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Original article

Effect of adding Metformin to Insulin therapy in the third trimester of pregnant women with uncontrolled type I Diabetes as regard pregnancy outcome

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Abstract

Objective: To examine if addition of metformin to insulin is an effective alternative to insulin alone, to lower insulin dose, hospital stay, maternal and neonatal complications in pregnant women at third trimester with uncontrolled type I Diabetes Mellitus, particularly in a resource-poor setting. **Material and method:** Our randomized controlled trial included 80 patients, who were distributed into two equal groups; group A treated with metformin and insulin and group B treated with insulin alone, in Beni-suef and Cairo University hospitals. **Results**: We found that metformin and insulin group (Group A) showed significant outcomes regarding shortened hospital stay, lower insulin dose and lower maternal weight gain during pregnancy (p values: 0.04, 0.02 and 0.03 respectively). Most of maternal and neonatal complications were non-significantly lower in group A. **Conclusion:** Oral metformin therapy is an effective and safe additional treatment option for diabetic women with type I diabetes during pregnancy to lower insulin requirements, hospital stay and most maternal and fetal complications, especially in settings with limited economic resources.

1. Introduction:

Diabetes mellitus could happen with pregnancy, either diagnosed before pregnancy, being type I or type II or diagnosed during pregnancy; gestational diabetes. Obesity, family history of diabetes, increased maternal age, past history of Gestational diabetes mellitus (GDM) and fetal macrosomia are risk factors for developing GDM (1) . GDM is known as glucose intolerance first diagnosed or developed during pregnancy (2). Both maternal and fetal adverse effects include preeclampsia, cesarean section, fetal macrosomia, neonatal hypoglycemia, hyperbilirubinemia, birth trauma, death, and obesity or diabetes later in life. Also half of these mothers will develop type 2 DM and/or GDM later in life (1,2).

Current methods of glycemic control include lifestyle modification, self-monitoring of blood glucose (SMBG) and pharmacological agents such as insulin, Metformin and Glypuride (3). Many randomized controlled trials and observational studies compared Metformin with insulin and glyburide (4). After insulin, Metformin may be considered the preferred first-line option when an oral agent is chosen by the patient or provider as it has better fetal outcome compared to Glyburide.

Many studies showed that Metformin has beneficial effects as lower maternal weight gain and lower risk of pregnancy induced hypertension (PIH). Other benefits include a lower rate of maternal hypoglycemia than insulin or glyburide, lower cost and less need for SMBG. However, its association with increased rate of preterm deliveries was debatable among different studies. Two meta-analyses of studies for continued use of Metformin during pregnancy in patients with polycystic ovary syndrome (PCOS) showed a lower risk of abortion and preterm delivery with Metformin (5,6).

Recent meta-analyses and other studies did not report any increase in preterm deliveries with the use of Metformin 7-9. Another meta-analysis comparing Metformin versus Glyburide, Metformin was associated with lower rates of neonatal death, while glyburide was associated with increased risk of neonatal hypoglycemia, higher birth weight and greater incidence of macrosomia and higher maternal weight gain (10). Other meta-analysis demonstrated the effect of Metformin on reducing the risk of preeclampsia, macrosomia, large for gestational age (LGA), neonatal hypoglycemia and NICU admission 8. Also, Metformin was better than insulin or glyburide as regards macrosomia, PIH, LGA and respiratory distress, but has highest rate of preterm birth in obese GDM women (11).

American college of Obstetrics and Gynecology (ACOG) recommends that insulin be the preferred treatment if glycemic control is not achieved by non-pharmacologic methods. If a patient cannot take insulin or

declines, Metformin can be used after counseling the patient about the possible risks 12. A systematic review and meta-analysis by Bao et al., reported that Metformin may have potential maternal, fetal or neonatal benefits with no major adverse effects in GDM 13,14. However, more studies are required to provide more evidence for the use of Metformin for type I DM during pregnancy. Regarding insulin, the cost and system of parenteral dosing, it may not be appropriate in settings with limited resources, patient illiteracy and insulin lacking. The cost and multiple parenteral administrations represent a problem. In addition, the risk of hypoglycemia and maternal weight gain are undesirable effects. The oral route of administration, low cost and excellent patient compliance makes Metformin superior 15. Moreover, the evidence is lacking as regards the effect of the combined Metformin and insulin therapy use on pregnancy outcomes in type I DM. This raised the need to perform this randomized controlled study. In our study we aim to show the Effect of adding metformin to Insulin therapy in pregnant women with uncontrolled type I Diabetes.

