Effect of Oral Hypoglycemic Drugs on the Outcome of Pregnancy in Type 2 Diabetes Mellitus

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Abstract: Background: Type 2 diabetes mellitus (T2DM) is a progressive and complex disorder that is difficult to treat effectively in the long term. The majority of patients are overweight or obese at diagnosis and will be unable to achieve or sustain near normoglycemia without oral antidiabetic agents; a sizeable proportion of patients will eventually require insulin therapy to maintain long-term glycemic control, either as monotherapy or in conjunction with oral antidiabetic therapy. The frequent need for escalating therapy is held to reflect progressive loss of islet β-cell function, usually in the presence of obesity-related insulin resistance. Today's clinicians are presented with an extensive range of oral antidiabetic drugs for T2DM. **Objective**: This article will discuss the various effects of oral hypoglycemic drugs on the outcome of pregnancy with T2DM. **Material And Methods**: Patients were attending the combined outpatient clinic for Internal Medicine Department, Endocrinology Unit and Obstetrics Department of Zagazig University Hospital, were entered into a database. The following maternal, fetal and neonatal items were retrieved from the database. Maternal outcome (pre-eclampsia, pre-term delivery, Cesarean section) and fetal and neonatal outcome (macrosomia, congenital malformations, perinatal mortality, neonatal hypoglycemia) were analyzed as well HbA1c levels, planning of pregnancy, gestational age at first antenatal visit. One hundred-fifty pregnant female were classified into three groups. All pregnant females were subjected to full medical history with thorough medical examination, routine laboratory investigations include (fasting blood glucose [FBG] level, 2-hours post prandial glucose level [2-hpp]), glycosylated hemoglobin (HbA1c) and pelvi-abdominal ultrasonography. **Results**: In the present study, 50 pregnancies in T2DM have delivery and they incidentally continued the use of their oral anti-diabetes (OADs) (e.g., sulphonylurea and biguanides) before realizing that they had got pregnant for a period from 1-4 weeks. As regards, the relation between fetal macrosomia and types of OADs; there were nonsignificant statistically value occurred in all studied groups used biguanides. The relation between neonatal hypoglycemia and types of OADs; there is nonsignificant value in the OADs group of the studied groups. Also, there is nonsignificant value between OADs types and neonatal polycythemia, hyperbilirubinemia and respiratory distress. There were nonsignificant value in the cases of studied groups with birth injury and types of OADs, but it did not occur with biguanide use. There was nonsignificant statistical value between intra uterine foetal death and types of OADs. There were significant statistical value between CS and types of OADs use in the studied groups. Also, there is nonsignificant statistical value in the incidence of abortion and types of OADs (weeks). It occurred mostly with sulphonylurea, and did not occur with biguanide use. As regards, the results obtained the relation between incidence of preeclampsia and types of OADs, there was nonsignificant statistical value, it occurred mostly with sulphonylurea and did not occur with biguanide in cases of the studied groups. There was relation between polyhydramnios and the types of OADs. There were nonsignificant statistical value occurred only with the use of sulphonylurea in cases of the studied groups. **Conclusion**: The use of oral hypoglycemic drugs on the outcome of pregnancy in type 2 diabetes during early pregnancy increases the incidence of maternal complication. **Recommendations**: 1) Preconception counseling and assessment of glycemic control before conception and during early gestation (first 6 to 8 weeks) is the primary determinant of the risk for various congenital anomalies and early pregnancy loss. 2) Pre pregnancy management should be initiated 3to 6 months before intended conception; the goal is to obtain A1c level within normal range. 3) Oral hypoglycemic drugs must not be taken during early pregnancy. 4) Insulin should be used during pregnancy.

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1. Introduction

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both[1-3]. Insulin deficiency in turn leads to chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism[4]. As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy[5,6], neuropathy[7,8], nephropathy[9,10], cardiovascular complications[11,12] and ulceration[13]. Thus, diabetes covers a wide range of heterogeneous diseases.

Diabetes is the most common endocrine disorder and by the year 2010, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the disease by 2025[14].

Type 2 diabetes is the commonest form of diabetes and is characterized by disorders of insulin secretion and insulin resistance[15]. In Western countries the disease affects up to 7% of the population[16]. Globally, it affects 5-7% of the world's population[17].

Diabetes should optimally be under tight control before conception. During the first trimester before the placenta increases the production of hormones, nausea, and increased insulin sensitivity (possibly by estriol) may place the mother at risk for hypoglycemia. Women must be counseled that their insulin requirements in the first trimester are likely to decrease by 10-20%[18]. This is especially true at night when prolonged fasting and continuous fetal glucose utilization places the woman at even a higher risk for hypoglycemia[19].

Diabetes is a chronic progressive disorder, with multiple biological defects, which necessitates the use of a range of different classes of drugs in order to optimize disease control over the patients' life span. To date there have been oral drug classes such as the biguanides, sulphonylureas, and injectable insulin options such as human and analogue insulin, which have become household names in the treatment of diabetes. New treatment options that target the incretin system are now available. These now widen the choices for commencing treatment for Type 2 diabetes [20].

It is important to understand the mechanism of action of these drugs to fully comprehend the mode and extent of glucose control that can be achieved as well as the side effects that could be anticipated[21].

