Perinatal Outcomes in Cystic Fibrosis Women: Data From the Italian Cystic Fibrosis Registry.

Rita Padoan (✉ ritaf54@gmail.com)

Università degli Studi di Brescia <https://orcid.org/0000-0002-0624-8125>

Serena Quattrucci

Lega Italiana Fibrosi Cistica onlus

Annalisa Amato

Lega Italiana Fibrosi Cistica onlus

Marco Salvatore

Istituto Superiore Di Sanità, Roma

Barbara Giordani

Lega Italiana Fibrosi Cistica onlus

Donatello Salvatore

Cystic Fibrosis Center, San Carlo Hospital, Potenza

Giuseppe Campagna

Università degli Studi di Roma Dipartimento di Medicina Clinica e Sperimentale

Research article

Keywords: Cystic fibrosis, Italian Cystic Fibrosis Registry, pregnancy outcomes, birth weight, caesarean delivery

Posted Date: July 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-46020/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Acta Obstetrica et Gynecologica Scandinavica on June 14th, 2021. See the published version at <https://doi.org/10.1111/aogs.14190>.

PERINATAL OUTCOMES IN CYSTIC FIBROSIS WOMEN: DATA FROM THE ITALIAN CYSTIC FIBROSIS REGISTRY.

Rita Padoan^{a,b}, Serena Quattrucci^{b,c}, Annalisa Amato^c, Marco Salvatore^{b,d}, Barbara Giordani^c, Donatello Salvatore^{b,e}, Giuseppe Campagna^{e,f}

Authors' affiliations:

- a) Cystic Fibrosis Center, Department of Pediatrics, University of Brescia, Brescia, Italy
- b) Scientific Board, Italian Cystic Fibrosis Registry, Rome, Italy
- c) Lega Italiana Fibrosi Cistica ONLUS-LIFC, Rome, Italy
- d) National Center Rare Diseases, Undiagnosed Rare Diseases Interdepartmental Unit, Istituto Superiore di Sanità, Rome, Italy
- e) Cystic Fibrosis Center, Hospital San Carlo, Potenza, Italy
- f) Department of Clinical and Molecular Medicine – University of Rome “La Sapienza”

*Corresponding author:

Rita Padoan, MD

Cystic Fibrosis Regional Support Center, Lombardy Region,
Department of Pediatrics, University of Brescia, Brescia, Italy
Piazzale Spedali Civili 1, 25123 Brescia, Italy

E mail: ritaf54@gmail.com

Tel: +39 030 3998764

ABSTRACT

Data from the Italian Cystic Fibrosis Registry (ICFR) concerning pregnancies in the period 2010-2015 were used to investigate the association between the pre-conception clinical status and perinatal outcomes of women with CF.

The assessed clinical variables were genotype, pre-conception age, the body mass index (BMI), and the percentage of predicted forced expiratory volume in one second (ppFEV₁); the analysed outcomes were gestational age, birth weight (BW), and the frequency of caesarean deliveries.

Complete information concerning mother and child was available for 56 pregnancies that came to term. The median pre-conception age was 30.8 years (18.7-42.3); median BMI was 21.5 kg/m² (16.5-26.8); and median ppFEV₁ was 73.9% (30-128%). Twenty-four women (42.8%) carried class I-III mutations, and 25 (44.8%) at least one mutation conferring residual CFTR function or having variable clinical consequences.

The median duration of pregnancy was 37 weeks (31-41), and the frequency of prematurity was 28.30%. Median BW was 2,910 g (1,300-3,650). There was a positive correlation between BMI and ppFEV₁ in comparison with BW ($\rho=0.29$ and $\rho=0.31$ by $p=0.048$ and $p=0.032$, respectively), but no correlation between age and BW. The overall frequency of caesarean sections was 63.64%, but it was 77.27% among the women with severe genotypes. A lower ppFEV₁ corresponded to a lower BW ($p=0.047$). Respiratory function had no effect on the percentage of caesarean deliveries.

