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Review

Pregnancy in cystic fibrosis: Review of the literature and expert recommendations

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ABSTRACT

Cystic fibrosis (CF) was historically a disease largely afflicting children. Due to therapeutic advancements, there are now more adults with CF than children. In the past decade, medications including Cystic Fibrosis Transmembrane conductance Regulator (CFTR) modulators became available that treat the underlying cause of CF and are dramatically improving lung function as well as quality and quantity of life for people with CF. As a result, more women with CF are becoming pregnant. We gathered a panel of experts in CF care, family planning, high risk obstetrics, nutrition, genetics and women with CF to review current literature on pregnancies and to provide care recommendations for this unique population.

1. Introduction

Cystic Fibrosis (CF) is an autosomal recessive life limiting illness caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Historically, few people survived to adulthood. With the advent of improved therapies and care models, the median predicted survival is now in the late fourth decade of life and is projected to continue to rise [1]. This progressive change in survival allows women with CF to consider important life choices, including the decision to reproduce. A recent survey found that almost 80% of young women with CF desire future children [2]. In addition, data from the United States CF Foundation Patient Registry (CFFPR) in 2019 shows a progressive increase in number of pregnancies over the past several years [1]. As highlighted in the following patient perspectives, there is limited evidence to guide the care of pregnant women with CF. In this review, we comprehensively summarize the literature and provide recommendations for pre-pregnancy, intrapartum, and postpartum care for women with CF.

From a mother with CF: "Family planning and navigating pregnancy while having CF is not a time to play a guessing game, but that is what a lot of my care decisions felt like when I was

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pregnant. Don't get me wrong, the CF and Ob/Gyn care teams supported me through both pregnancies and I appreciate all of their hard work. But without research and data, my clinicians were forced to make their best guess with limited evidence to guide my care. Complications arose when different specialists trying to coordinate care did not agree on a plan of action. There just isn't enough clear science to support one plan of care over another. Through trial and error the care teams were able to find which medications were safe, when and how to treat an exacerbation of a highly resistant *Pseudomonas*, what state of lung health was safest to start planning, and how to balance my care while caring for a newborn. These are all topics that were not as relevant before but especially in the age of highly effective modulator therapy, these topics are going to become a lot more important. Both patients and doctors desire a clear path to safely navigate family planning and pregnancy and I am happy these issues are being brought to the forefront."

From a woman with CF who had undergone a lung transplant: "I have received care at a CF center my entire life and my care team has never discussed family planning with me – neither options for becoming a parent nor options for pregnancy prevention. Family planning seems to be a luxury not afforded to the sickest patients. My pulmonary status declined throughout my 20 s and I had more and more frequent episodes of actue illness. Discussions with my care team focused on my immediate survival. Long term planning in my case meant maintaining eligibility for transplant.

I assumed that carrying a child was not an option because of my low lung function and now is not recommended because I am taking anti-rejection drugs post-transplant. I still wonder about becoming a parent through adoption or surrogacy and my partner and I would like to know our options so that we can plan for the future. We have so many questions, such as the cost of adoption and surrogacy, whether my eggs are viable for retrieval, the risks of caring for a newborn as an immunocompromised individual, and the impact my health and life expectancy would have on a child. I don't expect my CF team to have all the answers, but I do expect them to be able to broach the subject of parenting and to refer me to resources. All women with CF, regardless of their health status, deserve accurate information and adequate support to balance pregnancy and parenthood with our complex chronic condition."

2. Pre-pregnancy planning and considerations

2.1. Fertility

In women with CF, one report found the rate of infertility and subfertility to be 35% [3], significantly higher than the 5–15% described in the general population [4,5]. CFTR is highly expressed in women's reproductive organs, including the cervix and the endometrial endothelium [6]. For women with CF, the alteration in CFTR function results in several pathophysiological processes that potentially reduce fertility, including the production of abnormally viscous and pH imbalanced cervical mucus due to altered bicarbonate exchange that block sperm transport and limit sperm capacitation [7,8].

Newly available CTFR modulator therapies, oral drugs that correct the underlying CFTR defect at the protein level, are now widely available worldwide and include ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor (ETI). Of these, ivacaftor and ETI are considered highly effective modulator therapies (HEMT) because of their profound impact on lung function, quality of life and decreased hospitalizations [9–12]. Pregnancy rates have increased among women with CF since the advent of HEMT and nearly doubled in the G551D CF population after ivacaftor was made available [1,13,14]. While the mechanism of action of HEMT in improving CFTR function in the reproductive tract is not yet known, it is hypothesized that cervical mucus is less viscous and pH increased, thus improving conditions for capacitation. Additional proposed HEMT effects include improvements in lung function and nutritional status that optimize the health of women with CF, thus, facilitating easier conception [13,15]. We recommend that CF care teams consider the potential improved fertility in women with CF and counsel them on the possibility of unplanned pregnancies and contraceptive options if pregnancy is not desired.