Less is known of the pregnancy outcome in women with pre-gestational type 2 diabetes mellitus. During the last decade, five surveys have been published which show that maternal, fetal and neonatal outcomes are similar to, if not worse than those in pregnancies with pre-gestational type 1 diabetes[22]. Pre-gestational type 2 diabetes is an emerging problem especially since type 2 diabetes has become a global epidemic[23]. This means that type 2 diabetes occurs with increasing frequency in younger age groups. Since, at the same time, the maternal age of first and subsequent pregnancies has risen in modern society, more and more women are confronted with the problems and burden of diabetes type 2 during pregnancy[23].

Type 2 diabetes in pregnancy is also associated with additional potentially harmful factors. A considerable number of women are of migrant origin and language and cultural barriers may exist, impairing adequate pre-gestational care and counseling[24]. This may result, for example, in late reporting for initial antenatal care. Medication poses additional problems. Not only are some women continuing to take oral glucose-lowering medication while pregnant, but a considerable number of women may also use anti-hypertensive and anti-hyperlipidemic drugs. Some of these drugs are associated with congenital malformations[25].

Diabetes complicates up to 14% of pregnancies, and with the rising prevalence of obesity and diabetes in younger population groups it may become an even greater problem. Poor metabolic regulation is a precipitating factor for unfavorable pregnancy outcome or fetal macrosomia[26].

Different oral hypoglycemic and antihyperglycemic agents have diverse mechanisms of action to correct or improve the pathological lesion responsible for glucose intolerance. Therefore, these drugs provide an enhanced approach to the treatment of type 2 diabetes[27].Furthermore; combination therapies will further improve the effect of these drugs on glucose metabolism. Insulin therapy, in contrast to therapy with oral agents, is designed to mimic the physiological secretion of endogenous insulin. Oral agents are a pragmatic alternative to insulin therapy in pregnancy because they are easy to administer and noninvasive and therefore user-friendly[28].

The introduction of any new drug in pregnancy will raise concerns about fetal and maternal safety. The ultimate proof that a drug cannot affect the fetus during pregnancy is founded on its inability to cross the placenta. The majority of drugs used in pregnancy cross the placenta[29]. Thus, even if a new drug cross the placenta, it remains to be proven that it will cause a teratogenic effect on the fetus in utero. If there is no adverse effect on the fetus, the drug can be used[30].

From the preconception phase on ward, fasting blood glucose levels should be maintained between 90 and 105 mg /dl with 2 hours post-prandial readings less than 140 mg/dl constant glucose monitoring system that continually plot blood glucose levels over a 72–hours period are useful in detecting nocturnal hypoglycemia or demonstrating a- progressive over night rise in glucose levels (the dawn phenomenon). An insulin pump with a programmable progressive increase in basal insulin delivery through the night is the most effective way of combating the dawn phenomenon[31].

The possible treatment options for women with diabetes are reviewed, with special reference to novel treatment[32]. Although type 2 diabetes in pregnancy is related to adverse outcomes[33]. In this retrospective study, we will review the effect of oral hypoglycemic drugs on the outcome of pregnancy in type 2 diabetes mellitus. We can choose the appropriate drugs for optimal control of diabetes targeting specific pathophysiological defects.

2. Subjects and Methods

This prospective descriptive study was carried out during the period from November 2009 to September 2010. Patients with a diagnosis of type 2 diabetes

mellitus (T2DM), who delivered in the studied period attending the combined outpatient clinic for Obstetrics and Internal Medicine Department, Endocrinology Unit of Zagazig University Hospital, were entered into a database. The department serves as a multiple medical center.

Patients had to have a diagnosis of pre-gestational type 2 diabetes (T2D) based on a previous medical diagnosis and/or abnormal biochemical data and/or use of oral medication and/or insulin. Patients who were referred to our center based on their obstetric pathology were excluded, as they were first seen after 30 wk of gestation.

Subjects

The total number of deliveries during the period of the study was 150 pregnant female. They were classified into three groups.

Group I (control group): It included 50 healthy pregnant females their ages ranged between 19-35 years old. They had no history of diabetes proved by both clinical and laboratory evaluation.

Group II: It included 50 pregnant females with type 2 diabetes their ages ranged between 19-32 years old and the duration of diabetes ranged from 1-8 years and they used insulin from early pregnancy.

Group III: It included 50 pregnant females with type 2 diabetes, their ages ranged between 23-36 years old and the duration of diabetes ranged from 1-10 years and they incidentally continued the use of their oral anti diabetes (Sulfonylurea and biguanides) before realizing that they had got pregnant for a period ranging from 1 weeks – 4 weeks.

Methods

All patients were subjected to the following:

- Full medical history with thorough medical examination.

Maternal investigations

- Age
- Weight and length (body mass index (BMI))
- Parity
- Planning of pregnancy (use of folic acid and/or evidence of pre-gestational counseling and actions in the medical files)
- Gestational age at first antenatal visit (counted from the last of day of the last menstruation, thus normally a minimum of 4 wk)
- Duration of clinical diabetes
- Insulin use during pregnancy
- Incidence of preeclampsia
- Incidence of spontaneous abortion (before week 20)
- Abortion due to severe malformations
- Pre-term delivery (20-37 wk)
- Fetal death
- Mode of delivery

Fetal or neonatal delivery

- Congenital malformations (major malformations, defined as malformations which result in death, require major surgical intervention or result in physical handicaps including major cosmetic handicaps)
- Birth weight
- Macrosomia (defined separately as birth weight >4000g, or birth percentile ≥90 (large-for gestational age (LGA)); severe macrosomia defined separately as birth weight >4500g, or birth percentile ≥97.7 (very-large-for gestational age (VLGA)) – Neonatal hypoglycemia (plasma glucose ≤2.6 mmol/l)
- Severe neonatal hypoglycemia (plasma glucose ≤2.0 mmol/l and/or use of intravenous glucose infusion)
- Hyperbilirubinemia requiring at least one period of phototherapy

