

Reproductive Issues



When it comes to understanding the reproductive and gynecological ramifications of CFS, we have few definitive answers. But the research to date reveals some intriguing aspects of the illness.

By Pamela Young, Director of Publications, CFIDS Association of America

When Nancy Klimas, MD, was recently asked what she'd say about research on chronic fatigue syndrome and reproductive issues if she had only the duration of an elevator ride to convey the facts, her reply was telling. "I'm afraid the conversation would be over by about the second floor."

As director of the Department of Immunology at the University of Miami School of Medicine and as a well-known CFS clinician and researcher, Klimas is in a position to know what key advances have been made in this area, so her answer is especially sobering. In a disease that affects three to five times more women than men, relatively little direct research has been focused on how CFS impacts reproductive and gynecological functions.

Challenges to research

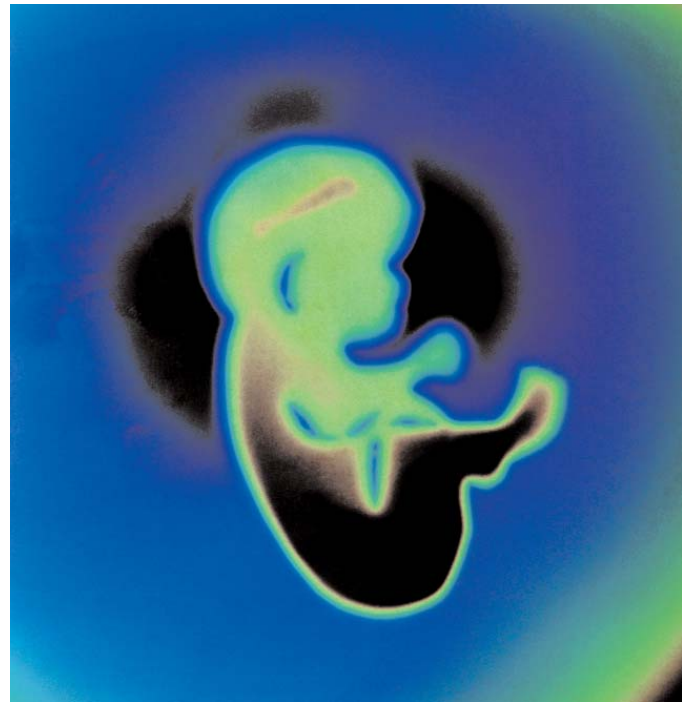
Why hasn't more research been conducted into how CFS affects reproductive issues? Clinicians cite myriad reasons, but the challenges fall into three main categories: trouble finding appropriate samples to study, a lack of gynecologists specializing in CFS and a scarcity of funding.

To determine how CFS impacts fertility, a researcher would need to find a statistically viable sample of women of childbearing age, diagnosed with CFS, attempting to get pregnant and well enough to participate in ongoing monitoring. And with a multisystemic disease as complex as CFS, many clinical subsets may exist. Even a clinician with a sizable practice may have trouble finding a large enough sample to conduct a thorough study. Furthermore, only recently have multicenter collaborative studies become more feasible through Internet-linked technology.

Another hindrance to specific research into this area relates to the history of CFS itself. In 1985 CFS

was thought to be caused primarily by a viral agent. As a result, virology and immunology received most of the focus, and the clinicians involved came primarily from that background. In the mid-1990s the focus broadened to autonomic control and then eventually expanded to neuroendocrine factors. Because of these focuses, few gynecologists have been involved in ongoing research.

And, of course, there is the issue of funding. Charles Lapp, MD, one of the earliest physicians involved in recognizing and treating CFS, sees federally funded research stagnating and private sources challenged to come up with enough funds to underwrite studies into the many facets of CFS. Specific to reproductive and gynecologic research, he notes that one logical candidate, the Office of



Research on Women's Health, "has few research dollars of its own and is not an NIH institute with a long history of landmark research."

Anthony Komaroff, MD, one of the leading researchers in this field, echoes Lapp's view on funding. "There are not enough resources, whether you're talking about CFS or diabetes or other illnesses," he explains. In such a climate, research into possible causes and treatments garners more attention than research into related areas like reproduction and gynecology, no matter how relevant the issue is in patients' lives.

What has been studied?

Still, some research has been achieved in this area, including Komaroff's own 1998 study with Bernard Harlow, PhD, and other colleagues, which examined whether menstrual and gynecological abnormalities precede the onset of CFS.¹ Though Komaroff also researches other aspects of CFS, he returned to the reproductive front with Richard Schacterle, PhD, in 2004 to conduct the most comprehensive study to date on pregnancy and CFS—surveying 86 women about 252 pregnancies that occurred before or after the onset of their CFS and comparing the effects and outcomes.² Along with a 1997 retrospective review of pregnancy-related patient data collected by Lapp, this constitutes the majority of direct study of the reproductive ramifications of the disease, particularly relating to pregnancy.

