



Cystic Fibrosis: Its Impact at Women's Fertility and their Pregnancy. A Narrative Review

C. Loukopoulou

Medical Student, University of Ioannina, Greece

F. Gkrozou

Department of Obstetrics and Gynaecology,
Medical School, University Hospital of Ioannina, Greece

A. Geroula

Medical Student, University of Ioannina, Greece

N. Mantzoukidou

Medical Student, University of Ioannina, Greece

A. Zoi

Department of Obstetrics and Gynaecology,
Medical School, University Hospital of Ioannina, Greece

C. Skentou

Department of Obstetrics and Gynaecology,
Medical School, University Hospital of Ioannina, Greece

A. Vatopoulou

Department of Obstetrics and Gynaecology,
Medical School, University Hospital of Ioannina, Greece

O. Tsonis

Assisted Conception Unit,
Guy's and St Thomas' NHS Foundation Trust, London, UK

Abstract

Women with cystic fibrosis (CF) leave more years than in the past. This is the reason why this population has increased expectations for a more "normal" life. We aimed to assess current maternal and fetal outcomes in women with CF with varied pre-pregnancy lung function, in addition with fertility outcome after artificial reproductive technology (ART). A review of relative literature was conducted, using the MEDLINE database, the ScienceDirect database and Google scholar and relevant keywords. Studies confirmed that more women with CF are considering pregnancy. Unplanned pregnancies also are happening, and women need the right guidance. Most women will have normal pregnancies, but preterm births are common. Optimization of treatment is recommended during family planning or pregnancy. Reduced fertility may be overcome with ART. With careful multidisciplinary

antenatal and intrapartum management, successful outcomes have been obtained in women with CF.

Keywords: Cystic Fibrosis, fertility, pregnancy complications, reproductive medicine

INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive disease that results from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene at chromosome 7, that cause the CFTR protein to become dysfunctional, which is normally responsible for the transport of chloride and indirectly sodium and water across luminal cell membranes. This genetic disorder can lead to thickened and desiccated secretions throughout the respiratory and alimentary tracts, sweat ducts, and the reproductive organs. In other words, CF affects many different organs and patients are often suffering from pancreatic insufficiency, malabsorption, respiratory failure due to chronic infection, bronchiectasis, and progressive lung destruction, diabetes mellitus and cirrhosis. Therefore, the life expectancy is reduced (1). However, over the last few years the median predicted survival is above 50 years and the prognosis of CF has been improved due to earlier diagnoses based on neonatal screening, the existence of specialized centers and new treatments (2).

It is well known that 95% of CF males are infertile. The ejaculatory fluid of low volume does not contain sperm (azoospermia) because of the bilateral absence of the vas deferens. On the other hand, the impact of CF on female fertility is not so clear (3). Women with CF may have thicker cervical mucus and more anovulatory cycles than women without CF. The impact of these mechanisms on fertility is not yet completely defined and the true fertility rate is yet to be understood (4). According to Cystic Fibrosis Foundation due to increased life expectancy even more women are becoming pregnant and increasing numbers of children are born to women with CF each year (5). However, there is a significant percentage of women who have dilemma on whether to become pregnant or not, as the CF has a huge impact on their life. They cited concerns about possible CF complications during and after pregnancy and that their reproductive choices would maybe worsen their disease and decrease their lifespan (1,4,6-12). All this is a result of lack of knowledge about the CF and its effect not only on pregnancy but also on fertility. There are complains about major gaps in sexual and reproductive health (SRH) because they are uninformed about SRH from their CF team (3,4,7-15). Although the frequency of contraceptions between people with CF and people without CF is similar (7).

Further study on this group of population is necessary, as there is need for women with CF to be informed about fertility and pregnancy. We should also highlight the importance of communication between patients and the CF team in correlation with SRH decisions, as the current guidelines suggest that all members of CF team play a major role in educating and informing women about CF and pregnancy-fertility. The aim of this study is to present the current knowledge of the pregnancy outcomes, the maternal pathology, the potential risks, the postpartum follow up, the fertility issues and the ways to sort out these fertility problems on women with cystic fibrosis.

METHODS

A review of relative literature was conducted, using the MEDLINE database, the ScienceDirect database and Google scholar. The keywords that were used are "Cystic Fibrosis and fertility",

"Cystic Fibrosis and young women", "Cystic Fibrosis and IVF", "Cystic Fibrosis and ICSI", "Cystic Fibrosis and hormonal treatment" and "Cystic Fibrosis and pregnancy". Based on those keywords 189 articles have been found but only 28 of them were more related to the subject "Cystic Fibrosis and fertility in women".

RESULTS

Pregnancy Outcomes

It is well known that physiological changes happen in all pregnant women. However, these changes in patient with lung disease such as cystic fibrosis can lead to difficulty in excreting sputum and these mechanisms might cause maternal and neonatal complications (16). Poor pregnancy outcomes in women with CF are associated with maternal pulmonary status. The major factors (16) that affect the outcome of pregnancy is lung function ($FEV_1 < 40\%$ or forced vital capacity $< 50\%$), nutritional status ($BMI < 18 \text{ kg/m}^2$), poorly controlled diabetes and therefore some authors support that woman with $FEV_1 < 60\%$ and worse lung function should terminate the pregnancy or avoid it (17,18). However, this advice may not be justified (5).

