



Prorenin periconceptionally and in pregnancy: Does it have a physiological role?

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ABSTRACT

Pregnancy demands major cardiovascular, renal and endocrine changes to provide an adequate blood supply for the growing fetus. The renin-angiotensin-aldosterone system plays a key role in this adaptation process. One of its components, prorenin, is released in significant amounts from the ovary and uteroplacental unit. This review describes the sources of prorenin in the periconception period and in pregnancy, including its modulation by in-vitro fertilization protocols, and discusses its potential effects, among others focusing on preeclampsia. It ends with discussing the long-term consequences, even in later life, of inappropriate renin-angiotensin-aldosterone system activity in pregnancy and offers directions for future research. Ultimately, a full understanding of the role of prorenin periconceptionally and during pregnancy will help to develop tools to diagnose and/or prevent reproductive complications.

1. Introduction

Successful conception and the subsequent physiologic adaptation to pregnancy involves the complex coordination of different organ systems, including the endocrine, cardiovascular and renal systems, to ensure the well-being of the mother and the fetus during pregnancy. These changes start in the luteal phase of the menstrual cycle and peak at the end of the first trimester prior to the increase in metabolic demands of mother and fetus and in anticipation of growing needs in the second half of pregnancy (Fig. 1). Systemic vasodilation occurs as early as 3 weeks post-conception (5 weeks gestation) (Chapman et al., 1998), and is accompanied by a decrease in peripheral vascular resistance, reaching a nadir during the mid-second trimester. A first reduction in maternal systolic, diastolic and mean arterial blood pressure is observed at a median of 6 weeks gestation, with a return to non-pregnant levels during the last month of pregnancy (Mahendru et al., 2012; Chapman et al., 1998; Robson et al., 1989; Capeless and Clapp, 1989; Robb et al., 2009). Heart rate increases in early pregnancy, while cardiac output and left atrial dimension increase from preconception to mid-gestation, with a decline after 32–35 weeks of gestation. Carotid femoral pulse wave

velocity and augmentation index decline continuously from baseline preconception levels. Reductions in renal afferent and efferent arteriolar resistance result in rises in renal plasma flow, ([RPF], by 50–80%) and glomerular filtration rate ([GFR], by 40–65%) (Sims and Krantz, 1958; De Alvarez, 1958; Assali et al., 1959; Roberts et al., 1996; Dunlop, 1981). This will increase creatinine and urea clearances, thereby lowering their plasma level (Roberts et al., 1996; Sims and Krantz, 1958; Kuhlback and Widholm, 1966; Nice, 1935).

The renin-angiotensin-aldosterone system (RAAS) is a key player in this adaptation process. Renin cleaves angiotensin (Ang) I from angiotensinogen, which is subsequently converted by ACE into Ang II, a potent vasoconstrictor and growth factor which also stimulates the synthesis of aldosterone. Increases in Ang II and aldosterone levels are necessary to achieve the 30–40% increase in intravascular volume that is required in normal pregnancy to allow the above-described changes. Rises in Ang II particularly depend on increases in renin and angiotensinogen, and to a lesser degree on increases in angiotensin-converting enzyme (ACE) (Danser et al., 1998, 2007). Remarkably, the levels of renin's precursor, prorenin, also increase substantially in pregnant women. This is unexpected, since prorenin is inactive (due to the fact

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that a so-called prosegment covers its active site; Fig. 2), raising the question why prorenin would rise at all. Normally under conditions where the RAAS is activated, e.g. in heart failure and patients with renal artery stenosis, it is renin rather than prorenin which rises (Danser et al., 1997; Klotz et al., 2009). Indeed, particularly during additional blockade of the RAAS with RAAS inhibitors, renin rises may be > 100-fold (Balcarek et al., 2014; Klotz et al., 2009). To display activity, prorenin needs to be converted to renin. This proteolytic process involves the cleavage of the prosegment by an as yet unknown enzyme, and is limited to the kidney. Of interest, under physiological conditions (pH 7.4, 37 °C), a small fraction of prorenin (≈1% or less) occurs in a so-called ‘open’ conformation, i.e., a conformation where the prosegment has moved out of the enzymatic cleft (Schalekamp et al., 2008) (Fig. 2). Hence, it no longer covers the cleft, and thus such prorenin is able to display enzymatic activity to the same degree as renin, although its prosegment is still present (Schalekamp et al., 2008). Theoretically, particularly under conditions where prorenin levels are high (like in pregnancy) this ‘non-proteolytic’ activation of prorenin could contribute to Ang I generation in blood. Studies in transgenic animals with excessively high prorenin levels (Campbell et al., 2009) support this view, but in-vivo data in humans confirming this phenomenon are lacking. A further possibility, actively studied over the last 20 years, is that prorenin binds to a receptor, which then facilitates non-proteolytic activation. According to this theory, prorenin might contribute to angiotensin generation at any non-renal tissue site simply by binding to its receptor, without the need for a prosegment-cleaving enzyme. This is a very attractive theory, particularly because humans have relatively high prorenin levels which increase even further due to unknown reasons in conditions like pregnancy and diabetes. The presence of a receptor would finally explain why prorenin exists at all. A putative candidate was proposed nearly 20 years ago, the so-called (pro)renin receptor (Nguyen et al., 2002). It not only allowed prorenin to display Ang I-generating activity, but also to act as an angiotensin-independent agonist. However, prorenin-(pro)renin receptor interaction required prorenin levels in the nanomolar range (Batenburg et al., 2011), i.e.

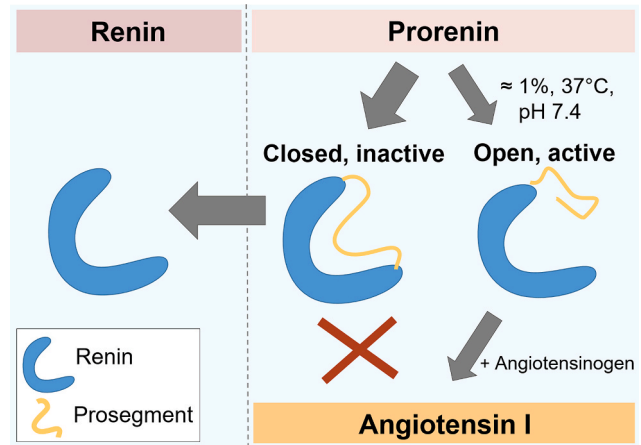


Fig. 2. Renin and prorenin conformations. Under physiological conditions (pH 7.4, 37 °C), a small fraction of prorenin (≈1% or less) occurs in the so-called ‘open’ conformation, i.e., a conformation where the prosegment has moved out of the enzymatic cleft, thus allowing it to react with angiotensinogen to yield angiotensin I. Yet, the majority of prorenin is closed and inactive. Cleavage of the prosegment (also known as ‘proteolytic’ activation) occurs exclusively in the kidney, and depends on an as yet unidentified enzyme.

many orders of magnitude above its normal levels, even under conditions where its levels have increased (like in pregnancy). Thus, such interaction is highly unlikely to ever occur in vivo (except in transgenic animals), and more recent studies suggest that the (pro)renin receptor rather exerts RAAS-independent functions (Lu et al., 2016; Ren et al., 2018).

This paper describes the source(s) of prorenin during the peri-conception period and in pregnancy, and discusses its regulators and potential role(s), among others focusing on preeclampsia, where elegant transgenic models have yielded novel insights. It ends with discussing the long-term consequences of inappropriate RAAS activity in

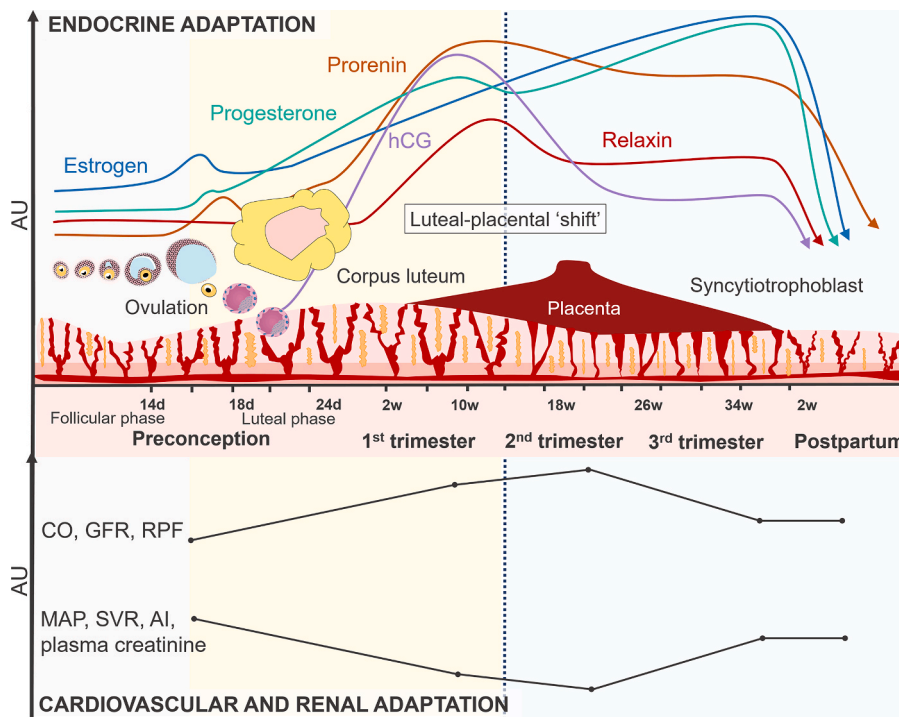


Fig. 1. Adaptation of endocrine, cardiovascular and renal parameters from preconceptional baseline throughout pregnancy and postpartum. AI, augmentation index; AU, arbitrary units; CO, cardiac output; GFR, glomerular filtration rate; hCG, human chorionic gonadotropin; MAP, mean arterial pressure; RPF, renal plasma flow; SVR, systemic vascular resistance.

pregnancy, and offers directions for future research.