More studies have been directed toward the neuroendocrine and hormonal physiology of CFS. At least five studies of the hypothalamic-pituitary-adrenal (HPA) axis have shown that the function of the hypothalamus, and possibly the pituitary gland, may be disordered in CFS.^{3,4,5} Two studies of the hypothalamic-pituitary-gonadal (HPG) axis have uncovered less evidence of dysfunction.^{6,7} A score of other studies have explored specific hormone levels and neuroendocrine functions in CFS and FM patients. But these studies come to varying conclusions, and almost all encourage more research into the issue to arrive at determinative facts. What's more, the underlying causes of apparent hormonal perturbations in CFS patients remain elusive.

Researchers have also sought to uncover genetic components to CFS. A 2001 twin study led by Dedra Buchwald, MD, explored the genetic influences in the expression of CFS.⁸ Several immunology studies have uncovered increases

How Does Pregnancy Affect the Symptoms of CFS?

A 2003 study published in the Archives of Internal Medicine showed a variety of symptomatic dynamics in 86 women with CFS.

Unchanged both during and after the pregnancy	30%
Improved during but worsened after the pregnancy	26%
Worsened during and remained worse after the pregnancy	16%
Worsened during but improved after the pregnancy	13%
Unchanged during but worsened after the pregnancy	9%
Improved during and remained improved after the pregnancy	4%
Unchanged during but improved after the pregnancy	3%

in certain human leukocyte antigens (HLA-II), suggesting a sort of marker for vulnerability to CFS.^{9,10} However, details vary from study to study and more exploration is needed to arrive at conclusive findings.

What we know about pregnancy

Even the sparse amount of research conducted has uncovered some interesting data on pregnancy in women with CFS, including effects on symptoms, complications during pregnancy and genetic links.

For example, Komaroff and Schacterle's 2004 comparison study reported that pregnancy didn't consistently worsen the symptoms of CFS. In 41% of pregnancies that followed the onset of CFS, there was no change in symptoms. An improvement of symptoms was reported in 30% of the pregnancies, while a worsening of symptoms was reported in 29%.² Lapp found a similar split in his 1997 retrospective exploration of CFS and pregnancy. As for postpartum effects, Komaroff and Schacterle found that 50% of participants reported a worsening of symptoms following pregnancy, yet 30% reported no change, and 20% felt improvement.² As Komaroff notes, "Our study indicates that the impact can be quite different from one woman to another. We do not know how to predict who will feel better or worse."

While there is no evidence to suggest that pregnancy improves symptoms in most women with CFS, anecdotal evidence indicates that for those who experience an improvement, the impact can be quite dramatic. Klimas describes one patient whose first clue she was pregnant with her third child was that her CFS symptoms cleared up so suddenly. This observed improvement might be attributed to

What about Hormone Replacement Therapy?



Because research indicates that people with CFS experience neuroendocrine dysfunction affecting the levels of hormones such as estrogen, testosterone, prolactin, growth hormone, DHEA and ACTH, clinicians have been exploring various types of hormone replacement therapy (HRT) for their patients. Reproductive hormones like estrogen have a long history of use in women, but the HERS (Heart and Estrogen/Progestin Replacement Study), which warns of increased risk for heart problems and breast cancer associated with estrogen HRT, changed the way many clinicians are prescribing this therapy.

How are doctors balancing these risks and using HRT with CFS patients? Here, three leading clinicians speak out on the subject:

“Some clinics are exploring hormonal manipulation to treat all the symptoms of CFS. Because we don’t yet know long-term outcomes, I don’t use hormones to manipulate CFS itself. However, when people with CFS become hormone deficient, replacing those hormones helps tremendously. Menopausal women with CFS, for instance, often experience amplified symptoms. I feel justified to use HRT to calm down these symptoms for patient relief.”

Lucinda Bateman, MD
Fatigue Consultation Clinic, Salt Lake City

“Generally speaking, HRT with estrogen increases the chance for cancer of the breast and uterus and shouldn’t be used for the treatment of CFS. In cases of severe menopausal problems, one could consider using HRT for a limited time. I feel the use of DHEA is different. It’s also a hormone, but it has promising effects in the brain without the same known risks as estrogen.”

R.C.W. Vermeulen, MD, PhD
CFS Research Center, Amsterdam

“Birth control pills in premenopausal women can help minimize the predictable premenstrual relapsing of CFS symptoms. In peri- and postmenopausal women, it can also be helpful to measure testosterone levels, which are normally present in women in low but predictable levels. If testosterone is low and estrogen therapy is already being considered, it may be helpful to add very small doses of testosterone. In all instances, however, the risk of estrogen therapy must be weighed against the potential benefit. In women with a history of deep vein thrombosis or hypercoagulable disorder, or with a strong family history of estrogen-sensitive tumors such as ovarian cancer or postmenopausal breast cancer, estrogen should be avoided.”

Nancy Klimas, MD
University of Miami School of Medicine

a combination of factors such as increased blood volume and the immunologic boost associated with pregnancy.

