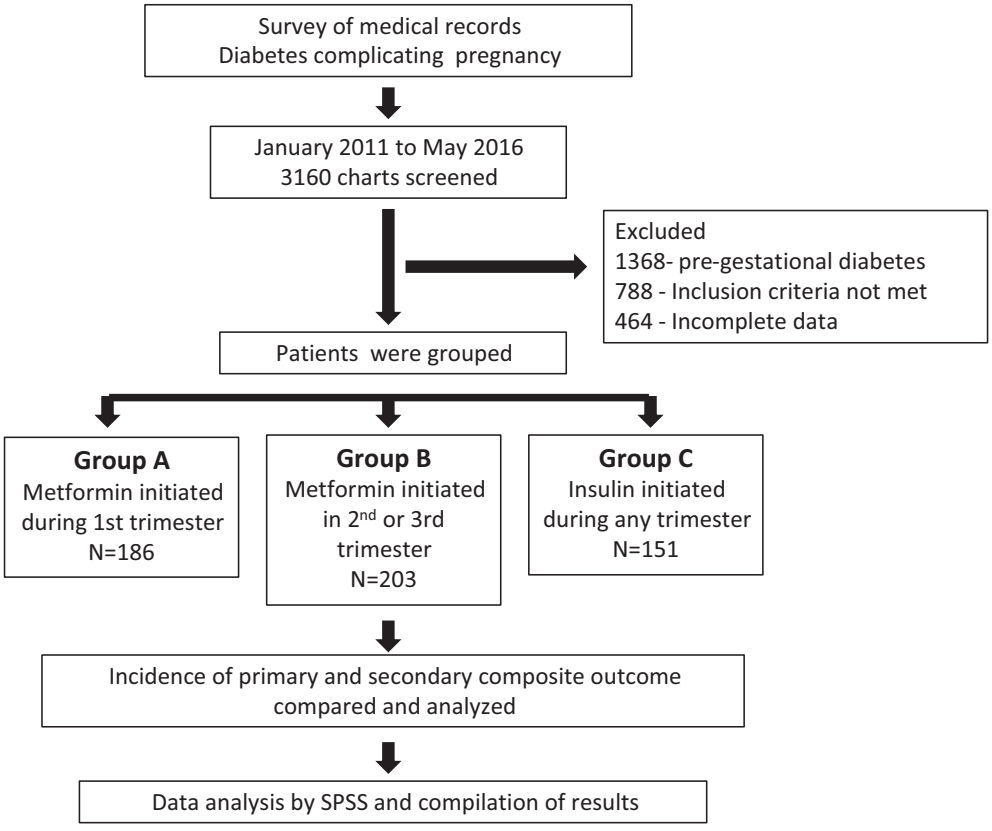

Fig. 1 – Diagrammatic algorithm of the study.

The baseline characteristics of each group have been outlined in Table 1.

Though all the groups were comparable according to the age, Group A had patients diagnosed with GDM in early pregnancy, requiring intervention in the form of oral Metformin in the first trimester. A greater number of patients in Group A had reported a previous history of GDM (28.5% vs 18.23% (group B) & 22.52% (group C)) and a positive family history of diabetes mellitus (66.13% vs 57% (group B) & 53% (group C)) rendering them at a higher risk for GDM. The 2 h OGTT values were significantly higher in Group C who were initiated on insulin.

3.1. *Comparison of primary and secondary outcomes: Group A vs Group B*

The comparison of the primary and secondary outcomes between Group A and Group B are outlined in Table 2. There was no statistically significant difference in the individual primary or secondary outcomes between the two groups. Although the number of premature births was higher in the Group A, it was not found to be statistically significant (p = .619). Maternal glycemic control was adequate in 172 (92.5%) subjects in Group A and in 183 (90%) subjects in Group B (p = .976). On post-partum OGTT, 67 (36.02%) subjects in Group A compared to 69 (33.99%) subjects in Group B had persistent hyperglycemia (p = .342) while the incidence of macrosomia was comparable among the Group A (1.61%) and Group B (2.46%) subjects (p = .257).

