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THE USE OF METFORMIN IN TREATMENT OF POLYCYSTIC OVARY SYNDROME AND GLUCOSE CONTROL IN PREGNANT WOMEN WITH GESTATIONAL DIABETES MELLITUS AT TRIPOLI MEDICAL CENTER

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ABSTRACT

Normal pregnancy is associated with metabolic changes leading to decreased insulin sensitivity and reduced glucose tolerance. However, 3-5% of pregnant women proceed to develop gestational diabetes mellitus (GDM). Researchers elsewhere studied the use of metformin in many fields and the benefit to risk balance of using metformin during pregnancy and the risk of fetotoxic. In this study, the use of Metformin to control Glucose in pregnant women with gestational diabetes mellitus (GDM) was examined and its safety use during the first trimester of pregnancy was evaluated.A group of pregnant patients with gestational diabetes mellitus from the first trimester of pregnancy, non-smoking with no family history of congenital malformation disease, aged between (20-45 years) and have no liver diseases and who had indicating good compliance at more than one visit over several month until delivery put on Metformin were participated in this trial. The results show that all the studied group of pregnant women using metformin 500mg daily delivered healthy babies.Meta-analysis by mother risk program showed no increase in incidence of malformations by use of Metformin during the first trimester of pregnancy.A hundred outpatients were participated in the survey on the general knowledge and awareness of diabetic patients to their illness and medication used their aged between 20-40 years old. It was realized that 90% of physicians are not giving patients full information about their illness and the use of Metformin during pregnancy. Also, about 65% of patients did not know about the nutritionist in the hospital, the right control diet for diabetes, courses on first aid, rapid diagnosis of poisoning and follow the written procedures to dealing with such cases.

Key words: Gestational Diabetes, Malformations, Metformin, pregnancy.

INTRODUCTION

Metformin is an oral anti-diabetic drug in the biguanide class, first described in the scientific literature in the 1922, by Werner and bell (Warner & Bell, 1922), as a product in the synthesis of N,N-dimethylguanidine. First synthesized in 1929 and then clinically developed in the late 1950s by the French physician Jean Sterne, who gave it its first trade name, Glucophage ("glucose eater") for the drug and published his results in 1957 (Campbell, 2007). It's the drug of choice for the treatment of type-II

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diabetes, particularly in over weight patients, and is also used in treatment of polycystic ovary syndrome. Metformin disposition is unaffected by presence of diabetes and only slightly affected by the use of oral formulations. It has an absolute oral bioavailability of 40-60% and gastrointestinal absorption is completed within 6 hours (Royal College of Physicians, 2008; Amarican Diabetes Association, 2009). Metformin hydrochloride works in a number of ways to decrease the amount of sugar in the blood of the patients with type-II diabetes. It first reduces the amount of sugar produced by the cell in the liver, then it increases the sensitivity of the muscle cells to insulin; this enables the cell to remove sugar from the blood more effectively, and finally, it delays absorption of sugar from the intestines into the blood stream after eating (Royal College of Physicians, 2008). Over all, Metformin reduces blood sugar levels between and directly after meals. The daily dose must be established by the physician for each individual patient. Usual adult dose for Diabetes Mellitus Type-II is 500 mg orally twice a day (with the morning and evening meals) and for the extended release thedose should be between 500 to 2000 mg orally once a day (with the evening meal). Maximum daily dose is 2500 mg (www.drugs.com). Metformin should be used cautiously, if at all, in patients with renal and liver disease as well as elderly knowing that it can precipitate lactic acidosis in these patients (Complications report of WHO consultation Part1). Doses may be increased by 500 mg every week or 850 mg every other week based on patient tolerance and response (www.drugs.com). The maximum recommended daily dose is 2.55g. Metformin may be used concomitantly with oral sulfonylurea. Transfer of patients from other oral hypoglycemic agents should be done conservatively to prevent hypoglycemia. It has been assigned to pregnancy category B by the FDA. Insulin remains the mainstay of therapy for gestational diabetes due to the close glucose control it affords and Metformin is only recommended for use during pregnancy when benefit outweighs risk (WHO Model list of essential medicines, 2010). Metformin may rarely cause a serious and sometimes fatal condition called lactic acidosis (Graham, 2011). Most of these cases have occurred in diabetic patients who also have certain kidney problems. The risk of lactic acidosis may be greater if patient have liver problems, kidney problems or heart failure. The risk may also be greater in patients who are elderly or drink alcohol. Lab tests, including kidney function, may be performed while taking Metformin.There are no data on the excretion of Metformin into human milk. Metformin is excreted into the milk of rats and achieves milk concentrations comparable to those found in plasma (PM Encyclopedia, 2007).