2. Patients and Methods:

A total of 80 uncontrolled diabetic pregnant patients in the 3rd trimester seeking medical advice and met the eligibility criteria, were asked about participation in the trial and given information pamphlets describing the study. Patients who agreed to join the trial gave written informed consent. The study was approved by the Ethics Committee of faculty of medicine, Beni-Suef University. This randomized controlled clinical trial was conducted in Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo and Department of Obstetrics and Gynecology, Beni-Suef University Hospital, Beni-Suef, Egypt. The Randomized control trial (RCT) registration ID was NCT03928340 on 20th April 2019.

Inclusion and exclusion criteria:

We included; pregnant patients with type I diabetes with no other chronic disorders, on insulin therapy since start of gestation, singleton pregnancy with no apparent congenital anomalies and HbA1c level between 7% to 11% done at start of the third trimester. We excluded patients with type 2 or gestational diabetes, intolerance or hypersensitivity to Metformin, congestive heart failure or a history of congestive heart failure, renal or hepatic insufficiency, severe vomiting requiring intravenous fluids or hospitalization, diabetic ketoacidosis or a history of diabetic ketoacidosis or lactic acidosis, higher order pregnancies (twins, triplets, etc.) and fetal lethal anomaly were excluded. Masking was followed using envelopes which were numbered serially and in each envelope the corresponding letter which detect the targeted group (A or B) was put according to computer based

randomization then all envelops were closed and put in one box.

Intervention:

The patients were assigned to one of 2 groups: Group A (study group); included 40 patients who were treated with Metformin (as Cidophage 500 mg, CID Pharmaceuticals, Cairo, Egypt) given at a dose of 2000 mg, divided into two doses, taken with the 2 main meals, in addition to previous adjusted insulin dose. Insulin therapy was given subcutaneous by insulin syringes, the dose was calculated as 0.7 to 1.0 units/kg/d, the total dose was given in two divided doses of a mixture of regular insulin and neutral protamine Hagedorn insulin (NPH) at a ratio of 3:7, 100 IU/ml (Insulin Mixtard 70/30, Novo Nordisk, Bagsværd, Denmark): two-thirds in the early morning (7–8 am) and one third in the evening (5–7 pm)16. Glycemic response to Metformin treatment was assessed by checking fasting and 2-h postprandial blood glucose 5 days after the treatment was started. Group B (control group); included 40 patients who were treated with insulin alone, as described before (Insulin therapy was given subcutaneous by insulin syringes, the dose was calculated as 0.7 to 1.0 units/kg/d, the total dose was given in two divided doses of a mixture of regular insulin and neutral protamine Hagedorn insulin (NPH) at a ratio of 3:7, 100 IU/ml (Insulin Mixtard 70/30, Novo Nordisk, Bagsværd, Denmark): two-thirds in the early morning (7–8 am) and one third in the evening (5–7 pm))16. Poor glycemic control was defined as fasting blood glucose [95 mg/dl and/or 2-h postprandial blood glucose 120 mg/dl or more] 17.

All patients underwent full history taking, thorough clinical examination, fundus examination at Ophthalmology clinic, laboratory investigations; CBC, HbA1c, coagulation profile, liver and kidney function at time of participation, at 28-32 weeks. FBS, 2h postprandial blood sugar were done weekly till time of delivery.

Also follow up included daily fetal kick count, weekly fetal weight gain, maternal weight gain, fundal level in relation to period of amenorrhea, CTG and fetal Ultrasound. Subsequent management for uncontrolled cases were followed up weekly in the High Risk Pregnancy outpatient clinic until 36 weeks and then admitted to High Risk Pregnancy department for termination of pregnancy.

Resistant uncontrolled cases were admitted immediately to the High Risk Pregnancy department where capillary blood sugar was measured 7 times daily. Inpatient follow up included daily fetal surveillance by fetal kick count, CTG and regular fetal ultrasound every 3 days.

At time of termination, assessment was done by fasting blood sugar, 2 hours postprandial blood sugar and HBA1C in addition to the routine preoperative labs. Also assessment included estimated fetal weight and maternal

weight. Neonatal assessment after delivery included APGAR score, neonatal weight, incidence of transient tachypnea of newborn (TTN), respiratory distress syndrome (RDS), neonatal hypoglycemia and neonatal Intensive care unit (NICU) admission.

