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Gender Differences in Abdominal Aortic Aneurysms

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Abstract

Abdominal aortic aneurysms (AAAs) comprise the 10th leading cause of death in Caucasian males 65–74 years of age, and accounted for nearly 16,000 deaths overall in the year 2000. Therefore, understanding the pathophysiology of AAAs is an important undertaking. Clinically, multiple risk factors are associated with the development of AAAs, including increasing age, positive smoking history, and hypertension. Male gender is also a well-established risk factor for the development of an AAA with a 4:1 male to female ratio. The reason for this gender disparity is unknown. The pathogenesis of AAA formation is complex and multifactorial. Histologically, AAAs are characterized by early chemokine driven leukocyte infiltration into the aortic wall. Subsequent destruction of elastin and collagen in the media and adventitia ensues due to excessive local production of matrix degrading enzymes, and is accompanied by smooth muscle cell loss and thinning of the aortic wall. At present, there are no medical therapies available to treat patients with aortic aneurysms, using only the crude measurement of aortic diameter as a threshold for which patients must undergo life-threatening and costly surgery. Defining the early mechanisms underlying gender-related differences in AAA formation are critical, as understanding differences in disease patterns based on gender may allow us to develop new translational approaches to the prevention and treatment of patients with aortic aneurysms.

Introduction

Abdominal aortic aneurysms (AAAs), defined as an aortic diameter (AD) > 3.0 cm,¹ are a common clinical condition in adult patients and can lead to serious life-threatening complications if not addressed. According to the National Center for Health Statistics, AAAs are the cause of over 12,000 deaths annually and ranks as the 15th leading cause of death among all individuals aged 55–85.² Recent advances in screening and therapy, such as endovascular aneurysm repair, have led to improved detection and lower mortality rates.^{3–8}

The pathogenesis of AAAs involves a complex series of events that have not been fully elucidated yet, as most studies of AAAs primarily involve cohort studies from the end-stage of the disease process. Characteristics of aneurysm development include: degradation of elastin and collagen in the media and adventitia, release of cytokines and chemokines, and an oxidative burst resulting from a catalytic process that occurs following infiltration of inflammatory cells into the aortic wall.^{9–13}

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Clinical Impact of Gender on AAA

Clinical risk factors for AAA including advanced age, family history, smoking history, atherosclerosis, hypertension, and chronic obstructive pulmonary disease (COPD), are equally distributed between males and females.^{5, 14, 15} In contrast, females seem to be protected from developing AAAs. Lederle et al. documented that female gender was considered a negative risk factor for developing a small AAA [OR 0.47 (CI 0.32–0.69) for AD 3.0–3.9 cm, OR 0.18 (CI 0.07–0.48) for AD > 4.0 cm].⁵ In contrast, the prevalence of AAAs amongst males greater than 50 years old is 4–5 times greater than females of the same age.^{15, 16} As one ages, the prevalence of AAAs increases with males, reaching a peak prevalence of 5.9% at 80–85 years of age and then decreasing afterwards. In women the prevalence increases to 4.5% after age 90 years of age.¹⁷ After analyzing population based screening studies, Bengtsson et al. demonstrated that AAAs develop 10–15 years later in women.¹⁷ Speculation as to why this occurs may be due to decreased circulating levels of estrogen in post-menopausal women, as has been suggested by investigational studies in rodents.¹⁸

Observations such as these have diminished the enthusiasm for screening women for AAAs, even those with a significant number of risk factors for developing an AAA. Currently, the United States Preventive Task Force provides a grade D recommendation for screening for AAA among women due to the low prevalence of the disease.¹⁹ However, this recommendation conflicts with the Society of Vascular Surgery and the Society for Vascular Medicine and Biology who recommend screening for women aged 60–85 with cardiovascular risk factors or greater 50 years old with a family history of AAA.²⁰ Derubertis et al. recently documented that women of advanced age (≥ 65 years) with a history of smoking or heart disease should be considered for AAA screening.²¹

