Original Article

Title-Efficacy of metformin as monotherapy in gestational and pre-gestational diabetic pregnant women

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ABSTRACT

Diabetes is the most common medical disorder in pregnancy in UAE affecting between 7.9% to 37.7% of women. Recommendations for Metformin use in pregnant diabetics vary between societies. Through this study, we explored the effectiveness and safety of metformin monotherapy in women with diabetes during pregnancy and analyzed the clinico-demographic profile of cases with successful metformin use. This is a retrospective study conducted in Abdulla Bin Omran Hospital, RAK between January 2018 and December 2019 including women with GDM and PGDM requiring pharmacological treatment for blood sugar control. The effectiveness of metformin was assessed with Glycemic control FBG, 1HPG, and 2HPG levels at definite intervals and pregnancy outcomes. Clinico-demographic profiles for the successful use of Metformin were analyzed. Descriptive, inferential, and regression model analyses were done by using SPSS version 24. This included 271 patients with GDM and 56 with PGDM(total 327).Metformin was as effective as insulin for the control of blood glucose in both GDM and PGDM. Insulin is more effective in control of FBG abnormalities but is associated with higher preterm labor rates(p=.0009).Women with higher BMI (≥40) and FBG levels at diagnosis are significantly more likely to need supplemental insulin(p= .00008 and .0001). This is not associated with factors like age, parity, ethnicity, class1 or class-2 obesity. There were no abnormalities or differences in babies at a 2-year follow-up. Metformin is a safe and effective option for both PGDM and GDM in carefully selected patients without any adverse effect on offspring.

Keywords: Metformin, Gestational diabetes, Pregestational diabetes, Monotherapy

Introduction

Diabetes is the most common medical disorder in pregnancy, particularly in this part of the world. According to the International Diabetes Federation in 2021, UAE was 18th in the world with the highest prevalence of diabetes [1]. This subsequently increased the number of women with diabetes during pregnancy. Pregnant diabetics are divided into 2 categories. Women who developed diabetes during pregnancy for the first time (after 24 weeks of gestation) are called Gestational diabetics (GDM) whereas those who were diabetic prior to pregnancy or whose diabetes developed before 24 weeks of gestation are referred to as Pre-gestational diabetics (PGDM). Diabetes during pregnancy (both types) can adversely affect the mother and fetus. The rate of GDM in the United Arab Emirates (UAE) is reported to vary from 7.9% to 37.7% in the published literature, depending on the use of different diagnostic criteria [2-5]. A recent study shows the rate to be 27% among women with twin pregnancies [6]. Metformin is an oral hypoglycemic agent that acts as an insulin sensitizer, decreases serum insulin levels, and inhibits transepithelial glucose transport in the intestine [7-9]. It is a biguanide and is used abundantly across the world to control blood glucose (BG) levels. Commercially

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produced Insulin has long been the gold standard approach to achieving glycemic control during pregnancy. The NICE guideline states that women with diabetes may be advised to use metformin as an adjunct or alternative to insulin in the preconception period and during pregnancy when the likely benefits from improved blood glucose control outweigh the potential for harm. It also recommends offering metformin to women with GDM if blood glucose targets are not met using lifestyle changes within 1–2 weeks. Furthermore, to offer insulin instead of metformin to women with GDM if metformin is contraindicated or unacceptable [10]. Recently The American College of Obstetricians and Gynecologists (ACOG) has issued clinical management guidelines offering an update on the pharmacologic treatment of gestational diabetes mellitus (GDM) stating that when pharmacologic treatment of GDM is indicated, insulin is considered the preferred treatment for diabetes in pregnancy and in women who decline insulin therapy or will be unable to safely administer insulin, or who cannot afford insulin, metformin is a reasonable choice (Level B) [11]. The 2022 American Diabetes Association (ADA) guidelines recommend Insulin as the first-line agent for the treatment of GDM, and metformin should only be used in the first trimester of pregnancy to treat PCOS. Metformin was not recommended as a first-line treatment for GDM because they are known to cross the placenta and safety concerns for offspring [12]. Most communities do not advocate the use of other agents like metformin which is ideally used routinely in patients with type-2 diabetes, obesity, and Polycystic ovary syndrome (to regularize menstrual cycles) [13]. The advantages of metformin are that it is familiar, inexpensive, it's easy to administer with higher patient compliance. In pregnancy, added benefits of metformin over insulin are fewer incidences of maternal weight gain, preeclampsia, and maternal hypoglycemia and it is associated with clear benefits as a treatment of hyperglycemia in pregnancy [14-17]. Published data from post-marketing studies have not reported a clear association between metformin and major birth defects, miscarriage, or adverse maternal or fetal outcomes when it was used during pregnancy [15, 18].

