



# Interactions Between Inflammation and Female Sexual Desire and Arousal Function

Tierney K. Lorenz<sup>1</sup>

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## Abstract

**Purpose of Review** To describe the current state of research on interactions between inflammation and female sexual function. **Recent Findings** Inflammation may interfere with female sexual desire and arousal via direct (neural) and indirect (endocrine, vascular, social/behavioral) pathways. There are significant sex differences in the effect of inflammation on sexual function, arising from different evolutionary selection pressures on the regulation of reproduction. A variety of inflammation-related conditions are associated with the risk of female sexual dysfunction, including cardiovascular disease, metabolic syndrome, and chronic pain.

**Summary** Clinical implications include the need for routine assessment for sexual dysfunction in patients with inflammation-related conditions, the potential for anti-inflammatory diets to improve sexual desire and arousal function, and consideration of chronic inflammation as moderator of sexual effects of hormonal treatments. Although the evidence points to a role for inflammation in the development and maintenance of female sexual dysfunction, the precise nature of these associations remains unclear.

**Keywords** Inflammation · Sexual desire · Sexual arousal · C-reactive protein · Cytokines · Interleukin-6

## Introduction

Despite much research on interactions between immunity and female reproductive health [1], there is much less known about the effect of immunity on women's sexual wellbeing. The present review examines one important aspect of immune response – inflammation – and its potential effects on women's sexual desire and arousal (see Fig. 1 for visual summary). While there is much indirect evidence for important interactions between inflammation and female sexual function, causal studies are lacking; thus, the broader purpose of this review is to encourage future research.

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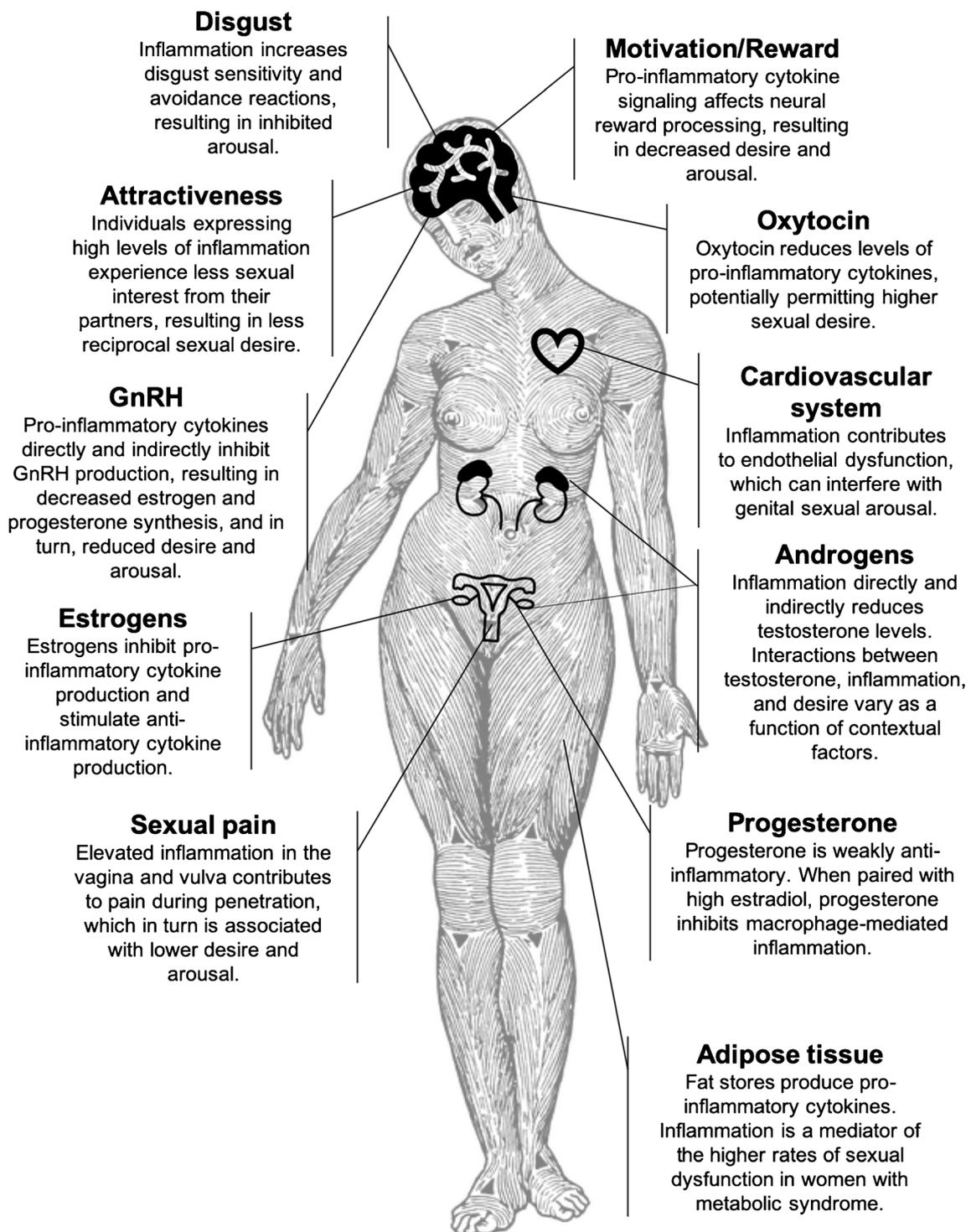
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✉ Tierney K. Lorenz  
tierney.lorenz@unl.edu

