ORIGINAL INVESTIGATION

A Comparison of Pregnancies That Occur Before and After the Onset of Chronic Fatigue Syndrome

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Background: Many women with chronic fatigue syndrome (CFS) fear that pregnancy will worsen their condition, increase the risks of maternal complications of pregnancy, or threaten the health of their offspring. Little empirical evidence, however, has been published on this matter.

Methods: A detailed questionnaire was administered to 86 women regarding 252 pregnancies that occurred before or after the onset of CFS and the outcomes of these pregnancies were observed.

Results: During pregnancy, there was no change in CFS symptoms in 29 (41%), an improvement of symptoms in 21 (30%), and a worsening of symptoms in 20 (29%) of 70 subjects. After pregnancy, there was no change in CFS symptoms in 21 (30%), an improvement of symptoms in 14 (20%), and a worsening of symptoms in 35 (20%) of the subjects. The rates of many complications were similar in pregnancies occurring before the onset and in those occurring after the onset of CFS. There was a higher frequency of spontaneous abortions in the pregnancies occurring after, vs before, the onset of CFS (22 [30%] of 73 pregnancies after vs 13 [8%] of 171 before; $P<.001$), but no differences in the rates of other complications. Developmental delays or learning disabilities were reported more often in the offspring of women who became pregnant after, vs before, the onset of CFS (9 [21%] of 43 children vs 11 [8%] of 139 children; $P=.01$).

Conclusions: Pregnancy did not consistently worsen the symptoms of CFS. Most maternal and infant outcomes were not systematically worse in pregnancies occurring after the onset of CFS. The higher rates of spontaneous abortions and of developmental delays in offspring that we observed could be explained by maternal age or parity differences, and should be investigated by larger, prospective studies with control populations.

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CHRONIC FATIGUE SYNdrome (CFS) is a debilitating illness characterized by fatigue, muscle and joint aches, headache, sleep disruption, and cognitive impairment that, by definition, last at least 6 months.[1] Studies in the past decade indicate that an underlying biological process involving the central nervous system and the immune system is present.[2] Typically, the onset of CFS is sudden, and the chronic debility that follows usually lasts many years.[3] Many patients who seek medical care for CFS are women in their childbearing years who want to become pregnant but are fearful of possible adverse consequences for themselves and their offspring.

There is a paucity of information describing the reciprocal effects of pregnancy and CFS. Does being pregnant improve, worsen, or leave unchanged the symptoms of CFS? Do women who have CFS experience more frequent complications of pregnancy? Is the health of the offspring affected by CFS? One could speculate that the physical and mental stress of being pregnant adversely affects a woman's symptoms, particularly the fatigue. However, anecdotal evidence from one of the author's (A.L.K.) practice indicates that some patients with CFS feel better during pregnancy, particularly in the first trimester. To address these questions, we asked the female patients followed in the practice to provide detailed information about all of their pregnancies.

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METHODS

During 15 years, more than 400 male and female patients with the chief complaint of at least 6 months of chronic fatigue were seen in consultation at Brigham and Women's Hospital in Boston, Mass. Each was evaluated by a

Table 1. Reasons Given for Not Having Children After the Onset of Chronic Fatigue Syndrome (CFS)

Reasons	Patients, No. (%) (n = 18)
I am afraid that CFS would interfere with my ability to raise small children	17 (94)
I am afraid that my children would not be healthy because of CFS	10 (56)
I am afraid that pregnancy would make CFS symptoms worse	9 (50)
I do not want to stop medications during pregnancy	4 (22)
The doctor advised me not to have children	2 (11)

Table 2. Percentage of Pregnancies in Which Symptoms of Chronic Fatigue Syndrome Improved or Worsened

Changes in Symptoms	%
Improved during and remained improved after the pregnancy (A)	4
Improved during but worsened after the pregnancy (B)	26
Unchanged during but improved after the pregnancy (C)	3
Unchanged during but worsened after the pregnancy (D)	9
Unchanged both during and after the pregnancy (E)	30
Worsened during but improved after the pregnancy (F)	13
Worsened during and remained worse after the pregnancy (G)	16
Improved during the pregnancy (A + B)	30
Unchanged during the pregnancy (C + D + E)	41
Worsened during the pregnancy (F + G)	29
Improved after the pregnancy (A + C + F)	20
Unchanged after the pregnancy (E)	30
Worsened after the pregnancy (B + D + G)	50

standardized interview, a physical examination, and a battery of laboratory tests, as described elsewhere.[4]

Pregnancy questionnaires were mailed to 220 female patients and 137 (62%) responded. The mean ± SD age of respondents and nonrespondents was similar (49.9 ± 10.0 years vs 51.2 ± 12.4 years; $P = .57$) as well as their educational background (66% vs 60% of college graduates; $P = .42$), duration of illness (15.7 ± 5.0 years vs 15.7 ± 5.4 years; $P = .72$), and severity of illness (16% vs 25% were regularly bedridden or shut-in; $P = .18$). Of these respondents, 126 (92%) met the 1994 Centers for Disease Control and Prevention case definition for CFS[1] but 40 had never been pregnant. The results of this study are based on the answers of the 86 remaining women.