- Routine laboratory investigations:
  - Fasting blood glucose level.
  - 2 hours post prandial glucose level.
- Glycosylated Hemoglobin (HbA1c): (for the second and third groups).
  - Normal range in diabetic pregnancy is from 4-6%
  - Good glycemic control < 6.5%
  - Fair glycemic control is from 6.5 – 7.5%
  - Poor glycemic control > 7.5%
- Pelvi-abdominal ultrasonography

Statistical analysis

All analysis was performed using SPSS for windows (SPSS Inc., Chicago, IL, USA, version 15.0). Results are given for continuous variables as mean and standard deviation (X±SD) with normal distribution. Categorical variables are given as percentages. Differences between groups are tested with the appropriate (non-)parametric tests for continuous variables with the χ^2-test or F-test for categorical variables. The level of statistical significance was set at $P < 0.05$. Parameters with $p < 0.10$ were entered into a multivariate regression modal to test for independence if multiple determinants were found.

3.Results

This prospective descriptive study was conducted to discuss the effect of oral hypoglycemic drugs on the outcome of pregnancy in type 2 diabetes mellitus (T2DM). Results from the study population were compared with those from the general population. In this study, 100 pregnant T2DM were conducted and classified to two groups according to age, duration of diabetes, types of oral hypoglycemic drugs, and insulin used, and compared to 50 healthy pregnant females as control group who had no history of diabetes.

The demographic and clinical characteristics of all the subjects in each group are summarized in **Table 1**.

The individual pregnant T2DM and control group represented as a mean value ± standard deviation (X±SD). As regard, age of group I (control group) without T2DM their ages ranged from (20-36) was 29.2±4.3 years, and group II with T2DM and duration of diabetes ranged from 1-8 years and used insulin from early pregnancy ranged from (19-32) was 28.8±4.1 years, and group III with T2DM and duration of diabetes ranged from 1-10 years and they use the oral hypoglycemic drugs before realizing that they had got pregnant for a period 1 week to 4 weeks, age ranged from (32-37) was 29.9±3.6 years. There were nonsignificant statistically differences between control and studied groups (p value = 0.38). As regard, the parity, weight, and height have nonsignificant statistical differences between patient groups comparing to control group. Also, we found that there was statistical significant increasing in systolic BP in group II comparing to group III and control group (p value = 0.002). On the other hand, there were statistical nonsignificant decrease in group III comparing to control group and group II with diastolic BP (p value = 0.06).

In the present study, **Table 1** show an increase in duration of diabetes (in years) in group II used insulin ranged from 1-8 years comparing to group III used oral hypoglycemic drugs; it ranged from 1-10 years, there were statistical nonsignificant differences in insulin group (Group II) versus OADs group (group III) (p = 0.26).

On the other hand, there was statistical highly significant increasing in fasting blood glucose level (FBG), 2-hpp and HbA1c levels in studied groups comparing to control group (p <0.001). There were non-significant increasing in poor glycemic control comparing with fair glycemic control had nonsignificantly decreased between groups II and III (**Table 1**).

Table 2 showed that there was a decrease in systolic BP at 0-3 months between control group and studied groups also, there was changes at 6 months and had statistical highly significant differences between control group and studied groups (p <0.001). As regard, with diastolic BP, there were nonsignificant differences between control group and studied groups (at 0 month p < 0.01, 3 months p = 0.72 versus 6 months p < 0.001). Also, there were statistical highly significant decrease in fasting blood glucose (FBG) at 0-6 months between control group and studied groups (p < 0.001). As regard, there was an increase in 2-hpp at 0-3 months in groups II and III comparing to control group, also, there was an increase of 2-hpp in group III comparing to group II and control group at 6 months. There were statistical highly significant differences between control group and studied groups (p < 0.001).

On the other hand, there were statistical highly significant differences in HbA1c (%) at 0-6 month, in groups II and III versus control group (p < 0.001) (**Table 2**).

Table 3 showed that there were highly significant differences between control group and studied groups with cesarean section (CS) and normal vaginal delivery (NVD) (p < 0.001) comparing to abortion had statistical nonsignificant differences between control group and studies groups (p = 0.39).

In the present study, there were statistical nonsignificant differences between control group and studied group with preeclampsia (χ^2 = 2.79; p value 0.2). As regard, comparing with polyhydramnios, also there were statistical significant differences (χ^2 = 6.08; p value 0.04) (**Table 4**).

Table 5 showed that the comparison between poor and fair glycemic control as regard maternal and fetal complications and outcomes. In this table we found that hypoglycemia, polycythemia, normal vaginal delivery, and preeclampsia have statistical significant differences, and its incidence is increased with fair control. On the other hand, in macrosomia, hyperbilirubinemia, respiratory distress, birth injury, intra uterine foetal death, cesarean section, abortion, and polyhydramnios had statistical nonsignificant differences and its incidence is increased with poor control.