The nutritional status and respiratory function of CF mothers correlate with their newborn's BW. Caesarean sections are very frequent, even in young women with normal lung function.

Key words: Cystic fibrosis; Italian Cystic Fibrosis Registry; pregnancy outcomes; birth weight; caesarean delivery

INTRODUCTION

Cystic Fibrosis (CF) is the most frequent autosomal recessive disease among Caucasians due to alterations in the CF transmembrane regulator (CFTR) gene. This multi-organ disease reduces the life expectancy of affected subjects. There have been noticeable improvements in the prognosis of CF patients over the last 20 years due to earlier diagnoses as a result of neonatal screening, improved patient management at specialised Centres, and the use of treatments that improve CFTR protein function, all of which have led to a median predicted survival of >50 years for subjects born after 2000 [1] and an increase in the adult CF population [2,3].

The first report of a full-term pregnancy in a woman with CF was published in 1960 [4], when early death at pre-school age was prevalent. However, the subsequent improvements in diagnostic and therapeutic methods leading to longer and healthier life have meant that women with CF could plan a pregnancy as a real possibility. A number of reports [5-10] have documented the effect of pregnancy on the clinical status of women with CF, but less is known about perinatal outcomes [11-13]. Other than the annual number of pregnancies, the American, British, Canadian and Australian CF registries provide no information in terms of gestational age or type of labour; only the French registry reports some data concerning perinatal outcomes [14,15].

Clinicians are consequently very interested in learning more about the management and outcomes of pregnancy in fertile women with airway disease and possibly reduced respiratory function [16], and so the aim of this study was to investigate the perinatal outcomes of women with CF who gave birth in the period 2010-2015 using data from the Italian CF Registry (ICFR).

METHODS

In order to evaluate the effects of the mothers' clinical status on perinatal outcomes, we retrospectively studied the clinical data of women with CF who had at least one pregnancy during the study period of 2010-2015. The considered variables were genotype, age at pregnancy, lung function as the percentage of predicted of forced expiratory volume in one second (ppFEV₁), and nutritional status in terms of the body mass index (BMI) in the year of conception of their first pregnancy, and the analyzed outcomes were the type of labour, and the newborns' gestational age and birth weight (BW). Missing data were acquired by means of a dedicated phone interview and collected from each CF Centre.

All of the patients had given their informed consent before being included in the ICFR (<http://www.registroitalianofibrosicistica.it/>), and this study of anonymous patient data was approved by the Scientific and Steering Committees of the ICFR on 27 February 2017. The terms of

use of the provided data are governed by the Italian law in accordance with European data protection legislation.

Statistical analysis

The continuous variables are recorded as mean values $\pm$ standard deviation (SD) when they were normally distributed, verified using the Shapiro-Wilk test, and as median values and ranges when they were not, and the correlations between them were measured using Spearman's coefficient. The application of the Box-Cox procedure not identified a suitable mathematical function to make the data normal. Comparisons between the continuous variables and subjects with absent/minimal function vs. those with residual function/variants with varying clinical consequences were made using the *t* test, normally distributed data, or the Mann-Whitney test, not normally distributed data. Differences in the continuous variables in relation to ppFEV₁ levels were tested using the Kruskal-Wallis test and the *post hoc* analysis was made using the Steel-Dwass test. Homoscedasticity was verified by Levene and Brown-Forsythe tests.

The categorical variables are recorded as absolute numbers and percentages, and the associations between them were evaluated using the χ^2 test. The Cochran-Armitage test was used to verify the associations and trends of the categorical variables of ppFEV₁ levels and chronic *Pseudomonas aeruginosa* infection.

The statistical analyses were made using SAS v. 9.4 and JMP v. 15 software (SAS Institute Inc., Cary, NC, USA). A $p\text{-value} \leq 0.05$ was considered statistically significant.

