Chapter 5

Cystic Fibrosis and Fertility

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Additional information is available at the end of the chapter

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Abstract

In the last 20 years, the prognosis of cystic fibrosis (CF) has slightly increased and nowadays more than 50% of CF patients are adults. An obvious consequence of this deep change is the increasing question about fertility in both males and females.

Almost 97% of male CF patients are infertile, having significant anatomical abnormalities of the reproductive tract, in most cases a congenital bilateral absence of the vas deferens (CBAVD); even if anatomical defect plays an important role, cystic fibrosis transmembrane conductance regulator (CFTR) is directly involved in many aspects of male reproduction, with well-known consequences in spermatozoa capacitation and bicarbonate secretion.

Actually, male CF patients can become parents with assisted fertilization techniques: intracytoplasmic sperm injection (ICSI), currently the most used fertilization treatment worldwide, has dramatically improved the assisted reproduction outcomes for men with obstructive azoospermia.

Most CF women have a normal reproductive tract and may be able to conceive spontaneously, but multifactorial fertility problems can affect them also: the main cause could be the difficult transport of sperm through the female reproductive tract, secondary to thick secretions, but also lung function and nutritional status at the time of conception significantly influence their fertility.

Keywords: Cystic fibrosis, CFTR, Congenital bilateral absence of the vas deferens, Fertility, In vitro fertilization, Pregnancy

1. Introduction

As the life expectancy of cystic fibrosis (CF) patients continues to increase, and more patients become adults with a chronic disease, researching the impact of this disorder on male and female infertility has become increasingly important.

Although most men with CF have significant anatomical abnormalities of the reproductive tract causing infertility, most women with CF have anatomically normal reproductive tracts and up to half of them may be able to conceive spontaneously.

Assisted reproductive technologies can help both infertile male and female patients with CF in achieving successful parenthood. In addition, for women more health characteristics including baseline pulmonary function have to be evaluated as predictors of health and pregnancy outcomes.

2. Fertility in men with cystic fibrosis

CF is a systemic illness that affects multiple organ systems, including lungs, endocrine and epithelial tissues, gastrointestinal system, pancreas, and reproductive tract. Because of the dramatic improvement made in prognosis in CF population in the last two decades, reproductive function has become one of the new red flags in the management of CF adult patients. Infertility in CF males has been extensively studied and found in most cases to be secondary to atrophy or malformation of the vas deferens, leading to an obstructive azoospermia (Figure 1).

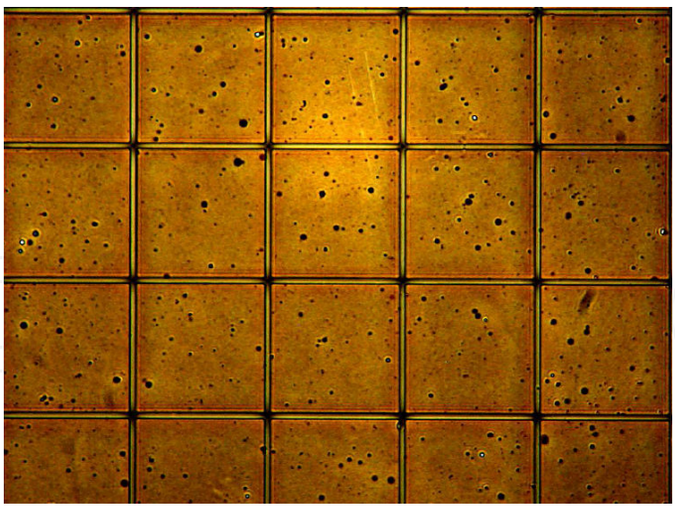

Figure 1. Spermiogram performed in our 34-year-old patient affected by CF documents azoospermia

2.1. Pathogenesis

Cystic fibrosis transmembrane conductance regulator (CFTR) is a gene located on chromosome 7 (7q31.2), encoding for a protein located in the apical membranes of epithelial cells; it was

identified in 1989 and its role in the pathogenesis of CF is now well known. CF is a disease characterized by a defect in electrolyte and fluid transport in exocrine tissues; it could present several different clinical manifestations, including chronic lung disease, pancreas insufficiency, and infertility [1].

In literature, it is reported that almost 97% of male CF patients are infertile [2]: this infertility is primarily secondary to an obstructive azoospermia. The defective CFTR ion channel function causes an early obstruction of male genital tract, due to the dehydrated secretions: this mechanism drives to deep structural changes in reproductive tract, causing in most cases a congenital bilateral absence of the vas deferens (CBAVD). In early studies on CF adult patients with azoospermia, CBAVD was reported in all the population studied. At the light of these findings, Holscalaw et al. [3] speculated a unique genetic cause of CF and CBAVD. Usually, the proximal part of epididymis is present and this allows the sperm collection in CF patients to obtain spermatozoa.