<sup>1</sup> Department of Psychology and Center for Brain, Biology and Behavior, University of Nebraska–Lincoln, C66 East Stadium, Lincoln, NE 68588-0156, USA

## Definition of Desire and Arousal

Sexual desire is a motivational state, reflecting the interest in or receptiveness to sexual activity either with or without a partner [2]. As such, it has been characterized as either an acute response to sexual cues [3] (including sexual arousal [4, 5]) or as an ongoing orientation towards sexual stimuli [2, 6]. Sexual arousal, on the other hand, is typically defined as a temporary state that occurs in response to sexual stimulation. Female sexual arousal involves thoughts and emotions as well as physiologic responses including both sympathetic nervous system activation (e.g., increased heart rate, blood pressure, and breathing rate) and arousal of the sex organs (e.g., engorgement of the vulva and vaginal lubrication) [7]. There are common psychological and physiologic foundations for both arousal and desire, including some shared neural networks [8, 9]; moreover, in healthy females, desire can lead to arousal, and vice versa, in a cyclical feedback loop [5, 10]. Insofar as inflammation influences sexual desire, it will likely also impact arousal.



**Fig. 1** Summary of research on inflammation and female sexual desire and arousal function. Image design credit: Anneliis Sartin-Tarm

## Primer on Inflammation

Inflammation is a suite of immune processes that respond to pathogens and toxins, identify and clear out damaged cells, and stimulate and direct the adaptive immune system. In the acute phase, stimulated immune cells exert a variety of

inflammatory actions: increasing blood flow and permeability of blood vessels to permit diffusion of plasma into the tissues; phagocytosis of pathogens and cellular waste; release of substances such as histamines that damage foreign cells; and generation of acute-phase products such as coagulation factors and complement proteins. The acute inflammatory response

generally resolves rapidly, as it relies on the presence of stimulating factors which degrade rapidly as the harmful agents are removed. However, if these stimulating factors remain, the inflammatory response evolves to a chronic phase that can result in lasting tissue damage and contributes to future immune hypersensitivity and autoimmunity [11, 12] as well as a number of chronic diseases such as metabolic and mood disorders [13].

In addition to its critical role in immune defense, inflammation contributes to somatic maintenance. For example, many of the tasks faced by the female reproductive system (e.g., menstrual cycling [14], ovulation [15], implantation [16], and parturition [17]) rely on inflammation processes that assist with tissue repair, vascular reorganization, and coordination with endocrine and nervous systems. One of the negative effects of chronic inflammation on reproduction is disruption of the normal activity of acute inflammation and subsequent loss of these important functions.

