Pregnancy in Cystic Fibrosis: Review of the Literature and Expert Recommendations

[a]Jain Raksha, [b]Kazmerski Traci M, [c]Zuckerwise Lisa C, [d]West Natalie E, [e]Montemayor Kristina, [f]Aitken Moira L, [g]Cheng Edith, [h]Roe Andrea H, [i]Wilson Alexandra, [j]Mann Caitlin, [k]Ladores Sigrid, [l]Jacqui Sjoberg, [m]Taylor-Cousar Jennifer

[a] Raksha Jain, MD, MSc (Corresponding author)
Department of Medicine
Associate Professor of Medicine, University of Texas Southwestern
5323 Harry Hines Blvd., Dallas TX 75390-8558
raksha.jain@utsouthwestern.edu
Phone: 214-648-2546

[b] Traci M. Kazmerski, MD, MS
Department of Pediatrics
Assistant Professor, University of Pittsburgh School of Medicine
120 Lytton Ave. Suite M060 University Center, Pittsburgh, PA 15213
traci.kazmerski@chp.edu
Phone: 412-692-5630

[c] Lisa C. Zuckerwise, MD
Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine
Assistant Professor of Obstetrics and Gynecology, Vanderbilt University Medical Center
1161 21st Avenue South, B-1100 MCN, Nashville, TN 37232
lisa.zuckerwise@vumc.org
Phone: 615-343-6275

[d] Natalie West
Department of Medicine
Assistant Professor, Johns Hopkins University
1830 E. Monument St. 5th Floor, Baltimore, MD 21205
Nwest5@jhmi.edu
Phone: 410-502-7044

[e] Kristina Montemayor, MD, MHS
Department of Medicine
Instructor, Johns Hopkins University
1830 E. Monument St. 5th Floor
Baltimore, MD 21205
kmontem1@jhmi.edu
Phone: 410-502-7044

[f] Moira L. Aitken, MD, FRCP
Department of Medicine
Professor, University of Washington

1959 NE Pacific Street - Rm BB 1361, Seattle WA 98195-6522
moira@u.washington.edu
Phone: 206-685-8434

[g] Edith Cheng, MD
Professor and Chief of Service, Obstetrics
Division Chief, Maternal Fetal Medicine
Maternal Fetal Medicine
and Medical Genetics
University of Washington
chengels@uw.edu
Phone: 206-543-3729

[h] Andrea H. Roe, MD, MPH
Department of Obstetrics and Gynecology
Assistant Professor, University of Pennsylvania Perelman School of Medicine
3400 Spruce Street, 1000 Courtyard
Philadelphia, PA 19106
andrea.roe@pennmedicine.upenn.edu
Phone: 267-254-0225

[i] Alexandra Wilson, MS, RDN, CDE
Department of Medicine
Manager, Cystic Fibrosis Clinical Research, National Jewish Health
1400 Jackson Street, K333b, Denver, CO 80206
wilsona@njhealth.org
Phone: 303-270-2517

[j] Caitlin Mann, MGC, CGC
Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine
Assistant Director of Obstetrical Genetic Counseling
Senior Associate in Obstetrics and Gynecology, Vanderbilt University Medical Center
1161 21st Avenue South, B-1100 MCN, Nashville, TN 37232
caitlin.mann@vumc.org
Phone: 615-343-6275

[k] Sigrid Ladores, PhD, RN, PNP, CNE, FAAN
School of Nursing
The University of Alabama at Birmingham, NB 470L
1720 2nd Avenue South, Birmingham, AL 35294-1210
sladores@uab.edu
Phone: 205.934.6835

[l] Jacqui Sjoberg
Adult with Cystic Fibrosis
237 Russell St.
Oceanside, CA 92058
Jacquisjoberg@gmail.com

[n] Jennifer L. Taylor-Cousar, MD, MSCS
Departments of Medicine and Pediatrics

Professor, National Jewish Health
1400 Jackson Street; J318
Denver, CO 80206
Taylor-CousarJ@NJHealth.org
Phone: 303-270-2764

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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 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 having babies. 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.

