

# Case Study: Conception as a Potential Consequence of Diabetes Treatment

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## PRESENTATION

M.M. is a 45-year-old white woman with a medical history of type 2 diabetes, polycystic ovarian syndrome (PCOS), hypertension, and gastroesophageal reflux disease. She had a history of one normal, healthy pregnancy and delivery without complication. The patient was diagnosed with diabetes in 1994, and after 2000 developed painful diabetic neuropathy and microalbuminuria.

At 42 years of age, she was being followed by both her primary care physician (PCP) and collaboratively by a clinical pharmacist within the same academic practice. At that time, she was prescribed 30 mg pioglitazone daily, 1,000 mg metformin twice daily, 10 mg glipizide twice daily, 2.5 mg enalapril daily, 25 mg hydrochlorothiazide daily, and 81 mg aspirin daily. For neuropathic pain, she was receiving 5 mg methadone three times daily, 300 mg gabapentin three times daily, and 40 mg fluoxetine daily. She had been receiving metformin since 2001, and pioglitazone since 2003.

At the time of pioglitazone initiation, she was counseled regarding the possible effects of the medication on increasing fertility in women with PCOS. She said she did not want to become pregnant, but she refused hormonal contraceptives or an intrauterine device. Both she and her husband were counseled to use barrier contraception methods.

By February 2004, her pioglitazone had been titrated to 30 mg once daily. Her weight was 233 lb and height 64 inches, for a BMI of 40 kg/m<sup>2</sup>. Her most recent hemoglobin A<sub>1c</sub> (A1C) was 6.2%,

and her serum chemistries were within normal limits.

Her PCP noted that she was recently nonadherent with both glipizide and metformin because of her concern about low blood glucose. Discussion revealed that she had not experienced hypoglycemia, and her understanding of what constituted hypoglycemia was incorrect. She did not understand her glycemic goals. She became concerned that glucose readings < 120 mg/dl were too low, and she discontinued diabetes medications. When an increase in her home blood glucose values was noted after medication discontinuation, her PCP instructed her to restart metformin at the previous dose and glipizide at a reduced dose.

On 18 May 2004, the patient was seen by the clinical pharmacist and complained of early morning nausea and vomiting. She thought she was pregnant because her last menstrual period had been ~ 6 weeks earlier. A urine pregnancy test confirmed her pregnancy, and she was contacted and scheduled to return 2 days later.

At that time, her A1C was 6.7%. She expressed the desire to maintain her pregnancy and was given instructions to taper off both methadone and gabapentin during the next 2 weeks, and she was provided lidocaine 5% patches to manage her neuropathic pain. Her enalapril and oral antidiabetic medications were discontinued, and she was initiated on 35 units NPH insulin at bedtime and 5 units lispro with evening meals. She was scheduled to be seen in the high-risk obstetric clinic within 1 week, but she missed this appointment.

Her next visit was 17 June 2004. She reported having a miscarriage on 30 May 2004, which was evaluated at an outside hospital. She and her husband expressed the desire to attempt another pregnancy; however, she was asked to defer further attempts until her obstetric visit the following week. At that appointment, she was urged to improve her glycemic control and blood pressure before attempting another pregnancy.

Her blood pressure was 141/98 mmHg. However, in the previous 4 months, it had ranged from 106 to 136 mmHg systolic over 60 to 90 mmHg diastolic.

Once again, she declined hormonal contraception or an intrauterine device, and she was encouraged at a minimum to use barrier methods of contraception.

## QUESTIONS

1. What factors may have increased M.M.'s likelihood of pregnancy?
2. Why is preconception planning essential for women with diabetes?
3. What are the usual actions needed before a woman with diabetes should attempt to become pregnant?

## COMMENTARY

Insulin resistance is present in a significant proportion of women with PCOS. Hyperinsulinemia is then thought to promote the abnormalities in steroid production in patients with PCOS, resulting in excessive ovarian androgen production and leading to anovulation.<sup>1</sup> Thiazolidinediones and metformin are postulated to promote fertility in women with PCOS by two potential mechanisms. By increasing insulin sensitivity

and decreasing circulating serum insulin concentrations, these agents may then decrease ovarian androgen production.<sup>1</sup> Additionally, these agents increase serum concentrations of sex hormone-binding globulin, thereby decreasing free testosterone concentrations.<sup>2</sup> Ovulation may therefore potentially be stimulated by these agents in women who may have previously considered themselves to be infertile, even in older women.

In one case, a 46-year-old woman with PCOS who was using both metformin and rosiglitazone experienced an unplanned pregnancy very similar to the patient in this case.<sup>3</sup> The authors who reported this patient's case noted that unplanned pregnancy at age 46 to be rare and theorized that the risk may be increased by "stockpiling" of ovarian follicles. Education regarding this potential increased likelihood of pregnancy is of paramount importance and necessitates proactive intervention on the part of providers caring for women with PCOS who are prescribed these medications.

Despite the risks of spontaneous abortions and fetal malformations resulting from elevated blood glucose levels during embryogenesis, an estimated two-thirds of women with diabetes have unplanned pregnancies;<sup>4</sup> this may increase the risk of entering the first trimester of pregnancy with inadequate glycemic control.<sup>5</sup>

Preconception care is generally inadequate in women with diabetes. One retrospective review revealed that only 25% of women aged 18–40 years had documented preconception counseling, whereas 74% of these patients had no documentation of preconception counseling or counseling regarding contraceptive measures.<sup>6</sup>

The American Diabetes Association's glycemic goals for women with diabetes during the preconception period include an A1C < 1% above the normal range, premeal capillary plasma glucose between 80 and 110 mg/dl, and 2-hour postprandial concentrations < 155 mg/dl.<sup>4</sup>

We believe that women < 50 years of age should be counseled about the risks of pregnancy before reaching their glycemic goals and advised to use contraception, even if pregnancy is desired, until these targets are met.

Available data on the use of oral hypoglycemic agents during pregnancy are limited, and this is not routinely recommended.<sup>7</sup> It may be advisable to attain glycemic control with insulin alone before a planned conception. Statin medications alter cholesterol biosynthesis in fetal tissue and have been found teratogenic in animals; they are contraindicated during pregnancy.<sup>8</sup> A recent retrospective cohort study suggests a potential teratogenic effect of angiotensin-converting enzyme (ACE) inhibitors when used during the first trimester of pregnancy.<sup>9</sup> Both of these medication classes should be discontinued before conception to avoid the potential for untoward effects on the fetus.

Women with diabetes may be able to decrease their risk of fetal complications during pregnancy to a level similar to that of the general population with the proper medical treatment.<sup>4</sup> Given the overall high risk potential of these pregnancies, we advocate regular preconception dialogues with women who have diabetes to determine their intentions regarding conception and make clinical adjustments. Once these patients reach their preconception goals, we advocate referral to a high-risk obstetric-gynecologist for consultation and management.

### CLINICAL PEARLS

- Clinicians should know the potential of metformin and thiazolidinediones to increase the fertility of women, particularly those with PCOS.
- Preconception dialogues should be carried out routinely to allow for appropriate clinical adjustments in preparation for pregnancy or for education on the need for contraception.
- Tight glycemic goals should be met before conception to reduce the risks

of spontaneous abortions and fetal malformations.

- Medication alterations to improve safety during pregnancy should include, but are not limited to, discontinuation of oral hypoglycemic agents, statins, and ACE inhibitors.

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