On the other hand, there are reports of successful pregnancy despite the poor lung function and most new-borns are healthy (6,12,17–21). According to a French survey (6) 87% of women with CF had at least one pregnancy, 85% of these pregnancies were successful and only a small percentage of 1% had an abortion because of fetal abnormalities. Similar findings were confirmed by a different survey (5), where 93,3% of population had live births and only one fetal anomaly was detected.

Pregnancies of women with cf lead to premature delivery (< 37 weeks) in a percentage rate of 19% (6), 28,3% (2), 25% (8) and these infants are more likely to have disorders such as, respiratory distress syndrome, sepsis, cerebral haemorrhage, hypoglycaemia, growth retardation (iugr) and be small for their gestational age (sga) (8). More frequently, in women with cfrd (cystic fibrosis-related diabetes) or poor lung function (19) and after lung transplantation up to 50% of infants are born premature (8) and 20% have intrauterine growth restriction (iugr). These happen due to chronic hypoxia in women with chronic respiratory disease and severe hypoxia during labor might result in fetal death. (1) in a multicenter-retrospective cohort study (16), women with cf were categorized as mild and moderate-to-severe disease. Patients with mild cf had $FEV_1 > 60\%$ and a $BMI > 21 \text{ kg/m}^2$, whereas women with moderate to severe disease had either $FEV_1 \leq 60\%$ or a $BMI \leq 21 \text{ kg/m}^2$ before pregnancy. Women with moderate to severe cf had more preterm births and neonatal disorders than women with mild cf. Pancreatic insufficiency and severe lung function are related to sga newborns with no difference in the percentage of sga babies between these two disorders (complications) (16). Although recently, pancreatic status has become a less important evidence (12). Furthermore, cf predispose to pulmonary infection such as pneumonia, pulmonary hypertension (pht) and fetal loss and 44% of women with pneumonia had preterm labor (1). Women with cf also are more likely to deliver infants with congenital anomalies, including cardiac anomalies at a rate 7 times higher than in pregnancies of mothers without cf (21).

Moreover, the frequency of cesarean sections was 63,64% at women with CF (2). Women with poor respiratory function ($FEV_1 < 60\%$) tend to deliver by cesarean section because of premature delivery unlike women with $FEV_1 > 60\%$ (17). At the same time, as regards spinal anesthesia is

preferred over general anesthesia (19). Vaginal delivery is also preferred to Cesarean when this is possible because surgical recovery can increase atelectasis and retention of airway secretions (18).

Furthermore, maternal and gestational diabetes are more common in women with CF during pregnancy and in these circumstances cesarean section is preferred over vaginal delivery (8,19). Diabetes is a significant factor for the outcome of pregnancy and the health of both infant and mother, since complications may occur(1,8). Poor glycemic control mainly during the first trimester is related to a great risk of fetal malformations (19). For that reason, the European Cystic Fibrosis Society recommend that an oral glucose tolerance test must be done pre-pregnancy and multiple times during pregnancy. However, Frayman K-B et al reported that cystic fibrosis-related diabetes (CFRD) did not affect the fetus and there were no differences in the frequency of preterm births and the birth weight (12).

Generally, most drugs used in the long-term therapy of CF are considered generally harmless except immunosuppressant drugs for lung transplantation as well as rifamycins, azoles, and tetracyclines. Additionally, careful consideration should be taken while choosing intravenous and oral antibiotics for treatment of acute respiratory exacerbations (19).

According to long-term CFTR modulator therapy, it is claimed that all four authorized medications are safe, but a notable concern is that there is lack of human evidence and data (19,21). Modulators were found in cord blood, newborn plasma, and breast milk at minor concentrations and moreover in maternal plasma, at predicted quantities (21). Despite the fact of placental transfer, CFTR modulators do not have teratogenic effects at standard human dose levels and they are classified in category B3 in pregnancy (18,20). In pregnancies of women that used CFTR modulators there were no maternal or fetus deaths, no cataracts in infants, no neonatal abnormalities (20,21) and no miscarriage rate increase (19,21). Due to a lack of knowledge about their safety during gestation, efforts to withdraw CFTR modulators led to clinical instability, a reduction in pulmonary function, and an escalation in pulmonary exacerbations (18,20,21). Even a case of maternal fatality has been documented because of modulator withdrawal (21). Thus, it is important to evaluate the advantages and disadvantages of modulator treatment for each woman individually throughout pregnancy and lactation (18). However, CFTR modulators, specifically the Lumacaftor/Ivacaftor (LUM/IVA) combination, during pregnancy were associated with one infant and two maternal complications. Due to the use of LUM/IVA infants were delivered earlier than 37 weeks (20,21). One of the maternal complications occurred during pregnancy and was a pulmonary exacerbation; however, the writers are uncertain if this was because of LUM/IVA (Lumacaftor/Ivacaftor) or the existing CF condition. A postpartum detection of acute myeloid leukemia (AML) was the second unfavorable outcome that was thought to be connected to LUM/IVA (12,20,21). The researchers assume that the occurrence of AML may not have been directly associated with LUM/IVA, because there have not been reported any similar cases, but instead could have been an unfortunate concurrence (20). Current recommendations unlikely suggest not to give CFTR modulators during pregnancy as the long-term consequences of the exposure of the infant to the medication is not yet completely understood (12,21).

