Chapter 6

Role of the Renin-Angiotensin System in Healthy and Pathological Pregnancies

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http://dx.doi.org/10.5772/66748

Abstract

Introduction: Pregnancy is a physiological process that necessitates many cardiovascular and hemodynamic adaptations to ensure the survival of the foetus and well-being of the mother. The renin-angiotensin system (RAS) has been suggested as key player in many of these changes as it is critical for blood pressure control as well as fluid and salt homeostasis in the non-pregnant state.

Body: Normal pregnancy is characterized by an increase in the circulating levels of prorenin, renin, angiotensinogen and angiotensin-II. However, this is coupled to a diminished endothelial sensitivity to angiotensin-II, which may explain the lack of increase in blood pressure in pregnancy. Conversely, an increase in circulating levels of aldosterone and anti-diuretic hormone during pregnancy can be observed and could contribute to the enhanced renal sodium and water reabsorption, respectively. Moreover, dysregulation of the RAS has been implicated in the development of gestational hypertensive disorders such as preeclampsia.

Conclusion: The difference in the RAS effects observed during normal pregnancy may be attributable to local modifications of the RAS as well as to non-classic RAS such as the angiotensin-(1-7) axis. These adaptations may be dysregulated during preeclampsia and may contribute to the development of the disease.

Keywords: gestation, reproductive system, cardiovascular adaptations to gestation, preeclampsia, exercise training

1. Menstrual cycle, implantation and pregnancy

The female reproductive system includes the ovaries, fallopian tubes, uterus, cervix and vagina. It is involved in the production and transportation of gametes, the production of sex hormones and development of embryo. The oviducts extend from the uterus to the ovaries. The egg bursts from the ovary and moves through the oviduct towards the uterus. In humans, an egg lives approximately 6–24 hours, unless fertilization occurs, which results in zygote formation. A developing embryo normally reaches the uterus after several days, and then implantation occurs. During implantation, the embryo embeds in the uterine lining, which has been prepared to receive it. The lining of the uterus, called the endometrium, participates in the formation of the placenta, which has a main role in supplying nutrients needed for embryonic and foetal development [1]. At menarche (first menstrual period), females undergo monthly reproductive cycles regulated by the hypothalamus, pituitary gland and ovaries. This so-called menstrual cycle prepares the reproductive system for pregnancy. As shown in **Figure 1**, each menstrual cycle is composed of an ovarian and an uterine cycle based on processes taking place in the ovary and uterus, respectively [1, 2].

