



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

Anthony J Yun <sup>a,\*</sup>, Stephanie M. Daniel <sup>b</sup>

<sup>a</sup> *Stanford University, Department of Radiology, 470 University Avenue, Palo Alto, CA 94301, United States*

<sup>b</sup> *Palo Alto Institute, Palo Alto, CA, USA*

Received 15 March 2005; accepted 19 March 2005

---

**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  $\beta_1$  (TGF $\beta_1$ ), 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.

© 2005 Elsevier Ltd. All rights reserved.

---

\* Corresponding author. Tel.: +1 650 387 6667; fax: +1 650 325 5028.

E-mail address: [ayun@stanford.edu](mailto:ayun@stanford.edu) (A.J. Yun).

## Hypothesis

Uterine fibroids are the leading cause of hysterectomy and account for the fifth most common gynecologic condition of reproductive-age women hospitalized for conditions unrelated to pregnancy [1]. Risk factors associated with uterine fibroids include obesity, early menarche, low parity, late age of first pregnancy, and long interval since last pregnancy [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 progesterone and estrogen remain inconclusive [2,5]. Furthermore, the weakness of the sex steroid hypothesis is evident in the myriad of other factors well known to be associated with fibroids that cannot be easily explained. Chlamydia infection and pelvic inflammatory disease are positively associated with uterine fibroids. A negative association exists among women with a history of abnormal Pap smears [3,4]. Hypertension requiring medication 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 contributes to the formation of fibroids, independent of the sex steroid status. We also propose that fibroids represents a modern maladaptation that partly results from decreasing exposure to seminal fluid, which contains catecholamines, transforming growth factor  $\beta_1$  (TGF $\beta_1$ ), vasopressin, oxytocin, aldosterone, and prostaglandins that normally modulate the uterine environment to sympathetic and T helper (Th)2 bias [6].

## Evidence

Systemic autonomic and T helper balance demonstrate 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, presumably as adaptations for increased physiologic demands 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 attributes 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 fibroids. Factors associated with reduced risk of fibroids also represent potential surrogates for increased 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. Obesity, which is associated with an increased risk of fibroids, is also associated with a lower frequency of penile-vaginal intercourse [8]. While these epidemiologic risk factors are consistent with the traditional 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 hypothesis but could be explained by exposure to seminal fluid. Chlamydia infection and pelvic inflammatory disease are associated with higher risk of fibroids. These infections are generally painful and are generally 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 seldom 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  $\beta_1$  (TGF $\beta_1$ ), vasopressin, 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 uterine epithelial cells, seminal fluid promotes pro-inflammatory Th2 cytokine synthesis including IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) [20,21]. Condom-protected intercourse does not induce maternal inflammatory response [22]. This phenomenon may reflect an evolutionary 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 fetal allograft. Birth rates for assisted reproduction techniques are higher when the females are exposed to seminal fluid around the time of embryo or gamete transfer [6]. In cases of recurrent pregnancy 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

- [1] Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. *Obstet Gynecol* 1997;90(6):967–73.
- [2] Samadi AR, Lee NC, Flanders WD, et al. Risk factors for self-reported uterine fibroids: a case-control study. *Am J Pub Health* 1996;86(6):858–62.
- [3] Faerstein E, Szklo M, Rosenheim N. Risk factors for uterine leiomyoma: a practice-based case-control study. I. African-American heritage, reproductive history, body size, and smoking. *Am J Epidemiol* 2001;153(1):1–10.
- [4] Faerstein E, Szklo M, Rosenheim N. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. *Am J Epidemiol* 2001;153(1):11–9.
- [5] Walker CL, Cesen-Cummings K, Houle C, et al. Protective effect of pregnancy for development of uterine leiomyoma. *Carinogenesis* 2001;22(12):2049–52.
- [6] Bazar K, Yun AJ, Lee PY. Immunomodulatory function of seminal catecholamines may be an adaptation for reproduction. *Med Hypotheses* 2004;63(1):168–71.
- [7] Yun AJ, Lee PY, Bazar KA. Temporal variation of autonomic balance and diseases during circadian, seasonal, reproductive, and lifespan cycles. *Med Hypotheses* 2004;63(1):155–62.
- [8] Brody S. Slimness is associated with greater intercourse and lesser masturbation frequency. *J Sex Marital Ther* 2004;30:251–61.
- [9] Frega A, Stentella P, De Ioris A, et al. Young women, cervical intraepithelial hyperplasia and human papillomavirus: risk factors for persistence and recurrence. *Cancer Lett* 2003;196(2):127–34.
- [10] Stafford EM, Stewart Jr RS, Teague GR, et al. Detection of human papillomavirus in cervical biopsies of summer camp ROTC cadets with abnormal papanicolau smears. *J Pediatr Adolesc Gynecol* 1996;9(3):119–24.
- [11] Schiott A, Widegren B, Sjogren HO, Lindvall M. Transforming growth factor-beta 1, a strong costimulator of rat T-cell activation promoting a shift towards a Th2-like cytokine profile. *Immunol Lett* 1999;67(2):131–9.
- [12] Nocera KPM, Chu TM. Transforming growth factor beta as an immunosuppressive protein in human seminal plasma. *Am J Reprod Immunol* 1993;30(1):1–8.