In the present study, 50 pregnancies in T2DM have delivery and they incidentally continued the use of their oral anti-diabetes (OADs) (e.g., sulphonylurea and biguanides) before realizing that they had got pregnant for a period from 1-4 weeks. **Table 6** show that the relation between types of OADs and the maternal and fetal complications. As regard the relation between fetal macrosomia and type of OADs; there were nonsignificant statistically value occurred in all studied groups used biguanides. As regard, the relation between neonatal hypoglycemia and types of OADs; there is nonsignificant value in the OADs group of the studied groups. Also, there is nonsignificant value in OADs types and neonatal polycythemia, hyper-bilirubinemia and respiratory distress. There were non significant value in the cases of studied group with birth injury and types of OADs, but it did not occur with biguanide use. There was nonsignificant statistical value between intra uterine foetal death and types of OADs. There were significant statistical value in CS and types of OADs use in the studied groups. Also, there was non-significant statistical value in the incidence of abortion and types of OADs (weeks). It occurred mostly with sulphonylurea, and did not occur with biguanida use. Also, the results obtained the relation between incidence of preeclampsia and types of OADs. There was nonsignificant statistical value, it occurred mostly with sulphonylurea and did not occur with biguanida in cases of the studied groups. There was relation between polyhydramnios and the types of OADs. As regard, there were nonsignificant statistical

value occurred only with the use of sulphonylurea in cases of the studied groups.

Table 1: Demographic and clinical characteristics of control and studied groups

Variables	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	*F*	*P* value
Age (years)					
X±SD	29.2±4.3	28.8±4.1	29.9±3.6	0.95	0.38
Range	(20-36)	(19-32)	(32-37)		
Parity					
Gravidity	2.98±1.25	2.68±1.24	2.76±1.46	0.76	0.47
Parity	1.92±1.22	1.95±1.32	1.58±1.34	1.31	0.27
Blood pressure					
Systolic BP	117.3±7.9	126.4±12.8	122.6±17.6	6.1	0.002*
Diastolic BP	73.1±5.9	76.8±13.6	78.4±14.7	2.72	0.06
Weight (kg)	76.5±7.2	74.5±8.7	76.9±13.1	0.86	0.42**
Height (cm)	165.7±6.5	167.2±5.4	168.1±6.5	2.02	0.13**
Duration of diabetes (years)					
X±SD	-	4.26±3.2	3.65±2.2	$t = 1.2$	0.26**
Range	-	(1-8)	(1-10)		
Duration of OADs					
X±SD	-	-	2.1±0.75	-	-
Range	-	-	(1-4)		
FBG					
X±SD	80.0±6.59	200.3±62.2	201.7±60.3	140.7	<0.001***
Range	(70-110)	(87-380)	(89-388)		
2-hpp					
X±SD	100±15.32	263.0±72.6	273.0±74.7	140.07	<0.001***
Range	(110-140	(160-450)	(158-477)		
HbA1c (%)					
X±SD	5.4±0.9	8.64±1.67	8.36±1.6	52.87	<0.001***
Range	(4.2-6.7)	(7-11)	(6.7-11.8)		
Glycemic control		**No** **%**	**No** **%**		
Poor		32 64.0%	35 70.0%	$\chi^2 = 0.41$	0.52**
Fair		18 36.0%	15 30.0%		
Good		0 0.0%	0 0.0%		

BP: blood pressure **OADs**: oral anti-diabetes **FBG**: Fasting blood glucose **2-hpp**: 2-hours pos prandial
* *P* value < 0.05 = significant ** *P* value > 0.05 = nonsignificant *** *P* value < 0.001 = highly significant

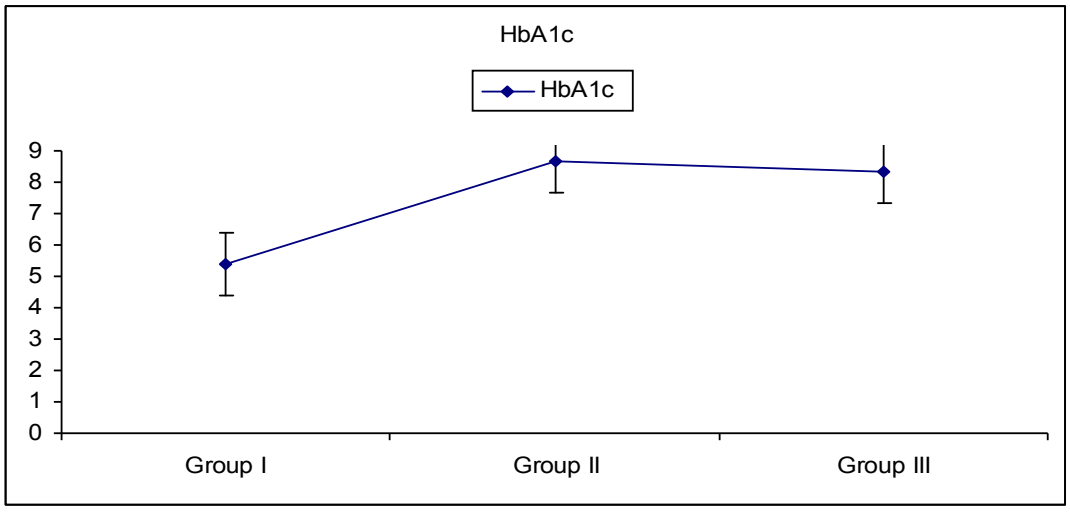

Figure 1: HbA1c-levels before and during pregnancy. Data are means ± SD.