Last but not least, data from the US National Transplantation Pregnancy Registry showed that more than 50% of transplant recipient had premature infants and neonatal complications were

reported in 71% (12), such as reduced weight of birth (18) and congenital abnormalities caused by drugs (12). According to pregnant lung transplant recipients, they may be more likely to experience acute organ rejection (1,12,18) and organ failure (1). Additionally, they may be more susceptible in developing preeclampsia, hypertension during pregnancy (8,18), gestational diabetes, and even postpartum death. (18). Women after lung transplantation and with excellent lung function for at least three years before pregnancy and with limited transplant-related comorbidities have the best pregnancy outcomes (12). For that reason, recommendations suggest women to wait for at least 2 years after transplantation before conception (1,9,11).

Maternal Pathology During Pregnancy-Risks

It was initially thought that there is a high risk for all pregnant women with CF (11) and that due to normal adaptations of respiratory system and lung function during pregnancy, women with lung disease would be in a high-risk position (9). New data have showed that a successful pregnancy is possible even in severe cases of respiratory diseases (21). In general, pregnancy of women with CF can be safe and without much risk to them or the fetus (12), but still literature supports that the ones with CF have more complications related to themselves or their fetus when they are compared with healthy women (12,21). Some women with CF even decided to proceed to termination of pregnancy, although some case-control studies noted that there is no correlation between pregnancy and mental or physical condition (11). Padoan R et al in a study that took place between 2010 and 2015, showed that out of the 81 pregnant women, 9 were led to the termination of pregnancy, either voluntarily or due to miscarriage. (2)

Adverse prognostic factors for a pregnancy are poor lung function, cystic fibrosis-related diabetes (CFRD), and infection with the *Burkholderia cepacia* complex (18,21). An increased risk occurs in cases of poor dietary intake and unsuccessful weight gain during pregnancy (11), while BMI <18 kg/m² indicates a poor prognosis (18). Moreover, pre-existent pancreatic insufficiency (21) and liver disease (18) can deteriorate pregnancy.

Lung function is thought to be the primary predictor of pregnancy outcome (1), particularly at conception (5), suggesting that pregnancy might have a major impact on women with decreased pulmonary function, causing further impairment and altering the prognosis. (1) Low pulmonary function, and possibly more crucially, unsteady pulmonary function, is related with worse maternal and newborn outcomes (11,18). On the other hand, pregnancy doesn't affect CF women with adequate and stable lung function (12). When lung function is inadequate, challenges such as shorter pregnancy time, increased mother and newborn problems, greater cesarean rate, and decreased chance of breastfeeding are more common (1). Additionally, maternal decline of pulmonary function and hastened deterioration after pregnancy is observed in pregnant women with CF with low pulmonary function, serious clinical manifestations, and diabetes. (1)

A multicenter retrospective cohort study, that classified the individuals with CF as mild or moderate-severe disease, showed that during pregnancy, women with moderate and severe illness experienced greater complications related to cystic fibrosis than women with mild disease. (16) Nevertheless, there was no difference in FEV₁ (forced expiratory volume in the first second) and BMI between the two groups. In addition, moderate-severe patients had increased pulmonary exacerbations in all three time periods, but no wide variations in trends

were seen when data were analyzed over time. FEV1 decreased more significantly in infected individuals with *Pseudomonas aeruginosa* (PA) and in individuals with pancreatic insufficiency during pregnancy, but it afterward stabilized. Particularly, chronic PA infected individuals manifested more mild pulmonary exacerbations and CF patients with pancreatic insufficiency were correlated with severe pulmonary exacerbations, leading them to alter or initiate antibiotics. Pregnancies with moderate-severe illness were more likely to be complicated by gestational diabetes. Regardless of categorization criteria, patients with poorer condition spent more days on intravenous antibiotics throughout pregnancy rather than only oral antibiotics (16). In summary, these results show that even women with serious CF disease can tolerate a pregnancy, and no significant progression of the condition is anticipated during or after pregnancy (16). In case of diminishing function or infection, measures and antibiotic therapy should be vigorous and initiated as soon as possible (18).

It has been reported that pregnant and nonpregnant women with CF have higher resting metabolic rate than healthy pregnant women, leading to reduced weight gain during pregnancy. To achieve 10 to 12 kg gain weight during pregnancy, it is vital for pregnant women with CF to take care of their dietary condition (19). A common issue in patients with CF is malabsorption and due to the nutritional demands, that rise during pregnancy, it is difficult to meet those nutritional needs (9). According to Frayman et al (12), reduced BMI before pregnancy has been observed in CF women, in comparison with general public. Nutritional status during pregnancy is crucial, since low BMI is related with intrauterine growth retardation, premature birth, and low birth weight. The CF care team might have to start or increase oral/enteral vitamin and food supplements to improve BMI (18). Also, an increase in fiber and water consumption may help avoid constipation (19).

