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COMPARISON OF METFORMIN VERSUS OTHER TREATMENT MODALITIES IN GESTATIONAL DIABETES MELLITUS

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ABSTRACT

INTRODUCTION: Despite evidence to prove both its efficacy and safety, use of metformin is at most restricted to only as an adjunct to insulin preparations. We compared the maternal, fetal and neonatal outcomes associated with GDM in women treated with metformin versus those treated with diet alone and diet plus insulin. **Method:** An observational study was carried out over a period of six months in 104 GDM patients. Study groups were 43 patients on diet alone (group A), 42 on metformin plus diet (group B), and 19 on diet plus insulin (group C). Maternal, fetal and neonatal outcomes were compared. **Results:** Fourteen patients in group B subsequently required supplemental insulin. Gestational hypertension 5(12%), 4(10%), 5(26%) (p=0.8) and wound infection among 2(5%), 1(2%), 0(0%) (p=0.6) were seen in groups A, B and C respectively. Four patients with polyhydramnios were seen in group B. Mean birth weights were A=3.07kg, B=3.07kg, C=3.1kg (p=0.96). Macrosomia 5 (12%), 3 (7%), 3 (16%) (p=0.2), neonatal hypoglycemia 2 (5%), 2 (5%), 2 (11%) (p=0.4), five minute Apgar scores 9.9, 9.7, 9.9, and neonatal jaundice 5(12%), 4(10%), 3(16%) (p=0.04) were noted in in groups A, B and C respectively. Single case of respiratory distress was seen in the insulin group. Shoulder dystocia and perinatal deaths were not observed. **Conclusion:** Maternal and perinatal outcomes were similar among diet alone, diet plus metformin, and diet plus insulin groups. Cost-effectiveness, easy administration, safety profile and convenience of storage would make metformin an attractive option in the management of gestational diabetes mellitus.

KEYWORDS: Gestational diabetes mellitus, pregnancy, metformin, diet, insulin.

INTRODUCTION

In most Asian countries, increasing economic prosperity has caused a change lifestyles and this has in turn resulted in a change in disease patterns which is called the "epidemiological transition".[1] This has caused a rise in obesity and diabetes mellitus evident in most urban communities.[2,3,4,5] In keeping with this rise in diabetes, the prevalence of gestational diabetes (GDM) also has risen with a reported prevalence of over 17% in a community based study done in an urban community in South India in 2008.[6] Incidence of GDM in Australia among age-adjusted South Asian women is three times that of women born in Australia.[7]

Poorly controlled GDM is associated with an increased risk of fetal macrosomia that may give rise to shoulder dystocia, perinatal morbidity due to birth asphyxia, still birth and a rise in caesarean sections.[8,9] As suggested by Barker glucose intolerance during pregnancy may predispose the fetus to an increased risk of glucose intolerance in adult life by permanent gestational programming in-utero.[10] Gestational hypertension and preeclampsia are some of the maternal complications of GDM.[11] Active management of GDM has been found to reduce the incidence of macrosomia and perinatal morbidity.[12,13] Although diet and lifestyle modifications are the first line interventions in the management of GDM, if normoglycaemia was not achieved insulin was traditionally considered to be the next option.

The MiG trial[14], a large randomized prospective study comparing metformin and insulin for the treatment of GDM demonstrated that metformin is a safe alternative to insulin as the perinatal complication rate was not increased in the metformin group. It was also found to be more acceptable with a lesser risk of hypoglycemia.[14, 15, 16] It is also comparatively easier to administer than insulin preparations which require detailed guidance for safe self-administration to avoid hypoglycaemia. Storage

and cost advantages of metformin over insulin preparations are also important factors that need consideration.

Metformin crosses the placenta, as concentrations as high as those seen in the mother have been observed in women taking metformin throughout pregnancy.[17, 18] A meta-analysis evaluating the safety of oral hypoglycemic in the first trimester found that there was no difference in the rate of major anomalies or neonatal deaths.[19] The use of metformin throughout pregnancy in 109 women with polycystic ovarian syndrome (PCOS) found normal growth and motor development in infants followed up to 18 months.[20] Despite evidence on its efficacy and safety, metformin is at most restricted to only as an adjunct to insulin. Published literature on the use of oral hypoglycaemics during pregnancy in Sri Lanka are scarce. Therefore this study was designed to assess the maternal, fetal and neonatal outcomes associated with gestational diabetes mellitus in women treated with metformin compared to insulin and diet alone.