RESULTS

During the study period, 81 women underwent a total of 84 pregnancies; nine women (11.1%) experienced pregnancy interruptions, equally distributed between miscarriages and abortions.

Complete information concerning mother and child was available for 56 pregnancies that came to term: 52 single pregnancies and four twin pregnancies. The median pre-conception age of the women was 30.8 years (18.7-42.3); their median BMI was 21.5 kg/m² (16.5-26.8); and their median ppFEV₁ was 73.9% (30-128%). Twenty-four women (42.8%) had two mutations leading to minimal CFTR function; 25 (44.8%) had at least one mutation conferring residual function (RF) or a variant with varying clinical consequences (VVCC); and remaining seven (12.5%) carried CFTR alterations of undetermined function.

Median gestational age was 37 weeks (31-41), and median birth weight was 2,910 grams (1,300-3,650). The frequency of prematurity (gestational age <37 weeks) was 28.30%, and the overall frequency of caesarean section was 63.64%. One newborn was diagnosed as having CF.

Tables 1 and 2 show the mothers' clinical data and perinatal outcomes by CFTR function (minimal vs. RF/VVCC). The between-group difference in ppFEV1 was significant ($p=0.0032$), but there was no difference in perinatal outcomes except for the greater frequency of caesarian deliveries among the women with minimal CFTR function (77.27 vs. 47.83; $p=0.042$).

Table 1. Mothers' clinical data by CFTR function (minimal vs. RF/VVCC)

Parameter	Minimal function	RF/VVCC	p
	mean $\pm$ SD ; (95%CI) n=23	mean $\pm$ SD ; (95%CI) n=23	
Age, years	29.57 $\pm$ 4.88; (27.46 to 31.68)	30.90 $\pm$ 6.77; (27.97 to 33.83)	0.45
BMI, kg/m ²	21.10 $\pm$ 2.22; (20.14 to 22.06)	21.99 $\pm$ 2.79; (20.79 to 23.20)	0.24
ppFEV1%	63.60 $\pm$ 21.85; (54.15 to 73.05)	83.83 $\pm$ 22.15; (74.25 to 93.41)	0.0032

Table 2. Perinatal outcomes by CFTR function (minimal vs. RF/VVCC)

Parameter	Minimal function	RF/VVCC	p
	median (min to max) n=23	median (min to max) n=23	
Gestational age, weeks	37 (32 to 41)	38 (32 to 41)	0.09
Premature births, n (%)	7/21 (33.33%)	6/23 (26.09%)	0.60
Birth weight, grams	2820 (1300 to 3650)	2930 (1840 to 3600)	0.51
Newborns weighing <2500 g, n (%)	4/20 (20.00%)	4/21 (19.05%)	0.94
Caesarean deliveries, n (%)	17/22 (77.27%)	11/23 (47.83%)	0.042

Tables 3 and 4 show that neither maternal age (<30 or ≥ 30 years) nor pre-conception nutritional status (BMI <22 or ≥ 22) had any effect on perinatal outcomes.

The highest frequencies of caesarean deliveries were associated with maternal malnutrition (100.0%), severe lung disease (ppFEV₁ <40; 80.0%), genotypes with minimal CFTR function (77.27%), pregnancies ending before the 37th week of gestation (70.5%), and a younger maternal age (<30 years; 68.0%).

Table 3 - Effect of pre-conception age on perinatal outcomes

Parameter	Age<30 years	Age≥30 years	p
	median (min to max) n=26	median (min to max) n=30	
Gestational age, weeks	38 (33 to 41)	37 (31 to 40)	0.16
Birth weight, grams	2970 (1300 to 3600)	2820 (1670 to 3650)	0.30
Caesarean deliveries, n (%)	17/25 (68.00%)	18/30 (60.00%)	0.54

