Comparison of pregnancy outcome with use of metformin versus insulin in management of gestation diabetes mellitus: An interventional study

Dr. Venish Panchal[1§], Dr. Deepali Jain[2]

[1]Post graduate Residents, Department of Obstetrics and Gynecology, JLN Medical College, Ajmer (Rajasthan), India
[2]Senior Professor, Department of Obstetrics and Gynecology, S.M.S Medical College, Ajmer (Rajasthan), India
[§]Corresponding author's

Abstract—*Gestational Diabetes Mellitus (GDM) is a problem which may occur during pregnancy. For treatment of GDM either the Metformin or Insulin is used. So this prospective randomized multicenter trial in women with GDM was conducted to compare the treatment outcomes of metformin and insulin. This study was conducted at Rajkiya Mahila Chikitsalaya, in Obstetrics & Gynaecology Department of Jawaharlal Nehru Medical College, Ajmer. This study was done on 110 women who were diagnosed GDM by DIPSI criteria with a singleton pregnancy and meet entry criteria are randomized to insulin or metformin treatment (55 cases in each group).It was observed that metformin is equally efficacious and safe as insulin with a lot of advantages like less costly, better compliance, less weight gain, less change of hypoglycaemic attack and more feasible as insulin require several daily injection with not much difference in perinatal outcome except statistically significant difference in baby weight, mean cord blood sugar level at birth, large for gestation age. So it can be concluded that Metformin treatment is suitable for non-obese as well as obese type 2 diabetes patients in pregnancy without complications. Metformin is a safer alternate to insulin in GDM management with no adverse maternal and fetal outcome.*

Keywords: Gestational Diabetes Mellitus (GDM), pregnancy outcomes.

I. INTRODUCTION

Gestational Diabetes Mellitus (GDM) is defined as any degree disturbance of glucose metabolism with onset or first recognition during pregnancy.[1,2] The prevalence of GDM varies worldwide from 1 to 25% according to the ethnic population and the criteria used in the diagnosis.[3] Screening policies regarding GDM and the diagnostic criteria vary according to the different recommendations.[4]

The initial recommendation for using 75-g Oral Glucose Tolerance Test (OGTT) in pregnancy was from the World Health Organization (WHO). The WHO used the same criteria for diagnosing diabetes both during and outside of pregnancy.[5] This approach was criticized, as it ignored the physiological changes in carbohydrate metabolism that occurs during pregnancy. In 1999, the WHO lowered the threshold for FPG from 7.8 mmol/L (140 mg/dL) to 7.0 mmol/L (126 mg/dL) and recommended that pregnant women meeting the criteria for diabetes mellitus or impaired glucose tolerance (IGT) be classified as having GDM[5]. The current 75-g International Association of the Diabetes and Pregnancy Study Groups criteria (IADPSG) criteria have been devised keeping this fact in mind and evaluating evidence that associates abnormal glucose tolerance in pregnancy with adverse perinatal outcomes.[6]

Unblinded studies since 1995 have shown adverse perinatal outcomes to be linearly linked with glycemic levels in gestation[7]. The landmark study in this respect was the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[8]. The HAPO study was a large, multicenter, multinational, epidemiologic study in which 23,316 women (30 times larger than the O'Sullivan cohort) underwent

blinded 2-hour, three-sample, 75-g OGTTs at 24–32 weeks of gestation. All women with a fasting plasma glucose (FPG) 5.8 mmol/L (105 mg/dL) and 2 hours values up to 11.1 mmol/L (200 mg/dL) were included.[7,8]

GDM is associated with an increased risk of a variety of maternal and perinatal complications, including preeclampsia, caesarean section, macrosomia, shoulder dystocia, instrumental delivery, birth injuries, hypoglycemia and respiratory distress syndrome (RDS), Neural Tube Defect (NTD), cardiac anomaly like VSD, ASD , still birth , neonatal death resulting from excess transfer of glucose from mother to fetus.[8,10]

The treatment of GDM improves pregnancy outcomes by reducing the incidence of macrosomia, pre-eclampsia and hypertensive disorders.[11] Diet therapy and self-monitoring of blood glucose concentrations are key factors in the treatment of GDM.[12,13] Traditionally, Insulin therapy has been the first line medical treatment in GDM, but recently oral hypoglycemic agents, especially Metformin and Glyburide have been under investigation. Women with GDM are known to carry an almost eight-fold risk of subsequent Diabetes Mellitus later in life. In addition, GDM has been found to be associated with a later risk of Metabolic Syndrome (MetS) and cardiovascular diseases. The offspring of women with GDM have an increased risk of later Obesity, Diabetes and Metabolic Syndrom (MetS).[14,15]

So this comparative randomized trial was conducted to compare the effects of Metformin and Insulin in treatment of GDM.