Much research on inflammation indexes the level of cytokines, proteins secreted both by immune cells (e.g., macrophages) and other tissues (e.g., endothelial cells). Like hormones, these proteins act on receptors to produce an effect, including regulating inflammation processes; notably, cytokines can also act on cells outside the immune system such as the nervous system (e.g., neurons and microglia [18]) and endocrine system (e.g., gonads [19]). Cytokines may exert either a pro- or anti-inflammatory effect, depending on contextual factors such as where they are secreted, sender and receiver cell type, and activity of other cytokines, hormones, or neurotransmitters. However, there are a few cytokines that are typically indexed for their pro- or anti-inflammatory action. The triad of IL-6, IL-1 $\beta$ , and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) are thought to have a predominantly pro-inflammatory role [20, 21], as each encourages the inflammatory action of macrophages and stimulates the production of acute-phase proteins and prostaglandins (see below). The action of these cytokines on the nervous system are also critical for the psychological and behavioral aspects of sickness [22]. In contrast, IL-4 and IL-10 are thought to be anti-inflammatory as they inhibit the action of pro-inflammatory cytokine signaling [23] and encourage the development of Th2 cells, which regulate acute inflammation and moderate tissue damage [24, 25].

Another commonly indexed marker of inflammation is C-reactive protein (CRP). Acute-phase proteins like CRP aid in the disposal of dead cells and pathogens by binding to their surface and attracting other immune actors to dispose of them. The liver produces CRP in response to cytokine signaling from across the body, making it a useful index of system-level inflammation.

Finally, prostaglandins are compounds that exert a hormone-like effect to moderate inflammation processes [26]. Like cytokines, prostaglandins can exert direct action

on receptors in the nervous system, resulting in pain [27]. Of note, prostaglandin action in the central nervous system is an important mediator of anorexia (loss of appetite) associated with sickness [28]; there is speculation that prostaglandins may moderate other motivation systems as well including, potentially, female sexual desire [29–31]. Outside the brain, prostaglandins can serve a pro-sexual role by promoting vasodilation, including that associated with genital arousal in both males and females [32].

## Mechanisms by Which Inflammation May Influence Female Sexual Desire and Arousal

### Central Nervous System

Cytokines can exert a powerful effect on the central nervous system, contributing to behavioral responses, potentially including the sexual response. Areas of the brain that have been shown to be relevant for coordination of sexual desire and arousal, such as the mesolimbic reward system, cingulate cortex, and thalamus [8, 33], have been shown to respond to cytokine signaling, both directly on neuronal receptors [34, 35] and indirectly through interactions with dopamine [36] and other neurotransmitters [37, 38]. Several studies have found that, even at levels too low to trigger other symptoms such as fever, pro-inflammatory cytokines can interfere with neural processing associated with motivation and reward [39, 40].

A number of animal studies suggest that pro-inflammatory cytokines can lower interest in sexual behavior, particularly among females. When given a dose of IL-1 $\beta$  or lipopolysaccharide (LPS, a substance that induces robust inflammatory responses), female rats had significantly reduced interest in sexual activity. At an equivalent dose, male rats showed no decrease in sexual interest (and, at high doses, even showed *increased* sexual interest) [41, 42]. The desire-suppressing effect of inflammation appears to be the result of interactions between multiple cytokine systems, including IL-1 $\beta$  and TNF- $\alpha$  [42, 43••], as well as increased prostaglandin synthesis and activity in the hypothalamus [31].

These findings have not yet been thoroughly replicated in humans, but preliminary evidence suggests convergence. In a small exploratory study of premenopausal women, higher levels of CRP and IL-6 predicted lower levels of self-reported sexual desire, arousal, and pleasure during sexual activity [44]. In contrast, a small study of men found significant *positive* correlations between high sexual desire and TNF- $\alpha$  (but not CRP) [45]. In a separate study of 11 healthy men, Haake et al. found sexual arousal was associated with increases in IL-6 and TNF- $\alpha$ , albeit non-significantly [46]. Together, these findings echo the sex differences noted in animal models, with markers of inflammation associated with lower desire and arousal in females, but either no effect or higher desire/arousal in males.