Metformin can be used for various indications during pregnancy like GDM, PGDM, prevention of pregnancy complications in patients with PCOS, and prevention of occurrence of GDM in pregnancies at high risk of developing GDM (i.e history of GDM in previous pregnancy) but the use for the latter indication is uncommon [19-21]. In a recent study from UAE, it was found that in women with twin gestation and GDM, the majority were treated successfully with lifestyle management (71.5%) followed by Insulin (14.7%), Metformin (11.9%) and both insulin and Metformin (1.8%) [6]. Recent years have seen metformin becoming increasingly acceptable for use in pregnancy in UAE. However, no study was done on women in UAE specifically addressing the efficacy of the use of metformin alone and the outcome of its use. Metformin is a drug that is readily available, affordable, and has been in use for a long time. The major concern with metformin is also the unpredictable need to add insulin to control blood glucose. There are not enough studies that focus on the clinico-demographic profile of patients in whom metformin alone was effective in controlling blood glucose during pregnancy [20]. Most of the previous studies also have incomplete data on maternal (e.g. weight gain, hypertension, operative interference) and neonatal (e.g. high birth weight, prematurity, perinatal mortality, neonatal issues i.e. hypoglycemia, jaundice, neonatal admissions) complications seen with metformin use in pregnancy [12, 20, 21]. Knowing whether metformin can be used as a monotherapy in this population and understanding the clinico-demographic profile of the women where metformin alone was able to control blood glucose in the local population will help in improving the choice of treatment options leading to better management of this common but serious condition during pregnancy.

Aims and objectives

Our primary objective was to find out whether metformin as monotherapy is effective in controlling blood glucose levels in women with Gestational and Pre-gestational diabetes. Furthermore, the secondary objective was to study the clinico-demographic profile of the women where metformin alone was able to control blood glucose.

Materials and Methods

This is a retrospective study conducted in Abdulla Bin Omran Hospital, Ras Al Khaimah between January 2018 and December 2019. After due ethical clearance (Approval Reference No: MOHAP/REC/20201 22 -2020-VG- M), case records of patients were studied to include them in GDM and PGDM groups. The antenatal records, delivery records, and neonatal case records were studied. In diabetic women, those who needed medication for diabetes were included and the data from those who received metformin was compared to those who received insulin. Pregnant women with GDM or PGDM who are well controlled with lifestyle changes (diet and exercise) alone without the need for Metformin or Insulin, those who refused any treatment, and cases where blood sugar is not controlled were excluded.

The case files of those who received Metformin as monotherapy were studied for further analysis. Data was collected in data collection sheets where the effectiveness of metformin was assessed with Glycemic control in GDM and PGDM by Fasting blood glucose (FBG), 1-hour (1HPG), and 2-hour postprandial blood glucose (2HPG) levels. Dose, schedule, and duration of use were also noted. Blood sugar control was noted 2 weeks after diagnosis, 4 weeks after diagnosis, and at the time of delivery. As per general practice guidelines, in the metformin group, the maximum dose was 2500 mg per day. Insulin was added if targets could not be reached on metformin alone at maximum doses. Treatment glycemic targets of FBS < 5.3 mmol/L, 1HPG < 7.8 mmol/L, and 2HPG < 6.4 mmol/L recommended by the National Institute for Health and Care Excellence [10] were taken as the standard of control for the study. If blood glucose targets were not met with diet and exercise changes within 2 weeks, pharmacological treatment was offered. In cases, where

insulin was added for control of BG, the dose of insulin used, was recorded.

The data was analyzed using SPSS version 24. Descriptive statistical analysis (i.e., relative numbers, median, and measures of dispersion) was used for the majority of the data. Inferential statistical analysis was used as applicable (i.e., chi-square test for categorical variables, and student t-tests to compare differences between group means for continuous variables). Multivariate or univariate regression model analyses were done to quantify the association as applicable. Correlations were tested at different levels of significance (i.e., 5%, 1%, and 0.1%) and a p-value of 0.05 was taken as significant.