Regarding different thresholds for AAA repair among gender, the 2005 ACC/AHA practice guidelines recommends an AAA diameter of 5.5 cm as a lower limit with no mention of variation between sexes.¹ However, numerous studies have documented that females consistently suffer significantly higher mortality rates compared to males following elective AAA (eAAA) repair (Figure 1), ruptured AAA (rAAA) repair, and endovascular AAA repair (EVAR).^{4, 16, 22–24} Methods suggested to decrease mortality rates in females include referral to high volume hospitals²³ or decreasing the diameter threshold for repair.^{3, 25} According to Dimick et al., there were significant decreases in mortality rates for women undergoing AAA repair when they were admitted to a high-volume hospital, versus a low-volume hospital. (Table 1).²³ In addition, numerous retrospective studies have suggested an almost paternalistic approach by caregivers for women with AAAs, as females were less likely than males to undergo eAAA repair, rAAA, or EVAR.^{4, 16, 22} Anatomical contraindications, such as small iliac arteries or a small aortic bifurcation diameter, and increased intraoperative morbidity, such as iliac artery occlusions, dissections, and ruptures, are factors which occur more frequently in females, and may preclude women from undergoing EVAR, with its attendant lower short term mortality.²⁶

A lower threshold for eAAA repair in women at AD of 4.5 cm to 5.0 cm, which is in contradiction to the 2005 ACC/AHA practice guidelines, has been recommended by the American Association for Vascular Surgery and Society of Vascular Surgery.³ Evidence to support this recommendation was primarily based on a study by Brown et al. which reviewed risks of small aneurysm rupture in patients undergoing ultrasound surveillance. The study documented that female sex was significantly associated with aneurysm rupture (HR 4.50, CI 1.98–10.2, $p = 0.001$) and that mean AD at rupture was 5 cm in women versus 6 cm in men.²⁵ Reasons for these differences may be that aneurysms of the same size in both sexes represent more advanced disease in the females, who generally have smaller initial

aortic diameters.^{27, 28} An alternative hypothesis is that, while AAAs occur less frequently in females, women have faster growth rates of their aorta compared to males secondary to increased inflammation in the aortic wall once they have a small AAA.^{29, 30}

There are other disease states associated with an increased incidence of aortic aneurysms, such as polycystic kidney disease (PKD), in which the severity of the disease is associated with alterations in gonadal hormones. A recent study by Smith suggested that testosterone is associated with a decline in renal function, while estrogen was protective in mice with juvenile cystic disease.³¹ A link between steroid hormones and MMP9 and MMP1 in patients with PKD has been established.³² A link between Turner syndrome, a chromosomal deletion leaving patients with an XO sex linked chromosome pair, and aortic disease is also well documented.³³ Observations such as these have led some to suggest that: *“Males and females have different patterns of illness Understanding the basis of these gender-based differences is important to developing new approaches to prevention, diagnosis, and treatment.”*³⁴

Increasing Incidence of AAAs in Males in Rodent Experimental Models

The mechanism(s) by which aneurysms are initiated and the series of events by which an AAA forms are poorly understood.³⁵ While the specific etiology is unclear, AAAs are initiated by some unknown aortic wall injury. In a conducive genetic and environmental background, recruitment of leukocytes into the aortic wall media and adventitia by chemokines appears to be an early and critical event. These chemokines may be secreted by a number of cells, including leukocytes and smooth muscle cells. Subsequent leukocyte infiltration into the aortic wall is associated with the production of many pro-inflammatory cytokines as part of the innate inflammatory response. It is during this stage that a number of matrix degrading enzymes are released, leading to aortic wall elastin and collagen degradation. With continued aortic wall thinning secondary to SMC apoptosis³⁶ and elastin fragmentation, AAA formation occurs.

Three published reports have directly compared male and female animals in experimental AAA models and have suggested that, similar to humans, females are protected from AAA formation.^{18, 37, 38} Daugherty documented in ATII-induced AAAs in apolipoprotein E $-/-$ and LDL receptor $-/-$ mice, males are more susceptible to aneurysm development than females.³⁹ Interestingly, in the initial report using this model³⁸ describing suprarenal aortic aneurysm formation, female mice were used exclusively and only 20% and 33% of mice developed an AAA. In subsequent studies, male mice have been used primarily and develop an AAA approximately 80% of the time.³⁸

In the elastase-induced rodent aortic aneurysm model, a report from our laboratory documented that males form AAAs more often than females, and that this was associated with an increase in the number of MMP9 secreting macrophages in the aortic wall.¹⁸ The mean increase in aortic diameter 14 days after elastase perfusion in male (M) aortas was $200 \pm 38\%$, while female (F) aortas had an increase of only $69 \pm 27\%$ ($P=.023$). The incidence of AAAs, defined as a 100% increase in aortic diameter from baseline, was 82% in males compared to 29% in female rats ($P=.023$). A follow-up study in the rat elastase model in males using microarrays also suggested that early (day 3) during AAA development the androgen receptor and the estrogen-related α receptor are down regulated 50 fold and 126 fold, respectively, compared to control animals.⁴⁰ A number of other cytokines, including IL-1, were also found to be down-regulated in females compared with males.⁴¹ (Table 2)