METHODS

An observational study was carried out over a period of six months from 1st May 2013 at the Professorial Obstetric unit of the North Colombo Teaching hospital. All women with GDM managed in the unit during the study period were included in the study. Patients were grouped into three groups; diet alone, diet and metformin, and diet and insulin. Data were collected using an interviewer administered questionnaire and from patient's clinical records. Diagnosis of GDM was made, if either the fasting blood glucose exceeded 126 mg/dl or the two hour blood glucose exceeded 140 mg/dl in an oral glucose tolerance test (OGTT) using 75g glucose occurring for the first time in the index pregnancy.[21] Outcome measures were defined as follows; Gestational hypertension as hypertension that was detected after 20 weeks of pregnancy in a previously normotensive woman according to the International Society for the study of Hypertension in Pregnancy **(**ISSHP) classification[22]; Pre-eclampsia as the presence of recent onset proteinuria (two 'clean-catch-midstream' or catheter specimens of urine collected > 4 hours apart with proteins ≥2+) in a patient with pregnancy induced hypertension[22]; Infection as wound breakdown with purulent discharge of either episiotomy site or caesarean section wound; Macrosomia as infants above the 90th birth weight centile for gestational age, using sex specific charts[23]; 5-min Apgar score was obtained as per standard practice[24]; Polyhydramnios when the deepest vertical amniotic fluid pool was greater than eight centimetres[25]; Shoulder dystocia as delivery requiring MacRobert's position and/or suprapubic pressure to achieve delivery[26]; A perinatal death as a still birth occurring after 28 weeks of gestation or a death of a neonate up to seven days of birth[27]; Respiratory distress of the neonate as respiratory compromise (cyanosis, tachypnoea, grunting, and subcostal recession) up to 4th day of life with radiological evidence of ground glass appearance and air bronchogram[28]; Hypoglycaemia as serum glucose concentration less than 40 mg/dl requiring dextrose infusion[29]; and neonates who required phototherapy according to national institute of clinical excellence (NICE) treatment threshold graphs were considered as those with significant jaundice.[30] The criterion for supplemental insulin in metformin group was the presence of polyhydramnios, macrosomia or poor glycaemic control on a four point blood sugar series as per NICE guidelines.[31] Data were analyzed using Statistical packages for Social sciences version 20.0. Significance was considered at 5% level. Analysis of variance and logistic regression were used to describe the results. Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya (Number P/30/03/2013).

RESULTS

One hundred and four women were included in the study. Of these, 43 women were managed with diet alone while 19 received only insulin. The remaining 42 were initially put on metformin but 14 of them needed supplemental insulin later on. The baseline characteristics of age, parity, BMI did not differ between the study groups. However there was a statistically significant difference in the 2nd hour OGTT value between the groups, with patients who received insulin having the highest and patients managed with diet having a marginally elevated level (Table 01).

Table 01. Maternal baseline characteristics

	Diet (Mean and 95% CI)	Metformin (Mean and 95% CI)	Insulin (Mean and 95% CI)	F value in ANOVA	Significance
Age (yrs)	30.7 (30.0-32.4)	32.9 (31.2-34.6)	32.2 (30.0-34.4)	1.625	0.202
Parity	3.5 (3.2-3.8)	4 (3.3-4.7)	4.5 (2.9-6.1)	1.172	0.314
BMI	29.1 (27.9-30.3)	29.2 (27.7-30.7)	29.1 (27.6-30.6)	0.007	0.993
OGTT (mg/dl)	**154.5** (145.9-163.1)	**197** (173.5-220.5)	**255** (210.7-299.2)	16.48	0.001

There were no significant differences in the incidences of gestational hypertension, pre-eclampsia, polyhydramnios and wound infection among the three groups (Table 02). But a significant difference was observed in the gestational age at delivery between the diet only group [270 days (267.3-272.7)] in comparison to other two groups [263 days (260.5-268.6) in the metformin group and 263 days (259.8-266.2) in the insulin group]. Birth weight did not differ among the three groups.

Table 02. Maternal outcomes for the 3 main groups

	Diet (n=43)	Metformin (n=42)	Insulin (n=19)	Test	Significance
Gestational hypertension/ Pre-eclampsia	5	4	5	-0.278 #	0.782
Polyhydramnios	0	4	0		
Gestational age at delivery	270 (267.3-272.7)	263 (260.5-268.6)	263 (259.8-266.2)	7.24 *	.001
Wound infection	2	1	0	0.563 #	0.576

- T value in Logistic regression
*- F value in ANOVA
** - Standard error

No differences were observed in fetal outcomes; macrosomia, 5 minute Apgar scores and neonatal hypoglycemia. Single case of respiratory distress was seen in the insulin group (Table 03). There were no cases of shoulder dystocia or perinatal deaths.