Obstructive dysfunction is not the only cause of infertility in males with CF: further studies demonstrated that CFTR may also play a critical role in spermatogenesis and sperm maturation [4]; an increased CFTR mutation frequency in a population of men with reduced sperm quality is also reported [5]. Histological examination of CF testicular biopsies shows a wide range of spermatogenesis abnormalities, including a decreased count of mature spermatids and maturation arrest. These findings could be the expressions of CFTR abnormalities in seminiferous tubules or spermatozoa.

CFTR plays a role in many aspects of male reproduction, with well-known consequences in CBAVD and CF. It has not only ion channel functions but also it is a versatile signaling molecule and interacts with more than 180 other proteins. CFTR is expressed throughout the whole genital tract [6], but we do not know yet what is CFTR's role in the male accessory glands other than the epididymis.

A significant role in sperm function was also suggested by the involvement of CFTR in uterine HCO_3^- secretion and its effect on the fertilizing capacity of sperm [7]. CFTR is present in human sperm and it is involved in both sperm motility and capacitation phases. CF mice sperm has reduced sperm motility and capacitation with reduced fertility rate in vitro and in vivo [8]: these findings suggest a significant role of CFTR in sperm functions also.

2.2. CBAVD

CBAVD is a congenital condition in which vas deferens fails to develop properly, causing male infertility because of the total obstruction of reproductive tract. CBAVD accounts for approximately 1–2% of all infertility in males and is the result of genetic abnormalities [9]. More than half of the men with CBAVD (62–80%) carry a CFTR mutation and this condition is considered to be one of the most common CFTR-related diseases. Anatomical abnormalities include bilateral or unilateral absence of the vas deferens and seminal vesicles anomalies.

Subjects with CBAVD usually have no clinical symptoms of CF, but the finding of subclinical CF features is not uncommon (mild chloride elevation at sweat test, chronic sinusitis, nasal polyps) and actually many experts consider CBAVD as a mild CF form [9].

2.3. Other genital abnormalities

Genital abnormalities may develop early in CF, but in children these are less common than described in adults. In 2002, Blau et al. [10] described genital abnormalities in male children with CF, performing pelvic and scrotal ultrasonography in 12 CF boys aged 2–12 years. They found seminal vesicles hypoplasia, testicular microlithiasis, and abnormalities of the epididymal head, such as cysts, hypo-, or hyper-echogenicity. These findings are more frequent in pancreatic-insufficient than in pancreatic-sufficient CF patients. The reported experience represents a very small population of CF children, and larger longitudinal studies will be necessary to better define the onset and progression of urogenital abnormalities in CF males.

In CF adults, testes are usually symmetric and have a normal echogenicity, but mild inhomogeneity or striated appearance can be documented with ultrasounds. Focal inhomogeneities seem to be rare, as testicular nodules. Didymus cysts, epididymal cysts (also multiple) with sediments and/or calcifications are common. Usually, vas deferens is absent, but a structure attributable to spermatic cord could be revealed bilaterally or unilaterally in some cases, usually with a significant stenosis.

Several features can influence the anatomical genital phenotype in these patients (as genotype, clinical features, age), and further studies will be crucial to find risk factors and significant correlation for these abnormalities in CF.

2.4. Fertility management in men with CF

Over the last 20 years, the relevant improvement in survival of CF patients and the concomitant development of new assisted conception methods have significantly increased the opportunities for these patients to become parents. It is therefore very important to start an early and effective management of fertility issues in males with CF.

The clinical management of reproductive issues in males affected by CF has to begin during puberty with periodic evaluation of testicular volume/consistency and all the other virilization signs, indicating a congruous testosterone production. Hormonal levels (as LH, FSH, and testosterone serum concentration) are usually normal in male CF, indicating a regular spermatogenesis in most cases. It could be also useful as a deeper examination to detect the presence of vas deferens (usually palpable in the upper portion of scrotum), but the definitive diagnosis of CBAVD can be made with radiological exams.

There is not a considerable literature about the morphological study of the scrotum in adult CF patients, but trans-rectal ultrasounds could be considered a good instrument to evaluate abnormalities in shape, volume, and structure of testes, epididymis, and spermatic cord.

Also scrotal ultrasound with high-definition instruments is non-invasive and executable without any discomfort for the patient and could be useful in order to analyze the extra pelvic portion of the vas deferens (from the groin to the testicle) and all the scrotal structures.

The diagnosis of azoospermia could be simply supported and confirmed by semen analysis. In case of seminal vesicles abnormalities, semen analysis will also show an acid pH, due to lack of fructose concentrations in sperm, and often the volume of ejaculate is low: in these

cases, the sperm is produced by the prostate, with no contribute from vesicles. Typically, men with the absence of the vas deferens have low-volume (often less than 0.5 ml) and acidic semen [11].

2.5. Assisted reproduction in men with CF

2.5.1. Counseling

CF men and their partners, who want to start assisted reproduction treatments, need an adequate genetic, medical, and psychological counseling. Genetic tests have to be performed in the patient (if not already done) and in the partner, in order to define the risk of generating an affected child. In case of incomplete genetic assessment or high risk of CF recurrence, prenatal or pre-implantation genetic diagnosis could also be recommended; it is important to consider ethic and legislative issues, because in some countries pre-implantation genetic tests are not allowed. All these procedures have relevant psychological, ethical, and sanitary costs, so alternative measures (as adoption or use of sperm donor) could be considered.