Recent experiments in our laboratory have confirmed that the phenotypic changes that occur in rats also occur in mice in the elastase-induced AAA model. In these experiments, male and female mice underwent isolated elastase or heat-inactivated elastase aortic perfusion. The

results were similar to rats, in that male mice form larger AAAs with increased incidence compared with female mice. (Figure 2A) In addition, MMP9 and MMP2 activity as determined by zymography is increased in the mouse aortic wall in males compared with females. (Figure 2B)

Recruitment of Leukocytes is Critical during Early AAA Formation

The pathogenesis of AAAs involves a complex series of events, characterized ultimately by the degradation of elastin and collagen in the media and adventitia through a catalytic process that occurs following infiltration of inflammatory cells into the aortic wall.^{10, 12, 42–45} The macrophage, in particular, has been implicated as critical in the pathogenesis of AAAs.⁴⁶ The importance of the neutrophil during AAA formation, while not as well studied, has also been established in humans^{47–49} and, recently, in a mouse model of aneurysm formation.⁵⁰

The broad context for another study from our laboratory using a neutrophil depletion strategy prior to AAA formation was to better define the role of the neutrophil in the sequence of events leading to AAA formation.⁵⁰ Briefly, control, rabbit serum treated, (RS, n=27) or anti-neutrophil antibody treated (Anti-PMN, n=25) C57BL/6 mice underwent aortic elastase perfusion to induce experimental aneurysms. Control mice 14 days after elastase perfusion exhibited a mean aortic diameter (AD) increase of $104\% \pm 14\%$ ($P < 0.001$), and 67% developed AAAs, while Anti-PMN-treated mice exhibited a mean AD increase of only $42\% \pm 33\%$ with 8% developing AAAs. Tissue neutrophils and macrophages 14 days after elastase perfusion were significantly decreased in the Anti-PMN group compared to controls. Earlier time-points (4 and 7 days) reflected these differences as well.

The mechanism by which neutrophils and macrophages are recruited into the aortic wall during aneurysm formation are critical early events during AAA formation,⁵¹ and appear to be mediated by two primary mechanisms: 1) soluble mediators, including chemokines and cytokines, and 2) cell specific receptors such as the selectins. Multiple chemokines and cytokines have been studied in both human and experimental AAAs. The CC chemokines appear to be critical during AAA formation and have previously been shown to be important intermediaries during the initial inflammatory process leading to AAA formation.^{52, 53} Each of these chemokines, while not completely selective, tends to recruit a particular cell type to sites of inflammation. For example, MIP2 and KC (human IL8) are primarily associated with recruitment of neutrophils, while MIP1 α and MCP-1 (CCL2) are involved in the recruitment of macrophages.^{52, 53} MIP-1 α has been shown to be up-regulated in macrophages in response to in hyperlipidemic apo E^{-/-} and Ldlr^{-/-} mice that form AAAs.⁵⁴ MCP1 is leukotriene LTD₄ essential for monocyte recruitment *in vivo* in several different inflammatory models,^{55–57} and is up-regulated in both mouse and human AAAs.^{58, 59} The importance of MCP1, in particular, during AAA formation is also supported by the observation that mice deficient in CCR2 receptor fail to develop aneurysms in the ATII-induced apo E^{-/-} mice.⁶⁰ This observation is associated with a marked decrease in monocyte-mediated inflammation in the aortic wall and an increase in IL1 β expression.

In separate experiments in mice using the elastase perfusion AAA model, the temporal course of MCP1 expression and protein levels was defined.⁵⁸ Mouse aortic diameter (mean $\pm$ SEM) increased to aneurysmal proportions 14 days after elastase perfusion (from 0.51 ± 0.03 mm to 1.34 ± 0.32 mm; 163% increase; $P < .05$). Aortic wall messenger RNA expression increased 28-fold for MCP1 on day 4, with maximal production of chemokine protein on day 7. These data suggest that increased aortic wall expression of MCP1 occurs early in development of elastase-induced AAAs before the onset of the chronic

inflammatory response. The source of MCP1 was aortic SMCs, providing an important link between enzymatic injury, leukocyte recruitment, and aneurysmal degeneration of the aortic wall.