For women with CF who are not able to naturally conceive, there are a number of different assisted reproductive technology options, but the ones most commonly used in women with CF are *in-vitro* fertilization (IVF) and intrauterine insemination (IUI) of sperm [16]. IVF allows sperm to fertilize the egg outside a woman's body in a culture dish. The embryo that is formed is implanted back into the uterus of the woman. Additional embryos, if any, can be frozen for later use. IVF offers the opportunity for preimplantation genetic testing, which may be desired by a patient with a CF carrier partner. IUI is the process of delivering sperm (or an embryo), past the thickened cervical mucus and into the uterus using a catheter to increase the chances of fertilization. IUI can be performed without having to take medications, but fertility specialists may offer ovulation-stimulating drugs before starting the procedure. IUI is associated with a risk of infection due to insertion of the catheter. In the case of IVF, the success rates for women in general vary between 20 and 40 percent and women may have to undergo multiple cycles of IVF before pregnancy is achieved. [17] Multiple pregnancies are common for those undergoing IVF. The success rates of IUI alone are lower than those of IVF (5 to 25 percent) [17]. Options for women to have children who are not able to become pregnant or whose health is not conducive to pregnancy include surrogacy (implanting embryo into a surrogate mother) or adoption. All of these options of parenthood should be discussed with women with CF so that they can make informed decisions.

2.2. Genetic counseling

An important aspect of pre-pregnancy planning for people with CF includes genetic testing. As CF is autosomal recessive in inheritance, any infant of a woman with CF will be an obligate carrier of one CFTR mutation. Carrier screening for reproductive partners should be offered preconception to refine the risk of having a child with CF [18]. As there are over 300 disease causing mutations identified in the CFTR gene [19], CFTR mutation carrier screening panels that test only for the twenty-five most common mutations can lead up to 30% of affected pregnancies being missed, particularly in non-Caucasian individuals [20]. Next-generation sequencing allows for more comprehensive CF carrier screening and is recommended for all partners of people with CF regardless of race or ethnicity [21]. If the reproductive partner is identified as a CF carrier, additional genetic counseling is recommended for discussion of reproductive options, including sperm or ovum donation, preimplantation genetic testing, and prenatal diagnostic testing [18].

2.3. Pre-pregnancy evaluation

Health status at the time of conception can serve as an important prognostic indicator of obstetric and neonatal outcomes [22–25] Specific aspects of maternal health that contribute to outcomes of pregnancy (in CF) include: pre-conception weight, pulmonary and cardiac function, pancreatic insufficiency, CF related diabetes control, and bacterial burden [23,24,26]. Thus, multi-organ pre-conception evaluation is advised.

Pre-conception consultation by a specialist in high risk obstetrics, Maternal-Fetal Medicine (MFM), in collaboration with the CF

team is ideal. Tailored counseling regarding prognosis in pregnancy should be offered and overt risks of a pregnancy identified. For example, although a rare complication of CF, pulmonary hypertension is widely accepted as an absolute contraindication to pregnancy, as recent data suggests a several-fold higher rate of death, severe maternal morbidity, and adverse pregnancy outcomes in these pregnancies [27,28].

Spirometry and, specifically, percent predicted forced expiratory volume in 1 s ($ppFEV_1$) is one of the primary markers of lung health in a person with CF. Low $ppFEV_1$ ($\leq$ 50%–60%) carries a higher risk of both maternal and neonatal adverse outcomes, including destabilization of health in the mother and premature delivery, delivery by caesarean section and adverse fetal outcomes such as low birthweight [22,24,29]. We generally do not advise women with low lung function to become pregnant but there have been successful pregnancies in this group [25]. In addition, women colonized with bacteria such as specific subgroups of *Burkholderia cepacia*, known to potentially result in rapid deterioration in lung function, have been reported to decline in health during pregnancy [30,31]. There are case reports of 4 women with *Burkholderia cepacia* that deteriorated in health during pregnancy, 3 out of 4 of these babies were delivered prematurely and 1 underwent termination due to fetal abnormalities [30,31]. Women colonized with *B. cepacia* should be counseled on the high risk scenario if they are considering pregnancy.

