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Original Article

Pregnancy outcome in women with cystic fibrosis and poor pulmonary function

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ABSTRACT

Background: To investigate how poor pre-gestational pulmonary function influenced pregnancy outcome and clinical status evolution in women with cystic fibrosis.

Methods: Pregnancies in women without lung transplantation with a first delivery reported to the French cystic fibrosis registry between 2000 and 2012 were identified. Pregnancy outcomes and clinical trends (body mass index – BMI, and pulmonary function) over a 4-year follow-up in women with poor pre-gestational pulmonary function, defined as forced expiratory volume (FEV_1) ≤ 50%, were compared to those in women with FEV_1 > 50%.

Results: A total of 149 women had a first delivery and 36 (24.2%) of these had pre-gestational $FEV_1 \leq 50\%$. There was no significant difference in age or frequency of assisted conception between the 2 groups. The rate of cesarean section was significantly higher in women with $FEV_1 \leq 50\%$ (43.7% vs. 21.1%, $p = .01$). The frequency of preterm birth did not differ significantly between the two groups, but median infant birthweight was significantly lower in women with $FEV_1 \leq 50\%$ (2705 g; range: 650–3700 vs. 3044 g; range: 1590–3860, $p = .003$). Despite significantly lower FEV_1 and BMI the year before pregnancy for women with poor pulmonary function, the decline in these parameters during the study period did not differ significantly between the two groups.

Conclusion: Poor pre-gestational pulmonary function in women with cystic fibrosis was associated with a higher rate of cesarean section and a clinically significant impact on fetal growth, but was not associated with more important pulmonary and nutritional decline over the study period.

1. Introduction

Improved survival and overall health in cystic fibrosis (CF) [1] has led to an increased number of CF women making childbearing decisions and long-term survival does not appear to be negatively impacted by pregnancy [2–5]. Women with CF who become pregnant have been found to have similar respiratory decline compared to non-pregnant women with CF [5,6]. A number of studies have shown that CF itself does not affect maternal pregnancy survival [2,7] and does not affect maternal lung function, nutrition, and exacerbation rate [8]. We recently reported no increased risk of deterioration of maternal pulmonary and nutritional status in CF women with pre-pregnancy diabetes [9]. Negative outcomes seem mostly associated with poor lung function ($FEV_1 < 50\%$) [10,11]. Since the published pregnancy outcome data are limited for CF women with poor pulmonary function (<50%), we compared pregnancy outcome and clinical evolution (body mass index and pulmonary function) of women with and without poor pre-gestational pulmonary function over a total period of four consecutive years starting the year before pregnancy until two years after pregnancy.

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2. Methods

Study population, collected data, outcome measures were previously described [9]. According to the current French legislation, institutional review board approval was not needed; the study did receive approval from the relevant data protection agencies (*Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé*, registration number 10536, December 2015) and from the national data protection commission (*Commission Nationale de l'Informatique et des Libertés*, registration number 1202233, February 2016). For the purpose of the analyses herein we studied CF women with a first pregnancy leading to birth between January 1, 2001 and December 31, 2012, and with a two-year follow up delivery without a second pregnancy. Women were categorized according to their pulmonary status the year before pregnancy: poor pulmonary function ($FEV_1 \leq 50\%$) and non-poor pulmonary function ($FEV_1 > 50\%$). Women with lung transplantation were excluded from the study. Endpoints were outcomes of pregnancy and change in FEV_1 and BMI evolution over the study period. To analyze FEV_1 and BMI, we considered for each women a study period of four consecutive years starting the year before pregnancy until two years after pregnancy. Data were therefore collected over the 2000 to 2014 period. Clinical data are exctracted from the French CF registry which is completed annually for each patient. Data extracted for the present study included forced expiratory volume in one-second (FEV1) (best value of the year) and body mass index (BMI; value measured at the time of best FEV1). These values are the one considered in the Registry and correspond to the best result of the year for each patient for FEV1. None of the patients included were treated with CFTR modulators.

