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Two Unanticipated Pregnancies While on Cystic Fibrosis Gene-Specific Drug Therapy

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Abstract

Women with cystic fibrosis (CF) desire to become pregnant and accomplish the same life goals as women without CF. The underlying pathology of CF and medications used to treat this genetically transmitted disease can affect women's reproductive potential. An interview with Ana (pseudonym), who became pregnant twice while taking the medication lumacaftor/ivacaftor (LUMA/IVA), was analyzed using thematic analysis. She described her experiences related to "Fertility and Pregnancy Surrounding LUMA/IVA," the major theme that emerged from her narrative. While there are anecdotal reports of infants conceived by women on LUMA/IVA and other CF precision medications, pregnancy rates and outcomes are not systematically tracked. Education about risks and benefits of these medications should be provided as part of comprehensive clinical care.

Keywords

cystic fibrosis, reproductive health, pregnancy, CFTR modulators

Introduction

Cystic fibrosis (CF) is a genetic disorder that affects approximately 30 000 people in the United States and 70 000 people worldwide (1). It is the most common genetic disorder among Caucasians and affects men and women equally (1). More than half of the CF population is older than 18 years, and the median predicted survival age is above 40 years (1). Cystic fibrosis is a genetically transmitted, multisystem, life-limiting disease that primarily affects the pulmonary and gastrointestinal systems (1). The defective gene alters the sodium chloride transport channel and results in tenacious mucus that obstructs the lungs, pancreas, and reproductive organs (1). In women with CF, the abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein causes a reduced or absent level of chloride and bicarbonate ion transported across epithelial membranes (2) leading to an altered fluid microenvironment within the reproductive organs and thickened cervical mucus that blocks sperm from effectively reaching the egg for fertilization (3). Both of these underlying pathophysiological processes negatively affect the woman's fertility and ability to conceive.

Background

Due to rapid advances in research and medical care, people with CF are now living long enough to consider careers, attend college, or even start a family (1). They are meeting developmental milestones similar to their non-CF counterparts (4). In fact, women with CF have a conception rate of 67% compared to 85% in women without CF unless they have end-stage lung disease or are severely malnourished due to CF's associated malabsorption syndrome (5). While the literature on pregnancy rates and outcomes in women with CF is scarce, reports indicate that they do become pregnant, carry to term, and deliver healthy babies (6). Additionally, women with CF who become pregnant do not have

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shorter lives than women with CF who have not been pregnant (7). With the rising survival age, women with CF are now having to face decisions about their sexual and reproductive health much the same as women without CF (8). Despite facing similar decisions as women with CF, according to a recent study, over 20% reported that did not know how CF affected their fertility, and 4% thought they might be infertile, thus, indicating a risk for unplanned pregnancy (9).

The recent discovery and approval of CFTR modulator therapy, considered a "game-changer" in the CF-specific landscape of precision medicine, contributes another layer of challenges when educating women with CF about these medications' possible, and currently largely unknown, impact on reproductive health (6). Cystic fibrosis transmembrane conductance regulator modulators are targeted therapeutics prescribed per the individual's specific CF mutation(s) (10). It is the umbrella term for 2 major CF drug categories known as "potentiators" and "correctors" (11). Potentiators work to improve CFTR chloride transport on the cell surface, whereas correctors allow CFTR to be properly expressed on the cell membrane by correcting misfolding of the protein that leads to degradation of CFTR (11). An example of a CFTR potentiator is ivacaftor (Kalydeco), hereafter referred to as IVA. It was the first CFTR modulator approved by the US Food and Drug Administration (FDA) in 2012 and prescribed to those with 38 different CF mutations (12). An example of a CFTR corrector is lumacaftor (LUMA), and it is used in combination with IVA, hereafter referred to as LUMA/IVA (Orkambi). It was FDA approved in 2015 and prescribed to treat the single most common CF mutation known as DF508 (13). Simplistically, these CFTR modulators help to correct the basic underlying problem of the defective sodium chloride channel, resulting in normalization of sweat chloride levels and improvement of lung function and overall quality of life (11).

Safety profiles for these CFTR modulators are currently not well established. Current prescribing recommendations include avoiding or discontinuing the medication during pregnancy or while breastfeeding, based on limited human data during pregnancy and no human data while breastfeeding (2). The drugs' fetal effects are largely unknown, and data on pregnancy and fetal/infant outcomes are not collected by the CF Foundation Patient Registry. Thus, the number of women who became pregnant on CFTR modulators and those who remained on the drugs during pregnancy or while breastfeeding despite current prescribing recommendations are unknown (14). Anecdotal reports and case studies provide the beginning evidence regarding CFTR modulators' effects on women's fertility and reproductive health. Ladores, Kazmerski, and Rowe presented a case of an unanticipated conception in a woman on IVA therapy who had a healthy pregnancy and an equally healthy infant (15). Another case report of a woman on LUMA/IVA described a healthy pregnancy, safe delivery, and successful breastfeeding while on the drug (16). The report also showed that both components of the combination drug LUMA/IVA were detected in the infant's plasma and the mother's breastmilk. Ivacaftor has been associated with cataract development in children, thus, it is imperative that infants exposed to the drug in utero be closely monitored (17). While CFTR modulators have been hypothesized to affect numerous factors that improve fertility in women with CF, there are no studies to date that show that the drugs directly increase fertility (6).

As noted above, unanticipated pregnancies do occur in women taking CFTR modulators and can result in devastating consequences for the woman and/or infant, including loss of lung function for the woman and growth retardation from hypoxia and premature birth for the infant (3). Additional risks to the mother and/or infant while on CFTR modulator therapy are still largely unknown (14). The purpose of this case report is to describe the experiences of a woman with CF who had 2 unexpected pregnancies while on LUMA/IVA.

