

Sex-specific Prenatal Programming

A Risk for Fibromyalgia?

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Women are four to eight times more likely to be affected by fibromyalgia syndrome (FMS). A lack of cortisol, potentially due to an adrenocortical deficit is postulated in FMS. The cause of such adrenal insufficiency is unknown. It could be assumed that stress exposure during critical periods contributes to vulnerability for FMS. These critical periods might include prenatal periods in which adversities may lead to an impaired development of the adrenal cortex, especially in females. More than 50% of FMS patients report major life events before the onset of the disease. Possibly due to adrenal insufficiency they may not be able to dampen their stress response by secreting sufficient glucocorticoids. Thus, stress mediators, such as catecholamines and pro-inflammatory cytokines, may be disinhibited and affect brain function. This might result in an enhanced responsiveness to external and internal pain- and fatigue-eliciting stimuli. In a study with female FMS patients ($N = 93$) those patients with a shorter gestational length (<38 weeks) showed a lower cortisol awakening response (CAR) than FMS subjects with a gestational length >38 weeks ($F_{(3,31)} = 2.94, P = 0.038$). Additionally, more than 70% reported severe psychological stress alone or in combination with other factors at disease onset.

Key words: fibromyalgia; prenatal programming; adrenal insufficiency; sex specific; cortisol awakening response (CAR)

Introduction

Fibromyalgia syndrome (FMS) is a disorder of unknown etiology characterized by widespread, chronic musculoskeletal pain and pressure hyperalgesia. In the United States, FMS constitutes the second most common rheumatologic disorder behind osteoarthritis, with a prevalence between 0.5% and 3.4% in the general population.¹ Women comprise 80–90% of the affected population.^{2,3} Both genetic and environmental factors seem to play a prominent role in triggering the de-

velopment of FMS, suggesting a multifactorial condition.⁴

Early adversities have recently been discussed as major risk factors for many stress-related disorders. There is growing evidence that life stress in childhood and/or adulthood confers an increased risk of chronic pain conditions, such as FMS.⁵ For example, one study compared the rate and the impact of life events between FMS patients and healthy volunteers.⁶ Results revealed that during childhood or adolescence, half of the FMS patients (51%) had experienced severe adverse events, as compared to 28% of the healthy controls. Before disease onset, 65% of FMS patients faced some negative life event. Concerning very negative life events during the last year, the rate was

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significantly higher in the patient group (51%).⁶ Although these numbers are impressive, it must be noted that all these assessments were made after the onset of FMS, which may itself provoke the report of higher incidences of stressful events or the evaluation of events as more stressful.⁷ So far, prospective studies are lacking.

Low cortisol levels have been observed in FMS patients in terms of 24-h urinary free cortisol levels⁸⁻¹⁰ and basal cortisol levels in plasma and serum,⁹⁻¹¹ supporting the assumption of a mild hypocortisolism in this patient group. In addition, pharmacological stimulation tests and exercise studies have revealed hypocortisolemic stress responses at the adrenal level in FMS patients. For example, exaggerated adrenocorticotrophic hormone (ACTH) responses in the corticotropin releasing-hormone (CRH) test and insulin tolerance test have been accompanied by unchanged cortisol levels in some studies,^{8,9,12} which has been interpreted as a hyper-reactivity of the pituitary corticotroph level and concomitant reduced adrenal responsiveness to elevated ACTH levels in FMS patients. It has to be noted that some studies have reported contradicting results in terms of unchanged or elevated basal cortisol concentrations in FMS patients.^{13,14} Overall, however, it seems that the majority of studies investigating hypothalamo-pituitary-adrenal (HPA) reactivity in FMS patients suggest hypocortisolemic stress responses on the adrenal level.

The question arises how such lack of cortisol availability in FMS patients may contribute to disease symptomatology. The way Munck and colleagues¹⁵ conceptualized the role of glucocorticoids (GC) might shed some light on this question. They postulated that GC suppress the stress response, thus preventing it from being pathologically overactivated.¹⁵ This idea first came up in the late 1940s when GC were discovered to be anti-inflammatory agents.¹⁶ Munck and colleagues proposed that “(a) the physiological function of stress-induced increases of GC levels is to protect not against the source of stress itself, but against the nor-

mal defence reactions that are activated by stress; and (b) the GC accomplish this function by turning off those defence reactions, thus preventing them from overshooting and themselves threatening homeostasis.”¹⁵ This hypothesis implies that in hypocortisolemic disorders, like FMS, the body's defense reactions against stress are out of control due to a lack of inhibition by cortisol.

