Maternal and Fetal Outcome in Gestational Diabetes Mellitus (GDM) Treated with Diet and Metformin - A Preliminary Retrospective Analysis

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Abstract: *Context*: Metformin therapy for treatment of GDM (Gestational Diabetes Mellitus) is not yet approved by FDA.

Objectives: To assess the glycaemic control in women with GDM who received metformin therapy and to know the maternal side-effects and effects on the fetus-neonate.

Material and Methods: A preliminary retrospective cohort analysis of 38 women with GDM who received metformin along with dietary advice for control of GDM. The maternal analysis included the time of initiation of metformin therapy, the glycaemic control, the need to add insulin and the side-effects. Fetal outcome analysis included Apgar score at birth, birth weight, neonatal hypoglycaemia, still birth rate and congenital malformations. The goals of glycaemic control were achieved by a pre-prandial Blood sugar of 60-70 mg%; post prandial blood sugar of 120-140mg%.

Results: The mean age was 27.5 years and gestational age at diagnosis and initiation of metformin therapy was 24 weeks and 3 days. Twenty-four percent were diagnosed during first trimester. Ninety percent achieved glycaemic control with a dose of 1500 mg of metformin. Ten percent required an increment in dose up to 2250 mg and an addition of small dose of insulin only after 35 weeks of gestation. The mean birth weight was 3.12 kg and 13% were LGA. There were no cases of maternal or neonatal hypoglycaemia and no stillbirths, congenital anomalies or neonatal deaths.

Conclusion: Metformin therapy resulted in optimum control of blood sugar in most of the women with GDM without any significant side-effects in the mother or in the fetus-neonate.

Keywords: GDM, Metformin therapy, Glycaemic control, hypoglycaemia, congenital malformations.

INTRODUCTION

The conventional treatment of GDM is diet control and Insulin therapy when indicated. For advocating insulin therapy most often women need to get hospitalised for a prolonged period and the occurrence of hypoglycaemia also needs to be monitored carefully as hypoglycaemia is more dangerous to the fetus leading to sudden fetal demise. Oral hypoglycaemic agents during pregnancy were blamed to be associated with congenital malformations. There are no randomized controlled trials on which conclusions can be drawn regarding the teratogenicity of these oral agents and futher it is the level of metabolic control that is important to achieve good out come of the pregnancy and not the mode of therapy [1]. Hence search is on for an oral agent which does not cause congenital malformations and does not lead to hypoglycaemia. Glyburide is being used by some obstetricians but it is found to cause hypoglycaemia. Metformin is a Class B drug and does not cause hypoglycaemia and hence it can be administered during pregnancy though it is not yet approved by FDA. There is a controversy regarding its usage during pregnancy as it crosses the placenta and some studies have reported it being associated with increased incidence of pre-eclampsia and adverse perinatal outcome though others did not find any such association. In this context we have undertaken this preliminary retrospective analysis of women with GDM who received metformin therapy along with dietary advice during the past 6 years.

MATERIAL AND METHODS

The maternal health records of patients who received metformin for control of GDM were analysed with respect to the time of diagnosis (gestational age) of GDM and initiation of metformin therapy, the glycaemic control ,the need to add insulin and side-effects especially hypoglycaemia. Fetal outcome was also analysed which included Apgar score at birth, birth weight, neonatal hypoglycaemia, still birth rate and congenital malformations and their nature. The goals of glycaemic control were achieved by a pre-prandial Blood sugar of 60-70 mg%; post prandial blood sugar of 120-140mg%. GDM was diagnosed by performing OGTT with 100 gm oral glucose on out-patient basis and the timing of the test was according to the risk stratification during pregnancy. All the pregnant women with a diagnosis of GDM or IGT (impaired glucose tolerance) based on NDDG criteria were hospitalised and blood sugar profile was carried out which included the following samples; Fasting; 2 hours post breakfast ; pre-lunch and 2 hr post lunch; pre-dinner and 2 hour post-dinner and at 2 AM. All the women were adviced 1500 to 2000 K cal diet emphasising to consume the low glycaemic index foods and they started taking Metformin 500mg after the three large meals (after breakfast; after lunch and after dinner). Tablet methylcobalamine was given once daily to prevent vitamin B12 deficiency associated with metformin therapy. Oral

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Table 1. Clinical Profile

S. No	Characteristic	Value (n=38)
1	Mean age in yrs	27.5
2	Mean Gestational age at diagnosis in weeks+days	24+3
3	Family history of DM	(15) 39.5%
4	History of Recurrent Pregnancy loss	(5) 13%
5	Hypothyroidism	(8) 21%
6	Primigravidae	(16) 42%

informed consent was taken after explaining that metformin was the alternative oral treatment for GDM which is being advocated by some for GDM. The side-effects and advantages of metformin and the necessity of taking injections of Insulin as the standard treatment was also told and those women who chose to take metformin were only given the same . All the maternal records that were analysed included the patients treated by both the authors only. The Blood sugar profile was repeated after a minimum period of 72 hrs and when the glycaemic levels were within control they were discharged to home with advice to take the same dose and repeat a fasting and postprandial blood sugars every 2 weeks and come for antenatal check-up to OPD. At this visit they were reviewed and dose adjustment was carried out. The maximum dose which we advocated was 750 mg three times daily and if the blood sugar profile was not within the targeted values they were hospitalised and injection Human mixtard was added and dose titration was done. All the patients were monitored antepartum by Nonstress test from 32 weeks and USG was performed whenever indicated and mode of delivery was invidualised according to the present and past obstetric conditions and other associated complications. All the neonates were seen at birth by paediatricians and they were monitored for hypoglycaemia and other neonatal problems according to the hospital protocol.