Another group of soluble mediators involved early in the cascade of events that occurs during AAA formation are cytokines, which serve as cytotoxic mediators damaging SMCs in the aortic wall. Two well-studied cytokines, TNF α and IL1 β may play a central role in the gender disparity seen during AAA formation. Importantly, increased serum and tissue levels of TNF α and IL1 β have been documented in patients with aortic aneurysms.^{61, 62} These two cytokines are particularly relevant during AAA formation as they both inhibit Type I and III collagen synthesis.^{63, 64} In general, while often cited as having similar effects in inflammatory and septic models, a recent study has demonstrated enhanced TNF α expression without corresponding changes in IL1 β in small AAAs.⁶⁵ Temporal and concentration differences in the expression of these two cytokines may be critical during the observed differential phenotypic expression of AAA between males and females. The expression of MMPs and TIMPs are also controlled in part at the transcriptional level by cytokines.

In addition to the multiple potential soluble mediators of early leukocyte recruitment during AAA formation, various cell-based receptors are also critical during this process. One group of adhesion molecules that may be relevant is the selectins. The selectins are a family of three adhesion molecules: 1) E-selectin on the surface of activated endothelial cells, 2) P-selectin on the surface of activated platelets and endothelial cells, and 3) L-selectin constitutively expressed on the surface of most leukocytes (PMNs and macrophages).^{66, 67} The primary function of selectins is to promote leukocyte capture to sites of inflammation. Without selectins, inflammatory cell recruitment is significantly diminished.^{68–72}

The critical role of L-selectin in AAA formation in male rodents has been studied extensively in our laboratory.⁷³ Briefly, male rat abdominal aortas were perfused with saline or elastase and studied on post-perfusion days 1, 2, 4, 7, and 14. L-selectin expression and protein levels in aortic tissue were determined by PCR and western blot, respectively. Elastase perfused aortic diameters were significantly increased compared to control aortas at all time points except day 1 ($P < .05$). L-selectin mRNA expression in elastase perfused aortas were 18 ($P = .018$), 17 ($P < .001$) and 8 times ($P = .02$) times greater than control aortas at days 1, 2, and 4, respectively. Western blot demonstrated a significant 69% increase in L-selectin protein at day 7 in elastase compared to saline perfused aortas ($P = .005$). Subsequent experiments involved studies on post-elastase perfusion days 4, 7, and 14 of aortas from C57Bl Wt ($N = 21$) and L-selectin knockout (LKO) mice ($N = 19$). LKO mice had significantly smaller aortic diameters at day 14 compared to Wt mice. PMN counts were significantly greater in elastase perfused Wt mouse aortas compared to LKO mouse aortas at day 4 post-perfusion (12.8 vs. 4.8 PMNs/HPF, $P = .02$). Macrophage counts were significantly greater at all time points in elastase perfused WT mouse aortas compared to elastase perfused LKO mouse aortas, with a maximum difference at day 7 post-perfusion (13.3 vs. 0.5 macrophages/HPF, $P < .001$).

In separate experiments from our laboratory to document phenotypic and mechanistic changes in AAA formation, male Wt ($n=17$) and P-selectin knock-out ($n=10$) $-/-$ mice (PKO) underwent elastase perfusion, and aortic diameters were determined post-perfusion day 14.⁷⁴ The results document that, even to a greater extent than L-selectin $-/-$ mice, the absence of P-selectin inhibits AAA formation ($P < 0.001$). (Figure 3)

Manipulation of Gonadal Hormones Alters Leukocyte Trafficking and Aortic Wall Degradation

While few studies have examined the role of pharmacologic or surgical alteration of gonadal hormones on leukocyte recruitment during AAA formation, a protective role for estrogen and its derivatives in AAA formation receives indirect support from a number of studies. A study in the AT-II induced AAA model suggested that 17 β -estradiol implanted subcutaneously attenuates aneurysm development.⁷⁵ Inhibition of proinflammatory genes, including MCP1, was proposed as the mechanism responsible for this effect. It has been suggested that orchidectomy, not ovariectomy, is capable of altering gender-specific rates of AAA formation.⁷⁶

Our laboratory confirmed the inhibitory effects of estradiol in the aortic elastase-perfusion rodent model.¹⁸ Male rats were randomized to implantation of an estrogen pellet or sham implantation (n=13, each). Rat aortas from both groups were subjected to elastase perfusion 5 days later. The aortic size was then determined 14 days following elastase perfusion and the aorta was excised for study. By day 14, male rats receiving estradiol (**ME**) had significantly smaller aneurysms ($241\% \pm 57$) compared to sham rats (**MS**, $538\% \pm 105$, $P=.023$).¹⁸ ED-1 positive cell counts (mononuclear leukocyte lineage) were 1.8 ± 0.3 cells/HPF in males receiving estradiol (ME) versus 5.2 ± 0.5 cells/HPF male sham (MS) rats (* $P=.0006$).