So far several studies have demonstrated altered sensibility to pain as well as altered brain processing of nociceptive and non-nociceptive somatic stimuli in FMS patients. For instance, patients with FMS or chronic back pain show enhanced sensitivity for thermal or mechanical pain stimuli,¹⁷⁻¹⁹ which is reflected in enhanced activity in brain areas that are active during painful stimulation.²⁰ In patients with FMS it was demonstrated that especially brain areas associated with the evaluative-affective pain component are more active during painful stimulation than in healthy controls. These areas are the anterior cingulate cortex and the insula. Both areas are involved in processing of visceral sensations as well as the integration of somatosensory and visceral input. They are also involved in the processing of immune responses. The enhanced responsiveness of brain areas related to integrative aspects of body sensations and visceroreception in patients with FMS might also be related to altered body perception. The assumption of an altered body perception, especially visceroreceptive functioning, is supported by many findings showing numerous somatic symptoms including gastrointestinal complaints in FMS patients. Thus it is important to address FMS not only from the pain perspective but also to combine this effort with psychoneuroimmunologic results. So far the correlation between dysfunctions of the HPA axis and the extent of pain perception in FMS is unclear. For a better understanding of the phenomenon it would be important to know how the findings of hypocortisolism in FMS patients are connected to the processing of painful stimuli in the brain.

Prenatal Glucocorticoid Programming in FMS: Hypothesis and Evidence

We here propose the following sequence of events, which may put women at risk for FMS: (1) Enhanced GC levels of the mother during pregnancy may impair the development of the adrenal cortex in the female fetus. (2) This may diminish the ability of the daughter to adequately dampen a stress response in later life. (3) When exposed to intense physical or psychological stress, stress-mediators, such as catecholamines and pro-inflammatory cytokines, may be disinhibited in these women and affect brain function. (4) In consequence, these patients may develop plastic alterations in the brain that result in enhanced responsiveness to external and internal pain- and fatigue-eliciting stimuli, which later constitutes the symptomatology.

We suggest that many of the alterations described above may already develop during gestation under various conditions, as for example prenatal exposure to maternal stress or synthetic GC.^{21,22} It is known from animal studies that GC influence maturation of fetal organs and play an important role in "GC programming."^{23,24} Recent studies and reviews emphasize the possibility of GC programming not only in animals but also in humans.^{25–27} Early adverse environments can be related to enhanced HPA and autonomic responses to stress later in life. Those changes in neuroendocrine systems may provide risk factors for cardiovascular disease, psychopathologies, and stress-related bodily disorders. A recent study in humans reported an association between high cortisol levels at 30–32 weeks of gestation and infant negative reactivity.²⁸ Also maternal mood is associated with neuroendocrine alterations in the offspring: In a study by O'Connor and colleagues,²⁹ prenatal maternal anxiety predicted cortisol elevations more than 10 years postpartum, and Van den Bergh, Van Calster, Smits, Van Huffel, and Lagae³⁰ showed that antenatal anxiety can be related to high cortisol profiles

in adolescents and can predict depressive symptoms in female adolescents only. Also preterm birth has been linked to altered HPA function in children.³¹

The HPA axis and its key limbic regulator, the hippocampus, are particularly sensitive to GC and their perinatal programming actions.^{32,33} In general, the placenta forms a structural and biochemical barrier to maternal GC. This results from the placental expression of 11 β -hydroxysteroid dehydrogenase (11 β -HSD).³⁴ There are two isoforms of 11 β -HSD, type 1 interconverts cortisol and corticosterone to inactive products (cortisone, 11-dehydrocorticosterone) and vice versa (bidirectional) and type 2 converts cortisol to cortisone only (unidirectional). This barrier is incomplete, as 10–20% of maternal GC cross intact to the fetus.³⁵ It has been shown that a positive relationship between maternal and fetal GC concentrations exists. One can imagine that with 10–20% passage of maternal cortisol through the placenta, fetal cortisol increase is still substantial, if the maternal levels are elevated to a certain degree.^{36,37}

One key mechanism of persisting alterations of physiological functions in the prenatal programming hypothesis is reduced glucocorticoid receptor (GR) expression and thus impaired negative feedback function, which is discussed as an explanation for the long lasting effects on the HPA axis.^{22,38,39}