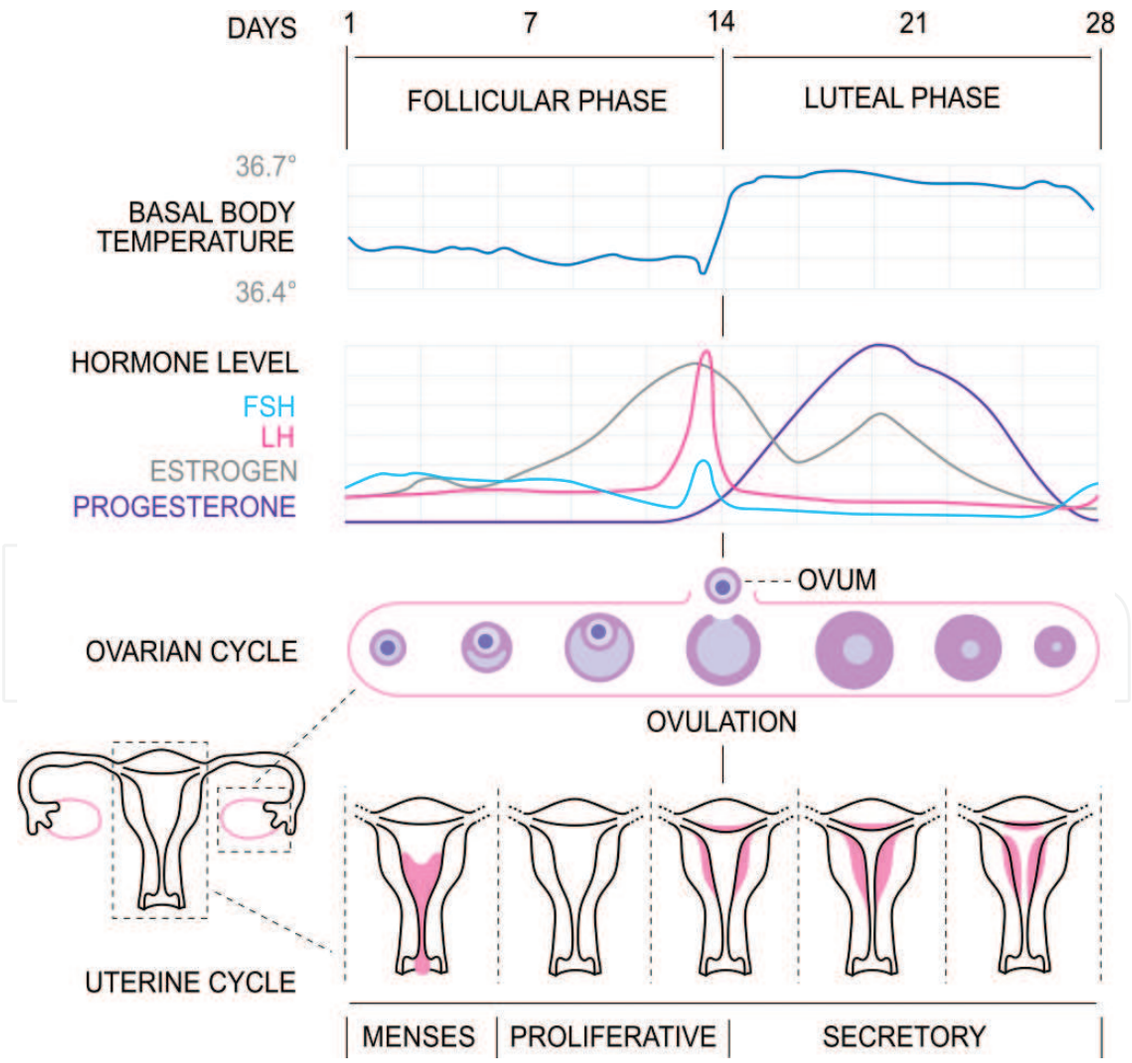

Figure 1. Human ovarian and menstrual cycles. Diagram of the menstrual cycle (based on several different sources) by Isometrik through Wikimedia Commons licensed under CC BY-SA 3.0.

http://dx.doi.org/10.5772/66748

The ovarian cycle begins with the menstrual phase from day 1 and lasts, on average, for 5 days. The menstrual phase is followed by the follicular phase, which ends at ovulation at approximately day 14. The third phase is called the luteal phase which lasts from day 14 to 28 and ends with the beginning of menstruations and the start of a new cycle (**Figure 1**) [3]. During the ovarian cycle, there are two hormones released from the anterior pituitary by the stimulatory action of the gonadotropin-releasing hormone (GnRH): the follicle-stimulating hormone (FSH), which stimulates the development of ovarian follicles and production of estrogen by the follicular cells, and the luteinizing hormone (LH), which serves as the trigger for ovulation and stimulates the follicular cells and corpus luteum to produce progesterone [2]. The cyclic changes in the ovaries with hormonal stimulation of FSH and LH allow follicle maturation and oogenesis, and lead to the release of the secondary oocyte into the oviduct during a process called ovulation (**Figure 1**) [1].

Estrogen and progesterone produced by the ovarian follicles and corpus luteum during the ovarian cycle cause cyclic changes in the endometrium of the uterus, also known as the uterine cycle. Both ovarian and uterine cycles last on average 28 days. Menstruation, characterized by the endometrium's breaking down, is the first phase of the uterine cycle and lasts from day 1 to day 5. It also spans part of the follicular phase of the ovarian cycle. Menstruation is followed by the proliferative phase, characterized by estrogen secretion from the primary follicles and lasts for almost 9 days. This phase, which coincides with the growth of the ovarian follicles in the ovarian cycle, leads to increasing thickness of the endometrium. At the very end of the proliferative phase on day 14, the ovulation occurs. After that, the uterine secretory phase begins. This phase lasts for 13 days and coincides with the formation, function and growth of the corpus luteum in the ovarian cycle [1, 2]. During days 15–28, increased production of progesterone by the corpus luteum in the ovary causes the endometrium of the uterus to double or triple in thickness [1]. This phenomenon prepares the endometrium for receiving the developing embryo in the short period of receptivity known as the window of implantation [4]. If fertilization does not occur, the corpus luteum degenerates and the concomitant decrease in progesterone level causes timely destruction of the fully developed endometrium, leading to menstruation. However, if fertilization occurs, the zygote cleavage (increase in cell number without increase in mass) takes place. Following blastocyst formation, the embryo implantation occurs, typically on the sixth day of the luteal phase. This leads to the secretion of the human chorionic gonadotropin (hCG) by the syncytiotrophoblasts of the developing placenta, which acts on the ovaries to maintain the secretion of estrogen and progesterone and prevent the degradation of the corpus luteum. As a result, the luteal phase is prolonged, which prevents the start of the menstrual cycle, and the endometrium continues to grow and undergoes further morphological and molecular changes to provide sufficient support for the growing embryo during the pregnancy [2].

