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Metformin Vs. Insulin in The Managment of Gestational Diabetes Mellitus

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Abstract

Objective

To examine the effectiveness & safety of Metformin vs. Insulin in the treatment of pregnancy complicated by gestational diabetes mellitus (GDM) .

Design Open –labelled prospective randomized controlled study .Setting

Basra maternity and children(tertiary level) hospital in Basra city . Sample

121 women with GDM who did not attain normoglycemia with diet during the period between January-December/2018. Method

Women were randomized to two groups :treatment by Insulin n= 60 & by Metformin n=61.Main outcome measure

The efficacy &safety of the use of oral Metformin in controlling hyperglycemia among women suffering from uncontrolled GDM by diet only; as compared to Insulin.

Result

There were no significant differences in the incidence of neonatal morbidity nor mortality including macrosomia (10 (20%) versus 8(16%)) ,intra uterine growth restriction (2(3%) vs. 5(3%)),mean birth weight(gm)(3923±412 vs. 3426±632),perinatal mortality (0 in both groups),birth trauma (0(0%)vs. 1(2%)),congenital anomaly(2(3%) in each group),neonatal hypoglycemia (8(13%)vs9(15%)),neonatal hyperbilirubinemia (17(28%)vs. 19(32%),& apgar score in Min 1&Min2 (7±1vs 6±1 &8±1 vs. 9±1)in Metformin vs. Insulin group. There was a tendency to a higher rate of deliveries by caesarean section (23(38%)vs. 13(22%)) &more spontaneous labor (34(56)%vs. 21(35%)) in the metformin group ,but induction of labor nearly same in both groups(25(41%) vs29(48%)) . Still both groups have comparable other maternal complications apart from less chance of developing hypertension (2(3%)vs13(22%)),less hypoglycemic episodes(11 (18%)vs33 (55%)), more hyperglycaemic postprandial episodes (18(30%)vs7(12%)) ,less weight gain throughout the pregnancy (1.4±3.20 vs. 3.9 ±3.5)in Metformin group, in spite of comparable fasting blood glucose level in both groups(6.5±0.7 vs. 6.0±0.5) . 9 (15%) of the Metformin treated women were failed to obtain normoglycemia and so ; needed supplemental Insulin to be added. Those women who failed to have controlled glycemic status by monotherapy and needed combined therapy, were

more obese,(mean BMI=36.2±3.4 vs. 30.6±1.4 kg/m²), had higher fasting blood glucose level (7.4 ±1.2 vs. 6.1±0.5 mmol/L) and needed medical treatment for GDM earlier in pregnancy (about 26±3.2 vs. 32±3.4 wks)& their newborns had higher incidence of macrosomia(3(33%)vs. 7(13.5%)) than women who were normoglycemic with monotherapy.Conclusion

Metformin is effective in the control of maternal hyperglycemia & prevention of fetal macrosomia &other feto- neonatal events , especially in non obese women developing GDM in late pregnancy. Women with considerable obesity , high fasting blood glucose and those who need for early pharmacological treatment during pregnancy may better be treated by Insulin alone or as adjuvant to the Metformin .

INTRODUCTION

1.1. Gestational diabetes mellitus (GDM)

1.1.1. Definition:

Is “a state of impaired glucose tolerance recognized for the first time during pregnancy” .It is a common obstetric problem with a variable prevalence world wide ranging from 1% to 30% according to WHO records from(2005 to 2015).the prevalence is more in middle east and the least in Europe .[1]

1.1.2. Glucose metabolism in normal pregnancy

In pregnancy, metabolism of glucose is modified ,as secretion of insulin stimulated by eating is stronger than in non pregnant women, still postprandial glucose levels are higher than in non-pregnant women. This increase in Insulin secretion is due to the estrogen and progesterone hormones; causes enlargement of the islets of Langerhans and pancreatic b-cells hyperplasia ; hepatic insulin sensitivity is increase stimulating basal hepatic glucose production and decreasing the level of fasting blood glucose. Glucose metabolism may also be affected by the haemodilution during pregnancy, the transfer of glucose from the placenta to the fetus and inadequate production of glucose during pregnancy. [2,3]

