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Pregnant women with type 1 diabetes mellitus treated by glargine insulin

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Pregestational diabetes mellitus complicates approximately 0.2-0.5% of pregnancies. Type 1 diabetes was 35% of pregestational diabetic women and 65% was type 2 diabetes mellitus. Pregnancy in diabetes is associated with an increase in risk to both the fetus and the mother. The risk of complications increased in poor glycemic control and decreased in nearly normal glucose levels. Tight control of blood glucose is mandatory in both type 1 and type 2 during pregnancy. The goals of glycemic control in type 1 diabetes sometimes very difficult especially in brittle's diabetes mellitus. With the use of long acting insulin, such as glargine insulin in addition of premeals, short acting insulin makes the control easier in such patients. There is no clear safety of glargine insulin in pregnancy. With very well-known hazards of high blood glucose during pregnancy without known hazards glargine insulin, we decided to use it in difficult cases of type 1 diabetes.

Type 1 diabetes treated by glargine insulin and became pregnant advised either to continue or to change to other insulin. Pregnant women with uncontrolled type 1 diabetes mellitus treated by insulin other than glargine insulin were also advised to be treated by glargine insulin. The safety of the glargine insulin and the hazards of high glucose during pregnancy were discussed with the patients. Glargine insulin was initiated or continued if the patients agreed and signed the consent forms. The total daily insulin doses were calculated according to the body built (0.7 unit/kg) and 50% of it was glargine insulin given once daily either afternoon or in the evening. The other daily dose was given as a short acting insulin (regular insulin) and was divided into 3 premeals doses. The doses of the glargine insulin and short acting insulin were adjusted according to the blood glucose levels. We aimed to lower the fasting blood glucose less than 100 mg/dl and postprandial less than 130 mg/dl. They were followed in monthly bases during the pregnancy in our clinic and followed by the obstetrician. They had all the antenatal investigation and follow up. Home glucose monitoring pre and post meals were carried out by the patients and reviewed in each visits. Glycosylated hemoglobin was carried out in the first month of pregnancy and every 3 months thereafter. Fetal monitoring by ultrasound was carried out in the first trimester and repeated every 3 months thereafter. The fetal sizes, heart pulses, and any abnormalities were reported by ultrasound. The methods of the delivery, fetal apgar scores and fetal sizes were noted at deliveries.

Eleven patients with type 1 diabetes became pregnant and were treated by glargine insulin. All went through pregnancy without any problems except for one abortion. The dose of glargine insulin ranged between 30-80 units per day. The glycosylated hemoglobin in the first trimester was ranging from 7.8-12.4% (the mean was 9.93%). At the end of the pregnancy, the glycosylated hemoglobin reduced to 5.9-7.4% (the mean 6.54%). All antenatal visits revealed no abnormalities. Fetal heart and sizes were normal through all pregnancy. Mild hypoglycemic events reported 3 times in different patients and managed without any complications. Normal spontaneous vaginal delivery was the way of delivery in 7 patients and 3 by cesarean section due to poor progression and fetal distress. All patients were informed to discontinued the glargine insulin during delivery and treated only by short acting insulin. All fetuses were healthy (4 boys and 6 girls). There was no congenital anomalies found in all of them. Their sizes were ranging between 2.8-4.34 kg (mean 3.26%) (**Table 1**). All patients except one were discharged from the hospital after 24 hours of delivery.

Type 1 diabetes mellitus is a common disease in our country. Women with type 1 diabetes has the capability to conceive and high blood glucose has many drawback effects on the mother and the fetus.

Table 1 - Important findings on patients treated by glargine insulin during pregnancy.

Patients	HA1c- before glargine insulin (%)	HA1c* (%)	Weight of the baby (kg)	Mode of delivery	Congenital anomalies	Fetal complications
1	9.3	6.7	3.4	SV	Absent	Absent
2	9.7	6.92	3.6	CS	Absent	Absent
3	10.2	7.4	4.34	CS	Absent	Absent
4	9.2	6.5	3.1	SV	Absent	Absent
5	10	6.2	2.9	SV	Absent	Absent
6	12.4	6.8	3.3	CS	Absent	Absent
7	11.6	6.1	2.85	SV	Absent	Absent
8	8.9	5.9	2.8	SV	Absent	Absent
9	7.8	6.2	3.1	SV	Absent	Absent
10	10.2	6.7	3.2	SV	Absent	Absent