3.2. *Comparison of primary and secondary outcomes: Group A vs Group C*

The comparison between the primary and secondary outcomes among Group A and Group C have been outlined in Table 3. Although there were numerical differences among the variables in groups A & C, they were not statistically significant. As compared to group A, group C had gestational hypertension in 16 (10.5%) (p = .495), uncontrolled maternal glycaemia in 20 (9.85%) (p = .976), impaired postpartum glucose tolerance in 69 (33.99%) (p = .342), macrosomia in 5 (2.46%) (p = .257) and birth length > 50 cm in 15 (7.4%) (p = .415).

Logistic regression did not show any statistical difference in the composite primary outcomes [OR: 1.738 (CI 0.657–4.597)] or the composite secondary outcomes [OR: 1.617 (CI 0.618–4.115)] between groups A and B. There were also no statistically significant differences in the composite primary outcomes [OR: 1.717 (CI 0.715–4.119)] or the composite secondary outcomes [OR: 1.720 (CI 0.619–4.117)] between groups A and C.

We further did a subgroup analysis comparing the primary and secondary outcomes among patients started on metformin (Group A) and patients started on insulin within the first trimester of pregnancy (Group C-1), though there were no statistically significant differences between the groups (Table 4).

Additionally, informative secondary outcome variables like anthropometric measures and maternal hypoglycemia were compared between the three groups (Table 5). Though

Table 1 – Baseline characteristics of the groups A, B and C at diagnosis with gestational diabetes.

Characteristics	Group A (Metformin in the 1st trimester) Mean ± SD (N = 186)	Group B (Metformin in the 2nd trimester) Mean ± SD (N = 203)	Group C (Insulin) Mean ± SD (N = 151)	*p*-value (Group A vs Group B)	*p-value* (Group A vs Group C)
Age of subject (years)	29.41 ± 4.64	28.8 ± 5.12	28.9 ± 4.03	.16	.11
Gestational age at diagnosis (weeks ± days)	10.04 ± 1.8	22.45 ± 5.4	23.67 + 7.65	.03	.04
History of GDM	53 (28.5%)	37 (18.23%)	34 (22.52%)	.06	.05
Family history of diabetes mellitus	123 (66.13%)	109 (53.7%)	80 (53%)	.04	.03
Fasting Plasma Glucose*	108 ± 32.2	–	–	–	–
0hr 75 g OGTT plasma glucose (mg/dl)	–	102 ± 26.5	120 ± 40.8	.11**	.15**
2hr-postprandial plasma glucose (mg/dl)#	188 ± 46.7	–	–	–	–
2hr post 75 g OGTT plasma glucose (mg/dl)	–	174 ± 39.8	210 ± 53.7	.05##	.04##
Duration of hospital stay during delivery (days)	5.58 ± 1.2	5.55 ± 1.09	6.07 ± 1.16	.25	.18
Birth length (cm)	47 ± 2.66	48.07 ± 2.89	48.16 ± 2.35	.43	.38

* Fasting and 2 h-postprandial plasma glucose used for diagnosis of GDM in first trimester.
** Comparison between fasting plasma glucose in group A and 0 h-75 g OGTT plasma glucose in Groups B and C.
# 2-h postprandial plasma glucose used for diagnosis of GDM in first trimester.
Comparison between 2 h-postprandial plasma glucose in group A and 2 h-75 g OGTT plasma glucose in Groups B and C.

Table 2 – Individual comparison of primary and secondary outcome characteristics between Group A (Metformin in 1st trimester) vs Group B (Metformin in 2nd or 3rd trimester).