2. Circulating renin-angiotensin-aldosterone system in pregnancy: source(s) of prorenin

Circulating angiotensinogen levels increase 3-5-fold in pregnant women (Verdonk et al., 2015). This is due to estrogen-stimulated upregulation of hepatic angiotensinogen synthesis (Klett et al., 1992; Uijl et al., 2019). The rise in angiotensinogen is accompanied by a modest (≈ 1.5 -2-fold) rise in the concentration of plasma renin, either due to the decrease in blood pressure (affecting renal afferent/efferent arteriolar tone and renal JG cell responsiveness) or the fact that progesterone acts as an antagonist towards the mineralocorticoid receptor (Landau and Lugibihl, 1958). Together, the upregulation in plasma renin concentration and angiotensinogen result in a 2-3-fold rise in plasma renin activity (PRA), thereby raising Ang I and II levels throughout pregnancy. Remarkably, the Ang II elevation does not result in a rise in blood pressure. In fact, the constrictor sensitivity to exogenous Ang II is diminished in pregnancy. This could relate to a down-regulation of constrictor Ang II type 1 (AT₁) receptors, an upregulation of dilator Ang II type 2 (AT₂) receptors, and/or the upregulation of counterbalancing dilator mechanisms including nitric oxide (NO), prostaglandins and the Ang-(1-7)/Mas receptor axis (Mishra et al., 2019; Gant et al., 1980; Verdonk et al., 2014; South et al., 2019). Renin levels fall within 24 h after delivery, thus allowing a rapid post-pregnancy normalization of circulating Ang II and aldosterone (Derkx et al., 1987). Angiotensinogen levels fall less rapidly, possibly due to puerperal activity of the corpus luteum, resulting in continued estrogen release after birth (Wier et al., 1975; Weiss and Rifkin, 1975; Conrad et al., 2019a).

Prorenin levels increase 4-5-fold by week 8, and drop only slowly after delivery over a period of several days (Sealey et al., 1985; Derkx et al., 1987). The latter contrasts with the rapid decrease of renin after pregnancy, and is suggestive for an extrarenal source of prorenin with continued activity after birth. The much higher rise in prorenin rapidly after conception and during pregnancy (versus renin) also supports an extrarenal source. Studies in pregnancies lacking a corpus luteum (Fig. 3) have revealed that the corpus luteum is the major contributor to this rise in circulating prorenin, as well as its continued synthesis after birth. Indeed, no such increase in circulating prorenin was seen in

pregnancies without a corpus luteum (Derkx et al., 1987). In such pregnancies, the prorenin rise was as modest as the rise in renin, and prorenin decreased in parallel with renin after parturition (Sealey et al., 1985; Derkx et al., 1987). Recent data obtained in 277 women with either no corpus luteum, 1 corpus luteum or >1 corpus luteum further confirmed the direct relationship between corpus luteum number and prorenin levels (Wiegel et al., 2020). Taken together, these data indicate that renin upregulation in pregnancy is kidney-driven, while the ovaries are the main source of prorenin levels in pregnant women.

Chorionic and amniotic fluid contain prorenin levels that are many orders of magnitude above those in blood. Early in pregnancy the chorionic cavity is larger, while it disappears after 8 weeks, when human chorionic gonadotropin (hCG) levels decline and the amniotic cavity becomes predominant (Itskovitz et al., 1992). The amniotic tissue does not synthesize prorenin, and it is believed that chorionic prorenin passes through the amnion into the amniotic fluid. Since the amniotic fluid levels of prorenin were normal in pregnancies without a corpus luteum (Derkx et al., 1987), it appears that chorionic prorenin does not contribute to the levels of prorenin in plasma. Other potential sources of circulating prorenin are the uterus and placenta. Indeed, making use of the isolated perfused cotyledon setup, Lenz et al. were able to demonstrate prorenin release to the maternal but not the fetal circulation (Lenz et al., 1991). Direct evidence for decidual prorenin release into the circulation is not available. Yet, it may contribute to gestational fluid prorenin (Shaw et al., 1989). Moreover, Brar et al. demonstrated prorenin release from the uteroplacental unit in pregnant women (Brar et al., 1986). This conclusion was based on the presence of higher prorenin levels in uterine venous blood versus arterial blood. No such differences were observed for renin. In summary, next to the ovary and kidneys, a third (and probably modest) source of circulating prorenin in pregnancy is the uteroplacental unit. Lenz et al. estimated that <5% of circulating prorenin in pregnancy originates from the placenta (Lenz et al., 1991). The very modest rises in prorenin in a woman without a corpus luteum, also at late term (Derkx et al., 1987), is in agreement with this view.

Prorenin levels in blood normally are around 10 times higher than those of renin (Danser et al., 1998). In pregnancy, with renin increasing <2-fold, and prorenin increasing 4-5-fold, this results in renin levels representing <5% of total renin (=renin + prorenin). Under such conditions, a small fraction of prorenin displaying activity (Fig. 2) might

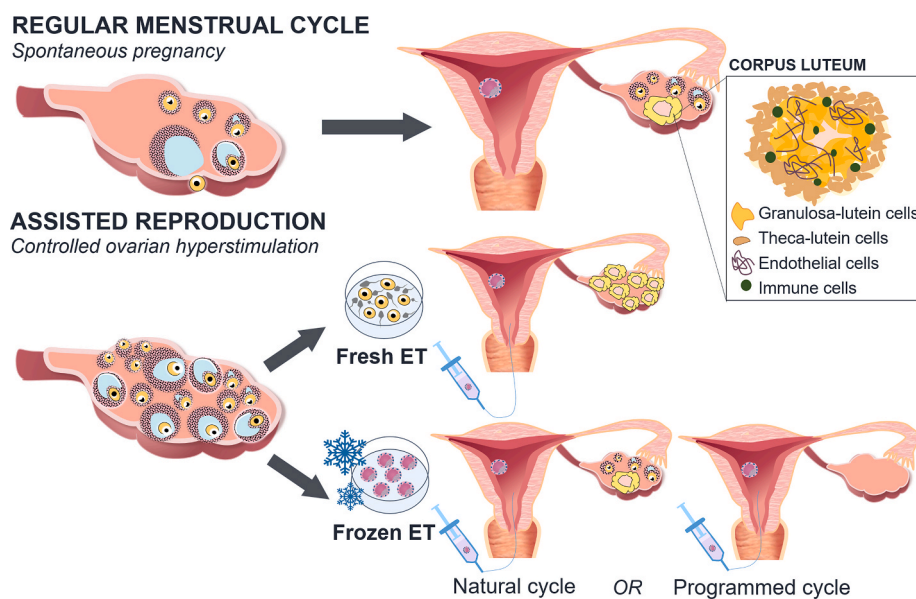


Fig. 3. Physiological follicle development followed by spontaneous conception with one corpus luteum compared to pregnancies achieved through assisted reproduction with fresh embryo transfer (ET) after superovulation with multiple corpora lutea or frozen ET in a natural cycle with one corpus luteum or frozen ET in a programmed cycle after suppression of the pituitary-ovarian axis in the absence of a corpus luteum.

contribute to Ang I generation in blood to the same degree as renin. Initial studies linked prorenin to vasodilation, albeit via an unknown mechanism (Sealey et al., 1991, 1996). Direct prorenin-induced effects (e.g., independent of Ang II formation) may involve a receptor, and although the (pro)renin receptor has been suggested to be this receptor (Pringle et al., 2015), convincing evidence that it plays such a role in vivo is lacking (Batenburg et al., 2011).

3. Corpus luteum, early gestational hemodynamic adaptation and circulating prorenin

In conceptions lacking a corpus luteum the systemic and renal adaptations in the first weeks of pregnancy are attenuated. This is suggestive for a critical role of corpus luteum factors in the maternal hemodynamic adaptation in early gestation (von Versen-Höynck et al., 2019; Conrad et al., 2019b). Indeed, the corpus luteum is considered a 'functional ovarian cyst' during early pregnancy, i.e., before the luteal-placental shift, when placental hormones (synthesized by syncytiotrophoblast cells) become of greater importance. Moreover, prospective cohort studies in infertile populations showed that the risk to develop preeclampsia is doubled in women who lack a corpus luteum (von Versen-Höynck et al., 2019; Ginstrom Ernstad et al., 2019). The corpus luteum evolves from remnant tissue of the ovulated follicle with the preovulatory surge of luteinizing hormone (LH) from the pituitary gland as the main stimulus. It has significant steroidogenic and angiogenic activity in both the luteal phase of a menstrual cycle and in early pregnancy (Devoto et al., 2009). Transformation of the follicle into the corpus luteum involves vascular endothelial cells undergoing intense proliferation and the formation of a rich vascular network, essential for the delivery of substrates.

A physiological pregnancy is preceded by one corpus luteum. In contrast, pregnancies achieved via ovulation stimulation treatment often begin in a non-physiological endocrine milieu due to suppression of the pituitary-ovarian axis and the absence of the corpus luteum or due to superovulation with the presence of more than one corpus luteum (Fig. 3). Corpus luteum function is controlled by the interaction of several hormones secreted by the pituitary gland, and in case of pregnancy, by the decidua and the placenta. It contains steroidogenic cells (theca-lutein [small luteal cells] and granulosa-lutein cells [large luteal cells]) and non-steroidogenic cells (endothelial cells, pericytes, fibroblasts and immune cells) (Davis and Rueda, 2002; Alila and Hansel, 1984). The corpus luteum synthesizes hormones, growth factors, angiogenic factors and vasoactive substances to establish and maintain pregnancy. These include 17 β -estradiol, progesterone, prostaglandins, relaxin, oxytocin, vasopressin, inhibin, vascular endothelial growth factor, endothelin-1 (ET-1), and prorenin (Ebisch et al., 2008; Kampfer et al., 2014). In the absence of pregnancy, the corpus luteum will cease synthesis and the structure will regress in size over time (Rowan et al., 2008).