II. METHODOLOGY

This prospective comparative interventional study was conducted on 110 women with GDM at Rajkiya Mahila Chikitsalaya, in Obstetrics & Gynaecology Department of Jawaharlal Nehru Medical College, Ajmer (Rajasthan) India. This study was aproved from institutional ethical committee.

For this study, all single tone pregnant women, who were diagnosed GDM as per Diabetes in Pregnancy Study Group India (DIPSI) criteria, delivered in Obstetrics & Gynecology department at Rajkiya Mahila Chikitsalaya, Ajmer were included. Out of these women, women either previously diagnosed DM or having previous bad obstretic history was excluded from study. Even women sensitive to either Metformin or Insulin were also excluded from study. Those refusing to give consent to participate in the study were also excluded from study.

HbA1C was done for all women whose blood sugar level (BSL) were 140mg/dl and referred to a diabetologist and managed with joint care. If BSL was normal, the screening criteria was repeated between 24 and 28 weeks of gestation and same screening criteria was applied.

Subjects have been followed through their index pregnancy and blood glucose level monitored. Blood Glucose monitoring by a Glucometer was encouraged. Target blood sugar levels was aimed at FBS equal or less than 100 mg/dl and 1 hour postprandial level equal or less than 140 mg/dl. Initially GDM has been managed by diet and exercise for two weeks. If blood glucose was not controlled, Pharmacotherapy has been instituted. These women were enrolled for the study. Finaly 110 eligible women participated in this study.

Sample size was calculated 49 subjects for each of the two groups at alpha error 0.05 and power 80% assuming minimum difference of means to be detected of 2HPG between the two (Metformin and

Insulin) groups, 4mg/dl with standard deviation 0. 22 mmol/l (Rowan JA *et al*., 2008[16]). To estimate an appropriate sample size the following formula was used

$$N \text{ (per group)} = Z\left[\frac{\left(z\frac{a}{2}+z_a\right)a}{\Delta}\right]^2$$

Where n = sample size (per group), $Za/_2$ = (1.96) for 95% confidence (i.e a =0.05)

Za = cut off value for power (1 – β), a = Common standard Deviation of both groups, Δ = Mean difference to be detected (From a previous study (Rowan JA *et al*., 2008[7]), a minimum difference of 4mg/dl (0. 22 mmol/l) was estimated in the mean 2HPG between the two groups)

After taking written informed consent from the all eligible 110 participants, a detailed history was taken. H*eight* in *cms* and *weight* in *kgs* was recorded and *BMI was* calculated. A general, systemic and obstetric examination was done.

Then these women were randomized into 2 groups. One group given tablet Metformin orally and the other group given injection Insulin subcuteneously. In the Metformin group, the starting does of Metformin was 500 mg once a day and increased gradually over time according to blood sugar values. The maximum dose allowed per study protocol was 1500 mg per day. Insulin was added if targets were not reached on Metformin alone at maximum doses. In the Insulin group, Insulin was administered subcutaneously in the thigh or abdomen. Insulin doses were adjusted by Diabetologist as per BSL (blood sugar level). Frequency of monitoring was being decided based on BSL. The total dose of insulin was titrated for each patient to achieve the optimum Glycemic targets. The women were asked for follow up monthly till 28 weeks. Then fortnightly till 36 weeks following which a weekly follow up was recommended. More frequent visits were advised if necessary. USG was done at 7 weeks for viability, at 12 weeks for Nuchal transparency (NT), at 18 - 20 weeks for anomalies, at 32-34 weeks growth scan and more often if required. The frequency of visits was increased if any complication developed. After 30 weeks all pregnant women were counselled to keep a daily fetal movement count. Neonatal hypoglycemia was defined as a blood glucose level <40 mg/dl in any infant, regardless of gestational age and whether or not symptoms were present. Blood glucose levels were checked at 1, 2, 3, 6, 12 and 24 hours. Additional blood glucose testing was done as per Paediatric / Neonatologist recommendation. Glucose was measured with Chemstrip BG. Reading <40mg/dl should be checked rapidly by a clinical laboratory. The infant was fed orally or given IV glucose by 1 hour of age.