Although it was once thought to be a systemic entity, the presence of local tissue-specific renin-angiotensin systems (RASs) has been recently demonstrated. Indeed, different tissues have been found to express all the functional components of the RAS [5, 6]. The reproductive system and placental RAS play a key role in ovulation, implantation, placentation and development of the uteroplacental and umbilicoplacental circulations [7]. Additionally, this local RAS contributes to the activity of circulating maternal renin-angiotensin-aldosterone system (RAAS), and as such, influences maternal cardiovascular and renal function [8]. Moreover,

the reproductive system RAS has been shown to be implicated in different aspects of reproduction, from fertility to embryo implantation and later through pregnancy [9, 10]. Important modulations of the RAS are observed from the very beginning of pregnancy and aberrant changes in RAS component expression can cause gestational problems such as preeclampsia [11–13]. The implication of the RAS in both normal and pathological pregnancy will be discussed in this book chapter.

2. RAS in the reproductive system

2.1. RAS and ovary and follicular development

Prorenin is produced by the ovarian follicular cells at different stages in oocyte maturation. As the ovarian follicle undergoes maturation, the prorenin concentration increases and remains elevated until the end of the luteal phase, near the start of menstruation, where it falls in parallel with progesterone levels [14]. Prorenin secretion in the ovary is regulated by gonadotropins, and thus, the rise in plasma-luteinizing hormone (LH) levels shortly precedes the elevation of plasma prorenin, secreted into circulation mainly by the ovary [15, 16]. Of note, concentrations of prorenin, the inactive precursor of renin, are typically higher in the reproductive system than those of renin and it was originally postulated that it was locally activated by an unknown process. As such, studies demonstrating the expression of cathepsin B, a potential activator of prorenin, in the maturating oocyte suggest that the increase in prorenin expression in the ovary can contribute to the rise in renin levels in the follicular fluid. Moreover, prorenin can activate the prorenin/renin receptor ((P)RR) and thus become active as well as stimulate Ang-II-independent pathways, which are associated to this receptor [17]. For instance, binding of prorenin to the (P)RR can promote cell growth and oocyte maturation [18]. More specifically, the (P)RR has recently been suggested to induce resumption of meiosis in oocytes [19].

Similarly to prorenin, local ovarian renin activity has been shown to be increased following the LH surge in rats, rabbits and human [20–22]. Moreover, increased renin mRNA expression has been measured in rat and primate following follicle-stimulating hormone (FSH), estradiol or human chorionic gonadotropin (hCG) stimulation [23], suggesting that prorenin could be activated locally in the ovary and could contribute to the stimulation of the local RAS [15].

The ovarian expression of angiotensinogen (Agt) has been studied in rats and humans and has been shown to vary between species. In rat, Agt expression is found in ovaries, more specifically during the mid- and late-maturation of follicles (not during maturation of early-primary or primary follicles) [24]. The timing of Agt expression in maturing follicles matches the expression of gonadotropins. As such, given that Agt expression has been shown to be stimulated by estradiol in rat liver, it has been suggested that Agt expression in maturating follicles could be driven by gonadotropin-stimulated-estradiol local production. In humans, Agt has been measured in the follicular fluid and its levels are comparable or lower to circulating Agt [7]. However, there is no evidence of local ovarian Agt mRNA expression, suggesting that local ovarian Agt protein levels are derived from the circulation [15].