Given the suboptimal maternal hemodynamic adaptation in pregnancies lacking a corpus luteum, it is likely that this insufficient adaptation relies at least also on one or more of the factors released by the corpus luteum into the circulation. Prorenin is produced by the mature ovarian follicle and the corpus luteum in response to gonadotropin stimulation (Derckx et al., 1987). Its levels directly relate to the number of ovarian follicles, with a modifying role for the hormones applied in the in-vitro fertilization (IVF) protocol (Itskovitz and Sealey, 1987; Itskovitz et al., 1987; Wiegel et al., 2020). The former also applies to relaxin, which, unlike prorenin, is exclusively produced by the corpus luteum (Weiss et al., 1993; Mushayandevu et al., 1998; Arthur et al., 1996; Haning et al., 1996; Kristiansson et al., 1996; Conrad et al., 2019a). In other words, relaxin is entirely absent in pregnancies lacking a corpus luteum. Relaxin causes relaxation via NO and prostacyclin, and thus potentially contributes to the systemic and renal vasodilation and the increase in GFR in early pregnancy. Indeed, the absence of relaxin associated with a diminished increase in GFR and higher serum sodium

and creatinine levels. Moreover, lower relaxin levels ultimately promote preeclampsia (Conrad and Davison, 2014; Post Uiterweer et al., 2020). Relaxin also stimulates prorenin production (Poinsner et al., 1990). Finally, estrogens promote vasodilation via NO and prostacyclin, by stimulating endothelial NO synthase (eNOS) and cyclooxygenase-1, respectively. This increases blood flow, particularly in the uterine vascular bed. The latter likely involves 17 β -estradiol-induced upregulation of dilator AT₂ receptors (Mishra et al., 2019). As discussed, estrogen additionally upregulates angiotensinogen, allowing an increase in Ang II levels. Simultaneously, estrogens stimulate 11 β -hydroxysteroid dehydrogenase 2, thereby preventing glucocorticoids from increasing blood pressure via binding to mineralocorticoid receptors (Baggia et al., 1990). Progesterone, like 17 β -estradiol, promotes vasodilation via eNOS and cyclooxygenase-1 (Simoncini et al., 2007; Hermenegildo et al., 2005), and is thus able to antagonize Ang II-induced vasoconstriction (Nakamura et al., 1988). Summarizing, the corpus luteum secretes multiple factors that, through modulation of circulating RAAS activity, affect maternal hemodynamic adaptation to pregnancy (Fig. 4). Yet, why it secretes prorenin in large amounts cannot be deduced from the above findings. A further possibility is that prorenin exerts effects locally, in the ovaries, uterus and/or placenta.

4. Prorenin synthesis in the ovaries, uterus and placenta: does it have a local function?

Extrarenal cells that synthesize prorenin during pregnancy include theca cells, chorionic cells, decidual cells and placental cytotrophoblasts. Prorenin, in contrast to renin, is not stored in vesicles, and thus its local synthesis is likely to result in direct release, yielding high prorenin levels in the immediate surrounding of prorenin-synthesizing cells, i.e., in follicular, chorionic, and amniotic fluid. Indeed, chorionic prorenin levels were the highest ever measured in the human body: they amounted to 1000 times the normal prorenin levels in the circulation (Itskovitz et al., 1992). At such high levels, given that up to 1% of prorenin occurs in the open (active) conformation (Schalekamp et al., 2008), Ang I generation is likely to take place even in the absence of any prorenin-renin conversion. In fact, assuming that sufficient angiotensinogen is available, the degree of Ang I generation under such conditions might be 100 times above the normal PRA. This implies that this prorenin, at least locally, is capable of promoting Ang II-mediated effects.

4.1. Ovaries

Prorenin levels in follicular fluid are approximately 10-fold higher than those in plasma, both in normal and stimulated menstrual cycles (Fernandez et al., 1985; Glorioso et al., 1986). Theca cells of the follicle and the luteinized thecal cells of the corpus luteum after ovulation are the source of this prorenin. Prorenin synthesis occurs in response to the gonadotropic hormones LH and hCG, and involves the adenylyl cyclase-cyclic adenosine monophosphate (cAMP) pathway (Sealey et al., 1985; Itskovitz et al., 1987; Brunswig-Spickenheier and Mukhopadhyay, 2003; Do et al., 1988). Activation of protein kinase C (PKC), e.g. by tumor necrosis factor (TNF)- α , inhibits this process (Brunswig-Spickenheier and Mukhopadhyay, 1993). High follicular prorenin levels correlate with atresia (characterized by high testosterone levels and a low estradiol/progesterone ratio, together resulting in granulosa cell degeneration), while low follicular prorenin levels associate with immature follicles (Itskovitz et al., 1991). In other words, follicular prorenin levels should be in an ideal range, and not be too low or too high. Possibly, this is related to the need for 'optimal' Ang II levels. Multiple effects of Ang II in the ovaries have been described, ranging from stimulation of steroidogenesis to oocyte maturation, ovulation and atresia (Itskovitz et al., 1991; Cornwallis et al., 1990; Yoshimura et al., 1992; Peterson et al., 1993; Pellicer et al., 1988; Morris and Paulson, 1993; Paulson et al., 1989; McNatty et al., 1979; Seibel et al., 1989; Lightman et al., 1987). Ang II might also display vascular effects in the

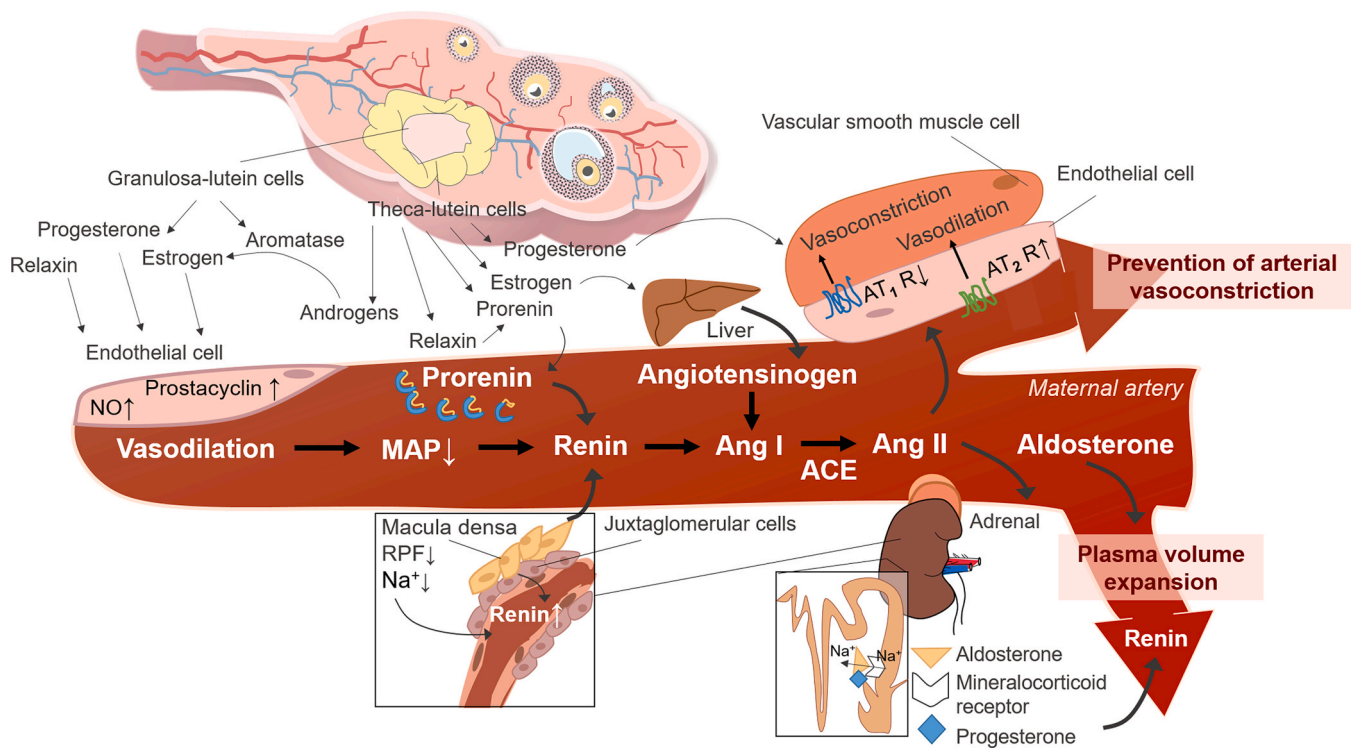


Fig. 4. The corpus luteum secretes multiple factors that directly or indirectly modulate circulating RAAS activity and affect maternal hemodynamic adaptation during early human pregnancy. Progesterone acts as a mineralocorticoid receptor antagonist, thus blocking the effects of aldosterone. Ang, angiotensin; AT₁R, angiotensin II type 1 receptor and AT₂R, angiotensin II type 2 receptor; GFR, glomerular filtration rate; MAP, mean arterial pressure; Na⁺, sodium; NO, nitric oxide; RPF, renal plasma flow.

follicular microcirculation (affecting blood flow) and facilitate the process of neovascularization that is required for appropriate corpus luteum formation (Fernandez et al., 1985; Stirling et al., 1990). Many of these Ang II effects are controversial (Naftolin et al., 1989; Yoshimura,

1997). Both AT₁ and AT₂ receptor stimulation have been implied, with the AT₂ receptor being the predominant Ang II receptor in the ovaries (Yoshimura et al., 1996). Here it is of interest to note that AT₂ receptor stimulation requires higher Ang II levels than AT₁ receptor stimulation