People with CF often have increased protein, fat, and sodium requirements due to malabsorption from pancreatic insufficiency, infection and inflammation. Better pulmonary function is closely associated with improved nutritional status [1,32]. Poor nutritional status, defined as an imbalance of energy and nutrient intake such that physiologic requirements are not met, is also a risk for poor outcomes including premature and low birth weight babies [31,33]. Importantly, a better pre-pregnancy BMI correlates with better health outcomes for women with CF and a BMI of at least 22 kg/m2 is recommended prior to pregnancy [34]. Historically, a weight gain of at least 11 kg during pregnancy was recommended for women with CF [35], however, more recently recommendations by the Institute of Medicine were defined based on pre-pregnancy BMI [36]. For a woman with a pre-pregnancy BMI of 18.5–24.9 kg/m^2, a weight gain of 11.5– 16.0 kg is recommended [36]. For a woman with a pre-pregnancy BMI less than 18.5 kg/m^2, a weight gain of 12.5–18.0 kg/m^2 is recommended [36]. Additional recommendations are available for overweight and obese individuals [36]. More aggressive nutritional intervention ranging from oral calorie supplementation to enteral or parenteral nutrition support should be considered in the absence of adequate weight gain [23,37]. Vitamin supplementation is often required and should be adjusted based on serum and plasma micronutrient levels with the goal of maintaining levels in the normal range [38]. Iron and folate supplementation is similar to that of women without CF though some literature supports high dose folate supplementation in CF particularly in those at high risk for deficiency [23]. Due to fat-soluble vitamin malabsorption in CF, CF-specific multivitamins contain vitamin A, largely as beta-carotene [39,40], which is water soluble [41] and not found to be associated with congenital defects. [42] Guidelines recommend vitamin A dosing of $<$ 10,000 IU per day [23]. It is recommended that vitamin A levels be monitored closely if giving doses higher than 10,000 IU per day as avoidance of this high-dosing is recommended in the non-CF population based on the associated increased risk of miscarriage and congenital malformations. Up to 30–50% of women in their reproductive ages have CF-related diabetes (CFRD) [1,43]. Hyperglycemia related to inadequate diabetic control can cause major fetal anomalies [44,45]. Pre-conception health assessment allows for attempts at optimization of lung function, nutritional status, vitamin levels and glycemic control to prevent maternal mortality or neonatal morbidity.

2.4. Effect of pregnancy on maternal health

With increased pregnancy rates in women with CF (**Fig. 1**) [1], the impact of pregnancy on the health of women in the modern era is important to evaluate. Researchers have investigated the impact of pregnancy on respiratory health focusing on lung function and pulmonary exacerbations. With one recent exception [46], studies overall demonstrate no significant difference in lung function decline between pregnant and non-pregnant women with CF when compared from baseline to follow-up visits [47–49]. A study of all pregnant CF women seen in the Toronto CF clinics over a 37-year period demonstrated that women had a 1.6% decline in $ppFEV_1$ per year, which is similar to what is observed in the total Toronto CF population [48]. In a French CF registry study, pregnant women were stratified by lung function severity and found to have no significant difference in $ppFEV_1$ decline over a four-year study period (the year before pregnancy until two years after pregnancy) [25]. Finally, a large study using the U.S. CF Foundation Patient Registry (CFFPR) showed no survival difference in women who experienced pregnancy versus those who did not [50]. Importantly, in this study, women who became pregnant had a higher baseline lung function than those that did not [50]. As women with lower basline lung function are able to conceive on HEMT, it will be important to determine whether pulmonary function and survival remain equivalent between pregnant and non-pregnant women with CF [50].

While other studies demonstrated no difference in pulmonary exacerbation rates between pregnant and non-pregnant CF women, data from the Epidemiologic Study of CF did show that pregnant women with CF received more intravenous (IV) and inhaled antibiotics in the 18 months before pregnancy and during pregnancy than non-pregnant women with CF [51]. Furthermore, pregnant women with CF had a 33% increase in outpatient visits compared to baseline (and 62% more frequent than non-pregnant women) as well as an increase in hospitalization rates. [51] As in the CF registry study by Goss et al., women who became pregnant had higher baseline lung function than those who did not become pregnant [50]. Given that the use of IV antibiotics did not increase during the same period, the authors believed pregnant women were being admitted more frequently for closer surveillance or for potential obstetric complications [47]. We, therefore, recommend that clinicians discuss the potential increase in clinic visits and antibiotics use that may occur during pregnancy as women are planning their pregnancies.