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In contrast to the other RAS components mentioned above, the angiotensin-converting enzyme (ACE) expression in the ovary does not follow gonadotropin-stimulated cyclic expression pattern during the oestrous cycle since high ACE levels are found in the early stages of follicle maturation and in atretic follicles with very low levels in preovulatory follicles. This suggests that ACE has a role in early maturation of the follicles as well as their atresia [15].

Angiotensin II (Ang II) has been found to be produced and secreted by rabbit and rat ovaries in response to hCG elevation [21]. Since renin activity is stimulated by gonadotropins during preovulation, this increased renin activity probably drives the production of local Ang II. Similar observations have been made in women with natural or gonadotropin-stimulated cycles [25].

Ang II mediates its actions in the ovary through both AT1R and AT2R. However, each receptor has different functions within the reproductive system. Indeed, AT1R has been reported to be mainly involved in the maintenance of ovarian vasculature which supplies nutrients to the developing follicles [26], whereas AT2R would be implicated in both the follicular development as well as in the regression of the luteal vasculature towards the end of the ovarian cycle. However, the timing of AT2R expression during oocyte maturation is uncertain and varies between species. Indeed, a study using autoradiography and gene expression measurements reported the expression of AT2R in granulosa cells of rat atretic follicles while it is almost absent in healthy follicles [27]. In contrast, studies in bovine ovaries demonstrate that AT2R expression is increased during follicular growth and maturation [15]. As such, it is very difficult to conclude on a clear role of the ATRs in the ovary. In addition, the signalling pathways involved in AT2R modulation of follicular growth and maturation have not yet been studied. However, neuronal studies of AT2R signalling demonstrate that the MAPK pathway and activation of nitric oxide promotes cell differentiation and could be putative pathways involved in follicular maturation in the ovary [28]. On the other hand, studies in rabbits have shown that ovarian RAS activation leads to estradiol production through AT2R stimulation. Based on the fact that gonadotropins stimulate the expression of many components of the RAS cascade, an intra-ovarian paracrine or autocrine loop would exist between Ang II and estradiol [15]. However, the mechanisms responsible for the control of the autocrine loop are not well understood and more data are needed to confirm its activity in other species such as rodents and humans.

2.2. RAS during ovulation

The process of ovulation depends on different signalling cascades involving cAMP release, steroids, prostaglandins and other chemical mediators [29, 30]. Several *in vitro* and *in vivo* studies have demonstrated that the RAS, especially through AT2R stimulation, has a role to play in ovulation. In particular, studies using *in vitro* perfused ovaries have demonstrated a dose-dependent effect of Ang II on estradiol and prostaglandin secretion, correlating with the initiation of ovulation [31]. Therefore, the use of ACE inhibitors (which would lead to a decrease in Ang II production) for the treatment of hypertension in women who want to become pregnant may not be recommended. Of note, insulin-like growth factor 1 (IGF-1), through the activation of the plasminogen activator (PA), has been proposed to increase Ang

II production, leading to the production of prostaglandins necessary for the rupture of the follicular wall and ovulation [32]. Hence, this could be a mechanism by which the IGF-1 produces its important effects on ovarian physiology and follicle development [33].

Studies on human follicular fluid samples collected from *in vitro* fertilization samples suggest that RAS activity correlates with follicular development. In particular, prorenin activity in follicular fluid is associated with the development, maturity and viability of the oocytes [18]. Indeed, low levels of follicular prorenin are associated with immature follicles while high prorenin levels are correlated with atretic follicles, the latter being characterized by high levels of testosterone and low levels of estradiol. Intermediate levels of prorenin would therefore be necessary for normal ovulation to proceed. Interestingly, in our recently characterized model of preeclampsia superimposed on chronic hypertension, mice that overexpress both human renin and angiotensinogen (R^+A^+), we observed that these mice have reduced litter size [34]. Given that this is not associated with increased foetal or neonatal mortality, this suggests that hypertension or the overexpression of the RAS in the reproductive system may decrease fertility by modulating ovulation or embryo implantation.