Case Presentation

Ana (pseudonym) is a 29-year-old woman, diagnosed with CF at 4 months old, and carries the mutation of homozygous DF508, the most common genetic mutation in CF (17). Ana had been trying to become pregnant with her husband for 2 years with no success. Two weeks after she started LUMA/IVA, she became pregnant. Starting LUMA/IVA was the only change in her CF care regimen, and she vehemently attributed her unexpected (and welcomed) pregnancy to the drug. She also described that almost immediately after starting LUMA/IVA, her pulmonary function improved by 6 percentage points. She also noted that her chronic sinus congestion improved as well as her overall energy level and vitality. Upon discovering that she was pregnant, she shared the happy news with her CF care team who advised her to discontinue LUMA/IVA due to its unknown safety profile in pregnant women. She advocated that she remain on the drug throughout her pregnancy, and her son is now a healthy toddler. She then became pregnant with a second unplanned pregnancy while on the drug when her son was 7 months old.

Methods

The first author (S.L.) conducted a telephone, audio-recorded interview with Ana during her second pregnancy. Ana consented to being interviewed. Since this interview was with one person only, Institutional Review Board approval was not necessary. A pseudonym was given to ensure privacy and protect the interviewee's identity. The interview lasted approximately 80 minutes. The recording was transcribed verbatim and analyzed independently by the 3 authors. Intercoder agreement was high at approximately 90%. Using Braun and Clarke's method of thematic analysis, codes were developed into the major theme and subthemes (18). The steps of thematic analysis include independent analysis of the transcribed interview by the 3 authors to

establish codes, then analyzing the codes for recurring themes.

Results

The overarching theme of "Fertility and Pregnancy Surrounding LUMA/IVA" emerged from the interview data. Three subthemes depicted Ana's experiences: (1) fertility prior to LUMA/IVA (2) fertility after starting LUMA/IVA, and (3) pregnancy while on LUMA/IVA.

Fertility Prior to LUMA/IVA

Ana described how she first learned about potential fertility challenges due to CF: "My parents were very open about it [fertility] . . . they were very aware that I possibly couldn't have kids, and they made me very aware of it at a young age." As she became older and engaged in romantic relationships, she disclosed the reproductive implications of CF with her partners. Within 3 months of dating her now-husband, she explained to him: "I'm not on birth control because I have blood clots, but also because most likely, I can't get pregnant." Additionally, because of her potential infertility or subfertility, she thought about using a gestational surrogate: "I have a really good friend of mine who offered to carry [the baby] for me if I was not able to have kids or if I wanted them and couldn't carry." Ana and her husband engaged in regular unprotected sexual intercourse in an attempt to conceive a child with no success.

Fertility After Starting LUMA/IVA

Ana began taking LUMA/IVA 7 months after getting married and became pregnant 2 weeks after starting the drug. Ana shared the positive changes that she noticed after starting LUMA/IVA: "I was definitely less congested lung-wise just a few days after." She went on to add that, "I had a feeling that also means that the mucus that I had covering my cervix also thinned out." Once Ana became pregnant, she spoke to her CF care team about her pregnancy and described their reactions: "There was one or two doctors who had warned me previously that they didn't support pregnancy in CF patients because it's dangerous." Despite the initial negative reception to her pregnancy announcement, Ana eventually found support from her health-care providers.

Pregnancy While on LUMA/IVA

Regarding the continued use of LUMA/IVA during pregnancy, most of Ana's CF care team was either neutral on the topic or encouraged her to consider discontinuation of the drug: "They [health-care providers] weren't sure at that point if it [LUMA/IVA] was safe or not safe. There wasn't any information on it so they said, 'It's up to you.'" Ana chose to stay on LUMA/IVA for the entirety of her pregnancy because she "felt a lot better on it than she did off it."

When her first son was approximately 7 months old, Ana was placed on intravenous antibiotics for a CF exacerbation. She described how the LUMA/IVA and being on the antibiotics resulted in her second unanticipated pregnancy: "It [antibiotic] caused me to ovulate twice. It threw off my ovulation so much [that] I got pregnant the month after I was in the hospital." She shared that the second pregnancy was an even bigger surprise compared to the first. However, with the shock also came anxiety: "The danger of being pregnant hit me more . . . having a child already and knowing [that] something could happen to me and [I may have to] leave him." Lastly, Ana spoke about the changing needs of women with CF: "I don't think that, up until recently, there was a need for them [health-care providers] to understand reproductive issues because we weren't living as long to have families."

Discussion/Lessons Learned

This case study depicted one woman's experience with fertility and pregnancy related to the use of LUMA/IVA throughout 2 pregnancies. The needs of women with CF are changing due to recent drug discoveries like LUMA/IVA and the related improvement in overall quality and quantity of life, which provides them an opportunity to reach new developmental milestones, including motherhood. Likewise, health-care providers must adapt and meet the emerging needs of this uniquely vulnerable population of women. This case study illustrated the following key messages: (1) LUMA/IVA has the potential to affect fertility and reproductive health in women with CF; (2) It is possible to conceive and deliver a healthy infant while taking LUMA/IVA; (3) Pregnancy rates and outcomes in women taking CFTR modulators must be tracked; and (4) Health-care providers need to include reproductive health education during routine CF clinic appointments as part of comprehensive clinical care.

Conclusion

Targeted therapeutics in CF can affect fertility and result in unanticipated pregnancies, thus, women must be counseled about risks and benefits before its initiation.

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We acknowledge that the work is our own. This manuscript has not been previously published and is not under consideration for publication elsewhere. Since this manuscript is based upon an interview with one person, approval from the Institutional Review Board was not necessary. A pseudonym was given to the interviewee to ensure privacy.

Declaration of Conflicting Interests

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