The impact of cystic fibrosis upon the evolution of pregnancy, fetus and newborn

Impactul fibrozei chistice asupra evoluției sarcinii și a dezvoltării fetusului și nou-născutului

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Abstract

International statistics confirm that in recent years more and more women with cystic fibrosis report pregnancy. In the past, pregnancy was associated with a high rate of miscarriage, premature birth, and newborn mortality. We report a case of a 22-year-old female with cystic fibrosis who got pregnant being in an advanced stage of the disease, associating COPD, bilateral saccular bronchiectasis, multiple air cysts of the right upper lobe, pulmonary fibrosis, chronic pulmonary infection with Pseudomonas aeruginosa, Burkholderia cepacia, second-degree chronic respiratory failure, exocrine pancreatic insufficiency associated with severe weight and height growth disorders (body weight: 43 kg, height: 158 cm, BMI: 17.22). At the term of 35 weeks of gestation the patient underwent the planned caesarean section, giving birth to a live newborn male with a body mass of 1470 g, height: 40 cm, head circumference: 29 cm, thoracic circumference: 23 cm, Apgar score: 7/8. The pregnancy in this patient with a severe form of cystic fibrosis, chronic pulmonary destructive changes, severe height and weight deficiencies was carried on with complications and negative impact upon the child with chronic intrauterine hypoxia, intrauterine growth retardation, highly marked morphological and functional immaturity.

Keywords: ***cystic fibrosis, pregnancy, intrauterine growth retardation***

Rezumat

Publicațiile internaționale confirmă faptul că tot mai multe femei cu fibroză chistică (FC) raportează sarcină, mai ales în timpul ultimului deceniu. În trecut, sarcina la femei cu FC era asociată cu o rată înaltă de avort spontan, naștere prematură și mortalitate a nou-născutului. În lucrare este prezentat cazul unei femei în vârstă de 22 ani cu FC care a rămas gravidă fiind într-un stadiu avansat de FC, cu bronșită cronică obstructivă, bronșiectazii bilaterale sacciforme, pneumatocele în lobul superior drept, fibroză pulmonară, infecție pulmonară cronică cu Pseudomonas aeruginosa, Burkholderia cepacia, insuficiență respiratorie cronică de gradul II, insuficiență pancreatică exocrină asociată cu tulburări severe de greutate și de creștere a taliei (greutate corporală: 43 kg, înălțimea: 158 cm, IMC: 17,22). La termenul de 35 de săptămâni de gestație, pacienta a fost supusă operației cezariene planificate, dând naștere unui băiat viu, cu o masă corporală de 1470 g, înălțimea de 40 cm, circumferința capului de 29 cm, circumferința toracică de 23 cm și scor Apgar 7/8. Sarcina la o pacientă cu o formă severă de fibroză chistică, modificări pulmonare cronice și tulburări nutriționale severe evoluează cu complicații și efecte negative asupra copilului, cu hipoxie cronică intrauterină, întârzierea creșterii intrauterine, imaturitate morfologică și funcțională extrem de marcantă.

Cuvinte-cheie: ***fibroză chistică, sarcină, întârzierea creșterii intrauterine***

Introduction

Cystic fibrosis (CF) is one of the most frequent monogenic diseases, autosomal recessive transmitted in the Caucasian population, being characterized by severe respiratory, digestive and nutritional conditions, with progressive chronic evolution and potential fatality. In the Republic of Moldova, according to preliminary information, the frequency of this genetic disease is 1:2000 live newborns. Studies show that every 25th European is a healthy carrier of a mutation in the CFTR gene responsible for CF [(1)].

The medical and social importance of this disease is determined by the low life expectancy, which in developed countries was in 1969 of 14 years of age, in 1990 - 28 years, for those born in 2000 the estimated lifespan is 30-32 years, while for those born in 2010 the lifespan is greater than 40 years of age. For developing countries, the lifetime since diagnosis is between 2 to 16 years of age, with a modest future expectancy (22-26 years). The newest health care therapeutic trends for patients with cystic fibrosis have led to important progress in preventing CF complications or delaying their onset, improvement of life quality and life expectancy, increasing the chances for proper fertilization in adult patients, especially in women with CF.