2.3. Corpus luteum

Following ovulation, the remaining follicular cells undergo rapid remodelling and capillary invasion. Studies have shown that microvascular endothelial (MVE) cells in the corpus luteum express ACE and can convert Ang I to Ang II [26]. Both AT1R and AT2R have been detected in MVE cells with different levels of expression throughout the ovarian cycle: AT1R expression levels seem unchanged, whereas AT2R expression is lowest during the mid-luteal phase and highest during the late luteal phase [26]. The regulation of angiogenic processes is a crucial step to ensure the constant flow of growth, maturation and demise of the corpus luteum. This angiogenic step requires the secretion of angiogenic factors such as the basic fibroblast growth factor (bFGF). Ang II would be one of the drivers of this rapid capillary invasion through AT1R-dependent stimulation of bFGF expression. Hence, in luteal cells, the surge in LH that precedes ovulation would lead to increased Ang II production and enhanced AT1R stimulation which would drive the expression of bFGF. This would then promote angiogenesis and appropriate maintenance of the corpus luteum [35]. In contrast, the regression of the luteal vasculature would be attributed to the Ang II-AT2R axis of the RAS [36].

2.4. Atresia

At the beginning of each ovarian cycle, several primordial (immature) follicles undergo maturation. Due to the inefficient nature of folliculogenesis, most of those primordial follicles will not reach the final stage of maturation, and in humans, only one follicle will undergo ovulation. The remaining follicles degenerate through a process known as atresia. Atretic follicles are characterized by abnormally high prorenin levels associated with a low estradiol/progesterone ratio [37]. These follicles have a thin layer of degenerated granulosa cells and the remaining active theca cells secrete prorenin [38]. In atretic granulosa cells, the Ang II receptor isoform that is most expressed is AT2R, which has been shown to drive apoptosis

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[27]. In follicles, FSH acts as a mild repressor of AT2R expression, so apoptosis cannot be triggered during the maturation phase of follicular development. However, in the luteal phase, FSH levels are reduced which relieves the inhibition on AT2R expression. As such, given the high Ang II level, AT2 stimulation increases granulosa cells apoptosis, promoting the atresia of immature follicles.

2.5. RAS and the placenta

The placenta is an organ that provides nutrients and oxygen to the developing foetus and removes toxic waste products from the foetal circulation [39]. The formation of the placenta starts with the implantation of the embryo (at this developmental stage, the blastocyst) in the endometrium (known as the decidua during pregnancy). The blastocyst is composed of an inner cell mass (which will give rise to the foetus and the amniotic cavity) and the trophoblastic cells (a 'sticky' layer of cells forming the outer layer of the blastocyst). Implantation is initiated when the trophoblastic cells adhere to the surface of the decidua. This stimulates the proliferation of the trophoblastic cells, which divide into two cell types: the syncytial trophoblasts and cellular trophoblasts (also known as the chorion). The syncytial trophoblastic cells are multinucleated cells which are highly invasive. They secrete proteolytic enzymes that are responsible for the destruction of the decidua which creates cavities (known as endometrial lacunae). Simultaneously, the proliferating trophoblastic cells form protrusions, known as the chorionic villi, which become highly branched as well as vascularised by ramifications of the umbilical vein and artery. The endometrial lacunae will then be invaded by the branching chorionic villi, allowing the blastocyst to penetrate into the decidua and establishing the interface between the maternal and foetal blood where nutrients, blood gas and wastes will be exchanged. By the end of the first trimester, the uteroplacental circulation is fully established [40]. Maintaining optimal placental blood osmotic pressure and flow is crucial for the production of a viable offspring. Placental RAS is a key player in the regulation of maternal-foetal blood flow during pregnancy [41]. Since many components of the RAS have been shown to be expressed in whole human placental extracts, human placental cell lines (human umbilical venous endothelial cells (HUVEC)), and in isolated primary placental cell fractions (primary trophoblastic cells fraction, primary macrophage-rich fraction and primary villous endothelial cells) [42–44], the RAS is believed to have a considerable influence in this organ [11, 45–48]. However, functional data of the placental RAS are very rare. RAS proteins have different level of expression in various areas of the placenta. Agt, renin, Ang I, Ang II, ACE, AT1R, and AT2R have been localized to the human and rat maternal decidua [49, 50], whereas Ang II and ACE have also been found in pericytes of endometrial spiral arteries. RAS components such as Agt and renin have also been detected in foetal capillaries [51] and AT1R has been found in cytotrophoblastic and syncytiotrophoblastic cells as well as in foetal capillaries. Many studies have suggested the implication of the placental RAS in promoting trophoblastic cell migration, proliferation of the foetal vascular endothelium and vasodilation of the maternal vasculature [52, 53]. Hence, changes in placental RAS potentially contribute to alterations in uteroplacental perfusion, which are associated with gestational complications such as preeclampsia [54].