Variable		Group A (Metformin in the 1st trimester) (N = 186)	Group B (Metformin in the 2nd trimester) (N = 203)	OR (CI)	*p*-value
Premature birth	Yes	23 (12.37%)	20 (9.85%)	1.434	.619
	No	163 (87.63%)	183 (90.15%)	(0.528–3.895)	
Respiratory distress	Yes	1 (0.53%)	0	6.280	1.000
	No	185 (99.46%)	203 (100%)	(0)	
Birth trauma	Yes	1 (0.53%)	0	0.389	.505
	No	185 (99.46%)	203 (100%)	(0)	
5 min Apgar <7	Yes	0	2 (0.99%)	6.280	.999
	No	186 (100%)	201 (99.01%)	(0.980–1.045)	
Neonatal hypoglycemia	Yes	3 (1.61%)	0	1.795	1.000
	No	183 (98.39%)	203 (100%)	(0.16–20.18)	
Need for phototherapy	Yes	1 (0.54%)	2 (0.99%)	1.013	.468
	No	185 (99.46%)	201 (99.01%)	(0.988–1.038)	
Gestational Hypertension	Absent	158 (84.94%)	181 (89.16%)	0.675	.545
	Present	28 (15.05%)	22 (10.84%)	(0.189–2.410)	
Maternal glycemic control	Adequate	172 (92.5%)	183 (90.15%)	0.983	.976
	Not adequate	14 (7.53%)	20 (9.85%)	(0.323–2.985)	
Post-Partum Glucose Tolerance	Normal	119 (63.97%)	134 (66.01%)	0.457	.342
	Impaired	67 (36.02%)	69 (33.99%)	(0.091–2.301)	
Baby's birth weight (kg)	<4	183 (98.4%)	198 (97.54%)	2.541	.257
	>4	3 (1.61%)	5 (2.46%)	(0.51–12.730)	
Baby's birth length (cm)	<50	163 (87.6%)	188 (92.7%)	1.556	.415
	>50	23 (12.4%)	15 (7.4%)	(0.538–4.503)	
Pre-eclampsia (%)	–	5	4	–	.35
Gestational age at delivery (weeks)	–	36.16 + 5.88	37.81 ± 7.06	-	.04

Table 3 – Individual comparison of primary and secondary outcome characteristics between Group A vs Group C.

Variables		Group A (Metformin in the 1st trimester) (N = 186)	Group C (Insulin) (N=151)	OR (CI)	*p*-value
Premature birth	Yes	23 (12.37%)	9 (6.27%)	1.805	.236
	No	163 (87.63%)	142 (93.73%)	(0.694–4.695)	
Respiratory distress	Yes	1 (0.53%)	0	6.280	1.000
	No	185 (99.46%)	151 (100%)	(0)	
Birth trauma	Yes	1 (0.53%)	1 (0.66%)	0.389	.505
	No	185 (99.46%)	150 (99.33%)	(0.024–6.260)	
5 min Apgar <7	Yes	0	0	1.009	1.000
	No	186 (100%)	151 (100%)	(0.992–4.695)	
Neonatal hypoglycemia	Yes	3 (1.61%)	2 (1.32%)	0.978	.195
	No	183 (98.38%)	149 (98.67%)	(0.948–1.009)	
Need for Phototherapy	Yes	1 (0.53%)	1 (0.66%)	1.009	1.000
	No	185 (99.46%)	150 (99.33%)	(0.992–1.027)	
Gestational Hypertension	Absent	158 (84.9%)	135 (89.5%)	0.667	.495
	Present	28 (15.1%)	16 (10.5%)	(0.159–2.339)	
Maternal glycemic control	Adequate	172 (92.5%)	110 (92.4%)	0.990	.988
	Not adequate	14 (7.3%)	9 (7.6%)	(0.321–2.782)	
Post-Partum Glucose Tolerance	Normal	119 (63.97%)	99 (65.7%)	0.502	.347
	Impaired	67 (36.02%)	52 (34.3%)	(0.071–2.320)	
Baby's birth weight (kg)	<4	183 (98.4%)	146 (96.68%)	2.542	.261
	>4	3 (1.61%)	5 (3.31%)	(0.407–11.721)	
Baby's birth length (cm)	<50	163 (87.6%)	131 (86.5%)	1.563 (0.578–4.302)	.423
	>50	23 (12.4%)	20 (13.5%)		
Pre eclampsia (%)	–	5	3	–	.44
Gestational age at delivery (weeks ± days)	–	36.16 + 5.88	37.25 ± 6.72	–	.04

Table 4 – Individual comparison of primary and secondary outcome characteristics between Group A vs Group C-1.