As pregnancy advances , Insulin sensitivity decreases, till reaches 33-78% of that of non-pregnant women at the third trimester. maternal adiposity and insulin-desensitizing effect of the placental hormones, progesterone and placental growth hormone (PGH))cause insulin resistance [3]. Glycosylated hemoglobin (HbA1c) during pregnancy is less by 0.6% unit than in non pregnant since the mean blood glucose level is decreased and the count of red blood cell is increased[4]and their life span is reduced from ~ 120 to ~ 90 days, and thus the HbA1c-value reflects the glycemic level over a shorter period of time than in non-pregnant women.[5]

1.1.3. Glucose metabolism and pathogenesis of GDM

Fasting blood glucose level tend to be higher in GDM than in normal pregnancies, while the basal hepatic glucose production remain similar. Insulin sensitivity in GDM is lower than that in normal pregnancies. In severe GDM, Insulin resistance is increased by 40% in late pregnancy in comparism to normal pregnancies .[3]GDM occurs when the pancreatic b-cells do not produce enough insulin to counteract the increased insulin resistance. Chronic insulin resistance and /obesity are the most important factors that predispose to b-cell dysfunction and predispose to GDM. Some GDM ladies (< 10%) have auto antibodies against Insulin, pancreatic b-cells , and/or islet cells, some (1-5%) have maturity-onset diabetes of the young (MODY) with autosomal dominant heredity[6]. Leptin and tumor necrosis factor (TNF-a) the biochemical mediators which associated with insulin resistance are increased; while adiponectin decreased in GDM. Especially in late pregnancy complicated by GDM, serum C-reactive protein (CRP) concentration is increase too.[7]

1.1.4. Maternal risks of GDM

1.1.4.1. Short-term risks: There is 2-3 folds increase in the risk of pre-eclampsia and other pregnancy associated hypertensive disorders, and 2 folds increase in the rate of cesarean deliveries compared to non-GDM women[8], also infertility, Infection, preterm labor, traumatic delivery, postpartum bleeding, polyhydramnios, retinopathy, hypoglycemia because of treatment [9].

1.1.4.2. Long-term risks : A high risk for developing type 2 diabetes in the future,especially in obese persons (9 folds over 9 years)[9,10]. Independent of obesity, in another study, the relative risk of the metabolic syndrome was 2.4[10]. Over 11 years after GDM, a risk of cardiovascular diseases (CVD) rises 13% [11]. Renal problems, retinopathy, over weight and its impact on the musculoskeletal system, and cancer are possible risks too.[10]

1.1.5. Fetal and neonatal risks of GDM: They can be at risk even in cases of mild hyperglycemia complicating pregnancy .[12]

1.1.5.1. Short-term risks: Macrosomia is the main problem linked to other fetal complications. Perinatal death , prematurity, birth trauma like brachial plexus palsy and/or bone fractures), hypoglycemia, ,recurrent abortions, malformations ,respiratory distress syndrome (RDS) and hyperbilirubinemia. Mother hyperglycemia causes passive glucose transport through the placenta to the fetus stimulates excessive release of fetal Insulin which act as a growth factor(anabolic effect) causing macrosomia[13,17].Both hyperglycemia and hyperinsulinemia found to increase risk of antepartum and /or intrapartum asphyxia.[15,18]

1.1.5.2. Long-term risk: Children born to mothers with GDM complicated pregnancies have 3.5-4 folds Increase risk of the metabolic syndrome ,high risk of CVD.[13] They tend to be overweight with high incidence of type 2 diabetes mellitus(1.6-7.8 folds more).The

association could be explained by environmental factors or by hereditary factors. [18]Studies also showed increased risk of hyper activity attention deficit, and other forms of autism[15.]

1.2 Diagnosis : Oral glucose tolerance test (OGTT) is the most popular test to diagnose GDM, other test which is less popular is glucose challenge test.
According to International Association of Diabetes and Pregnancy Study Group (IADPSG) in 2010 , diagnostic criteria include a fasting blood glucose level of ≥5.0 mmol/L, 1-hour blood glucose level≥9.3mmol/l , 2-hour level≥7.9 mmol/l[1] .

