Case Study: Conception as a Potential Consequence of Diabetes Treatment

Alexander B. Guirguis, PharmD, BCPS; Robert M. Malone, PharmD, CDE, CPP; Paul R. Chelminski, MD, MPH; and Michael Pignone, MD, MPH

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/m². Her most recent hemoglobin A₁c (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.¹ 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. Additionally, these agents increase
serum concentrations of sex hormone–
binding globulin, thereby decreasing free
testosterone concentrations. 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 meflo-
formin and rosiglitazone experienced
an unplanned pregnancy very similar to
the patient in this case. 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 poten-
tial increased likelihood of pregnancy is
of paramount importance and necessi-
tates 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 result-
ing from elevated blood glucose levels
during embryogenesis, an estimated
two-thirds of women with diabetes
have unplanned pregnancies; this may
increase the risk of entering the first
trimester of pregnancy with inadequate
glycemic control.

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 coun-
seling or counseling regarding contra-
ceptive measures.

The American Diabetes Association’s
glycemic goals for women with dia-
betes 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.

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 contra-
ception, 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. It may be advisable to
attain glycemic control with insulin alone
before a planned conception. Statin medica-

dations alter cholesterol biosynthesis in fetal tissue and have
been found teratogenic in animals; they
are contraindicated during pregnancy.
A recent retrospective cohort study
suggests a potential teratogenic effect of
angiotensin-converting enzyme (ACE)
inhibitors when used during the first
 trimester of pregnancy. Both of these
medication classes should be discon-
tinued 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. Given the
overall high risk potential of these preg-
nancies, we advocate regular preconcep-
tional 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-gynecol-
ogist for consultation and manage-
ment.

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 edu-
cation 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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Alexander B. Guirguis, PharmD, BCPS,
is an assistant professor at the Univer-
sity of Tennessee College of Pharmacy,
Knoxville campus. Robert M. Malone,
PharmD, CDE, CPP, is an assistant
professor of medicine; Paul R. Chelmin-
ski, MD, MPH, is an assistant profes-
sor of medicine; and Michael Pignone,
MD, MPH is an associate professor of
medicine and chief of the Division of
General Internal Medicine & Epidemiol-
ogy at the University of North Carolina
Department of Medicine in Chapel Hill.
Dr. Pignone is also an associate editor
of Clinical Diabetes.