Key words: Cystic Fibrosis

Introduction:

Cystic Fibrosis (CF) is an autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR codes for a chloride channel which regulates ion exchange, located on the epithelial cell surface of several organs. 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 this review, we include patient perspectives, 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 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 specialtists trying to coordinate care did not agree on a plan of action. There just isn't enough clear science to back a 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 *Psuedomonas*, 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.”

Pre-pregnancy planning and considerations

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 in the U.S. and include ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor. Of these, ivacaftor and the triple combination elexacaftor/tezacaftor/ivacaftor are considered highly effective modulator therapies (HEMT) because of their profound impact on lung function, quality of life and decreased hospitalizations.[9-11] Pregnancy rates have markedly increased among women with CF on HEMT.[12] 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.[12,13]

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 to refine the risk of having a child with CF, either in preconception or early pregnancy.[14] As there are over 2000 mutations identified in the CFTR gene,[15] 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.[16] Next-generation sequencing allows for more comprehensive CF carrier screening.[17] Additional genetic counseling is recommended if the reproductive partner is identified as a CF carrier for discussion of reproductive options, including sperm or ovum donation, preimplantation genetic testing, and prenatal diagnostic testing.[14]

Pre-pregnancy Evaluation:

Health status at the time of conception is an important prognosticator of obstetric and neonatal outcomes.[18] 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. Thus, multi-organ pre-conception evaluation is advised.

Pre-conception consultation by a specialist in 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.[19,20]

Spirometry and, specifically, percent predicted forced expiratory volume in 1 second ($ppFEV_1$) is one of the primary markers of lung health in a person with CF. Low $ppFEV_1$ (≤ 50%-60%) carries a higher risk of both maternal and neonatal adverse outcomes.[21] Patients with CF often have increased protein, fat, and sodium requirements due to malabsobtion from pancreatic insufficiency, infection and inflammation. Better pulmonary function is closely

associated with improved nutritional status.[1,22] 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. Weight gain of at least 11 kg during pregnancy is recommended for women with CF as opposed to 12.7 to 15.9 kg in women without CF.[23,24] More aggressive nutrition intervention ranging from oral calorie supplementation to enteral or parenteral nutrition support should be considered in the absence of adequate weight gain.[23,25] 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.[26] Iron and folate supplementation is similar to that of women without CF.[23] Due to fat-soluble vitamin malabsorption in CF, CF-specific multivitamins contain vitamin A, largely as beta-carotene,[27,28] which is water soluble[29] and not found to be associated with congenital defects.[30] Up to 50% of women in their reproductive ages have CF-related diabetes (CFRD).[31] Hyperglycemia related to inadequate diabetic control can cause major fetal anomalies.[32,33] 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.

Maternal outcomes in pregnancy:

With increased pregnancy rates in women with CF (Figure 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,[34] 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.[35-37] 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% predicted decline in ppFEV$_1$ per year, which is similar to what is observed in the total Toronto CF population.[36] 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).[38] 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.[39]

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 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.[40] 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. 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.[35]

Recommendations and considerations once pregnant

Medication Management:

When considering the use of medications during pregnancy, the known and unknown risks of the medication for the fetus must be weighed against the risk to the woman's health resulting from therapy discontinuation. Recent comprehensive reviews of medication considerations for pregnant women with CF are published.[41-43] See **Table 1** for considerations when prescribing the most commonly used chronic therapies in CF. Here we will discuss data on two particular categories of medications used in the chronic management of people with CF: chronic azithromycin and CFTR modulators.

Based on the positive pulmonary health impacts of the macrolide, azithromycin in people with CF,[44,45] its use is recommended for chronic daily or every other day therapy.[46] However, the

safety of its use during pregnancy has been a subject of recurrent study and discussion.[47-51] 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,[52,53] 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 with unknown risk to the mother if azithromycin is discontinued.[54]

The global and profound impacts of CFTR modulators on the health of the mother, including improved lung function and weight, and decreased pulmonary exacerbations,[10,11,55,56] these medicaitons may indirectly benefit the infant during pregancy. In additiion, there are case series reporting marked health decline and even death in people who abruptly discontinued CFTR modulators.[57,58] 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.[59-62] Furthermore, data in pregnant women, limited to case reports and case series, do not suggest harm.[63-68] 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.[69] 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. In combination, the limted available clincal data are reassuring for the safety of use of CFTR modulators during preganancy, however, larger and ideally prospective studies are needed.