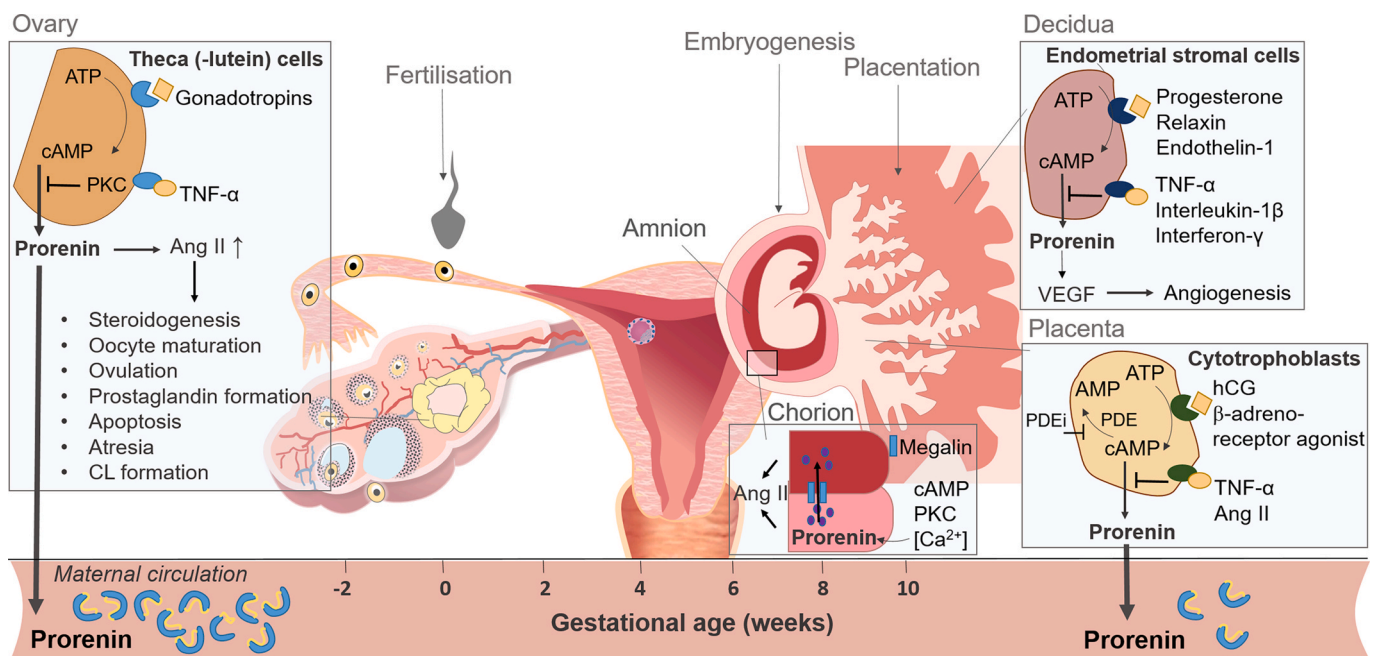


Fig. 5. Local prorenin synthesis in the ovaries, uteroplacental unit and fetal membranes, known stimulators and inhibitors of prorenin synthesis, and possible functions (local and systemic) of prorenin. ATP, adenosine triphosphate; Ca²⁺, extracellular calcium; cAMP, cyclic adenosine monophosphate; hCG, human chorionic gonadotropin; PDE, phosphodiesterase; PDEi, phosphodiesterase inhibitor; PKC, protein kinase C; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

(Schalekamp and Danser, 2013). Thus, high prorenin levels might indeed lead to Ang II levels that are high enough to stimulate atresia via AT₂ receptor stimulation (Kotani et al., 1999). Prostaglandins often act as intermediates, and since both AT receptors upregulate different prostaglandins this may explain part of the controversy (Jaiswal et al., 1991; Glance et al., 1985). After decades of work, the only unifying concept is that the ovarian Ang II effects occur in a model- and species-dependent manner.

4.2. Uteroplacental unit

The decidua, the maternal bed of the placenta, originates from differentiating endometrial stroma cells. This 'decidualization' process (involving cell growth, proliferation and angiogenesis) is primarily coordinated by ovarian steroids (Shah et al., 1991). It occurs during the secretory phase of the endometrial cycle, to prepare the receptive endometrium for implantation, and is maintained during pregnancy. Both the endometrium and decidua release prorenin, although quantitatively the decidual contribution is most important (Shaw et al., 1989). Most groups investigating prorenin release from decidual cells additionally find 'renin' activity, i.e., Ang I-generating activity even without converting prorenin to renin. Yet, in reality this represents the fact that, as discussed, a small fraction of prorenin occurs in the open conformation (Fig. 5) (Martini et al., 2017). Martini et al. investigated whether decidual cells possibly release prorenin in the 'open' conformation, based on the concept that the low pH conditions under which its synthesis and release occur favor the open conformation (Schalekamp et al., 2008). If so, prorenin would display local activity, in the immediate surrounding of its release, before returning to its closed, inactive conformation at greater distance from its release site. Unfortunately, no evidence for this concept could be obtained. Among the stimulators of decidual prorenin synthesis are progesterone (Shah et al., 1991) and relaxin (Poisner et al., 1990). Remarkably, ET-1, known to suppress renin synthesis in the kidney (Verdonk et al., 2015), actually stimulated decidual prorenin production (Poisner et al., 1990; Chao et al., 1993), while TNF- α , interleukin-1 β and interferon- γ inhibited it (Poisner et al., 1991; Jikihara et al., 1995, 1996). Like in theca cells, the adenylyl cyclase-cAMP pathway is the intracellular mediator of this process, with modulatory roles for PKC and calcium (Poisner et al., 1991; Chao et al., 1994). Decidual prorenin production has been linked to vascular endothelial growth factor expression through local RAAS activation (Lumbers et al., 2015). Since vascular endothelial growth factor is a well-known contributor to de novo vessel formation, prorenin may thus facilitate decidualization. Interestingly, altered endometrial AT₁ and AT₂ receptor expression has been suggested to underlie recurrent miscarriage (Qi et al., 2020).

The placental cells that synthesize prorenin are the cytotrophoblasts (Poisner et al., 1994). Cytotrophoblasts decrease in number during gestation, when they fuse to syncytiotrophoblasts. As a consequence, placental prorenin levels are low at term, and hence prorenin release into the maternal circulation at the end of pregnancy will be similarly low. Stimulators of placental prorenin production are hCG and β -adrenoceptor agonists (Downing et al., 1994). This involves the adenylyl cyclase-cAMP pathway (Poisner et al., 1994; Downing et al., 1994). Phosphodiesterase inhibitors (blocking cAMP degradation) further upregulate prorenin release (Poisner et al., 1994; Downing et al., 1996), while Ang II and TNF- α block it (Poisner, 1995).

The fetal membranes, chorion and the amnion, originate from the outer trophoblast layer of the implanting blastocysts. Only chorionic cells (cytotrophoblasts) synthesize and release prorenin (Pinet et al., 1988; Duncan et al., 1990). Prorenin is capable of passing through the amnion, thus explaining why amniotic fluid contains high prorenin levels, despite the fact that amniotic cells do not synthesize prorenin (Acker et al., 1982; Itskovitz et al., 1992). A potential candidate facilitating prorenin passage is megalin (Sun et al., 2020). Megalin is a 600 kDa endocytic receptor, highly expressed in placental

syncytiotrophoblasts, which is thought to contribute to transport functions (Akour et al., 2013). Decidual cells are an unlikely source of prorenin in the gestational sac, given the fact that the gestational prorenin levels were normal in tubal pregnancy, when decidualization is absent (Itskovitz et al., 1992). Chorionic prorenin synthesis depends on cAMP, PKC and extracellular calcium (Duncan et al., 1990). To what degree the high prorenin levels in chorionic and amniotic fluid play a role beyond Ang II formation remains a matter of debate. Possible roles of Ang II concern its effects on angiogenesis, growth and vascular constriction/dilation (the latter mediated via vasodilator prostanoids) (Fernandez et al., 1985; Glance et al., 1985; Magness et al., 1992; Anton et al., 2008; Pringle et al., 2011; Franklin et al., 1974).

5. Prorenin and preeclampsia: lessons from animal models

The hemodynamic adaptation process in pregnancy, i.e. the expansion of plasma volume and the decrease in vascular resistance, is less pronounced in preeclampsia (Spaanderman et al., 2001). Pregnancies complicated by preeclampsia are characterized by diminished uteroplacental flow (Schuchter et al., 2001), suggesting that the normally occurring expansion of plasma volume and increase in cardiac output are essential for the maintenance of a sufficient uteroplacental flow. Remarkably, despite this reduction in circulating volume, renin and angiotensinogen are downregulated in preeclampsia compared with normal pregnancy (Verdonk et al., 2015). Whether this is a physiological response to the increased blood pressure or an active contributor to the pathophysiology of preeclampsia is unknown. Circulating prorenin levels in preeclampsia are in the normal range (Nicholson et al., 1987; Verdonk et al., 2015; Brar et al., 1987), although data during early pregnancy in this condition are lacking. Thus, we do not know whether the follicular/corpus luteum release of prorenin in early pregnancy is altered in women who develop preeclampsia. Data on prorenin levels in the uteroplacental unit (chorion, amnion, placenta) of preeclamptic women are conflicting, with evidence for decreases, increases and no alteration (Brar et al., 1987; Singh et al., 2004; Kalenga et al., 1996; Poranen et al., 2009; Herse et al., 2007). The rise in ET-1 in preeclampsia (Verdonk et al., 2015), given its stimulatory effect on prorenin release in decidual cells (Chao et al., 1993), might support local prorenin upregulation. Nevertheless, in view of the normal circulating prorenin levels in preeclamptic women, prorenin upregulation, if occurring at all in either ovaries or the uteroplacental unit, is most likely modest. Herse observed decidual AT₁ receptor upregulation in preeclamptic women, and no change in decidual and placental renin, angiotensinogen or ACE, nor AT₁ receptor upregulation in the placenta (Herse et al., 2007). From these gene expression studies, it is difficult to conclusively state that there is selective RAAS upregulation at one or more sites in the uteroplacental unit.