1.3. Treatment :

1.3,1. Nutritional treatment: The primary treatment for GDM is through modifying the life style and diet habits; Ideally, this should be tried even before pregnancy especially in risky women (overweight with BMI≥25 kg/m^2 , family history of DM, previous history of having macrosomic baby ,previous history of stillbirth ,history of recurrent fetal demise, cigarette smoking ,previous GDM, polycystic ovary syndrome, advanced age ,grand multiparty, woman with physically in active lifestyle ,multiple pregnancy, women live under stress like having depression) . Yoga , aerobic exercise for ≥ 30 minute daily is advisable. For obese GDM mothers, should have less weight gain during pregnancy (ideally220 gm/wk for obese vs. 420gm/wk for healthy pregnant lady) . increase fibres intake and nuts, decrease fat, proteins ,red meat, decrease carbohydrate congestion to 35-40% of total calories for overweight/ obese pregnant women [1,19]. GDM patients should be advised to measure their blood glucose values before breakfast and 1-2 hours after meals two time weekly to make sure that glycemic control is achieved. Measuring abdominal circumference (AC) of the fetus and detection of polyhydramios (by ultrasound) may be helpful in detecting uncontrolled GDM and the need for pharmacological treatment[20]. HbA1c values may be helpful in confirming good glycemic control during the last three months. Short term glycemic control can be checked by measuring plasma Fructosamine level, particularly in the third trimester.[21]

1.3.2. Medical treatment:

I.3.2.1. Insulin: is safe to be used in pregnancy in uncontrolled GDM; as it is not cross the placenta. Often using intermediate-acting and/or rapid acting insulin . by subcutaneous single or more injections, which is relatively painful for some patients, need training for use and special environmental conditions for storage (need refrigerator to prevent destruction by room temperature) , it can cause hypoglycemia and it increases appetite and weight .[22]

1.3.2.2. Oral antidiabetic agents:

Glibenclamide is a sulfonylurea, act by binding to pancreatic b-cell ATP (adenosine triphosphate) raises the intracellular calcium content in these stimulating release of insulin also named glybride .[23]
Metformin (1,1-dimethylbiguanide), is a derivative of biguanide, described for the first time in 1921 .Its transport through liver, small bowel and kidneys actively by OCT1 and OCT2

transporters. It is mainly absorbed from the small bowel with oral bioavailability about 50-60%[24]. It has different mechanisms of action in controlling hyperglycemia: by decreasing the production of liver glucose by inhibiting gluconeogenesis and glycogenolysis in the liver. In skeletal muscles; It is an insulin sensitizer , It also delays absorption of glucose from the small bowel, may reduce weight by decreasing appetite . It inhibits lipolysis so improves metabolism of lipids , and it reduces free fatty acids and triglycerides levels in the plasma. It does not increase production of Insulin, so, does not lead to hypoglycemia[25,26] . The plasma concentration is reached the peak within 1-3 hours after oral ingestion of immediately release tablets or within 4-5 hours after ingestion of extended release one. Its half-life is about 6.5 hours. It is not metabolized, so is excreted unchanged into the urine by renal tubules in 90% of total concentration. Platue level is reached within 24 to 48 hours . Its maximum dose per day is 3 g . Its clearance in normally functioning kidney is over 400ml/min.[27] The main side effects are the gastrointestinal; still, lactic acidosis is the most serious adverse effect which is happen in 5-9 per 100 000 persons per a year. It can cause Foliate deficiency and vit. B12 deficiency if used for≥ 4 years. [28]

1.4. Metformin in pregnancy :

1.4.1. Effet of pregnancy on Metformin:

Renal clearance of Metformin rises by 29% during pregnancy in comparism to non pregnant women. Plasma concentration-time curve of the drug decreases in 20% during pregnancy than non pregnant women, so less side effects is anticipated [29].

1.4.2. Effect of Metformin in GDM:

Metformin crosses the placenta; still ,glucose transport through the placenta is not affected. Studies show that Metformin use can control both maternal weight and fetal weight gain more than diet regimen or glibenclamide use during pregnancy complicated by diabetes, different studies show that vitamin B12 level , holotranscobalamin and homocysteine concentrations measured in GDM patients on metformin are remain unchanged[30-31] . No significant congenital malformation, fetal acidosis, vitamin B12 or follate deficiency found in blood sample of newborns, nor growth ,motor and social development or any metabolic or hormonal abnormality found in blood samples of children of diabetic mothers treated by Metformin. Lactation during treatment by Metformin found to be safe .[30,31,35-37].