3. Recommendations and considerations once pregnant

3.1. Medication management

When considering the use of medications during pregnancy, the known and unknown risks of medications to the fetus must be weighed against the risk to the mother's health resulting from therapy discontinuation. Recent comprehensive reviews of medication considerations for pregnant women with CF are published [52–54]. See **Table 1** for considerations when prescribing the most commonly used chronic therapies in CF. Here we will discuss data in detail on two particular categories of medications used in the chronic management of people with CF: azithromycin and CFTR modulators.

Based on the positive pulmonary health impacts of the macrolide, azithromycin, in people with CF [55,56], its use is recommended for chronic daily or every other day therapy [57]. However, the safety of its use during pregnancy has been a subject of

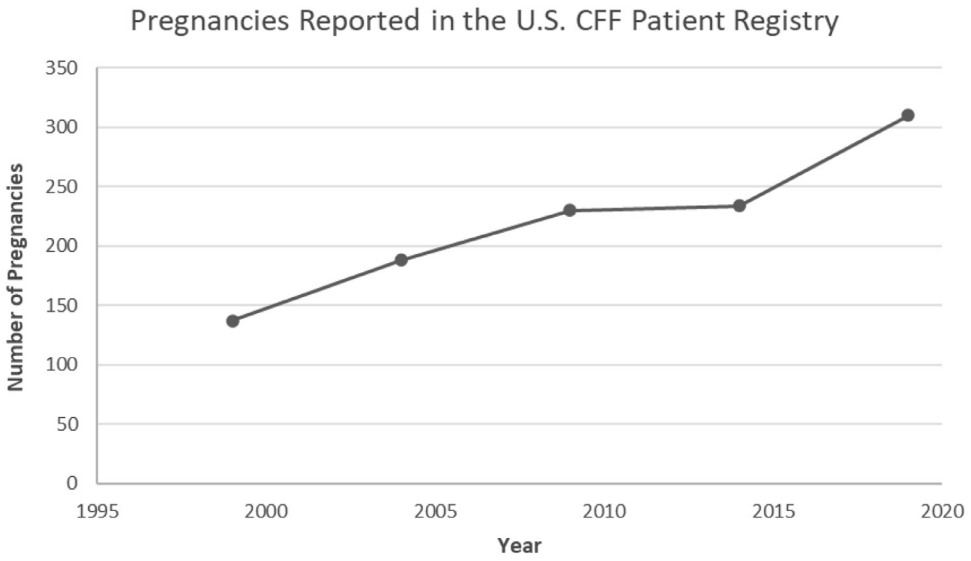

Fig. 1. Depicted is the number of pregnancies per year in women with CF in the U.S. CF Foundation patient registry from 1999 to 2019 [1].

Table 1
Most common therapies used in the chronic treatment of CF.

Medication	Route of Administration	Considerations	Use in Pregnancy	Use in Lactation
Inhaled mucolytics Dornase alpha Hypertonic saline	Inhaled	Limited to no systemic absorption	Yes	Yes
Inhaled antibiotics Tobramycin Aztreonam Colymycin Levofloxacin	Inhaled	Limited to no systemic absorption	Yes, if necessary for mother's health	Yes
Pancreatic enzymes	Oral	Benefits of appropriate nutrition outweigh risks	Yes	Yes
Fat soluble vitamin replacement (A, D, E, K)	Oral	Monitor vitamin A levels if giving doses higher than 25,000 IU per day	Yes	Yes
CFTR modulators (ivacaftor, tezacaftor/ivacaftor, lumacaftor/ ivacaftor, elexacaftor/tezacaftor/ivacaftor)	Oral	No harm observed of individual components given in animal models, but human data is limited	Yes, if necessary for mother's health	Yes, if necessary for mother's health
Chronic azithromycin	Oral	Multiple epidemiologic studies show very low risk of congenital anomalies in pregnant women with short term use.	Yes, if necessary for mother's health	Yes

recurrent study and discussion [58–62]. Data suggest low risk in pregnancy, leading the European Respiratory Society/Thoracic Society of New Zealand statement to rate the drug as "probably safe" in pregnancy. Because of the prolonged presence of azithromycin in white blood cells [63,64], the majority of obstetricians continue to prescribe azithromycin for acute infections. We suggest that women with CF who consider continuing use of chronic azithromycin during pregnancy be counseled regarding the very small potential risks to the fetus. At the same time, it is important to note that risk to the mother if azithromycin is discontinued is unknown [65].