In 1996, a mouse model was described with severe maternal hypertension during pregnancy, when mating transgenic females expressing human angiotensinogen with males expressing human renin (Takimoto et al., 1996). Here it is important to note that human renin does not react with mouse angiotensinogen (and vice versa), so that the single transgenic mice did not have a hypertensive phenotype. Interestingly, pregnancy-associated hypertension did not occur when crossing females expressing human renin with males expressing human angiotensinogen. The authors concluded that the placenta releases renin but not angiotensinogen into the circulation. Indeed, human renin could be demonstrated in maternal plasma at levels of 2.7 ng/mL, i.e., around 1000 times the normal renin level in humans (Campbell et al., 2009). Importantly, human prorenin levels in these mice were 57 ng/mL, which is also around 3 orders of magnitude above its normal levels in humans (and 100 times above the prorenin levels in pregnant women). Thus, in full agreement with the observations in humans, the placental release largely concerned prorenin. Furthermore, given that the human renin levels represented only a small fraction of the total human renin levels, it is likely that this in reality was prorenin in the open, active

conformation. The fact that there was no placental angiotensinogen release suggests that either angiotensinogen, unlike (pro)renin, cannot be released from its placental generation sites, or that there simply is no placental angiotensinogen production. The latter explanation is the most likely, since the placental angiotensinogen levels, unlike those of prorenin, are identical at different placental tissue sites (chorion leave, amnion, chorion plate and chorion fondrosom) (Lenz et al., 1989). This argues against a specific production site. Moreover, placental angiotensinogen is washed away during perfusion with buffer (Lenz et al., 1991). The fact that the follicular/amniotic fluid levels resemble those in plasma suggests that also in the ovaries, angiotensinogen is derived from maternal blood (Glorioso et al., 1986; Paulson et al., 1989).

The double transgenic approach (human angiotensinogen females x human renin males) also yielded hypertension, proteinuria and growth restriction in pregnant rats, and this model is therefore suggested to be representative for preeclampsia. These rats displayed a PRA that was roughly 100 times the normal PRA in pregnant women (Verdonk et al., 2015; Bohlander et al., 2000), while their angiotensinogen levels were in the normal pregnancy range. Human prorenin levels were not determined in this model. But given that normally the placental contribution to plasma prorenin in pregnancy is <5% (Lenz et al., 1991), and assuming that the rise in PRA largely reflects the activity of open prorenin, it can be estimated that the placental release of human prorenin in these transgenic rodents must have been phenomenally high, possibly >10.000 times normal. When combined with human angiotensinogen, it is not surprising that this results in severe hypertension. Haase recently reported that human angiotensinogen siRNA targeted to the maternal liver suppressed the phenotype (Haase et al., 2020), raising the possibility that targeting the maternal RAAS may be beneficial in preeclampsia. However, whether this model truly mimics preeclampsia remains doubtful, since in reality preeclamptic women display significantly suppressed PRA levels. If the proteinuria and growth restriction in this animal model are due to the elevated PRA, this model may turn out to be less representative for the human situation. Nevertheless, these transgenic studies elegantly support the release of prorenin from the uteroplacental unit into blood, and prove that such release, if excessive, disturbs the normal maternal hemodynamic adaptation to pregnancy.

6. Prorenin and (patho)physiology of pregnancy course and outcomes

Most of the adverse pregnancy outcomes are likely to originate in the first trimester of pregnancy (Stegers-Theunissen et al., 2013). Insufficient hemodynamic adaptation preconception and during early pregnancy may also underlie fetal growth restriction (FGR) (Duvekot et al., 1995; Vasapollo et al., 2004; Salas et al., 2006; De Paco et al., 2008). To what degree this concerns suppressed circulating RAAS activation (like in preeclampsia) is unknown, although an impaired plasma volume expansion in the third trimester and low birthweight have been linked to low PRA and circulating aldosterone levels in late pregnancy (Salas and Rosso, 1998; Salas et al., 2006). Moreover, first trimester plasma angiotensinogen levels correlated positively with birth weight (Al Kadi et al., 2005). Since low birth weight is a substantial determinant of a child's health and a major risk factor for several noncommunicable diseases (Barker, 2007), these data indicate that dysregulated circulating RAAS activation in early pregnancy may also affect health later in life.

Low follicular/amniotic fluid prorenin levels might reduce local RAAS activity, thus diminishing the growth-stimulating and angiogenic effects of Ang II. A downregulation of placental AT₁ receptors, as observed in FGR pregnancies (Knock et al., 1994; Li et al., 1998), would have a similar effect.

Pregnancies achieved through IVF treatment are characterized by more frequent early and late vascular-related pregnancy complications. The risk factors for these complications are identical to those for women who conceive naturally and develop pregnancy complications, and

include high maternal age, a high body mass index, chronic hypertension and diabetes mellitus (Bartsch et al., 2016). These risk factors are characterized by RAAS alterations and oxidative stress. For instance, diabetes mellitus, like pregnancy, associates with high prorenin levels (Byrer-Ash et al., 1983; Franken et al., 1990). Interestingly, pregnant women with diabetes mellitus who additionally develop preeclampsia displayed the highest prorenin levels (Ringholm et al., 2011). Oxidative stress impacts placental health during the critical hypoxic state (Jau-niaux et al., 2006; Burton et al., 2003) This may affect local renin regulation via epigenetic pathways (Wang et al., 2013).

7. Conclusions and future directions

Prorenin is among the factors released by the corpus luteum that determine maternal hemodynamic adaptation in early gestation. Animal data suggest that prorenin release by the placenta, if excessive, leads to hypertension, proteinuria and growth restriction. There is no evidence for conversion of this ovarian/placental prorenin to renin, and normally, at most a very small fraction of prorenin displays Ang I-generating activity without prosegment removal. This implies that only under conditions where prorenin release is far beyond normal (like in transgenic animals) such prorenin rises would substantially upregulate Ang II generation in the circulation. In humans this might also be the case in chorionic fluid, with its prorenin levels that are >1000-fold those in blood, and possibly in the immediate surrounding of cells that synthesize prorenin in the decidua and placenta. The angiotensinogen that is needed to allow local prorenin activity is of maternal origin, implying that it must be capable of passing the placental barrier. Angiotensinogen siRNA targeted to the maternal liver may thus help to prevent excessive RAAS activation, both in the mother and fetus. However, the pregnancy complication preeclampsia is characterized by low RAAS activity, and this may also be true for FGR. A wide range of local effects of Ang II in the ovary and uteroplacental unit has been described, ranging from oocyte maturation and decidualization to angiogenesis and regional blood flow modification. A remaining question is whether prorenin exerts effects beyond Ang II. Here its interaction with the (pro)renin receptor is of interest, although even the prorenin rises in pregnancy appear to be too limited to match the nanomolar affinity of this receptor. It has been argued that prorenin is a direct vasodilator, but the underlying mechanism remains unknown. A novel prorenin receptor is megalin, a transporter protein which is also abundantly present in the placenta. Its relationship with prorenin in the placenta remains to be determined. Future studies correlating prorenin levels with utero (placental) outcome and oxidative stress parameters could help to further determine the function of this prohormone. Careful linking of prorenin to other corpus luteum factors, corpus luteum number and IVF protocol will yield insight into its regulation and release. Here both relaxin and ET-1 are of great interest as prorenin modifiers. Low or absent relaxin levels (as occurring in women without a corpus luteum) promote preeclampsia, while ET-1 is upregulated in this condition. Since both relaxin and ET-1 upregulate prorenin, a unifying hypothesis might be that prorenin levels need to be in a specific range to allow optimal Ang II formation, with for instance too low levels resulting in insufficient AT₁ receptor stimulation (required for corpus luteum formation and decidualization), and too high levels leading to deleterious AT₂ receptor stimulation (inducing atresia).

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Abbreviations

ACE angiotensin-converting enzyme

Ang	angiotensin
AT ₁	Ang II type 1
AT ₂	Ang II type 2
cAMP	cyclic adenosine monophosphate
eNOS	endothelial NO synthase
ET-1	endothelin-1
FGR	fetal growth restriction
GFR	glomerular filtration rate
hCG	human chorionic gonadotropin
IVF	in-vitro fertilization
LH	luteinizing hormone
NO	nitric oxide
PKC	protein kinase C
PRA	plasma renin activity
RAAS	renin-angiotensin-aldosterone system
RNA	ribonucleic acid
TNF	tumor necrosis factor

