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# Effects of intrauterine growth restriction and female sex on future blood pressure and cardiovascular disease

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## Abstract

**Purpose of the Review—**It is well-established that the age-related increase in blood pressure is augmented after menopause. Yet, the prevalence of hypertension is enhanced in low birth weight women relative to normal birth weight counterparts by 60 years of age suggesting that adverse influences during fetal life heighten cardiovascular risk in later life.

**Recent Findings—**A changing hormonal milieu may contribute to increased cardiovascular risk that occurs after the menopausal transition. Low birth weight is associated with early age at menopause. A recent study indicates that a shift towards testosterone excess following early reproductive senescence may contribute to the etiology of age-dependent increases in blood pressure in a rodent model of low birth weight.

**Summary—**This review will highlight current findings related to postmenopausal hypertension and discuss potential mechanisms that may contribute to the enhanced cardiovascular risk that develops with age in low birth weight women.

### Keywords

Women's Health; Low Birth Weight; Blood Pressure; Menopause; Sex Steroids; Cardiovascular Disease

## Introduction

Cardiovascular (**CV**) disease is the leading cause of death in women in the United States (1). Hypertension is a major risk factor for the development of CV disease and the etiology of hypertension includes lifestyle choices, such as diet and exercise, as well as genetic mechanisms. Yet, numerous studies suggest that adverse influences during fetal life also promote the development of CV risk including hypertension (2). Males and females exhibit a different timecourse in the onset of hypertension and CV risk that originates during fetal

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life (3, 4, 5, 6, 7). Experimental studies indicate that unlike their male littermates, females exposed to an insult during fetal life do not develop an increase in blood pressure or CV risk in young adulthood relative to female controls (3, 4, 5, 6, 8, 9. Sex differences in blood pressure are also observed within the general population with men having higher blood pressure relative to women prior to menopause (10). Numerous mechanisms contribute to sex differences in primary hypertension with a role for sex steroids implicated in the progression of CV risk (11. Sex steroids may also contribute to sex differences in the onset of increased blood pressure that has its origins in fetal life (12).

Blood pressure increases with age and the prevalence of hypertension is higher among the elderly (13). After age 50, the prevalence of hypertension is greater in women versus men (14). Furthermore, the prevalence of hypertension is enhanced in low birth weight women relative to normal birth weight counterparts by 60 years of age (15) implicating a fetal origin in the etiology of heightened CV risk in women born small. Accelerated reproductive aging is a risk factor for CV disease (16). Low birth weight is associated with early age at menopause (17) and recent experimental studies demonstrate the development of early reproductive senescence in female offspring exposed to an adverse environment during fetal life. Whether accelerated reproductive aging in low birth weight women *directly* contributes to enhanced CV risk is not known. Yet, recent studies indicate a role for sex steroids in the development of age-dependent increases in blood pressure in an experimental model of low birth weight (12).

Clinical studies reveal that intensive hypertension treatment is advantageous in lowering systolic blood pressure and improving overall health (18). Although the prevalence of controlled hypertension is greater in women relative to men at 60 years or older, the percentage of uncontrolled hypertension in women at this age is almost 50% (19) suggesting that current knowledge regarding appropriate sex- and age-specific therapeutics is lacking. Birth weight and/or other perinatal factors are not yet a standard consideration in the treatment of hypertension. Thus, the purpose of this review is to examine the role of sex steroids in the etiology of increased blood pressure and CV risk following the onset of menopause and to explore potential mechanisms by which CV risk is enhanced in later life in women born low birth weight.