Due to the global and profound impacts of CFTR modulators on the health of the mother, including improved lung function and weight and decreased pulmonary exacerbations [10,11,66,67], these medications may indirectly benefit the infant during pregancy. In addition, there are case series reporting marked health

decline and even death in both non-pregnant [68,69] and pregnant women [70–74] who abruptly discontinued CFTR modulators. With little long-term data, the decision to continue or stop modulators is complicated.

Animal reproduction models did not demonstrate fetal harm at normal human doses of CFTR modulators [75–78] Furthermore, data in pregnant women, limited to case reports and case series, do not suggest harm [70–72,79–81]. Recently, Nash and colleagues reported maternal and infant outcome data from 61 live births in women who were on CFTR modulators for all or part of their pregnancy [73]. The miscarriage rate for women with CF on modulator therapy was 4.7% (lower than that reported in the general population of pregnant women). Critically, cessation of modulator therapy resulted in clinical decline in 9 women, prompting resumption of CFTR modulator therapy during pregnancy. These data were collected in an era prior to ETI. Since the release of ETI in the United States, Taylor-Cousar and Jain collected additional data and found that of 45 mothers exposed to ETI during pregnancy, complications in two mothers and in three infants (2 born to mothers with poorly controlled diabetes) were reported by submitting physicians as possibly or suspected to be related to ETI exposure. Two of the infants had severe congenital malformations reported. However, in one instance the mother had the known risk factor for congenital malformations of poorly controlled diabetes and the other mother had two previous first trimester miscarriages. Thus the providers reported both instances of congenital malformations as unrelated to ETI [82]. In combination, the limited available clinical data are reassuring for the overall safety of use of CFTR modulators during preganancy, however, larger and ideally prospective studies are needed to further understand the safety of CFTR modulator use in pregnancy.

3.2. Diabetes management in pregnant women with cf

Diabetes is common in pregnancies complicated by CF. Of those without CFRD, 14–20% will receive a diagnosis of gestational diabetes (GDM) while pregnant [33,48,83]. The likelihood of either CFRD or GDM is even higher for patients with severe pancreatic insufficiency [84]. Complications of hyperglycemia in pregnancy include macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia, and increased cesarean delivery rate. The management of diabetes shares similar goals as for women without CF and is based on risk mitigation of adverse pregnancy outcomes related to hyperglycemia. Glucose monitoring in pregnancy is typically assessed at least four times daily, including fasting and 1- or 2 h postprandial after each meal or with a continuous glucose monitor. Commonly used targets for adequate glycemic control include: $<$ 95 mg/dL fasting and $<$ 140 or 120 mg/dL for 1- and 2 h postprandial values, respectively [85]. Postprandial and fasting targets are evidence-based in pregnancy and are associated with improved glycemic control and lower associated maternal and fetal complications [85–88].

Insulin is considered a first-line agent for glycemic control in pregnancy due to its favorable safety profile, lack of transport across the placenta, and ability to be continuously titrated [89,90]. Insulin is dosed to achieve target fasting and post-prandial glucose values with a combination of intermediate or long-acting insulin for basal needs and short-acting insulin for meal-time coverage. Women with CF may have higher insulin requirements due to their competing need for adequate nutritional intake. Oral alternatives including metformin and glyburide are commonly used for patients unwilling or unable to adhere to insulin therapy; however, these agents have less evidence supporting their use in GDM and are therefore more controversial. Additionally, failure to achieve adequate glycemic control may occur in almost 50% of patients who start with metformin [91]. While the Society for Maternal-Fetal Medicine endorses metformin as a viable first-line alternative to insulin, there is no data to support the use of metformin in people with CF in general and is not advised in pregnant women with CF [92]. The American College of Obstetricians and Gynecologists and the American Diabetes Association also maintains that current evidence supports the use of oral hypoglycemics only as second-line options due to limited data, lesser efficacy, and potential for long-term effects on offspring but again are not supported for use in CF or GDM in CF [88,90,93,94].

3.3. Timing and mode of delivery

Physiologic changes in all pregnancies begin early in the first trimester, increase steadily into the third trimester, and culminate at the time of labor and delivery. At delivery, maternal cardiac output increases up to 40% due to both increased intravascular volume and the effects of catecholamine release due to the pain and stress of labor [95,96]. Careful hemodynamic monitoring is essential, especially for patients with cardiac and pulmonary disease, as there is an increased circulating volume of about 300–500 mL due to uterine contractions, and also due to autotransfusion with placental separation. The increased cardiac output of about 50% poses an acute risk of heart failure in women with pulmonary hypertension or cor pulmonale.