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.[36,70,71] The likelihood of both CFRD and GDM is even higher for patients with severe pancreatic insufficiency.[72] 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-hour postprandial after each meal or with a continuous glucose monitor. Commonly used targets for adequate glycemic control include: < 95mg/dL fasting and < 140 or 120mg/dL for 1- and 2-hour postprandial values, respectively.[73] Postprandial and fasting values are evidence-based for use in pregnancy and are associated with improved glycemic control and lower associated maternal and fetal complications.[73-76]

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.[77,78] Insulin dosing targets the fasting and post-prandial values with a combination of intermediate or long-acting insulin for basal rate and short-acting for meal-time dosing. 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.[79] While the Society for Maternal-Fetal Medicine endorses metformin as a viable first-line alternative to insulin, other groups (American College of Obstetricians and Gynecologists and the American Diabetes Association) maintain 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.[76,78,80]

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.[81,82] Careful hemodynamic monitoring is essential, especially for patients with cardiac and pulmonary disease, as there is an increased circulating volume of about 300-500mL 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 anethesia 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.[18] 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).[83] 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 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 patients with CF than in patients 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.

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.[84] Of over 2 million reported singleton pregnancies ≥ 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 c-section and more likely to be delivered at <37 weeks. Additionally, infants of women with CF had more congenital anomalies, particularly cardiac anomalies. 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 2015-2017.[21] Amongst 71 pregnancies in women with CF, those with ppFEV$_1$ <60% had a higher chance of delivering premature, smaller babies.

<u>Considerations after delivery</u>

Postpartum clinic visits:

The CF Foundation (CFF) recommends individuals be evaluated by their CF care teams quarterly for routine care and management. In 2018 the average number of clinic visits per year for people with CF was 4.3.[85] with pregnant women averaging 1.45 visits to CF clinic. In the year

following pregnancy, the average number of clinic visits was 1.1 (**Figure 2**). 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 a time when the new parent with CF may be at highest risk for health decline,[34] CF care teams should consider alternative approaches to ensuring health care. 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.

Lactation:

Two key concerns of women when considering lactation are nutritional expenditure and use of medications. Lactation does require an estimated 500 kcal/day, and restriction of energy/ calorie intake is discouraged.[23,86] 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[25] and others not returning to their pre-pregnancy weight by 2 years postpartum.[87] To maintain adequate nutritional status, the postpartum woman with CF may need to consume at least 500 kcal/day.[88]

As with safety of medication use in pregnancy, recent and comprehensive review and recommendations of medications frequently used in lactating women with CF are published.[42,43] 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.[63] 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.[89] 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). No clinical studies of the use of tezacaftor or elexacaftor during lactation currently exist. 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.[42] For women who have undergone a lung transplant for end stage lung disease from CF, immunosuppression with cyclosporine (which has the most supporting clinical data across multiple medical conditions) and tacrolimus (which has low excretion into breastmilk) may be compatible with breastfeeding, but no lactation data exist for mycophenolate.

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".[90] 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.[91] Unfortunately, data are lacking on the longitudinal health impact of parenthood.

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.[92] 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.[93] As always,

specific comorbidities must be considered. The depot medroxyprogesterone injection may negatively impact bone mineral density and therefore may not be optimal for women with CF with osteopenia or osteoporosis.[94,95] 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.[96]

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, obstetricians, and MFM teams to collaborate in care. We have much to learn about the impact of medications used by these women with limited data on risks to the fetus. A large multicenter observational study, called Maternal and Fetal Outcomes in the Era of CFTR modulators (MAYFLOWERS), is funded by the U.S. Cystic Fibrosis Foundation, and will begin in 2021 with the goal of collecting granular data about pregnancy and infant outcomes in CF to further guide the CF community.