A total of 348 patient records were identified using the inclusion criteria. 21 case records were discarded due to grossly incomplete data. 327 records were studied in detail. 271 patients with GDM and 56 patients with PGDM were identified in our study. Neonatal records were available for 317 babies and 2-year follow-ups of the babies were possible for only 23 of them **(Figure 1)**. As the population dynamics in UAE are heterogeneous, nationality was recorded rather than ethnicity. In both PGDM and GDM patients, Southeast Asian patients were the highest [n=146 (53.8%) in GDM and n=33 (58.9%) in PGDM)] followed by MENA (the Middle East N Africa] region and others.

Results and Discussion

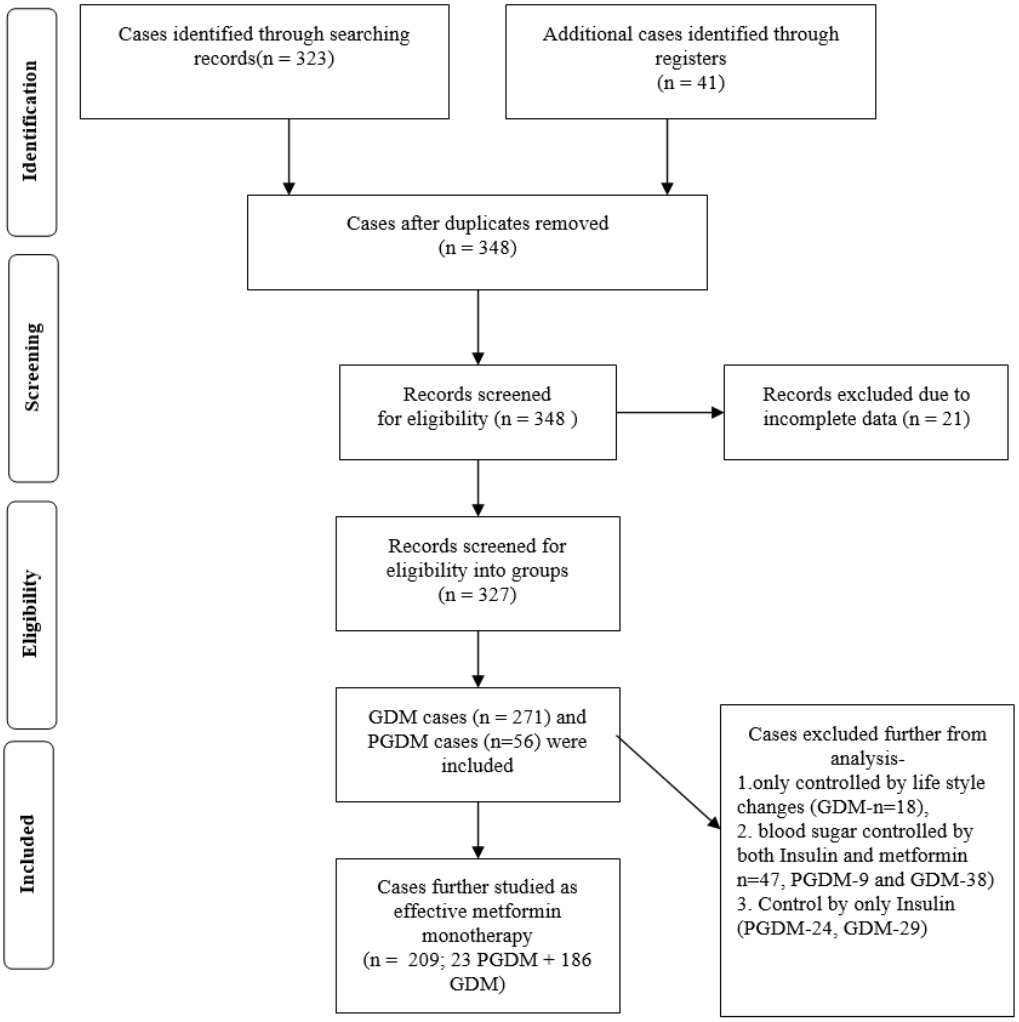

Figure 1. Case selection- Metformin use in pregnancy

PGDM

For comparison, patients were divided into 3 groups, Group 1 consisted of cases where control was successful using metformin only, group 2 consisted of cases where only insulin was used for control, and group 3 consisted of cases where insulin was added for blood sugar control.

37 patients with PGDM were on Metformin at the time of diagnosis of pregnancy and 32 were continued on Metformin. 24 women (19 patients were on Insulin and 5 who opted for Insulin treatment) received Insulin treatment since the diagnosis of pregnancy.

