**Cystic Fibrosis and Reproductive Outcomes: The Latest Insights into Fertility and Pregnancy**

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**Abstract**

**Introduction and purpose:** Due to improvement in treatment of people with cystic fibrosis (CF), the number of adult patients increases. CF patients are living longer, with better quality of life and a growing number of them are considering parenthood. Most people with CF are suffering because of reduced fertility, however the number of pregnant CF patients rises. The aim of this paper was to summarize the date available in the literature and recent reports about the fertility, pregnancy and treatment of pregnant CF patients.

**Material and methods:** The literature was reviewed in PubMed database, GoogleScholar and in European Cystic Fibrosis Society database with the use of keywords.

**State of knowledge:**78% of women with CF declare that they want to have a child in the future. Reduced fertility may be overcome with assisted reproduction technologies, which also gives an opportunity to do preimplantation genetic tests. CFTR modulators therapy during the pregnancy was described in a small number of studies, but the current experts statement declares that those drugs are probably safe for the infant, and discontinuing this therapy is connected with an increased risk of pulmonary exacerbation in mothers.

**Summary:** Women with CF nowadays have an opportunity to become parents. Despite fertility lower than in the general population, they are able to become pregnant. The decision about the conception should be planned before and consulted with the CF team. Planning the pregnancy gives time to prepare the mother, optimize her nutrition status and make sure medications she takes are safe for the fetus. Data about the use of CFTR modulators during pregnancy and breastfeeding are limited. In the future the MAYFLOWER study may determine the impact of CFTR modulators on pregnancy and breastfeeding.

**Key words:** “Cystic fibrosis”, “CFTR”, “Fertility”, “Pregnancy”

**Introduction**

Cystic fibrosis (CF) is an autosomal recessive genetic disease, caused by mutations in cystic fibrosis conductance regulator (CFTR) gene. The incidence of CF is estimated between 1/3000 and 1/6000 in Caucasian population according to newborn screening (NBS) programs [1] . CF patients suffer from severe pulmonary, pancreatic and gastrointestinal complications. This disease is a.o. connected with progressive lung dysfunction, recurrent acute pancreatitis leading to pancreatic insufficiency, CF related diabetes and CF related bone disease [2].

In the past it was exclusively pediatric disease, but nowadays the proportion of adult patients is higher than the number of children with CF. Research shows that the estimated median age of survival is close to 50 years old in newborn children with CF [3]. The elongation of lifetime in CF is a result of improvement in antimicrobial treatment and nutrition care, successful physiotherapy, screening programmes in newborns, standardization of care in multidisciplinary CF centers and new casual treatment - CFTR modulators. [4]

The growing population of adults with CF also requires medical care in reproductive health since many of them are considering parenthood. Recent study [5] showed that 78% of surveyed young women with CF wanted to have a child in the future, even though 72% of respondents were concerned that their future children might have CF.

**Purpose**

The paper presents the current state of knowledge on fertility and pregnancy in CF. The goal was to summarize the data available in literature, case reports and studies that analyzed the impact of CFTR modulators therapy on pregnancy and breastfeeding. Authors included both advantages and adverse effects of this group of medications.

**Material and methods**

A review of the PubMed database, GoogleScholar and European Cystic Fibrosis Society database was performed. The articles were searched with the use of keywords such as “cystic fibrosis”,”CF”, “fertility”, “pregnancy”, with a time limitation to years 2013-2023. The search provided 2817 positions, after rejecting scientific papers that did not meet authors’ criteria, 26 of articles were included in this paper.

**State of knowledge**

**Infertility in men**

According to research over 98% of men with CF are infertile [6] because of congenital bilateral absence of vas deferens with lower semen volume and abnormal semen pH. Partner pregnancy might be achieved by procedures such as in vitro fertilization or intra cytoplasmic injection. These procedures involve accessing spermatozoa from testicles by sperm aspiration or testicular biopsy [7]. Methods of assisted reproduction technologies should be considered individually since the cost of these procedures might be prohibitive. Furthermore, described methods would require female partners of men with CF to undergo a medical procedure despite their normal fertility.