Multiple observations from the trauma and sepsis literature suggest that gonadal hormones regulate leukocyte trafficking. Chaudry and others developed the hypothesis that leukocyte immune responses, through multiple soluble mediators, are depressed in males and enhanced in females following trauma and hemorrhage.^{77–82} Other models have also been used to examine the role of estrogen on leukocyte migration. In rat carotid arteries following acute balloon injury, a large number of leukocytes (neutrophils and macrophages) invade the carotid artery within 24 hours following injury. This response is markedly blunted by exogenous estrogen. Following ovariectomy in rats, estrogen therapy is able to negatively modulate the pro-inflammatory response by altering expression and protein levels of a number of chemokines and cytokines, including MCP1, IL1 β , and TNF α . Inhibition of these chemokines and cytokines by estrogen in oophorectomized animals translated into decreased migration of neutrophils in a chemotaxis assay.^{83–85} Estrogen also has a direct inhibitory effect on macrophage recruitment, through its effects on MCP1.^{86–89} Furthermore, increased estrogen levels in women, including those on estrogen replacement therapy, correlated with reductions in circulating MCP1 levels.

Gonadal hormones may also affect AAA formation through their effects on gonadal receptors. Multiple genetic studies have suggested a role for the estrogen receptors in influencing cardiovascular disease. While not examined in detail experimentally in the development of AAAs, vascular SMCs express functional estrogen receptor (ER) α and β . ER α polymorphisms are associated with premature coronary artery disease in men⁹⁰ and postmenopausal women.⁹¹ Similarly, a polymorphism in the ER β gene has been documented in post-menopausal Japanese women with hypertension,⁹² a known risk factor for aneurysm development.

Estrogen may also affect AAA development by directly inhibiting macrophage and SMC production of MMPs. For example, estrogen treatment of U937 cells decreases MMP-2 production directly.⁹³ In a study by Potier and others, estrogen and progesterone differentially regulated MMP-9 and MMP-2 expression and activity in aortic arch-derived smooth muscle cells isolated from atherosclerosis-susceptible and -resistant mice.⁹⁴ Animals

treated with estradiol also have decreased vascular smooth muscle cell contractility and proliferation.⁹⁵

A third possible mechanism by which gender might alter AAA formation is through the effect of gonadal hormones on aortic wall ECM proteins. In particular, the influence of sex hormones on aortic wall elastin and collagen degradation has been studied. Fischer and Swain examined the effects of castration in the presence of testosterone and estradiol in male rats and concluded that: 1) estradiol, in the presence or absence of testosterone, alters the proportions of collagen and elastin so that the vessel is more distensible, and 2) testosterone has the opposite, but markedly less, effect of estradiol on vascular tissue.⁹⁶ These studies were extended by Simpson and Cardeilhac who, following the administration of beta-aminopropionitrile (BAPN) in turkeys, demonstrated that 65% of BAPN-treated male turkeys died of dissecting aneurysms, while only 21% of females died of the same disease. Ultrastructural alterations in aortic collagen and elastin occurred more frequently in males.⁹⁷ Potier and others also suggested that estrogen differentially regulates collagen in atherosclerosis-susceptible and atherosclerosis-resistant mice.⁹⁴ In postmenopausal women, phytoestrogens result in decreased aortic stiffness.⁹⁸

Summary

Despite human epidemiologic and animal investigational data strongly supporting a gender bias in the development of AAAs, little is known about the specific mechanisms driving this disparity. This review provides data supporting the concept that gonadal hormones and their receptors work through multiple mechanisms, including: 1) inhibiting leukocyte recruitment and aortic wall inflammation, 2) altering MMP expression or activity, or 3) effecting levels of ECM proteins elastin and collagen, ultimately leading to gender-based differences in AAA formation. Clearly, leukocyte recruitment plays a critical role during early AAA formation and data suggest that this is influenced by gonadal hormones. Improved understanding of leukocyte trafficking during AAA formation will help to better elucidate the pathophysiologic mechanism of aneurysm formation in men and women, and may ultimately be expected to translate into novel therapies by which we might treat the large number of patients with small AAAs.