Out of 32 women, 9(28.1%) required the addition of Insulin for the control of blood sugar during pregnancy (group3), 23 belonged to Group 1, and 24 belonged to Group 2. There was

no difference between the 1st and 2nd groups regarding epidemiological characteristics **(Table 1)**. There was no significant difference between the groups regarding blood sugar control and maternal or fetal outcomes. Although there were anomalies in ultrasonography (USG) for expelled fetuses in second-trimester miscarriages, no congenital anomalies were detected at birth in either group **(Table 1)**.

Metformin was successfully used in 23 patients with a median dose requirement of 2000 mg per day. Although the number of patients requiring additional insulin in addition to metformin was small (n=9), in the comparison, successful use of metformin was associated with younger age (<35 years), BMI between 30 and 39.9, normal fasting blood glucose and lower values of fasting blood glucose at diagnosis (<7mmol/L). These were, however, not statistically significant (p>.05).

Table 1. Metformin Use in PGDM

Variables	Group-1 (n=23)	Group-2 (n=24)	Significance /p-value
Age	35.2 ± 5.01 years	35± 4.242 years	>.05
Parity [n (%)]			
-Nulliparous	5 (21.7)	3 (12.5)	>.05
-Multiparous	18 (78.2)	21 (87.5)	
Body Mass Index [Kg/Square meter] [n (%)]			
-<25	1 (4.3)	0	
-25-29.9	4 (17.3)	3 (12.5)	Obesity (BMI≥30Kg/ M^2)
-30-34.9	13 (56.5)	11(45.8)	
-35-39.9	3 (13)	6 (25)	
-≥40	2 (8.6)	4 (16.6)	p= .399
Antenatal complications [n (%)]			
- Hypo/Hyperthyroidism	3 (13)	1 (4.1)	Presence of complications p= .676
-Anaemia in pregnancy	5 (21.7)	7 (29.1)	
-Chronic hypertension	2 (8.6)	3 (12.5)	
-Others*	3 (13)	4 (16.6)	
Pregnancy outcome [n (%)]			
-Miscarriage	5 (21.7)	3 (12.5)	p= .399
-Preterm labor	4 (17.3)	2 (8.3)	p= .352
-Instrumental delivery/CS	3 (13)	5 (20.83)	p= .477
-PIH/PET	2 (8.6)	5 (20.83)	P= .242
-Others**	5 (21.7)	3 (12.5)	P= .365
Fetal/Neonatal outcome [n (%)]			
-Macrosomia/ LGA baby	6 (26)	8 (33.3)	p= .587
-Neonatal admission	7 (30.4) (MHS=1.85days)	9 (37.5) (MHS=2.11days)	p= .609
-Others***	3 (13)	2 (8.3)	p= .600

[MHS= Mean hospital stay

Others*: Obstetric cholestasis=1, Twin pregnancy=2, Toxoplasmosis under treatment=1, Rh negative pregnancy=2, Gestational thrombocytopenia=1

Others**: Antepartum hemorrhage=1, Postpartum hemorrhage=1, Urinary tract infection=2, Polyhydramnios=4

Others***: One newborn in each group had Neonatal jaundice, One neonate in the metformin group had Caput succedaneum and scalp abrasion each, and Intrauterine growth restriction was seen in 1 newborn in the Insulin group]

GDM

For comparison, patients were divided into 3 groups, Group 1 consisted of cases where control was successful using metformin only, group 2 consisted of cases where only insulin was used for control, and group 3 consisted of cases where insulin was added for blood sugar control.

Out of 271 women with GDM, 18 were controlled by diet and exercise only. 253 women required pharmacological treatment for blood sugar control. 38(16.9%) women needed the addition of Insulin for blood sugar control (group-3), 29 women received only insulin with a mean dose of 27.24±12.4 units (group-2) and 186 women received only metformin (group-1) at a median dose of 1000 mg per day [Mean-1408.6±614.33mg]. The rate of preterm labor (p=.0009) and other maternal complications (p=.0032) were higher in the Insulin group, but there were no significant differences between the groups regarding other outcomes **(Table 2)**.