Why would the nervous system respond to inflammation cues, and why would there be sex differences in the effect of inflammation on sexual desire? There is a suite of behavioral and psychological effects induced by increased inflammation, such as fatigue and anhedonia. These “sickness behaviors” may have evolved to focus resources on fighting infections by lowering activity levels and reducing exposure to new sources of infection (such as other animals) [47]. Signals of inflammation may thus reduce interest in all social interactions, including partnered sexual activity [48•]. Reproduction requires significant resources, more so for females than for males [49]. As such, modulation of sexual desire may be a means of timing female reproductive investment in accordance with resource availability (or likely future availability) [50]. Inflammation processes are energetically costly, precluding long-term investment in non-essential processes such as reproduction [51]. Thus, signals of inflammation may exert a more powerful effect on female sexual desire in order to delay reproductive investment to healthier times [52, 53].

The behavioral sequelae of inflammation are not limited to lower female sexual desire; there is a reason to believe inflammation may inhibit arousal via increased disgust sensitivity. Disgust is a form of “behavioral immunity,” reducing the chance of exposure to infection by producing an avoidance/withdrawal reaction to disease cues [54, 55]. When inflammation levels rise, disgust sensitivity and avoidance reactions become more pronounced [55–57]. Disgust can interfere with approach-related emotions, including sexual arousal [58, 59]. Experimentally induced disgust strongly inhibits female sexual arousal [60–62]. At a trait level, disgust is associated with higher rates of female sexual desire and arousal dysfunction [63]. The reciprocal inhibition between disgust and sexual arousal may be particularly evident in females, as the female body faces higher reproductive burden of sexually transmitted infection relative to males [58, 64, 65].

Taken together, these findings suggest that inflammation may act on the central nervous system to contribute to female sexual desire and arousal dysfunction via interference with reward processing (decreasing motivation for sex) and increased disgust (increasing avoidance and lowering arousal [65]).

### Endocrine Effects

In addition to the direct effects of cytokines on neural processing, inflammation can influence endocrine function. As noted above, there are significant interactions between female reproductive and immune systems that are thought to have evolved to balance tradeoffs between investing in reproduction vs. somatic maintenance [66•]. Alongside direct neural effects, these tradeoffs are often negotiated via immune interactions with sex steroid hormones (such as estrogens and androgens) and other hormones such as leptin [67, 68] and kisspeptin

[69]. A decidedly mixed literature has revealed that the normal function of these hormones is a necessary, but not sufficient factor in human sexual behavior: while their presence does not guarantee sexual function, their absence almost always impairs it.

### Estrogens and Progesterone

A large body of clinical and basic science research has documented the effects of estrogens and progesterone on inflammation. Notably, the action of each hormone depends on the level expressed and the presence of the other [70–72]. At high levels (e.g., during pregnancy), estrogens typically have an anti-inflammatory action, by inhibiting production of pro-inflammatory cytokines [73] such as IL-6 and TNF- $\alpha$  [74–77], stimulating production of anti-inflammatory cytokines such as IL-4 and IL-10 [78], and accelerating the resolution of ongoing inflammation [79]. However, at lower levels, estrogens can be pro-inflammatory as they stimulate the production of IL-1 $\beta$  [80, 81] and increase the inflammatory action of neutrophils and monocytes [82, 83]. Progesterone is typically weakly anti-inflammatory [84], but in the presence of high levels of estradiol, it can exert powerful inhibitory effects on macrophage-mediated inflammation processes [85, 86].

In turn, inflammatory processes suppress the production of sex steroid hormones and can modulate the action of their receptors. Inflammation processes inhibit the hypothalamic release of gonadotropin-releasing hormone (GnRH) [87, 88], which in turn reduces the production of gonadal hormones. Concurrently, pro-inflammatory cytokines activate the hypothalamic-pituitary-adrenal (HPA) axis via increased production of adrenocorticotropic releasing hormone [89], which further antagonizes production of GnRH [90]. More directly, TNF- $\alpha$  and IL-1 $\beta$  inhibit the production of progesterone and estradiol by ovaries [91–93], uterus [94], and breast tissue [95]. Women who have high circulating levels of IL-6 and IL-1 $\beta$  show significantly lower GnRH receptor sensitivity [96]. In animal models, inflammation is associated with a reduction in the number and sensitivity of the estrogen receptor- $\alpha$  (ER $\alpha$ ) [97]. In sum, inflammation can interfere with the synthesis and activity of estrogen and progesterone, reducing their potentially stimulatory effect on female sexual desire and arousal.

