Med. J. Cairo Univ., Vol. 88, No. 4, Septemper: 1967-1974, 2020
www.medicaljournalofcairouniversity.net

Metformin versus Insulin in Treatment of Gestational Diabetes

AHLAM NASIR ABOUD AL HAYANI, M.D.

The Department of Obstetrics and Gynecology, Ministry of Health, Faculty of Medicine, El Anbar University, Iraq

Abstract

Background: GDM affects both mother and baby during pregnancy and in the long term. Metformin was associated with a lower risk of neonatal hypoglycemia; however, metformin may slightly increase the risk of prematurity.

Aim of Study: The aim of the present study was to compare the safety and efficacy of metformin as an oral anti-diabetic drug with insulin as oral hypoglycemic drugs for management of gestational diabetes mellitus.

Patients and Methods: 120 pregnant women with gestational diabetes mellitus were included in this randomized controlled trial. Patients were randomly allocated into 2 groups as follows: Group I: Insulin group (n=64) and Group M: Metformin group (n=56). Follow-up was done every week by measuring fasting and post prandial blood glucose level. Maternal outcomes and neonatal outcomes were recorded.

Results: There were statistically significant differences as regard mean fasting and post prandial blood glucose level and mean birth weight in insulin and metformin group. Also, increased CS rate between insulin and metformin group. There were statistically significant differences between insulin group and metformin sub-groups patients as regards birth weight, Apgar score and serum glucose level.

Conclusion: We concluded that metformin is an effective and safe treatment option for women with GDM. Metformin is comparable with insulin in glycemic control, providing additional evidence for the use of metformin in GDM.

Key Words: *GDM – Metformin – Insulin.*

Introduction

GESTATIONAL Diabetes Mellitus (GDM) can be defined as 'glucose intolerance or hyperglycaemia (high blood glucose concentration) with onset or first recognition during pregnancy. GDM occurs when the body is unable to make enough insulin to meet the extra needs in pregnancy. The high blood sugars associated with GDM will usually return to normal after the birth of the baby [1].

Correspondence to: Dr. Ahlam Nasir Aboud Al Hayani, The Department of Obstetrics and Gynecology, Ministry of Health, Faculty of Medicine, El Anbar University, Iraq

The prevalence of diabetes in pregnancy has been increasing in the U.S. The majority is Gestational Diabetes Mellitus (GDM) with the remainder primarily preexisting type 1 diabetes and type 2 diabetes. The rise in GDM and type 2 diabetes in parallel with obesity both in the U.S. and worldwide is of particular concern. Both type 1 diabetes and type 2 diabetes in pregnancy confer significantly greater maternal and fetal risk than GDM, with some differences according to type of diabetes as outlined below [2].

GDM affects both mother and baby during pregnancy and in the long term. During pregnancy, women with GDM are at increased risk of pre-eclampsia, hypertension, early delivery, induction of labour and caesarean section. Long term, women with GDM have a greatly increased risk of developing type 2 diabetes mellitus (T2DM); Lee et al., documented the cumulative risk to be 25.8% at 15 years post-pregnancy in a moderate-risk population. The cumulative incidence of T2DM is as high as 70% in some populations [3].

In general, specific risks of uncontrolled diabetes in pregnancy include spontaneous abortion, fetal anomalies, preeclampsia, fetal demise, macrosomia, neonatal hypoglycemia, and neonatal hyperbilirubinemia, among others. In addition, diabetes in pregnancy may increase the risk of obesity and type 2 diabetes in offspring later in life [4].

Insulin may be required to treat hyperglycemia, and its use should follow the guidelines. Both multiple daily insulin injections and continuous subcutaneous insulin infusion are reasonable alternatives, and neither has been shown to be superior during pregnancy [5].

Metformin, an oral biguanide, may be a more logical alternative to insulin for women with GDM who are unable to cope with the increasing insulin

resistance of pregnancy. Metformin works primarily by decreasing hepatic glucose output, improving peripheral glucose uptake, and decreasing free fatty acid levels, thus reducing insulin resistance without as much risk of resulting hypoglycemia [3].

Metformin was associated with a lower risk of neonatal hypoglycemia and less maternal weight gain than insulin in 2015 systematic reviews; however, metformin may slightly increase the risk of prematurity. Furthermore, nearly half of patients with GDM who were initially treated with metformin in randomized trial needed insulin in order to achieve acceptable glucose control. Umbilical cord blood levels of metformin are higher than simultaneous maternal levels. None of these studies or meta-analyses evaluated long-term outcomes in the offspring [6-8].