Descriptive data are presented as median with range and number of available data. For comparisons between groups, the Chi-square or Fisher's exact test was performed for qualitative variables and Wilcoxon's test for quantitative variables. We fit a linear mixed effects model to examine whether the trend in FEV1 and BMI over time was different according the pulmonary status the year before the pregnancy. The time scale for the analysis was years since pregnancy. The model contained random- and fixed-effects of time since pregnancy, pulmonary status group (FEV1 > 50% vs FEV1 ≤ 50% the year before the pregnancy), and a time-by-group interaction. A Wald test of the interaction effect was used to test the change in trend between groups.

All analyses were performed using SAS software version 9.3 (SAS Institute; Cary, NC, USA). All *p*-values reported are two-tailed; values <0.05 were considered statistically significant.

3. Results

3.1. Women characteristics and pregnancy outcomes

A total of 149 pregnancies were analyzed: 36 (24.2%) pregnancies occurred in women with $FEV_1 \leq 50\%$ and 113 (85.8%) in women with $FEV_1 > 50\%$. No death or lung transplantation was observed during the two years of follow-up after pregnancy. Age was not significantly different between the two groups ($p = .70$), and median BMI was lower for $FEV_1 \leq 50\%$ women ($p \leq .001$). Data concerning chronic colonization with *Pseudomonas aeruginosa* were not available. No significant difference was observed between the two groups for diabetes (10/36 (27.8%) in the group with $FEV_1 \leq 50\%$ and 23/111 (20.7%) in the group with $FEV_1 > 50\%$, $p = .38$; two missing data), or the pancreatic insufficiency (respectively 30/35 (85.7%) and 81/96 (84.4%), $p = .85$, 18 missing data). There was no significant difference in the frequency of assisted conception between women with $FEV_1 \leq 50\%$ (35.3%) and women with $FEV_1 > 50\%$ (39.4%), $p = .80$; and the frequency of cesarean section was significantly higher in women with $FEV_1 \leq 50\%$ (43.7% vs. 21.1%, $p = .01$). The frequency of preterm birth did not differ significantly between the two groups. Median infant birthweight was significantly lower in women with $FEV_1 \leq 50\%$ (2705 g, range: 650–3700 vs. 3044 g, range: 1590–3860; $p = .003$; Table 1).

Table 1
Women characteristics the year of pregnancy and newborns characteristics.

	Women with $FEV_1 \leq 50\%$ $n = 36$	*Women* with $FEV_1 > 50\%$ $n = 113$	p
Women characteristics			
Median age, in year (range)	26 (18–41)	26 (17–41)	0.70
Median FEV_1, in % (range)	42.3 (32.5–49.9)	76.6 (50.1–131.5)	≤ 0.001
Median BMI, in Kg/m^2 (range)	19.3 (15.6–28.8)	21.1 (13.0–34.5)	≤ 0.001
Median IV antibiotic courses, in day/year (range)	30.0 (0–105.0)	0 (0–89.0)	≤ 0.001
Median IV antibiotic courses, in number/year (range)	2.0 (0–14.0)	0 (0–6.0)	≤ 0.001
Pregnancies characteristics			
Medically assisted conception (%)	12 (35.3)	39 (39.4)	0.80
Cesarean-section delivery (%)	14 (43.7)	20 (21.1)	0.01
Medical interruption of pregnancy (%)	2 (5.6)	2 (5.6)	0.13
Abortion (%)	0	7 (6.2)	0.13
Newborns characteristics			
Premature birth (%)	13 (41.9)	27 (28.7)	0.17
Birth weight in g (range)	2705 (650–3700)	3044 (1590–3860)	0.003
Dead newborns (%)	0	0	

BMI: Body Mass Index, FEV_1: Forced Expiratory Volume in 1 s (%), g: grams.