**Fertility in women**

Subfertility in women with CF has been described since the 1970s. In a retrospective multinational study [8] it was provided that 35% of women with CF who attempted conception are infertile or subfertile, while according to WHO data the subfertility and infertility rate in the general population is about 17,5% [9]. Reduced fertility in women with CF may result from a variety of etiologies. In one study [8] it was shown that subfertility was significantly associated with pancreatic insufficiency. There was also strong association of subfertility and advanced age, which suggest that reduced fertility may be combined with ovarian and hormonal reserve. However, another paper, published in 2023, did not support the hypothesis that reduced ovarian reserve has a major role in decreased fertility in women with CF [10]. It was also pointed out that chronic colonization with Pseudomonas aeruginosa, pulmonary exacerbations, body mass index and lung function were not associated with infertility [8].

Women with CF more frequently than healthy women suffer from anovulation [7]. They have elevated levels of testosterone and lower levels of estrogen and progesterone. Those hormonal variations along with hypersecretion of insulin are similar to those in polycystic ovarian syndrome, however examined women had normal follicles by sonography [11].

Historically, it was believed that women with CF experienced menarche at a more advanced age than their relatives, but an Australian study [12] did not find any significant difference in Tanner stage and menarche age between CF girls and healthy control subjects.

Reduced fertility problems may be usually overcome with assisted reproduction technologies (ART), such as intrauterine insemination or in vitro fertilization (IVF). IVF has a huge advantage, as it gives an opportunity to do preimplantation genetic tests in the case of partners with CFTR mutation. One study [8] showed that 80% of subfertile or infertile women became pregnant due to ART or after more than a year of attempts to conceive.

**Planning of parenthood**

Reproductive decision making should be consulted with the multidisciplinary CF team but women with CF often are in fear of being advised not to childbear, so they may not want to talk about it [13]. In a paper [13] that studied decision making related to pregnancy in CF, interviewed women pointed out that they want to “feel normal, like someone who didn’t have CF [and] could have a baby”. It is important to remember that the decision whether to conceive or not belongs to the woman and the CF team should respect her own choice.

It has to be considered that a mother with CF must have time not only for taking care of an infant, but also for her regular treatment and to rest. Before making the decision about procreation the mother should know if she will have some home support to be able to take care of both – the infant and herself. Planning of pregnancy guarantees more time to prepare for not only enlargement of the family, but also to prepare the mothers health and optimize the nutrition status. Poor nutritional status is connected to worse outcomes, such as prematurity and low birth weight, therefore in some patients with low preconceptional BMI even enteral feeding should be considered [14].

In a paper that analyzed association between unplanned pregnancies and maternal pulmonary exacerbations (PEx) it was shown that there is an increased frequency of PEx in unplanned pregnancies in patients with CF compared to planned pregnancies in patients with CF [15]. Higher risk of PEx might potentially affect an increase in infant complications, such as pre-birth or lower APGAR scale [15].

In patients that take CRTF modulators there have been described cases of improved fertility and unplanned pregnancies in women that previously were reported as infertile [16]. In a study [17] it was noticed that women with the mutation G551D have reported an increased number of pregnancies after periods of CFTR modulators trial. To avoid unwanted pregnancies, health providers should discuss with their CF patients who start to take CFTR modulators about potential of increased fertility.

It is also important to notice that women with CF may want to do genetic tests on their partner, to assess the risk for CF disease or carrier status of the offspring. According to study [5] 79% of wwCF would elect to do genetic testing for CF for their future children. Planning of pregnancy gives time for medical providers to not only do genetic tests but also optimize lung function, nutrition and medications before conception [18].

When pregnancy is planned, both the woman and her partner should be tested to specify the genotype of the future mother, and to assess whether the man is a CFTR mutation carrier. It provides data to discuss with a genetic counselor about the risk of an infant having CF [19]. If the partner is a carrier or his genotype cannot be tested, prenatal diagnosis can be performed to verify whether the fetus has CF.