So, the aim of the present study was to compare the safety and efficacy of metformin as an oral anti-diabetic drug with insulin as oral hypoglycemic drugs for management of gestational diabetes mellitus.

Patients and Methods

After approval from the Institutional Ethics Committee, informed consent was obtained from each of the 120 pregnant women diagnosed with gestational diabetes mellitus.

This study was conducted at Especial Clinic for Obseteric and Gynecology, Al-Ramady, Iraq from 2017-2020.

This is a randomized controlled trial included pregnant women with gestational diabetes mellitus not controlled by diet with gestational age 29 th to 35th weeks, and with singleton pregnancy. Women with pregestational diabetes mellitus, renal or hepatic dysfunction, fetal congenital anomalies and with previous adverse reaction to metformin-were excluded from the current study.

Patients enrolled in the study, were admitted to the hospital for glycemic control followed by history taking, general examinations, abdominal examination, laboratory investigations (routine investigations, fasting and post prandial blood glucose level, liver and kidney function tests, urine analysis for proteinuria), obstetric ultrasound (to rule out congenital fetal malformation, confirm gestational age and polyhydramnios).

All patients are divided in to two groups according to electronic randomization Fig. (1). Each group included 60 patients.

- *Group I (insulin Group):* Received human NPH insulin with starting dose was 0.8 unit/kg/day, with 2/3 of the dose being administrated in the morning (before breakfast) and 1/3 in the evening (before dinner). The doses were adjusted to achieve adequate glycemic control. If pre-prandial glucose levels and post prandial glucose levels were high, regular insulin (1 unit/10mg/dl) over target value was added half an hour before meal.
- *Group M (metformin Group):* Received metformin with initial dose of 500mg once daily with food and increased 500mg every one week if blood glucose not controlled up to a maximum dose of 2000mg in divided doses. In case of metformin therapy, if there was poor control even after maximum dose was reached; those patients were shifted to insulin treatment.
- *Follow-up:* Done every week by measuring fasting and post prandial blood glucose level.
- *Endpoint:* Maternal outcomes and neonatal outcomes.

Data analysis:

Data was analyzed by using SPSS 24.0.

Quantitative data was presented as mean ± standard deviation while qualitative data was presented as frequency and percentages.

Comparison betweenthetwo groups as regards Quantitative variables was made by using independent samples (t) test or Mann-Whitney tests between two groups and ANOVA test was used between more than two groups.

Significantresults were defined when the p-value was less than 0.05.

Results

As in Fig. (1), this study included 120 pregnant women having GDM, 60 of them were treated with metformin, and the remaining number (60) was treated with insulin. After one week of follow-up, 20 women were controlled by 500mg metformin once daily and 40 were uncontrolled and needed to increase dose of metformin. After two weeks of follow-up, 15 of 40 women were controlled by 500mg metformin twice daily and 25 were uncontrolled and needed to increase dose of metformin. After three weeks of follow-up, 14 of 25 women were controlled on 500mg metformin three times daily and 11 were uncontrolled and needed to increase dose of metformin. After four weeks of follow-up, 7 of 11 women were controlled on 500mg metformin four times daily and the remaining 4 women needed to shift to insulin.

In (Table 1), there were non-significant differences between the two study groups as regards age, gravidity, parity, gestational age and body mass index ($p>0.05$).

In (Table 2) and Figs. (2,3), showed statistically significant differences between insulin and metformin groups as regards fasting and postprandial glucose level after one week of treatment with higher mean among insulin group. After two, three and four weeks there were statistically significant differences between insulin and metformin subgroups as regards fasting and postprandial glucose level with higher mean among metformin group, while after five weeks insulin group had significantly higher mean of fasting and postprandial glucose level.

In (Table 3) and Fig. (4), there were statistically significant differences between insulin and metformin groups as regards mode of delivery as insulin group has higher percentage than metformin groups in cesarean delivery.

Table (4) and Fig. (5) showed statistically significant differences between insulin group and metformin sub-groups patients as regards neonatal birth weight, Apgar score and serum glucose level.