Variables		Group A (Metformin in the 1st trimester) (N = 186)	Group C-1 (Insulin in the 1st trimester) (N=57)	OR (CI)	*p*-value
Premature birth	Yes	23 (12.37%)	5 (8.77%)	1.63	.34
	No	163 (87.63%)	52 (91.22%)	(0.594–3.165)	
Respiratory distress	Yes	1 (0.53%)	0	5.190	1.000
	No	185 (99.46%)	57 (100%)	(0)	
Birth trauma	Yes	1 (0.53%)	1 (1.76%)	0.246	.445
	No	185 (99.46%)	56 (98.24%)	(0.011–3.610)	
5 min Apgar <7	Yes	0	0	0.989	1.000
	No	186 (100%)	57 (100%)	(0.866–4.383)	
Neonatal hypoglycemia	Yes	3 (1.61%)	3 (5.26%)	0885	.232
	No	183 (98.38%)	54 (94.74%)	(0.799–1.509)	
Need for Phototherapy	Yes	1 (0.53%)	1 (1.76%)	1.118	1.000
	No	185 (99.46%)	56 (98.24%)	(0.955–1.029)	
Gestational Hypertension	Absent	158 (84.9%)	49 (85.97%)	0.717	.375
	Present	28 (15.1%)	8 (14.03%)	(0.320–3.677)	
Maternal glycemic control	Adequate	172 (92.5%)	53 (92.99%)	0.916	.828
	Not adequate	14 (7.3%)	4 (7.01%)	(0.556–2.686)	
Post-Partum Glucose Tolerance	Normal	119 (63.97%)	35 (61.41%)	0.612	.420
	Impaired	67 (36.02%)	22 (38.59%)	(0.094–1.998)	
Baby's birth weight (kg)	<4	183 (98.4%)	55 (96.49%)	2.216	.137
	>4	3 (1.61%)	2 (3.51%)	(0.398–9.615)	
Baby's birth length (cm)	<50	163 (87.6%)	50 (87.72%)	1.453	.414
	>50	23 (12.4%)	7 (12.28%)	(0.499–5.732)	

Table 5 – Comparison of additional secondary outcome characteristics between Group A, B and C.

Characteristics	Group A (Metformin in the 1st trimester) Mean ± SD (N = 186)	Group B (Metformin in the 2nd trimester) Mean ± SD (N = 203)	Group C (Insulin) Mean ± SD (N = 151)	*p*-value (Group A vs Group B)	*p-value* (Group A vs Group C)
BMI at diagnosis (kg/m^2)	29.8 ± 5.6	28.5 ± 7.1	30.2 ± 6.6	.34	.18
Weight gain during gestation (kg)	7.9 ± 4.1	7.7 ± 3.9	8.4 ± 5.1	.22	.08
Weight loss from delivery to postpartum visit (kg)	7.4 ± 3.8	7.1 ± 4.2	6.8 ± 4.4	.11	.09
Maternal hypoglcyemia (%)	3.7%	3.1%	6.3%	.40	.06

not statistically significant, patients in group C receiving insulin had greater weight gain during pregnancy, lesser weight loss following pregnancy and higher incidence of maternal hypoglycaemia.

The overall rate of pregnancy loss was 2.59% (14/540) with the overall incidence of stillbirths/IUD being 1.3% (7/540), with 3.23% (6/186) in Group A and 0.5% (1/203) in Group B. There was only one case of early pregnancy loss (0.18%) due to spontaneous abortion in Group A. Total congenital anomalies reported were 1.11% (6/540), of which 4 (2.15%) were in group A and 2 (1.32%) in Group C. Overall, the anomalies noted included cardiac anomalies in 2, spina bifida in 3 and rhizomelia in 1. All the pregnancies with congenital anomalies had medical terminations of pregnancy.