Likewise, those women who experience postpartum problems often report a similarly strong experience, much like a harsh CFS relapse. Lucinda Bateman, MD, an internist who focuses her entire practice on CFS and fibromyalgia (FM), describes this postpartum risk as “the biggest issue” she addresses with prospective parents. She suspects this risk is magnified by the standard rigors of caring for a new baby—such as increased physical activity and sleep disruption—and how that affects someone with CFS.

Komaroff and Schacterle also reported a fourfold increase in the frequency of miscarriages occurring in pregnancies after the onset of CFS, but no significant differences in the rates of other complications such as gestational diabetes or toxemia.² The study was careful to point out, however, that increased rates of miscarriage could potentially be explained by maternal age or parity differences in the study and should be investigated further. When compared with figures from a population-based study in Denmark of maternal age and fetal loss,¹¹ the miscarriage rates found by Komaroff and Schacterle may indeed be higher than normal even when adjusted for age, but no additional research has been done on women with CFS.

What about the question of whether a mother can pass CFS on to her child? Buchwald’s twin study found that the concordance rate for CFS was higher in monozygotic (identical) than dizygotic (fraternal) twins, suggesting that genes may play a role in the etiology of the disease. Even when Buchwald refined the sample to exclude twins if either had a history of major depression, the difference in concordance rates remained statistically significant.⁸ However, most clinicians are quick to say that mothers don’t pass CFS directly to their offspring even though there may be an inherited predisposition. As Bateman puts it, “I believe that certain people are more genetically prone to developing this illness.” But she warns, “there are many other factors involved.”

The lack of evidence-based research has implications for clinical care and how physicians advise patients. Endocrinologist and gynecologist R.C.W. Vermeulen, MD, PhD, of the CFS Research Center in Amsterdam, notes, “We still have no

definitive idea of the risks involved in pregnancy for women with CFS. The suggestion that it's okay to be pregnant is not yet substantiated by science." He concludes, "I will not tell my CFS patients to postpone pregnancy. But I must tell them that we don't know enough about the dangers."

What we know about gynecological abnormalities

Pregnancy is just one gynecological issue facing women with CFS. According to Bateman, "Dysmenorrhea (painful periods) and PMS are almost the rule in most women with CFS." Other complications include anovulatory cycles (absence of ovulation), irregular periods, intermenstrual bleeding (between periods), ovarian cysts and a worsening of CFS symptoms at menopause.¹ There is also anecdotal evidence to suggest that instances of pelvic congestion syndrome may be increased.

Two other commonly mentioned abnormalities are endometriosis and polycystic ovary syndrome (PCOS). The 1998 study of reproductive correlates found symptoms of PCOS reported more often in women with CFS, but researchers did not conduct further studies to confirm that specific finding.¹ Other research suggests that endometriosis and PCOS are prevalent in those with FM, but several studies suggesting that endometriosis may be more common in patients with CFS are, in Komaroff's words, "still very preliminary."

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— DR. R.C.W. VERMEULEN

Much left to investigate

With anecdotal data, but relatively little direct research into the reproductive and gynecological impact of CFS, there is still much to uncover. Experts readily point out many areas of needed research. Bateman, Klimas, Komaroff and Lapp all agree that more research is needed on the effects of pregnancy. As Lapp says, "There has been retrospective study but nothing prospective, examining women who are currently pregnant." Or as Klimas puts it, "There are just observational

What about Men?

Chronic fatigue syndrome affects an estimated 266,000 men in the United States, and millions worldwide. Men with CFS experience many of the same symptoms as women and suffer from similar neuroendocrine dysfunction. Yet we know even less about the reproductive ramifications of CFS in men than we do in women.

Charles Lapp, MD, of the Hunter-Hopkins Center in Charlotte, North Carolina, reports that the most common reproductive issue in male CFS is decreased libido. Although some investigation has been directed at male hormone deficiency and hypogonadism (low gonadal hormone production), no formal research has directly studied how CFS may impact male fertility and reproductive functions.

Some men with CFS take supplements for their reported ability to stimulate libido and boost testosterone levels, but there's no evidence from clinical trials to demonstrate the effectiveness of such treatments.

studies that tell us what patients report and not any biology." Komaroff agrees. He'd like to determine whether there are biological differences that conclusively explain why some women have fewer symptoms during pregnancy while others feel the same or worse. Also high on Komaroff's list of research topics is further investigation into miscarriage rates.

"In terms of patient care and management," Bateman says, "I'd like to know how female hormone levels and hormone shifts relate to CFS symptoms. That's a clinically relevant topic I face each day in treating people." Klimas lists hormonal factors, CFS in menopause and female-related oncology as areas requiring more study. Lapp cites lack of libido, estrogen replacement and osteoporosis as "biggies" with "many questions not answered so far."

Perhaps Klimas sums it up best: "We suspect things from clinical practice, but we don't have the studies we need. There just has not been enough research done. This leaves us with many more questions than answers." ■

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