Table 4 - Effect of BMI on perinatal outcomes

Parameter	BMI<22	BMI≥22	p
	median (min to max) n=31	median (min to max) n=24	
Gestational age, weeks	37 (33 to 41)	38 (32 to 40)	0.50
Birth weight, grams	2850 (1300 to 3650)	2990 (1670 to 3450)	0.17
Caesarean deliveries, n (%)	20/30 (66.67%)	15/24 (62.50%)	0.75

Tables 5 and 6 show the effect of ppFEV₁ on the mothers' condition and perinatal outcomes. A younger age and the absence of *Pseudomonas aeruginosa* chronic infection significantly correlated with a better ppFEV₁ (p=0.038 and p<0.0001). *Post hoc* analysis showed a significantly older maternal age between the mothers with a ppFEV₁ of 40-70% (32.5 years) and those with a ppFEV₁ of 70-90% (27 years) (p=0.046) (Fig. 1A).

There was a positive correlation between maternal BMI and ppFEV₁ in comparison with BW ($\rho=0.29$ and $\rho=0.31$ by p=0.048 and p=0.032, respectively), but no correlation between maternal age and BW. BW was distributed by ppFEV₁ class (p=0.047): *Post hoc* analysis showed a difference between the BW of the newborns of mothers with a ppFEV₁ of <40% and that of the newborns of mothers with a ppFEV₁ of ≥90% (p=0.041) (Fig. 1B). No significant relationship was found between the frequency of caesarean sections and the severity of lung function impairment.

Table 5 - Effect of severity of respiratory on clinical mothers' data

Parameter	ppFEV ₁				P
	<40	≥40; <70	≥70; <90	≥90	
	median (min to max) n=5	median (min to max) n=21	median (min to max) n=15	median (min to max) n=14	
Age, years	33.2 (28.5 to 37.1)	32.5 (24.8 to 40.6)	27.0 (18.7 to 40.5)	30.4 (19.8 to 42.3)	0.038
BMI, kg/m ²	18.7 (16.6 to 23.6)	21.2 (18.4 to 26.8)	23.0 (16.5 to 26.4)	21.4 (18.7 to 26.3)	0.067
Chronic <i>Pseudomonas Aeruginosa</i> infection, n (%)	100.00% (5/5)	76.19% (16/21)	46.67% (7/15)	7.14% (1/14)	<0.0001

Age: *Post-hoc* analysis: p(≥40; <70 vs. ≥70; <90)=**0.046**

Table 6 - Effect of severity of respiratory on perinatal outcomes

Parameter	ppFEV ₁				P
	<40	≥40; <70	≥70; <90	≥90	
	median (min to max) n=5	median (min to max) n=21	median (min to max) n=15	median (min to max) n=13	
Gestational weeks, weeks	35 (34 to 37)	37 (31 to 40)	38 (32 to 41)	38 (36 to 41)	0.056
Birth Weight, grams	2160 (1800 to 2850)	2845 (1300 to 3650)	3000 (1670 to 3600)	2940 (2480 to 3250)	0.047
Cesarean deliveries, n (%)	80.00 (4/5)	76.19 (16/21)	53.33 (8/15)	53.85 (7/13)	0.11

Birth Weight: *Post-hoc* analysis: p(≥40 vs. ≥70; <90)=**0.041**

Figure 1 – Box-plot between maternal age and ppFEV₁ (A) and between birth weight and ppFEV₁ (B)

DISCUSSION

As an extension of a study of pregnancies in Italian CF women [10], this paper describes for the first time the good perinatal outcomes documented by the Italian CF Registry (ICFR) data of 2010-2015. The previous study evaluated the effects of pregnancy on the women's clinical condition, and showed that the majority of Italian CF women starting a pregnancy became mothers regardless of the severity of their genotype or lung function impairment; the only adverse effect was on their nutritional status. This suggests that pregnancy is feasible in CF women, and can be successfully managed by the integrated multidisciplinary care provided by specialised CF centres following specific recommendations [17].