It should be noted that the effect of estrogens and progesterone on inflammation appear to differ if these hormones are endogenous (i.e., those produced by the body) vs. exogenous (administered). Whereas endogenous estrogens can have an anti-inflammatory effect, the use of exogenous estrogens is associated with increased levels of inflammation, particularly when administered orally [70, 98–100]. There is no consensus as to the effect of hormonal treatments (such as oral contraceptives or hormone replacement therapies) on sexual desire

and arousal in healthy women [101, 102]. However, a number of studies have documented that at least a subset of patients reports either decreased sexual desire [103–105] or lack of improvement in sexual desire [106, 107] while taking these medications. Given the strong associations between endocrine and immune systems, it is likely that inflammatory effects partially mediate some of the negative effects of estrogen and progesterone treatments on women's sexual desire and arousal; clearly, this is an area needing further research.

### Testosterone

Early work characterized testosterone and other androgens as universally immunosuppressant, as males typically have a lower immune response (and lower rates of autoimmune disorders) than do females [108]. It is now clear that, like estrogens, endogenous androgens can have either pro- or anti-inflammatory actions in females, depending on the menstrual cycle phase [109], menopausal status [110–114], and even level of sexual activity [115]. Treatment with exogenous testosterone similarly can have either a pro- or anti-inflammatory effect, again depending on the menstrual cycle phase and/or menopausal status [109, 116, 117]. Studies of androgen treatment in hypogonadal women have found no significant effect of testosterone on CRP [118, 119] or other markers of inflammation [120]. In the other direction, inflammation is known to reduce gonadal production of testosterone [121, 122] (except in the case of polycystic ovarian syndrome [123]). Moreover, high levels of IL-6 and TNF- $\alpha$  stimulate aromatase activity [124, 125], which converts testosterone to estrogen, further decreasing bioavailable testosterone.

There have been similarly inconsistent reports of the effects of testosterone on female sexual desire and arousal function: some studies have found significant positive associations [126–128], others negative [129, 130], and others no association [131, 132]. Of note, women who are regularly sexually active with a partner have *lower* endogenous testosterone than single (and sexually inactive) women [133, 134]. Systematic reviews suggest that while testosterone treatment for low libido can be effective in postmenopausal women [135, 136], it is not significantly better than placebo for premenopausal women with normal gonadal function [137, 138]. The inconsistency across both lines of literature makes it difficult to draw definite conclusions regarding the interactions among testosterone, inflammation, and female sexual desire; however, it is clear that these interactions will be sensitive to contextual factors such as menopausal status, menstrual cycle phase, and sexual partnership.

### Oxytocin

Finally, oxytocin plays an important role in female sexual function, as it is released during sexual arousal and orgasm

[139], and contributes to the sense of intimacy and pleasure associated with sexual activity [140, 141]. Women with low scores on the FSFI arousal and lubrication subscales have lower levels of oxytocin than women who are satisfied with their sexual function [142]. In addition to its role in coordinating sociosexual behavior, oxytocin reduces the level of pro-inflammatory cytokines produced by macrophages [143, 144] and microglial cells of the nervous system [145]. Thus, it is possible that the high levels of oxytocin associated with sexual activity (and particularly with orgasm) may provide a permissive environment for sexual desire by reducing cytokine signaling in the nervous system.