## The Developmental Origins of Chronic Health and Disease

In the early 1980's Dr. David Barker hypothesized a role for the fetal environment in the determination of CV risk in later life (20). Recognition of this phenomenon, now referred to as the developmental origins of chronic health and disease, was based on observations by Barker and colleagues that demonstrated an association between adverse influences during fetal life and adult mortality due to ischemic heart disease (20). Birth weight and blood pressure are also inversely related (21) further supporting the theory that susceptibility to CV disease can initiate *in utero.* The inverse relationship between birth weight and blood pressure is observed in both men and women (21). However, a study by Vos et al. showed that CV risk is two-fold greater in low birth weight men relative to low birth weight females in young adulthood (7) indicating a sex difference in susceptibility to CV risk that originates in fetal life. Andersson and colleagues reported that the prevalence of hypertension is

heightened in low birth weight women in later life relative to normal birth weight counterparts suggesting that low birth weight exacerbates age-related increases in CV risk. Yet, the effect of sex on CV risk in low birth weight individuals has not been studied in depth. Furthermore, studies investigating age as an additional insult are also very limited.

## Experimental Models of Developmental Origins

Numerous experimental models are utilized to study the mechanisms by which insults during perinatal life are associated with an increased risk for hypertension and CV disease (3, 4, 6, 8, 9). Many of these mimic the pathophysiological causes of low birth weight and maternal conditions that impact fetal growth and increase later CV risk in the offspring (3, 4, 5, 6, 8, 9). Preeclampsia is a major cause of fetal morbidity and mortality in the Western world (22). This pregnancy-specific disease is characterized by improper remodeling of the spiral arteries resulting in poor nutrient and oxygen delivery to the fetus (22), low birth weight (22) and increased blood pressure in the offspring (23). Alexander reported that placental insufficiency in the rat induced via reduced uterine perfusion results in intrauterine growth restriction (**IUGR**) associated with a significant increase in blood pressure in male IUGR offspring at 3 months of age (3). Yet, female IUGR offspring remain normotensive relative to female control offspring (3) suggesting that females in young adulthood are less susceptible to a developmental insult that programs increased CV risk in their male littermates (3). Other models of developmental origins also demonstrate a sex difference in blood pressure. Fetal undernutrition is the initiating insult in the hypothesis formulated by Dr. Barker (24). Utilizing protein restriction as a mediator of undernutrition, Woods and colleagues reported that a modest reduction in maternal protein intake programs hypertension in male (4) but not female low protein rat offspring (5) in young adulthood (approximately 5 months of age). Betamethasone is used clinically to accelerate lung development in preterm infants. Ortiz and colleagues observed a similar sex difference in blood pressure at 6 months of age in offspring exposed to prenatal dexamethasone (6). Bourque et al. reported that prenatal exposure to hypoxia (8) also induces sex-specific programming of CV risk with females protected relative to their male counterparts; a similar finding was demonstrated by Xiao and colleagues in a model of developmental origins induced by prenatal nicotine (9). However, recent studies indicate that females exposed to a developmental insult do not remain protected across the lifespan. Blood pressure is increased by 12 months of age in female IUGR offspring exposed to placental insufficiency (12, 25) or maternal protein restriction (26). CV risk is also increased with age in female exposed to prenatal nicotine (27). Thus, these studies suggest that protection against programmed CV risk is lost with age in females.

## Models of Post-Menopausal Hypertension

Recent studies evaluating the prevalence of hypertension within the general population report that men in young adulthood exhibit a greater occurrence of hypertension compared to age-matched women (19). During mid-life (50–64 years of age), this difference subsides so that men and women display a similar prevalence of hypertension (19). However, as men and women age, the increase in blood pressure after menopause is accelerated in women compared to age-matched men (19). Production of E2, the predominant estrogen before

menopause, is greatly decreased after menopause (28). Production of estrone (**E1**), the predominant estrogen in postmenopausal women (**PMW**), is also decreased but to a lesser degree than E2 leading to an increase in the E1/E2 ratio (28). Testosterone increases after menopause (28) and is positively associated with blood pressure in women after menopause (29, 30). Despite studies that show a correlation between changes in sex steroids and increased CV risk in women as they age, the exact contribution of sex steroids remains unclear.