The prevalence of gestational diabetes is higher in women with cystic fibrosis than in women of general population (12). Notably, pregnancy-related complications might arise from CF-related diabetes (CFRD) (9). Preterm birth, maternal problems including pre-eclampsia, and infant anomalies are just a few of the negative impacts of diabetes during pregnancy (18). Early detection of gestational diabetes should occur, and if negative, further testing should be performed at regular intervals. Glycemic control during pregnancy is crucial for women with newly diagnosed gestational diabetes or CFRD. This includes regular glucose testing and could necessitate insulin therapy (18).

It doesn't seem that pregnant women with CF experience long-term pulmonary function decline (17) and there is no indication of faster disease progression throughout pregnancy in women with cystic fibrosis (12). However, they often need more hospital appointments, they manifest more respiratory exacerbations (9–12,17) and they have a poorer life quality during pregnancy than non-pregnant women (10–12). Pregnancy hospital admissions are more common, pharmaceutical treatments are more necessary, CFRD diagnoses, and treatment are increased compared to general population (9,11). Meanwhile physiotherapy intervention is quite often necessary and diabetic monitoring are better documented compared to general population (17). Nevertheless, long-term survival is not impacted by pregnancy (1,5,17,21). In fact, data have shown that even in women with significant respiratory impairment (particularly $FEV1 < 40\%$), the 10-year survival is equal or better for CF women who get pregnant, in comparison with the non-pregnant CF women (5,11,17).

CF pregnant women with poor pulmonary function, low body mass index, or CFRD experience higher rates of mortality (1). Reduced survival was also correlated with pancreatic insufficiency and colonization by *Burkholderia cepacia* (1). Pregnancy is absolutely contraindicated in cases of pulmonary hypertension and respiratory failure, particularly when FVC < 50% (1), and termination is suggested (11). Absolute numbers of pulmonary function might not be the best prognostic factor; but the pace of deterioration may be more essential (1). An expected FEV1 of more than 60 to 70 percent is suggested, although safe pregnancies have been reported in women with significantly poorer lung function (1,11). There are also several relative contraindications, such as liver disorders and *Burkholderia cepacia* colonization (1,11).

Postpartum Follow Up

Airway clearance and mobilization should be a priority and should not be neglected in cases of cesarean delivery, extended vaginal birth, or impaired pulmonary function (8). It is essential to appropriately relieve pain for this to occur, since it may result in less successful airway management and delayed mobilization (8,19). If necessary, oxygen should be supplied, and manual cough aid should be provided. Additionally, ventilator assistance should be ensured if the respiratory muscles are inadequate and exhausted. Depending on the mother's physical state, treatment meetings can require more time or may have to be split into smaller ones (8). Even in women with CF who have no pancreatic insufficiency, further vitamin D supplements might become necessary during breastfeeding due to the prevalence of inadequate levels (8). Regarding lactation, normal concentrations of proteins and electrolytes have been detected in breast milk from mothers with CF (8,18), but there have also been findings of reduced levels of cholesterol and fatty acids (8).

There are some main determinants influencing suggestions for breastfeeding for CF women (21). The most important factor is the capacity of mother to keep her weight stable despite the significant calorie requirements of breastfeeding (21). After giving birth, women with cystic fibrosis must make a continuous effort to preserve their nutritional and respiratory health because breastfeeding involves a considerable amount of time and nourishment. This leads to conclusion that it may not be suitable for women with CF, specifically those who have nutritional insufficiency (18). Nevertheless, it is believed that mothers should be motivated to carry on breastfeeding for as long as feasible, without exhausting themselves and also using a feeding bottle as a complementary food, as long as the nutritional and caloric condition of mother and newborn is constant (8,11) and mother is physically or psychologically incapable to continue breastfeeding (8). Dehydration is another significant concern in CF women because it might develop distal intestine obstructive syndrome. Therefore, CF women require an additional two liters of liquids to stay hydrated.(8)

It is not recommendable to use some pharmaceuticals during pregnancy or the postpartum period because they are excreted during breastfeeding (21). When a woman with CF decides to lactate, her medicines should be assessed. Because preterm newborns and infants younger than one-month-old absorb drugs in different proportions than older babies, the infant's age substantially impacts drug safety (8). Table 1 summarizes some important factors post-delivery for women with CF.

A retrospective cohort study that categorized patients depending on-the severity of the disease, the pancreatic sufficiency, and the *P. Aeruginosa* status showed that during the first postpartum

year, neither of the groups experienced any further struggles, however, women with moderate to severe condition were found to have additional CF-related difficulties (16). Usually, after pregnancy, the respiratory function improves and returns to normal (3). There is no indication of exacerbated CF progression during postpartum time when CF patients who were pregnant were compared with those who were not pregnant. Furthermore, in comparison to pregnant CF women who did not have cystic fibrosis-related diabetes, the researchers did not find any notable variation in the deterioration of FEV1 or BMI in patients with CFRD during the postpartum time of 2 years. CF mothers with serious obstructive pulmonary illness and lower BMI, moreover, did not present any faster reduction in FEV1 or BMI throughout the first 2 postpartum years when compared to women with FEV1 greater than 50% (12).