Table 2: Comparison of variable investigations in the control and studied groups

Variables	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	*P* value
Blood pressure				
Systolic BP				
0 month	107.0±7.2 (100-120)	121.2±13.6 (100-160)	122.6±17.6 (100-170)	<0.001***
3 months	108.0±6.4 (100-115)	*107.3±14.4 (90-155)	*113.6±12.2 (90-150)	<0.001***
6 months	100.0±5.36 (90-110)	*107.4±12.6 (100-145)	*108.3±11.7 (100-130)	<0.001***
Diastolic BP				
0 month	70.0±6.2 (60-80)	76.5±13.9 (62-120)	78.4±14.7 (60-130)	<0.01*
3 months	72.6±6.3 (60-90)	*72.7±8.62 (65-115)	*73.8±9.77 (60-110)	0.72**
6 months	*60.0±6.7 (50-70)	*73.3±6.2 (70-90)	*70.0±6.3 (60-80)	<0.001***
FBG				
0 month	80.0±6.59 (70-110)	121.2±13.6 (100-160)	122.6±17.6 (100-170)	<0.001***
3 months	82±7.1 (70-100)	*107.3±14.4 (90-155)	*113.6±12.2 (90-150)	<0.001***
6 months	*78±7.3 (65-90)	*107.4±12.6 (100-145)	*108.3±11.7 (100-130)	<0.001***
2-hpp				
0 month	100±15.32 (110-140)	263.0±72.6 (160-450)	273.0±74.7 (158-477)	<0.001***
3 months	103±15.4 (110-145)	270.8± 42.2 (200-400)	273.7±53.1 (200-410)	<0.001***
6 months	*95±15.6 (100-120)	*250.7±32.7 (190-230)	*261.7±34.0 (215-305)	<0.001***
HbA1c (%)				
0 month	5.4±0.9 (4.2-6.7)	8.64±1.7 (7-11)	8.36±1.6 (6-11.8)	<0.001***
3 months	5.7±1.2 (4.5-7)	8.2±2.1 (7.2-10)	8.19±1.1 (6.6-10.2)	<0.001***
6 months	5.0±1.3 (4.1-7)	8.5±2.1 (7-11)	*7.27±0.4 (6.7-7.6)	<0.001***

BP: blood pressure **FBG**: Fasting blood glucose **2-hpp**: 2-hours post prandial blood glucose level
* *P* value < 0.05 = significant ** *P* value > 0.05 = nonsignificant *** *P* value < 0.001 = highly significant

Table 3: Comparison of pregnancy outcome between control and studied groups

Variables	Group I (n = 50)		Group II (n = 50)		Group III (n = 50)		χ^2	*P* value
	No	%	No	%	No	%		
CS	12	24.0	39	78.0	37	74.0	37.34	< 0.001***
NVD	35	70.0	10	20.0	9	18.0	37.67	<0.001***
Abortion	3	6.0	1	2.0	4	8.0	1.85	0.39**

CS: cesarean section **NVD**: normal vaginal delivery
** *P* value > 0.05: nonsignificant *** *P* value < 0.001: highly significant

Table 4: Comparison of maternal complications between control and studied groups

Variables	Group I (n = 1)		Group II (n = 10)		Group III (n = 10)		χ^2	*P* value
	No	%	No	%	No	%		
Preeclampsia	1	2.0	4	8.0	5	10.0	2.79	0.2**
Polyhydramnios	0	0.0	6	12.0	5	10.0	6.08	0.04*

* *P* value < 0.05: significant ** *P* value > 0.05: nonsignificant

Table 5: Comparison between poor and fair glycemic control as regard maternal and fetal complications and outcomes

Complications	Poor control (n = 67)	Fair control (n = 33)	χ^2	*P* value
Macrosomia (78)	54	24	0.8	0.37**
Hypoglycemia (54)	31	23	4.89	0.02*
Polycythemia (27)	13	14	5.95	0.014*
Hyperbilirubinemia (23)	19	4	3.29	0.06**
Respiratory distress (27)	21	6	1.94	0. 16**
Birth injury(caput medusa) (7)	4	3	0.03	0.87**
Intra Uterine Fetal Death (3)	2	1	0.37	0.54**
Cesarean section(76)	53	23	1.07	0.3**
Normal vaginal delivery(19)	3	16	27.82	0.001*
Abortion(6)	6	0	1.76	0.18**
Preeclampsia (9)	9	0	4.87	0.02*
Polyhydramnios (11)	10	1	2.1	0.14**

* *P* value < 0.05: significant ** *P* value > 0.05: nonsignificant

Table 6: Effect of oral anti-diabetes (OADs) drugs on the outcome of pregnancy in T2D and maternal and fetal delivery (n = 50)

Parameters	Sulphonylurea (n = 38)	Biguanides (n = 4)	Combination (n=8)	X^2	*P* value
Macrosomia	30	4	6	1.15	0.56**
Hypoglycemia	21	1	4	1.34	0.51**
Polycythemia	10	3	2	4.2	0.12**
Hyperbilirubinemia	7	1	2	0.25	0.88**
Respiratory distress	10	1	4	1.82	0.4**
Birth injury (caput medusa)	2	0	1	0.89	0.64**
Intra Uterine Fetal Death	2	0	1	0.89	0.64**
Cesarean section (CS)	28	4	5		0.019*
Abortion	4	0	1	0.51	0.7**
Preeclampsia	4	0	1	0.51	0.7**
Polyhydramnios	5	0	0	1.75	0.41**

* *P* value < 0.05: significant ** *P* value > 0.05: nonsignificant

4.DISCUSSION

The use of oral hypoglycaemic drugs in pregnancy is not recommended because of reports of foetal anomalies and other adverse outcomes in animal studies and in some human cases. However, recent studies have suggested that some oral hypoglycaemic drugs may be used in pregnancy[34].