International statistics confirm that more women with CF report pregnancy, especially during the last decade. In the past, pregnancy in CF mothers was associated with a high rate of miscarriage, premature birth, and newborn mortality. The recent data confirm that the results for pregnancy in women with CF are: the rate of live newborn reaches 70-90%, the miscarriage rate is not higher than in the general population, and the prematurity index is 8-46% for different countries. Some pregnant women with CF have a poor health condition, including severe impairment of respiratory function, triggering therefore the premature births[(2-6)].

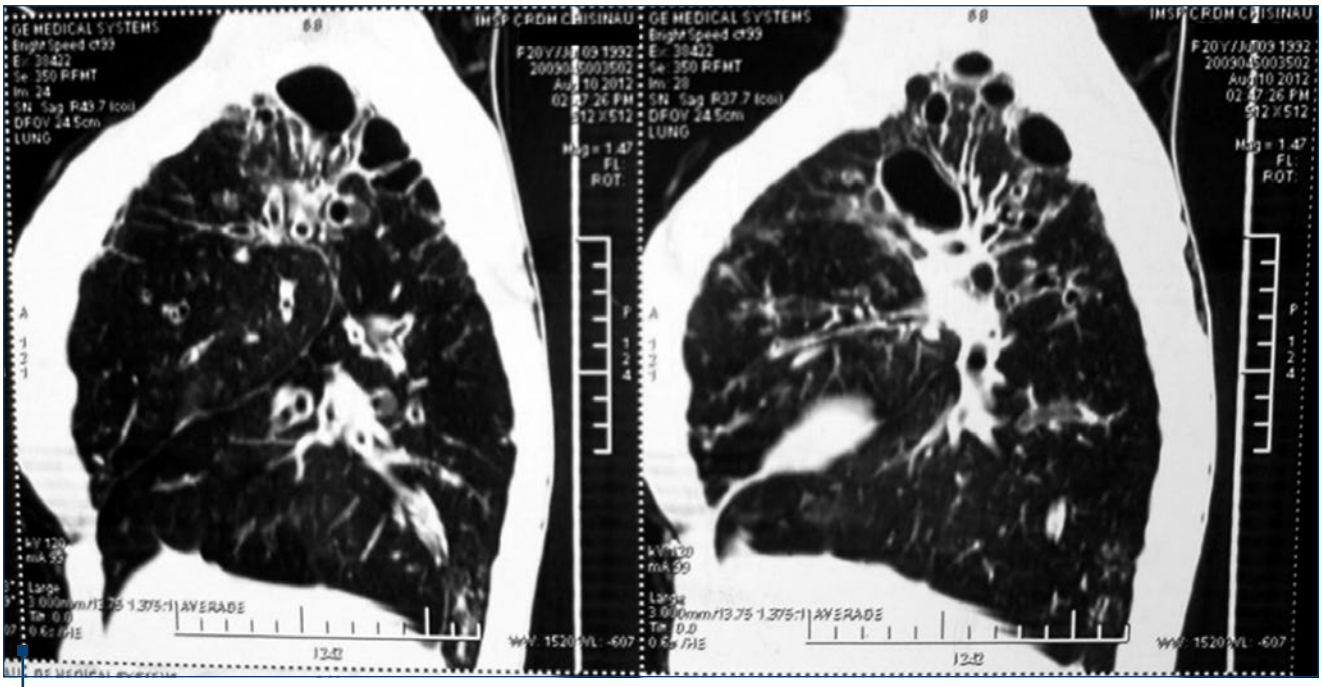

Figure 1. *CT of the patient with cystic fibrosis*

Clinical case

The female patient, born in 1992 (22 years of age), was first diagnosed with CF at the age of 9. Her medical history showed high respiratory infectious morbidity since infancy, at the age of 18 months having a bronchopneumonia followed by episodes of bronchitis, recurrent wheezing, pneumonias which clinically manifested with painful cough, difficult elimination of bronchial secretions and noisy breathing. The recurrent bronchopulmonary infections during the first 3 years of her life were usually 5-8 episodes per year, thus the child became frequently sick and the respiratory diseases had a slow evolution with the development of pulmonary complications (pleural effusion, destructive pulmonary lesions). At preschool and school age, a persistent chronic cough syndrome installed, which was a result of the frequent respiratory infections. The cough was accompanied by sticky, adherent, gluey secretions with infectious bacterial component, mucopurulent (yellow or green colored), abundant, sometimes with fetid smell; the cough also appeared during the night, being paroxysmal and tiresome. The clinical respiratory manifestations constantly included the obstructive syndrome described by wheezing, prolonged expiration, in the context of respiratory infectious episodes.