2.6. RAS and the uterus/endometrium

Most components of the RAS can be found in both myometrium and endometrium of the uterus. However, the role of the RAS in the non-pregnant uterus is still unknown [55]. Elevated expression and secretion of prorenin in stromal cells have been associated with decidualisation of the endometrium in early to mid-proliferative phase [56]. Activation of the (P)RR by prorenin has been shown to promote vascular endothelial growth factor (VEGF) expression and could thus increase vascularity of the decidua to ensure an adequate blood flow to the placenta [56]. In addition, Ang II as well as AT1R and AT2R show a cyclical pattern of expression depending on the phase of the uterine cycle. First, AT2R is expressed at higher levels compared to AT1R, although both receptors show a similar expression pattern. Their expression gradually increases during the proliferative phase, reaching a maximum in late proliferative and early secretory phases, followed by a gradual decrease in expression through the rest of the secretory phase [57]. In comparison, plasma Ang II levels gradually increase through the menstrual cycle, reaching a peak in the late secretory phase [58]. Moreover, in the early to mid-proliferative phase, endometrial Ang II levels and ATRs expression are mostly localized to the glandular and stromal cells of the endometrium, which could highlight a role for the RAS in modulating decidualisation and neovascularisation of the endometrium. Alternatively, in late secretory phase, they are localized mostly around blood vessels, where Ang II could contribute to the vasoconstriction of spiral arterioles which is necessary for the induction of menstruation [57]. In addition, angiotensin-(1-7) (Ang-(1-7), a heptapeptide generated from Ang II cleavage by the enzyme ACE 2) and its receptor MAS (MAS-R) have been shown to be expressed in the endometrium. While MAS-R expression is localized to the epithelial and stromal cells and does not change throughout the menstrual cycle, Ang-(1-7) concentrations are highest in the glandular epithelium and in the stroma of the endometrium in mid- to late-secretory phase [59]. Although the function of the Ang-(1-7)—Mas-R axis is not well understood in the endometrium, by its vasodilatory, antiangiogenic and antimitotic properties, Ang-(1-7) could counterbalance Ang II actions and, possibly regulate endometrial regenerating processes according to homeostatic needs.

3. Pregnancy and RAS

Pregnancy is characterized by an elevation in the levels of maternal circulating estrogen. Consequently, maternal circulating prorenin and renin are also increased during pregnancy. Prorenin reaches a peak within 20 days after conception and remains high until parturition while plasma-renin activity rises during the first few weeks of pregnancy [60]. ACE is the only RAS component that decreases during pregnancy [61] while plasma Agt and Ang II levels are particularly elevated during the last trimester of normal gestation [62]. The elevated Ang II levels could be attributed in part to the stimulatory effect of estrogen on Agt expression but also to the elevated renin levels [63]. In addition, increased urinary and plasma aldosterone levels are observed during pregnancy which produces the increased plasma volume required for the growing placenta and foetus [64].

The increase in RAS in pregnant women should normally be associated with an increase in blood pressure. However, elevated blood pressure in not typically observed during normal

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pregnancy. On the contrary, due to the vasodilating effect of progesterone, a decrease in blood pressure is typically seen in the first and second trimesters, returning to baseline by delivery [65]. Indeed, although Ang II levels are increased during pregnancy, normotensive pregnant women are actually refractory to its vasopressor effects. Studies have reported a twofold increase in plasma Ang II levels concomitantly with a twofold decrease in the sensitivity to Ang II vasoconstrictive effects [66, 67]. Moreover, studies in pregnant women and animals have demonstrated that the elevation of plasma Ang-(1-7) would contribute to the reduction in blood pressure during pregnancy by counterbalancing the vasoconstrictor actions of elevated Ang II [68–70]. It was also demonstrated in rats, that arteries were more responsive to the vasodilatory effects of Ang-(1-7) during pregnancy [71]. The capacity of Ang-(1-7) to stimulate the release of the vasodilatory molecules prostaglandins would potentiate its own vasodilatory actions and would oppose Ang II effects [72]. A balance of the two biologically active peptides of the RAS, Ang II, a vasoconstrictor and angiogenic molecule, and Ang-(1-7), a vasodilator and anti-angiogenic molecule, may therefore be essential for the maintenance of normal pregnancy [11, 73].