The questionnaire, which included questions on the following topics, was administered for each of a patient's pregnancies regardless of the outcome: pregnancy duration; patient's age; pregnancy occurrence relative to onset of CFS; effect of pregnancy on CFS symptoms; maternal complications of pregnancy (gestational diabetes, hypertension/preeclampsia, toxemia, vaginal bleeding in each trimester, severe nausea or vomiting, premature rupture of membranes, premature labor, difficult or prolonged labor, and placental insufficiency); maternal outcome of the pregnancy (live birth with vaginal or cesarean delivery, spontaneous abortion, ectopic pregnancy, induced abortion, or stillbirth); and information about the health of the newborn and subsequent child development.

Because of the potential for recall bias in the patients' responses, except for vaginal bleeding, we did not ask about specific periods during pregnancy (ie, trimester) or the postpartum. We also asked respondents to describe the effect of pregnancy on their CFS symptoms as a whole, rather than request that they remember specific CFS symptoms—which, in many cases, had occurred several years previously.

Because of the typically discrete onset of CFS, the respondents had little difficulty in identifying which pregnancies occurred before or after the onset of CFS. The questionnaire and study were approved by the institutional review board of Brigham and Women's Hospital. Because the patients came from a wide geographic area and had their pregnancies managed in many distant practices and hospitals, it was not feasible to confirm their reports by medical record review.

Data from the pregnancies occurring prior to and after the onset of CFS were separately analyzed. For each group of pregnancies, we calculated incidence rates for different maternal and neonatal complications and outcomes and for later complications in the offspring. Incidence rates between the 2 groups were tested for statistical significance using 2-tailed χ^2 or Fisher exact tests.

RESULTS

STUDY POPULATION

Among the 86 subjects there were 252 pregnancies, with an average of 2.9 pregnancies per subject. The mean ± SD age of those who became pregnant prior to the onset of CFS was 24.8 ± 4.3 years, and it was 33.0 ± 4.5 years for those who became pregnant after the onset. Most pregnancies (176 [70%]) occurred prior to the patient's onset of CFS.

One reason why there were fewer pregnancies after the onset of CFS was concern about the illness. Eighteen (21%) of the patients reported that they decided not to have children (or more children) because of the illness. **Table 1** summarizes the reasons given for this decision, the most common being that the debility caused by CFS would impair the patient's ability to raise children.

Interestingly, women who had children before the onset of CFS and decided to continue to have children had more pregnancies after the onset. Among the 19 patients (22%) who reported pregnancies both before and after the onset of CFS, 30 pregnancies occurred before and 46 occurred after the onset.

SYMPTOMS OF CFS

Table 2 summarizes the effect of pregnancy on the symptoms of CFS reported by patients whose pregnancy occurred after they had been diagnosed with the syndrome. No predominant pattern was observed. During pregnancy, there was no change in CFS symptoms in 41%, an improvement of symptoms in 30%, and a worsening of symptoms in 29% of subjects. After pregnancy, there was no change in 30%, an improvement in 20%, and a worsening in 50% of patients.

MATERNAL COMPLICATIONS AND OUTCOMES

Table 3 shows the incidence of maternal complications. There were no differences in the rates of complications between the pregnancies that occurred before and those that occurred after the onset of CFS. **Table 4** shows the incidence of maternal outcomes. There was a significantly higher rate of spontaneous abortions, and a correspondingly lower rate of live births by vaginal delivery, in the pregnancies that occurred after the onset of

Table 3. Maternal Complications of Pregnancy Before and After the Onset of Chronic Fatigue Syndrome

Complication	No. (%) Before Onset (n = 154)	No. (%) After Onset (n = 75)	*P* Value
Gestational diabetes	6 (4)	5 (7)	.56
Pregnancy-induced hypertension and/or preeclampsia	10 (6)	4 (5)	.96
Toxemia and/or eclampsia	2 (1)	1 (1)	.55
Vaginal bleeding in 1st trimester	24 (16)	16 (21)	.37
Vaginal bleeding in 2nd or 3rd trimester	14 (9)	5 (7)	.71
Severe nausea and or vomiting	43 (28)	24 (32)	.63
Premature rupture of membranes	4 (3)	2 (3)	.68
Premature labor with bed rest and/or hospitalization	14 (9)	5 (7)	.71
Difficult or prolonged labor	36 (23)	12 (16)	.27
Placental insufficiency	1 (1)	1 (1)	.81