Outcomes:

The primary outcome measures were HbA1c after 8 to 10 weeks from start of intervention, fasting blood sugar (after fasting for 8 hours), 2 hours postprandial blood sugar after 2, 4, 8 weeks of start of intervention. Secondary Outcome Measures were maternal weight gain in kilograms all through pregnancy, weekly estimated fetal weight gain by ultrasound, the dose of insulin taken by patient, attacks of maternal hypoglycemia (plasma glucose level below 65 mg/dl), intra uterine fetal death (IUFD) in the third trimester, neonatal weight in kilograms, preterm birth, neonatal respiratory distress, neonatal hypoglycemia (plasma glucose level below 45 mg/dL (2.5 mmol/L)), neonatal Intensive care unit (NICU) admission.

Sample size:

Sample size calculation was done using the comparison of HbA1c level between pregnant women with type I DM treated with insulin alone and those treated with insulin plus metformin, as it was the primary outcome of our study. As reported in previous publication15.the mean ± SD of HbA1c in diabetic pregnancy treated with insulin was approximately 5.7 ± 0.6%, and we assumed that addition of metformin will achieve at least 10% improvement in HbA1c. Accordingly, we calculated that the minimum proper sample size was 24 participants in each group to achieve 80% power at $\alpha = 0.05$ level using Student's t test for independent samples. Sample size calculation was done using Stats Direct statistical software version 2.7.2 for MS Windows, Stats Direct Ltd., Cheshire, UK.

Statistical methodology:

• The data was collected on Microsoft Excel Sheet 2010. Data were statistically described in terms of mean ± standard deviation (± SD) or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Mann Whitney U test for independent samples. For comparing categorical data, Chi-square (±2) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 were considered statistically significant using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

3. Results:

Eighty pregnant females participated in the study divided into two groups. Table I and II show the demographic characteristics and antenatal follow up criteria in the studied groups, there were no significant difference in the baseline terms as age, education,

profession and BMI (p-value >.05). Maternal weight gain > 10kgs from start of pregnancy till time of termination showed statistical significant difference between both groups, where group A showed less weight gain (p-value is 0.02).

The duration of DM (in years) was non-significantly higher in group A than in group B (17.18±7.66, 15.73±5.65, ρ0.34). No significant difference between the two groups regarding the resistant uncontrolled cases (who were admitted to high risk pregnancy department) or regarding pregnancy associated hypertensive disorders. As regards the change in insulin dose, the increase in insulin dose was 30% and 80% (p 0.03), while 10%, 0% (p<0.001) has decreased dose and 60%, 20% (p<0.001) did not change the dose of insulin in Metformin and insulin only groups, respectively. Figure 1 shows hospital stay in a high risk pregnancy unit in days, it was more in patients of group B, where there was a statistically significant difference as regard number of days in both groups with p-value being 0.04. The number of hypoglycemic attacks was non-significantly lower in group A than in group B (0.18±0.55, 0.50±1.04, ρ0.84). Severe preeclampsia developed in 1 (2.5%) of cases, and 2 (5%) in group A and group B, respectively (p 0.55), while mild cases were equal in both groups 3 (7.5%). At time of termination, the estimated fetal weight by ultrasound was similar in group A and group B (p 0.9). The AFI was non-significantly lower in group A than in group B (p 0.37). The Resistance index (RI) of umbilical artery Doppler was non-significantly higher in group A than in group B (0.60±0.08, 0.59±0.05, p 0.45). Table III shows intra-partum, immediate postpartum care criteria. 80% of cases of group A terminate pregnancy (showed signs of fetal maturity) less than 39 weeks gestation, while 60% of cases of group B terminate pregnancy before 39 weeks and 40% necessitated to postpone delivery (waiting for signs of fetal maturity). As regard mode of termination of pregnancy in both groups, there was no statistical significant difference as regard vaginal or CS delivery (p-value is 0.79). Table IV shows neonatal outcome in the studied groups. No statistically significant differences were found as regard data of neonatal outcomes, where p value in each was > 0.05.

Table I: Demographic and antenatal follow up criteria in the studied groups

Variable	Group A (n=40)	Group B (n=40)	P-value
Maternal age (mean ±SD)	32.45±6.28	30.90±4.62	0.21
Parity: - Primipara, n (%)	5 (12.5%)	6 (15.0%)	
-Multipara, n (%)	35 (87.5%)	34 (85.0%)	0.75
Education: -Illiterate, n (%)	5 (12.5%)	9 (22.5%)	0.56
-Primary/middle school, n (%)	10(25%)	10(25%)	
-University, n (%)	24 (60.0%)	19 (47.5%)	
-Postgraduate, n (%)	1 (2.5%)	2 (5.0%)	
Profession: -working, n (%)	12 (30.0%)	13 (32.5%)	0.81
Body mass index at booking (BMI) (mean±SD)	31.95±4.38	30.71±4.76	0.23
Maternal weight gain> 10kg at the time of termination, n (%)	8(20%)	18(45.0%)	0.02*
Fundal level in relation to period of amenorrhea:			0.49
Equivalent, n (%)	28(70.0%)	26(65.0%)	
Above expected, n (%)	10(25.0%)	9(22.5%)	
Below expected, n (%)	2(5.0%)	5(12.5%)	
Vaginitis/cervicitis: Moniliasis, n (%)	8(20.0%)	7(17.5%)	0.92
Vaginosis, n (%)	4(10.0%)	5(12.5%)	