The nutritional status of the patient indicated insufficient weight growth during infancy, thus at the age of 12 months she had 9,1 kg, and afterwards the weight growth deficiency was between the 3rd and the 10th percentile, leading to stature growth deficiencies. The patient's life history shows that she was born at term, without complications in her mother's first pregnancy. Her birth weight was 3250 g, with 50 cm height. She also had prolonged neonatal jaundice. There have been mentioned chronic respiratory diseases in her father's relatives (chronic bronchitis in her mother and sisters). The clinical- and exploratory-based CF diagnosis in this patient was done late – at the age of 9-years-old, and was based on high values in the sweat test (87.2 mmol/l) and the genetic examination of the *CFTR* gene, that allowed identifying the mutation *ΔF508* in heterozygote state. At this age, she developed COPD, moreover the FVC and FEV_1 values went under 50% of predicted value, with pulmonary fibrosis, bronchiectasis, pulmonary infection with *S. aureus and H. influenzae*; after 5 years she developed an infection with *Pseudomonas aeruginosa*, at the age of 21 - an infection with *Stenotrofomonas maltofilia*, and at the age of 22 - an infection with *Burkholderia cepacia*.

At the age of 22, after 2 years of living with her partner, she got pregnant, being at a CF stage associated with COPD, bilateral saccular bronchiectasis, multiple air cysts of the right upper lobe, pulmonary fibrosis (Figure 1), chronic pulmonary infection with *Pseudomonas aeruginosa* and *Burkholderia cepacia*, second-degree chronic respiratory failure (Table 1), exocrine pancreatic insufficiency associated with weight and height growth severe disorders (body weight: 43 kg, height: 158 cm, BMI: 17.22).

At the term of 27-30 weeks of gestation, the patient was hospitalized in the intensive care unit of the Mother and Child Institute maternity in critical status due to acute pulmonary infection, SaO_2 being under 90%. The chest X-ray performed on arrival showed chronic pulmonary changes with bilateral saccular bronchiectasis, polisegmentar pneumonia with right sero-fibrinous pleurisy, air cysts and atelectasis of the right upper lobe. The abdominal ultrasound showed a liver right lobe of 130 mm, left lobe: 65 mm; portal vein: 8 mm; pancreas: 20x11x17 cm, regular shaped, homogenous parenchyma, highly echogenic; spleen: 101x51 mm, homogenous; splenic vein: 5 mm; right kidney: 106x43 mm; left kidney: 114x45 mm, parenchyma: 15 mm, and deformed left renal pelvis. The

