Sympathetic and T helper (Th)2 bias may ameliorate uterine fibroids, independent of sex steroids

Anthony J Yun a,*, Stephanie M. Daniel b

a Stanford University, Department of Radiology, 470 University Avenue, Palo Alto, CA 94301, United States
b Palo Alto Institute, Palo Alto, CA, USA

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Summary We propose that inadequate sympathetic bias and Th2 bias in the uterine environment contributes to the formation of fibroids, independent of the sex steroid status. We also propose that fibroids represent a modern maladaptation that partly results from decreasing exposure to seminal fluid, which contains catecholamines, transforming growth factor β1 (TGFβ1), aldosterone, prostaglandins, and other factors that shift the uterine environment to sympathetic and T helper (Th)2 bias. Lower risk of fibroids is associated with pre-menarche, post-menopause, pregnancy, exposure to contraceptives, smoking, earlier age of first pregnancy, shorter interval since last pregnancy, higher parity, and non-obesity. These associations are currently attributed to alterations of sex steroids. However, the association may also be explained by the observation that pre-menarche, post-menopause, pregnancy, and smoking represent periods of sympathetic and Th2 bias. Furthermore, use of contraceptives, early age of first pregnancy, short interval since last pregnancy, high parity, abnormal pap smear, and non-obesity may represent surrogates for increased sexual activity and increased exposure to seminal fluid. Catecholamines, aldosterone, TGF, and prostaglandins are among the seminal fluid components that promote sympathetic and Th2 bias. Vasectomized copulations protect against fibroids, an observation that undermines the steroid hypothesis and supports our hypothesis. The putative mechanism of action of uterine artery embolization (UAE) for fibroid treatment is starvation of blood supply, but the extensive collaterals that protect uterine perfusion would presumably also buffer against fibroid hypoperfusion. Instead, the sympathetic and Th2 responses to UAE-related ischemia may contribute to fibroid regression. A potential explanation for the association of fibroids with intrauterine devices may be a Th1 cell-mediated immune response to the foreign body, which may also enhance the contraceptive effect. Novel methods of preventing and treating fibroids by promoting sympathetic and Th2 shift through natural, pharmacologic, and neuromodulatory means are envisioned. Fibroids are likely a modern dysfunction given the high Darwinian fitness cost of fibroid-related infertility, and may be attributable to reduced intercourse frequency. Fibroids have been observed among animals in captivity that are presumably reproductively isolated.

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Hypothesis

Uterine fibroids are the leading cause of hysterec-
tomy and account for the fifth most common gyn-
cologic condition of reproductive-age women hospi-
talized for conditions unrelated to pregnancy [1]. Risk factors associated with uterine fibroids in-
clude obesity, early menarche, low parity, late age of first pregnancy, and long interval since last preg-
nancy [2–4]. Decreased risk of uterine fibroids is
associated with cigarette smoking, pregnancy, use of oral contraceptives, pre-menarche and post-
menopause [3,4]. The sex steroid hypothesis is the
dominant incumbent framework to explain these associations. However, the data on proges-
terone and estrogen remain inconclusive [2,5]. Fur-
thermore, the weakness of the sex steroid hypo-
thesis is evident in the myriad of other factors well known to be associated with fibroids that can-
not be easily explained. Chlamydia infection and pel-
vic inflammatory disease are positively associ-
ated with uterine fibroids. A negative association
exists among women with a history of abnormal Pap smears [3,4]. Hypertension requiring medica-
tion was found to have a positive association with uterine fibroids, though an explanation has not
been found [4].

We propose that inadequate sympathetic bias and Th2 bias in the uterine environment contrib-
utes to the formation of fibroids, independent of the sex steroid status. We also propose that fib-
roids represent a modern maladaptation that partly results from decreasing exposure to seminal
fluid, which contains catecholamines, transforming growth factor β1 (TGFβ1), vasopressin, oxyto-
cin, aldosterone, and prostaglandins that normally modulate the uterine environment to sympathet-
ic and T helper (Th)2 bias [6].

Evidence

Systemic autonomic and T helper balance demon-
strate temporal variation during the human life-
span [7]. Sympathetic bias and Th2 bias is highest
during childhood and senescence and lowest during the reproductive years [7]. Pregnancy is also
marked by sympathetic bias and Th2 bias, presum-
ably as adaptations for increased physiologic de-
mands for gestational immune tolerance [7]. Smokers exhibit clear traits of sympathetic bias and Th2 bias. Lower risk for fibroids is associated
with pre-menarche, menopause, aging, smoking, and pregnancy. While conventional wisdom attrib-
utes these associations to sex steroids, we pro-
pose that sympathetic bias and Th2 bias could
help account for these associations.