Polycystic ovary syndrome

Polycystic ovary syndrome is a heterogeneous endocrine disorder that affects about one in 15 women worldwide. The major endocrine disruption is excessive androgen secretion or activity, and a large proportion of women also have abnormal insulin activity. Many body systems are affected in polycystic ovary syndrome, resulting in several health complications, including menstrual dysfunction, infertility, hirsutism, acne, obesity and metabolic syndrome (Nestler and Jakubowicz, 1996; 1998). Women with this disorder have an established increased risk of developing type-II diabetes and a still debated increased risk of cardiovascular disease. The diagnostic traits of polycystic ovary syndrome are hyper-androgenism, chronic an ovulation, and polycystic ovaries, after exclusion of other conditions that cause these same features. A conclusive definition of the disorder and the importance of the three diagnostic criteria relative to each other remain controversial. The cause of polycystic ovary syndrome is unknown, but studies suggest a strong genetic component that is affected by gestational environment, lifestyle factors, or both. Several studies have recorded the use of Metformin in women with PCOS. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. While Metformin starts to improve the prospects for fertility in few weeks, a reduction in unwanted hair growth would be expected to take some months and be slower than conventional treatment. Women can find weight loss easier when taking Metformin even though it is not a traditional weight reducing agent. One placebo-controlled trail has shown that Metformin is better than placebo in inducing ovulation in women with PCOS. The effectiveness of Metformin has been best demonstrated in obese women and it is likely that women of normal weight would benefit very little from this drug (Jakubowicz *et al.*, 2002).

Monitoring the use of Metformin

Tests at the start of Metformin and every 2 months thereafter Menstrual cycle diary for 6 months (recall), Weight, Urinalysis LH, FSH, Testosterone, Glucose, HbA1c, U&E, Cholesterol, triglycerides, HDL, LDL and fasting insulin is optional. Stop taking Metformin if pregnancy occurs. There is no particular time limit for the use of Metformin, if no effect is seen in six months then there is no point in continuing (Palomba *et al.*, 2005). After one year the goals of future treatment should be reviewed. The long term place of Metformin in PCOS is not clear. It is strongly recommended that the use of Metformin is monitored either in an official trail or as a formal audit in a specialist unit in order that the effectiveness of this treatment can be clearly documented (Vanky *et al.*, 2004). The aim of this study is to investigate if Metformin has any congenital effect when taken during pregnancy and assist the outcome of using Metformin during pregnancy also a survey on the knowledge of patients to their medication and how to control their illness.

Study One

Patients and Method

After local research Ethics committee Approval by Tripoli Medical Center Tripoli-Libya had been obtained.The study groups were pregnancy women outpatient suffering from diabetes andwere currently taking Metformin compared with a group taking placebo.The study was limited to small number of outpatient for logistical reasons but was intended to be extended if promising result was obtained. The patients were reviewed at more than one visit until deliveryand files of the patients were reviewed.We investigate effect of Metformin on pregnant diabetic patient:Ten outpatients who had Metformin indicating good compliance at more than one visitover several months until delivery with no liver diseases, non-smoking and no family history of malformation or congenital diseasewere participated in this study

Cases Results

Case 1

-Patient was 30 years old women married for 3 years the patient weight was 71kg.
-Blood group (A+).
-last year the patient had an abortion the baby girl was 3 weeks when she died
-The patient was in rolled to hospital with 4 weeks discovered GDM.
-pregnant with a 7 weeks baby girl
-The patient is taking Metformin 500mg 3times a day, no other drugs given.
Baby was born with no defects

Case 2

-Patient was 33 years old women married
-Blood group (B+)
-the patient is diabetic and had an abortions at the first trimmest,
-she is now 35 weeks pregnant
-she has no other diseases
-Patient is taking Metformin 500mg 3 times a day and insulin
-Baby was born 2.88kg with no defects

Case 3:

-Patient is 35 years old is pregnant with twins.
-Blood group (O+).
-She is treated with Metformin and folic acid.
-She is newly discovered GDM.
-The twins were born with no defect

Case 4

-Patient is 39 years old married for 10 years no children.
-Blood group (A).
-The patient was taking Clomied for 3 months before pregnancy.
-She is now pregnant 11 weeks
-She is a newly discovered diabetic.
-She is now taking Metformin 500mg 3 times a day.
-Baby is born with no defects.

COMMENT AND CONCLUSIONS

All the patients participated in this study deliver healthy babies. Doctors were asked to report to us any congenital defects on any of their patients. Metformin treatment from first trimester to delivery did not reduce pregnancy complications in PCOS.

Study 2

AIMS AND OBJECTIVES

The objective of this survey was to see the diabetic patient's general knowledge on their medication.

Patients and method

After Ethics committee Approval by Tripoli Medical Center Tripoli-Libya had been obtained. The study groups were random women outpatient suffering from diabetes and were currently taking Metformin compared with placebo, by using a questionnaire. The study group was 100 outpatient patients their ages between (20-40) years old.The survey was done to see the patients knowledge and information about their medication and there problems.

RESULTS

The results of the questionnaire survey on Metformin are shown in Table 1 and depicted graphically in figures (1-4).

Comment: the results give us a glimpse on the public general knowledge on their medication, and their ability to adapt to their illness.

