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Cystic fibrosis and pregnancy: counseling, obstetrical management and perinatal outcome.

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Abstract. The progress in research of in vitro fertilization and fetal-maternal medicine allows more women and men, with fertility problems due to cystic fibrosis, to have a baby. In the majority of cases, pregnancy in women with cystic fibrosis results in favorable maternal and fetal outcomes. However, the incidence of preterm delivery, intrauterine growth restriction, caesarean section and deterioration of the maternal health are increased. Pre-pregnancy counseling is a crucial component of overall obstetric care, especially in women with poor pulmonary function. Additionally, closer monitoring during pregnancy with a multidisciplinary approach is required. The value of serial ultrasound scans and fetal Doppler assessment is important for the control of maternal and fetal wellbeing, as well as for the definition of the appropriate timing of delivery. In this article, clinical issues of pregnant women with cystic fibrosis are reviewed; counseling, obstetrical management and perinatal outcomes are being discussed.

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Fibrosis quística y embarazo: asesoría, manejo obstétrico y del resultado perinatal.

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Palabras clave: fibrosis quística, prematuridad, retraso crecimiento fetal, ultrasonido.

Resumen. Los avances en la investigación de la reproducción asistida y también en la medicina fetal, permiten cada vez a más mujeres y hombres con infertilidad debido a la fibrosis quística tener un hijo. En general, el embarazo en las mujeres con fibrosis quística tiene buen resultado perinatal, aunque hay mayor riesgo de prematuridad, de retraso crecimiento del feto, cesárea y un posible empeoramiento de la enfermedad de la madre. El rol de la asesoría antes del embarazo es un componente particularmente importante del control obstétrico general, especialmente en mujeres con pobre función pulmonar. Aún más, se requiere una vigilancia más estrecha del embarazo, con la participación de médicos de diversas especialidades. La valoración de los ultrasonidos sucesivos y del examen Doppler fetal son importantes y necesarios para el control del bienestar maternal y fetal, así como para la determinación del tiempo apropiado para la culminación del embarazo. En este artículo, se analizan los problemas clínicos que surgen durante el embarazo en mujeres con fibrosis quística. También se analizan la asesoría, el manejo obstétrico y el resultado perinatal.

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INTRODUCTION

Physiologic changes associated with pregnancy may adversely affect women with cystic fibrosis. Young and healthy women easily adapt to pulmonary, cardiovascular and metabolic changes of pregnancy. Pregnant women with cystic fibrosis require special medical care.

We searched Medline, Google Scholar (up to September, 1994) and the Cochrane Library for cystic fibrosis and pregnancy in English and French languages. Large retrospective studies or case series were thoroughly evaluated.

Pulmonary changes during pregnancy include increased oxygen consumption and minute ventilation. Functional residual capacity (FRC) decreases up to 20% and closing volume exceeds FRC in all pregnant women in supine position at term, making them prone to hypoxemia and oxygen desaturation (1, 2). These normal physiologic changes deteriorate the marginal pulmonary function of women with cystic fibrosis. Inflammation, chronic pulmonary infection and maternal hypoxemia have been associated with intrauterine growth restriction (IUGR) and preterm labor (3, 4).

Adaptive cardiovascular mechanisms of pregnancy include increased cardiac output, heart rate and blood volume and decreased systemic vascular resistances. These effects may cause right heart strain or even right heart failure in women with cystic fibrosis and moderate to severe pulmonary disease. Pulmonary hypertension and cardiovascular compromise usually be-

come more apparent after delivery. More interestingly, gestational pulmonary hypertension is a serious complication with maternal mortality rates as high as 50% (3, 4).

Normal weight gain during pregnancy ranges between 12-16 kg while total caloric needs of pregnancy range between 80.000-124.000 kcal. This correlates well with a daily caloric intake increase of 50-100 kcal in the first weeks of pregnancy to 200-300 kcal at term (2, 5). Energy requirements increase to meet accelerated maternal and fetal metabolic demands. Altered carbohydrate, fat and protein metabolism favors fetal growth and development. Twenty five percent of adults with cystic fibrosis have body mass index (BMI) <19 (5). Pregnant women with cystic fibrosis cannot compensate the increased energy requirements. Patients gradually lose adipose tissue and lower their metabolic rates in order to meet fetal growth demands. Low BMI in pregnancy has been associated with an increased risk for IUGR and preterm labor. Edenborough *et al*. (6) showed that mothers with cystic fibrosis who delivered prematurely gained significantly less weight and had more complications requiring treatment.

High levels of estrogens, progesterone and placental galactogen result in decreased glucose tolerance during normal pregnancies. Renal plasma flow and glomerular filtration rate increase and mild glycosuria is common among 5-50% of pregnant women (1). Glucose tolerance is already decreased in patients with cystic fibrosis. Twenty four percent of patients with cystic fibrosis and 14% of pregnant women with cystic fibrosis suffer diabetes (7, 8). Diabetes mellitus is common in pregnant women with cystic fibrosis and screening is therefore mandatory. Current guidelines (9) suggest two glucose challenge tests in the 20th and the 28th week of gestation, even if the first test was normal. Women with pre-gestational diabetes are at increased risk for abortion, congenital anomalies, hydramnion, macrosomia, IUGR, preterm labor and intrauterine death (9). Neonates born from women with diabetes are also at increased risk for jaundice, polycythemia, hypocalcemia and hypomagnesemia. Mothers with gestational diabetes are also prone to pre-eclampsia, infection and tissue trauma during labor. Caesarian section rates are higher for this category (1,4). For pregnant women with cystic fibrosis, it is important to maintain glucose levels close to their baseline (1, 2, 5, 9).