- [13] Tremellen KP, Seamark RF, Robertson SA. Seminal transforming growth factor beta1 stimulates granulocyte-macrophage colony-stimulating factor production and inflammatory cell recruitment in the murine uterus. *Biol Reprod* 1998;58(5):1217–25.
- [14] Kelly RW, Critchley HO. Immunomodulation by human seminal plasma: a benefit for spermatozoon and pathogen. *Hum Reprod* 1997;12(10):2200–7.
- [15] Elenkov IJ, Papanicolaou DA, Wilder RL, Chrousos GP. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. *Proc Assoc Am Physician* 1996;108(5):374–81.
- [16] Brotherton J. Vasopressin: another pregnancy protein in human seminal plasma. *Andrologia* 1990;22(4):305–7.
- [17] Goverde HJ, Bisseling JG, Wetzels AM, et al. A neuropeptide in human semen: oxytocin. *Arch Androl* 1998;41(1):17–22.
- [18] Pandya IJ, Cohen J. The leukocytic reaction of the human cervix to spermatozoa. *Fertil Steril* 1985;43(3):417–21.
- [19] Robertson SA, Allanson M, Mau VJ. Molecular regulation of uterine leukocyte recruitment during early pregnancy in the mouse. *Trophoblast Res* 1998;11:101–20.
- [20] Robertson SA, Mau VJ, Tremellen KP, Seamark RF. Role of high molecular weight seminal vesicle proteins in eliciting the uterine inflammatory response to semen in mice. *J Reprod Fertil* 1996;107(2):265–77.
- [21] Robertson SA, Sharkey DJ. The role of semen in induction of maternal immune tolerance to pregnancy. *Semin Immunol* 2001;13(4):243–54.
- [22] Robertson SA, Sharkey DJ, Tremellen KP, Danielsson KG. Semen elicits immunological changes in the human cervix. *J Soc Gynecol Invest* 2001;9(Abstract 502):228A.
- [23] Coulam CB, Stern JJ. Effect of seminal plasma on implantation rates. *Early Pregnancy* 1995;1(1):33–6.
- [24] Burbank F. Childbirth and myoma treatment by uterine artery occlusion: do they share a common biology. *J Am Assoc Gynecol Laparosc* 2004;11(2):138–52.
- [25] Yun AJ, Lee PY, Bazar KA. Clinical benefits of hydration and volume expansion in a wide range of illnesses may be attributable to reduction of sympatho-vagal ratio. *Med Hypotheses* 2005;64(3):646–50.
- [26] Wollen AL, Sandvei R, Mork S, Marandon JL, Matre R. In situ characterization of leukocytes in the fallopian tube in women with or without an intrauterine contraceptive device. *Acta Obstet Gynecol Scand* 1994;73(2):103–12.
- [27] Randic L, Haller H, Susa M, Rukavina D. Cells adherent to copper-bearing intrauterine contraceptive devices determined by monoclonal antibodies. *Contraception* 1990;42(1):35–42.
- [28] Walzer A, Kübber-Heiss A, Bauder B. Spontaneous uterine fibroleiomyoma in a captive cheetah. *J Vet Med* 2003;50:363–5.
- [29] Thomas SL, Ellertson C. Nuisance or natural and healthy: should monthly menstruation be optional for women? *Lancet* 2000;355(9207):922–4.

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