## Other Mechanisms

### Endothelial Dysfunction

One of the ways in which inflammation serves immune defense is by encouraging local blood vessels to dilate and increase permeability; this allows defensive and wound-healing factors from plasma to perfuse the inflamed tissue [146]. However, chronically high inflammation can interfere with nitric-oxide-mediated vasodilation, which is necessary for genital arousal [147]. In males, high levels of TNF- $\alpha$  and IL-6 are associated with erectile dysfunction [148–150], even when controlling for a variety of other factors such as age, metabolic syndrome, and blood pressure [151]. Specifically, TNF- $\alpha$  has been demonstrated to reduce synthesis of nitric oxide in erectile tissue [152], reducing the capacity to support genital arousal. To date, these effects have not been replicated in females; however, given similar mechanisms underlying erectile function in the penis and the clitoris [153], it is very likely that high levels of TNF- $\alpha$  would interfere with genital arousal function in females.

### Sexual Pain

One of the key clinical signs of inflammation is pain (*dolor*), and thus it is not surprising that women who report significant pain with penetration also have elevated markers of inflammation, both locally in the vulva and vagina [154] and systemically [155, 156]. Women with sexual pain disorders report significantly lower sexual desire and arousal than women without such disorders [157]. Thus, it is reasonable to expect that to the degree that inflammation contributes to pain during sex, it will also contribute to lower sexual desire.

### Attractiveness

In rodent models, males are significantly less likely to initiate or be receptive to sexual activity with a female who has been treated with IL-1 $\beta$  [158] or LPS [159], suggesting that the attractiveness of potential sexual partners was reduced when

they were expressing higher levels of inflammation. From an evolutionary perspective, mating with an unhealthy female can be both risky (in terms of potential exposure to infection) and counterproductive (in terms of likelihood of spontaneous abortion). Humans are similarly able to detect experimentally induced increases in inflammation via olfactory and visual cues [160, 161]. In one study, the faces of participants who had been injected with LPS were rated significantly less sexually attractive than the faces of the same participants following saline injection [162]. Insofar as sexual desire can be responsive to partner initiation [163], these findings suggest that individuals who are expressing higher levels of inflammation may experience less interest from their partners, and in turn, less desire themselves.

### Sexual Desire and Arousal Function in Populations with Inflammation-Related Conditions

Further evidence of the negative impact of chronic inflammation on female sexual desire and arousal function comes from clinical observations in populations with inflammation-related conditions. In each case, sexual desire appears to be impacted more severely than other aspects of sexual function such as orgasm.

#### CVD

There is a well-known connection between cardiovascular disease (CVD) and erectile dysfunction in men [164], which is mediated via chronic inflammation and subsequent endothelial dysfunction [165–167]. Although less well documented, the associations among inflammation, CVD, and sexual arousal dysfunction have also been observed in women [168–170]. Similarly, hypertensive women report lower sexual desire and arousal function than normotensive women [171], although it should also be noted that anti-hypertensive medications are known to have iatrogenic effects on sexual function [171, 172].

#### Metabolic Syndrome

Chronic low-grade inflammation is also associated with obesity and metabolic syndrome, as adipose tissue generates pro-inflammatory cytokines which in turn impair insulin sensitivity [173]. Across numerous studies, metabolic syndrome is associated with significantly higher levels of sexual desire dysfunction among women [174–176]. In studies that include both pre- and post-menopausal women, there are higher rates of sexual desire dysfunction among women with metabolic syndrome than in women without; however, arousal and orgasm function are similar across groups [177, 178]. In one study of women with and without metabolic syndrome, scores on a validated index of sexual function were inversely related

to levels of serum CRP [179], further evidence that inflammation may partially mediate the higher rates of sexual dysfunction in women with metabolic syndrome.

#### Chronic Pain

Although the etiology of chronic pain is complex, there are many pain conditions for which inflammation plays a significant role [180]. There are higher rates of sexual desire and arousal dysfunction among women with inflammatory bowel diseases [181, 182], rheumatoid arthritis [183], fibromyalgia [184], and chronic pelvic pain [185]. Among women with rheumatoid arthritis, sexual desire and arousal dysfunction is predicted by higher levels of CRP [186].

### Effects of Anti-inflammatory Treatments on Female Sexual Function

As noted above, inflammation-related conditions can have a deeply negative effect on female sexual function. However, the effect of treatments for these conditions has mixed effects on sexual function: while anti-inflammatory diets and lifestyle interventions appear to have a positive effect, anti-inflammatory medications can have a negative effect. In considering this paradox, it should be noted that cytokines and prostaglandins have a variety of homeostatic functions not limited to inflammation *per se* [187]; external manipulation of these systems may have iatrogenic effects that environmental or behavioral interventions lack.