Table II: Maternal, fetal and neonatal examination and investigations data in the studied groups

Variable	Group A (n=40)	Group B (n=40)	P-value
Abnormal CTG[a] at time of termination, n (%):	3 (7.5%)	3 (7.5%)	0.66
FBS [b] after 4wk (mean± SD)	128.38±36.33	136.00±28.17	0.3
FBS after 8wk (mean± SD)	140.36±164.18	125.74±27.39	0.59

FBS (at termination) (mean± SD)	**132.45±38.85**	**131.20±32.52**	**0.88**
2hPP[c] after 4wk (mean± SD)	**169.83±44.53**	**185.05±38.87**	**0.11**
2hPP after 8wk (mean± SD)	**148.28±45.66**	**168.26±32.52**	**0.03***
2hPP (at termination) (mean± SD)	**177.33±47.29**	**182.35±44.09**	**0.62**
HbA1C[d] (initial) (mean± SD)	**8.14±1.24**	**7.92±1.07**	**0.39**
HbA1C:8-10 wks later (mean± SD)	**7.68±1.18**	**7.80±1.13**	**0.64**
Follow up of fetal growth by Ultrasound: at 28 weeks:			**0.05**
-equivalent, n (%)	**36 (90.0%)**	**28 (70.0%)**	
-Above, n (%)	**4 (10.0%)**	**9 (22.5%)**	
Below, n (%)	**0 (00.0%)**	**3 (7.5%)**	
Follow up of fetal growth by Ultrasound: at 32weeks:			**0.23**
-equivalent, n (%)	**32 (80.0%)**	**26 (65.0%)**	
-Above, n (%)	**7 (17.5%)**	**10 (25.0%)**	
-Below, n (%)	**1 (2.5%)**	**4(10.0%)**	
Follow up of fetal growth by Ultrasound: at 36 weeks:	**Total (38 cases)**	**Total (39 cases)**	**0.37**
-equivalent, n (%)	**25 (65.8%)**	**25(64.1%)**	
-Above, n (%)	**12 (31.6%)**	**10 (25.6%)**	
-Below, n (%)	**1 (2.6%)**	**4 (10.3%)**	

Table III: Intra-partum and immediate postpartum criteria in both groups.

Variable	GroupA (n=40)	GroupB (n=40)	p- value
Time of termination in weeks:			**0.05**
≤39 weeks (n, %)	**32(80%)**	**24(60%)**	
>39 weeks (n, %)	**8(20%)**	**16(40%)**	
Mode of delivery:			**0.79**
Vaginal delivery, n (%)	**8 (20.0%)**	**9(22.5%)**	
Caesarean section, n (%)	**32 (80.0%)**	**31(77.5%)**	

Table IV: Neonatal Outcome in the studied groups.

Variable	Group A (n=40)	Group B (n=40)	P-value
Preterm labour:, n (%)	2(5.0%)	1(2.5%)	0.56
Birth trauma:, n (%)	3(7.5%)	1(2.5%)	0.31
Neonatal Birth weight in grams (mean± SD)	3,430.00±628.88	3,433.75±515.20	0.98
Apgar-1 (mean± SD)	6.93±1.526	6.90±1.566	0.94
Apgar-5 (mean± SD)	8.50±1.155	8.33±1.403	0.54
Hospital stay in High risk pregnancy unit in days (mean± SD)	0.28±0.45	0.50±0.51	0.04*
Neonatal hypoglycemia:, n (%)	16 (40.0%)	9(22.5%)	0.091
Transient tachypnea of newborn (TTN): n (%)	10(25.0%)	7(17.5%)	0.412
Respiratory Distress Syndrome (RDS): n(%)	7(17.5%)	3(7.5%)	0.176
NICU admission>24hours: n(%)	9(22.5%)	11(27.5%)	0.606
Neonatal death: n(%)	1(2.5%)	0(0.0%)	0.314