Table 4. Pregnancy Outcomes Before and After the Onset of Chronic Fatigue Syndrome

Outcome	No. (%) Before Onset (n = 171)	No. (%) After Onset (n = 73)	*P* Value
Live birth, vaginal delivery	116 (68)	33 (45)	.002*
Live birth, cesarean delivery	20 (12)	9 (12)	.94
Spontaneous abortion	13 (8)	22 (30)	<.001*
Ectopic pregnancy	2 (1)	1 (1)	.61
Induced abortion	19 (11)	8 (11)	.85
Stillbirth	1 (1)	0 (0)	.66

*The difference is statistically significant ($P<.05$).

Table 5. Outcomes in the Offspring of Pregnancies Occurring Before and After the Onset of Chronic Fatigue Syndrome

Outcome	No. (%) Before Onset (n = 139)	No. (%) After Onset (n = 43)	*P* Value
Birth weight, g*	3475 ± 590	3502 ± 650	.8
Female sex	66 (48)	21 (49)	.9
Premature birth (3 wk before due date)	12 (9)	5 (12)	.51
Low birth weight (<2495 g)	10 (7)	0 (0)	.10
Breech presentation	14 (10)	0 (0)	.03†
Birth defects‡	7 (5)	2 (5)	1.00
Developmental delays, learning disabilities§	11 (8)	9 (21)	.01†

*As some patients could not recall their children's birth weights, results are based on 123 responses in the before onset group and 40 responses in the after onset group.
†The difference is statistically significant ($P<.05$).
‡They include such conditions as Down syndrome or muscular dystrophy.
§They include such conditions as dyslexia.

CFS. There were no significant differences in the rates of other maternal outcomes.

OFFSPRING OUTCOMES

Table 5 displays the incidence of adverse outcomes in offspring. Developmental delays or learning disabilities were significantly more frequent in children born from pregnancies that occurred after the onset of CFS, and there were more breech presentations in the pregnancies that occurred before the onset of CFS. There were no other differences.

COMMENT

Our study offers some reassurance to women with CFS who fear adverse consequences of pregnancy. The study showed that during pregnancy, symptoms were unchanged or improved in 71% of patients, and that in the postpartum period, symptoms were unchanged or improved in 50% of patients. While some women reported a worsening of their CFS symptoms during pregnancy, an equal number reported some improvement. Unfortunately, we cannot predict into which category an individual will fall.

Many women were afraid that their offspring would also be adversely affected, but there was little evidence that this happened. Although there was a higher reported rate of developmental delays and learning disabilities when pregnancies occurred after the onset of CFS, that difference could be explained by confounders such as the older age of women.

There also was little evidence that the rates of various maternal complications during pregnancy, or outcomes of the pregnancy, were different in pregnancies that occurred following the onset of CFS compared with those that occurred before. One exception was the significantly greater number of spontaneous abortions in the pregnancies that occurred after the onset of CFS. This difference also could be explained by confounding, particularly by age or parity. We compared rates of spontaneous abortions in patients with CFS of different age and parity (nulliparous vs multiparous) with rates in a population-based Danish survey of 1 221 546 pregnancy outcomes,[5] and did not find clearly higher rates in our patients.

Our study has 3 important limitations. First, the participation rate of 63% was suboptimal, although respondents were similar to nonrespondents with respect to several important criteria, suggesting that no substantial bias was introduced. Second, because the study was designed as a case series, it did not include healthy comparison groups. Rather, we used the patients as their own controls by comparing rates of various complications and outcomes in women with CFS before and after they became pregnant. The premise underlying this design is that biological changes that develop as a result of becoming ill with CFS might alter the course of subsequent pregnancies. It is possible that some underlying biological process might already be at work in the asymptomatic years prior to the onset of CFS, a process rendering individuals vulnerable to the developement of CFS. If that were true, the before vs after design would not be adequate. Third, the data were based on self-report. It was not fea-

sible to compare patient self-report with their medical records because the patients came from a wide geographic area and had received obstetric care in many different practices.

In summary, this study did not find evidence that pregnancy worsens the symptoms of CFS in most women. Likewise, most maternal and offspring outcomes when pregnancies occurred after the onset of CFS were not systematically worse. Larger, prospective studies with control populations are needed to determine if there are higher rates of spontaneous abortions and developmental delays in the offspring of women with CFS.

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