Table 2. Metformin Use in GDM

Variables	Group-1 (n=186)	Group-2 (n=29)	Significance/p-value
Age	33.27 ± 4.82 years	30.63± 2.56 years	>.05
Gestational age at diagnosis	26.00± 2.29 weeks	27.75± 3.29 weeks	>.05
Parity [n (%)]			
-Nulliparous	8 (4.3)	2 (6.8)	.53
-Multiparous	178 (95.6)	27(93.1)	
Body Mass Index [Kg/Square meter] [n (%)]			
-<25	4 (2.1)	1 (3.4)	
-25-29.9	35 (18.8)	3 (10.3)	Obesity (BMI≥30Kg/M^2)
-30-34.9	98 (52.6)	14 (48.2)	
-35-39.9	32 (17.2)	7 (24.1)	p= .368
-≥40	17 (9.1)	4 (13.7)	
Antenatal complications [n (%)]			
-Hypo/Hyperthyroidism	3 (1.6)	1 (3.4)	Presence of any complication p= .101
-Anemia in pregnancy	23 (12.3)	5 (17.2)	
-Chronic hypertension	5 (2.6)	3 (10.3)	
-Others*	13 (6.9)	2 (6.8)	
Pregnancy outcome [n (%)]			
-Preterm labor	11(5.9)	7 (24.1)	.0009
-Instrumental delivery/CS	17 (9.1)	6 (20.6)	.0612
-Polyhydramnios	14 (7.5)	5 (17.2)	.0864
-Urinary tract infection	21 (11.2)	3 (10.3)	.8804
-Others**	5 (2.6)	7 (24.1)	.0032
Fetal/Neonatal outcome [n (%)]			
-Macrosomia/ LGA baby	41 (22)	7 (24.1)	.801
-Neonatal admission	23 (12.3)	4 (13.7)	.829
-Neonatal jaundice	19 (10.2)	6 (20.6)	.101
-Others***	9 (4.8)	4 (13.7)	.059

[LGA= Large for gestational age; CS= Cesarean section

-Others***: there were 2 stillbirths in group-1 and 1 in group-2, 5 neonates in group-1 and 2 in group-2 had scalp injuries as caput or abrasion, Neonatal sepsis was seen in 2 babies in group-1 and 1 in group-2

- Others**: Postpartum hemorrhage=4, Preeclampsia=3, Perineal tear extensions (anal sphincter injury)=5

*Others: Obstetric cholestasis=1, Twin pregnancy=5, Rh negative pregnancy=7, Gestational thrombocytopenia=2]

Blood glucose reduction was seen with both Metformin and Insulin use. Although Insulin was significantly more effective in reducing fasting blood glucose abnormalities (p= < .001), this was not significant for 1HPG or 2PG values **(Table 3)**.

Table 3. Metformin Use in GDM -Glycemic profile

	Group-1 (n=186)	Group-2 (n=29)	p-value
Mean blood glucose at diagnosis (mmol/L)			
Mean FBG	6.29±1.63	10.31±1.77	< .00001
Mean 1HBG	9.91±1.2	11.12±1.18	.025
Mean 2HBG	8.13±1.29	9.32±1.79	.0380
Mean blood glucose at delivery (mmol/L)			
Mean FBG	5.42 ±1.18	6.72 ±1.72	Decrease in FBG- p= < .001
Mean 1HBG	7.56 ±1.43	9.87 ±2.31	Decrease in FBG- p= .853
Mean 2HBG	7.26 ±2.13	8.95 ±1.66	Decrease in FBG- p= .781

[FBG= Fasting blood glucose; 1 HBG= 1 hour post prandial blood glucose; 2 HBG= 2 hour post prandial blood glucose]

The use of Metformin monotherapy for the control of blood glucose revealed women with class-1 or class-2 obesity, and minimal or absent FBG abnormalities were well controlled with Metformin therapy. Women needing supplemental insulin had higher mean BMI (p= .00008) and higher FBG values at diagnosis (p= .0001). The parameters like age, parity, ethnicity, and gestational age at diagnosis did not significantly affect the need for supplemental insulin for blood sugar control **(Table 4)**.