Another important issue is the prognosis of the potential father affected by CF. This delicate aspect asks the intervention of CF-clinician and psychologist, together with an experienced fertility specialist.

2.5.2. Sperm collection

Sperm retrieval is a procedure used to obtain sperm for fertility purposes. In general, it is necessary in case of azoospermia or if men are unable to ejaculate. In almost all cases, sperm retrieval must be utilized in combination with in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) for reasonable pregnancy rates to be obtained [12].

The sperm collection could be performed by aspiration from epididymis or directly from the testis. In CF the proximal part of the epididymis is usually present, so the procedure is usually quietly simple. The techniques of collection include:

- Percutaneous epididymal sperm aspiration (PESA) from the caput of the epididymis, usually simple to localize and good reservoir of sperm; aspiration is performed with fine needle after local anesthetization and is usually fast and well tolerated by the patient
- Microsurgical epididymal sperm aspiration (MESA)
- Percutaneous testicular aspiration (TESA) performed with local anesthetization (Figure 2) as for PESA
- Testicular surgical biopsy (Figure 3)
- Testicular sperm extraction (TESE), an in vivo microdissection of testicular tubules finalized to the identification of normal tubules (Figure 4), suitable for an effective sperm collection

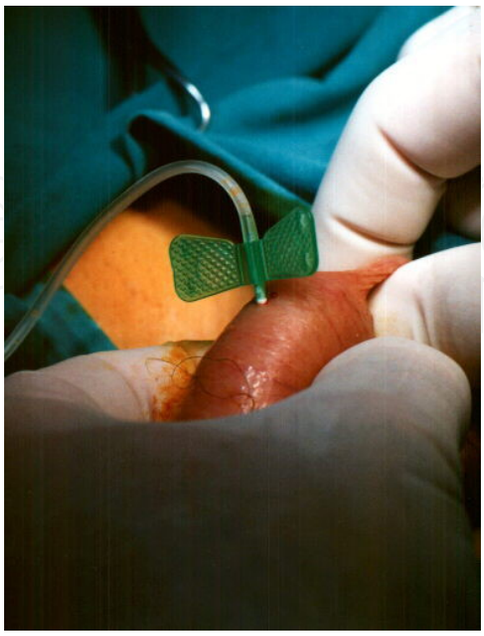

Figure 2. Percutaneous testicular aspiration (TESA) performed with local anesthetization

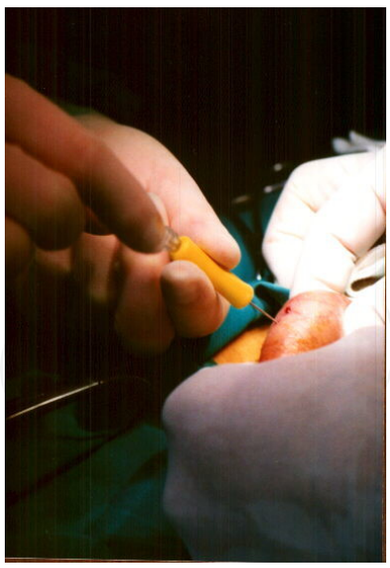

Figure 3. Percutaneous testicular biopsy

Cryopreservation of sperm is possible and represents a good chance for future use, but usually repeated epididymal aspiration is required. These procedures are usually performed on the same day of the partner's oocytes collection (Figure 5) to assure high counts of motile sperm in the time of fecundation.

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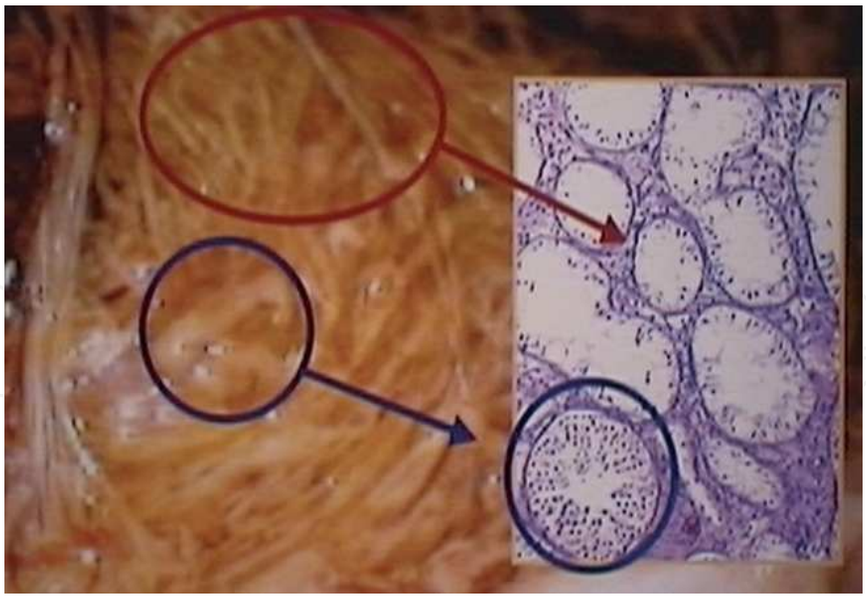

