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Sex-specific contributions of endothelin to hypertension

Eman Y. Gohar, Ph.D, David M. Pollock, Ph.D.

Section of Cardio-Renal Physiology & Medicine, Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA. 35233

Abstract

Purpose of review—Men and women differ in the prevalence, pathophysiology and control rate of hypertension in an age-dependent manner. The renal endothelin system plays a central role in sex differences in blood pressure regulation by control of sodium excretion and vascular function. Improving our understanding of the sex differences in the endothelin system, especially in regard to blood pressure regulation and sodium homeostasis, will fill a significant gap in our knowledge and may identify sex-specific therapeutic targets for management of hypertension.

Recent Findings—The current review will highlight evidence for the potential role for endothelin system in the pathophysiology of hypertension within three female populations; (i) postmenopausal women, (ii) women suffering from preeclampsia or (iii) pulmonary arterial hypertension.

Summary.—Clinical trials that specifically address cardiovascular and renal diseases in females under different hormonal status are limited. Studies of the modulatory role of gonadal hormones and sex-specific mechanisms on critically important systems involved, such as ET-1, are needed to establish new clinical practice guidelines based on systematic evidence.

Keywords

sex; endothelin; postmenopausal; preeclampsia; pulmonary hypertension

Introduction

Hypertension affects one in three Americans [1] and is more prevalent in men compared to age-matched premenopausal women [2]. Hypertension is a major risk factor for cardiovascular disease, which is the leading cause of morbidity and mortality in men and women. Despite the availability of numerous antihypertensive medications; hypertension is still not fully managed.

Corresponding author: David M. Pollock, Ph.D., Section of Cardio-Renal Physiology and Medicine, Division of Nephrology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL 35233, Phone: 205-975-7526, Fax: 205-975-7520, davidpollock@uabmc.edu.

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Endothelin-1 (ET-1) is the most potent vasoconstrictor agent discovered to date. It has remarkable long lasting effects on vascular tone [3, 4]. This peptide is composed of a 21 amino acid chain, which is released primarily from endothelial cells. However, other cell types including the epithelial cells also produce the peptide [4]. ET-1 circulating levels reflect its biosynthesis and release from endothelial cells, as well as clearance rates [4, 5]. ET-1 binds to two cell surface G-protein coupled receptors; ET type A (ET_A) receptor and ET type B (ET_B) receptor. ET_A receptors are located mainly on smooth muscle cells. Activation of ET_A receptors results in vasoconstrictor, inflammatory and proliferative effects. On the other hand, ET_B receptors are located mainly on endothelial and renal epithelial cells. ET_B receptor activation to promote vasodilation and natriuresis, although there are limited numbers of ET_B receptors on vascular smooth muscle that can contribute to vasoconstriction. ET-1 plays a central role in maintaining body fluid and electrolyte balance. Defects in the capacity of the kidneys to excrete Na⁺ are a fundamental mechanism involved in the initiation of hypertension [6, 7]. Therefore, it is vital that we broaden our understanding of the varied mechanisms of blood pressure regulation and renal Na⁺ handling in both sexes hoping to pinpoint sex-specific therapeutic targets for hypertension and other cardiovascular diseases.

Abnormalities of the ET-1 signaling system have been linked to development of hypertension and impaired sodium handling. Inhibition of the ET_B receptor function, either pharmacologically or genetically, results in salt-sensitive hypertension [8, 9]. Further, ET_B dysfunction is associated with elevated ET-1 levels and ET_A receptor activation such that ET_A receptor blockers are particularly effective in lowering blood pressure in patients with salt-dependent as well as resistant hypertension [10].

Evidence has emerged that there are sex differences at various levels in the ET-1 signaling pathway including circulating peptide levels and tissue concentrations, receptor expression, receptor function and downstream signaling. We recently reviewed the role of ET-1 in the sexual dimorphism in cardiovascular and renal diseases [11]. In the current review, we will focus on clinically relevant advances and potential future possibilities in targeting ET-1 signaling to regulate blood pressure particularly within the female population, hoping that future clinical studies will target at-risk populations. It is important to note that problems with drug dosing, toxicity, patient selection and study design have contributed to failure of many previous clinical trials for ET_A receptor antagonists [12].