4. Discussion

The perinatal effects of metformin when initiated, on diagnosis of diabetes, in the 1st trimester of pregnancy compared to it being initiated later in pregnancy has not been specifically studied in women with gestational diabetes without preconception exposure to metformin. Several studies have however looked into the effects of exposure to metformin in the 1st trimester of pregnancy while on treatment for PCOD and have reported its relative safety [3,7,11–16]. Though majority of the international guidelines have not officially approved metformin for treatment of gestational diabetes in early pregnancy, evidence has accumulated favouring its safety and efficacy in early GDM. Though insulin is the standard

treatment of choice for GDM, it has several disadvantages including multiple daily injections, dose adjustments, risk of hypoglycaemia, and issues with storage. As such, a safe and effective oral therapy, akin to metformin, is generally favoured among women with GDM, more so in a developing country like India.

The main objective of this study was to compare the primary and secondary composite maternal and fetal outcomes of initiating metformin in the 1st trimester (Group A) with that of initiating metformin after the 1st trimester (Group B) and that of insulin alone initiated in any trimester (Group C) for glycaemic control. Of the 540 subjects screened, 186 patients diagnosed with diabetes had to be initiated on metformin in their 1st trimester itself. These women had a mean gestational age of 10.04 ± 1.8 weeks at diagnosis with significant number among them having risk factors such as a positive family history of diabetes and a previous history of GDM. Early diagnosis of hyperglycaemia in this group had permitted timely intervention in the form of medical nutritional therapy and oral metformin, thereby favouring a better perinatal outcome despite an exposure to an earlier and more prolonged duration of hyperglycaemia [17].

Overall, 47.30% subjects taking metformin (group A + B) required supplementary insulin in our study which is comparable to the findings in the MiG Trial (46.3%) [7]. A subgroup analysis was done comparing patients taking metformin alone (A-1) with those requiring supplemental insulin (A-2). The findings (Table 6) failed to show any significant difference in outcomes. Although it was not statistically significant, a higher fasting plasma glucose level was recorded at the time of diagnosis in Group A (108.67 ± 32.2 mg%) as compared to Group B (102 ± 26.5 mg%). This along with early onset of hyperglycemia necessitating intervention (1st trimester vs. 2nd or 3rd trimester), may have contributed to the higher rate of requirement of supplemental insulin for glycemic control in Group A (99/186 (53.22%)) as compared to Group B (85/203 (41.87%)).

Among the primary outcome variables, premature births were numerically higher in Group A (12.37%) when compared to Group B (9.85%) and Group C (6.27%), with most deliveries being associated with spontaneous labour. Though there was no statistical difference among the groups A and B with regard to premature birth ($p = .12$), it was statistically significant when either A or B (metformin groups) were compared to group C (Insulin group) ($p = .03$). This is similar to the findings of the MiG Trial, wherein a preterm birth rate was reported in 12.1% subjects in the Metformin group and 7.6% subjects in the insulin group ($p = .04$) [7]. Similar findings have also been reflected in the meta-analysis carried out by Gui et al. and Poolsup et al. [18,19]. The impact of diabetes on spontaneous preterm birth though not explained has been widely reported [20]. The HAPO study, and subsequent findings by Ngai et al., have reported a positive association between the timing of the diagnosis of gestational diabetes mellitus (GDM) and preterm delivery [21,22]. Therefore the higher incidence of prematurity may be due to the earlier onset of hyperglycaemia and the causal association with metformin which remains to be investigated further. None of the other individual variables of the primary composite outcome have shown statistically significant differences between the groups, thereby suggesting the safety of metformin when initiated within the first trimester. Similar findings have been reported in a published meta-analysis on metformin in pregnancy [18,19].

Comparing the secondary composite outcomes, there were no statistical difference between the groups, further lending credence to the maternal and fetal safety of metformin initiated early in pregnancy. Birth weight above 90th percentile was seen in only 1.61% infants in Group A, 2.46% in Group B and 3.31% in Group C while the MiG Trial had birth weight >90th percentile in 19.3% of metformin group and 18.6% of insulin group [7]. Adherence to stringent HAPO criteria and strict glycaemic control, which took effect after the MiG Trial, could probably account for this difference in findings. Moreover, ethnic variations in the birth weight of infants between Indian and Western populations, which is well recognized also needs to be considered [23]. Post partum OGTT revealed impaired glucose intolerance among 36.02%, 33.99% and 34.3% patients in Group A, B and C respectively which is consistent with published reports. Even though Group A had early onset DM when compared to group B, the lack of difference in the incidence of persistent postpartum hyperglycaemia between these two groups can be possibly attributed to inadequate follow-up and the retrospective nature of the

Table 6 – Comparison of primary and secondary outcome characteristics between Group A-1 and A-2.