3.2. Change in FEV_1 and BMI over the study period

The median (range) FEV_1 at Y-1 was 42.3% (32.5–49.9) and 76.6% (50.1–131.5) respectively in the group with $FEV_1 \leq 50\%$ and $FEV_1 > 50\%$; it was 41.1% (24.3–59.9) and 73.7% (31.8–118.9) the year of pregnancy, 39.0% (22.1–93.2) and 70.4% (24.4–131.4) at Y + 1, and 38.3% (18.3–67.5) and 69.2% (13.7–128.4) at Y + 2, respectively. The mean FEV_1 change per year over the four-year study period was −0.9% (95% CI: −2.5 to 0.8, $p = .31$) in the group $FEV_1 \leq 50\%$ women whereas it was estimated at −2.3% (95% CI: −3.3 to 0.6) in the group $FEV_1 > 50\%$ women. The change in FEV1 over time was not significantly different between groups ($p = .16$, Table 2).

The median (range) BMI at Y-1 was 18.7 (15.4–25.1) and 20.4 (15.1–34.1) respectively in the group with $FEV_1 \leq 50\%$ and $FEV_1 > 50\%$; it was 19.3 (15.6–28.8) and 21.1 (13.0–34.5) the year of pregnancy, 19.1 (14.5–27.6) and 20.7 (14.5–31.2) at Y + 1, and 18.7 (14.9–28.0) and 20.0 (15.8–37.0) at Y + 2, respectively. The mean BMI change per year over the four-year study period was estimated at −0.1 kg/m^2 (CI95%: −0.4 to 0.1) in the group $FEV_1 \leq 50\%$ women and was not significant ($p = .25$). No significant difference in BMI change over time was shown between groups ($p = .41$).

Table 2
Results of linear mixed-effect model analysis of change in FEV1 according to the pulmonary status the year before pregnancy.

Factor	Coefficient (SD)	[CI95%]	p-Value
Intercept*	41.8 (2.9)	[36;47.6]	<0.01
Time (in year)**	−0.9 (0.8)	[−2.5;0.8]	0.31
$FEV_1 > 50\%$	33.7 (3.4)	[27;40.3]	<0.01
Time * $FEV_1 > 50\%$***	−1.4 (1)	[−3.3;0.6]	0.16

SD: Standard Deviation, CI: Confident Interval.
* mean FEV1 inthe year of pregnancy for women in the group with FEV1 ≤ 50%.
** slope i.e. mean FEV_1 change per year for women in the group with $FEV_1 \leq 50\%$.
*** change in slope for women in the group with $FEV_1 > 50\%$.

Table 3
Results of linear mixed-effect model analysis of change in BMI according to the pulmonary status the year before pregnancy.

Factor	Coefficient (SD)	[CI95%]	p-Value
Intercept*	19.3 (0.4)	[18.4;20.1]	<0.01
Time(in year)**	−0.1 (0.1)	[−0.4;0.1]	0.25
$FEV_1 > 50\%$	1.9 (0.5)	[0.9;2.9]	<0.01
Time ∗ $FEV_1 > 50\%$***	0.1 (0.1)	[−0.2;0.4]	0.41

SD: Standard Deviation, CI: Confident Interval.
* Mean BMI (kg/m^2) in the year of pregnancy for women in the group with FEV1 ≤ 50%.
** Slope i.e. mean BMI change per year for women in the group with $FEV_1 \leq 50\%$. Data from the year beforepregnancy were excluded of the linear mixed-effects model analyses given the nonlinear trend in BMI before and after pregnancy.
*** Change in slope for women in the group with $FEV_1 > 50\%$.

Considering only a three-year study period starting the year of pregnancy for BMI evolution analysis given the nonlinear trend in BMI before and after pregnancy, we observed a significant mean BMI change per year in the group $FEV_1 \leq 50\%$ ($-0.5\,kg/m^2$; CI95%: −0.8 to −0.1; $p = .02$). The change in BMI over time was not significantly different in the group $FEV_1 > 50\%$ compared to the group with $FEV_1 \leq 50\%$ ($p = .52$, Table 3).