Figure 4. Microsurgical identification of tubules with spermatogenesis (TESE technique)

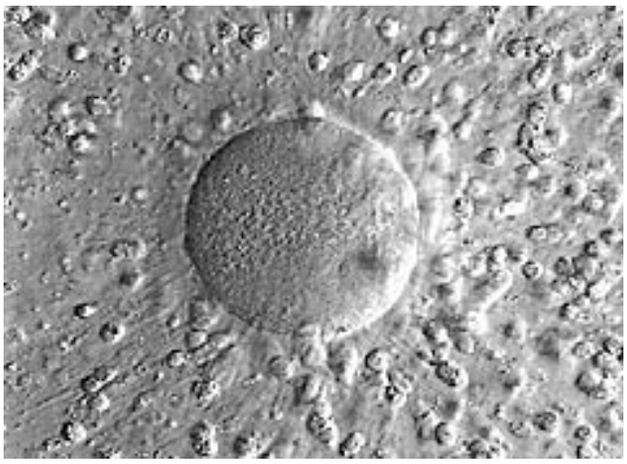

Figure 5. Oocytes culture

2.5.3. Assisted reproduction treatments

The first experience of in vitro fertilization with sperm obtained by epididymal aspiration was in 1985 [13]; in the next years, several experiences also in CBAVD patients have been reported [14]. In that period, the fertilization rates were low (less than 20%), with very poor birth rates.

A dramatic increase in assisted reproduction outcomes for men with obstructive azoospermia has been represented by ICSI, introduced first in the 1990s. The first large experience with ICSI in the United States was published by Sherins et al. in 1995 [15]. This technique is generally performed following an in vitro fertilization procedure to extract one to several oocytes from a woman. The procedure is done under a microscope, using multiple micromanipulation devices, in order to allow the direct injection of a single sperm in a human oocyte.

This technique is currently the most used fertilization treatment worldwide and it has deeply increased the chances of successful fertilizations and pregnancies; ICSI technique allows to have the same fertilization and pregnancy rates between CF males and men with no vas deferens obstructive disease (Figure 6).

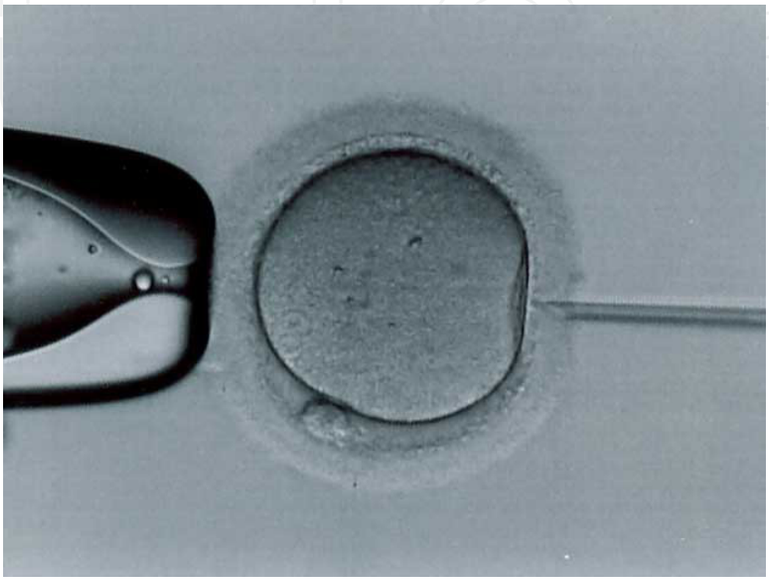

Figure 6. ICSI technique

3. Fertility in women with cystic fibrosis

Although most men with CF have significant anatomical abnormalities of the reproductive tract, most CF women have an anatomically normal reproductive tract and may be able to conceive spontaneously, but in literature it is reported that only slightly more than half of them have spontaneous pregnancies. The fertility problems in CF female are multifactorial: the main cause would be the difficult transport of sperm through the female reproductive tract, secondary to thick secretions; but certainly also the underlying medical conditions (especially lung function and nutritional status) have a major impact on fertility in these patients. The improved health and longevity of CF women naturally leads to an increased number of CF women who become or desire to become pregnant.

The first reported successful pregnancy in a CF woman was in 1960 [16], and in 1966 13 pregnancies in 10 different patients were reported [17]. These early reports were discouraging. However, with aggressive management of infections and significant improvement in pulmonary and nutritional interventions, pregnancies today are well tolerated in CF, especially in women with mild to moderate disease [18, 19]. The North American CF Registry reported in 2007 that 3–4% of CF women over 17 years old become pregnant each year [20].