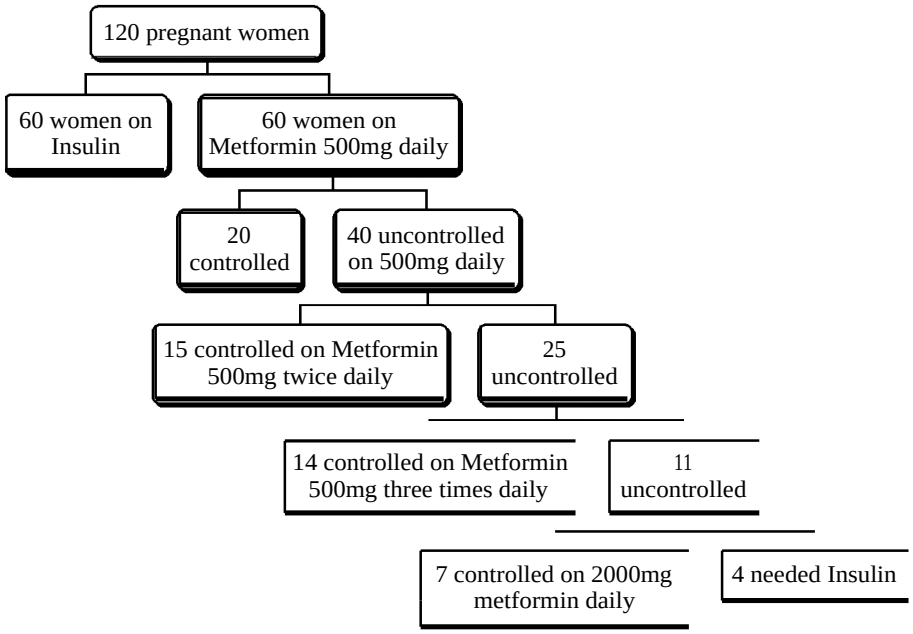
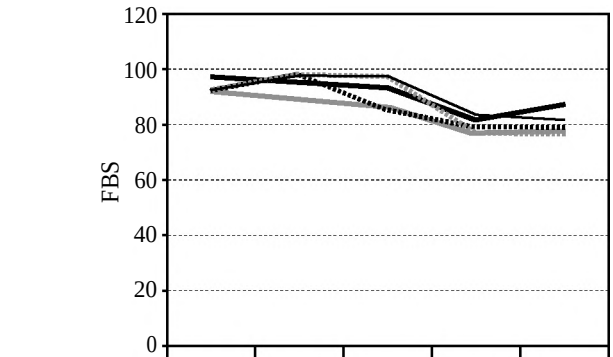
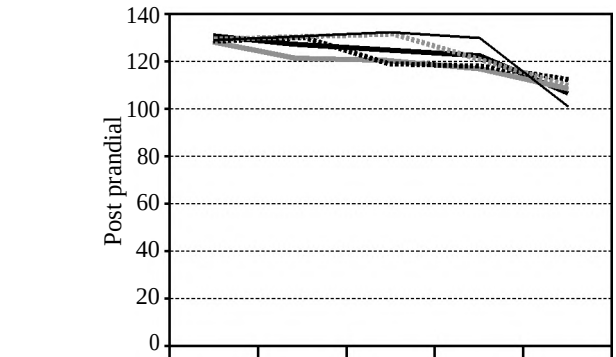


Fig. (1): Flow chart of patients allocation.



	Week 1	Week 2	Week 3	Week 4	Week 5
Insulin	97.13	94.53	92.62	81.26	86.92
500mg	91.92	88.41	86.02	76.82	77.3
1000mg	91.92	97.62	85.31	78.92	78.7
1500mg	91.92	97.62	96.81	76.81	76.4
2000mg	91.92	97.62	96.81	83.46	81.2

Fig. (2): Comparison of fasting bloob glucose level between insulin group and metformin groups after 1, 2, 3, 4 and 5 weeks of treatment.



	Week 1	Week 2	Week 3	Week 4	Week 5
Insulin	130.23	126.51	125.42	122.15	106.2
500mg	127.6	120.67	119.42	116.56	107.42
1000mg	127.6	130.22	118.51	117.87	111.82
1500mg	127.6	130.22	131.43	120.21	109.11
2000mg	127.6	130.22	131.43	129.42	100.12

Fig. (3): Comparison of post prandial bloob glucose level between insulin group and metformin groups after 1, 2, 3, 4 and 5 weeks of treatment.

Table (1): Demographic data of patients of group I and group M.