The data analysed in the present study show that neither severe lung disease nor malnutrition affect successful pregnancies in Italian women with CF, and that most pregnancies come to term and lead to the birth of babies with a good neonatal weight.

Multiple logistic regression analyses of the data comparing more than one thousand pregnancies in CF women with pregnancies in non-CF women in the largest study of pregnancy outcomes [18] showed that the former were more likely to go into premature labour. Depending on the characteristics of the studied populations and the survey period, it has been reported that between 8% and 46% of the pregnancies of CF women end in premature births [11]. The frequency of prematurity (28.3%) in our population is in line with range, and significantly higher than the 7% observed in the general Italian population [19]. Premature birth usually affects birth weight but, despite the high percentage of prematurity in our pregnant CF women, the average birth weight is in line with that reported by Girault *et. al* [11]. Use of the general linear model (GLM) showed that prematurity was not related to the mothers' pre-conception respiratory function but, in addition to

spontaneous pre-term labour, may be due to prudential medical indications for anticipating childbirth in order to avoid respiratory worsening.

In relation to the type of birth, it has been reported that 41.9% of CF women with a ppFEV₁ of <50% [15] and 45.4% of those giving birth prematurely [13] undergo caesarean sections, whereas we found that a much higher proportion of cases (63.64%) were managed by means of a caesarean delivery. Our data show that there is no association between caesarean delivery and the severity of pre-conception respiratory function impairment, the age of the mother or her nutritional status by genotype, but there is a more significant association with a severe genotype than with the presence of at least one RF or VCC variant ($p = 0.042$).

The rate of caesarean deliveries in Italy is generally very high (up to 35%) [19], and this may be reflected in the case of CF women. However, a high percentage was also observed among younger women, those with normal respiratory function, and those with full-term pregnancies, which may be due to the widely held opinion of medical staff that CF women poorly tolerate vaginal birth.

Our study refers to a period preceding the availability of CFTR modulators in Italy, whereas a number of cases of successfully completed pregnancies in women receiving these drugs have recently been reported [20]. It is therefore realistic to believe that the innovative treatments of precision medicine will improve the clinical status and fertility of many CF women, thus making it easier for them to become mothers. One of the main aims of CF registers in the future will be to follow the pregnancy outcomes of women receiving CFTR modulators. [21]

In conclusion, analysis of the ICFR data relating to this large cohort of mother-child dyads showed that CF women can successfully undergo pregnancy, and that this often leads to the birth a full-term newborn of adequate weight. The very high percentage of caesarean sections transversally related to various factors is often an *a priori* choice rather than being determined by the clinical condition of the mother, and deserves further investigation.

Acknowledgements

We would like to thank the *Lega Italiana Fibrosi Cistica ONLUS-LIFC* for financially supporting all of the activities of the Italian Cystic Fibrosis Registry (ICFR), the patients who allow their data to be collected, and the Directors of the Italian CF centres who transmit the data to the registry. We would also like to thank Vincenzo Carnovale, MD (Centro Regionale Fibrosi Cistica, Sezione Adulti, Università di Napoli Federico II, Naples, Italy), Domenica Taruscio (National Center for Rare Diseases, Istituto Superiore Sanità) and Giovanna Floridia (Unità di bioetica, Istituto Superiore Sanità) of the ICFR Scientific Board, and Gianluca Ferrari (LIFC) and Fabio Majo (CF Center, Bambino Gesù Paediatric Hospital, Rome) of the Technical Committee for their support.

We would also like to thank Kevin Smart for the linguistic revision of the manuscript.