Insulin has long been the mainstay of treatment for women with gestational diabetes and type 2 diabetes in pregnancy. Although oral hypoglycemic agents or oral anti-diabetic agents (OADs) were used in these patients in the 1970s and 1980s, concerns arose from some studies that found increased rates of perinatal mortality and neonatal hypoglycemia[35]. Because of these concerns, the use of OADs in pregnancy was strongly discouraged. However, more recent data on oral agents in women with gestational diabetes suggest that an important paradigm shift is occurring regarding their use in pregnancy[36].

There is now a changing trend in the acceptability of using oral hypoglycemic agents in non-insulin dependent pregnant diabetics. There are some oral hypoglycemic drugs which may be safe and therefore, useful especially for those who are only mildly to moderately hyperglycemic and who do not desire multiple daily insulin injections[37].

Sulfonylureas act by increasing insulin secretion from the pancreas. They bind to the sulfonylurea receptor on the pancreatic ß cells, leading to inhibition of the potassium channel and reduction of the resting membrane potential[38]. This leads to the opening of the calcium channel and an increase in intracellular calcium, resulting in the release of insulin from secretory granules. **Elliot *et al*.[39]** tested 4 sulfonylureas for placental transfer using the human placental cotyledon perfusion model. This model replicates the *in vivo* situation more closely than do subcellular or cell culture systems, obviating the need for human *in vivo* studies and avoiding the inappropriate use of animal models[40]. The investigators found that, while the first-generation sulfonylureas crossed the placenta readily (21.5% for tolbutamide, 11% for chlorpropamide), the second-generation sulfonylureas crossed to a much lesser extent (glipizide 6.6%)[39]. In particular, a small percentage (3.9%) of glyburide (glibenclamide) crossed.

In some countries where the use of insulin may not always be possible, the option of using oral hypoglycemic agents may be particularly attractive. Among the sulphonylureas, only glibenclamide has been shown not to cross the placenta[41]. Moreover, the best and strongest evidence available so far in terms of safety and efficacy is that of glibenclamide as shown in a randomized controlled study involving a large number of subjects and a direct head-to-head comparison with the gold standard use of insulin in the treatment of gestational diabetes[34]. However, it would be reassuring to have more of such randomized controlled studies comparing glibenclamide and insulin to confirm these findings[42].

Biguanides (metformin) work to lower blood glucose levels primarily by decreasing hepatic gluconeogenesis[43]. Other mechanisms of action include increased peripheral glucose disposal and reduced intestinal glucose absorption. Metformin has been shown to pass freely across the placenta[44]. Two *in vivo* studies measured maternal and cord blood samples in women taking metformin throughout pregnancy (850 mg twice daily in 15 women[45] and 2000 mg/day in 8 women) [46]. The results of these trials showed that the fetus is exposed to concentrations as high or higher than those seen in the mother.

The present study of pregnant women with type 2 diabetes mellitus (T2DM) during 2009–2010 emphasizes that T2DM in pregnancy comprises a serious problem. This study, discussed the effect of different oral hypoglycemic drugs (e.g., sulfonylurea and biguanides) which there is still an increased frequency of adverse pregnancy outcomes in women with T2DM with emphasis on an increased frequency of congenital malformations, preeclampsia, macrosomia and neonatal hypoglycemia.

The present study shows that the age had nonsignificant differences between control group and studied groups. As regard, the parity, weight, and height have nonsignificant differences in studied groups comparing to control group. Also there were nonsignificant statistically difference in duration of diabetes (years).

The clinical characteristics of control and studied groups showed that there were highly significant statistically increasing in FBG, 2-hpp, and HbA1c in groups II and III comparing to control group. Regarding, there were non-significant increasing in poor glycemic control comparing with fair glycemic control had non-significantly decreased between groups II and III.

In this study, the outcome was compared with available national data for the general population. Since the aim was to determine the outcome in T2DM compared to the normal population, we did not use the data from the population of other patients because this population was selected specifically in view of the nature of our center. The group of T2DM patients was considered to be well-representative of the normal diabetes population, since many patients originated from the general outpatient clinic. The planning of pregnancy with pre-gestational optimization of glycemic control is of paramount importance.

This study showed that a majority of patients in our population did indeed plan their pregnancy. To define the planning of pregnancy, the use of folic acid or pre-gestational attention and early visits to the clinic were considered. Although folic acid is part of the recommended treatment in early pregnancy, its use in the general population of Egypt is much lower than the 65% seen in this study. Some kind of planning was seen in more than 70% of patients which was consistent with the high level of birth planning in the Egyptian society.

Hypoglycemic control counseling means that the HbA1c level should be maintained as low as possible, Furthermore, counseling should achieve the cessation of treatment with oral hypoglycemic medication, the starting or adjusting of insulin treatment if necessary and the discontinuation of other potentially teratogenic medication. A complicating factor may be that many patients with type 2 diabetes are treated by a general practitioner. In view of the complications of diabetes in pregnancy and the intensive end complex therapies required, all patients who express the desire to become pregnant should be referred for specialist care before conception.