Basline characteristics	Group I N=60	Group M N=60	*p*-value
Age (years): Mean ± SD	29.97±4.13	30.09±4.1	0.423•
Gravidity: Mean ± SD	2.1±1.3	2.1±1.5	0.726•
Parity: Mean ± SD	1±1.2	1±1	0.817•
G.A: Mean ± SD	30.4±1.32	30.6±2.02	0.564•
BMI Kg/m ^{2}: Mean ± SD	29.13±2.43	30.21±2.25	0.284•

•: Independent *t*-test used. *: Statistical significant when *p*-value <0.05.

Table (2): Comparison of mean glucose level between insulin group and metformin groups after 1, 2, 3, 4 and 5 weeks of treatment.

	Mean Glucose level	Group I N=60	Group M N=60	*p*-value
	Week one:			
	• *Fasting:*			
	Range	84-99	80-96	0.002•*
	Mean ± SD	97.13±3.15	91.92±3.01	
	• *Postprandial:*			
	Range	115-145	110-140	0.003•*
	Mean ± SD	130.23±6.17	127.6±6.97	

Week two	Group I N=60	500mg N=20	1000mg N=40	*p*-value
• *Fasting:*				
Range	88-110	85-100	90-132	0.002#*
Mean ± SD	94.53±3.84	88.41±4.21	97.62±4.73	
• *Postprandial:*				
Range	116-139	110-135	114-149	0.041•*
Mean ± SD	126.51±5.02	120.67±4.62	130.22±6.07	

Week three	Group I N=60	500mg N=20	1000mg N=15	1500mg N=25	*p*-value
• *Fasting:*					
Range	87-111	84-99	83-101	92-139	0.003#*
Mean ± SD	92.62±3.73	86.02±3.87	85.31±3.73	96.81±3.31	
• *Postprandial:*					
Range	115-137	109-133	104-135	114-152	<0.001#*
Mean ± SD	125.42±5.32	119.42±3.31	118.51±3.04	131.43±5.17	

Week four	Group I N=60	500mg N=20	1000mg N=15	1500mg N=14	2000mg N=11	*p*-value
• *Fasting:*						
Range	79-100	75-95	77-97	77-98	79-130	0.035#*
Mean ± SD	81.26±6.14	76.82±5.19	78.92±6.11	76.81±3.31	83.46±6.16	
• *Postprandial:*						
Range	110-131	109-130	108-133	109-130	110-148	0.032#*
Mean ± SD	122.15±3.21	116.56±4.21	117.87±3.67	120.21±4.65	129.42±3.78	

Week five	Group I N=64	500mg N=20	1000mg N=15	1500mg N=14	2000mg N=7	*p*-value
• *Fasting:*						
Range	80-111	75-85	76-88	77-86	75-87	0.022#*
Mean ± SD	86.92±3.31	77.3±4.2	78.7±3.2	76.4±3.2	81.2±3.4	
• *Postprandial:*						
Range	99-110	102-111	105-115	100-114	98-110	0.012#*
Mean ± SD	106.2±3.2	107.42±3.03	111.82±3.41	109.11±3.24	100.12±3.7	

•: Independent *t*-test used. #: ANOVA test used. *: Statistical significant when *p*-value <0.05.

Table (3): Comparison of maternal outcomes between groups.

Maternal outcome	Group I N=64	Metformin subgroups				*p*-value
		500mg N=20	1000mg N=15	1500mg N=14	2000mg N=7	
Pre-term labour	7 (10.9%)	1 (5%)	2 (13.3%)	2 (14.3%)	4 (57.1%)	0.072•
Hypertension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Cesarean delivery	38 (59.4%)	8 (40%)	7 (46.7%)	8 (57.1%)	4 (57.1%)	0.024•*

•: Fisher exact test used.
*: Statistical significant when *p*-value <0.05.

Table (4): Comparison of neonatal outcomes between groups.

Neonatal outcome	Group I N=64	Metformin subgroups				*p*-value
		500mg N=20	1000mg N=15	1500mg N=14	2000mg N=7	
Birth weight: Mean ± SD	4.0±0.12	3.16±0.23	3.2±0.19	3.26±0.15	3.0±0.22	0.038•*
Apgar score: Mean ± SD	8.7±0.9	9.7±0.1	9.6±0.2	9.7±0.09	9.8±0.2	0.048•*
2hrs serum glucose level (mg/dl): Mean ± SD	40.18±1.2	44.09±0.9	44.53±1.2	43.15±1.8	42.36±1.7	0.042•*

•: ANOVAtest used.
*: Statistical significant when *p*-value <0.05.