ET-1 in postmenopausal hypertension

After menopause, the prevalence of hypertension among women increases sharply to levels that equal or surpass those of men implicating an important role for ovarian hormones in cardiovascular and renal protection [13–19]. It is also evident that hypertension is less well controlled in aging women compared to aging men [20]. The mechanisms responsible for elevated blood pressure after menopause is not well understood and it may require multiple drug therapy to treat postmenopausal hypertension. Previous studies suggest that imbalances in the ET-1 signaling pathway may contribute to the etiology of postmenopausal hypertension. Postmenopausal women exhibit elevated plasma ET-1 levels that may contribute to elevated blood pressure and cardiovascular risk in this population [21, 22].

Previous studies have demonstrated that enhanced ET-1 in the circulation may result in endothelial dysfunction and arterial stiffness. Hormonal replacement therapy decreased plasma ET-1 in hypertensive postmenopausal women [21, 23]. In addition, exercise decreased blood pressure and plasma ET-1 in postmenopausal hypertensive women [24], suggesting that exercise might be employed as a means of reducing ET-1 and subsequent cardiovascular risks in postmenopausal women. Webb et al. found that short-term intracoronary administration of estradiol resulted in a significant decrease in coronary sinus concentrations of ET-1 in postmenopausal women with coronary artery disease [25]. A recent study has shown that ET_B-mediated vasodilatory capacity is decreased in postmenopausal women, compared to young women (Figure 1)[26]. This interesting finding suggests that impaired ET_B-mediated vasodilatory function may be responsible, at least in part, for endothelial dysfunction manifested after menopause [26].

Consistent with the data from humans, animal studies have demonstrated that ovariectomy and hormone replacement modulate expression of ET_A and ET_B receptors in renal tissues [27]. More specifically, ovariectomy significantly decreased renal cortical ET_A and ET_B receptor expression [27]. This effect was prevented by supplementation of OVX rats with estradiol [27]. On the other hand, ovariectomy increased the expression of ET_A and ET_B expression in the renal inner medulla and supplementation of OVX rats with estradiol prevented this increase [27]. These findings are particularly relevant because the inner medulla of the kidney produces the largest amounts of ET-1 peptide and has the highest expression of renal tubular ET_B receptors [28]. In addition, renal medullary salt loading stimulated natriuresis in intact female and OVX rats. It was further shown that both ET_A and ET_B receptors contribute to this natriuretic response only in OVX rats, but not intact females [29]. Blockade of ET_A and ET_B receptors prevented the natriuretic response to renal medullary purinergic receptor activation only in OVX and not intact females [29], suggesting that the renal medullary ET-1 system in OVX rats, a crude model of postmenopause, may play a more important role in renal salt handling compared to intact female rats, which model pre-menopause. In related studies, the endothelial impairment manifested in ovariectomized rats can be prevented by chronic vagus nerve stimulation, through mechanisms that may include ET-1 reduction [30]. In an effort to model of postmenopausal hypertension, Lima et al. [31] used aged spontaneously hypertensive rats to demonstrate that ET_A receptor blockade causes an additional reduction in blood pressure, compared to treatment with angiotensin converting enzyme inhibitor and arachidonic acid metabolism inhibition. This observation supports the notion that postmenopausal hypertension is multifactorial and involves pathophysiological changes in different signaling systems including the ET-1 pathway.