Characteristics-n(%)		Group A-1 (Metformin alone) (N = 205)	Group A-2 (Supplemental insulin) (N = 184)	*p*-value
Premature birth	Yes	26 (12.6%)	21 (11.4%)	.42
Respiratory distress	Yes	1 (0.48%)	0	–
Birth trauma	Yes	1 (0.48%)	1 (0.54%)	.56
5 min Apgar <7	Yes	1 (0.48%)	1 (0.54%)	.70
Neonatal hypoglycemia	Yes	2 (0.97%)	2 (1.08%)	.89
Need for Phototherapy	Yes	1 (0.48%)	1 (0.54%)	.94
Gestational Hypertension	Present	30 (14.8%)	22 (12.1%)	.38
Maternal glycemic control	Not Adequate	16 (7.8%)	15 (8.2%)	.48
Post-Partum Glucose Tolerance	Impaired	76 (37.3%)	71 (38.6%)	.51
Baby's birth weight (kg)	>4 kg	4 (1.9%)	4 (2.2%)	.66
Baby's birth length (cm)	>50 cm	26 (12.6%)	23 (12.3%)	.52

study. The postpartum study of pregnancies which were complicated by diabetes, by Kitzmiller et al. had reported that 34.3% of the study group (N = 527) demonstrated post- partum glucose abnormalities [24]. In the MiG study, 23.0% in the metformin group and 20.6% in the insulin group had impaired glucose tolerance post-partum [7]. Though maternal glycemic control was comparable among groups A, B and C, our study had the limitation of using subjective measurements of maternal glycemic control owing to its' retrospective nature. The use of objective measurements like high Hba1c and persistent hyperglycemia with unusual insulin requirements would have been better to define maternal glycemic control. The institute protocol was to treat all women with overt DM with insulin at diagnosis. Thus, there were no patients with overt DM in the Group A, since all of them belonged to Group C. Hence comparison of outcomes between GDM and Overt DM groups initiated early on metformin or insulin could not be ascertained.

The teratogenic effects of diabetes probably start early in pregnancy. The increased risk of congenital abnormalities found in diabetic mothers may be associated to poor metabolic control during the period of organogenesis that occurs in the first trimester of pregnancy, though the exact mechanisms remain elusive [21]. In our study, we found a total of 1.11% congenital anomalies, 2.15% in the metformin group vs 1.32% in the insulin group. It is almost similar to that of 3.03% congenital anomalies reported in the metformin group in the MiG trial, though much less in the insulin group at 4.86% [7].

5. Conclusion

Our study is the first analysis of maternal and fetal outcomes with early initiation of metformin in GDM mothers of Asian Indian origin over a period of 5 years. Our findings suggest that metformin is a safe, convenient and effective option that can be initiated in the first trimester for the management of diabetes mellitus complicating pregnancy, with or without insulin. Initiation of metformin in the first trimester of pregnancy is not associated with an increase in the adverse outcomes like neonatal hypoglycaemia, need for phototherapy, respiratory distress, birth trauma, 5 min APGAR < 7, high birth weight or birth length, poor maternal glycaemic control, post-partum hyperglycaemia or gestational hypertension. However, vigilance for spontaneous onset of labour aiming at early medical attention is advisable in view of the increased rates of preterm deliveries.

Therefore, our study suggests that the initiation of metformin within the 1st trimester of pregnancy has no significant maternal and fetal adverse effect. However, a cautious approach is strongly recommended in view of the higher number of premature births that were reported in those patients where in metformin exposure was present throughout pregnancy.

Conflicts of interest

None.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2018.01.002.

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