Nevertheless, cases of death have been reported in mothers with severe or moderate CF disease, who did not show improvement in their lung function after giving birth (3). In another retrospective study that studied forty-eight pregnancies, death occurred in the first 18 months postpartum in three of five patients with FEV1 less than 40%. In addition, four out of the nine patients who had FEV1 between 40 and 50% passed away within two and eight years after childbirth. (17)

Regarding to lung transplantation and pregnancy, death will occur in the first 5 years postpartum in most mothers with CF, or retransplantation may be vital (12). According to information gathered from the National Transplantation Pregnancy Registry of the US, half of the 11 pregnant CF women who had received lung transplantation had a graft function loss within two years (11). A case series shows, also, that 4 of 10 pregnant lung transplant recipients with CF passed away 26 months after giving birth. (11)

A considerable issue is the high likelihood of the newborn to have inherited the CF disease (11) and CF screening in infants is a valuable method to early diagnose the condition and take the necessary measures (22). Another significant concern is the high risk of maternal death during the first years of a child's life (11). The main determinant factor is the preexisting pulmonary function of mother (17). Regarding the postnatal depression, is uncertain how common it is (8,11). However, adequate screening and preventive measures are essential and should not be neglected (8,18).

Fertility Issues

CF impairs fertility of both sexes, although men are more severely affected. Congenital bilateral absence of vas deferens is responsible for obstructive azoospermia which is present in 98% of cases (11). A study found that 39.6% of women with CF were subfertile (23). According to a questionnaire concerning pregnancy planning and outcome of women with cystic fibrosis, the median time to pregnancy was twelve months, which is defined as a subfertility indication. Moreover, 37% failed to conceive without infertility treatment (6). Even though the exact process by which CFTR mutations can lead to subfertility is not fully understood yet, many mechanisms have been proposed.

CFTR is expressed in the cervix, endometrium, fallopian tubes, and hypothalamus (11). The expression of CFTR in the cervical epithelium and its role in mucus thickness is a possible cause of the observed subfertility among women with CF. The abnormally thick mucus that is produced due to deficient CFTR is a barrier to sperm permeability and fertilization (24). More

specifically, the normal cyclical variations in water content of the cervical mucus are not observed in women with CF. Thus, decreased hydration and increased viscosity of the mucus during ovulation blocks the passage of sperm through the cervix (1,14,21). Moreover, sperm capacitation could be impaired due to a dysregulation of the uterine fluid and bicarbonate secretion(11). Although the anatomy of the reproductive tract is normal in most women (9,21), a relation between congenital absence of uterus and vagina (CAUV) and CF is possible since common CFTR mutations are two times more frequent among women with CAUV compared to the incidence in the general population (15). In addition, endocervical polyps and mucus plugs have been reported in patients with CF, and they have been associated with the use of hormonal contraception. (1)

Hypothalamic suppression is the main cause of menstrual irregularities in women with CF (18), and anovulation is more common among these patients in comparison to healthy women (19). It is suggested that defective CFTR in the hypothalamus and the pituitary gland could contribute to the abnormal GnRH pulsatile secretion (18). Moreover, anovulatory women have shown a decrease in estrogen with an increase in testosterone, which is comparable to the polycystic ovary syndrome findings. Interestingly, studies on mice have shown that CFTR regulates the activation of aromatase and the production of estrogen. Also, it has been reported that women with CF have lower levels of anti- Mullerian hormone, suggesting a decreased ovarian reserve (19). Moreover, according to a cohort study the LEP gene which encodes the hormone leptin has been found to be associated with the CFTR gene. Thus, Leptin is proposed to be a potential link between CFTR and ovarian function since this hormone has been related to HPG axis function (25). This study also found that specific CFTR mutation loci are associated with the development of oocytes and the embryo. However, validation of these findings is required due to the lack of sufficient number of patients.

Finally, pancreatic insufficiency has been associated with subfertility (12,23,24,26). According to a recent review, genotype, and cystic fibrosis due to diabetes (CFRD) are not related to subfertility, although CFRD is found to be associated with increased need for fertility assistance. Moreover, anovulatory women with CF have shown pathological insulin response during oral glucose tolerance test (26). According to a multicenter study, older age at first conception attempt (>31 years old) (18) has also been strongly associated with subfertility. Although malnutrition is considered a factor of subfertility, because of the amenorrhea and the anovulatory cycles (3), no association was found with BMI in this study (24). In 2016, a retrospective study found that lung function, disease exacerbations' rate and *Pseudomonas* colonization are not significant variables for fertility (23). A 2020 cohort study that collected data on pregnant women with CF during 1986-2018 confirmed that patients with cystic fibrosis related diabetes, as well as patients with chronic *pseudomonas aeruginosa* infection, have shown increased rates of fertility assistance, while fertility was not found to be associated with disease severity estimated by FEV1 (16).