Sex-specific Prenatal Programming of the Stress Response

A substantial number of animal studies focusing on adversity during the prenatal period have been performed with male animals only.^{38–41} It is important to note, though, that studies including male and female animals suggest sex-specific prenatal programming. There is a great body of evidence indicating that prenatal restraint stress affects the adrenocortical stress response in female offspring to a greater extent than in male offspring.^{42–45}

Furthermore, offspring of mothers exposed to ACTH during the last trimester of pregnancy had reduced adrenal weight and aberrant morphology, which was more pronounced in the adrenals of females than of males, again suggesting that females were more vulnerable to the prenatal treatment.⁴⁶ In line with these results, in a human male twin population, salivary cortisol responses to stress exposure in the Trier Social Stress Test (TSST)⁴⁷ were significantly and inversely related to the subjects' birth weight.⁴⁸ Further support comes from a study in children, where a negative relationship between birth weight and salivary cortisol responses to the children's version of the TSST was reported in boys but not in girls.³³ Recently, it has been suggested that prenatal programming might affect primarily the adrenocortical response in men and the sympathoadrenal response in women. This idea is further supported by the finding that women who were small at birth demonstrated increased sympathetic and decreased parasympathetic activity as well as reduced baroreflex sensitivity.^{27,49} Thus, there is evidence for increased effects of prenatal stress in female offspring. An earlier study provides a possible reason for this effect: Montano, Wang, and vom Saal⁵⁰ demonstrated greater GC transfer across the placenta of female compared to male mice fetuses. Studies in humans, where placental 11 β -HSD-2 concentrations were determined at birth, suggested higher levels in females than in males. Also in line with these findings are observations suggesting reduced placental 11 β -HSD-2 expression in female but not male alcohol-exposed fetuses.⁵¹ Thus, placental 11 β -HSD-2 concentrations might be more affected by maternal adverse conditions in females than in males, exposing the female fetus to higher amounts of maternal GC, which may result in adrenal hypotrophy of the female offspring postnatally.^{46,52} As a further mechanism explaining sex-specific programming, morphological changes in the hypothalamic paraventricular nucleus (PVN) can be considered, since chronic maternal stress during the last trimester

of pregnancy has been found associated with stress-induced apoptosis in the PVN of female but not male fetuses in rats.⁵³

Recent studies support the hypothesis of FMS being a hypocortisolemic disorder with characteristic changes on the adrenal level. In one study, the endocrine response to the TSST was investigated in female FMS patients. Despite a normal ACTH release in response to the TSST, diminished cortisol secretion was observed.⁵⁴ This discrepancy between pituitary and adrenal outcomes revealed the expected insufficient adrenocortical cortisol release in response to stress-induced ACTH release in FMS patients. Preliminary observations from this study further suggested an enhanced increase of IL-6 in patients with shorter gestational length ($N = 10$; unpublished). Interestingly, a second study found evidence for similar endocrine alterations in female young adults with a history of prenatal stress experience. Stress reactivity was investigated in subjects whose mothers reported to have experienced severe stress during pregnancy. Like prenatally stressed males, females presented with increased ACTH secretion in response to the TSST.^{55,56} While in male prenatally stressed subjects total cortisol secretion was also higher compared to a male nonstressed group, female subjects exposed to prenatal stress exhibited a lower cortisol response than the nonstressed comparison group. Thus, in prenatally stressed female subjects only, a discrepancy between the pituitary and adrenal stress response can be observed.⁵⁶ Considering the large increase in ACTH in the prenatally stressed females, their total cortisol response is not proportional, possibly reflecting an adrenal insufficiency. The same is suggested for FMS patients (see findings in Ref. 54). In another study, size for gestational age has been used as a proxy, since it has been related to prenatal maternal stress, as reviewed by Mulder and colleagues.⁵⁷ Stress-induced salivary cortisol secretion was compared in young adult subjects born small for gestational age (SGA) respectively appropriate for gestational age. While SGA males