Data thus collected were compiled as master chart in MS EXCEL 2010 worksheet. Qualitative data were expressed in percentage and proportion. Quantitative data were expressed in mean and standard deviation. Chi-square test was used to infer the difference on proportions whereas unpaired 't' test was used to infer difference on means of these two groups.

III. RESULTS

Metformin and Insulin group were well comparable i.e. without significant difference, as per studies demographic characteristics like age, parity etc. Mean age was observed 30.5 ± 3.2 years and 32.3 ± 3.4 years in Metformin and Insulin group respectively, which was without significant difference (p>0.05). Likewise, mean parity was observed 2.4 ± 1.3 and 2.9 ± 1.4 in Metformin and Insulin group respectively, which was also without significant difference (p>0.05). Mean gestational age was observed 11.1 ± 4.9 weeks and 10.2 ± 5.6 weeks in Metformin and Insulin group respectively, which was without

significant difference (p>0.05). Mean randome blood sugar (RBS) and mean fasting blood sugar (FBS)of both the group was also without any significant difference (p>0.05). (Table 1)

Table 1
Comparison of Clinico-demographic characteristics of Metformin and Insulin group

S. No.	Variables	Metformin (N=55)	Insulin (N=55)	*p value	LS
1	**Age (Mean ± SD)** *(in years)*	30.5 ± 3.2	32.3 ± 3.4	0.07	NS
2	**Parity (Mean ± SD)**	2.4 ±1.3	2.9 ± 1.4	0.12	NS
3	**Gestational age at registration (Mean ± SD)** *(in weeks)*	11.1 ± 4.9	10.2 ± 5.6	0.07	NS
4	**Basal RBS at registration (Mean ± SD)** (in mg/dl)	188.7 ± 31.5	204.3 ± 19.8	0.82	NS
5	**Basal FBS at registration (Mean ± SD)** (in mg/dl)	136.0 ± 39.7	140.1 ± 27.6	0.29	NS

by Unpaired 't' test

As far as the clinical profile of both the group was concerned, it was also without significant difference (p>0.05). In Metformin group 66.67% were GDM and other were T2DM whereas in Insulin group it was 62% and %. (Table 2)

In Metformin group associated morbidly was Essential Hypertension in 7.27%, Hypothyroidism 1.82% and Anemia in 1.82% whereas in Insulin group it was 5.45%%, 0% and 1.82% respectively. It was also comparable (p>0.05). (Table 2)

Table 2
Comparison of clinical profile of Metformin and Insulin group

S. No.	Variables		Metformin (N=55)	Insulin (N=55)	*p value	LS
1	**Type of Diabetes**	GDM	33 (60%)	30 (54.55%)	0.7	NS
		T2DM	22 (40%)	25 (45.45%)		
2	**Co-morbidity**	Essential Hypertension	4 (7.27%)	3 (5.45%)	0.679	NS
		Hypothyroidism	1 (1.82%)	0 (0%)		
		Anemia	1 (1.82%)	1 (1.82%)		

by Chi-square test

When maternal outcome in both the groups were compared, it was also found without any significance difference (p>0.05) as per studied variable i.e. weight gain during pregnancy (p=0.09), gestational age at delivery (p=0.3), presence of pre-eclampcia (p=0.7), presence of polyhydramnios (p=0.12) and mode of delivery (p=0.999). (Table 3, Figure 1, 2 & 3)