Management of Fertility Problems

Subfertility of women with Cystic Fibrosis can be treated with Assisted Reproductive Technology (ART), which according to records has a success rate of 80-85% (Figure 1). The use of ART can decrease the negative effect that cervical obstruction has on fertility, as well as overcome any possible hormonal imbalances of the women with CF. Intrauterine insemination (IUI) after induction of ovulation with gonadotropins and in vitro fertilization (IVF) are both

used (16,19). Clomiphene citrate as well as gonadotropin injections can be administered to stimulate ovarian follicle development. IUI is minimally invasive and with this method the thick cervical mucus is bypassed efficiently (18). However, considering the importance of preimplantation genetic testing (PGT) in order to detect whether the partner is a CFTR mutation carrier, IVF is suggested to be more advantageous compared to IUI (19).

Fertility assistance of women with cystic fibrosis is not yet extensively studied, even though assisted reproductive technology carries risks that are of great importance, considering the compromised health of these women (11,18). For example, multiple pregnancy and ovarian hyperstimulation syndrome are risks that should be considered when ART is used. Moreover, ART has been associated with a higher risk of neonatal adverse outcomes. Intracytoplasmic sperm injection is related to an increased risk of genetic malformations. Another disadvantage of ART is that some procedures are expensive. The high cost of IVF (18) can be a discouraging factor for women with CF who wish to become pregnant (14).

Genetic counselors have an important role in decision making and in educating women on the methods of assisted reproduction (22). Furthermore, genetic screening of partner of a woman with cystic fibrosis is important, in order to detect possible mutations in CFTR gene. However, there is a possibility that standard mutation panels which are used for the screening of the CFTR gene could fail to detect some of the existing mutations. For example, men with Congenital absence of the vas deferens, which is caused by mutations of the CFTR gene, do not show CF symptoms and are at a higher risk of their mutations to be undetectable.(27)

Spontaneous pregnancy achievement has been reported as a result of initiation of ELX-TEZ-IVA treatment in women with a history of infertility, indicating that CFTR has an important role in fertility. According to O'Connor et al., 8 weeks (range, 1-17 weeks) after the initiation of ELX-TEZ-IVA treatment, 14 spontaneous pregnancies occurred among 200 women with CF. Four of the women that achieved pregnancy were previously considered infertile, and seven of them were not using optimal contraception and did not wish to conceive. (28)

CFTR modulators could increase the chance of pregnancy with many suggested mechanisms. These include the modulators' direct thinning effect on cervical mucus viscosity, the achievement of a more suitable cervical pH, the change of hormonal responses, the improved nutrition of patient and the better regulation of menstrual cycles (10,20). CFTR modulators could also increase fertility by adjusting the hypothalamic-pituitary-adrenal axis (12).

CFTR modulators are associated with improved nutritional status of women with CF, resulting in increased fertility. According to a report, between 12 infertile women, 7 achieved pregnancy 3.2 months (range 1–8.5) after initiating therapy with ivacaftor medication. Moreover, an increase in unplanned pregnancies has also been observed (21).

Considering effectiveness of contraception while using CFTR modulator therapy, it has been found that lumacaftor leads to induction of the CYP3A enzyme of the P450 pathway (12) . Co-administration of CYP3A inducers and oral contraceptives may decrease the effectiveness of contraceptives, due to the reduction of circulating estrogens. As a result, an increase of unplanned pregnancies is possible, underlying the importance of properly informing women

who are taking this type of medication. This interaction is not observed with drugs like Ivacaftor, Tezacaftor and Elexacaftor (12).

CONCLUSION

The life expectancy and overall health of people with CF is improving, such as the number of achieved pregnancies. The CF care team is responsible to recognize act appropriately, when issues regarding menstruation, fertility, sexual activity, contraception, pregnancy planning or prevention and menopause are present. The same team should organise multidisciplinary approach with multiple specialities in reproductive endocrinology, maternal-fetal medicine, and family planning to maximize the reproductive health of women with CF. We have much to learn about the optimal management strategies for our women with CF who choose to become parents. Future questions remain, including the impact of medications used by women with CF that have limited human data on risks to the fetus. Prospective studies are necessary to improve our knowledge and be able to offer the best options to our patients.

Disclosure

All authors don't have any financial relationship with the companies that may have a financial interest in the information contained in the manuscript.