Although the increased prevalence of hypertension in women following menopause is well documented, few animal models are available to study the mechanisms of chronic disease related to the transition into reproductive senescence. Rodents in addition, to non-human primates, and other species are used to study the etiology and investigate potential therapies for chronic conditions and disease related to menopause (31, 32, 33). Menopause involves a gradual transition that occurs over a 5- to 10-year period that is referred to as perimenopause. Perimenopause is characterized by irregular cycle lengths and fluctuating estrogen levels. Ovariectomy is commonly used to induce a change in the hormonal milieu to investigate the importance of sex steroids on blood pressure. However, a major limitation for this model involves the abrupt loss of estrogens rather than a gradual decline in E2 levels due to a slower depletion of ovarian follicles. Other limitations to studies that utilize ovariectomy include the loss of ovarian tissue as an endocrine secreting organ, and experiments conducted in females in young adulthood that fail to reproduce outcomes specific to females in later life. A more recently developed model of menopause uses repeated daily injections of a ovotoxic chemical, 4-vinylcyclohexene diepoxide (**VCD**), to produce a gradual depletion of ovarian follicles in rodents in association with retention of ovarian tissue and androgen secreting potential (31). This model mimics the natural transition into menopause and includes a period of perimenopause during induction (31). Another well-characterized animal model is the aged spontaneously hypertensive rat (**SHR**) (32), an experimental model that mimics the sexual dimorphism of human hypertension. Blood pressure is reduced in female SHR in young adulthood relative to age-matched male SHR (32). Yet, blood pressure increases in age in association with a decrease in E2 levels and an increase in testosterone levels in intact-aged SHR females relative to female counterparts in young adulthood, and loss of the sex difference in blood pressure in the aged female SHR relative to the age-matched male SHR (32, 34).

## The Renin Angiotensin System, Sex Steroids, Menopause and Blood Pressure

The renin-angiotensin system (**RAS**), a major hormonal system involved in the regulation of arterial blood pressure and sodium homeostasis, is implicated in the etiology of postmenopausal hypertension (35). Recent studies suggest that regulation of the RAS via E2 may contribute to the development of hypertension that occurs after menopause. Dean and colleagues reported that ovariectomy in the female rat is associated with an increase in angiotensin converting enzyme (**ACE**) and angiotensin II type 1 ($\mathbf{AT_1}$) receptor expression (36), components of the classic vasoconstrictor arm of the RAS. They further demonstrated that these increases are abolished by E2 replacement (36) suggesting direct regulation of the RAS by E2. In a study by Ji et al., ovariectomy decreased the activity of ACE2 (37); Baiardi et al. reported a similar effect on $AT_2$ receptor expression in female rats (38) implicating that

physiological changes in E2 can also alter the counter-regulatory arm of the RAS. In a study by Dai and colleagues, treatment with an $AT_2$ receptor agonist attenuated salt/DOCA–induced hypertension in female rats in conjunction with increased ACE2 and $AT_2$ receptor expression (39). Thus, this study by Dai et al. demonstrated that direct activation of the $AT_2$ receptor is cardio-protective in the female rat (39). However, whether hypertension in females after reproductive senescence involves an imbalance in the ACE/Ang II pathway versus the ACE2/$AT_2$ receptor pathway of the RAS is not yet clear. Furthermore, whether modulation of the RAS via E2 as noted in experimental studies conducted in young female rats (36, 37, 38, 39) translates towards the etiology of postmenopausal hypertension is not known.

Yanes and colleagues, using the aging female SHR as a model of postmenopausal hypertension, reported that plasma renin activity and circulating angiotensinogen are elevated in aged female SHR relative to younger counterparts that exhibited an elevated blood pressure in later life (40). Although blockade of the RAS with losartan, an inhibitor of the $AT_1$ receptor, resulted in a partial reduction in blood pressure in aged female SHR, losartan did not fully normalize blood pressure in aged female SHR equivalent to blood pressure in young female SHR (40). Thus, this study indicates that although the RAS contributes to the increase in blood pressure that occurs with aging in the female SHR, other factors may also be involved. Yanes and colleagues also demonstrated that blockade of the RAS reduces blood pressure to a greater degree in aged male SHR relative to aged female SHR (34) implicating a sex difference in the blood pressure response to RAS blockade in aging rats. However, it is important to note that numerous clinical studies report that use of RAS blockade is beneficial against hypertension after menopause (41) suggesting a potential caveat for interpretation of results obtained from experimental models of postmenopausal hypertension. Fernández-Vega and colleagues found that blockade of the RAS significantly decreased blood pressure and enhanced blood pressure control in a cohort of post-menopausal women (42). Yet, no beneficial effect on blood pressure was observed in postmenopausal women treated with hormone replacement therapy (**HRT**) (42). Clearly, additional studies are needed to determine if E2-mediated regulation of the RAS contributes to the increase in blood pressure that occurs after menopause.