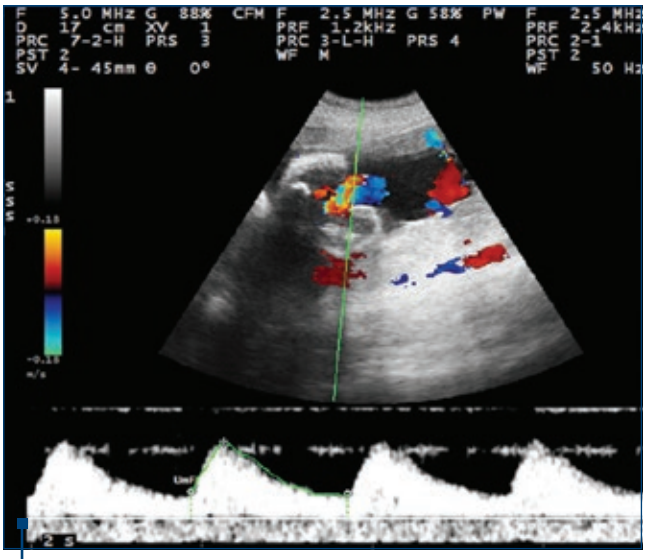

Figure 2. *Doppler velocimetry of the umbilical artery*

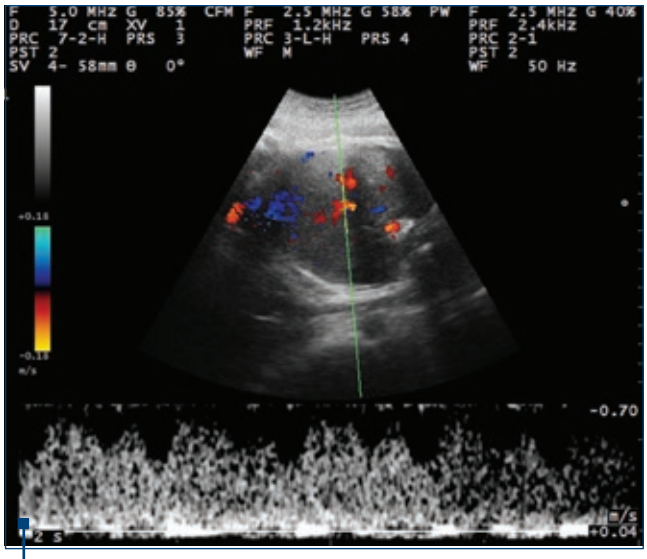

Figure 3. *Doppler velocimetry of the ductus venous*

pregnancy ultrasound showed chronic intrauterine fetal hypoxia with chronic fetoplacental failure, which has been induced by the severe chronic pulmonary disease of the pregnant, associated with severe nutritional disorders due to CF.

A complex therapeutic approach was started: antibiotic therapy with ceftazidime, amikacin and meropenem, bronchodilators for the obstructive syndrome, oxygen therapy, pancreatic ferments therapy (pancreatinum), ursodeoxycholic acid, vitamins and minerals. The treatment allowed the control of the pulmonary infection with the improvement of respiratory function, nutritional status recovery of the patient, followed by a proper pregnancy evolution. During the following 2 weeks the patient had taken CF medication at home, in addition to the antibiotic therapy (tobramycin inhalation) to control the *Pseudomonas aeruginosa* infection.

The next planned hospitalization of the patient was for the 33rd week of gestation. At that time, pregnancy evaluation tests were performed, a check for the anatomic and functional status of the fetus and the caesarean section for the pregnant was planned. The patient had a I–II degree anatomic narrow pelvis and a severe form of CF. The obstetrical examination showed a soft and non-tender abdomen, ovoid and normotonic uterus, mucous vaginal secretions and the fetus movements were well felt, with rhythmic, clear toned fetus heartbeats with a frequency of 146 per minute.

The ultrasound examination found an asymmetric type intrauterine growth retardation (IUGR), as the abdominal circumference and the estimated fetal weight were under the 3rd percentile, the presumptive weight - 1450 g, and the other biometric indices such as the head circumference, biparietal diameter and the femur length were according to the term of gestation. The Doppler examination of the umbilical artery (RI: 0.68 and PI: 1.18) and uterine arteries (left UA RI: 0.56 and PI: 1.05; right UA RI: 0.6, PI: 0.4) did not show signs of fetal circulatory failure. The medial cerebral artery Doppler registered the velocimetry curve with hemodynamic values appropriate for the gestation term (RI: 0.81, PI: 2.12), and the cerebral/placental ratio appeared to be above unit, which let us conclude that there was no evidence of fetal hypoxia. The Doppler results evaluation of the blood flow in the venous duct showed the presence of the diastolic component, establishing a compensatory fetal state as a result. After the complex Doppler ultrasound examination, we concluded: fetal asymmetric type IUGR, absence of circulatory failure and fetus hypoxia with a compensatory condition (Figure 2 and Figure 3).

At the term of 35 weeks of gestation, the patient underwent the planned caesarean section, giving birth to a living newborn male, with a body mass of 1470 g, height: 40 cm, head circumference: 29 cm, thoracic circumference: 23 cm, Apgar score: 7/8. During the operation an appendectomy was also performed, due to acute phlegmonous appendicitis.

The clinical examination of the newborn found intrauterine growth retardation with a weight and stature deficiency caused by mother's severe pulmonary disease and nutritional disorders, induced by the severe form of CF. The imagistic examination of the child showed no pathologic pulmonary and abdominal organ changes. The cardiac ultrasound examination performed in the early neonatal period showed the patent foramen ovale with a 2 mm diameter and the persistence of the arterial channel about 1.1 mm, first-degree tricuspid valve insufficiency, and first-degree pulmonary artery valve insufficiency. During the first 3 weeks the child has gained 210 g, and at the age of 3 months his body mass was 2600 g (Figure 4).