**Psychological support**

Couples considering pregnancy should talk with a specialist at the pre-pregnancy counseling stage, since parenthood with a chronic life-limiting disease may be extremely emotionally taxing. Some older papers [20] suggested that up to 20% of mothers with CF will die before their children's 10th birthday. Today these data might be outdated, but psychological support is definitely an important issue in providing healthcare for people with CF.

Psychological support may be necessary, because some women with more advanced disease might have to deal with advice to avoid pregnancy, despite their drive to have a child. It might be hard for them to cope with it. Even women with relatively good health may need professional psychological help to discuss difficult issues such as the possibility of death while the children are still young [19].

After childbirth women can experience postnatal depression. The rate of this issue in CF is unknown, but in the general population it is seen in 10-20% of mothers [19]. This disorder is connected with feelings of worthlessness, guilt, difficulties in concentration, disturbances in sleep. Treatment of postnatal depression includes antidepressant medications and cognitive-behavioral therapy. Screening of this issue should be considered by the CF team.

**Treatment of CF in pregnancy**

There are a small number of case reports for women who chose to continue or discontinue CFTR modulators therapy during pregnancy. The first study presenting a case series of the outcome of women taking CRTR modulator through part or entire pregnancy was published in 2020. [21] The paper provides that the available CRTF modulator therapies are generally well tolerated in pregnancy. Among identified 64 pregnancies in 61 women taking Ivacaftor (IVA), Lumacaftor/Ivacaftor (LUM/IVA), Tezacaftor/Ivacaftor (TEZ/IVA), 60 resulted in live births and only two maternal complications that were deemed related to CRTR modulators occurred - one with pulmonary exacerbation and one with acute myelocytic leukemia (AML), however there are no other reports of AML in association with CFTR modulators intake. There were no CFTR modulators-related complications in infants exposed in utero, however children were examined for a limited amount of post-partum time. It is possible that effects of CFTR modulators during pregnancy can be apparent later in chldrens’ lives.

Cases report [22] published in 2021 described 5 women who had unplanned pregnancies during ETI therapy. Two of them developed elevated transaminases suspected secondary to Elexacaftor-Tezacaftor-Ivacaftor (ETI) treatment. No other maternal or infant complications occurred. Another study [23], published in the same year, analyzed outcomes in women with CF who used ETI during pregnancy and/or lactation. In this study 45 pregnancies with fetal exposure to ETI resulted in 29 live births and 7 on-going uncomplicated pregnancies. Only one maternal complication - cholecystitis was deemed related to ETI use. Complications in 2 women and 3 infants were deemed in unknown relation with ETI use. In this study, 5 women that discontinued ETI therapy experienced clinical decline in pulmonary health.

Discontinuing CFTR modulators therapy during pregnancy might yield decreased lung function or increased risk of pulmonary exacerbation, but there is limited data and this subject should be investigated in future research [24][25].

Despite limited data from case reports and case series, experts support the ongoing use of CFTR modulators during pregnancy [26]. This therapy not only decreases the severity of pulmonary issues, but also improves the nutritional status, which is crucial during pregnancy and breastfeeding [27]. In 2020 the official statement of European Respiratory Society/Thoracic Society of Australia and New Zealand considered CFTR modulators to be “probably safe” and maternal benefits may outweigh potential risk during pregnancy and/or breastfeeding [28].

**Breastfeeding and CFTR modulators**

Women with CF require medical help to maintain nutritional health, especially if they decide to breastfeed. Before making the decision to breastfeed it should be consulted with the dietetic to ensure that the nutrition status of the woman provides enough calories for the mother and the child. Although many mothers with CF are not able to maintain breastfeeding for six months, they should be encouraged to continue it as long as possible; however each woman with CF has to be individually assessed and advised whether her clinical condition and circumstances allow her to breastfeed [19].