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References:

1. Cystic Fibrosis Foundation Patient Registry Report. 2019.
2. Kazmerski TM, Sawicki GS, Miller E, et al. Sexual and reproductive health behaviors and experiences reported by young women with cystic fibrosis. *J Cyst Fibros.* 2018;17(1):57-63.
3. Shteinberg M, Lulu AB, Downey DG, et al. Failure to conceive in women with CF is associated with pancreatic insufficiency and advancing age. *J Cyst Fibros.* 2019;18(4):525-529.
4. Munster E, Letzel S, Passet-Wittig J, et al. Who is the gate keeper for treatment in a fertility clinic in Germany? -baseline results of a prospective cohort study (PinK study). *BMC Pregnancy Childbirth.* 2018;18(1):62.
5. *Fertility: Assessment and Treatment for People with Fertility Problems.* 2004.
6. Tizzano EF, Silver MM, Chitayat D, Benichou JC, Buchwald M. Differential cellular expression of cystic fibrosis transmembrane regulator in human reproductive tissues. Clues for the infertility in patients with cystic fibrosis. *Am J Pathol.* 1994;144(5):906-914.
7. Stead RJ, Hodson ME, Batten JC, Adams J, Jacobs HS. Amenorrhoea in cystic fibrosis. *Clin Endocrinol (Oxf).* 1987;26(2):187-195.
8. Tomaiuolo G, Rusciano G, Caserta S, et al. A new method to improve the clinical evaluation of cystic fibrosis patients by mucus viscoelastic properties. *PLoS One.* 2014;9(1):e82297.
9. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med.* 2011;365(18):1663-1672.
10. Middleton PG, Mall MA, Drevinek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med.* 2019;381(19):1809-1819.

11. Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet.* 2019;394(10212):1940-1948.

12. Taylor-Cousar JL. CFTR Modulators: Impact on Fertility, Pregnancy, and Lactation in Women with Cystic Fibrosis. *J Clin Med.* 2020;9(9).

13. Hughan KS, Daley T, Rayas MS, Kelly A, Roe A. Female reproductive health in cystic fibrosis. *J Cyst Fibros.* 2019;18 Suppl 2:S95-S104.

14. Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions. *Obstet Gynecol.* 2017;129(3):597-599.

15. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med.* 2004;6(5):387-391.

16. Beauchamp KA, Johansen Taber KA, Grauman PV, et al. Sequencing as a first-line methodology for cystic fibrosis carrier screening. *Genet Med.* 2019;21(11):2569-2576.

17. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). *Genet Med.* 2020;22(8):1288-1295.

18. Thorpe-Beeston JG, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancies in women with cystic fibrosis--single centre experience 1998-2011. *BJOG.* 2013;120(3):354-361.

19. Thomas E, Yang J, Xu J, Lima FV, Stergiopoulos K. Pulmonary Hypertension and Pregnancy Outcomes: Insights From the National Inpatient Sample. *J Am Heart Assoc.* 2017;6(10).

20. Sliwa K, van Hagen IM, Budts W, et al. Pulmonary hypertension and pregnancy outcomes: data from the Registry Of Pregnancy and Cardiac Disease (ROPAC) of the European Society of Cardiology. *Eur J Heart Fail.* 2016;18(9):1119-1128.

21. Ashcroft A, Chapman SJ, Mackillop L. The outcome of pregnancy in women with cystic fibrosis: a UK population-based descriptive study. *BJOG.* 2020.

22. Stallings VA, Stark LJ, Robinson KA, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc.* 2008;108(5):832-839.

23. Edenborough FP, Borgo G, Knoop C, et al. Guidelines for the management of pregnancy in women with cystic fibrosis. *J Cyst Fibros.* 2008;7 Suppl 1:S2-32.

24. American College of O, Gynecologists. ACOG Committee opinion no. 548: weight gain during pregnancy. *Obstet Gynecol.* 2013;121(1):210-212.

25. Cheng EY, Goss CH, McKone EF, et al. Aggressive prenatal care results in successful fetal outcomes in CF women. *J Cyst Fibros.* 2006;5(2):85-91.

26. Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis and their infants: a review of five cases. *J Am Diet Assoc.* 1994;94(2):159-165.

27. Michel SH, Mueller DH. Nutrition for pregnant women who have cystic fibrosis. *J Acad Nutr Diet.* 2012;112(12):1943-1948.

28. Vitamin Comparison Chart. https://www.cff.org/Life-With-CF/Daily-Life/Fitness-and-Nutrition/Nutrition/Getting-Your-Nutrients/Vitamin-Comparison-Chart-for-CF-Specific-Multivitamins.pdf. Accessed August 8, 2020.