Endothelin receptor A as a therapeutic target for preeclampsia

Preeclampsia is a pregnancy specific syndrome that is associated with elevated blood pressure, increased renal vascular resistance and endothelial dysfunction. Despite being one of the major causes of maternal and perinatal morbidity and mortality, no specific therapeutic interventions have been developed yet due to incomplete understanding of the mechanisms involved in the pathophysiology of preeclampsia [32, 33]. Preeclampsia is a multisystem disorder involving abnormalities in multiple signaling pathways including the

ET-1 system. A recent meta-analysis study of 16 published cohort studies, including 1739 hypertensive cases and 409 controls, revealed that ET-1 plasma concentrations are elevated in hypertensive pregnant women as compared to normotensive controls [34]. Further, umbilical vein concentrations of ET-1 in preeclampsia are higher than in normal pregnancy [35]. In different experimental models of preeclampsia, tissue ET-1 levels were increased in the placenta and kidneys [36].

Growing evidence supports the concept that placental ischemia triggers enhanced ET-1 biosynthesis, which contributes to preeclampsia [37]. Recent data suggest that pharmacological induction of hemoxygenase-1 or bilirubin decreases ET-1 release in response to placental ischemia [38], thus providing a potential strategy to block this pro-hypertensive pathway in preeclampsia. ET-1 also appears to induce oxidative stress in preeclampsia [39, 40]. Importantly, ET_A receptor blockade provides protection against preeclampsia [36, 41–43]. ET_A receptor antagonism prevents/reduces the hypertension in many experimental models of preeclampsia, highlighting that ET-1 signaling is a common contributor to elevated blood pressure in pregnancy [44]. However, ET_A receptors are essential for fetal growth during the first trimester. Therefore, considering ET_A receptor antagonists for preeclampsia would have to be limited until after the first trimester, if at all. Alternatively, development of an ET_A receptor antagonist that does not cross the placental barrier would greatly advance the potential utility of ET_A receptor blockade in preeclampsia. Thaete et al., reported that the ET_A receptor antagonist, ABT-546, has limited access across the placenta from the maternal to the fetal compartment [45]. In this study, the plasma concentration of ABT-546 in the fetal circulation was 2% of those in the maternal circulation [45]. Whether this would be considered an acceptable risk is unclear. Thus, while the results of ET_A antagonism in preeclampsia are promising, additional studies are needed to evaluate the benefit risk ratio.

As already discussed, ET-1 may provide a link between placental ischemia and elevated blood pressure in preeclampsia (Figure 2)[36]. The reason for this may be through a link between ET-1 and anti-angiogenic factors. The hypoxic placenta releases anti-angiogenic molecules such as soluble fms-like tyrosine kinase 1 (sFlt-1) into the circulation [46]. sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor Flt1 lacking the transmembrane and cytoplasmic domains and acts as a potent antagonist of VEGF and placental growth factor [47, 48]. Similar to ET-1, sFlt-1 appears to contribute to the pathogenesis of preeclampsia and may be a predictor for the severity of preeclampsia [32, 49, 50]. Importantly, plasma ET-1 correlates positively with sFlt-1 in preeclampsia-in maternal circulation [51, 52]. This observation strengthens the possibility that ET-1 mediates the pathogenesis of preeclampsia secondary to the anti-angiogenic factors released in response to the hypoxic environment within the placenta [52]. This is further supported by data showing that ET_A receptor blockade completely abolished the hypertensive response to sFlt-1 in pregnant rats [41]. These findings suggest that ET-1 contributes to production of sFlt-1.

Besides the well-established contribution for ET_A to the pathophysiology of preeclampsia, dysfunction of ET_B receptors has recently been linked to preeclampsia [38, 53]. Cutaneous vascular responses to ET-1 are normally attenuated by ET_B dependent vasodilation that was

significantly reduced in previously preeclamptic women postpartum [53]. ET-1 via ET_B receptors also appears to impair trophoblast functions such as migration and invasion in human first trimester trophoblasts [54]. The mechanisms behind changes in receptor function need to be resolved in future studies.