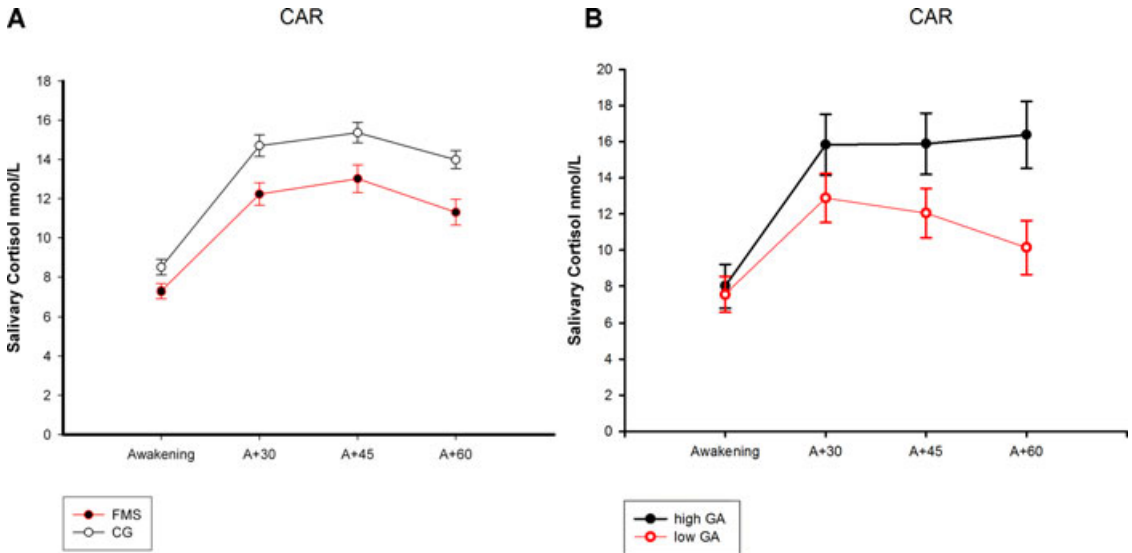


Figure 1. (A) Cortisol awakening response (CAR) in FMS patients and healthy controls. **(B)** Cortisol awakening response in FMS patients with and without prenatal risk indicated by high versus low gestational age (GA).

had a rather hyper-responsive cortisol response, SGA females did not show an increase in cortisol secretion, suggesting that prenatal insults compromising growth had a different impact in males and females.^{58,59}

Material and Methods

Ninety-three female FMS patients with a rheumatologist's attest confirming the diagnosis (mean age: 51.4 ± 8.8) were compared to 100 female teachers (mean age: 44.4 ± 9.0). All subjects answered a questionnaire (Prenatal Stress Questionnaire, PSQ, unpublished) assessing birth variables (such as birth weight, birth size, gestational length). In some cases, this information is recall data from the subjects' parents, but subjects are also asked to show birth records and "U-Hefte," which are used in Germany to monitor medical tests during the first year of life. Furthermore, every subject gave information about socioeconomic variables (including financial constraints and family income), partner-related variables (such as death and divorce), and individual variables (such as chronic or traumatic stress). In addition,

all subjects collected native saliva with a straw and eppivette on two consecutive working days at awakening, and 15, 30, and 60 min later. Free cortisol levels were analyzed with a time-resolved immunoassay with fluorescence detection as described elsewhere.⁶⁰ Values for the 2 days were computed to a mean value to obtain a reliable measure. The data were subjected to a repeated measure ANOVA, with time as within-subjects factor and group as a between subjects factor.

To assess the events triggering the symptomatology of FMS, patients were asked this question in a questionnaire. The answers were coded by a trained rater in five categories: physical stress (for example, working as elderly care nurse), psychological stress (including severe worrying about or stress with children, spouse, or job), disease (such as hepatitis), mixed category (several events from different categories), and missing value/missing answer.