2. Aim of the study :

To evaluate the efficacy of Metformin in controlling hyperglycemia &prevention of maternal and neonatal complications in comparison to insulin in pregnant women with GDM.

3.Method :

In Basra maternity and children hospital, which is the main obstetrical referral hospital in Basra city at a period of time between January-December 2018, 168 pregnant ladies were selected from the outpatient clinic referred with uncontrolled GDM for pharmacological

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treatment ; only 121 of them were followed up till one week after delivery .the participants with GDM ,having singleton pregnancy at a gestational age between 12-34 weeks . Maternal baseline parameters included maternal age in years ,parity ,BMI at first visit ,education and HbA1c level were registered .The GDM was diagnosed by measuring the fasting blood glucose level , and 1.5 hour after the main meals(postprandial) . The target levels were < 5.3 mmol/L , > 6.7 m mol/L respectively .The participants were checked their blood glucose level in the hospital every 2-4 weeks. Pharmacological treatment was started when the fasting or postprandial glucose levels exceeding the target level twice. Before starting medication ,normal liver &renal function were ensured by checking serum electrolytes, transaminases and creatinine after an overnight fast, in addition, serum glycosylated haemoglobin (GHbA1c) was checked . Exclusion criteria were :severe pre-eclampsia, Essential hypertension requiring antihypertensive drugs liver &/renal impairment . The participants were randomised to be treated by either Metformin only group (n=61) or Insulin only group (n=60). We used long acting insulin to normalize fasting blood sugar ,and rapid acting insulin to normalize postprandial blood glucose level .The dose of medication used was adjusted in coordination with a specialist physician according to the results of the biochemical studies.

Medication was discontinued (or modified) if significant side effect noticed or if normoglycemia was not achieved in spite of treatment for 2 weeks .Then supplemental Insulin was tried . Criteria of those who failed to achieve normoglycemia were observed in comparism to those who achieve glycemic control by Metformin only therapy including (BMI at first antenatal visit, fasting blood glucose level ,gestational age at randomization ,birth weight(gm), macrosomia, and apgar score at 1&5 min.).The women continue to measure their capillary glucose level daily twice a week . They were followed up at the outpatient clinic every 4 weeks between the 12th-32nd weeks of gestation, then every 2 weeks between 32nd-36th weeks of gestation ,and once or twice a week after 36th weeks of gestation till 1 week after delivery. Babies checked by echo cardio graph to exclude cardiac anomalies. The neonatal outcome(macrosomia , intrauterine growth retardation (IUGR), mean gestational age (by wks) at delivery, mean birth weight, neonatal hypoglycemia which need intravenous glucose treatment ,hyper billirubinaemia need management by phototherapy ,perinatal deaths, congenital anomalies and birth injuries, the Apgar score in 1 and 5 minutes were recorded .The maternal outcome included the effectiveness of use of Metformin in controlling fasting glucose level, episodes of hypoglycaemia, postprandial glycemic control, mode of delivery, birth canal injury, post partum haemorrhage , mild hypertension during pregnancy ,weight gain during pregnancy ,transfer to ICU and death were registered and compared in both groups understudy . The significance of the differences between the groups understudy was assessed by Chi-square test and t –tests as appropriate ,statistical significance was defined as p<o.o5 , P<o.o1 ,and p<0.001.

4.Result

121 women with GDM were randomized in two groups: Insulin group of 60 patients,& Metformin group of 61 patients (according to the type of medication they recieve to contral their disease).