Sex differences in the efficacy of ET_A receptor antagonists for pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a condition characterized by pulmonary vascular remodeling and increased pulmonary artery pressure leading to right ventricular failure [55]. PAH is a female-predominant disease. However, prognosis is worse in male patients [56]. It is well documented that ET-1 plays a major role in the pathogenesis of PAH through its vasoconstrictor and mitogenic effects. Previous studies showed that plasma and lung ET-1 levels are increased in PAH. ET_A receptor antagonists are commonly used as first line therapy for treatment of PAH since 2001 [57]. Currently, three ET_A receptor blockers, bosentan, macitentan and ambrisentan, are FDA approved for management of PAH.

A recent study indicates that women have better improvements of right ventricular functions and hemodynamics following optimal medical therapy [58]. Retrospective studies have pointed to a sex-related discrepancy in the therapeutic response ERA receptor blockers. Gabler et al. analyzed patient data from 1,130 participants enrolled in six randomized placebo-controlled trials of ET_A receptor blockers for management of PAH [59]. The authors found that women have greater therapeutic responses to ET_A receptor antagonists. These clinical findings suggest that female PAH patients may benefit more from ET_A receptor antagonists [60]. On the other hand, men with PAH showed greater improvement in response to phosphodiesterase type 5 inhibitors compared to women [61]. This sex-related difference in the efficacy of antihypertensive regimens suggests that the molecular mechanisms involved in the pathophysiology of PAH are sexual dimorphic. The robust effect of the female sex predicting better response to ET_A receptor blockers and the male sex predicting better response to phosphodiesterase type 5 inhibition can inform personalized treatment decisions. We hypothesize that differential effects on the ET_A and ET_B receptor systems could explain why females have more frequent risk for pulmonary hypertension, yet not as severe as in males (Figure 3). Future studies addressing sex differences in the therapeutic response to different treatment regimens can provide a foundation to revisit the guidelines for management of PAH to include the sex as a variable.

Conclusion

Studies published in recent years generally reinforce the importance of sex and sex hormones in determining quality of life and prognosis of cardiovascular diseases including hypertension. Increasing evidence demonstrates that pathophysiology, manifestations and complications of hypertension differ in men, premenopausal, hormonally supplemented and non-supplemented postmenopausal patients, indicating that female sex hormones play a central role in the maintenance of cardiovascular health in the female population. Thus, the management strategies evaluated in the general population may differ significantly between men, premenopausal female and postmenopausal female patients with and without hormonal

replacement therapy. The number of trials that specifically address cardiovascular and renal diseases in females under different hormonal status remains small. When results of needed studies of the modulatory role of gonadal hormones on critically important systems involved in cardiovascular and renal control, such as ET-1 system, and other relevant topics become available, new clinical practice guidelines based on a systematic evidence will need to be developed.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Go AS, et al., Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*, 2014 129(3): p. e28–e292. [PubMed: 24352519]
2. Mendelsohn ME and Karas RH, The protective effects of estrogen on the cardiovascular system. *N Engl J Med*, 1999 340(23): p. 1801–11. [PubMed: 10362825]
3. Granger JP, et al., Endothelin, the kidney, and hypertension. *Curr Hypertens Rep*, 2006 8(4): p. 298–303. [PubMed: 16884660]
4. Davenport AP, et al., Endothelin. *Pharmacol Rev*, 2016 68(2): p. 357–418. [PubMed: 26956245]
5. Levin ER, Endothelins. *N Engl J Med*, 1995 333(6): p. 356–63. [PubMed: 7609754]
6. Hall JE, et al., Hypertension: physiology and pathophysiology. *Compr Physiol*, 2012 2(4): p. 2393–442. [PubMed: 23720252]
7. Eljovich F, et al., Salt Sensitivity of Blood Pressure: A Scientific Statement From the American Heart Association. *Hypertension*, 2016 68(3): p. e7–e46. [PubMed: 27443572]
8. Pollock DM and Pollock JS, Evidence for endothelin involvement in the response to high salt. *Am J Physiol Renal Physiol*, 2001 281(1): p. F144–50. [PubMed: 11399655]
9. Speed JS, et al., High salt diet increases the pressor response to stress in female, but not male ETB-receptor-deficient rats. *Physiol Rep*, 2015 3(3).
10. Weber MA, et al., A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet*, 2009 374(9699): p. 1423–31. [PubMed: 19748665]
11. Gohar EY, et al., Role of the endothelin system in sexual dimorphism in cardiovascular and renal diseases. *Life Sci*, 2016 159: p. 20–29. [PubMed: 26939577]
12. Kohan DE, et al., Clinical trials with endothelin receptor antagonists: what went wrong and where can we improve? *Life Sci*, 2012 91(13–14): p. 528–39. [PubMed: 22967485]
13. Schulman IH, et al., Surgical menopause increases salt sensitivity of blood pressure. *Hypertension*, 2006 47(6): p. 1168–74. [PubMed: 16618835]
14. Wassertheil-Smoller S, et al., Hypertension and its treatment in postmenopausal women: baseline data from the Women's Health Initiative. *Hypertension*, 2000 36(5): p. 780–9. [PubMed: 11082143]
15. Burt VL, et al., Prevalence of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension*, 1995 25(3): p. 305–13. [PubMed: 7875754]