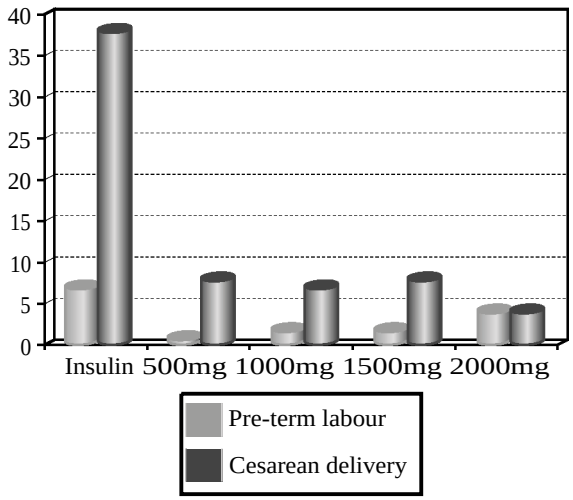


Fig. (4): Maternal outcomes among study groups.

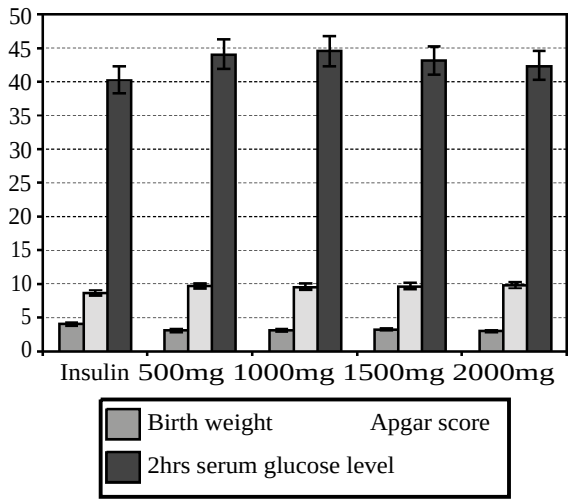


Fig. (5): Neonatal outcomes among study groups.

Discussion

The management of GDM is important because appropriate therapy can decrease many of its adverse pregnancy outcomes. Effective treatment regimens consist of dietary therapy, exercise, self-blood glucose monitoring, and administration of insulin if target blood glucose values are not met with diet regulation alone **[9]**.

RCTs and cohort studies have revealed that there were no substantial differences in maternal or neonatal outcomes attendant upon the use of metformin compared with insulin in women with GDM. However, as metformin can cross the placenta, there continues to be controversy regarding the safety of metformin for pregnant women and their infants **[10]**.

A recent meta-analysis of eight large studies has shown that the use of Oral Hypoglycemic Agents (OHAs) in treating GDM was not associated with neonatal hypoglycemia, macrosomia or increased incidence of cesarean section **[11]**.

The present study was conducted to compare the effectiveness and safety of metformin in treating patients with GDM.

As regard patients' characteristics in both groups, there were no significant differences between the two groups regarding gestational age, gravidity, parity, GA and BMI.

Also, after introduction of the drugs, the average glycemic levels after the first week showed statis-

tically significant differences between insulin and metformin groups as regards postprandial glucose level with higher mean among insulin group.

This was in agreement with the studies of Rowan et al., [10] and Niromanesh et al., [12] who reported that the postprandial glycemic levels at the first week after randomization were significantly lower in the metformin treated group (117.0 ± 16.2 mg/dl versus 120.6± 18mg/dl in insulin treated group). The likely explanation is that it takes time for the patients to master the usage and dose-calculation of insulin. Our results were not in agreement with Refuerzo et al., which revealed that the fasting and 2-hour postprandial glucose levels were not statistically different between insulin and metformin group. In both groups the fasting values were <100mg/dl (p=0.400) and 2-hour postprandial glucose levels all averaged <120mg/dl in both groups (p=0.545). In that study, Refuerzo et al considered any postprandial glucose level below 120mg/dl to be normal irrespective of its exact value [13].

These values had differed significantly in the last fifth week in this study between insulin and metformin groups as regards fasting and postprandial glucose level with higher mean among insulin group a finding suggesting that glucose targets were reached sooner in the metformin group.