29. NIH Office of Dietary Supplements, Professional Fact Sheet.

30. Maia S. Vitamin A and pregnancy: a narrative review. *Nutrients.* 2019;11:681.

31. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care.* 2009;32(9):1626-1631.

32. Ludvigsson JF, Neovius M, Soderling J, et al. Periconception glycaemic control in women with type 1 diabetes and risk of major birth defects: population based cohort study in Sweden. *BMJ.* 2018;362:k2638.

33. Guerin A, Nisenbaum R, Ray JG. Use of maternal GHb concentration to estimate the risk of congenital anomalies in the offspring of women with prepregnancy diabetes. *Diabetes Care.* 2007;30(7):1920-1925.

34. Giordani B, Quattrucci S, Amato A, Salvatore M, Padoan R. A case-control study on pregnancy in Italian Cystic Fibrosis women. Data from the Italian Registry. *Respir Med.* 2018;145:200-205.

35. McMullen AH, Pasta DJ, Frederick PD, et al. Impact of pregnancy on women with cystic fibrosis. *Chest.* 2006;129(3):706-711.

36. Gilljam M, Antoniou M, Shin J, Dupuis A, Corey M, Tullis DE. Pregnancy in cystic fibrosis. Fetal and maternal outcome. *Chest.* 2000;118(1):85-91.

37. Ahluwalia M, Hoag JB, Hadeh A, Ferrin M, Hadjiliadis D. Cystic fibrosis and pregnancy in the modern era: a case control study. *J Cyst Fibros.* 2014;13(1):69-73.

38. Reynaud Q, Rousset Jablonski C, Poupon-Bourdy S, et al. Pregnancy outcome in women with cystic fibrosis and poor pulmonary function. *J Cyst Fibros.* 2020;19(1):80-83.

39. Goss CH, Rubenfeld GD, Otto K, Aitken ML. The effect of pregnancy on survival in women with cystic fibrosis. *Chest.* 2003;124(4):1460-1468.

40. Schechter MS, Quittner AL, Konstan MW, et al. Long-term effects of pregnancy and motherhood on disease outcomes of women with cystic fibrosis. *Ann Am Thorac Soc.* 2013;10(3):213-219.

41. Panchaud A, Di Paolo ER, Koutsokera A, et al. Safety of Drugs during Pregnancy and Breastfeeding in Cystic Fibrosis Patients. *Respiration.* 2016;91(4):333-348.

42. Middleton PG, Gade EJ, Aguilera C, et al. ERS/TSANZ Task Force Statement on the management of reproduction and pregnancy in women with airways diseases. *Eur Respir J.* 2020;55(2).

43. Kroon M, Akkerman-Nijland AM, Rottier BL, Koppelman GH, Akkerman OW, Touw DJ. Drugs during pregnancy and breast feeding in women diagnosed with Cystic Fibrosis - An update. *J Cyst Fibros.* 2018;17(1):17-25.

44. Saiman L, Anstead M, Mayer-Hamblett N, et al. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA.* 2010;303(17):1707-1715.

45. Saiman L, Marshall BC, Mayer-Hamblett N, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA.* 2003;290(13):1749-1756.

46. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2007;176(10):957-969.

47. Fan H, Gilbert R, O'Callaghan F, Li L. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. *BMJ.* 2020;368:m331.

48. Damkier P, Bronniche LMS, Korch-Frandsen JFB, Broe A. In utero exposure to antibiotics and risk of congenital malformations: a population-based study. *Am J Obstet Gynecol.* 2019;221(6):648 e641-648 e615.

49. Berard A, Sheehy O, Zhao JP, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiol Drug Saf.* 2015;24(12):1241-1248.

50. Mallah N, Tohidinik HR, Etminan M, Figueiras A, Takkouche B. Prenatal Exposure to Macrolides and Risk of Congenital Malformations: A Meta-Analysis. *Drug Saf.* 2020;43(3):211-221.

51. Zithromax-Azithromycin dihydrate tablet prescribing information. 2019.

52. Matzneller P, Krasniqi S, Kinzig M, et al. Blood, tissue, and intracellular concentrations of azithromycin during and after end of therapy. *Antimicrob Agents Chemother.* 2013;57(4):1736-1742.