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Figure 1.

Comparison of in-hospital mortality rates for elective AAA repair documenting increased mortality in females compared with males. * $P < .05$. (Reproduced with permission from Dimick JB, Stanley JC, Axelrod DA, et al. *Ann Surg.* 2002;235(4):579–585.)²³

Mouse elastase aneurysms

Figure 2.

(A) Bar graph representing greater increase in aortic diameters of male mouse aortas versus female mouse aortas at 14 days post-elastase perfusion. Y- axis indicates % enlargement of aortic diameter calculated as follows: $\{[post (AD - pre AD)/pre AD]*100\}$. Groups: M = male mice, F = female mice, E = elastase perfused aortas, C = inactivated elastase perfused aortas. (B) Bar graph representing MMP9 and MMP2 activity levels analyzed via zymography in male and female mouse aortas harvested at 14 days post-elastase perfusion. There was a significantly greater amount of MMP 9 activity in male elastase perfused aortas (ME) versus female elastase perfused aortas (FE) ($P = 0.016$). There was no significant difference in MMP2 activity levels between the two groups. The y-axis represents integrated optical density (IOD) of zymogen activity levels corrected for total protein.

Figure 3.

WT mice had significantly larger aortic diameters compared to PKO mice at day 14 post elastase perfusion (116 % vs. 38 %, $P < 0.001$). In addition, aortic aneurysm incidence was 52% in WT mice and 0% ($P = 0.01$) in PKO mice. An aortic aneurysm was defined as a 100% or greater increase in AD from pre-perfusion measurement. (Reproduced with permission from Hannawa KK, Cho BS, Sinha I, et al. *Ann N Y Acad Sci.* 2006;1085:353–359.)⁷⁴

Table 1
Differences in Hospital Death Rates between Genders

Unadjusted In-Hospital Mortality Rates for Patients Undergoing Repair of Intact and Ruptured Abdominal Aortic Aneurysm in the United States, 1996 to 1997.

	OVERALL MORTALITY RATE (%)	MORTALITY AT HIGH VOLUME HOSPITALS (%)	MORTALITY AT LOW VOLUME HOSPITALS (%)
INTACT ABDOMINAL AORTIC ANEURYSM REPAIR			
AGE < 65 YEARS			
Male [†]	1.6%	0.8%	2.5%
Female [†]	2.8%	1.9%	3.9%
AGE > 65 YEARS			
Male [†]	3.9%	3.2%	4.6%
Female [†]	5.6%	4.4%	7.1%
RUPTURED ABDOMINAL AORTIC ANEURYSM REPAIR			
AGE < 65 YEARS			
Male	29.8%	30.6%	29.1%
Female [†]	56.7%	50.0%	61.1%
AGE > 65 YEARS			
Male [†]	47.0%	41.5%	50.8%
Female [†]	57.1%	55.2%	58.2%

Modified from Dimick JB, Stanley JC, Axelrod DA, et al. *Ann Surg.* 2002;235(4):579–585.²³

Table 2

Superarray data from male and female elastase perfused AAAs documenting down regulation of a number of gene families in females compared with males.

Cytokine/Chemokine	Fold Decrease in Females
Bone Morphogenetic Protein (BMP) Family	
BMP-1	6.1
BMP-6	6.3
BMP-7	5.6
BMP-15	6.3
C-C Chemokine Ligand Family	
CCL 24	ND
CCL 25	ND
CCL 28	ND
C-C Chemokine Receptor Family	
CCR 2	ND
CCR-7	ND
CCR-8	ND
Interleukin (IL) Family	
IL-1	6.2
IL-2	6.1
IL-3	4.9
IL-5	4.9
IL-7	5.9
IL-11	6
IL-12	6.3
Transforming Growth Factor (TGF) Family	
TGF- β 1	4.1
TGF- β 2	4.2
Tumor Necrosis Factor (TNF) Family	
TNFSF-4	ND
TNFSF-6	ND
TNFSF-9	ND
TNFSF-15	ND
Vascular Endothelial Growth Factor Family	
VEGF-1	3.6
VEGF-2	3.6

ND- denotes expression was present in males, but not detectable in females

Modified from Sinha I, Cho BS, Roelofs KJ, et al. *Ann N Y Acad Sci.* 2006;1085:367–379.⁴¹