COUNSELING

The survival of patients with cystic fibrosis has improved over the last decades and thus more women are able to achieve pregnancy; however, outcomes of such pregnancies are not always encouraging. Normal physiological changes of pregnancy may adversely affect the course of the cystic fibrosis. Thorough screening during pregnancy, counseling and honest discussion of directives is often warranted. Counseling should be addressed not only to the mother but also to the couple as an entity.

Genetic screening is mandatory in pregnant women with cystic fibrosis. Screening of the partner is also obligatory in family planning. The gene that causes cystic fibrosis was first identified in 1986 and to date, more than 1856 mutations have been characterized. Cystic fibrosis is caused by mutations in a gene located on the long arm of chromosome 7 (7q31.2). The cystic fibrosis genotype is variable between patient populations (10, 11).

When genetic testing has confirmed that both parents are carriers of cystic fibrosis gene mutation, they should be informed about the risks of invasive prenatal screening and the option of preimplantation genetic diagnosis. When the partner

of a known cystic fibrosis carrier does not carry a mutation the chance they would have a child with cystic fibrosis is reduced but not eliminated due to the tremendous variability of mutations.

The changes in maternal physiology and the need for high caloric intake during pregnancy should be underlined to the couple. In case of compromised pulmonary function of the mother, it is important to inform the couple about the high morbidity and mortality rates and the increased risk for preterm labor. Beyond the consequences for the mother's health, the couple should also be aware of the direct and long-term complications of preterm labor to the baby.

An unexpected pregnancy is not an ideal situation for a woman with cystic fibrosis. In that case, the couple should refer to specialized centers for genetic screening and counseling, as soon as possible. The option of pregnancy interruption due to medical or social reasons should be also explained to the couple (12, 13). Pregnancy interruption in women with severe cystic fibrosis and FVC<40% or deteriorating pulmonary function may be suggested in some cases; however, pregnancies with successful outcomes for both, the mother and the fetus, have been reported, even in mothers with cystic fibrosis and severe pulmonary disease (14-16). When pregnancy interruption is suggested by the attendant Obstetrician/Gynecologist, it should be followed by unbiased counseling. The mother will take the final decision. Pharmaceutical pregnancy termination has proven to be safe in early pregnancy (14). Nonetheless, all women with cystic fibrosis should be informed about the advantages of contraception.

OBSTETRICAL MANAGEMENT

Care of pregnant women with cystic fibrosis includes many health practitioners; however, the role of the Obstetrician is crucial. The care plan should be tailored to each individual patient, taking into consideration the history and the exacerbations of cystic fibrosis disease. The role of the Anesthesiologist is also important because he has great involvement in appropriate management decisions throughout the perioperative period. Additionally, pregnant women with cystic fibrosis may meet their Anesthesiologists during crises, when critical life issues for both, the mother and the baby, have to be discussed (1, 17).

On pregnancy confirmation, routine screening tests are performed. According to guidelines for the management of pregnancy in women with cystic fibrosis (9), more frequent ultrasound and Doppler tests are required due to the risk of IUGR. Special attention should be given to the possible diagnosis of echogenic bowel during ultrasonographic examination. This finding is present in approximately 50-78% of the cases with fetal cystic fibrosis. This ultrasonographic marker is associated with several other conditions. The diagnosis of isolated echogenic bowel is due to fetal cystic fibrosis only in 10% of cases (2). However patients with this diagnosis should have further studies such as amniocenticis (2, 9, 12). If preterm labor is anticipated, corticosteroids are given before birth to speed up fetus's lung development. Close blood glucose level monitoring is often warranted, especially for women with pancreatic insufficiency (7). Insulin pumps and serial blood glucose measurements may be required throughout pregnancy.

The cooperation between the members of the multidisciplinary medical team in the management of pregnant women with cystic fibrosis is important. The chest pathologist has a major role in the follow-up. In the presence of inflammation of the respiratory system, aggressive treatment with intravenous antibiotics is needed. Additionally the

need for changes in the program of physiotherapy is common, especially in women with preexisting reduced pulmonary function (3).

The ideal time for labor depends on the well being of the mother and the fetus during pregnancy. The most common complication is preterm labor, due to iatrogenic etiology. Deterioration of pulmonary function may lead to the decision of preterm labor. Approximately, 25% of labors are preterm in this category of women. Pregnancies that reach the 37th week are electively terminated in the presence of respiratory symptoms (8, 14-16). In the absence of obstetrical indications, normal vaginal delivery is the favorable method for labor. Epidural anesthesia offers a labor without severe stress, while a shorter second stage is preferred (17). Instrumental extraction may reduce the duration of the second stage of labor, as well as the risk of deterioration of the pulmonary function of the mother due to the repeated pushing. The blood loss must be the lowest possible, because postpartum anemia may cause severe complications. During labor, normal saline 0.9% must be avoided. Caesarean section is followed only in the presence of obstetric indications.