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References

- Acker, G.M., Galen, F.X., Devaux, C., et al., 1982. Human chorionic cells in primary culture: a model for renin biosynthesis. *J. Clin. Endocrinol. Metab.* 55, 902–909.
- Akour, A.A., Kennedy, M.J., Gerk, P., 2013. Receptor-mediated endocytosis across human placenta: emphasis on megalin. *Mol. Pharm.* 10, 1269–1278.
- Al Kadi, H., Nasrat, H., Broughton Pipkin, F., 2005. A prospective, longitudinal study of the renin-angiotensin system, prostacyclin and thromboxane in the first trimester of normal human pregnancy: association with birthweight. *Hum. Reprod.* 20, 3157–3162.
- Alila, H.W., Hansel, W., 1984. Origin of different cell types in the bovine corpus luteum as characterized by specific monoclonal antibodies. *Biol. Reprod.* 31, 1015–1025.
- Anton, L., Merrill, D.C., Neves, L.A.A., et al., 2008. Activation of local chorionic villi angiotensin II levels but not angiotensin (1-7) in preeclampsia. *Hypertension (Dallas, Tex : 1979)* 51, 1066–1072.
- Arthur, I.D., Anthony, F.W., Adams, S., et al., 1996. Serum relaxin and the major endometrial secretory proteins in in-vitro fertilization and down-regulated hormone-supported and natural cycle frozen embryo transfer. *Hum. Reprod.* 11, 88–91.
- Assali, N.S., Dignam, W.J., Dasgupta, K., 1959. Renal function in human pregnancy. II. Effects of venous pooling on renal hemodynamics and water, electrolyte, and aldosterone excretion during gestation. *J. Lab. Clin. Med.* 54, 394–408.
- Baggia, S., Albrecht, E.D., Pepe, G.J., 1990. Regulation of 11 beta-hydroxysteroid dehydrogenase activity in the baboon placenta by estrogen. *Endocrinology* 126, 2742–2748.
- Balcarek, J., Sevá Pessôa, B., Bryson, C., et al., 2014. Multiple ascending dose study with the new renin inhibitor VTP-27999: nephrocentric consequences of too much renin inhibition. *Hypertension* 63, 942–950.
- Barker, D.J., 2007. The origins of the developmental origins theory. *J. Intern. Med.* 261, 412–417.
- Bartsch, E., Medcalf, K.E., Park, A.L., et al., 2016. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. *BMJ* 353, i1753.
- Batenburg, W.W., Lu, X., Leijten, F., et al., 2011. Renin- and prorenin-induced effects in rat vascular smooth muscle cells overexpressing the human (pro)renin receptor: does (pro)renin-(pro)renin receptor interaction actually occur? *Hypertension* 58, 1111–1119.
- Bohlender, J., Ganten, D., Luft, F.C., 2000. Rats transgenic for human renin and human angiotensinogen as a model for gestational hypertension. *J. Am. Soc. Nephrol.* 11, 2056–2061.
- Brar, H.S., Do, Y.-S., Tam, H.B., et al., 1986. Uteroplacental unit as a source of elevated circulating prorenin levels in normal pregnancy. *Am. J. Obstet. Gynecol.* 155, 1223–1226.
- Brar, H.S., Kjos, S.L., Dougherty, W., et al., 1987. Increased fetoplacental active renin production in pregnancy-induced hypertension. *Am. J. Obstet. Gynecol.* 157, 363–367.
- Brunswig-Spickenheier, B., Mukhopadhyay, A.K., 1993. Effects of tumor necrosis factor- α on luteinizing hormone-stimulated prorenin production by bovine ovarian thecal cells in vitro. *Endocrinology* 133, 2515–2522.
- Brunswig-Spickenheier, B., Mukhopadhyay, A.K., 2003. Local regulatory factors in regulation of ovarian function: role of prorenin-renin-angiotensin-system. *Indian J. Exp. Biol.* 41, 669–681.
- Bryer-Ash, M., Ammon, R.A., Luetscher, J.A., 1983. Increased inactive renin in diabetes mellitus without evidence of nephropathy. *J. Clin. Endocrinol. Metab.* 56, 557–561.
- Burton, G.J., Hempstock, J., Jauniaux, E., 2003. Oxygen, early embryonic metabolism and free radical-mediated embryopathies. *Reprod. Biomed. Online* 6, 84–96.
- Campbell, D.J., Nussberger, J., Stowasser, M., et al., 2009. Activity assays and immunoassays for plasma renin and prorenin: information provided and precautions necessary for accurate measurement. *Clin. Chem.* 55, 867–877.
- Capeless, E.L., Clapp, J.F., 1989. Cardiovascular changes in early phase of pregnancy. *Am. J. Obstet. Gynecol.* 161, 1449–1453.
- Chao, H.S., Poisner, A., Poisner, R., et al., 1993. Endothelins stimulate the synthesis and release of prorenin from human decidual cells. *J. Clin. Endocrinol. Metab.* 76, 615–619.
- Chao, H.S., Poisner, A.M., Poisner, R., et al., 1994. Endothelin-1 modulates renin and prolactin release from human decidua by different mechanisms. *Am. J. Physiol. Endocrinol. Metab.* 267, E842–E846.
- Chapman, A.B., Abraham, W.T., Zamudio, S., et al., 1998. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int.* 54, 2056–2063.
- Conrad, K.P., Davison, J.M., 2014. The renal circulation in normal pregnancy and preeclampsia: is there a place for relaxin? *Am. J. Physiol. Ren. Physiol.* 306, F1121–F1135.
- Conrad, K.P., Graham, G.M., Chi, Y.Y., et al., 2019a. Potential influence of the corpus luteum on circulating reproductive and volume regulatory hormones, angiogenic and immunoregulatory factors in pregnant women. *Am. J. Physiol. Endocrinol. Metab.* 317, E677–E685.
- Conrad, K.P., Petersen, J.W., Chi, Y.Y., et al., 2019b. Maternal cardiovascular dysregulation during early pregnancy after in vitro fertilization cycles in the absence of a corpus luteum. *Hypertension* 74, 705–715.
- Cornwallis, C.M., Skinner, S.L., Naydu, P.L., et al., 1990. Follicular fluid renin concentration and IVF outcome. *Hum. Reprod.* 5, 413–417.
- Danser, A.H., Batenburg, W.W., van den Meiracker, A.H., et al., 2007. ACE phenotyping as a first step toward personalized medicine for ACE inhibitors. Why does ACE genotyping not predict the therapeutic efficacy of ACE inhibition? *Pharmacol. Ther.* 113, 607–618.
- Danser, A.H., Derckx, F.H., Schalekamp, M.A., et al., 1998. Determinants of interindividual variation of renin and prorenin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. *J. Hypertens.* 16, 853–862.
- Danser, A.H., van Kesteren, C.A., Bax, W.A., et al., 1997. Prorenin, renin, angiotensinogen, and angiotensin-converting enzyme in normal and failing human hearts. Evidence for renin binding. *Circulation* 96, 220–226.
- Davis, J.S., Rueda, B.R., 2002. The corpus luteum: an ovarian structure with maternal instincts and suicidal tendencies. *Front. Biosci.* 7, d1949-78.
- De Alvarez, R.R., 1958. Renal glomerulotubular mechanisms during normal pregnancy. I. Glomerular filtration rate, renal plasma flow, and creatinine clearance. *Am. J. Obstet. Gynecol.* 75, 931–944.
- De Paco, C., Kametas, N., Rencoret, G., et al., 2008. Maternal cardiac output between 11 and 13 weeks of gestation in the prediction of preeclampsia and small for gestational age. *Obstet. Gynecol.* 111, 292–300.
- Derckx, F.H.M., Alberda, A.T., De Jong, F.H., 1987. Source of plasma prorenin in early and late pregnancy: observations in a patient with primary ovarian failure. *J. Clin. Endocrinol. Metab.* 65, 349–354.
- Devoto, L., Fuentes, A., Kohen, P., et al., 2009. The human corpus luteum: life cycle and function in natural cycles. *Fertil. Steril.* 92, 1067–1079.
- Do, Y.S., Sherrod, A., Lobo, R.A., et al., 1988. Human ovarian theca cells are a source of renin. *Proc. Natl. Acad. Sci. U.S.A.* 85, 1957–1961.
- Downing, G.J., Maulik, D., Poisner, A.M., 1996. Human chorionic gonadotropin stimulates placental prorenin secretion: evidence for autocrine/paracrine regulation. *J. Clin. Endocrinol. Metab.* 81, 1027–1030.
- Downing, G.J., Poisner, R., Poisner, A.M., 1994. Beta-adrenoceptor activation stimulates, and phosphodiesterase inhibition potentiates, placental prorenin synthesis and release. *J. Clin. Endocrinol. Metab.* 78, 41–47.
- Duncan, K.G., Haidar, M.A., Baxter, J.D., et al., 1990. Regulation of human renin expression in chorion cell primary cultures. *Proc. Natl. Acad. Sci. U.S.A.* 87, 7588–7592.
- Dunlop, W., 1981. Serial changes in renal haemodynamics during normal human pregnancy. *Br. J. Obstet. Gynaecol.* 88, 1–9.
- Duvekot, J.J., Cheriex, E.C., Pieters, F.A., et al., 1995. Maternal volume homeostasis in early pregnancy in relation to fetal growth restriction. *Obstet. Gynecol.* 85, 361–367.
- Ebisch, I.M., Thomas, C.M., Wetzels, A.M., et al., 2008. Review of the role of the plasminogen activator system and vascular endothelial growth factor in subfertility. *Fertil. Steril.* 90, 2340–2350.
- Fernandez, L.A., Twickler, J., Mead, A., 1985. Neovascularization produced by angiotensin II. *J. Lab. Clin. Med.* 105, 141–145.
- Franken, A.A., Derckx, F.H., Man in't Veld, A.J., et al., 1990. High plasma prorenin in diabetes mellitus and its correlation with some complications. *J. Clin. Endocrinol. Metab.* 71, 1008–1015.
- Franklin, G.O., Dowd, A.J., Caldwell, B.V., et al., 1974. The effect of angiotensin-II intravenous infusion on plasma renin activity and prostaglandins A, E, and F levels in the uterine vein of the pregnant monkey. *Prostaglandins* 6, 271–280.
- Gant, N.F., Worley, R.J., Everett, R.B., et al., 1980. Control of vascular responsiveness during human pregnancy. *Kidney Int.* 18, 253–258.