Table 3
Comparison of Maternal outcomes of Metformin and Insulin group

S. No.	Variables	Metformin (N=55)	Insulin (N=55)	*p value	LS
1	**Weight gain (Mean ± SD)** *(in kg)*	10.2 ± 5.7	11.3 ± 4.4	0.09	NS
2	**Gestational age at delivery (Mean ± SD)** *(in weeks)*	36.8 ± 2.0	37.9 ± 1.7	0.3	NS

by Unpaired 't' test

Figure 1

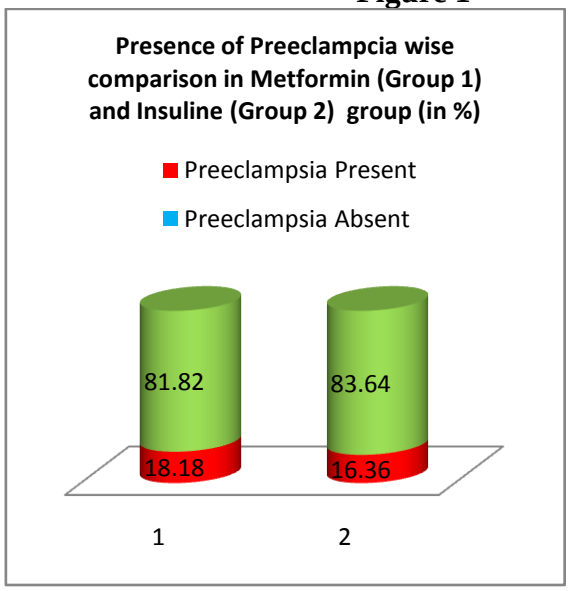


Figure 2

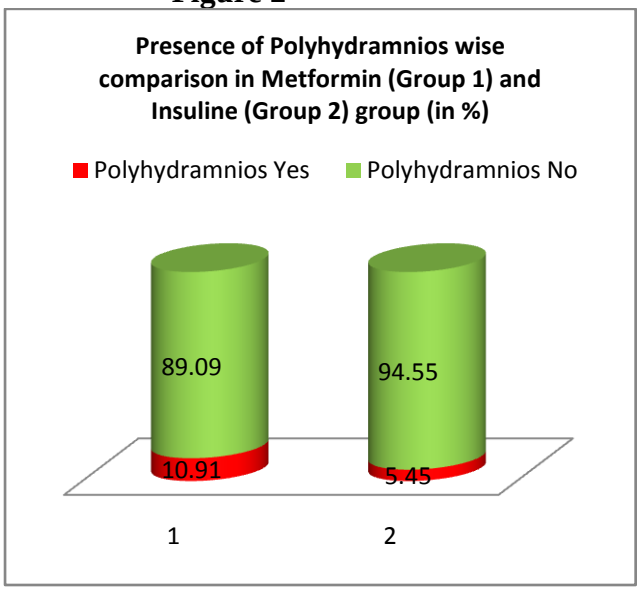
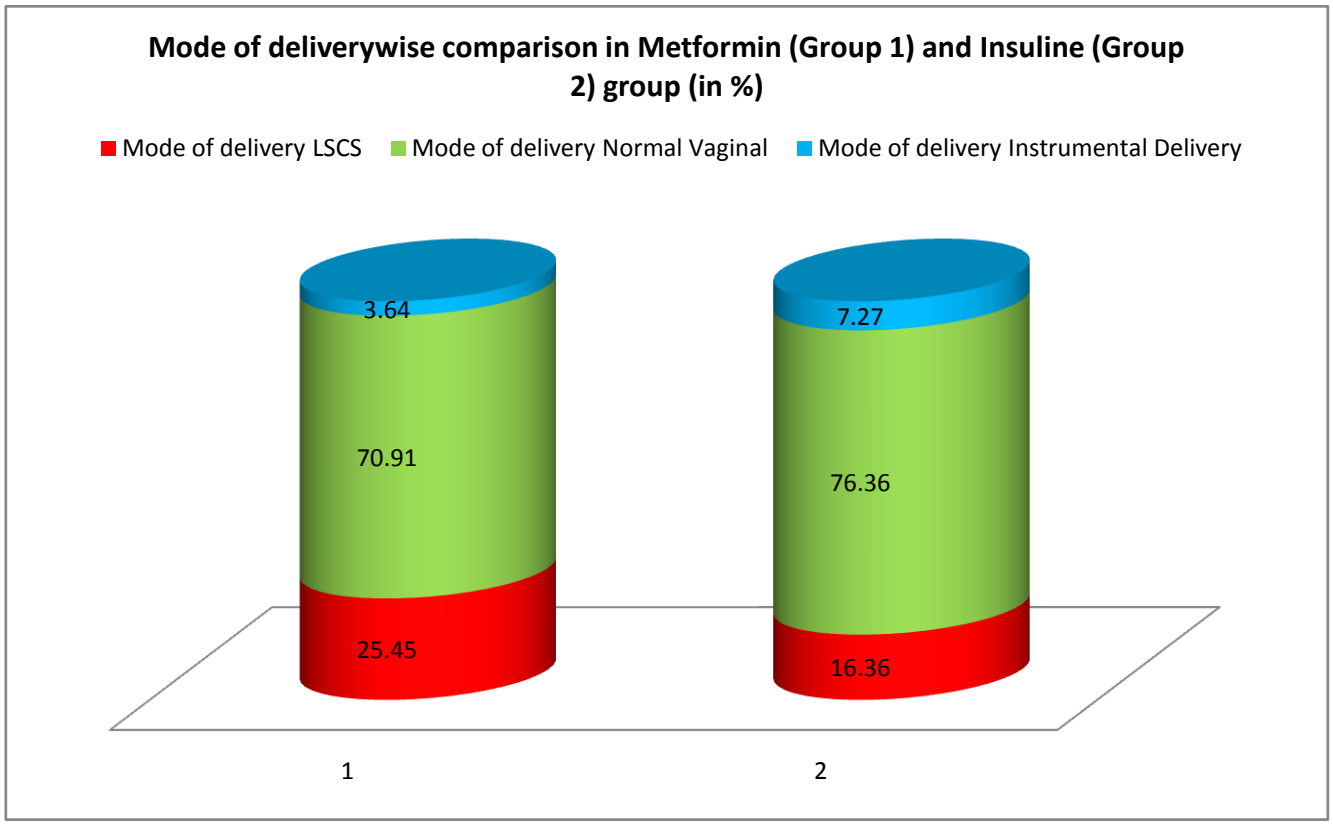