Results

As shown in Figure 1, compared to a healthy age-matched comparison group, the

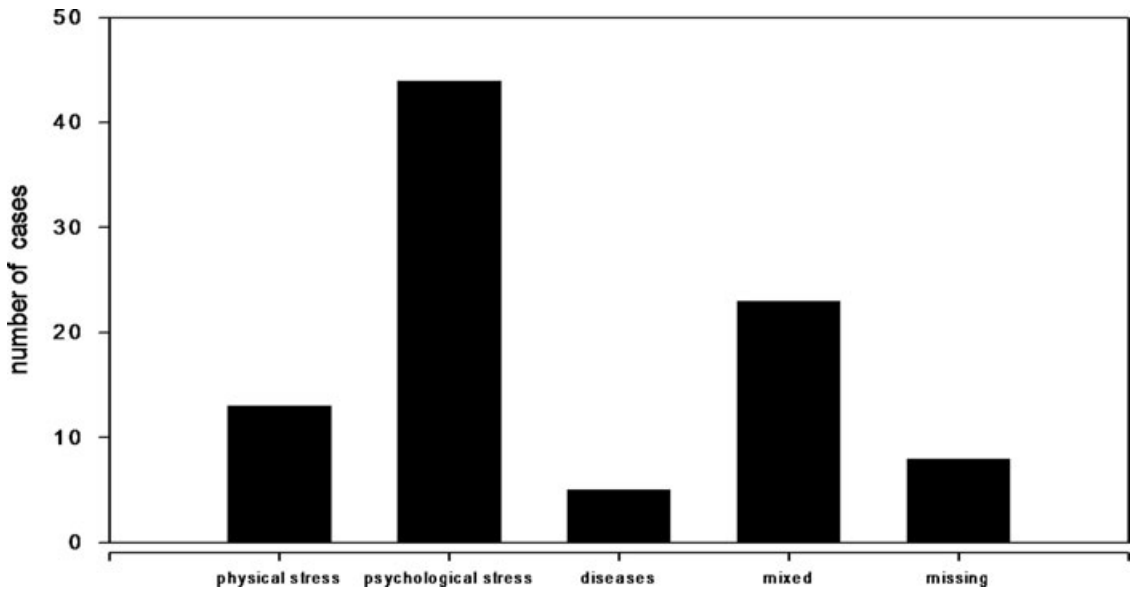


Figure 2. Triggering events that preceded FMS symptomatology in 93 patients.

FMS patients showed lower cortisol secretion during the first hour after awakening ($F_{(3,188)} = 3.55$, $P = 0.04$). About 62% of female FMS patients in this study reported short gestational length, as compared to 27% of the control group ($\chi^2 = 9.64$, $P = 0.002$). All in all, gestational length was reported shorter in the FMS group ($F_{(1,82)} = 5.91$, $P = 0.017$).

For exploring the meaning of prenatal risk factors for FMS, the patient group was split based on the median week of gestation (38 weeks), as maternal stress during pregnancy has been shown to be associated with reduced gestational length.⁶¹ Comparing the cortisol concentrations of those two FMS groups ($N_{GAshort} = 18$, $N_{GANormal} = 15$), lower cortisol concentrations after awakening were only observed in those female FMS patients that had been born with a shorter gestational length ($F_{(3,31)} = 2.94$, $P = 0.038$).

As described above, it has been suggested that onset of FMS symptomatology is often preceded by a period of severe stress or a traumatic event. This could be supported by 72% of FMS patients that participated in our study, who reported that severe stress had triggered their symptomatology (48% reported psychological stress only, while 24% reported psycho-

logical stress mixed with other factors). Women with evidence for both low cortisol levels and short gestational length reported significantly more often than controls that their mothers were exposed to adverse events ($P < 0.05$). However, such subjective recalls should be considered with caution.

Figure 2 summarizes stressful events that preceded onset of FMS in these 93 FMS patients.

Discussion

In this study, we observed that about 62% of female FMS patients report short gestational length, as compared to 27% of the control group. Given the positive feedback between maternal cortisol levels and placental CRH, one may expect a shorter gestational length. As recently reviewed by Smith and Nicholson,⁶² CRH derived from the placenta is thought to play a crucial role in the regulation of fetal maturation and the timing of delivery. Elevated CRH concentrations, as compared with gestational age-matched controls, occur in patients in preterm labor. Thus, short gestational length may indirectly reflect enhanced GC levels of the mother at that time of pregnancy.

In summary, there is evidence suggesting relative hypocortisolemia in FMS patients. This might have its origin in an adrenal insufficiency to appropriately respond to ACTH stimulation. Furthermore, there is evidence suggesting that this adrenal deficiency might be associated with stress exposure during pregnancy, which potentially compromised adrenal development. The possibility of *in utero* programming of hypocortisolism is further underlined by a study of babies of mothers who developed post-traumatic stress disorder (PTSD) after the terrorist attack on September 11, 2001. Those babies showed lower cortisol levels than babies of mothers who did not develop PTSD.⁶³ Interestingly, in some studies a lower adrenocortical stress response is only observed in prenatally challenged female subjects but not in their male counterparts. This suggests the occurrence of sex-specific programming, which might explain the sex-specific prevalence of FMS with females being affected significantly more often than males (reviewed above). This may put these women at risk to develop FMS, once an adaptation to a major physical or psychological stressor demands intact adrenal capacity. If the stress response cannot be sufficiently dampened, the central nervous system may be exposed to disinhibited stress modulators, such as pro-inflammatory cytokines.⁶⁴ It is intriguing to assume that under such conditions a pain memory and a fatigue memory may be established, similar to central manifestations of phantom pain.⁶⁵

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Conflicts of Interest

The authors declare no conflicts of interest.

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