3.1. Pathogenesis

Despite CF has long been associated with female infertility, the underlying causes remain unclear. Actually, we know that the majority of CF women have a normal fertility, but ovulation disturbance may occur in patients with advanced disease [21], also with amenorrhea in the most compromised subjects. Although most girls have normal menstrual cycles, there is a higher incidence of missed or irregular periods and amenorrhea. This is more likely in those with a reduced percentage of body fat and may occur in case of malnutrition or alimentary disorders.

Fertility problems may be related to lung disease severity, poor weight, and to an unsatisfying control of CF-related diabetes [22]. Historically, the predictors of poor pregnancy outcome for mother and/or fetus were a forced vital capacity (FVC) of less than 50% of the predicted value and poor nutritional status. In the past, an FVC of less than 50% of the predicted value was an absolute contraindication to pregnancy.

For several years, it has been postulated that the thickened cervical mucus present in CF women reproductive tract could lead to fertility disturbance. Normally, when the egg is released from the ovary, cervical and uterine mucus thins and allows easier passage of sperm into the uterus and fertilization. Increased thickness of this mucus in women with CF may theoretically act as a barrier to sperm penetration and could reduce fertility, but nowadays the majority of women with CF can become pregnant without any difficulty.

In 2008, Hodges et al. [23] studied the mouse model of CF, indicating that in CF mice the major cause of decreased fertility is the impaired sperm transport within female reproductive tract. In their experience, excess cervical mucus played a minor role, because instead of a physical barrier, the decreased fertilization seemed to be due to an inadequate fluid production in reproductive system, with a subsequent decrease in sperm number in the oviduct. CFTR could play not only an important role in female reproductive tract fluid control but also in sperm capacitation with its bicarbonate transport.

3.2. Impact of pregnancy on CF

The physiologic changes associated with pregnancy may contribute to increased morbidity and mortality risks for the mother in CF women. Volumetric increase of abdomen with the consequent upward displacement of diaphragm causes a decrease in functional residual volume, and the concomitant increase in resting minute ventilation can lead to a relevant breath disturbance. Also gas exchange has deep alterations in pregnant women, with an increased alveolar–arterial oxygen gradient, especially in supine position [24].

In a recent study [25], it is reported that adjusting for the FEV1 percent predicted, weight, height, and pulmonary exacerbation rate per year, pregnancy is not associated with an increased risk of death. Pregnancy did not appear to be harmful even in a subset of women with diabetes mellitus or with FEV1 less than 40% of predicted. Important predictors of pregnancy outcome for the fetus are the severity of maternal pulmonary impairment and nutritional status; in women with advanced lung disease, preterm delivery is very common.

McMullen et al. [26] in 2006 characterized health outcomes in CF pregnant women, comparing them with a group of never-pregnant CF population: this large observational study showed a nonsignificant difference in terms of FEV1 decline between the two groups (6.8% in pregnant group and 4.7% in never-pregnant, *P*=0.61). Respiratory exacerbations and hospitalizations were increased during pregnancy, as well as the number of outpatient visits and administered therapies.

The risk for congenital anomalies in the fetus is not increased in CF gravidas and breastfeeding is possible without complications.

3.3. Risk factors

The pregravid pulmonary function is clearly the greatest outcome predictor in CF women, but there are multiple clinical prognostic markers to consider. Women with poor nutritional status, pulmonary hypertension, and relevant decrease in pulmonary function during the first 3 months of gestation have to be informed about the high risk of maternal mortality and should consider therapeutic abortion [27].

3.3.1. Lung function

FEV1% predicted, PO2, and PCO2 are important predictors of pregnancy outcomes. In 1995, Edenborough et al. [28] reported that a pregravid FEV1 <60% caused greater pulmonary function decrease, a higher frequency of preterm infants, and also a higher mortality. However, successful pregnancies have been reported also in CF patients with compromised lung function (FEV_1 < 50% of that predicted), and most patients seem to return to baseline pulmonary status after pregnancy.

The only absolute contraindication to pregnancy in CF is represented by pulmonary hypertension, which is correlated with higher rates of mortality in pregnancy. An echocardiogram performed before pregnancy can be useful to individuate underlying pulmonary hypertension and cor pulmonale, in order to advise the patient about the high mortality risk in case of pregnancy [24].

3.3.2. Pancreatic insufficiency and diabetes mellitus

In old literature, pancreatic insufficiency was considered as a major risk factor in pregnancy outcomes. Actually, with the modern pancreatic enzymes supplementations, it is a nonsignificant issue in CF pregnancies.

CF women planning pregnancy have to be tested for glucose intolerance before conception and the test has to be repeated at 20 weeks of gestational age. Insulin therapy is indicated in case of abnormalities in blood glucose monitoring.

3.3.3. Nutritional status

Clinician should advise to reach a pregravid weight before conception up to 90% of the ideal body weight. Poor nutritional status is without any doubt one of the most relevant risk factor

for pregnancy outcomes in CF, and a severe malnutrition (BMI <18 kg/m^2) is a relative contraindication to pregnancy. A weight gain of 11–12 kg during pregnancy is recommended [29]; poor outcome is particularly associated with a maternal gain less than 4.5 Kg. A high caloric intake should be maintained and a poor weight gain is an indication for aggressive nutritional intervention (dietary supplementation, nasogastric, or gastrostomy feeding).