Table1 showed maternal baseline characteristics: There were no significant differences in the mean age of participants (33.1±5.1 vs 33.6±5.4), parity (2.4±1.2 vs 2.1±1.8),no.of nulliparous (16 (32%) vs 18 (36%), BMI at first ANC visit (30.8±1.2vs 32.2±0.5), fasting blood glucose level (5.7±0.6 vs 6.2±0.9), length of gestational enrolment (wk) (30.1±3.2 vs 30.2±3.3), number of non educated participants (12(20%) vs13(21%), HbA1c at randomization(5.8±0.2 vs 5.9±0.5) between Insulin &Metformin groups respectively). Table 2 showed the maternal outcome in both groups understudy: pregnancy complications like(hypertensive disorder was less in Metformin group;2(3%) vs13(22%) inInsulin group, otherwise, maternal injury 0 (0%) vs 1 (2%),postpartum haemorrhage(pph)0(0%) vs1(2%)transfer to ICU(2(3%) vs 1(2%),death 0(0%) vs0(0%), infection(6(10%) inInsulin group vs 10(16%)inMetformin group)were not different in both groups. Regarding the mode of delivery in this study, both number of spontanious vaginal deliveries and number of cesarion deliveries were segnificantly more in Metformin group (34(56%) vs21(35%))& 23(38%)vs13(22%) respectively (P≤ 0.001), while no segnificant differences in number of termination of pregnancy by induction of labor (24(40%)in Insulin vs 20(33%) in Metformin group). Weight gain at end of pregnancy was less in Metformin group(1.4±3.20kg) vs(3.9±3.50kg),(p≤0.001). Hypoglycemic episodes were significantly less with Metformin group of patients (11(18%) vs (33(55%),p≤0.001),post prandial episodes of hyperglycemia howevere were more in Metformin group(9(15%) vs 0(0%) in spite of normal fasting blood glucose level in both groups(6.2±0.5 in Metformin group vs 5.7±0.7 in Insulin group) . Those with hyperglycemic episodes needed suplimentory Insulin.Table 3 showed criteria of the women needed combined therapy ;they had greater BMI (36.2±3.4 vs. 30.6±1.4 kg/m^2), high fasting blood glucose level at presentation (7.4±1.2 vs. 6.1±0.5 mmol/l), and needed pharmacological treatment of earlier gestational age than women who were normo glycemic with monotherapy(26±3.2 vs.32±3.4 wk), more cases of macrosomic newborns (3(33%) vs. (7(13%)) (p≤0.002,0.001,0.001,0.001 respectively), and both showed no segnificant differences birth weight nor Agar score at delivery. Table4 showed no segnificant differences in the mean gestational age in weeks (wks) at delivery (38.3±1,1 vs 37,4±1.6)nor the mean birth weight(gm) (3430±630 vs 3920±410) between the two groups of participants, no segnificant differences in the percentage fo macrosomia (8(16%) vs 10(20%)), perinatal deaths(0 (0%) vs 0(0%)), birth ingury (1(2%) vs 0(0%)),neonatal congenital anomalies (2(3%) vs 2(3%))(,number ofcases having neonatal hypoglycemia that need treatment (9(15% vs 8 (13%)), hyperbillirubinemia (19(32%) vs 17(28%)), intra uterine fetal growth retardation(5(8%) vs 2(3%)) or Apgar score at 1min. &5min.post delivery (6±1 vs 7±1 & 9±1 vs 8±1)respectively.

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Table 1: Maternal basal characteristic

Character	In=60	M=61	P
Age In Year	**33.1 ± 5.1**	**33.6 ± 5.4**	N.S
Parity	**2.4 ± 1.2**	**2.1 ± 1.8**	N.S
Nulliparous	**19(32%)**	**22(36%)**	N.S
Bmi At The First Antenatal Visit	**30.8 ± 1.2**	**32.2 ± 6.5**	N.S
Fasting Blood Glucose Level Mmol/L	**5.7 ± 0.6**	**6.2 ± 0.9**	N.S
Length Of Gestational Enrollment-Wk	**30.1 ± 3.2**	**30.2 ± 3.3**	N.S
Education (Not) No .(%)	**14(23%)**	**12(20%)**	N.S
Hba1c% At Randomization	5.8 ± 0.2	5.9 ± 0.5	N.S

Data by means ± SD or no.(%).