E2 is decreased in women after menopause (28). Yet, not all studies indicate a positive effect of estrogen replacement on CV health in postmenopausal women (43, 44). The Heart and Estrogen/Progestin Replacement Study (**HERS**) (43) and the Women's Health Initiative (**WIH**) both sought to identify whether HRT would decrease the incidence of adverse CV events. The HERS study included postmenopausal women with coronary heart disease and concluded that HRT does not reduce adverse CV events in this population (43). The WIH trial was terminated early due to findings that estrogen + progestin increased the risk of breast cancer and stroke in healthy postmenopausal women (44). However, reevaluation of HRT in newly menopausal women versus aging patients indicates that HRT may exert less risk (45).

Like E2, testosterone is indicated in the regulation of the local RAS and as an influence on CV risk. In contrast to E2, testosterone inhibits $AT_2$ receptor expression in the female rat (46). Mishra et al. reported that $AT_2$ receptor mRNA and protein expression are lower in

male versus female Sprague Dawley rats (46). Their study also demonstrated that administration of exogenous androgen decreases $AT_2$ receptor expression in male and female rats, an effect that is reversed by treatment with the androgen receptor antagonist, flutamide (46). $AT_2$ receptor expression was also decreased *ex vivo* in the absence of confounding factors (46) implicating a direct effect of testosterone on $AT_2$ receptor expression. This study by Mishirea and colleagues also showed that blood pressure increases in response to an increase in exogenous androgens in the female rat (46) suggesting that testosterone may induce adverse CV events in the female. There is a positive association between testosterone and blood pressure in women (30). Whether testosterone is beneficial or permissive in the etiology of CV disease after menopause is controversial (47, 48). Yanes and Reckelhoff propose that a shift in the testosterone to estrogen ratio contributes to increased blood pressure after menopause (48). As highlighted above, increased testosterone can reduce expression of the protective arm of the RAS in the female. Thus, additional studies are needed to clarify the exact contribution of testosterone to blood pressure and CV outcomes in women after menopause.

### The Sympathetic Nervous System, Menopause and Blood Pressure

The SNS plays an important role in the regulation of blood pressure and renal function via activation of the renal sympathetic nerves (49). A study by Hart and colleagues demonstrated that an increase in sympathetic nerve activity is associated with an increase in blood pressure in women after menopause (50). Furthermore, this study showed that the sympathetic nervous system (**SNS**) plays a greater role in blood pressure control in women after menopause relative to women in young adulthood (50) suggesting that activation of the SNS contributes to the greater prevalence of hypertension in women as they age. Maranon and colleagues also demonstrated an important role for the SNS in the etiology of increased blood pressure in the aged female SHR, a model of postmenopausal hypertension (11). Their studies indicated that adrenergic blockade reduces blood pressure in young and old female SHR whereas renal denervation attenuates the increase in blood pressure to a greater extent in the aged female SHR relative to the young (11). Thus, these studies reinforce findings from a prospective study conducted in a large multi-ethnic cohort of postmenopausal women that reports beta-blockers are cardio-protective in women (51).