3.3.4. Microbiological issues

Burkholderia cepacia complex has been considered for several years a relative contraindication for pregnancy in CF, because this infection seemed to be related with a higher maternal mortality [30]. *B. cepacia* (particularly *B. cenocepacia* and *B. multivorans*) is also considered related to preterm delivery, weight loss, and rapid pulmonary function decline [31], but further studies are needed to better define its role in CF pregnancies.

3.3.5. Pulmonary transplantation

Limited cases of pregnancy after lung transplantation have been reported; most experience comes from renal transplantation. Compared to other solid organ transplants, lung recipients experience more frequent rejections during pregnancy and also a higher rate of graft loss postpartum [32]. Graft dysfunction is unpredictable and may occur anytime during pregnancy, leading to progressive decline and also eventual death after delivery. However, further studies are necessary to determine long-term maternal survival.

Prematurity and neonatal complications in these pregnancies are very high (56% and 33%, respectively), but no long-term consequences on children are reported [33].

3.4. Management of pregnancy in CF women

The management of pregnancy in CF requests necessarily a multidisciplinary approach. Most of the literature on pregnancy in CF is constituted by case reports and a few national centre based reviews. Unfortunately, at the moment, we have no available trials about any aspect of pregnancy management in CF. In 2008, Edenborough et al. [34] published the guidelines for the management of pregnancy in women with CF, based on the review of the literature and experience of pediatricians, adult and transplant physicians, nurses, physiotherapists, dietitians, pharmacists and psychologists experienced in CF, and also anesthetists and obstetricians with experience of CF pregnancy.

3.4.1. Counselling

Counselling consists in helping the CF patient planning pregnancy and her partner to explain the risks of their decision, such as medical implications, treatment options, and also the impact of a toddler on the everyday life of a CF woman.

Genetic features, such as the risk of recurrence of the disease, have also to be discussed with the couple. CF genotype, if not already known, have to be defined and the partner should also

be tested before conception. Genetic counsellors should be involved in order to discuss these delicate issues with the couple.

Genetic tests have a sensitivity <100% with detection rates from 70% to 95% of CFTR mutations. If the partner has not been tested, given a CF carrier frequency of 1:25, the risk of an affected infant is 1:50; while if the partner is a CF carrier, the risk is 1:2.

When the partner is a known carrier or if he has not been tested, clinicians should suggest to perform prenatal genetic diagnosis to the couple, with the analysis of chorionic villus sample (CVS) within the first trimester of gestation. This procedure includes technical risks that should be discussed with the couple.

Psychological counselling is also an important part of the counselling activities: CF team should provide information about sexual health and reproduction to all of their patients, particularly teenage girls. Psychologists and clinicians play an important role also in psychological counselling for CF women who want to become pregnant, even if women with advanced disease with a very strong wish to have a child may proceed whatever the advices.

3.4.2. Medications during pregnancy

Most drugs have not been tested on pregnant women. Relevant issues about their use in pregnancy are timing of exposure (periconception, first, second, third trimester, or perinatally), systemic availability of the drug, and its ability to cross the placenta. Side effects can consist in teratogenesis, growth retardation, death, renal insufficiency, neurological disorders, stillbirth, etc.

Many pregnancies are unplanned and drugs could have been taken at the time of conception and continued in the first weeks of pregnancy, and many women with serious illnesses required treatment to be continued. Even if nowadays there is experience to guide prescribing in pregnancy, the principle remains to avoid drug use where possible, except when the risk of the drug is outweighed by the risk of the condition being treated.

The Swedish FASS information catalog provides information on the risks of drugs to the fetus during pregnancy and to the infant during lactation. Each drug is classified to one category of safety:

1. Drugs that have been used widely during pregnancy and are assumed safe for the fetus
2. Drugs not known to cause harm to the human fetus but with insufficient experience to consider them safe. This category can be subdivided into
3. drugs that have been demonstrated to cause no harm in animal studies
4. drugs with insufficient animal data
5. drugs that have been demonstrated to harm the fetus only in animal studies
6. Drugs that could theoretically cause harm to the fetus by their pharmacological actions
7. Drugs known or believed to cause harm to the fetus

Patient's therapy should be reviewed during the discussion of a potential pregnancy, even if most of the routine CF medications are safe and could be continued. Contraindicated drugs have to be discontinued. β-lactams are safe in pregnancy and aminoglycosides at conventional doses have not showed toxic results. Once-daily tobramicin has been tested in second and third trimesters, showing safe results. Ciprofloxacin has been widely used during pregnancy with no certain side effects, but its use is indicated only if vital for the mother.

3.4.3. Lung function and infections

CF women can become pregnant in all pulmonary disease stage, but the outcome for the mother and the newborn is closely related to lung function (FEV1 predicted) and clinical stability. Lung function should be optimized and chronic infections may be suppressed before pregnancy: oral flucloxacillin could be administered in case of *Staphylococcus aureus* colonization; for *Pseudomonas aeruginosa* nebulized colistin or aminoglycoside treatment should be employed.