16. Khalil RA, Sex hormones as potential modulators of vascular function in hypertension. *Hypertension*, 2005 46(2): p. 249–54. [PubMed: 15983238]
17. Reckelhoff JF, Sex steroids, cardiovascular disease, and hypertension: unanswered questions and some speculations. *Hypertension*, 2005 45(2): p. 170–4. [PubMed: 15583070]
18. Tremollieres FA, et al., Coronary heart disease risk factors and menopause: a study in 1684 French women. *Atherosclerosis*, 1999 142(2): p. 415–23. [PubMed: 10030394]
19. Hajjar I and Kotchen TA, Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA*, 2003 290(2): p. 199–206. [PubMed: 12851274]
20. Kim JK, et al., Recent changes in cardiovascular risk factors among women and men. *J Womens Health (Larchmt)*, 2006 15(6): p. 734–46. [PubMed: 16910905]
21. Wilcox JG, et al., Endothelin levels decrease after oral and nonoral estrogen in postmenopausal women with increased cardiovascular risk factors. *Fertil Steril*, 1997 67(2): p. 273–7. [PubMed: 9022602]
22. Komatsumoto S and Nara M, [Changes in the level of endothelin-1 with aging]. *Nihon Ronen Igakkai Zasshi*, 1995 32(10): p. 664–9. [PubMed: 8551691]
23. Saltevo J, Puolakka J, and Ylikorkala O, Plasma endothelin in postmenopausal women with type 2 diabetes mellitus and metabolic syndrome: a comparison of oral combined and transdermal oestrogen-only replacement therapy. *Diabetes Obes Metab*, 2000 2(5): p. 293–8. [PubMed: 11225744]
24. Son WM, et al., Combined exercise reduces arterial stiffness, blood pressure, and blood markers for cardiovascular risk in postmenopausal women with hypertension. *Menopause*, 2017 24(3): p. 262–268. [PubMed: 27779565]
25. Webb CM, et al., 17beta-estradiol decreases endothelin-1 levels in the coronary circulation of postmenopausal women with coronary artery disease. *Circulation*, 2000 102(14): p. 1617–22. [PubMed: 11015337]
26. Wenner MM, et al., ETB receptor contribution to vascular dysfunction in postmenopausal women. *Am J Physiol Regul Integr Comp Physiol*, 2017 313(1): p. R51–R57. [PubMed: 28438762]
27. Gohar EY, Yusuf C, and Pollock DM, Ovarian hormones modulate endothelin A and B receptor expression. *Life Sci*, 2016 159: p. 148–152. [PubMed: 26776836]
28. Kitamura K, et al., Regional distribution of immunoreactive endothelin in porcine tissue: abundance in inner medulla of kidney. *Biochem Biophys Res Commun*, 1989 161(1): p. 348–52. [PubMed: 2658999]
29. Gohar EY, et al., Ovariectomy uncovers purinergic receptor activation of endothelin-dependent natriuresis. *Am J Physiol Renal Physiol*, 2017 313(2): p. F361–F369. [PubMed: 28468962]
30. Li P, et al., Chronic vagus nerve stimulation attenuates vascular endothelial impairments and reduces the inflammatory profile via inhibition of the NF-kappaB signaling pathway in ovariectomized rats. *Exp Gerontol*, 2016 74: p. 43–55. [PubMed: 26692419]
31. Lima R, et al., Roles played by 20-HETE, angiotensin II and endothelin in mediating the hypertension in aging female spontaneously hypertensive rats. *Am J Physiol Regul Integr Comp Physiol*, 2013 304(3): p. R248–51. [PubMed: 23220478]
32. Sava RI, March KL, and Pepine CJ, Hypertension in pregnancy: Taking cues from pathophysiology for clinical practice. *Clin Cardiol*, 2018 41(2): p. 220–227. [PubMed: 29485737]
33. Palei AC, et al., Pathophysiology of hypertension in pre-eclampsia: a lesson in integrative physiology. *Acta Physiol (Oxf)*, 2013 208(3): p. 224–33. [PubMed: 23590594]
34. Lu YP, et al., Plasma ET-1 Concentrations Are Elevated in Pregnant Women with Hypertension - Meta-Analysis of Clinical Studies. *Kidney Blood Press Res*, 2017 42(4): p. 654–663. [PubMed: 29212079]
35. Mastrogianis DS, et al., Potential role of endothelin-1 in normal and hypertensive pregnancies. *Am J Obstet Gynecol*, 1991 165(6 Pt 1): p. 1711–6. [PubMed: 1750465]
36. LaMarca B, et al., Hypertension in response to autoantibodies to the angiotensin II type I receptor (AT1-AA) in pregnant rats: role of endothelin-1. *Hypertension*, 2009 54(4): p. 905–9. [PubMed: 19704104]
37. LaMarca B, et al., Placental Ischemia and Resultant Phenotype in Animal Models of Preeclampsia. *Curr Hypertens Rep*, 2016 18(5): p. 38. [PubMed: 27076345]