Stavroula et al., found that maternal glycated hemoglobin-% at gestational week 36-37 was significantly lower in metformin group, indicating good glycemic control of metformin [14].

In the current study, there was a statistically significant difference between insulin and metformin groups as regards mode of delivery as insulin group has higher percentage than metformin groups in cesarean delivery. This was in agreement with studies of Susan et al., [15] Tertti et al., [16] but not in agreement with the study of Rowan et al., [10] who reported that the ratio of C.S in the metformin group were (49.1 %), while in insulin treated group were (73.4%), p=0.001.

This is inconsistent with the results of the meta-analysis which revealed that there was no significant difference between the metformin and insulin treatment groups in caesarean section [RR=0.93, 95% CI (0.75, 1.16), p=0.53] [11].

In the current study, there were statistically significant differences between insulin group and metformin sub-groups patients as regards birth weight, Apgar score and serum glucose level.

This is similar to a meta-analysis of sixteen studies (n=2165 in quantitative analysis) were included. Metformin lowered the risk of neonatal hypoglycaemia [risk ratio (RR)=0.63; 95% confidence interval (95% CI), 0.45 to 0.87] (Butalia et al., 2017).

In order to characterize and identify mothers needing insulin in addition to metformin, we compared the subgroups of metformin only. As regards patients' characteristics, women requiring supplemental insulin had a higher BMI at the time of diagnosis with p<0.001. The group requiring supplemental insulin also had a higher mean glucose level during the last week before introduction of medication.

As regards economic costs the insulin treatment was more costly than metformin treatment in terms of drug price, cost of blood tests and follow-up, cost of syringes used for insulin.

Therefore, providing a safe drug (metformin) alternative to insulin will save a lot of money, both at the national and individual levels.

Conclusion:

The findings of our study suggest that metformin is an effective and safe treatment option for women with GDM. Metformin is comparable with insulin in glycemic control, providing additional evidence for the use of metformin in GDM. However, this study showed that metformin as a promising drug on maternal and neonatal but larger multicenter studies is recommended to establish the long-term outcomes.

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الميتفورمين مقابل الآنسولين فى علاج السكرى الحملى

يعرف مرض السكرى الحملى تبعاً لما أقرته الجمعية الأمريكية لمرضى السكر بأنه أى درجة فى زيادة مستوى الجلوكوز فى الدم تحدث مع بداية الحمل أو يتم تشخيصه لأول مرة أثناء الحمل. وتقدر نسبة الإصابة به بحوالى ٧٪.

يعتبر الآنسولين هو العلاج التقليدى لمرضى السكرى الحملى لقدرته على السيطرة بصورة أفضل على مستوى الجلوكوز بالدم. وحيث أن مرض السكرى الحملى يتميز بوجود مقاومة للآنسولين، وكذلك إستخدام الآنسولين كعلاج له بعض العيوب مثل الوخز المتكرر، وكثرة التحاليل اليومية اللازمة لمتابعة نسبة الجلوكوز فى الدم لضبط الجرعة، وتدريب المريضة على إستخدام الآنسولين يحتاج إلى كثير من الوقت والجهد بالإضافة إلى التكلفة الإقتصادية العالية، لذا فإن العلاج بواسطة الأقراص المضادة للسكرى (مخفضات السكر) يعتبر العلاج الأمثل.

تقسم الأقراص المضادة للسكرى إلى أربع مجموعات هى: السلفانايل يورياز، والباى جوانيدز، ومثبطات ألفاجلوكوسيديز، وثايزولايدينداىونز.

وقد دعمت العديد من الدراسات التى تم إجرائها على المريضات المصابات بمتلازمة المبيض المتعدد الكيسات إستخدام عقار الميتفورمين من مجموعة الباى جوانيدز أثناء الحمل. وعلى الرغم من عبوره للمشيمة، لم يتم التوصل إلى دليل على وجود آثار سلبية له على الأجنة أو زيادة مخاطر التشوهات عند إستخدامه فى النساء الحوامل. لذلك ينصح بإستخدام عقار الميتفورمين فى علاج السكرى الحملى.