Table 2 : Maternal complications among Insulin therapy group vs. Metformin group:

Complications	**Insulin Group N=60**	**Metformin Group N=61**	**P-Value**
Death	**0 (0%)**	**0 (0%)**	**N.S**
Ht	**13(22%)**	**2(3%)**	**P≤0.001**
Maternal Injury	**1 (2%)**	**0 (0%)**	**N.S**
Pph	**1 (2%)**	**0 (0%)**	**N.S**
Transfer To Icu	**2(3%)**	**1(2%)**	**N.S**
Weight Gain (Kg)	**3.9±3.5**	**1.4±3.2**	**P≤0.002**
Preterm Labor	**2(3%)**	**5(8%)**	**N.S**
Infection	**6(10%)**	**10(16%)**	**N.S**
Hypoglycemic Episodes	**33(55%)**	**11(18%)**	**P≤0.001**
Fbs	**6.0±0.5**	**6.5±0.7**	**N.S**
Hyperglycemic Postprandial Episodes	**0(0%)**	**9(15%)**	**P≤0.001**
Mode Of Delivery			
Spontaneous Vaginal	**21(35%)**	**34(56%)**	**P≤0.001**
Induction Of Labor	**24(40%)**	**20(33%)**	**N.S**
C/S	**13(22%)**	**23(38%)**	**P≤0.001**

Data by mean ± SD or no.(%)

Table 3 : The baseline characteristics and neonatal outcomes in the monotherapy vs combined therapy group

	Monotherapy Group N=52	Combined Group N=9	P
BMI At Participation Visit	30.6 ±1.4	36.2 ±3.4	0.002
Fasting Glucose Serum Level	6.1 ±0.5	7.4 ±1.2	0.001
Gestational Age At Randomization	32 ±3.4	27 ±6.2	0.001
Birth Weight (G)Ms	3923 ±412	4179 ±600	N.S
Macrosomic	16(16%)	4(19%)	N.S
Apgar Score At			
1m	7 +1	7 +1	N.S
5m	9 +1	9 + 1	N.S

Data by mean ± SD or no.(%)

Data by mean ± SD or no.(%)

5.Discussion

GDM is a common & serious pregnancy related problem,as hyperglycemia affects adversely both maternal &neonatal outcomes. Studies showed that even minor degree of hyperglycemia may influence the outcomes of pregnancies complicated by GDM[12];so strict control of blood glucose level is necessary[32].In fact,life style &diet contlol is the corner stone for acheiving normoglycemia in GDM in about 90% of cases; which in tern should be started even before pregnancy especially in high risk group of women[1].If inspite of these attempts ,hyperglycemia can not be reached;so medication(s) should be prescribed. Basicly,normoglycemia was acheived by using subcutanious ingections of Insulin, which is safe in pregnancy as it not crosses the placenta to the fatal side[33.]However,it is not uncommon problem to have group of uncaoperative patients with poor compliance to the use of Insulin regularly &at proper timing becouse of its side effects like the need for training for the painful injections,relatively coasty,need to be stored in certain temprature &because of our hot wether it even need to refregrator for storrage,it may cause skin atrophy at site of injection,also may leads to frequent episodes of hypoglycemia & even loss of consciousness.In addition , it may lead to increase in appitite & body weight (BMI)[34].On the other hand, Metformin, the medication that used for many years to control Insulin resistance in polycystic ovarian syndrome,was tried recently by many centers warld wide to control GDM, although its efficacy &safety still a mater of discussion, espicially,it crosses the placenta to the fetal circulation.This,makes its safty regarding congenital/teratogenic side effect(s) uncertain[38].Diabetic patients prefer metformin to insulin[34],because it is easy to be used as it is available in the market as orally taken tablets ,cheeper than Insulin, easy storrage,not need special knowlage to use,suitable for multiple doses per day,can control appitite & body weight to certain limit ,as it dose so in ovarian polycystic patients,less side effects which are mainly gasrointestinal,simple,

tollarable& infrequent;not cause hypoglycemic episodes as Insulin dose with good glycemic control.In fact, it can cause lactic acidosis in≤9% of users if they have normal renal &liver function& not heavely alcoholics[28]. In varrious studies the metformin discontinuation rate was found in 2- 6% only and this was mainly due to intolerable gastrointestinal side effect.[32-34]