In concordance with this, the HbA1c levels were high significantly elevated in pregnancies in women with T2DM during the entire pregnancy compared with the normal range. However, compared with our well-characterized population of pregnant women with T2DM had comparable or better glycemic metabolic control but nevertheless a poorer pregnancy outcome. A few other studies find tendencies toward higher HbA1c, among women with type 2 diabetes, but only in the first part of pregnancy.[47] This indicates that factors in addition to glycemic control are related to the poor outcome of pregnancies complicated by T2DM.[48]

Glycemic control is a critical factor for a good course and outcome of pregnancy in women with diabetes. In this study we took HbA1c as the indicator of overall control. The mean level, of those in whom this was known, was close to 7% before pregnancy, decreasing during pregnancy (6.7-11%) and slightly increasing in the last trimester (7-11%). This pattern is well-known in pregnancy. The decrease in HbA1c during the first two trimesters is attributed to an increase in red cell production as well as to patients' action to improve control. The HbA1c levels were comparable to the Danish study done by **Clausen *et al*.**[49]

Clausen *et al.,* suggest that with targeted actions and good logistics, improved glycemic control is achievable[49].

Glycemic control also means that women should be encouraged to come to the clinic as soon as possible, approximately at week 4 to 5. The analysis of our group shows that three quarters of women report only after six weeks. When comparing our study group with other groups in published studies, the gestational age is much lower and the percentage of planned pregnancies is higher in our study group. **Clausen *et al.,***[49] reported that the mean gestational age at first visit was at week 13.

Risk to both the fetus and the mother in the diabetic pregnancy is associated with the degree of glycemic control. Glycemic control during the early phase of pregnancy decreases the risk of fetal congenital malformations and maternal complication[50].

In our study; fetal macrosomia occurred in 80% of

the OADs group and 76% of the insulin group and 14% of the normal group .In the OADs group it increased with increased durations of OADs use, with the use of biguanide, with poor glycemic control, but decreases with longer DM durations, in the insulin group it increased with poor glycemic control.

Excess glucose from the maternal circulation stimulates insulin production by fetal β-cells leading to increased anabolic processes, including the deposition of stored calories of fetal fat. Endocrine secretion by the fetal pancreas begins by the 11th gestational week, after that macrosomia may first be detected by ultrasonography[51].

Apart from increased attention to the problem of pregestational type 2 diabetes, this difference may also be due to logistical and cultural factors. A complicating factor may be that many women that they are pregnant in the first trimester and this limits the possibilities to achieve the beneficial regular life and work schedules. All these issues are a logical part of pre- and perigestational counseling. Interestingly, **Towner *et al.***[52] did not find an association between the incidence of congenital abnormalities and gestational age at first presentation[40]. However, glycemic control was poor in this compared to the other studies.

The major concerns regarding the use of oral hypoglycaemic drugs in pregnancy have been fetal anomalies, neonatal hypoglycaemia and the development of pre-eclampsia[34].

As was expected on the basis of earlier surveys, there was an increased incidence of adverse maternal and neonatal outcomes. In our study, spontaneous abortion occurred in 12% of the cases, which is comparable to the 11.3% incidence in the Danish study.[49] Preeclampsia has been linked to endothelial dysfunction and insulin resistance, thus the higher incidence is not surprising. This has also been shown in another study.[49]

There are some oral hypoglycaemic drugs which may be safe and, therefore, useful, especially for those who are only mildly to moderately hyperglycaemic and who do not desire multiple daily insulin injections. In some countries where the use of insulin may not always be possible, the option of using oral hypoglycaemic agents may be particularly attractive. Among the sulphonylureas, only glibenclamide has been shown not to cross the placenta[53]. Moreover, the best and strongest evidence available so far in terms of safety and efficacy is that of glibenclamide.

Sulphonylureas are known to cross the placental barrier depending on their molecular mass. Three hours after absorption tolbutamide attains a cumulative trans-plancental transfer 21.5%, chloropropamide 11% and glibenclamide (glyburide) only 3.9%[52]. Anecdotal data on fetal malformations after exposure to sulphonyl-ureas have been reported,[54] but the metabolic disorder *per se* has not been considered as a possible teratogenic factor[55].

In our study; the incidental use of metformin was not associated with neonatal birth injury (caput medusa), intrauterine fetal death, abortion, preeclampsia, or polyhydramnios, but related strongly to fetal macrosomia and cesarean section (CS) labor and to lesser extent to neonatal hypoglycemia, polycythemia, hyperbilirubinemia and respiratory distress.

In the present study; poor glycemic control was related to fetal macrosomia, neonatal hypoglycemia, polycythemia, hyperbilirubinemia, respiratory distress, birth injury, intra uterine fetal death (IUFD), CS, and to large extent to abortion, preeclampsia and polyhydramnios.

Women with T2DM and their health care professionals should be aware of the importance of optimizing metabolic control and treating diabetic complications before safe contraception is stopped. We found a very low risk of severe hypoglycemia in pregnant women with T2DM, most likely due to their considerable insulin resistance. The risk of hypoglycemia is therefore not expected to give the same limitations for strict metabolic control as in type 1 diabetes[54]. Although the number of pregnant women with T2DM is increasing, the absolute number is still relatively small, and it seems appropriate to centralize the treatment of these women. This would enable gathering of experience and a more standardized management, which may improve the outcome.

In our study; neonatal hypoglycemia occurred in 52% of the OADs group and in 56% of the insulin group and in 4% of the normal group of the studied groups, in the OADs group it increased with poor glycemic control and with the use of sulfonylureas, in the insulin group it increased with poor glycemic control.

Hypoglycemia is the most common metabolic problem in neonates. In children, a blood glucose value of less than 40 mg/dL (2.2 mmol/L) represents hypoglycemia. A plasma glucose level of less than 30 mg/dL (1.65 mmol/L) in the first 24 hours of life and less than 45 mg/dL (2.5 mmol/L) thereafter constitutes hypoglycemia in the newborn.[54] The incidence of neonatal hypoglycemia in the non diabetic pregnancies is associated with earlier gestational age and intrapartum fever[56].