53. Wilms EB, Touw DJ, Heijerman HG. Pharmacokinetics of azithromycin in plasma, blood, polymorphonuclear neutrophils and sputum during long-term therapy in patients with cystic fibrosis. *Ther Drug Monit.* 2006;28(2):219-225.

54. Taylor-Cousar JL, Jain R, Kazmerski TM, et al. Concerns regarding the safety of azithromycin in pregnancy - relevance for women with cystic fibrosis. *J Cyst Fibros.* 2020.

55. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *N Engl J Med.* 2010;363(21):1991-2003.

56. Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. *N Engl J Med.* 2017;377(21):2024-2035.

57. Trimble AT, Donaldson SH. Ivacaftor withdrawal syndrome in cystic fibrosis patients with the G551D mutation. *J Cyst Fibros.* 2018;17(2):e13-e16.

58. Carpino EA FE, Uluer AZ, Sawicki GS. Acute Clinical Outcomes Following Participation in Short-Term CFTR Modulator Trials in Adults with Cystic Fibrosis: A Retrospective Chart Review - Abstract. *Pediatr Pulmonol.* 2018;53(Suppl 2):260-261.

59. Pharmaceuticals V. https://pi.vrtx.com/files/uspi_ivacaftor.pdf. 2012.

60. Pharmaceuticals V. https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf. 2015.

61. Pharmaceuticals V. https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf. 2018.

62. Pharmaceuticals V. https://pi.vrtx.com/files/uspi_elexacaftor_tezacaftor_ivacaftor.pdf. 2019.

63. Trimble A, McKinzie C, Terrell M, Stringer E, Esther CR, Jr. Measured fetal and neonatal exposure to Lumacaftor and Ivacaftor during pregnancy and while breastfeeding. *J Cyst Fibros.* 2018;17(6):779-782.

64. Ladores S, Kazmerski TM, Rowe SM. A Case Report of Pregnancy During Use of Targeted Therapeutics for Cystic Fibrosis. *J Obstet Gynecol Neonatal Nurs.* 2017;46(1):72-77.

65. Vekaria S, Popowicz N, White SW, Mulrennan S. To be or not to be on CFTR modulators during pregnancy: Risks to be considered. *J Cyst Fibros.* 2020;19(2):e7-e8.

66. Mainz JG, Michl RK, Beiersdorf N, et al. Successful Pregnancy of a Patient with Cystic Fibrosis Genotype F508del/ F508del and Progressed Pulmonary Destruction on lumacaftor/ivacaftor. *Klin Padiatr.* 2019;231(5):271-273.

67. Kaminski R, Nazareth D. A successful uncomplicated CF pregnancy while remaining on Ivacaftor. *J Cyst Fibros.* 2016;15(1):133-134.

68. Jones GH, Walshaw MJ. Potential impact on fertility of new systemic therapies for cystic fibrosis. *Paediatr Respir Rev.* 2015;16 Suppl 1:25-27.

69. Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators - an international survey. *J Cyst Fibros.* 2020;19(4):521-526.

70. Renton M, Priestley L, Bennett L, Mackillop L, Chapman SJ. Pregnancy outcomes in cystic fibrosis: a 10-year experience from a UK centre. *Obstet Med.* 2015;8(2):99-101.

71. McArdle JR. Pregnancy in cystic fibrosis. *Clin Chest Med.* 2011;32(1):111-120.

72. Giacobbe LE, Nguyen RH, Aguilera MN, et al. Effect of maternal cystic fibrosis genotype on diabetes in pregnancy. *Obstet Gynecol.* 2012;120(6):1394-1399.

73. Group HSCR, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991-2002.

74. Landon MB, Spong CY, Thom E, et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N Engl J Med.* 2009;361(14):1339-1348.

75. de Veciana M, Major CA, Morgan MA, et al. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med.* 1995;333(19):1237-1241.

76. American Diabetes A. 13. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018;41(Suppl 1):S137-S143.

77. Blum AK. Insulin Use in Pregnancy: An Update. *Diabetes Spectr.* 2016;29(2):92-97.

78. Committee on Practice B-O. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol.* 2018;131(2):e49-e64.

79. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP, Mi GTI. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med.* 2008;358(19):2003-2015.