4. Discussion

The present study found that despite lower FEV_1 and BMI the year before pregnancy the change in these parameters following pregnancy was not greater for women with poor pre-gestational pulmonary function. We observed a similar rate of medically assisted conception in both groups of women. This is in favor of a similar fertility function in healthy and severely ill CF patients, with sufficient fertility in women with poor pulmonary function to achieve a spontaneous or medically assisted pregnancy [12]. The more frequent cesarean section for women with poor pulmonary function may be explained by the fear of poor tolerance of vaginal delivery for these patients. For such patients, an individual management plan for delivery should be made, taking in to account gestational age, ultrasound estimated fetal weight, disease severity, and assessed fetal wellbeing. In most cases, if maternal health is maintained and if the fetus is growing normally, vaginal delivery at term is an option and maternal lung function should be optimized prior to delivery [13]. One reason for higher rate of cesarean in women withlower pulmonary function might be that obstetrical center have different practices concerning delivery in CF without clear recommendations editing by expert. However, the birth weight of newborns was significantly lower in the group with $FEV_1 \leq 50\%$. This difference may partly be explained by the frequency of preterm birth, which was close to 42% in the group with poor pulmonary function, although not statistically significant. Furthermore, Cheng et al. demonstrated that mothers with an $FEV_1 < 50\%$ gave birth to infants of significantly lower weight despite similarities in gestational age [14]. One hypothesis may also be that women with low lung function spend more energy, therefore less of the gained energy is transferred to the growing baby.

As women affected by CF now live longer, pregnancy in those with poor pulmonary function is an important consideration for both medical teams and patients. It is of importance to discuss the decision to become pregnant and to explain the risk in terms of pregnancy outcomes and clinical course after pregnancy with such patients. Herein, we provide reassuring data as there was no significant difference in pulmonary and nutritional status decline according to FEV_1 status ($FEV_1 \leq 50\%$ vs. $> 50\%$). The reasons of such stability may be partly explained by reinforcement of treatment for pregnant CF women including specific nutritional and physiotherapy care, and more frequent CF center visits during pregnancy. However, a selection bias cannot be excluded that non-clinically stable CF women would not have chosen pregnancy. In addition, it is of note that there was no death or pulmonary transplantation related to pregnancy in the present study, but also that there was no case of colonized with *Burkholderia cepacia*. This could be of importance for pregnant CF patients as Tanser et al. reported that among 3 out of 4 case reports of death during pregnancy were colonized with this bacteria [15]. This study is retrospective and potential missing data may have induce bias and contribute to the absence of difference between our 2 groups. A sensitive analysis of women with very poor pulmonary function was not realized due to the small sample size of the group with low pulmonary function as it would not have been relevant on a statistical point of view, but might also contribute to the absence of difference.

In the present study, none of the patients were treated with CFTR modulators owing to the study period. However, fertility in healthy and severely ill CF patients could be theoretically improved by systemic treatments that improve CFTR functionality such as ivacaftor [16], however there is a lack of data from clinical trials [17]; the only data available are from unintended pregnancies which led to the birth of healthy babies [18,19].

5. Conclusion

The changes in maternal pulmonary and nutritional status during and after pregnancy in pregnant women with CF were not influenced by pre-gestational pulmonary function status. Further work is required to assess the risks and benefits of CFTR modulators in this context.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

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Authorship

Conception and design of the study: QR, SPB, MR, AD, ST, ID.
Acquisition of data: QR, SPB, AD, LL.
Drafting the article: QR, LL, ST, ID.
Final approval of the version to be submitted: QR, CRJ, SPB, AD, MR, LL, RNJ, SD, ST, ID.

Declarations of Competing Interest

None

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