Declaration of conflicting interests: None

Authorship

Study conception and design: RP, SQ, BG, GC

Data acquisition of data: AA, BG

Article drafting: RP, DS, SQ, MS

Statistical analysis: BG, GC

Scientific revision of manuscript: RP, SQ, DS, MS

Final approval of the submitted version: RP, SQ, AA, MS, DS, BG, GC

Availability of data

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

REFERENCES

1. Keogh RH, Szczesniak R, Taylor-Robinson D, Bilton D. Up-to-date and projected estimates of survival for people with cystic fibrosis using baseline characteristics: A longitudinal study using UK patient registry data. *J Cyst Fibr* 2018;17(2):218-227.
2. Zolin A, Naehrlich L, van Rens J. ECFSPR Annual Report 2015, 2017
3. Giordani B, Amato A, Majo F, et al. Registro italiano Fibrosi Cistica (RIFC). Rapporto 2015-2016 [Italian Cystic Fibrosis Registry (ICFR). Report 2015-2016]. *Epidemiol Prev*. 2019;43(4S1):1–36.
4. Siegel B, Siegel S. Pregnancy and delivery in a patient with cystic fibrosis of the pancreas. *Obstet Gynecol* 1960; 16:438-40.
5. Goss CH, Rubenfeld GD, Otto K, Aitken ML. The effect of pregnancy on survival in women with cystic fibrosis. *Chest* 2003;124(4):1460-8.
6. McMullen AH, Pasta DJ, Frederick PD, Konstan MW, Morgan WJ, Schechter MS, Wagener JS. Impact of pregnancy on women with cystic fibrosis. *Chest*. 2006;129(3):706-11.
7. Ahluwalia M, Hoag J, Hadeh A, Ferrin M, Hadjiliadis D. Cystic fibrosis and pregnancy in the modern era: a case control study. *J Cyst Fibros* 2014;13:69-73.

8. Burden C, Ion R, Chung Y, Henry A, Downey DG, Trinder J. Current pregnancy outcome in women with Cystic Fibrosis *Eur J Obstet Gynecol Reprod Biol* 2012;164(2):142-5.
9. Schechter MS, Quittner AL, Konstan MW, Millar SJ, Pasta DJ, McMullen A. Epidemiologic Study of Cystic Fibrosis. Long-term effects of pregnancy and motherhood on disease outcomes of women with cystic fibrosis. *Ann Am Thorac Soc* 2013; 10:213-9.
10. 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.
11. Girault A, Blanc J, Gayet V, Goffinet F, Hubert D. Maternal and perinatal outcomes of pregnancies in women with cystic fibrosis—A single centre case-control study. *Respir Med*. 2016; 113:22-7.
12. Thorpe-Beeston JG, Madge S, Gyi K, Hodson M, Bilton D. The outcome of pregnancy in women with Cystic fibrosis- single center experience 1998-2011 *BJOG* 2013; 120:354-61
13. Edenborough FP, Mackenzie WE, Stableforth DE. The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977-1996. *BJOG*. 2000;107(2):254-61.
14. Gillet D, de Braekeleer M, Bellis G, Durien I, French Cystic Fibrosis Registry. Cystic Fibrosis and pregnancy. Report from French data (1980-1999). *BJOG* 2002; 109:912-8.
15. 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.
16. 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):1901208.
17. Edenborough FP, Borgo G, Knoop C, Lannefors L, Mackenzie WE, Madge S, Morton AM, Oxley HC, Touw DJ, Benham M, Johannesson M; European Cystic Fibrosis Society. Guidelines for the management of pregnancy in women with cystic fibrosis. *J Cyst Fibros*. 2008;7 Suppl 1: S2-32.
18. 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. e1–98.e989.
19. Boldrini R, Di Cesare M, Basili F, Messia I, Giannetti A. Direzione Generale della Digitalizzazione, del Sistema Informativo Sanitario e della Statistica – Ufficio di statistica: Analisi dell'evento nascita - Anno 2016 - 2019: 46
20. 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: 72-77

21. Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators - an international survey [published online ahead of print, 2020 Mar 6]. *J Cyst Fibros*. 2020; S1569-1993(20)30067-9.

Figures

Figure 1

Box-plot between maternal age and ppFEV1 (A) and between birth weight and ppFEV1 (B)