80. Society of Maternal-Fetal Medicine Publications Committee. Electronic address pso. SMFM Statement: Pharmacological treatment of gestational diabetes. *Am J Obstet Gynecol.* 2018;218(5):B2-B4.

81. Ueland K, Hansen JM. Maternal cardiovascular dynamics. 3. Labor and delivery under local and caudal analgesia. *Am J Obstet Gynecol.* 1969;103(1):8-18.

82. Chestnut DH WC, Tsen LC, Ngan WD, Beilin Y, Mhyre J, Bateman BT, Nathan N. *Chestnut's Obstetric Anesthesia: Principles and Practice, 6th edition.* 2020.

83. Patel EM, Swamy GK, Heine RP, Kuller JA, James AH, Grotegut CA. Medical and obstetric complications among pregnant women with cystic fibrosis. *Am J Obstet Gynecol.* 2015;212(1):98 e91-99.

84. Jelin AC, Sharshiner R, Caughey AB. Maternal co-morbidities and neonatal outcomes associated with cystic fibrosis(). *J Matern Fetal Neonatal Med.* 2017;30(1):4-7.

85. Cystic Fibrosis Foundation Patient Registry Report. 2018.

86. Lactation ND. Washington (DC)1991.

87. Frangolias DD, Nakielna EM, Wilcox PG. Pregnancy and cystic fibrosis: a case-controlled study. *Chest.* 1997;111(4):963-969.

88. . *Nutrition During Lactation*. Washington (DC)1991.

89. Drugs and Lactation Database. Bethesda (MD): National Library of Medicine (US). 2006; Updated 2020 Apr 20.

90. Simcox AM, Hewison J, Duff AJ, Morton AM, Conway SP. Decision-making about pregnancy for women with cystic fibrosis. *Br J Health Psychol.* 2009;14(Pt 2):323-342.

91. 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;21(4):818-824.

92. Conde-Agudelo A, Rosas-Bermudez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA.* 2006;295(15):1809-1823.

93. Whiteman MK, Oduyebo T, Zapata LB, Walker S, Curtis KM. Contraceptive safety among women with cystic fibrosis: a systematic review. *Contraception.* 2016;94(6):621-629.

94. Wu M, Hunt WR, Putman MS, Tangpricha V. Oral ethinyl estradiol treatment in women with cystic fibrosis is associated with lower bone mineral density. *J Clin Transl Endocrinol.* 2020;20:100223.

95. Godfrey EM, Mody S, Schwartz MR, et al. Contraceptive use among women with cystic fibrosis: A pilot study linking reproductive health questions to the Cystic Fibrosis Foundation National Patient Registry. *Contraception.* 2020;101(6):420-426.

96. Roe AH, Traxler S, Schreiber CA. Contraception in women with cystic fibrosis: a systematic review of the literature. *Contraception.* 2016;93(1):3-10.

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	Inhaled	Limited to no systemic absorption	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 25,000IU 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	Yes, if necessary for mother's health	Yes

		women with short term use.		