- Ginstrom Ernstad, E., Wennerholm, U.B., Khatibi, A., et al., 2019. Neonatal and maternal outcome after frozen embryo transfer: increased risks in programmed cycles. *Am. J. Obstet. Gynecol.* 221, 126 e121-126.e118.
- Glance, D.G., Elder, M.G., Myatt, L., 1985. Prostaglandin production and stimulation by angiotensin II in the isolated perfused human placental cotyledon. *Am. J. Obstet. Gynecol.* 151, 387–391.
- Glorioso, N., Atlas, S.A., Laragh, J.H., et al., 1986. Prorenin in high concentrations in human ovarian follicular fluid. *Science (New York, N Y)* 233, 1422–1424.
- Haase, N., Foster, D.J., Cunningham, M.W., et al., 2020. RNA interference therapeutics targeting angiotensinogen ameliorate preeclamptic phenotype in rodent models. *J. Clin. Invest.* 130, 2928–2942.
- Haning Jr., R.V., Canick, J.A., Goldsmith, L.T., et al., 1996. The effect of ovulation induction on the concentration of maternal serum relaxin in twin pregnancies. *Am. J. Obstet. Gynecol.* 174, 227–232.
- Hermenegildo, C., Oviedo, P.J., Garcia-Martinez, M.C., et al., 2005. Progesterone stimulates prostacyclin production by human endothelial cells. *Hum. Reprod.* 20, 1554–1561.
- Herse, F., Dechend, R., Harsem, N.K., et al., 2007. Dysregulation of the circulating and tissue-based renin-angiotensin system in preeclampsia. *Hypertension* 49, 604–611.
- Itskovitz, J., Rubattu, S., Levron, J., et al., 1992. Highest concentrations of prorenin and human chorionic gonadotropin in gestational sacs during early human pregnancy. *J. Clin. Endocrinol. Metab.* 75, 906–910.
- Itskovitz, J., Rubattu, S., Rosenwaks, Z., et al., 1991. Relationship of follicular fluid prorenin to oocyte maturation, steroid levels, and outcome of in vitro fertilization. *J. Clin. Endocrinol. Metab.* 72, 165–171.
- Itskovitz, J., Sealey, J.E., 1987. Ovarian prorenin-renin-angiotensin system. *Obstet. Gynecol. Surv.* 42, 545–551.
- Itskovitz, J., Sealey, J.E., Glorioso, N., et al., 1987. Plasma prorenin response to human chorionic gonadotropin in ovarian-hyperstimulated women: correlation with the number of ovarian follicles and steroid hormone concentrations. *Proc. Natl. Acad. Sci. U.S.A.* 84, 7285–7289.
- Jaiswal, N., Tallant, E.A., Diz, D.I., et al., 1991. Subtype 2 angiotensin receptors mediate prostaglandin synthesis in human astrocytes. *Hypertension* 17, 1115–1120.
- Jauniaux, E., Poston, L., Burton, G.J., 2006. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. *Hum. Reprod. Update* 12, 747–755.
- Jikihara, H., Poisner, A.M., Handwerker, S., 1995. Tumor necrosis factor- α and interleukin-1 β inhibit the synthesis and release of renin from human decidua cells. *J. Clin. Endocrinol. Metab.* 80, 195–199.
- Jikihara, H., Poisner, A.M., Handwerker, S., 1996. Interferon- γ inhibits the synthesis and release of renin from human decidua cells. *Biol. Reprod.* 54, 1311–1316.
- Kalenga, M.K., Thomas, K., de Gasparo, M., et al., 1996. Determination of renin, angiotensin converting enzyme and angiotensin II levels in human placenta, chorion and amnion from women with pregnancy induced hypertension. *Clin. Endocrinol.* 44, 429–433.
- Kampfer, C., Saller, S., Windschutt, S., et al., 2014. Pigment-Epithelium Derived Factor (PEDF) and the human ovary: a role in the generation of ROS in granulosa cells. *Life Sci.* 97, 129–136.
- Klett, C., Ganten, D., Hellmann, W., et al., 1992. Regulation of hepatic angiotensinogen synthesis and secretion by steroid hormones. *Endocrinology* 130, 3660–3668.
- Klotz, S., Burkhoff, D., Garrelds, I.M., et al., 2009. The impact of left ventricular assist device-induced left ventricular unloading on the myocardial renin-angiotensin-aldosterone system: therapeutic consequences? *Eur. Heart J.* 30, 805–812.
- Knock, G.A., Sullivan, M.H., McCarthy, A., et al., 1994. Angiotensin II (AT1) vascular binding sites in human placenta from normal-term, preeclamptic and growth retarded pregnancies. *J. Pharmacol. Exp. Therapeut.* 271, 1007–1015.
- Kotani, E., Sugimoto, M., Kamata, H., et al., 1999. Biological roles of angiotensin II via its type 2 receptor during rat follicle atresia. *Am. J. Physiol.* 276, E25–E33.
- Kristiansson, P., Svardsudd, K., von Schoutz, B., et al., 1996. Supraphysiological serum relaxin concentration during pregnancy achieved by in-vitro fertilization is strongly correlated to the number of growing follicles in the treatment cycle. *Hum. Reprod.* 11, 2036–2040.
- Kuhlback, B., Widholm, O., 1966. Plasma creatinine in normal pregnancy. *Scand. J. Clin. Lab. Invest.* 18, 654–656.
- Landau, R.L., Luginbuhl, K., 1958. Inhibition of the sodium-retaining influence of aldosterone by progesterone. *J. Clin. Endocrinol. Metab.* 18, 1237–1245.
- Lenz, T., James, G.D., Laragh, J.H., et al., 1991. Prorenin secretion from human placenta perfused in vitro. *Am. J. Physiol. Endocrinol. Metab.* 260, E876–E882.
- Lenz, T., Sealey, J.E., August, P., et al., 1989. Tissue levels of active and total renin, angiotensinogen, human chorionic gonadotropin, estradiol, and progesterone in human placentas from different methods of delivery. *J. Clin. Endocrinol. Metab.* 69, 31–37.
- Li, X., Shams, M., Zhu, J., et al., 1998. Cellular localization of AT1 receptor mRNA and protein in normal placenta and its reduced expression in intrauterine growth restriction. Angiotensin II stimulates the release of vasorelaxants. *J. Clin. Invest.* 101, 442–454.
- Lightman, A., Tarlatzis, B.C., Rzasca, P.J., 1987. The ovarian renin-angiotensin system: renin-like activity and angiotensin II/III immunoreactivity in gonadotropin-stimulated and unstimulated human follicular fluid. *Am. J. Obstet. Gynecol.* 156, 808–816.
- Lu, X., Meima, M.E., Nelson, J.K., et al., 2016. Identification of the (pro)renin receptor as a novel regulator of low-density lipoprotein metabolism. *Circ. Res.* 118, 222–229.
- Lumbers, E.R., Wang, Y., Delforce, S.J., et al., 2015. Decidualisation of human endometrial stromal cells is associated with increased expression and secretion of prorenin. *Reprod. Biol. Endocrinol.* 13.
- Magness, R.R., Rosenfeld, C.R., Faucher, D.J., et al., 1992. Uterine prostaglandin production in ovine pregnancy: effects of angiotensin II and indomethacin. *Am. J. Physiol.* 263, H188–H197.
- Mahendru, A.A., Everett, T.R., Wilkinson, I.B., et al., 2012. Maternal cardiovascular changes from pre-pregnancy to very early pregnancy. *J. Hypertens.* 30, 2168–2172.
- Martini, A.G., Krop, M., Saleh, L., et al., 2017. Do prorenin-synthesizing cells release active, open prorenin? *J. Hypertens.* 35, 330–337.
- McNatty, K.P., Smith, D.M., Makris, A., et al., 1979. The microenvironment of the human antral follicle: interrelationships among the steroid levels in antral fluid, the population of granulosa cells, and the status of the oocyte in vivo and in vitro. *J. Clin. Endocrinol. Metab.* 49, 851–860.
- Mishra, J.S., Te Riele, G.M., Qi, Q.R., et al., 2019. Estrogen receptor-beta mediates estradiol-induced pregnancy-specific uterine artery endothelial cell angiotensin type-2 receptor expression. *Hypertension* 74, 967–974.
- Morris, R.S., Paulson, R.J., 1993. The ovarian renin angiotensin system: recent advances and their relationship to assisted reproductive technologies. *Assist. Reprod. Rev.* 3, 88–94.
- Mushayandebvu, T.I., Goldsmith, L.T., Von Hagen, S., et al., 1998. Elevated maternal serum relaxin concentrations throughout pregnancy in singleton gestations after superovulation. *Obstet. Gynecol.* 92, 17–20.
- Naftolin, F., Andrade-Gordon, P., Pellicer, A., et al., 1989. Angiotensin II: does it have a direct obligate role in ovulation? *Science* 245, 870–871.
- Nakamura, T., Matsui, K., Ito, M., et al., 1988. Effects of pregnancy and hormone treatments on pressor response to angiotensin II in conscious rats. *Am. J. Obstet. Gynecol.* 159, 989–995.
- Nguyen, G., Delarue, F., Burcklé, C., et al., 2002. Pivotal role of the renin/prorenin receptor in angiotensin II production and cellular responses to renin. *J. Clin. Invest.* 109, 1417–1427.
- Nice, M., 1935. Kidney Function during Normal Pregnancy I. The increased urea clearance of normal pregnancy. *J. Clin. Invest.* 14, 575–578.
- Nicholson, E.C., Gallery, E.D.M., Brown, M.A., et al., 1987. Renin activation in normal and hypertensive human pregnancy. *Pregnancy Hypertens.* 6, 453–464.
- Paulson, R.J., Do, Y.S., Hsueh, W.A., et al., 1989. Ovarian renin production in vitro and in vivo: characterization and clinical correlation. *Fertil. Steril.* 51, 634–638.
- Pellicer, A., Palumbo, A., DeCherney, A.H., et al., 1988. Blockage of ovulation by an angiotensin antagonist. *Science* 240, 1660–1661.
- Peterson, C.M., Zhu, C., Mukaida, T., et al., 1993. The angiotensin II antagonist saralasin inhibits ovulation in the perfused rat ovary. *Am. J. Obstet. Gynecol.* 168, 242–245.
- Pinet, F., Corvol, M.-T., Bourguignon, J., et al., 1988. Isolation and characterization of renin-producing human chorionic cells in culture. *J. Clin. Endocrinol. Metab.* 67, 1211–1220.
- Poisner, A.M., 1995. Regulation of utero-placental prorenin. *Adv. Exp. Med. Biol.* 377, 411–426.
- Poisner, A.M., Downing, G.J., Poisner, R., 1994. Prorenin secretion from villous placenta: regulation by cyclic AMP and angiotensin. *Placenta* 15, 487–499.
- Poisner, A.M., Thraikill, K., Poisner, R., et al., 1990. Relaxin stimulates the synthesis and release of prorenin from human decidua cells: evidence for autocrine/paracrine regulation. *J. Clin. Endocrinol. Metab.* 70, 1765–1767.
- Poisner, A.M., Thraikill, K., Poisner, R., et al., 1991. Cyclic AMP as a second messenger for prorenin release from human decidua cells. *Placenta* 12, 263–267.
- Poranen, A.-K., Aalto, M., Matinlauri, I., et al., 2009. Total renin in preeclamptic placenta. *Hypertens. Pregnancy* 15, 347–352.
- Post Uiterweer, E.D., Koster, M.P.H., Jeyabalan, A., et al., 2020. Circulating pregnancy hormone relaxin as a first trimester biomarker for preeclampsia. *Pregnancy Hypertens.* 22, 47–53.
- Pringle, K.G., Conquest, A., Mitchell, C., et al., 2015. Effects of fetal sex on expression of the (pro)renin receptor and genes influenced by its interaction with prorenin in human amnion. *Reprod. Sci.* 22, 750–757.
- Pringle, K.G., Tadros, M.A., Callister, R.J., et al., 2011. The expression and localization of the human placental prorenin/renin-angiotensin system throughout pregnancy: roles in trophoblast invasion and angiogenesis? *Placenta* 32, 956–962.
- Qi, R., Li, T.C., Chen, X., 2020. The role of the renin-angiotensin system in regulating endometrial neovascularization during the peri-implantation period: literature review and preliminary data. *Ther. Adv. Endocrinol. Metabol.* 11, 2042018820920560.
- Ren, L., Sun, Y., Lu, H., et al., 2018. (Pro)renin receptor inhibition reprograms hepatic lipid metabolism and protects mice from diet-induced obesity and hepatosteatosis. *Circ. Res.* 122, 730–741.
- Ringholm, L., Pedersen-Bjergaard, U., Thorsteinsson, B., et al., 2011. A high concentration of prorenin in early pregnancy is associated with development of preeclampsia in women with type 1 diabetes. *Diabetologia* 54, 1615–1619.
- Robb, A.O., Mills, N.L., Din, J.N., et al., 2009. Influence of the menstrual cycle, pregnancy, and preeclampsia on arterial stiffness. *Hypertension* 53, 952–958.
- Roberts, M., Lindheimer, M.D., Davison, J.M., 1996. Altered glomerular permeability to neutral dextrans and heteroporous membrane modeling in human pregnancy. *Am. J. Physiol.* 270, F338–F343.
- Robson, S.C., Hunter, S., Boys, R.J., et al., 1989. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am. J. Physiol.* 256, H1060–H1065.
- Rowan, K., Meagher, S., Teoh, M., et al., 2008. Corpus luteum across the first trimester: size and laterality as observed by ultrasound. *Fertil. Steril.* 90, 1844–1847.
- Salas, S.P., Marshall, G., Gutierrez, B.L., et al., 2006. Time course of maternal plasma volume and hormonal changes in women with preeclampsia or fetal growth restriction. *Hypertension* 47, 203–208.