## Low Birth Weight, Early Reproductive Aging and Cardiovascular Risk

Women typically enter menopause around 50–55 years of age (52). Low birth weight women; however, are more likely to experience menopause at 44–45 years of age compared to normal birthweight counterparts (17). Additionally, ovarian development is impaired in fetuses complicated by IUGR (53). Experimental models of low birth weight mimic this finding (54, 55, 56, 57, 58) (Table 1) and demonstrate that fetal exposure to maternal undernutrition and placental insufficiency program an accelerated depletion of ovarian follicles (53, 55, 58) and early age at cessation of estrous cyclicity (54, 55, 56) associated with a reduction in anti-Müllerian hormone (58) and an increase in circulating testosterone (57), factors indicative of reproductive senescence. In the rat model of IUGR induced by placental insufficiency, Intapad et al. demonstrated that timing of cessation of estrous cyclicity (54) coincides with the development of increased blood pressure in female IUGR

rats at 12 months of age (Table 1) (12, 25). An increase in blood pressure, associated with a depletion of ovarian reserve, was also observed in a bovine model of fetal undernutrition (Table 1) (57). Collectively, these findings suggest that fetal exposure to an adverse environment not only alters later CV health, but also influences reproductive aging in the female offspring (Table 1). It is well-established that early onset menopause is associated with greater CV risk (16). Andersson and colleagues reported that the prevalence of hypertension is increased in low birth weight women relative to normal birth weight women in later life (15). Yet, whether the association between early reproductive aging and enhanced CV risk in low birth weight women is correlative or causative is not yet known. Furthermore, the mechanisms that contribute to enhanced CV risk have not been elucidated. However, recent studies using experimental models of low birth weight are investigating the link between birthweight and later CV risk in female offspring and indicate that testosterone, the RAS and the SNS are all potential mediators of hypertension that develops with age.

## Testosterone, the Renin Angiotensin System, Blood Pressure and Models of Low Birth Weight

Using an experimental model of low birth weight induced via placental insufficiency in the rat, Alexander demonstrated that blood pressure is not increased in female IUGR offspring in young adulthood (3). However, other studies from the Alexander laboratory showed that blood pressure is increased by 12 months of age (25) in conjunction with the development of early reproductive senescence (54), a significant increase in circulating testosterone (12, 54) and renal expression of the $AT_1$ receptor in female IUGR offspring (12). Pharmacological blockade with flutamide, an androgen receptor antagonist, abolishes the age-dependent increase in blood pressure in female IUGR offspring (12). Renal expression of the $AT1_1$ receptor is also reduced in flutamide treated female IUGR relative to vehicle treated female IUGR (12). This study also reported that the age-dependent increase in blood pressure in female IUGR offspring at 12 months of age is abolished by blockade of the RAS using the ACE inhibitor, enalapril (12). Therefore, these findings suggest that activation of the RAS via testosterone may contribute to the etiology of hypertension that develops with age in the female IUGR rat. The RAS is implicated in the etiology of post-menopausal hypertension (41, 34); yet the relative importance of testosterone in postmenopausal hypertension remains unclear (47, 48). Whether testosterone contributes to *enhanced* CV risk in low birth weight women relative to normal birth weight women after menopause is not yet known suggesting that additional studies are needed to investigate the role of sex steroids as mediators of age-related enhanced CV in low birth weight women.

## Sex Steroids and Low Birth Weight

Circulating androstenedione and dehydroepiandrosterone (**DHEA**) levels are increased at 20 years of age in low birth weight women relative to normal birth weight counterparts (59) suggesting an altered adrenal synthesis of sex steroids. Androstenedione and DHEA serve as precursors to testosterone and estrogens. Like testosterone, circulating levels of androstenedione and DHEA increase during the menopausal transition (52). Testosterone is the most biologically active androgen during menopause (60) and the adrenals function as the primary site of androgen synthesis after menopause (52). Yet, adipose tissue is also an important site for aromatization of androgens to estrogens, providing another site for

production of testosterone and E2 after menopause (61). Visceral fat increases after menopause and is positively associated with testosterone in post-menopausal women (62). Thus, sex steroid production is altered in low birth weight women in early adulthood. Whether sex steroid production differs in low birth weight women as they transition through menopause is unknown. Furthermore, the role of sex steroids in the etiology of the enhanced prevalence of hypertension in low birth weight women in later life is not known.