#### NSAIDS

In men, long-term use of non-steroidal anti-inflammatories (NSAIDs) has been associated with erectile dysfunction, both in the exaggeration of pre-existing sexual dysfunction as well as new onset cases. Two studies found the association attenuated when considering a patient's underlying medical conditions [188, 189]; however, others have found increased risk even when controlling for indication and age [190, 191]. NSAIDs have their therapeutic action via inhibition of cyclooxygenase (COX) synthesis, which in turn reduces the activity of prostaglandins [192]. However, this, in turn, may interfere with prostaglandin-mediated vasodilation of erectile tissue [193]. The effect of NSAIDs on female sexual arousal is unknown. Given similar mechanisms of clitoral and penile erection [153], it is likely that NSAIDs would interfere with female sexual arousal as they do in males. However, in animal models, prostaglandins strongly suppressed female but not male sexual desire [31], suggesting potentially different effects across domains of female sexual function.

## Anti-inflammatory Diets

The Mediterranean diet—emphasizing whole grains, fresh fruits and vegetables, fish and poly-unsaturated fats—has been demonstrated to reduce markers of inflammation in both healthy weight [194, 195] and overweight women [196]. A Mediterranean diet has also shown benefits for sexual function for women with metabolic syndrome, particularly in sexual desire and arousal function [197–199, 200••]; these gains are mediated by decreased levels of CRP [197] (but see also [198]). Similarly, a calorie-restricted diet (also shown to reduce chronic inflammation [201]) has been shown to increase sexual desire and arousal in overweight women [202].

## Clinical Implications

Taken together, the above research strongly suggests that inflammation may play a significant role in female sexual desire and arousal function—although the precise nature of that role is still unknown. Thus, the following clinical implications should be considered speculative but worthy of future research.

Reducing chronic exposure to systemic inflammation is associated with improvements across a variety of domains of health and wellbeing; it is reasonable to suspect benefits for sexual function as well. As noted above, preliminary data strongly suggest that anti-inflammatory diets improve sexual desire and arousal, particularly among overweight women; given their high potential benefit and low risk of harm, these diets may be recommended as a preventive first-line treatment or adjunctive to treatments for sexual desire or arousal concerns. It is also reasonable to consider chronic inflammation as a possible contributing factor when assessing sexual desire and arousal concerns, particularly in women with immune conditions and in overweight women. Given interactions between immune and endocrine systems, it may be worthwhile to monitor changes in circulating markers of inflammation when introducing hormone regimens intended to treat sexual dysfunction; if a hormonal treatment not only stimulates desire through central mechanisms, but also increases systemic inflammation, the final result may be less dramatic than hoped. Finally, it is commonly accepted that, in men, sexual dysfunction may be an early warning sign of inflammation-related conditions such as CVD [203–205]; although much further research is needed, the evidence points to the same being true of women [206•], suggesting benefits for routine assessment of female sexual desire and arousal function in the context of preventative care.

## Conclusions

Chronic inflammation can contribute to dysfunction across metabolic, cardiovascular, endocrine, and neurological

systems. Thus, it is not surprising that inflammation may impact female sexual function. However, women's sexual desire and arousal may be particularly sensitive to the effects of inflammation, owing to the important interactions between female reproductive and immune systems. The aggregate evidence suggests that inflammation may interfere with female sexual desire and arousal by both direct (neural) and indirect (endocrine, endothelial, social/behavioral) mechanisms. However, this evidence comes mostly from animal studies, studies in males, and observations of higher rates of sexual dysfunction among clinical populations characterized by chronic inflammation. Direct evidence of the effects of inflammation on female sexual function is lacking. Future research elucidating the interactions between sexuality and immune function will likely be quite fruitful in uncovering new avenues for treatment for female sexual dysfunction.

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## Compliance with Ethical Standards

**Conflict of Interest** Tierney Lorenz declares no potential conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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