When a pregnancy is unplanned, pregnancy is frequently connected to a worsening in lung function: if necessary, one or more courses of IV antibiotic treatment could be administered in the usual format also during pregnancy (β-lactam + aminoglycoside).

During the first trimester, most patients will feel breathless and the frequency of hospitalizations could rise up: at each visit, physical examination, sputum cultures, weight and oxygen saturation measurement, and pulmonary function test should be performed.

3.4.4. Physiotherapy

If the pregnancy is planned, preconceptional period could represent a good opportunity to optimize the daily physiotherapy program. Inhalation therapies and techniques should also be reviewed and optimized; the timing of these treatments in relation to airway clearance therapy (ACT) is a relevant feature during pregnancy, especially in CF patients who produce big volumes of sputum. ACT adherence and technique have to be adapted in pregnant women. Advice on physical exercise and pelvic floor strength should be given as soon as possible.

The breathing pattern is affected by physiological and mechanical changes during pregnancy, and in the last trimester these features can lead to increase in closing volume and determine atelectasis. Physiotherapists should meet the pregnant patients weekly to optimize the physiotherapy regimen, monitor lung function and sputum production in terms of colour and quantity. Also maintaining exercise capacity should be useful during pregnancy and in last trimester.

3.4.5. Nutrition

Dietetic counselling is crucial in preconceptional period, because maternal nutritional state is one of the most important factors influencing outcomes for mother and infant. A low pre-pregnancy BMI is strictly associated with reduced birth weight. Preconceptional assessment is similar to non-CF population and should be performed by a CF specialist dietitian, who can advise not only on increasing energy density of the diet but also oral supplements and invasive

nutritional support (enteral tube feeding) can be purposed to the patient if nutritional status is unsatisfactory. Vitamin supplementation with folic acid, vitamin A, and vitamin D are recommended.

An overall weight gain of 12.5 Kg is considered normal and in CF it is recommended a weight gain of at least 11 Kg. Also gastro-oesophageal reflux, heartburn, nausea, recurrent vomiting, and constipation may occur more frequently in women with CF and required clinicians monitoring.

3.4.6. Diabetes care

A pre-pregnancy diagnosis of CF-related diabetes and gestational diabetes are associated with a poorer prognosis; in literature, it is reported that an unsatisfactory glycemic control in the first trimester is associated with an increased risk of teratogenesis. During preconceptional counselling an OGTT is recommended, if not already performed, and blood sugars have to be monitored during lung exacerbations. Usually, OGTT is repeated at 20 weeks gestation and glycaemia should be measured at every visit: if random values are high, another OGTT could be repeated at 28 weeks.

Insulin is the recommended treatment for diabetes in CF also during pregnancy. A high calorie intake should also be assessed in diabetic patients.

3.4.7. Termination of pregnancy

Guidelines about when to terminate pregnancy in a woman with advanced CF remain fluid. The indications may be psychosocial (in order to prevent serious injury to the mental health of the pregnant woman) or medical.

The only absolute contraindication to pregnancy is a pre-existing pulmonary hypertension with cor pulmonale; also chronic hypoxia could be considered a contraindication to pregnancy. There are no clear indications about the FEV1 cut-off to recommend pregnancy termination.

There are also some relative contraindications to pregnancy in CF women:

1. Poor nutritional status (BMI <18 kg/m^2; <85% ideal body weight)
2. Uncontrolled CF-related diabetes
3. *Burkholderia cepacia* infection
4. Significant liver disease

3.4.8. Delivery

Most pregnancies in CF end in spontaneous vaginal delivery. Caesarean section is indicated only in case of maternal or fetal sufferance, preferably with spinal anesthesia. In CF, a high proportion (26–46%) of pregnancies end up with a spontaneous or therapeutic preterm delivery, and the usual indication is represented by maternal conditions. Usually, failing lung function and hypoxia occur in patients with a significant low pre-pregnant lung function;

persisting hypoxia and onset of headache are in these cases severe signs and could request oxygen support or non-invasive ventilation.

In peripartum, pain and anxiety can lead to hyperventilation and decrease in alveolar gas exchanges; hypoxia, hypercarbia, and respiratory acidosis occur rapidly in patients with compromised lung function. An adequate analgesia should be performed, because it reduces pain, fear, and fatigue; oxygen support can be useful in case of desaturations.

4. Our experience

In our CF Center, we have 230 patients in regular follow-up and 153 of these are >18 years old. In the last few years, fertility issues increased significantly in our population, surely because of the significant improvement in prognosis and the easier access to the assisted reproduction treatments.

During the last 20 years, 12 of our male patients recurred to in vitro fertilization with sperm obtained by epididymal aspiration and in 6 cases had successful reproduction (with twin pregnancy in 2 cases and in 1 case triplet pregnancy). All the newborns enjoyed good health and no recurrence of CF has been detected (all the partners were tested for CFTR mutations before the conception). In the other six cases in vitro fertilization was not successful and one of these three patients decided to use heterologous fertilization by sperm donor, with a subsequent successful pregnancy.