No conflict of interest

Informed Consent

Informed Consent N/A

References

1. Edenborough FP. Respiratory diseases in pregnancy bullet 4: Women with cystic fibrosis and their potential for reproduction. *Thorax*. 2001 Aug 1;56(8):649–55.
2. Padoan RF, Quattrucci S, Amato A, Salvatore M, Salvatore D, Campagna G. Perinatal outcomes in women with cystic fibrosis: Data from the Italian Cystic Fibrosis Registry. *Acta Obstet Gynecol Scand*. 2021 Aug 14;100(8):1439–44.
3. Lyon A, Bilton D. Fertility issues in cystic fibrosis. *Paediatr Respir Rev*. 2002 Sep;3(3):236–40.
4. Kazmerski TM, Gmelin T, Slocum B, Borrero S, Miller E. Attitudes and Decision Making Related to Pregnancy Among Young Women with Cystic Fibrosis. *Matern Child Health J*. 2017 Apr 16;21(4):818–24.
5. Burden C, Ion R, Chung Y, Henry A, Downey DG, Trinder J. Current pregnancy outcomes in women with cystic fibrosis. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2012 Oct;164(2):142–5.
6. Tournier A, Murris M, Prevotat A, Fanton A, Bettiol C, Parinaud J. Fertility of women with cystic fibrosis: a French survey. *Reprod Biomed Online*. 2019 Sep;39(3):492–5.
7. Traxler SA, Chavez V, Hadjiliadis D, Shea JA, Mollen C, Schreiber CA. Fertility considerations and attitudes about family planning among women with cystic fibrosis. *Contraception*. 2019 Sep;100(3):228–33.
8. Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. *Journal of Cystic Fibrosis*. 2008 Jan;7:S2–32.
9. Gage LA. What Deficits in Sexual and Reproductive Health Knowledge Exist among Women with Cystic Fibrosis? A Systematic Review. *Health Soc Work*. 2012 Feb 1;37(1):29–36.

10. Leech MM, Stransky OM, Talabi MB, Borrero S, Roe AH, Kazmerski TM. Exploring the reproductive decision support needs and preferences of women with cystic fibrosis. *Contraception*. 2021 Jan;103(1):32–7.
11. Frayman KB, Sawyer SM. Sexual and reproductive health in cystic fibrosis: a life-course perspective. *Lancet Respir Med*. 2015 Jan;3(1):70–86.
12. Frayman KB, Chin M, Sawyer SM, Bell SC. Sexual and reproductive health in cystic fibrosis. *Curr Opin Pulm Med*. 2020 Nov;26(6):685–95.
13. Ladores S, Corcoran J, Campbell C, Bray L, Brown J, Woods B, et al. 230: State of fertility preservation counseling: Knowledge, experiences, and preferences of partners of women with cystic fibrosis. *Journal of Cystic Fibrosis*. 2021 Nov;20:S111–2.
14. Kazmerski TM, Prushinskaya O v., Hill K, Nelson E, Leonard J, Mogren K, et al. Sexual and Reproductive Health of Young Women With Cystic Fibrosis: A Concept Mapping Study. *Acad Pediatr*. 2019 Apr;19(3):307–14.
15. Sriramulu D, editor. *Cystic Fibrosis - Renewed Hopes Through Research*. InTech; 2012.
16. Cohen-Cymberknoh M, Gindi Reiss B, Reiter J, Lechtzin N, Melo J, Pérez G, et al. Baseline Cystic fibrosis disease severity has an adverse impact on pregnancy and infant outcomes, but does not impact disease progression. *Journal of Cystic Fibrosis*. 2021 May;20(3):388–94.
17. Thorpe-Beeston J, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis-single centre experience 1998-2011. *BJOG*. 2013 Feb;120(3):354–61.
18. Hughan KS, Daley T, Rayas MS, Kelly A, Roe A. Female reproductive health in cystic fibrosis. *Journal of Cystic Fibrosis*. 2019 Oct;18:S95–104.
19. Shteinberg M, Taylor-Cousar JL, Durieu I, Cohen-Cymberknoh M. Fertility and Pregnancy in Cystic Fibrosis. *Chest*. 2021 Dec;160(6):2051–60.
20. Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators – an international survey. *Journal of Cystic Fibrosis*. 2020 Jul;19(4):521–6.
21. Taylor-Cousar JL. CFTR Modulators: Impact on Fertility, Pregnancy, and Lactation in Women with Cystic Fibrosis. *J Clin Med*. 2020 Aug 21;9(9):2706.
22. Foil KE, Powers A, Raraigh KS, Wallis K, Southern KW, Salinas D. The increasing challenge of genetic counseling for cystic fibrosis. *Journal of Cystic Fibrosis*. 2019 Mar;18(2):167–74.
23. Shteinberg M, Lulu A ben, Blumenfeld Z, Gur M, Bentur L, Mussaffi H, et al. 223 Infertility among women with cystic fibrosis: prevalence and risk factors. *Journal of Cystic Fibrosis*. 2016 Jun;15:S108.
24. Shteinberg M, Lulu A ben, Downey DG, Blumenfeld Z, Rousset-Jablonski C, Perceval M, et al. Failure to conceive in women with CF is associated with pancreatic insufficiency and advancing age. *Journal of Cystic Fibrosis*. 2019 Jul;18(4):525–9.
25. VanWort TA, Lee JA, Karvir H, Whitehouse MC, Beim PY, Copperman AB. Female cystic fibrosis mutation carriers and assisted reproductive technology: does carrier status affect reproductive outcomes? *Fertil Steril*. 2014 Nov;102(5):1324–30.
26. Johannesson M, Landgren BM, Csemiczky G, Hjelte L, Gottlieb C. Female patients with cystic fibrosis suffer from reproductive endocrinological disorders despite good clinical status. *Human Reproduction*. 1998 Aug 1;13(8):2092–7.

