

Anakinra use during pregnancy: Report of a case with Familial Mediterranean Fever and infertility

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Abstract

Familial Mediterranean fever (FMF), affecting people of Mediterranean origin, is an endemic and sometimes problematic disease because of colchicine resistance/intolerance, with relative lack of treatment alternatives, and disease- or treatment-related issues, such as subfertility. Anakinra, being a rational and effective treatment alternative, has no conclusive human pregnancy data. Here we report a case of FMF with infertility who became pregnant with in vitro fertilization (IVF) under treatment with anakinra, along with the pregnancy outcome.

Keywords: Anakinra, Familial Mediterranean Fever, interleukin-1 β , pregnancy

Introduction

Interleukin-1 (IL-1), the blockade of which is a very attractive and rational primary treatment modality in various types of periodic fever syndromes as well as in cases of familial Mediterranean fever (FMF) resistant or intolerant to colchicine, is known to play physiological and pathological roles in early and late pregnancy, such as trophoblast motility and preterm labor, respectively (1). Pregnancy data with anti-IL1 β agents are scarce. Here we present a case of colchicine-resistant FMF with infertility who became pregnant with in vitro fertilization (IVF) under treatment with anakinra, along with the pregnancy outcome.

Case Presentation

A 27-year-old female, describing typical attacks of fever, peritonitis, and arthritis sometimes associated with pleuresy and diarrhea from infancy, was diagnosed with FMF 14 years ago. She had compound heterozygous M680I/M694V Mediterranean fever (MEFV) gene mutation with a positive family history. Attacks were precipitated by menstruation. Under 14 years of treatment with 1.5 to 2 mg/day colchicine, she had 6-12 attacks per year despite complete adherence to treatment. No proteinuria, subclinic interattack acute phase reaction, or any other sign of amyloidosis was evident. She was infertile for 4 years. She had regular menses beginning at the age of 14 years with a normal telarche and pubarche and other secondary sex characteristics. Despite intercourse without contraception, she could not get pregnant for 2 years after marriage. Her plasma prolactin and follicular phase levels of estradiol, luteinizing hormone, and follicle-stimulating hormone were normal. She had a normal hysterosalpingography. The male factor was excluded with a normal spermogram. Three cycles of in utero insemination (IUI) were not successful, and her gynecologist consulted her to our rheumatology department because of ongoing attacks with colchicine. Because of previous persistent diarrhea and vomiting with colchicine doses higher than 2 mg/day and a high frequency of attacks with 2 mg/day colchicine, anakinra (Kineret; Sobi Inc., Stockholm, Sweden) was started to be used at a 100 mg/day self-injected subcutaneous dose and colchicine was ceased. Before use, an intradermal provocation test was performed because of multiple drug allergies, and no reaction was observed. After 4 months of treatment with anakinra, she was attack-free, and IVF was planned by her gynecologist. She was informed about anakinra and pregnancy, but she wished to use the drug and became pregnant in the 5th month of treatment. She used the drug until labor. She had normal serum levels of alpha-fetoprotein, estradiol, and human chorionic gonadotropin, as measured in the early second trimester, in conjunction with a normal sonographic nuchal translucency. Findings of detailed fetal anatomic ultrasonography were also normal. No amniocentesis was performed. During the 34th week of gestation, she had the first attack of fever and mild arthritis due to an attempt of cessation of anakinra because of theoretic concerns about vaccine failure in the child. Anakinra was re-started after an interval of 5 days due to the risk of preterm labor. The attack subsided quickly. At the 38th week of gestation, she went cesarean section and gave birth to a child weighing 2700 g (2.2 percentile). Apgar scores were 9 and 10 in the 1st and 10th minutes, respec-



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tively. Findings of newborn examination were normal. The infant is now 13 months of age with normal anticipated development and is being breastfed from the time of birth without any health problem. It weighed between 3rd and 15th percentiles for 12 months after birth. The mother is still on anakinra, with no attacks after delivery.

Written informed consent was obtained from the patient who participated in this study.

Discussion

There are few reports in the medical literature about the use of anakinra during pregnancy. A total of 20 cases, 16 of which had pregnancy outcomes, have been reported (2-6). With regard to the other 3 available anti-IL1 β biologic agents, there are 2 ongoing pregnancy cases under treatment with canakinumab and no case of human pregnancy under treatment with rilonacept or gevokizumab. Four of the 20 reported cases had FMF and others had various periodic syndromes such as cryopyrin-associated periodic syndromes, tumor necrosis factor receptor-associated periodic syndrome, adult-onset Still's disease, and idiopathic recurrent pericarditis. All the FMF cases, all of which have been presented at the 2015 European League Against Rheumatism (EULAR) meeting, had uncomplicated and successful pregnancies and gave birth to healthy newborns (4). Only 1 FMF case was using anakinra from before the conception and the other 3 began to use it in the second trimester. This is particularly important because there are very few data (10 of the reported cases) about the use of anakinra during organogenesis. The potential teratogenic effects of anakinra must be theoretically seen if used in the early first trimester. Of the 10 reported pregnancies, 2 ended because of miscarriage and 1 had renal agenesis and fetal death occurred eventually. Along with the present case, 8 of 11 cases of first trimester uses of anakinra underwent successful pregnancies and gave birth to healthy newborns. IL1 β , which is a pro-inflammatory cytokine, is known to increase in vitro trophoblast motility via the urokinase plasminogen activator/plasminogen activator inhibitor-related pathway, and this effect can be blocked by the IL1 receptor antagonist (IL1Ra) (7, 8). This may be an explanation for miscarriages when this drug is used early

during pregnancy. Apart from its physiological role in early pregnancy, IL1 β may have some deleterious effects in late pregnancy (1). Along with IL1 α , it may have play role in preterm labor, and serum levels may predict this (9). Animal data are available for the use of IL1Ra to revert preterm labor (8). In animal studies, at doses 100 times the therapeutic dose, no harm in the offspring was evident, although it was detected in the amniotic fluid.

Despite having relatively frequent attacks, our case had a normal histerosalphingograpy. It was previously thought that peritoneal adhesions caused female FMF infertility. However, today, it is known that causes of infertility in FMF cases are similar to those in cases without FMF, although very rare complications, such as ovarian amyloidosis (and the male counterpart, testicular amyloidosis), may be seen (10). Amyloidosis in FMF is usually of the systemic AA type, and it is not expected for an FMF patient to have ovarian amyloidosis without renal involvement, which is screened by laboratory examination of proteinuria. Although it is known that colchicine increases the rate of miscarriage, it is again colchicine that improves the reproductive ability of FMF patients by controlling the disease activity. Concerns about colchicine and both male and female fertility have always been a matter of debate, but generally, they are not accepted as causes of subfertility in FMF patients. Attacks of disease and the eventual risk of amyloidosis must always be the primary concern in the management of FMF patients. It should also be noted that infertility and recurrent early pregnancy losses, i.e., miscarriages, must be differentiated in females with FMF, because recurrent early miscarriages due to uncontrolled disease may be confused with oligomenorrhea with irregular menses.

Anakinra seems to be safe in pregnancy, but there are very few data for conclusive interpretation, particularly in the first trimester. Subfertility in women with FMF is mostly the result of disease-related factors. Appropriate treatment and prevention of attacks are the key steps for fertility.

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