There is limited data on use of CFTR modulators in humans during lactation. In animal models IVA and LUM/IVA were present in breast milk [29][30]. The study that measured fetal and neonatal exposure to Lumacaftor and Ivacaftor during pregnancy and breastfeeding [31] suggested that both of those medicines pass into breast milk in low levels, but high enough to be detectable in infants' plasma. Although IVA is approved in infants with CF as young as 6 months of age [16], there is minimal data demonstrating safety of CFTR modulators during lactation.

It is also important to notice that IVA administered in 0,1 to 0,8 times of maximum recommended human doses in 7 to 35 days old rats led to development of non-congenital lens opacities (cataract) [30]. Non-congenital lens opacities have been also noticed in pediatric patients treated with CFTR modulators [29][30]. Considering this, it is advised that infants that were exposed to those medications in utero or while breastfeeding should be examined by an ophthalmologist. Furthermore, routine evaluation of infant liver function should be considered for infants exposed to CFTR modulators during breastfeeding, since there are concerns about the metabolism of these drugs in the liver [32].

Overall, as a matter of limited data, continuation of CFTR modulators should be individually assessed, with risk benefit discussion between the mother, the CF team and infant pediatrician.

**Pregnancy outcomes**

The authors of the study found a significant decrease in percent predicted forced expiratory volume in 1 second (ppFEV1) and body mass index (BMI) while comparing 1-year-pre-parenthood to 1 year after childbirth surveys, also 30% increase from pre- to post-parenthood in the number of IV antibiotics days annually [33]. The same study showed that the use of CFTR modulators mitigated the effect of parenthood on lung function, but had no impact on BMI or number of treatment days in pulmonary exacerbation.

In a study [34] 149 pregnancies were analyzed and the authors compared pregnancy outcomes in women with FEV1≼ 50% before the pregnancy and women with FEV1>50% before the pregnancy. It was shown that despite lower FEV1 the change in this parameter following pregnancy was not significantly different. Women with lower FEV1 more frequently delivered by the cesarian section than vaginally, but it could be explained by fear of poor tolerance of vaginal delivery. It also has to be mentioned that obstetrical centers may have different practices in delivery in CF, and there are no clear recommendations by experts. Reynaud et al. also noticed that the birth weight was significantly lower in infants born from mothers with FEV1≼50%. None of the women in this study was treated with CFTR modulators [34].

Overall outcomes in women with CF who experience pregnancy are good [35], but there is a need for a long-term study examining the impact of CFTR modulators on pregnancy and breastfeeding. In 2021 such a prospective study began - Maternal and Fetal Outcomes in the Era of Modulators - MAYFLOWERS [36]. This study takes place in 40 care centers across the USA and enrolls about 285 pregnant women with CF. It will be the first study to describe the detailed health outcomes of CFTR modulators therapy on pregnant women and their infants.

**Conclusions**

Nowadays people with CF live longer and this disease not only occurs in children, but also becomes a chronic disease in adults. The patient's estimated median age of survival is now close to 50 years. This fact gives an opportunity to people with CF to start their own families and become parents. Although almost every man with CF is infertile and about 35% of women with CF struggle with subfertility or infertility, the assisted reproduction techniques may help to achieve pregnancy. It is essential for women with CF to consult her decision about the conception with her CF team, who will help her to prepare her own health, nutrition status and also run some genetic tests to ensure if the partner is a CF carrier. Planned pregnancies in women with CF are connected with better outcomes than those unplanned. It is also important to provide pregnant women with CF psychological support, since they have to face up not only to changes connected with pregnancy but also perspective that they may not live long enough to see their children becoming adults.

This article summarized available data about pregnancy and breastfeeding during CFTR modulators therapy. Despite limited data experts suggest maintaining CFTR modulators therapy during pregnancy, however this decision should be taken individually considering advantages and disadvantages by CF patient and the CF team. The MAYFLOWERS study may clearly determine the impact of CFTR modulators on pregnancy and breastfeeding, but as the research is still ongoing, we shall await its conclusions.

**Disclosures**

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