Statistical Analysis

The results are analysed for the outcomes and calculated as percentages and proportions.

RESULTS

The clinical profile of the subjects is shown in Table **1**. The mean age is 27.5 yrs and 42% were primigravidae. There was family history of NIDDM in 39.5%. Thirteen percent gave history of recurrent pregnancy loss and 21% suffered from hypothyroidism. The mean gestational age at diagnosis was 24 weeks and 3 days.

Table **2** shows the time of initiation of metformin therapy soon after diagnosis. Majority (34.2%) were diagnosed in

Table 2. Gestational Age at Diagnosis and Initiation of Therapy

S. No	Gestational Age in Weeks	Number (n=38)	Percentage
1	≤12	9	23.7
2	>12 -28	8	21
3	>28-32	8	21
4	>32-38	13	34.2

Table 3. Maternal Outcome

S. No	Parameter Studied	Value (n=38)
1	Gestational Hypertension	(9) 23.7%
2	Premature rupture of membranes-	(6) 16%
3	Glycaemic control achieved with metformin alone	(34) 89.5%
4	Addition of Insulin	(4) 10.5%
5	LSCS	(19) 50%
6	Postnatal requirement of Metformin	(8) 21%
7	Maternal Morbidity and motality	nil

Table 4. Fetal/Neonatal Outcome

S. No	Parameter	Value (n=38)
1	Congenital malformations	Nil
2	Perinatal deaths	Nil
3	Mean birth weight	3.12 kg
4	Large for gestational age	(5) 13%
5	Neonatal complications	Nil

third trimester as expected because insulin resistance increases with increasing gestational age. The other reason is late presentation of the patient to our institute at later gestational age. However 23.7% were diagnosed during the first trimester.

Pregnancy outcome is shown in Tables **3** and **4**. Glycaemic control was achieved with diet and metformin (at a dose of 1500mg) alone in almost 90%. Remaining patients needed increment in dose up to 2250 mg and addition of small dose (10 Units) of insulin after 36 weeks of pregnancy. Gestational hypertension developed in 23.7% and there were no cases of pre-eclampsia. Sixteen percent developed premature rupture of membranes. Fifty percent underwent LSCS for various reasons. There were no significant side-effects due to metformin therapy that required stoppage of the drug and there were no cases of poor compliance.

All women were satisfied with the therapy and were happy that they did not have to take injections daily. There were no cases of morbidity and mortality. There were no congenital malformations though 23.7% received metformin during first trimester. There were no perinatal deaths and no significant morbidity. Metformin was stopped the day before induction of labour and or LSCS. There were no cases of neonatal hypoglycaemia or hyperbilirubinaemia. The mean birth weight was 3.12 kg and 13% were large for gestational age.

Table **5** shows the side-effects of metformin on mother and foetus that were specifically looked for and the efficacy of metformin along with diet.

DISCUSSION

India is considered to be the capital of Diabetes mellitus. Noninsulin dependent mellitus reveals itself during pregnancy as Gestational Diabetes Mellitus (GDM) and it is on the increase, the incidence in India being reported as high as 21% [2]. The standard treatment is insulin therapy when diet control fails. Insulin therapy is costly and requires skill to administer and requires special storage conditions like refrigeration. Women in developing countries may not comply with such treatment. Further, it causes hypoglycaemia when it is not properly administerd or when adequate diet is not consumed along with it. This is supported by an expert opinion of a large review of observational and controlled trials which compared insulin with Glyburide and metformin from 1960 to 2010 concluding that though insulin is an effective treatment for glycaemic control, it requires sufficient education and skills on the part of the patient to manage properly and may cause hypoglycaemia , anxiety, and fear .and oral treatment is more user friendly and useful for control of GDM. OHA s are as efficient as insulin and provide better quality of life though fear of congenital malformations still exists [3].

In this context, there is a great demand for an alternative drug which is easy to administer, does not cause hypoglycaemia, easily stored and is available at a cheaper rate. Metformin, a biguanide a Class B drug is the first line agent for NIDDM in non-pregnant state which has all these advantages. It can be administerd during pregnancy but as it is not approved by FDA for its use during pregnancy and for the fear of association of congenital malformations it has become difficult to undertake prospective trials. But with the report of Glueck and collegues [4] which was published in 2001 many obstetricians started using the drug keeping in mind its potential benefits. We started using the drug for treatment of Gestational Diabetes mellitus since 2002 in selected patients. Initially we used it for educated patients such as staff nurses of our hospital and our friends who could understand the implications and now we are using it for all other patients especially the illiterate GDM patients who find it difficult to take insulin at home.