Consultation prior to pregnancy with obstetricians and anesthesia allows for multidisciplinary delivery planning. While cesarean delivery should be reserved for usual obstetric indications, women with worse pulmonary function appear to have a higher incidence of cesarean delivery [22]. Early establishment of regional analgesia has several benefits for women with CF, including decreased catecholamine release, increased pain control and ability to rest, and potential avoidance of need for general anesthesia and intubation in the case that emergent cesarean delivery becomes necessary.

Patel and colleagues used a national database to examine outcomes of pregnancies in women with CF (N = 1119) [97]. At delivery, women with CF were more likely to have cardiac conduction disorders, diabetes, asthma, thrombophilia and anemia, and have a longer length of stay following vaginal delivery than that of women without CF. Furthermore, although the occurrence of deaths and need for mechanical ventilation did not occur frequently, they were much more likely to occur in women with CF than in women without CF.

For all women, and especially those with CF, early mobilization in the immediate postpartum period is paramount to reduce risks of thromboembolism, infectious morbidity, and deconditioning. Early chest physiotherapy is recommended, as is continued attention to medication use with possible resumption of medications that may have been paused due to pregnancy, depending on compatibility with lactation.

3.4. Infant outcomes in pregnant women with cf

Most large CF patient registries unfortunately do not collect detailed information on delivery and infant outcomes. [1] Jelin et al. examined maternal and perinatal outcomes for women with CF compared to those in the general population in the state of California [98]. Of over 2 million reported singleton pregnancies $\geq$20 weeks, 77 were complicated by maternal CF and infants born to these women had higher rates of jaundice, were more likely to be born via Cesarean-section and more likely to be delivered at $<$37 weeks. Additionally, infants of women with CF had more congenital anomalies (14.3%), particularly cardiac anomalies (3.9%) [98]. Neonatal and infant deaths were not more likely for women with CF.

More recently, Ashcroft and colleagues utilized the UK Obstetric Surveillance System to explore obstetric and neonatal outcomes

in women with CF between 2015 and 2017 [29]. Amongst 71 pregnancies in women with CF, those with a ppFEV$_1$ <60% had a higher chance of delivering premature, lower birth weight babies. As the health of people with CF has improved, a re-evaluation of maternal and infant outcomes in CF is needed to better understand the incidence and prevalence of complications

4. Considerations after delivery

4.1. Postpartum clinic visits

The U.S. CFF and European CF Society recommend individuals with CF be evaluated by their CF care teams quarterly for routine care and management. In 2018, based on data from the U.S. CFFPR, the average number of clinic visits per year for people with CF in the United States was 4.3 [99] with pregnant women averaging 1.5 visits to CF clinic. In the year following pregnancy, the average number of clinic visits was 1.1. These data suggest that it is difficult to maintain the recommended number of clinical visits while caring for a new baby. However, because the first year is commonly a time when the new parent with CF may be at highest risk for health decline [46], CF care teams should consider alternative approaches to ensuring health stability. Long-term postpartum care should be multidisciplinary and coordinated to optimize access and compliance with visits by scheduling multiple in person appointments in a single day or by utilizing telemedicine. With increasing numbers of successful pregnancies in women with CF, attention should now be directed to the postpartum course and care of these women with development of specific recommendations.

4.2. Lactation

Two key concerns of women when considering lactation are nutritional expenditure and use of medications. Lactation does require significant caloric expenditure and restriction of energy/calorie intake is discouraged [23,100]. Weight loss postpartum appears to be rapid in women with CF with some returning to their pre-pregnancy weight within the first 6 weeks postpartum [37] and others not returning to their pre-pregnancy weight by 2 years postpartum. [101] To maintain adequate nutritional status, postpartum women need to consume an extra 500 kcal/day and women with CF may require even more calories per day [102].

As with safety of medication use in pregnancy, recent and comprehensive reviews and recommendations of medications frequently used in lactating women with CF are published [53,54]. The most commonly used CF-related medications are considered safe to use during lactation, although extensive data are lacking (**Table 1**).

Data related to CFTR modulators and lactation remain extremely limited. Based on one case report, both ivacaftor and lumacaftor are excreted in breastmilk at subtherapeutic levels [71]. Due to the transient elevation of bilirubin and liver enzymes in this single case report, infant monitoring of these measures during breastfeeding may be considered [103]. In the survey conducted by Nash and colleagues on women with CF who continued ivacaftor, lumacaftor/ivacaftor, or tezacaftor/ivacaftor, no modulator-related complications were reported in infants exposed *in utero* and/or during lactation ($n = 27$). A recently published survey study by Taylor-Cousar and Jain similarly found no adverse effects of ETI exposure during breastfeeding of 26 infants although only 2 infants had formal cataract evaluation [82]. Overall, CFTR modulators are considered "probably safe" during lactation according to expert opinion, and the decision to use these medications while breastfeeding should be an individualized decision [53].