Breastfeeding in women with cystic fibrosis during the postpartum period is safe, as the milk does not consist of high levels of sodium. In cases of severe cystic fibrosis (5), breastfeeding could be an exhausting experience with a potential adverse effect on the disease. Counseling depends on the mother's general health condition and has to be individualized.

PERINATAL OUTCOME

The first case of pregnancy in a woman with cystic fibrosis was described in 1960; maternal death occurred six weeks postpartum. Nowadays, many studies focus on the perinatal outcome and rate of complications in pregnant women with cystic fibrosis (15-20) (Table 1). Women with cystic fibrosis have been, theoretically, 20% less fertile than the general population.

Kotloff *at al.* (21) reported that 31.6% of 111 pregnant women with cystic fibrosis were subjected to pregnancy termination. In the same study, the frequency of preterm labor was estimated in 25% and diabetes mellitus occurred in 4.5% of patients. Similarly, Kent *et al.* (22) documented an abortion rate of 4.6%, and therapeutic pregnancy termination in 13.8% of the cases. Maternal morbidity and mortality rates were high, with maternal death occurring within six months in 7.9% of the patients and two years in 13.6% of them. Perinatal death rates were also found to be very high (7.9% of the cases).

Recently, Thorpe-Beeston *et al.* (20) in a retrospective study of 46 gestations of women with cystic fibrosis, described the fetal and maternal outcomes. The fetal outcome could be characterized as favorable. No congenital anomalies and pregnancy terminations were observed. The mean gestational age at labor was 35.9 weeks. All neonates were liveborn and the medium birthweight centile was 31.9. Fifty-two percent of the women suffered pancreatic insufficiency and 35.4% were insulin-dependent. Women with FEV (Forced Expiratory Volume) < 60% were found to be at increased risk for preterm labor and cesarean section. Three out of seven patients with FEV< 40% died in the next 18 months postpartum while four out of eight patients with FEV 40-50% died within 2-8 years after labor. It seems that when the FEV>70%, pregnancy is considered to be safe for women with cystic fibrosis. Patients with a FEV<50%, pulmonary hypertension or right heart strain are associated with high mortality rates and adverse perinatal outcomes (15-20, 23, 24).

TABLE I
CLINICAL SERIES OF PREGNANCIES OF WOMEN WITH CYSTIC FIBROSIS: MATERNAL AND OBSTETRIC CHARACTERISTICS

	N° of pregnancies	Assistive reproduction techniques (%)	Pre-pregnancy FEV1 (mean,%)	Pre-pregnancy BMI (kg/m²)	Post pregnancy FEV1 (mean,%)	Preterm delivery (%)	Caesarian section (%)	Vaginal or instrumental delivery (%)
Thorpe-Beston *et al.*[20] (2013)	46	10.4	60.9	21.9	58.4	43.5	50	50
Burden *et al.*[15] (2012)	15	21	63.6	21.4	61.7	14	0	100
Lau *et al.*[16] (2011)	20	N/A	65.6	21	60.8	25	N/A	N/A
Cheng *et al.*[18] (2006)	16	N/A	61	21.2	N/A	43.7	18.8	81.2
Odegaard *et al.*[19] (2002)	33	N/A	76	54.9	N/A	43.5	24	76

In another study of eight women with cystic fibrosis who achieved 11 pregnancies and delivered 12 neonates, the fetal outcome was satisfactory as well (25). No miscarriages, terminations or neonatal deaths occurred. Three cases of preterm labor (25%) were noticed, whereas one infant was born with esophageal atresia.

Long-term outcomes of pregnancy in women with cystic fibrosis have also been studied (14, 26). It seems that satisfactory pre-gestational pulmonary function plays a crucial role in the course of the disease postpartum (1). Women with a FEV< 50% had lower decade-survival rates, while the same survival rates of women with a FEV>50% reached 89%. On the other hand, Goss et al. (26) found that pregnancy had no adverse effect on survival of women with cystic fibrosis. The researchers did not find evidence of correlation of FEV values or diabetes mellitus with poorer perinatal outcomes; however, 20% of the study population died 10 years postpartum and that rate doubled for women with a FEV<40% as predicted.

CONCLUSIONS

Although, in general, pregnancies of women with cystic fibrosis result in favorable perinatal outcomes, they are considered and managed as high risk pregnancies by an experienced multi-disciplinary team, including obstetrician-gynecologists, anesthesiologists, chest physicians, geneticists and physiotherapists, in specialized centers. Pre-pregnancy counseling is the cornerstone in obstetric care. During pregnancy, closer monitoring with serial ultrasound and fetal Doppler examinations are required because of the elevated risk for intrauterine growth restriction or preterm delivery, in order to estimate maternal and fetal wellbeing, as well as for the definition of the appropriate timing of delivery.

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