A recent case control study which compared metformin and insulin did not find any significant difference in the occurrence of gestational hypertension, pre-eclampsia and caesarean section rates. They reported a decreased weight

Table 5. Efficacy of Metformin

S.No	Effect	Value (n=38)
1	Maternal Glycaemic control with 1500 mg	89.5%
2	Maternal Hypoglycaemia	Nil
3	Maternal Lactic accidosis	Nil
4.	Neonatal hypoglycaemia	Nil
5	Neonatal Hyperbilirubinaemia	Nil

gain and improved fetal/neonatal outcomes in patients who received metformin compared to insulin [5].

A prospective cohort study which aimed to find out the incidence of GDM in PCOS women treated with metformin revealed the benefits of metformin by showing a statistically signifincant decrease in incidence of GDM and pre-eclampsia compared to those who did not receive metformin therapy [6]. As the increase in insulin resistance is greatest in the third trimester, GDM usually develops during this period. This is the reason for finding increasing number of women during the third trimester in the present study. At this time one cannot waste time depending only on diet and exercise which takes almost 2 to 4 weeks for their effect to be determined. As metformin does not cause hypoglycaemia one can administer this without fear of causing hypoglycaemia. The frequency of dose titration is not very much necessary with metformin at this gestational age when compared to Insulin. The maximum dose of metformin given in the present study is 2,250 mg when compared to 2500 mg employed in the MiG study [7 a]. The randomised control trial by Rowan and collegues [7 b] reported 46.3% taking metformin requiring addition of Insulin which is high when compared to the present study. The mean age of the patients in this study was 33 yrs when compared to 27 .5 yrs of the present study and the mean gestational age was also higher (30 weeks) when compared to 24 weeks. Gestational hypertension was present only in 7% of the subjects in their study where as 24% of our patients suffered from the same. None of the women complained of severe gastrointestinal side-effects in the present study whereas 10.7% of metformin group in Rowan's study complained of severe gastroinestinal side effects. An Indian study which compared insulin and metformin for treatment of GDM and type 2 gestational diabetes mellitus during pregnancy reported better glycaemic control with metformin one week after starting therapy [8] .

A significantly high perinatal mortality rate of 11.6% was reported with metformin when compared to insulin by Hellmuth and collegues [9]. However, there were many fitfalls in this retrospective cohort study such as the mismatch controls. Moore and colleagues did not report any such observations in a RCT of metformin versus Insulin [10]. Neonatal hypoglycaemia was found to be statistically less common in neonates of women treated with metformin when compared to insulin [7a,9,11]. In the study of Rai L and collegues more neonates in the Insulin group required NICU care for longer time because of hypoglycaemia and hyperbilirubinaemia [8]. In the present study no cases of neonatal hypoglycaemia were recorded and all the neonates were kept in Nursery for observation and were screened for hypoglycaemia. . This finding is encouraging as neonatal hypoglycaemia can lead to early neonatal death if not recognised and treated appropriately. This is one of the notable advantages of metformin, the mechanism being prevention of fetal hyperinsulinaemia as it crosses the placenta. There were no congenital malformations attributable for the usage of metformin in the few studies reported [9-11]. Rowan and Collegues reported 11 congenital malformations among 363 women who received metformin when compared to 18 anomalies among 378 women who received Insulin [7b]. The incidence of anomalies seems to be high in this population of GDM recruited by Rowan and collegues. There were no congenital anomalies in the present study though 23.7% received metformin during the first trimester. A meta-analysis of pregnancy outcome after first trimester exposure to metformin concluded that that there is no increased risk of major malformations (from eight studies) and commented on the need of larger studies in this aspect [12]. Only 13% of the infants were large for gestational age in the present study when compared to 22% in the study of Rowan and collegues. The incidence of macrosomia was also less (15.6%) in metformin group when compared to Insulin group (22.6%) in the study carried out byTertti K and collegues [11].

The largest review which included all the published articles from 1948 to 2008 on the usage of metformin for GDM found 33 articles out of which only 6 met the inclusion criteria. The authors concluded metformin to be an effective therapy for control of GDM but expressed concerns regarding safety [13]. Though the standard text books classify metformin as a class B drug Simmons and Collegues have termed it as Class C drug implying that the safety profile during pregnancy has not yet been established though it is not teratogenic [14]. Metformin is recently listed in the Model list of Essential drugs by WHO [15]. The literature reveals many benefits of metformin therapy to the mother and fetus hence more studies are required to establish the safety profile of this which is of immense benefit for the women of developing world. Our study is a small effort to contribute to the evidence.

ABBREVIATIONS

GDM	=	Gestational Diabetes Mellitus
FDA	=	Food and Drug Administration
NDDG	=	National Diabetes Data Group
OGTT	=	Oral Glucose Tolerance Test
LSCS	=	Lower segment Caesarean section
OPD	=	Out patient Department
WHO	=	World Health Organisation
RTC	=	Randomised Control Study

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