In the same period four of our female patients recurred to in vitro fertilization with two successful pregnancies (in one case twin pregnancy). Also in these cases the newborns enjoyed good health and no recurrence of CF has been detected (all the partners were tested for CFTR mutations before the conception).

In our population 12 of our patients (10 women and 2 men) had spontaneous conceptions with 18 successful pregnancies. Also in these cases no recurrence of the disease has been detected, even if in some cases the diagnosis of CF in these patients had been performed after the delivery and in most cases the partners had not been tested for CFTR mutations before the conception. Three of our female patients, after several attempts to become pregnant spontaneously, decided and obtained to adopt a child.

Actually, no literature is available about scrotal imaging in males affected by CF. We decided to realize an original study, performing scrotal ultrasound examination with high-definition technique, to better evaluate abnormalities in shape, volume, and structure of the testes, epididymis, and spermatic cord in a group of adult patients (>18 years) affected by CF. Preliminary results seem to show an increased incidence of testicular and epididymal abnormalities in comparison to the general population, but in most cases these seem to be secondary to the obstruction of vas deferens [FigureS 7,8,9].

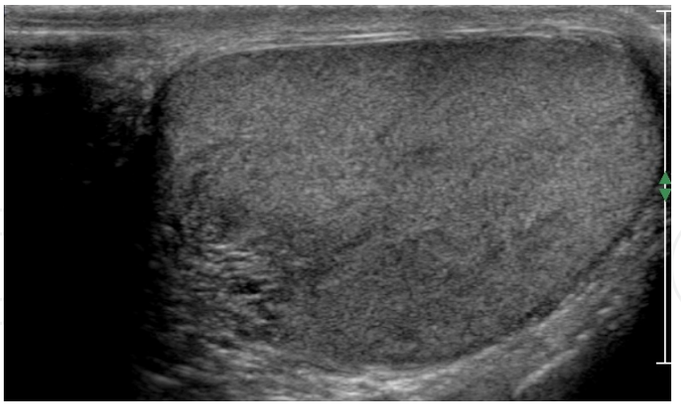

Figure 7. US Figure of rete testis ectasia with structure inhomogeneities in a CF patient

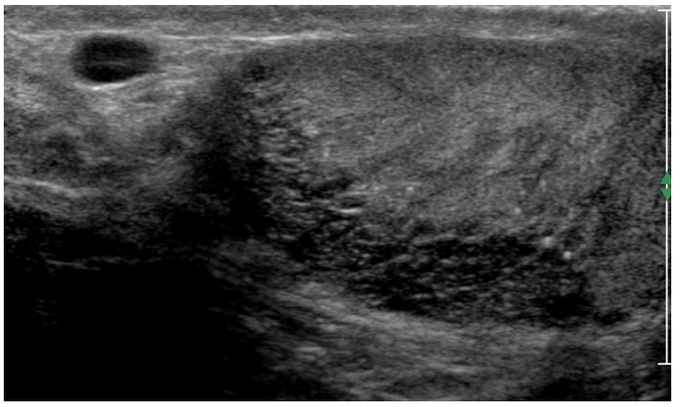

Figure 8. US Figure of rete testis ectasia with structure inhomogeneities with a little epididymal cyst in a CF patient

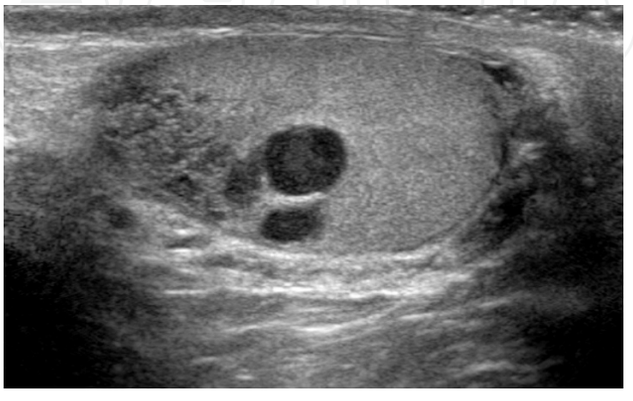

Figure 9. US Figure of intradidymal cysts (one with corpuscular content) in a CF patient

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Nomenclature

CF = Cystic fibrosis

CFTR = Cystic fibrosis transmembrane conductance regulator

CBAVD = Congenital bilateral absence of the vas deferens

LH = Luteinizing hormone

FSH = Follicle stimulating hormone

US = ultrasounds

IVF = in vitro fertilization

ICSI = Intracytoplasmic sperm injection

PESA = Percutaneous epididymal sperm aspiration

MESA = Microsurgical epididymal sperm aspiration

TESA = Percutaneous testicular aspiration

TESE = Testicular sperm extraction

FVC = forced vital capacity

FEV1 = Forced expiratory volume in 1 second

PO2 = Partial pressure of oxygen

PCO2 = Partial pressure of carbon dioxide

BMI = Body mass index

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