27. Danziger KL. Improved detection of cystic fibrosis mutations in infertility patients with DNA sequence analysis. *Human Reproduction*. 2004 Jan 29;19(3):540–6.
28. O'Connor KE, Goodwin DL, NeSmith A, Garcia B, Mingora C, Ladores SL, et al. Elexacafator/tezacaftor/ivacaftor resolves subfertility in females with CF: A two center case series. *Journal of Cystic Fibrosis*. 2021 May;20(3):399–401.

FIGURE LEGEND

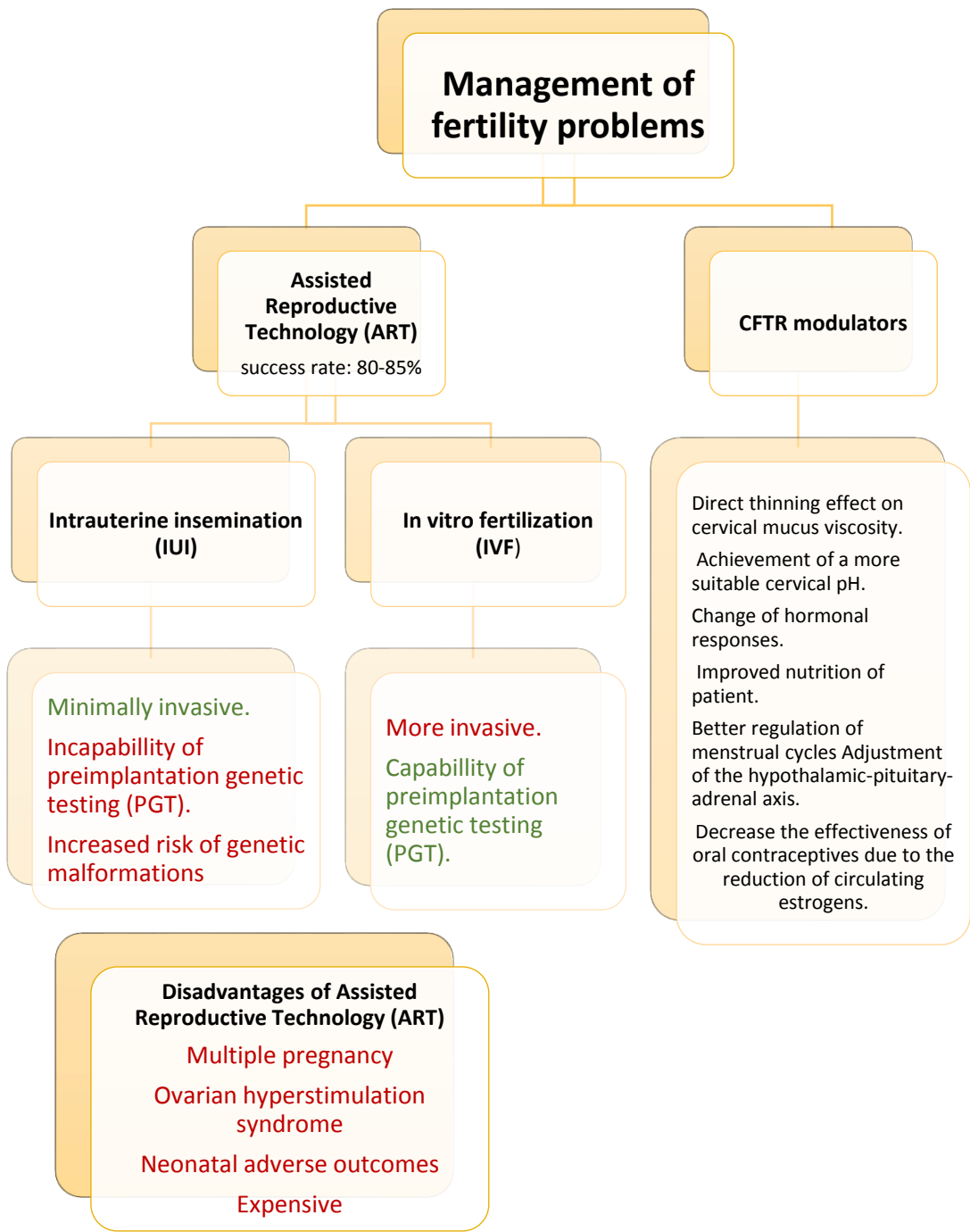


Figure 1. Fertility management

Table 1. What a woman with CF should pay attention to after pregnancy?

- Airway clearance and mobilization is a matter of greatest importance. Sometimes it may require oxygen supply, manual cough aid and ventilator assistance.
- Pain relief should not be neglected.
- Vitamin D supplements are very important during breastfeeding.
- The preservation of the weight and the nutritional status is vital. The use of a feeding bottle could be necessary for women to carry on with breastfeeding.
- An additional two liters of liquids is required in order women to stay hydrated.
- During lactation the evaluation of medicines is needed.