Table 03. Neonatal outcomes for the 3 main groups

	Diet (n=43)	Metformin (n=42)	Insulin (n=19)	Test	Significance
BW (kg)	3.07 (2.91-3.23)	3.07 (2.93-3.21)	3.1 (2.9-3.3)	0.041 *	0.96
Macrosomia	5	3	3	1.376 #	0.176
Apgar (SE**)	9.9 (0.04)	9.7 (0.24)	9.89 (0.07)	0.785 *	0.459
Neonatal jaundice	5	4	3	-2.078 #	0.04
RDS	0	0	1		
Hypoglycemia	2	2	2	0.758 #	0.453

- T value in Logistic regression
*- F value in ANOVA
** - Standard error

DISCUSSION

Although 14 of the 42 patients in the metformin group required supplemental insulin they were considered as a whole group in order to minimize a positive bias towards metformin. Thus our three groups were the diet only group, the metformin group which included patients with supplemental insulin as well, and insulin group. There was no difference in the incidence of gestational hypertension and pre-eclampsia among the three groups which was also comparable to the rates observed in the *MiG* trial.[14] There were four patients with polyhydramnios in the metformin group who required supplemental insulin. Although this would suggest poor glycaemic control, there was no difference in birth weight or macrosomia among the three groups. As birth weight and macrosomia are more objective measurements than the diagnosis of polyhydramnios it is possible that it could have been due to bias in assessment of liquor volume.[14]

The gestational age at delivery was longer in the diet alone group. This raises a question of whether there would have been a difference in birth weight as the patients in metformin and insulin groups were induced at an earlier gestation. However the gestational age at delivery was considered in categorization of macrosomia and the fact that there was no difference in the rate of macrosomia among the three groups further reiterates the comparable outcomes among the three groups.

There was no significant difference in the birth weight among the three groups. The mean birth weights of 3.07 kg, 3.07 kg and 3.1 kg for the diet alone, metformin and insulin groups respectively. They were lower than those observed in the *MiG* trial and by Ijas et al.[32] This is probably due to genetic predisposition and poor nutritional status in our patients compared to developed countries. There was also no significant difference in the occurrence of macrosomia among three groups. Ijas et al used a cut off of more than 4 kg to define macrosomia.[32] However in our study, sex specific charts which considered birth weight for gestational age were used rather than an arbitrary cut off of 4 kg as a definition of macrosomia. We feel the use of a centile based assessment is better as birth weight is related to gestational age as well. There was no difference in the 5-min Apgar values as well. The rate of neonatal jaundice requiring phototherapy was 11.6%, 9.5% and 15.8% in the diet alone, metformin and insulin groups respectively. Although it would appear as if metformin has a beneficial effect in terms of reducing the likelihood of phototherapy (p=0.04) data from the *MiG* trial did not suggest so as the rate of phototherapy was 8% and 8.4% among the metformin and insulin groups respectively.[14] The rate of hypoglycemia was 4.6%, 4.8% and 10.5% in the diet alone, metformin and insulin groups respectively. In our study, it appears that metformin, compared to insulin, is protective in terms of reducing the risk of hypoglycemia it was not statistically

significant, probably due to the small sample size. Data from Ijas et al suggests that metformin reduces the risk of hypoglycemia.[32]

The treatment allocation was determined by the treating physician. This may explain the difference of the 2nd hour OGTT values. The 2nd hour OGTT value in the diet alone [154.5mg/dl (145.9-163.1)] and metformin groups [197mg/dl (173.5-220.5)] were lower than in the insulin group [255mg/dl (210.7-299.2)]. Data from the *MiG* trial and Ijas et al also showed that severe cases; i.e.; those with higher blood glucose levels, obese patients and early gestation at diagnosis required supplemental insulin.[14,32] Therefore it is likely that the severe cases were subconsciously allocated to the insulin and metformin groups. Although this may seem a drawback for the study the recently updated NICE guideline also supports initial categorization of treatment modality on blood sugar level rather than the use of the standard step up model of diet, metformin and finally insulin.[33]

At the time of the study the criterion on diagnosing GDM was the WHO 1999 guideline.[21] however, there was universal concern regarding the fasting blood sugar value (FBS) of 126 mg/dl as it was considered to be too high.[34] Current WHO diagnostic criteria suggest that two hour value of 140 mg/dl as an acceptable alternative.[34] This point has been further clarified by the recently updated NICE guideline which has retained the two hour value at 140 mg/dl.[33]

In our study 14 out of 42 in metformin group subsequently required supplemental insulin. This was comparable to current available evidence from studies as 46% of patients receiving metformin in the MiG trial and 31.5% in the study done by Ijas et al required supplemental insulin.[14, 32] Overall 61 patients required supplemental treatment in addition to dietary measures, of which 19 were put on insulin at the outset while another 14 required supplemental insulin in addition to metformin. The other 28 patients were adequately managed with metformin alone. Therefore the use of metformin has reduced the total number of patients who would have otherwise required insulin from 61 to 33. This is a 46% reduction in the insulin requirement which would be advantageous in a resource poor setting as it would enable us to concentrate more efficiently on more severe cases that require insulin therapy.

CONCLUSION

Comparable maternal outcomes; gestational hypertension and wound infection were observed between the diet alone, diet and metformin, and diet and insulin groups. Perinatal outcomes; birth weight, macrosomia, Apgar score at 5 minutes, respiratory distress, neonatal jaundice requiring phototherapy and neonatal hypoglycemia were comparable between the three groups. It appears that metformin is a suitable alternative to insulin. Its cost-effectiveness, easy administration, safety profile and convenience of storage would make it an attractive option for developing countries.

There are no conflicts of interest.

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