Table 1. Results of the Questionnaire survey on Metformin

Questions	Results	
What is your general knowledge on blood glucose medication?	56% of patients were knowledgeable	44% of patients were unknowledgeable
Have you ever had problems controlling your blood glucose level?	60% of the patients were controlled	40% of patients were uncontrolled
Do you know what Metformin is?	96% of the patients were uninformed	4% of the patients were informed
Have u ever been advised to take Metformin during pregnancy?	91% of the patients were unadvised	9% of the patients were advised

Fig 1. Patients general knowledge on blood glucose medication

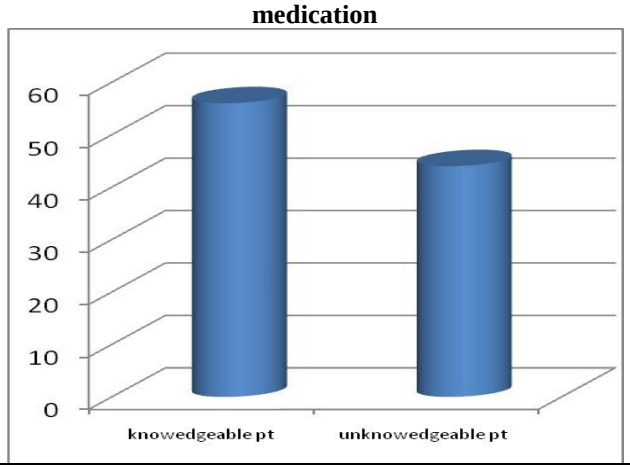


Fig 2. Patients problems in controlling blood glucose level

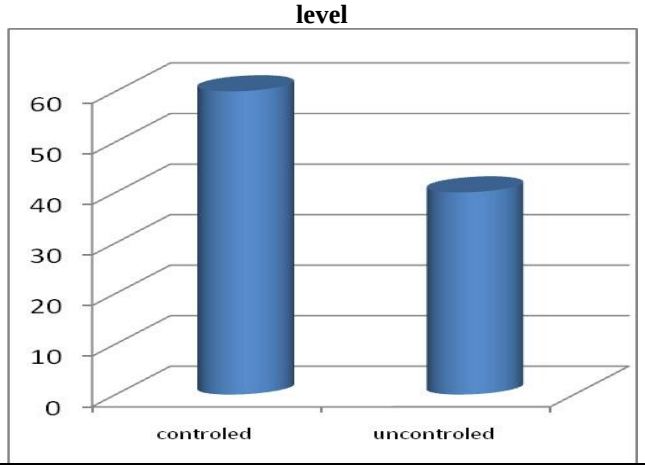


Fig 3. Patients knowledge about Metformin

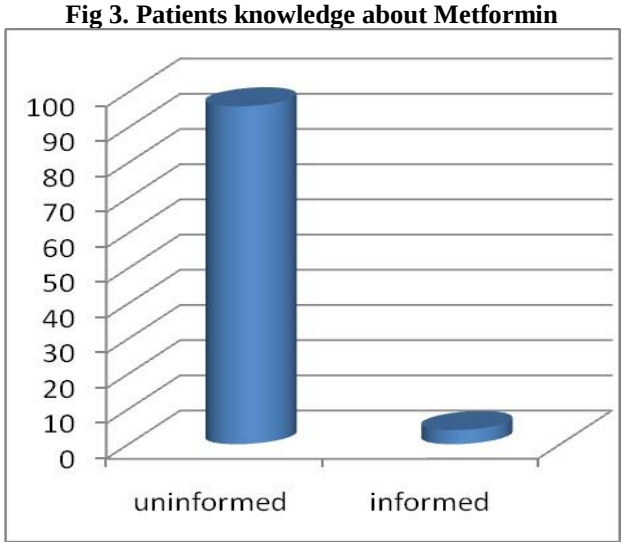
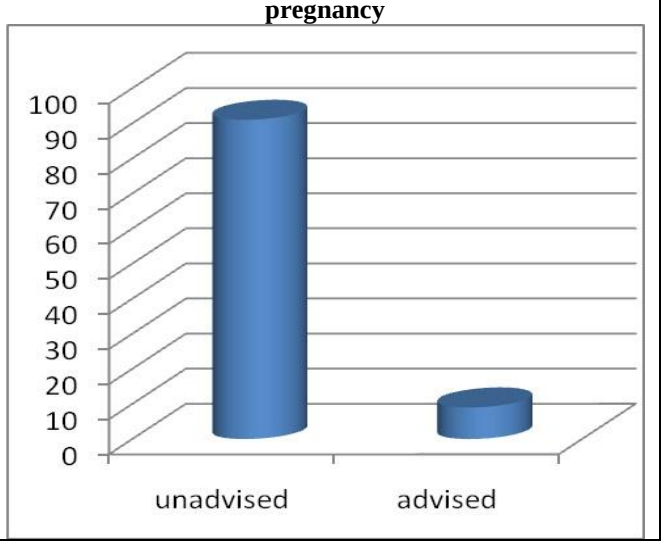


Fig 4. Advises taken for using Metformin during pregnancy



CONCLUSION

In this work we interview all patients; it was a very good experience for us. We got to acknowledge how patients try to deal with their chronic and how they alter their diet to soot their illness. Also in our survey we did realize that the doctors are not giving the patient information about their illness, a lot of the patients did not know about the nutritionist in the hospital and when we went to look for her she was located in the lower ground floor.

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