38. Bakrania BA, et al., Heme oxygenase-1 is a potent inhibitor of placental ischemia-mediated endothelin-1 production in cultured human glomerular endothelial cells. *Am J Physiol Regul Integr Comp Physiol*, 2018 314(3): p. R427–R432. [PubMed: 29212810]
39. Saleh L, et al., The emerging role of endothelin-1 in the pathogenesis of pre-eclampsia. *Ther Adv Cardiovasc Dis*, 2016 10(5): p. 282–93. [PubMed: 26755746]
40. Jain A, Endothelin-1: a key pathological factor in pre-eclampsia? *Reprod Biomed Online*, 2012 25(5): p. 443–9. [PubMed: 22995748]
41. Murphy SR, et al., Role of endothelin in mediating soluble fms-like tyrosine kinase 1-induced hypertension in pregnant rats. *Hypertension*, 2010 55(2): p. 394–8. [PubMed: 20026766]
42. George EM and Granger JP, Endothelin: key mediator of hypertension in preeclampsia. *Am J Hypertens*, 2011 24(9): p. 964–9. [PubMed: 21677700]
43. Saleh L, Danser JA, and van den Meiracker AH, Role of endothelin in preeclampsia and hypertension following antiangiogenesis treatment. *Curr Opin Nephrol Hypertens*, 2016 25(2): p. 94–9. [PubMed: 26717314]
44. Bakrania B, et al., The Endothelin Type A Receptor as a Potential Therapeutic Target in Preeclampsia. *Int J Mol Sci*, 2017 18(3).
45. Thaete LG, et al., Endothelin receptor antagonist has limited access to the fetal compartment during chronic maternal administration late in pregnancy. *Life Sci*, 2012 91(13–14): p. 583–6. [PubMed: 22406077]
46. Maynard SE, et al., Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. *J Clin Invest*, 2003 111(5): p. 649–58. [PubMed: 12618519]
47. Kendall RL, Wang G, and Thomas KA, Identification of a natural soluble form of the vascular endothelial growth factor receptor, FLT-1, and its heterodimerization with KDR. *Biochem Biophys Res Commun*, 1996 226(2): p. 324–8. [PubMed: 8806634]
48. Shibuya M, Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. *Cell Struct Funct*, 2001 26(1): p. 25–35. [PubMed: 11345501]
49. Karumanchi SA, Angiogenic factors in preeclampsia: implications for clinical practice. *BJOG*, 2018.
50. Karumanchi SA, Angiogenic Factors in Preeclampsia: From Diagnosis to Therapy. *Hypertension*, 2016 67(6): p. 1072–9. [PubMed: 27067718]
51. Verdonk K, et al., Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. *Hypertension*, 2015 65(6): p. 1316–23. [PubMed: 25870197]
52. Aggarwal PK, et al., The relationship between circulating endothelin-1, soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia. *J Hum Hypertens*, 2012 26(4): p. 236–41. [PubMed: 21451568]