Figure 3



When fetal outcome in both the groups were compared, although it was also found without any significance difference ($p>0.05$) as far as the birth weight and APGAR score of baby is concerned but Mean blood glucose level at birth of baby was found significantly more ($p=0.01$) in Insulin group. (Table 4)

Table 4
Comparison of Quantitative Fetal outcomes of Metformin and Insulin group

S. No.	Variables	Metformin (N=55)	Insulin (N=55)	*p value	LS
1	**Birth Weight (Mean ± SD)** (in kg)	3.5 ± 0.9	3.7 ± 0.7	0.04	S
2	**APGAR score at 5 minutes (Mean ± SD)**	7.6 ± 1.6	8.1 ± 0.8	0.07	NS
3	**Mean blood glucose level at birth (Mean ± SD)** (in mg/dl)	38.3 ± 8.6	41.4 ± 12.9	0.01	S

by Unpaired 't' test

When distribution of newborn baby between both the groups (Metformin and Insulin) was observed as per various complications, It was observed that there was no significance in both (Metformin and Insulin) the groups in study variables except large for gestational age babies were observed significantly more (p=0.03) in Insulin group. (Table 5)

No significant (p>0.05) difference in proportion of newborn either with Transient tachypnea NB or Respiratory distress syndrome or Neonatal Hypoglycemia or Neonatal Jaundice or Neonatal Sepsis was observed in both (Metformin and Insulin) the groups. Proportion of intra uterine fetal death and still births were also without significant difference (P>0.05). (Table 5)