### The Sympathetic Nervous System, Blood Pressure and Models of Low Birth Weight

Activation of the SNS contributes to increased blood pressure in menopausal women (48). A role for the SNS is also observed in the experimental model of low birth weight induced via placental insufficiency in the rat that exhibits a significant increase in blood pressure (25) associated with early reproductive senescence at 12 months of age (54). Intapad et al. demonstrated that bilateral renal denervation abolishes the age-dependent increase in blood in female IUGR rats at 12 months of age (25). In this study, Intapad and colleagues also reported that the significant increase in blood pressure at 12 months of age is also associated with an increase in total fat mass, visceral adiposity and circulating leptin levels in female IUGR rats relative to age-matched female controls (25). Leptin is a satiety hormone produced by adipose cells that stimulates sympathetic nerve activity (63). A role for activation of the SNS is reported in models of obesity-induced hypertension (64) suggesting that activation of the SNS is an important link between adiposity and increased blood pressure. Central adiposity is increased after menopause (65) with ovarian status linked to the change in fat distribution (66). Whether enhanced activation of the SNS contributes to the greater prevalence of hypertension in low birth weight women in later life relative to their normal birth weight counterparts has not yet been examined. However, findings from the study by Intapad and colleagues indicate a role for the SNS in the etiology of age-dependent hypertension in female IUGR rats.

## Conclusion

As women age, the incidence of high blood pressure increases indicative of a loss of CV protection after menopause relative to pre-menopause. Mechanisms that contribute to the age-related increase in blood pressure are in women are not well-understood. This review focuses on the role of sex steroids in the etiology of post-menopausal hypertension and also discusses potential mechanisms that may contribute to the enhanced prevalence of hypertension in low birth weight women in later life. Although it is well-established that birth weight and blood pressure are inversely related, few studies have investigated the effect of age on this association; fewer still have examined the effect of age on CV risk in low birth weight women. An experimental model of IUGR indicates a role for the RAS and the SNS in the etiology of hypertension that develops with age in the female rat; factors also implicated in the etiology of hypertension in PMW and in the aged female SHR, an experimental model of post-menopausal hypertension (Table 2). Testosterone is elevated in PMW and in the aged female SHR (Table 2). Testosterone is also elevated in female IUGR rats that develop an increase in blood pressure associated with early reproductive senescence at 12 months of age (Table 2); blockade of the androgen receptor abolishes age-dependent hypertension in the female IUGR rat. However, whether testosterone plays a permissive role

in the increased prevalence of hypertension in women after menopause, or the aged female SHR, is not yet clearly understood. Additionally, whether testosterone contributes to the enhanced CV risk reported in low birth weight women relative to age-matched normal birth weight counterparts after menopause is also not known. Developing a better understanding of mechanisms involved in the pathophysiology of the increased prevalence of hypertension in women as they age, in particular those born low birth weight, may lead to more effective therapeutics and pharmacological therapies.

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**Table 1**

Low birth weight and markers of early reproductive senescence: A comparison of the characteristic changes in the transition into menopause in low birth weight women and two experimental models of low birth weight.

| | Low Birth Weight | Placental Insufficiency | Maternal Protein Restriction |
|---|---|---|---|
| Early Onset Cessation of Estrous Cyclicity | Women (17) | Rat (54) | Rat (56, 57) |
| Depletion of Ovarian Reserve | Women (53) | --- | Rat (55)<br>Bovine (58) |
| Increased Testosterone | --- | Rat (12, 54) | Rat (56, 57) |

**Table 2**

A comparison of the markers of early reproductive senescence associated with increased cardiovascular risk in experimental models of low birth weight.

| | **Placental Insufficiency** | **Maternal Protein Restriction** |
|---|---|---|
| Early Onset Cessation of Estrous Cyclicity | Rat (54) | Rat (56, 57) |
| Depletion of Ovarian Reserve | --- | Rat (55)<br>Bovine (58) |
| Increased Testosterone | Rat (12, 54) | Rat (56, 57) |
| Reduced Anti-Müllerian Hormone | --- | Bovine (58) |
| Increased Blood Pressure | Rat (12, 25) | Rat (26)<br>Bovine (58) |