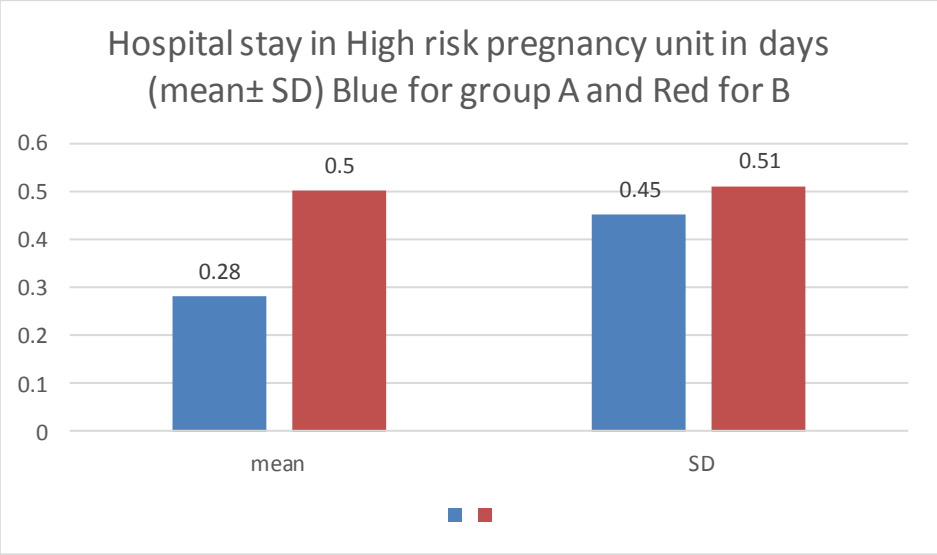

Figure (1): Hospital stay in days for both groups in a high risk pregnancy unit

4. Discussion:

Limited data is available, regarding combined use of Metformin and insulin for uncontrolled type I DM, during pregnancy. 80 patients were randomized into 2 equal groups in this study. Patients in the Metformin with insulin group and insulin only groups are nearly similar as regard demographic features.

Metformin has an advantage over insulin, being taken by an oral route, of low cost and has an excellent patient compliance. Glycogenic control of added effect of insulin was examined in this study. The effect of Metformin on HbA1c, fasting blood sugar, 2 hours postprandial blood sugar was not significant (except at 8 weeks, p 0.03). However, it does not stimulate insulin production and is therefore not associated with the risk of hypoglycemia[18].

Maternal weight gain in kilograms was significantly lower in Metformin group which agrees with other studies[9,19]. Whereas the estimated fetal weight gain by ultrasound was not significantly higher in Metformin group at 28 and 32 weeks and similar at 36 weeks.

A systematic review and meta-analysis by Bao et. al. showed that Metformin alone lowered the risk of neonatal hypoglycemia, macrosomia, large for gestational age babies and neonatal intensive care unit admission. In our study, the combined use of Metformin and insulin was not significantly effective in lowering those risks[20].

The increase in insulin dose was 30% and 80% in both groups (p 0.03), while 60%, 20% (p<0.001) did not change the dose of insulin in metformin and insulin only groups, respectively, which adds to the benefits of using combined metformin and insulin. These results are similar to other studies which show that 53.8% of the patients required insulin from their first visit due to 'overt' diabetes. In patients using oral hypoglycemic agents (OHAs), only 7.8% of cases needed to be switched from OHA to insulin [19].

The time of termination of pregnancy was ≤39 weeks in 80% of patients in the metformin group compared to 60% in insulin only group (p 0.05)[19].

The risk of developing preeclampsia in type I DM pregnant women is between 12% to 15%, with increased risk (50%) in preexisting nephropathy [20-22]. Compared to our study, the development of severe preeclampsia was non-significantly lower in the metformin group (1(2.5%), 2 (5%), p 0.55), while mild cases were equal in both groups (3(7.5%), 3(7.5%)).

In this study, the caesarean section rate, preterm birth or growth restriction did not increase by addition of metformin to insulin, which agrees with similar study[13]. However, opposing results are found in other studies [23-25].

Further follow-up is needed to establish long-term safety regarding the pregnancy outcome.

There were no serious adverse events associated with the use of metformin.

Long-term results were not included in the study due to difficulty to communicate with patients for follow up after labor. Future studies on larger sample of patients are needed to expand our understanding of the effect of combined metformin and insulin therapy in pregnancies complicated with type I DM.

The strength point in this study, consort statement of randomized study was followed, the good sample size and the follow up of intervention with small dropout. Our limitation is the lack of data and evidence in the topic of our study.

5. Conclusion:

Oral metformin therapy is an effective and safe treatment option for women with type I diabetes during pregnancy to lower the insulin requirements, hospital stay and most maternal and fetal complications. This may be of extreme importance, especially in settings with limited economic resources.

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