Seminal fluid exposure may reduce the risk of fib-
roids. Factors associated with reduced risk of fib-
roids also represent potential surrogates for in-
creased sexual activity or greater exposure to seminal fluid. Earlier age of first pregnancy, shorter
interval since last pregnancy, use of contraceptives,
and higher parity are not unreasonable surrogates
for greater and more recent sexual activity. Obes-
ity, which is associated with an increased risk of fib-
roids, is also associated with a lower frequency of
penile-vaginal intercourse [8]. While these epidemi-
ologic risk factors are consistent with the tradi-
tional sex steroid hypothesis, the pattern also fits
our current hypothesis. On the other hand, there
are numerous other risk factors for fibroids that
are not readily explained by the sex steroid hypo-
thesis but could be explained by exposure to seminal fluid. Chlamydia infection and pelvic inflamma-
tory disease are associated with higher risk of fibroids. These infections are generally painful and are gen-
erally perceived as deterrents for intercourse. In
contrast, a decreased risk of fibroids is associated
with abnormal Pap smears [4]. Abnormal Pap smears
are linked to human papilloma virus infections, and
both factors are not only positively associated with
the number of sexual partners [9,10], but also sel-
dom cause the degree of pain, discomfort or visible
infection that might discourage sexual activity.

Evidence suggests that seminal fluid is an under-
recognized source of sympathetic bias and Th2 bias
in the female reproductive tract [6]. Seminal fluid
components such as norepinephrine, aldosterone,
transforming growth factor β1 (TGFβ1), vasopres-
sin, oxytocin, and prostaglandin E2 (PGE2) have
been shown to dampen maternal Th1 immunity and promote Th2 immunity [6,11–17]. Seminal
fluid exposure alters leukocyte populations in the
superficial cell layers of the uterus [18,19]. In uter-
ine epithelial cells, seminal fluid promotes pro-inflammation Th2 cytokine synthesis including
IL-6 and granulocyte-macrophage colony-stimulating
factor (GM-CSF) [20,21]. Condom-protected intercource does not induce maternal inflammatory
response [22]. This phenomenon may reflect an evolu-
 tionary adaptation to ensure that the immune
environment in the female reproductive tract
remodels sufficiently towards Th2 bias, a state that
favors the survival of the male gametes and the fe-
tal allograft. Birth rates for assisted reproduction
techniques are higher when the females are ex-
posed to seminal fluid around the time of embryo
or gamete transfer [6]. In cases of recurrent preg-
nancy loss, exposure to seminal plasma pessaries
improves implantation rates [23].
Animal data provide additional support for our hypothesis. A recent study examined the incidence of fibroids among 4 groups of female Eker rats, who carry a gene mutation that results in the development of uterine fibroids with a frequency of 65% when not pregnant [5]. Fertile female Eker rats mated once with fertile male Eker rats exhibited a rate of fibroids that was statistically similar (71%) to the background rate [5]. In Eker rats that were pregnant with multiple litters, the incidence of uterine fibroids dropped down to 10%, which is consistent with the view that parity is protective and could support the sex steroid hypothesis. Strikingly, a significant reduction in the incidence of fibroids (41%) was found when Eker rats were allowed to mate with vasectomied males resulting in no pregnancy [5]. Furthermore, a similar reduction (35%) was experienced by infertile female Eker rats who were allowed to mate with non-vasectomied males [5]. The authors argue that the protection from fibroids is attributable to "pseudopregnancy" [5]. Alternatively, we postulate that exposure to seminal fluid helps protect against fibroids.

The response of fibroids to treatment also provides supporting evidence. Uterine artery embolization (UAE) is an emerging treatment for fibroids. The putative mechanism of UAE is starvation of blood supply to the fibroids during a period of transient uterine ischemia [24]. However, the extensive collaterals that protect uterine perfusion may offer a buffer to fibroid hypoperfusion. Perhaps a sympathetic and Th2 response to UAE-related ischemia contributes to fibroid regression. One possible explanation for the increased risk of fibroids among patients taking antihypertensive medication is that these drugs typically reduce sympathetic bias [4,25]. A potential explanation for the increased incidence of fibroids observed in women who use intrauterine devices may be an increased Th1 cell-mediated immune response to the foreign body, which may also contribute to the contraceptive effect [2,3,26,27].

**Implications**

Fibroids are likely a distinctly modern dysfunction given the high Darwinian fitness cost of fibroid-related infertility. The emergence of fibroids could be partly attributed to reduced seminal fluid exposure as a result of distinctly modern socio-cultural factors that dampen intercourse frequency. The lack of regular exposure to seminal fluid may be a circumstance rarely encountered in nature. Notably, fibroids have been observed among animals in captivity or in research laboratories that presumably are reproductively isolated [28]. The altered mating pattern argument has already been made to suggest that regular monthly menses, which presumably carries high metabolic costs and may attract predators, represent a distinctly modern maladaptation, since our prehistoric predecessors experienced far greater amenorrhea related to gestation and lactation [29]. If our hypothesis is validated, then a greater regularity of exposure to seminal fluid may represent a natural method to prevent and treat fibroids. Alternative methodologies may include pharmacologic agents, medical devices, and neuromodulation techniques that promote sympathetic activity and Th2 function in the female reproductive organs.

**References**