4.3. Parenthood

Many women with CF have greater concerns about being a parent rather than the process of becoming a parent through pregnancy or other means [2]. Common challenges include balancing the roles of parent and patient and the impact of parental health decline and early mortality on children. Parents with CF have described "being a parent on a compressed timeline" [104]. A recent systematic review found that, despite potential negative impacts on health and treatment adherence, people with CF report an overall positive outlook on parenting [105]. Unfortunately, data are very limited on the longitudinal health impact of parenthood, but retrospective and prospective studies are being designed.

4.4. Post-partum contraception

The postpartum period is an important time to consider contraceptive options in order to promote birth spacing, which improves both maternal and infant outcomes [106]. Combined hormonal contraception may be initiated at 3–6 weeks after delivery, depending on maternal comorbidities and delivery risk factors. In general, all contraceptive methods appear to be safe and effective for women with CF, though studies are limited by their small size [107]. As always, specific comorbidities must be considered. The depot medroxyprogesterone injection may negatively impact bone mineral density and therefore may not be optimal long term for women with CF with osteopenia or osteoporosis. [108,109] Similarly, presence of permanent venous access catheters, pancreatic insufficiency, CF-related liver disease, and use of certain medications may modify the choice of contraception for women with CF [110]. Among the available CFTR modulators, lumacaftor/ivacaftor reduces the effectiveness of hormonal contraception, while ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor do not [75–78].

5. Considerations for women with CF after lung transplantation

There are some unique challenges to consider in women with CF who have undergone lung transplantion such as maternal rejection of the transplanted lung (graft rejection) and infant complications secondary to status of maternal health or from immunosuppressive medications [23,30,111]. Maternal and fetal complications associated with pregnancy after a lung transplantation are unfortunately high. This issue was reported in a registry analysis in 2012 using data from the National Transplantation Pregnancy Registry [112]. Investigators found that in 30 pregnancies (12 of whom had CF), more than half of all women had live births, with few associated life-threatening complications and no reports of permanent disability in the infants [112]. However, the incidence of preterm birth was 60% and there were eleven infant complications and two neonatal deaths [112]. There was a higher rate of rejection during pregnancy in the women with CF (25% in CF vs. 11% in others) and there was a lower rate of spontaneous abortion in women with CF (25% in CF vs. 33% in others) [112]. Mean gestational age was similar but mean birth weight was lower in CF (1980 g in CF vs. 2349 g in others) [112]. From a study using the Transplant Pregnancy Registry International, 7% of 51 post transplant pregnancies resulted in graft loss within 2 years of pregnancy [113]. This complication is an important factor when considering pregnancy and is theorized to be due to the transplant recipient's immune system attacking the transplant organ. This immune phenomenon may occur spontaneously or due to providers and recipients decreasing immunosuppressive medications to protect the fetus or rarely due to antibody mediated rejection from human leukocyte antigen (HLA) sensitization [114]. For this reason, some lung transplant centers

Table 2
Practical checklist when caring for a pregnant woman or woman considering pregnancy with CF.

Pre-Pregnancy:
☐ Optimize lung function (ideally ppFEV1 > 60%) [29]
☐ Optimize BMI (ideally ≥22.0 kg/m^2) [36]
☐ If diabetic status is unknown, assess with an oral glucose tolerance test
☐ For those with diabetes, optimize glucose control for those with diabetes (ideally Hb A1C < 6.5%) [88]; consider continuous glucose monitoring device if not already in place
☐ Recommend genetic counseling with next-generation sequencing testing for partner
☐ Start prenatal vitamins (400 ug folic acid)
☐ Check iron, vitamin A, and other fat soluble vitamin levels and supplement as needed
☐ Discuss the impact of medications with specific attention to CFTR modulators [13], azithromycin [65] and inhaled tobramycin
☐ Refer woman to Obstetrician and ideally Maternal Fetal Medicine specialists
☐ Screen for anxiety (GAD-7) and depression (PHQ-9)
During Pregnancy:
(all management in collaboration with CF, Obstetrics/Maternal Fetal Medicine and Endocrinology teams)
☐ Maintain at least quarterly visits with CF team – monitor lung function and BMI
☐ Counsel and manage dyspnea
☐ Encourage exercise and activity
☐ Manage nausea – encourage hydration, consider antiemetics
☐ Manage reflux – offer appropriate diet and medication strategies
☐ Minimize constipation – encourage hydration, consider polyethylene glycol 3350
☐ Monitor weight - goal weight gain during pregnancy based on pre-pregnancy BMI [23,36]
☐ BMI <18.5 kg/m^2: weight gain of 12.5–18 kg
☐ BMI of 18.5 - 24.9 kg/m^2: weight gain of 11.5 – 16.0 kg
☐ BMI of 25.0 – 29.9 kg/m^2: weight gain of 7.0 - 11.5 kg
☐ Oral glucose tolerance test (at 12–16 weeks and 24–28 weeks) [23]
☐ Monitor fetal growth and well-being
☐ Monitor mental/emotional health
After Delivery:
☐ Recommend 1 month follow up in CF clinic and at least quarterly visits thereafter (potentially more frequent if breast feeding)
☐ Follow and manage PFTs and BMI
☐ Obstetrician follow up at 3–6 weeks with initiation of contraception
☐ Screen for post-partum depression
☐ Consider recommending infant LFT monitoring and infant cataract evaluation in those infants exposed to modulators in utero or during breastfeeding