Figure 1

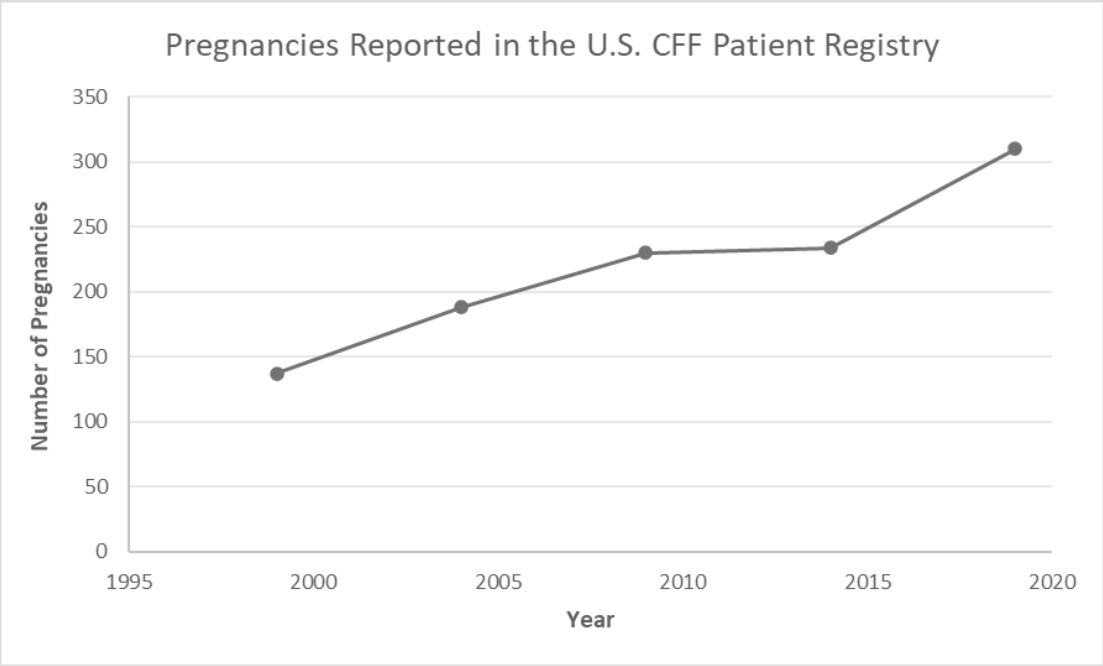

Figure 1: Depicted is the number of pregnancies in women with CF in the U.S. CF Foundation patient registry from 1999-2019.[1]

Figure 2.

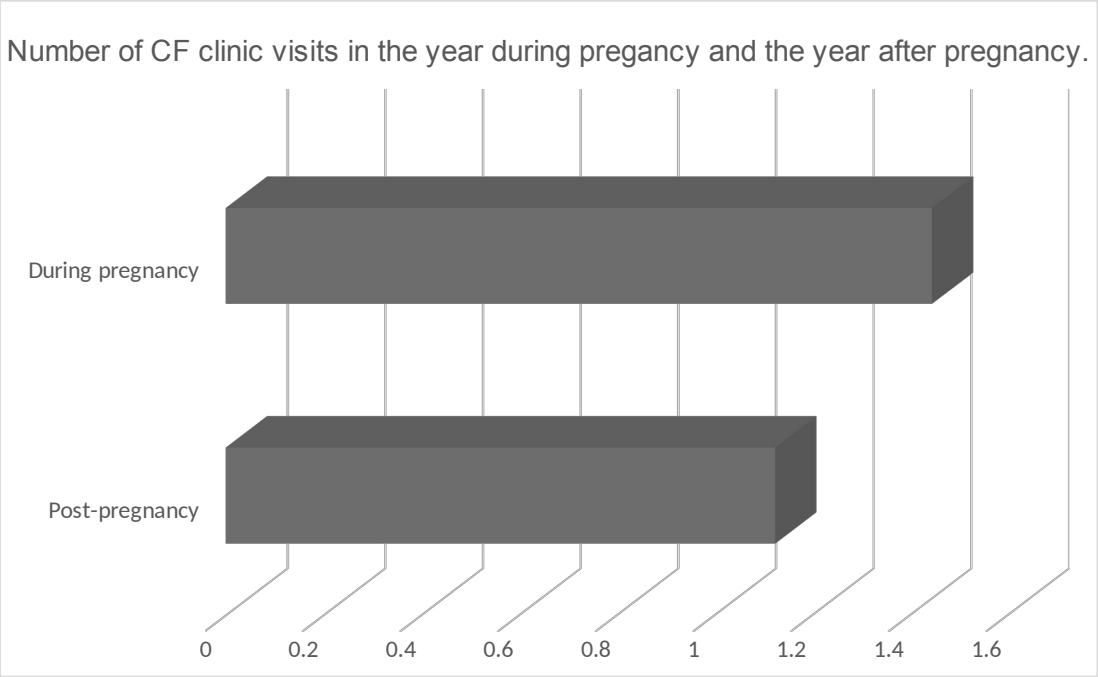

Figure 2: The CFF recommends 4 CF clinic visits per year for people with CF. Post-pregnancy, the average number of clinic visits decreased compared to the number of visits during pregnancy.[85]