Oral hypoglycaemic agents, which have been previously regarded as unsafe for pregnancy, are being re-evaluated for their use in non-insulin dependent pregnant diabetics. Most of the evidence available so far suggests that some of these drugs, when used in their normal non-pregnancy doses, may be safe and beneficial for women with gestational diabetes.

However, further well-conducted, large-scale clinical studies will be needed to confirm the safety and efficacy of these drugs for use in pregnant diabetics and to gather widespread acceptability in the medical community[34].

In our study, the incidence of neonatal polycythemia was 30% in the OADs group, 24%in the insulin group and 2% in the normal group, in the OADs group it increased with the use of sulfonylureas and with 2-weeks duration of OADs intake, in the insulin group it increased with poor glycemic control.

Burrow *et al.*,[57] had reported an increased incidence of neonatal polycythemia; it is explained by fetal anoxia secondary to placental insufficiency or the effect of fetal hyperinsulinism, which stimulates fetal erythropoietin production, increased levels of maternal HbA1c which bind tightly to oxygen ;reducing placental oxygen transfer. In some cases, a hyperviscosity may supervene .Affected infants have a plethoric appearance and venous hematocrit may be above 60%, intravascular slugging with tissue anoxia may result.

In our study, the incidence of neonatal hyperbilirubinemia was 20% in the OADs group, 26% in the insulin group and 2% in the normal group, in the OADs group it occurred more with poor glycemic control, with the use of sulfonylurea and with 2-weeks duration of OADs intake, in the insulin group it increased with poor glycemic control.

In our study; the incidence of respiratory distress was 32% in the OADs group, 24% in the insulin group and 6% in the normal group, in the OADs; it increased with sulfonylurea use,2-weeks duration of OADs intake and with poor glycemic control, in the insulin groups it increased with poor glycemic control. There is an intrinsic risk of respiratory distress syndrome in the infants of diabetic pregnancies, because of physiologic pulmonary immaturity, this risk increased when poor glycemic control is present[58].

In our study; the incidence of birth injury (caput medusa) was 6% in the OADs group and occurred with 2-weeks OADs intake and increased with poor glycemic control, in insulin group the incidence was 8% and occurred with poor and fair glycemic control. The infant of diabetic mothers have a higher incidence of birth injury; because of macrosomia, that is common in all types of diabetic pregnancies[58].

In our study; the incidence of intrauterine fetal death was 6% in the OADs group and 0.0% in the insulin group, in the OADs group it occurred totally with 3-weeks duration of OADs intake, increased with sulfonylurea use and with poor glycemic control.

Diabetes during pregnancy, particularly when it is poorly controlled, is associated with a 5% to 8% congenital anomaly rate which is responsible for 50% of the perinatal mortality,[59] still birth rates in pregestational diabetic pregnancies reported with 0% to 4% which is marked improvement[57].

In our study; the incidence of cesarean section was 74% in the OADs group, 78% in the insulin group and 24% of the normal group, in the OADs group it increased with the use of sulfonylurea, with 2-weeks duration of OADs intake, in the insulin group, it increased with poor glycemic control.

The rate of cesarean section in the diabetic mothers is at least twofold higher than for their non diabetics' counterparts, because of a combination of an increased incidence of preeclampsia and macrosomia.[57]

In our study; incidence of preeclampsia was 10% in the OADs group, 8% in the insulin group and 2% in the normal group, in the OADs group it increased with longer durations of OADs use, with the use of sulfonylureas and with poor glycemic control, in the insulin group; it occurred with poor glycemic control.

The risk of preeclampsia is threefold to fourfold higher than in normal pregnancies, preeclampsia rates range from 9 to 66%, the rate is increased with poor glycemic control, it is caused by the underlying vasculopathy, decreased glomerular filteration rate and sodium retensive properties of insulin[60].

In our study; the incidence of spontaneous abortion was 10% in the OADs group, 2% in the insulin group. In the OADs group it occurred totally with poor glycemic control, longer durations of OADs (2-4weeks) and sulfonylurea use. In the insulin group it occurred with poor glycemic control.

The risk of spontaneous abortions in diabetic pregnancies is increased with poorer glycemic control ,it may be explained by one or more of several factors; hyperosmolality, ketosis, inhibitors of various growth factors as IGF-1, DNA glycosylation, the generation of oxygen radicals or cell membrane lipid perooxidation[61].

In our study; the incidence of polyhydramnios was 10% in the OADs group, 12% in the insulin group, in the OADs group it occurred with 2-weeks duration of OADs use, poor glycemic control and the use of sulfonylurea, in the insulin group it increased with poor glycemic control.

The incidence of polyhydramnios increased in diabetic pregnancies, with higher rates in patients with poor glycemic control. Increased fetal urinary flow and altered osmolality of amniotic fluid may be possible causes[57].

In conclusion, type 2 diabetes is also still associated with an increased incidence of adverse pregnancy outcome despite a mean HbA1c level within normal ranges and a high incidence of planned pregnancies. Improvements in outcomes may be expected from more active specialist peri-gestational care, including pre-pregnancy referral to specialist care, and a tailored approach for women from migrant communities. At present, we still advocate caution in the use of oral hypoglycaemic agents in pregnancy, and

one should always consider the benefits and risks of giving these drugs.

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