Discussions

Women with CF and a good pulmonary function (FEV_1: 70-50%), and stable spirometry values before getting pregnant have a very good pregnancy tolerability and a low index of maternal mortality. On the contrary, women with CF and reduced pulmonary function have a high risk of improper pregnancy evolution. The long-

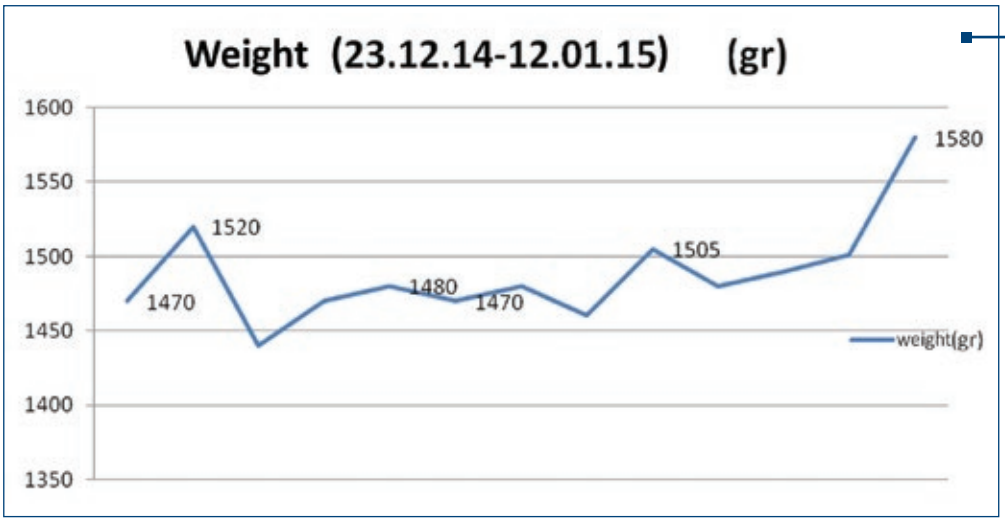

Figure 4. *Weight curve of a child born from a patient with cystic fibrosis*

Table 1 Spirometry of our patient with cystic fibrosis

Spirometry data (%)	2003	2005	2008	2012	2013	2014
FVC	51	48	41	29	33	33
FEV_1	40	47	39	19	19	20
TT	71	88	53	65	60	52
FEV_{25-75}	23	22	14	9	10	9
PEF	17	21	19	24	15	14
MEF_{75}	18	21	17	9	9	11
MEF_{50}	18	22	15	7	7	9
MEF_{25}	21	26	13	13	11	10

term prognosis for patients with stable pulmonary function is that pregnancy does not affect the health condition of the CF woman; however, it may have a negative impact on FEV_1 in less than 40% of patients [7].

Pulmonary hypertension and cor pulmonale in patients with CF are considered absolute pregnancy contraindications, being associated to a high probability of maternal death during pregnancy, birth and the postpartum period. The maternal infection with *Burkholderia cepacia* can be a relative pregnancy contraindication, as it may result in complications and maternal mortality risk associated with the presence of this pulmonary infection in the pregnant with CF.

Currently, there is a consensus that pregnancy does not reduce significantly the survival rate in women with CF. Unaffected health condition with stable pulmonary function is a good factor for the long-term prognosis for women with CF, thus ensuring the safety of a fine pregnancy evolution[7].

Conclusions

A pregnancy in a female patient suffering from cystic fibrosis is a major challenge for the mother, the fetus, the pulmonologist, the obstetrician and the neonatologist. Considering this is a rare situation, there are no guidelines for the approach of a pregnancy in a CF patient. The case we presented had a happy ending, but with severe suffering for the mother and fetus. There is a high risk of maternal death and development issues for the fetus. This should emphasise the importance of prenatal counseling, as a CF female patient should be aware of the possible complications of the pregnancy. The multidisciplinary approach of such a case – including the pulmonologist, the obstetrician and the neonatologist – should be the rule for these patients. ■

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