المرضى والوسائل: تم إختيار ١٢٠ سيدة مصابة بداء السكرى الحملى من المترددات على العيادات الخارجية بقسم النساء والتوليد بمستشفى الأزهر الجامعى، وقد توافرت فيهن الشروط الآتية:

- مدة الحمل من ٢٨ إلى ٣٤ إسبوع رحمى ويكون الحمل فى جنين واحد كما لم يستطيع هؤلاء المرضى الوصول إلى مستوى معتدل للجلوكوز فى الدم بعد إتباع النظام الغذائى.
- الحصول على موافقة خطية من كل مريضة لإدخالها فى البحث.

وقد تم إستبعاد الحالات الآتية:

- السيدات الحوامل اللاتى يعانين من مرض السكرى من النوع الأول أو الثانى.
- وجود حساسية لعقار الميتفورمين.

- وجود مرض يؤثر على نمو الجنين أو تصفية العقاقير مثل القصور المزمن فى وظائف الكلى أو الكبد.
- وجود عيوب خلقية فى الجنين تم تشخيصها عن طريق الأشعة التليفزيونية قبل البدء فى الدراسة.

شملت الدراسة الحالية ١٢٠ نساء حوامل مصابات بداء السكرى الحملى، عولج ٦٠ منهن بالميتفورمين، وتم علاج العدد المتبقى (٦٠) بالأنسولين. بعد إسبوع واحد من المتابعة، تم إستجابة ٢٠ إمرأة للعلاج ب٥٠٠ ملغ الميتفورمين مرة واحدة يومياً و٤٠ كانت غير مستجيبة وتحتاج إلى زيادة جرعة الميفورمين.

بعد إسبوعين من المتابعة، تم إستجابة ١٥ من ٤٠ إمرأة عن طريق ٥٠٠ ملغ الميتفورمين مرتين يومياً و٢٥ كانت غير مستجيبة وتحتاج إلى زيادة جرعة من الميتفورمين.

بعد ثلاثة أسابيع من المتابعة، تم إستجابة ١٤ من ٢٥ إمرأة على ٥٠٠ ملغ الميتفورمين ثلاث مرات يومياً و١١ كانت غير مستجيبة وتحتاج إلى زيادة جرعة من الميتفورمين.

بعد أربعة أسابيع من المتابعة، تمت إستجابة ٧ من ١١ إمرأة على ٥٠٠ ملغ من الميتفورمين أربع مرات يومياً، النساء الحوامل الأربع الباقيات، ٤ منهن لم تستجب لزيادة الجرعة. هؤلاء النساء الحوامل ٤ تم علاجهم بالأنسولين.

تم تقييم المواليد عن طريق الفحص الإكلينكى الذى إشتمل على فحص شامل لإستبعاد العيوب الخلقية وتحديد الوزن عند الولادة لحصر الحالات التى يزيد فيها وزن المولود عن ٤ كجم. كما تم القيام بالفحص المعملى عند الحاجة والذى يشمل قياس نسبة الجلوكوز فى الدم، قياس نسبة الصفراء فى الدم، وقياس نسبة الكالسيوم فى الدم.

\النتائج والمناقشة: تم تحليل النتائج إحصائياً بإستخدام الوسائل المناسبة كما تم إجراء مقارنة للخصائص الديموغرافية بين مجموعتين ولم يكن هناك فروق ذات دلالة إحصائية بين المجموعتين فيما يتعلق بعمر الأم، عدد مرات الحمل، عمر الحمل فى وقت التشخيص، ومؤشر كتلة الجسم فى وقت التشخيص.

بالإضافة إلى ذلك، لوحظ أن النساء فى المجموعة المعالجة بالميتفورمين وصلوا فى وقت أقرب إلى إنخفاض نسبة الجلوكوز بالدم كما لوحظ أن زيادة وزن الأمهات أقل فى المجموعة المعالجة بالميتفورمين.

وقد وجد أن النساء اللاتى إحتاجت الغلاج بالأنسولين الإضافى كان لديهن مؤشر كتلة الجسم أعلى، ومستويات أعلى من السكر الصائم ومستوى الجلوكوز فى ساعتين فى وقت التشخيص.

وكشف تحليل النتائج أن الميتفورمين كان دواء فعال للسيطرة على نسبة الجلوكوز فى الدم لدى النساء المصابات بداء السكرى الحملى الذين فشلوا فى تحقيق إنخفاض فى سكر الدم عن طريق إتباع نظام غذائى فقط.

\الإستنتاج: بهذه النتائج أثبتنا أن عقار الميتفورمين هو دواء فعال للسيطرة على الجلوكوز فى الدم عند إستخدامه فى حالات السكرى الحملى.