According to all of the above, many studies ,warld wide, were conducted to show the efficasy & safety of Metformin vs Insulin use in controlling hyprglycemia in GDM &then improve the pregnancy outcome. These were our aims of our study. Both groups of participants understudy had simillar general maternal characteristics including women age,parity ,BMI,fasting blood glucose level, gestational age at participation, education status,&HbA1c at enrollment. Maternal complications that may arise in pregnancies complicated by GDM like birth tract injury, postpartum bleeding ,transfer toICU, infections, glycemic control, death incidences were simillar in both groups .Still we regestered less number of cases had hypertensive disorders, less weight gain &hypoglycemic episodes in Metformin group .These findings were in line with those shown inLi-Ping Zhao et al,Genxia Li etal,Juan Gui et al.While Marico J Picon-Cesar et al showed no change in incidence of hypertention among women trated by Metformin as compared with those treated by Insulin .Studies which found the incidence of hypertention is less in Metformin group, regarded its use is prophylactic against its development.Inspite of similler (controlled)fasting blood glucose levels , still our study showed more frequent post prandial hyperglycemic episodes in Metformin group. This finding was against that shown in Maria J Picon-Cesar et al which found better glycimic control by using Metformin.The rate of failure of control in Metformin group was(about 15%) in our study,which is to some extant,comparable to2 previouse retrospective studies(13%&18%)mentioned in Terlti Ket al ,but much lower than that showed in Papa Dasari et al (around 25%), this dissimillarity may be infuenced by the small size of our sample understudy.Those group of women who failed to have controlled glycimic state by Metformin needed Insulin adjuvant therapy,they were more obese (higher BMI at participation,higher level of fasting blood glucose discovered to have GDM earlier in pregnancy,&their newborns had higher rates of macrosomia. Larger study in the future is hopeful to have more dependable results. Regarding the mode of delivery, both cessarion deliveries &spontanious vaginal deliveries were significantly more in Metformin group,while induction of labor was nearly the same in both groups.this was because of women worriness about fetal distress during induction of labor, as it would be longer in time with success rate around 65% in our hospital.The obstetricions themselves preffered cessarion deliveries for women with GDM whom were at advanced age or had bad obstetric history. These finding were disagrried with those of Maria J Picon-Cesar et al,as they found higer rate of induction of labor &rate of cessarion deliveries in Insulin group. Papa Dasari et al found no differences regarding rate of cessarion deliveries (differ with us) nor preterm labor (like our findings) between Metformin vs Insulin treated group. Our findings were parallel to that of Juan Gui et al regarding less weight gain &hypertention during the pregnancy in Metformin group,but we disagrreid with them regarding less gestational age in wks at delivery &less fasting blood glucose level during time of treatment by Metformin, as they found better glycimic control in Metformin

group while we found nearly equal levels of fasting blood glucose. Regarding other maternal outcomes found not differ between both groups in our study nor in other studies we used to compare with. Neonatal poor outcomes that may result from uncontrolled GDM include prematurity, abnormal body weight whether growth restriction or macrosomia, perinatal death, low apgar score, congenital anomally, hypoglycemia that need intravenous infusion,hyperbillirubinemia that need phototherapy; all were non significantly differ between the groups understudy. This was comparable with almost all studies we chose for comparism of results like Don-Qing Yu et al apart from some differences as the following : The incidence of both neonatal hypoglycemia & macrosomia were significantly lower in Metformin vs Insulin treated group shown in Rawan et al, Genexia Li et al & Juan Gui et al.. Hypoglycemia thought to be the leading cause of growth restriction or even stillbirth among women suffering from GDM. The later study & Juan Gui et al also showed higher rates of premature deliveries in Metformin group. Less macrosomia may be the leading cause of decreasing the rate of cessarion section in Metformin group of this study; Rawan et al also regestered a high rate of IUGR inInsulin treated group which might be explained by the high incidence of neonatal hypoglycemia in Insulin group of this study.It is important to say that not only the short term safety of the use of Metformin is needed to know &be insured,but long term both maternal &childhood safety to be guarantied;for that reason,future long &large meta analysis study is needed to vanish all doupts & to secure Metformin efficacy & safety .Till that time,Metformin looks suitable in controlling GDM in non obese pregnant women dicovered to have the diease in the second half of pregnancy with moderately high HbA1c.

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