53. Stanhewicz AE, et al., Alterations in endothelin type B receptor contribute to microvascular dysfunction in women who have had preeclampsia. *Clin Sci (Lond)*, 2017 131(23): p. 2777–2789. [PubMed: 29042489]
54. Majali-Martinez A, et al., Endothelin-1 down-regulates matrix metalloproteinase 14 and 15 expression in human first trimester trophoblasts via endothelin receptor type B. *Hum Reprod*, 2017 32(1): p. 46–54. [PubMed: 27864359]
55. Taichman DB and Mandel J, Epidemiology of pulmonary arterial hypertension. *Clin Chest Med*, 2007 28(1): p. 1–22, vii. [PubMed: 17338925]
56. Safdar Z, Pulmonary hypertension: a woman's disease. *Tex Heart Inst J*, 2013 40(3): p. 302–3. [PubMed: 23914026]
57. Rubin LJ, et al., Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*, 2002 346(12): p. 896–903. [PubMed: 11907289]
58. Kozu K, et al., Sex differences in hemodynamic responses and long-term survival to optimal medical therapy in patients with pulmonary arterial hypertension. *Heart Vessels*, 2018.
59. Gabler NB, et al., Race and sex differences in response to endothelin receptor antagonists for pulmonary arterial hypertension. *Chest*, 2012 141(1): p. 20–26. [PubMed: 21940766]

60. Marra AM, et al., Gender-related differences in pulmonary arterial hypertension targeted drugs administration. *Pharmacol Res*, 2016 114: p. 103–109. [PubMed: 27771466]
61. Mathai SC, et al., Sex differences in response to tadalafil in pulmonary arterial hypertension. *Chest*, 2015 147(1): p. 188–197. [PubMed: 25122150]

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Fig. 1.

Recent findings demonstrating differential vascular ET_B receptor function in the cutaneous circulation in young women (YW) and post-menopausal women (PMW). Cutaneous vascular conductance (i.e., vasodilatory responses) to local heating were measured during cutaneous microdialysis perfusions of ET_B (BQ-788) and ET_A (BQ-123) receptor antagonists (* $P < 0.05$ vs. control.) These findings demonstrate a role for ET_B receptors in control of microvascular function that is reversed following menopause. Used with permission from Wenner et al. [60].

Fig. 2.
Theoretical scheme for endothelin involvement in pregnancy induced hypertension.

Fig. 3. Hypothetical scheme demonstrating the paradoxical effects of estrogen in facilitating less severe pulmonary hypertension and yet being more responsive to ET receptor blockade.