*at the end of the pregnancy, SV - spontaneous delivery, CS - cesarean section

Tight glycemic control reduced many complications. Normalization of blood glucose concentrations before and early pregnancy reduce the risks of spontaneous abortion and congenital malformations nearly to general population.[1] Macrosomia is one of the most common complication of hyperglycemia during pregnancy and it reduces in those near normal blood glucose.[2] Frequents measurements of blood glucose are mandatory in women with type 1 diabetes mellitus during pregnancy. Glycosylated hemoglobin values provide the best assessment of degree of chronic glycemic control, reflecting the average of blood glucose concentration during the preceding 6-8 weeks. The lifespan of the red blood cells was shortened during pregnancy and the glycosylated hemoglobin can be measured every 4-6 weeks and even more frequently if the women glycemic control is poor. The recommended targets of glycemic control during pregnancy are as follows, fasting blood glucose of 60-90 mg/dl, one hour postprandial no higher than 130-140 mg/dl, and 2 postprandial no higher than 120 mg/dl. Insulin is only the available treatment of diabetes during pregnancy. Most women with type 1 diabetes require at least 3 injections of insulin per day. The average dose of the insulin in pregnant women with type 1 diabetes is 0.7 unit/kg in the first trimester, often increased to 0.8 unit/kg for weeks 18-26, 0.9 unit/kg for weeks 27-37, and 1 unit/kg for weeks 37 to the term.[3] A large maternal weight gain was associated with a greater increase in the insulin requirement. Type 1 diabetes mellitus sometime is very difficult to control and required 3-4 insulin injections with basal long acting insulin. Glargine insulin proved it efficacy in control hyperglycemia in those difficult cases.[4,5] Some of our patients with type 1 diabetes have controlled after addition of glargine insulin. Their blood glucose and glycosylated hemoglobin reduced than when they were treated by different types of insulin. Some women with this problem became pregnant, and we have the choice either to continue on same treatments, despite lacking of safety of glargine insulin in pregnancy, or to discontinue the glargine insulin with difficulties to controls other types of insulin. After discussing these issues with the patients, the author decided to continue the glargine insulin with agreements. The backgrounds of using glargine insulin in pregnancy despite there were no reports of safety are difficult cases of type 1 diabetes mellitus. There were no proved complications of glargine insulin while hyperglycemia has many complications during pregnancy.

We conclude from those cases that glargine insulin is safe and effective during pregnancy but more studies are needed.

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Table 1 - Showed side effects of tamoxifen in different doses.

Dose of Tamoxifen side effects	10 mg	20 mg	Total
Depression (%)	0	2	**2**
Dizziness (%)	2	4	**6**
Cephalalgia (%)	2	3	**5**
Total (%)	**4**	**9**	**13**

Tamoxifen effects on treatment fibrocystic breast disease in women

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Breast pain in women was first described in the early 19th century by Sir Astly Cooper, who suggested that women who sought advice for breast pain were "usually of a nervous and irritable temperament".[1] This sentiment persisted despite reports by Harris et al,[1] who said that women with breast pain were no more psychoneurotic than those having an operation for varicose veins. Mastalgia remains poorly characterized and not a reason for breast consultation in general practice.[1] The term fibrocystic or cystic breast disease is not a distinctive disease, but rather a term used to represent a group of breast tissue abnormalities that may occur separately or together. While we associate this "disease" with the menstrual cycle, it is important to remember that women can experience palpable breast irregularities regardless of menstruation. Pathologic descriptions of the disease were recorded as early as the 1880 with the term chronic cystic mastitis identified a decade later. Tamoxifen (Nolvadex) has been in use for over 20 years and currently the most prescribed anti-cancer medication in the world. It is an orally effective, synthetic, non-steroidal, estrogen antagonist and agonist agent. In studies and trials, it has been shown to have only limited side effects. It has produced regressions in women with fibrocystic changes, including precancerous ones, and in those with metastatic breast cancer, where its benefits were first observed. It has increased disease free survival (DFS) and overall survival (OS) rates when given as an adjuvant systemic type of therapy in women with early breast cancers, and it has reduced the incidence of contra lateral breast cancers.[3]

We examined the effect of tamoxifen therapy on several patients suffering from fibrocystic disease and mastalgia. The patients were followed and excluded those who had sonography and clinical examination that occurred at or subsequent to the diagnosis of fibrocystic disease. Sixty-two women underwent breast sonography for benign breast disease while in the trial; the remaining 202 women did not. We begin tamoxifen in doses of 10-20 mg daily for 2-4 months; during medication, one or 2 visits in a month is necessary. Over 3 years, tamoxifen treatment reduced the risk of benign breast disease and mastalgia by 78%, breast pain 21%, mild (deep palpation) and severe pain 19% (movement and rest) and moderate pain 38% (between 2). There were 62 women who underwent breast sonography, 85% showed cysts and fibrocystic change. Non-cyclic mastalgia (40%) and cyclical mastalgia (60%) were the most frequent. Thirteen percent of patients experienced some side effects, such as dizziness (6%), cephalalgia (5%) and depression (2%) (**Table 1**). Relief of pain and tenderness with a dose of 10 mg (11% of patients) and 20 mg (89% of patients) after 2-4 months treatment of tamoxifen were the most frequently reported. In addition, 3 (1.1%) patients discontinued the treatment and 78% of patients achieved pain control with the use of this drug. Sometimes referred to as fibrocystic disease, fibrocystic change, cystic disease, chronic cystic mastitis or mammary dysphasia is not a disease, but rather it describes a variety of changes in the glandular and stromal tissues of the breast. Symptoms of fibrocystic breasts include cysts (accumulated packets of fluid), fibrosis (formation of scar-like connective tissue), lumpiness, and areas of thickening, tenderness, or breast pain though sometimes painful, fibrocystic breast condition is not cancer. However,