Table 4. Insulin supplementation requirement in women receiving Metformin

Variables	Group-1 (n=186)	Group-3 (n=38)	Significance
Age	33.27 ± 4.82 years	33.39± 6.72 years	>.05
Gestational age at diagnosis	26.00± 2.29 weeks	26.23± 2.25weeks	>.05
Parity [n (%)]			
-Nulliparous	8 (4.3)	1 (2.63)	.63
-Multiparous	178 (95.6)	37 (97.3)	
Body Mass Index [Kg/Square meter] [n(%)]			
-<25	4 (2.1)	0	Mean BMI in Metformin only group= 35.82± 5.58 The mean BMI in Supplemental Insulin group= 32.62± 4.22 p= .00008
-25-29.9	35 (18.8)	9 (23.6)	
-30-34.9	98 (52.6)	12 (31.5)	
-35-39.9	32 (17.2)	12 (31.5)	
-≥40	17 (9.1)	5 (13.1)	
Blood glucose at diagnosis			
FBG [Mean±SD]	6.29±1.63	9.43±2.04	p= .0001
1HBG [Mean±SD]	9.91±1.2	10.96±1.67	p= .058
2HBG [Mean±SD]	8.13±1.29	8.92±1.57	p= .05672

[FBG= Fasting blood glucose; 1 HBG= 1 hour post prandial blood glucose; 2 HBG= 2 hour post prandial blood glucose]

A 2-year follow-up was done on the babies of the mothers with PGDM or GDM in pregnancy. Parents of only 23 of these babies consented to the study. 8 babies were from the Insulin arm and 15 from the Metformin arm. There was no significant difference between the groups regarding mean weight, mid-arm circumference, height, or psychomotor development.

There are numerous studies in the literature reporting the effectiveness of Metformin for controlling blood sugar and the prevention of complications in pregnant diabetics. A recent meta-analysis involving 35 studies including more than 8000 participants with moderate to low bias shows no significant differences in the risk of pre-eclampsia, preterm birth, gestational age at delivery, or likelihood of cesarean section. It showed a clear trend toward a reduction in the likelihood of pre-eclampsia and maternal weight gain during pregnancy, with metformin use. There were significant gastrointestinal side effects with Metformin use compared to Insulin used for all indications [17]. The findings are similar to our study where there are no differences in maternal outcomes. However, the current study included fetal/neonatal outcomes in addition to maternal outcomes. Similarly, another study from Pakistan (n=50) showed heavier babies and reduced cesarean deliveries in the Insulin group, which is in contrast with the findings of our study [22].

In our study, 16.9% of women with GDM and 28.1% with PGDM on Metformin, required the addition of Insulin for blood sugar control. The factors that were associated with the need for Insulin supplementation included high FBG values at diagnosis and class-3 obesity. In another similar study, 23.4% of women with GDM needed supplemental insulin, and Insulin supplementation in the metformin group was related to initial body mass index, HbA1c, oral glucose tolerance test (GTT), and first week mean fasting glucose level (Wk1-mFG) on therapy. The 1-h glucose level during initial GTT (Hr1-GTT) of >212 mg/dL (11.77mmol/L) and the Wk1-mFG of >95 mg/dL (5.3mmol/L) were the two independent parameters associated with requiring supplemental insulin with a risk ratio of 58.6 (p = 0.004) and 11.5 (p = 0.0008), respectively [23]. This is in contrast with our study where the FBG at diagnosis and BMI of 40 or more were better predictors of insulin need. However, the sample size in the previous study was small (n=46) as compared to the current study (n=224).

In a few of the previous studies, it was found that babies of a mother with GDM who received Metformin were significantly heavier (10.47 versus 9.85 kg, 95% CI 0.04-1.20) at 1 year of age, were taller and heavier at age of 18 months and had larger mid-upper arm circumferences (p = 0.002) at 2 years of life [23-25]. This is in contrast with our study. However, the motor, social, or language development evaluated at the age of 2 years did not differ between the groups in our study, similar to a previous study [25]. Unlike other studies, our study did not include body fat measurement, PCOS patients, or comparisons at later stages of life [24-26]. Moreover, as the sample size in the current study is small, further studies in this aspect are required.

There were various limitations of our study. There were a differential number of cases in the Metformin and Insulin arm,

the Insulin arm being smaller in both GDM and PGDM. In addition, the number of cases requiring additional Insulin in PGDM patients was too small for further analysis. This being a retrospective study, the follow-up of the babies at 2 years of age was grossly limited by the small number.

Conclusion

Metformin for the treatment of PGDM and GDM in women is as effective as Insulin for blood glucose control and prevention of maternal and fetal complications. The effectiveness is better regarding control of postprandial blood glucose levels (1HBG and 2HBG) as compared to FBG levels. There were no adverse effects on growth and development seen in babies born to women using metformin in pregnancy at 2 years of age. Metformin is a safe and valid option for the successful treatment of both PGDM and GDM in carefully selected patients.

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Ethics statement: The research was approved by the institutional research and ethics committee.

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