Table 5
Comparison of Qualitative Fetal outcomes of Metformin and Insulin group

S. No.	Variables		Metformin (N=55)	Insulin (N=55)	*p value	LS
1	**Live birth**	Yes	54 (98.18%)	55 (100%)	0.999	NS
		No (Still Birth)	1 (1.82%)	0 (0%)		
2	**Large for Gestational Age**	Yes	11 (20%)	16 (29.09%)	0.03	S
		No	44 (80%)	39 (70.01%)		
3	**Intra uterine fetal death**	Yes	0 (0%)	0 (0%)	0.999	NS
		No	55 (100%)	55 (100%)		
		Congenital Malformation	0 (0%)	0 (0%)		
4	**Transient tachypnea NB**	Yes	14 (25.45%)	16 (29.09%)	0.3	NS
		No	41 (74.55%)	39 (70.91%)		
5	**Respiratory distress syndrome**	Yes	10 (18.18%)	12 (21.82%)	0.8	NS
		No	45 (81.82%)	43 (78.18%)		
6	**NICU Admission**	Yes	21 (38.18%)	31 (56.36%)	0.08	NS
		No	34 (61.82%)	24 (43.64%)		
7	**Neonatal Hypoglycemia**	Yes	54 (98.18%)	55 (100%)	0.08	NS
		No	1 (1.82%)	0 (0%)		
8	**Neonatal Jaundice**	Yes	6 (10.91%)	5 (9.09%)	0.1	NS
		No	49 (89.09%)	50 (90.91%)		
9	**Neonatal Sepsis**	Yes	3 (5.45%)	4 (7.27%)	0.1	NS
		No	52 (94.55%)	51 (92.73%)		

by Chi-square test

IV. DISCUSSION

In this study, mean age of women with GDM was observed 30.5 ± 3.2 years and 32.3 ± 3.4 years in Metformin and Insulin group, mean parity was observed 2.4 ± 1.3 and 2.9 ± 1.4 and mean gestational age was observed 11.1 ± 4.9 weeks and 10.2 ± 5.6 weeks in Metformin and Insulin group respectively,

Mean randome blood sugar (RBS) and mean fasting blood sugar (FBS)of both the group was also without any significant difference (p>0.05).

In this study among women with GDM, in Metformin group 66.67% were GDM and other were T2DM whereas in Insulin group it was 62% and %. In Metformin group associated morbidly was Essential Hypertension in 7.27%, Hypothyroidism 1.82% and Anemia in 1.82% whereas in Insulin group it was 5.45%, 0% and 1.82% respectively.

In this study, no significant difference was observed in maternal as well as fetal outcome in both the groups except blood glucose level at birth of baby and large for gestational age babies were observed significantly more in Insulin group. Other studied variables like weight gain during pregnancy, gestational age at delivery), presence of pre-eclampcia, presence of polyhydramnios, mode of delivery, birth weight, APGAR score of baby, IU deaths, still births and proportion of babies with various complications were without significance difference in both (Metformin and Insulin) the groups in this study.

Niromanesh S etall[17] conducte a similar study on 80 GDM in Metforfine group and 80 in Insulin group and observed that two groups were comparable regarding the maternal characteristics. Two groups were similar in mean FBS (P=0.68) and postprandial measurements (P=0.87) throughout GDM treatment. The neonates of metformin group had less rate of birth weight centile >90 than insulin group (RR: 0.5, 95% CI: 0.3-0.9, P=0.012). Maternal weight gain was reduced in the metformin group (P<0.001). Two groups were comparable according to neonatal and obstetric complications (P>0.05). In metformin group 14% of women needed to supplemental insulin to achieve euglycemia.

So similar to the present study, they also found that Metformin is an effective and safe alternative treatment to insulin for women with GDM. This study does not show significant risk of maternal or neonatal adverse outcome with the use of metformin.

Li G etall[18] also concludes that Metformin is comparable with insulin in glycemic control and neonatal outcomes. It might be more suitable for women with mild GDM. This meta-analysis also provides some significant benefits and risks of the use of metformin in GDM and help to inform further development of management guidelines

Liang etall[19] also concluded that metformin is fastest in glucose control, with a more favorable pregnancy outcomes-would be a better option, but its rate of glucose control is the lowest.

V. CONCLUSION

This study concludes that Metformin is an effective treatment option for women with GDM/type 2 diabetes in pregnancy with or without add-on insulin who require pharmacological treatment for glycemic control in our resource poor setting. Metformin has advantages over insulin such as less maternal weight gain, no maternal hypoglycemia, being less costly, being oral therapy and requiring no vigorous monitoring and frequent hospital admissions with good compliance and acceptability. So, Metformin can be used in the management of gestational diabetes mellitus.