- Salas, S.P., Rosso, P., 1998. Plasma volume, renal function, and hormonal levels in pregnant women with idiopathic fetal growth restriction or preeclampsia. *Hypertens. Pregnancy* 17, 69–79.
- Schalekamp, M.A., Derkx, F.H., Deinum, J., et al., 2008. Newly developed renin and prorenin assays and the clinical evaluation of renin inhibitors. *J. Hypertens.* 26, 928–937.
- Schalekamp, M.A.D.H., Danser, A.H.J., 2013. How does the angiotensin II type 1 receptor 'trump' the type 2 receptor in blood pressure control? *J. Hypertens.* 31, 705–712.
- Schuchter, K., Metzenbauer, M., Hafner, E., et al., 2001. Uterine artery Doppler and placental volume in the first trimester in the prediction of pregnancy complications. *Ultrasound Obstet. Gynecol.* 18, 590–592.
- Sealey, J.E., Catanzaro, D.F., Lavin, T.N., et al., 1996. Specific prorenin/renin binding (ProBP) identification and characterization of a novel membrane site. *Am. J. Hypertens.* 9, 491–502.
- Sealey, J.E., McCord, D., Taufield, P.A., et al., 1985. Plasma prorenin in first-trimester pregnancy: relationship to changes in human chorionic gonadotropin. *Am. J. Obstet. Gynecol.* 153, 514–519.
- Sealey, J.E., von Lutterotti, N., Rubattu, S., et al., 1991. The greater renin system. Its prorenin-directed vasodilator limb. Relevance to diabetes mellitus, pregnancy, and hypertension. *Am. J. Hypertens.* 4, 972–977.
- Seibel, M.M., Smith, D., Dlugi, A.M., et al., 1989. Periovalvular follicular fluid hormone levels in spontaneous human cycles. *J. Clin. Endocrinol. Metab.* 68, 1073–1077.
- Shah, D.M., Higuchi, K., Inagami, T., et al., 1991. Effect of progesterone on renin secretion in endometrial stromal, chorionic trophoblast, and mesenchymal monolayer cultures. *Am. J. Obstet. Gynecol.* 164, 1145–1150.
- Shaw, K.J., Do, Y.S., Kjos, S., et al., 1989. Human decidua is a major source of renin. *J. Clin. Invest.* 83, 2085–2092.
- Simoncini, T., Fu, X.D., Caruso, A., et al., 2007. Drospirenone increases endothelial nitric oxide synthesis via a combined action on progesterone and mineralocorticoid receptors. *Hum. Reprod.* 22, 2325–2334.
- Sims, E.A., Krantz, K.E., 1958. Serial studies of renal function during pregnancy and the puerperium in normal women. *J. Clin. Invest.* 37, 1764–1774.
- Singh, H.J., Rahman, A., Larmie, E.T., et al., 2004. Raised prorenin and renin concentrations in pre-eclamptic placentae when measured after acid activation. *Placenta* 25, 631–636.
- South, A.M., Shaltout, H.A., Washburn, L.K., et al., 2019. Fetal programming and the angiotensin-(1-7) axis: a review of the experimental and clinical data. *Clin. Sci. (Lond.)* 133, 55–74.
- Spaanderman, M., Ekhart, T., Van Eyck, J., et al., 2001. Preeclampsia and maladaptation to pregnancy: a role for atrial natriuretic peptide? *Kidney Int.* 60, 1397–1406.
- Steegers-Theunissen, R.P., Twigt, J., Pestinger, V., et al., 2013. The periconceptional period, reproduction and long-term health of offspring: the importance of one-carbon metabolism. *Hum. Reprod. Update* 19, 640–655.
- Stirling, D., Magness, R.R., Stone, R., et al., 1990. Angiotensin II inhibits luteinizing hormone-stimulated cholesterol side chain cleavage expression and stimulates basic fibroblast growth factor expression in bovine luteal cells in primary culture. *J. Biol. Chem.* 265, 5–8.
- Sun, Y., Goes Martini, A., Janssen, M.J., et al., 2020. Megalin: a novel endocytic receptor for prorenin and renin. *Hypertension* 75, 1242–1250.
- Takimoto, E., Ishida, J., Sugiyama, F., et al., 1996. Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. *Science* 274, 995–998.
- Uijl, E., Mirabito Colafella, K.M., Sun, Y., et al., 2019. Strong and sustained antihypertensive effect of small interfering RNA targeting liver angiotensinogen. *Hypertension* 73, 1249–1257.
- Vasapollo, B., Valensise, H., Novelli, G.P., et al., 2004. Abnormal maternal cardiac function precedes the clinical manifestation of fetal growth restriction. *Ultrasound Obstet. Gynecol.* 24, 23–29.
- Verdonk, K., Saleh, L., Lankhorst, S., et al., 2015. Association studies suggest a key role for endothelin-1 in the pathogenesis of preeclampsia and the accompanying renin-angiotensin-aldosterone system suppression. *Hypertension* 65, 1316–1323.
- Verdonk, K., Visser, W., Van Den Meiracker, A.H., et al., 2014. The renin-angiotensin-aldosterone system in pre-eclampsia: the delicate balance between good and bad. *Clin. Sci. (Lond.)* 126, 537–544.
- von Versen-Höyneck, F., Schaub, A.M., Chi, Y.Y., et al., 2019. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. *Hypertension* 73, 640–649.
- Wang, Y., Pringle, K.G., Lumbers, E.R., 2013. The effects of cyclic AMP, sex steroids and global hypomethylation on the expression of genes controlling the activity of the renin-angiotensin system in placental cell lines. *Placenta* 34, 275–280.
- Weiss, G., Goldsmith, L.T., Sachdev, R., et al., 1993. Elevated first-trimester serum relaxin concentrations in pregnant women following ovarian stimulation predict prematurity risk and preterm delivery. *Obstet. Gynecol.* 82, 821–828.
- Weiss, G., Rifkin, I., 1975. Progesterone and estrogen secretion by puerperal human ovaries. *Obstet. Gynecol.* 46, 557–559.
- Wiegel, R.E., Jan Danser, A.H., Steegers-Theunissen, R.P.M., et al., 2020. Determinants of maternal renin-angiotensin-aldosterone-system activation in early pregnancy: insights from 2 cohorts. *J. Clin. Endocrinol. Metab.* 105, 3505–3517.
- Wier, R.J., Brown, J.J., Fraser, R., et al., 1975. Relationship between plasma renin, renin-substrate, angiotensin II, aldosterone and electrolytes in normal pregnancy. *J. Clin. Endocrinol. Metab.* 40, 108–115.
- Yoshimura, Y., 1997. The ovarian renin-angiotensin system in reproductive physiology. *Front. Neuroendocrinol.* 18, 247–291.
- Yoshimura, Y., Karube, M., Aoki, H., et al., 1996. Angiotensin II induces ovulation and oocyte maturation in rabbit ovaries via the AT2 receptor subtype. *Endocrinology* 137, 1204–1211.
- Yoshimura, Y., Karube, M., Koyama, N., et al., 1992. Angiotensin II directly induces follicle rupture and oocyte maturation in the rabbit. *FEBS Lett.* 307, 305–308.