ppFEV1 – percent predicted forced expiratory volume in 1 s, BMI – body mass index, HbA1C – hemoglobin A1C.
[1]PFTs – pulmonary function testing.
[2]LFT – liver function tests.

request that recipients avoid pregnancy all together, while others recommend waiting at least two years after transplantation to have the opportunity to safely achieve the lowest possible doses of immunosuppressive medicines prior to pregnancy.

Caution is also advised with immunosuppressive medication use during pregnancy. First, therapies such as cyclosporine and tacrolimus require frequent monitoring. As maternal weight changes, dose adjustments may be needed. Certain immunosuppressive agents should be avoided such as mycophenolate mofetil, which has known teratogenic effects [115]. Other immunosuppressant medications have limited information for guidance such as prednisone, azathioprine and calcineurin inhibitors. Breast feeding is generally not advised in a lung transplant recipient as many immunosuppressant medications pass through breast milk and may be harmful to the infant. Pregnancies are being followed in the National Transplant Pregnancy Registry long-term. Thus far, nine of the 36 recipients died and two reported reduced function [113]. Overall, successful pregnancies are possible after lung transplantation, but this option should be considered with extreme caution as these are high-risk pregnancies with associated risks for graft rejection, prematurity, and low birthweight infants. As such, some transplant centers advise against any women post lung transplant getting pregnant. An open discussion between care teams and transplant recipient is needed to discuss the risks and benefits surrounding pregnancy, and ideally would occur when a woman is considering at which transplant center she will undergo evaluation if she feels strongly about pregnancy.

6. Conclusions

The life expectancy and overall health of people with CF is improving, resulting in an increased number of women experiencing pregnancy. It is paramount for CF care teams and high risk obstetrical teams to collaborate in care. We have much to learn about the optimal management strategies for our women with CF who choose to become parents, but here provide a general summary from experts in the field (**Table 2**). Future questions remain, including the impact of medications used by women with CF that have limited human data on risks to the fetus. To further guide the community, a large multicenter observational study, called Maternal and Fetal Outcomes in the Era of CFTR modulators (MAYFLOWERS, NCT04828382), is funded by the U.S. CFF, and will begin in 2021 with the goal of prospectively collectin granular data about pregnancy and infant outcomes.

Declaration of Competing Interest

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CRediT authorship contribution statement

Raksha Jain: Conceptualization, Visualization, Writing – review & editing. **Traci M. Kazmerski:** Conceptualization, Visualization, Writing – review & editing, Writing – original draft. **Lisa C. Zuckerwise:** Writing – original draft, Writing – review & editing. **Natalie E. West:** Conceptualization, Visualization, Writing – review & editing, Writing – original draft. **Kristina Montemayor:** Writing – original draft, Writing – review & editing. **Moira L. Aitken:** Writing – original draft, Writing – review & editing. **Edith Cheng:** Writing – original draft, Writing – review & editing. **Andrea H. Roe:** Writing – original draft, Writing – review & editing. **Alexandra**

Wilson: Writing – original draft, Writing – review & editing. **Caitlin Mann:** Writing – original draft, Writing – review & editing. **Sigrid Ladores:** Writing – original draft, Writing – review & editing. **Jacqui Sjoberg:** Writing – original draft, Writing – review & editing. **Jennifer L. Taylor-Cousar:** Conceptualization, Visualization, Writing – review & editing, Writing – original draft.

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Supplementary materials

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