CONFLICT OF INTEREST

None declared till now.

REFERENCES

[1] World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1: diagnosis and classification of diabetes mellitus.2006.

[2] Metzger BE, Coustan DR. Summary and recommendations of the Fourth International Workshop-Conference on Gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care.1998;21 Suppl 2: B161 –7.

[3] THL National Institute of Health and Welfare. Perinatal Statistics: parturients, deliveries and newborns 2013. Finnish Medical Birth Register.2015. Accessed from: http://www.julkari.fi/handle/ 10024/116818.

[4] Kaaja R, Kivelä R, Kukkonen-Harjula K, Peränen N, Rönnemaa T, Saramies J, Soukka H, Tulokas S, Vääräsmäki M. Gestational Diabetes. Current Care Summary. Working group established by the Finnish Medical Society Duodecim, the Medical Advisory Board of the Finnish Diabetes Association and the Finnish Gynecological Association. 2014. Accessed from: http://www.kaypahoito.fi/web/kh/suositukset/suositus? id=hoi50068.

[5] World Health Organization. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus. WHO/NCD/NCS/99. 2nd ed. Geneva, Switzerland: World Health Organization; 1999.

[6] International Association of Diabetes and Pregnancy Study Groups Consensus Panel, Metzger BE, Gabbe SG, Persson B, et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classifiation of hyperglycemia in pregnancy. Diabetes Care. 2010;33(3):676–682.

[7] McIntyre HD, Colagiuri S, Roglic G, Hod M. Diagnosis of GDM: a suggested consensus. Best Pract Res Clin Obstet Gynaecol. 2015;29(2): 194–205.

[8] HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991–2002.

[9] World Health Organization. Diagnostic Criteria and Classification of Hyperglycaemia First Detected in Pregnancy: Report of a WHO Consultation. WHO/NHM/MND/13.2. Geneva, Switzerland: World Health Organization; 2013.

[10] Korucuoglu U, Biri A, Turkyilmaz E, Doga Yildirim F, Ilhan M, Hirfanoglu IM, Atalay Y. Glycemic levels with glucose loading test during pregnancy and its association with maternal and perinatal outcomes. Diabetes Res Clin Pract 2008; 80: 69–74.

[11] Falavigna M, Schmidt MI, Trujillo J, Alves LF, Wendland ER, Torloni MR, Colagiuri S, Duncan BB. Effectiveness of gestational diabetes treatment: a systematic review with quality of evidence assessment. Diabetes Res Clin Pract 2014;98(3): 396–405.

[12] Langer O, Yogev Y, Most O, Xenakis EM. Gestational diabetes: the consequences of not treating. Am J Obstet Gynecol 2005;192(4): 989–997.

[13] Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS, Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352(24): 2477–2486.

[14] Bo S, Monge L, Macchetta C, Menato G, Pinach S, Uberti B, Pagano G. Prior gestational hyperglycemia: a long-term predictor of the metabolic syndrome. J Endocrinol Invest 2004;27(7): 629–635.

[15] Boney CM, Verma A, Tucker R & Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115(3): e290–6.

[16] Scheen AJ. Clinical pharmacokinetics of metformin. Clin Pharmacokinet; 1996;30:359–371.

[17] Niromanesh S, Alavi A, Sharbaf FR, Amjadi N, Moosavi S, Akbari S. Metformin compared with insulin in the management of gestational diabetes mellitus: a randomized clinical trial Diabetes Res Clin Pract. 2012 Dec; 98(3):422-9. Epub 2012 Oct 12

[18] Li G, Zhao S, Cui S, Li L, Xu Y, Li Y. Effect comparison of metformin with insulin treatment for gestational diabetes: a meta-analysis based on RCTs Arch Gynecol Obstet. 2015 Jul; 292(1):111-20. Epub 2014 Dec 30

[19] Liang HL, Ma SJ, Xiao YN, Tan HZ. Comparative efficacy and safety of oral antidiabetic drugs and insulin in treating gestational diabetes mellitus: An updated PRISMA-compliant network meta-analysis. Medicine (Baltimore). 2017 Sep; 96(38):e7939.