Trophoblasts are rich in AT1Rs and are thus responsive to the changes in Ang II concentrations that occur during pregnancy [74]. Recent studies demonstrate that multiple genes are regulated by AT1R signalling and include those encoding secreted proteins associated with trophoblast invasion (e.g., plasminogen activator inhibitor-1, PAI-I) and angiogenesis (soluble fms-like tyrosine receptor-1, sFlt-1) which could promote endometrium decidualisation. Ang II signalling also activates NF-kappa B and stimulates NADPH-oxidase synthesis by trophoblasts which would promote trophoblastic proliferation and invasiveness [75].

4. RAS and gestational pathophysiological conditions

Since the RAS has a wide array of important functions in the body, any dysfunction in this system may lead to complications [41]. Studies have shown that the RAS is involved in reproductive conditions such as preeclampsia, polycystic ovary (PCOS) [76]. Moreover, it has a role in tumour progression in gynaecological cancers, highlighting the implication of the RAS in on tumour cell proliferation, vascular function and angiogenesis [54]. The following sections will describe the implication of RAS in the development of gestational pathologies, with the main emphasis being put on preeclampsia.

4.1. Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the leading cause of anovulatory infertility in women of reproductive age. Evidence of enhanced systemic RAS activity (increased plasma renin, Ang II and aldosterone) has been demonstrated to be responsible for the development of this disease [76, 77]. In PCOS patients, the maturation and oocyte quality are both affected by the increased intra-follicular renin level [54]. Moreover, there is evidence indicating that a polymorphism in ACE gene is associated to insulin resistance (IR) in women with PCOS [76, 78, 77]. Thus, treatment with ACE inhibitors aiming at increasing insulin sensitivity could result in an increased fertility in PCOS patients, but since RAS inhibitors are known to be teratogenic, further studies and much care would be needed to validate this therapeutic approach.

4.2. Ovarian cancer

Ovarian cancer is the most lethal gynaecological malignancy in women worldwide [79]. Ovarian cancer cells express Ang II and AT1R [80]. Elevated AT1R levels have been measured in borderline lesions and in invasive epithelial ovarian cancers [81]. Moreover, prognosis is worse for patients with tumours expressing high AT1R levels compared to patients with AT1R-negative tumours. The Ang II—AT1R pathway stimulates cell proliferation while the simultaneous increase in VEGF expression and Ang II levels promotes angiogenesis [54]. Therefore, targeting the Ang II-AT1R pathway could be part of a future treatment strategy for invasive epithelial ovarian cancer.

4.3. Endometrial cancer

Endometrial cancer (EC) is the most common gynaecological malignancy. Moreover, since obesity is a major risk factor, its incidence could increase in the future in parallel with the growing metabolic syndrome pandemic [82]. The endometrial RAS, like other tissue RASs, has been implicated in angiogenesis, neovascularisation and cell proliferation, which are processes involved in tumour growth and metastasis. Increased expression of Ang II, AT1R, AT2R, VEGF and estrogen receptor alpha (NR3A1) has been identified in EC tissues [83]. Moreover, a strong positive correlation has been detected between the levels of Ang II and AT1R/AT2R expression in endometrial tumours with advancing stage of the tumour [54, 83]. Overactivation of the RAS can often be attributed to single nucleotide polymorphisms (SNPs) in a RAS gene [84]. In a study by Freitas-Silva et al., an ACE polymorphism was described to be associated with early onset of EC. In summary, high activity of the local RAS in endometrial cancer is associated with higher incidence, earlier onset and increased rates of angiogenesis [54].

4.4. Preeclampsia

4.4.1. Definition of the pathology

Preeclampsia is a gestational complication that affects 2–5% of women in North America [85]. Preeclampsia risk factors include primiparity, multiparity as well as pre-existing conditions such as type 2 diabetes mellitus, obesity, hypertension and thrombophilia [86]. Moreover, women with preeclampsia are more likely to develop cardiovascular diseases later in life [87]. Clinical diagnostic is determined by the presence of new onset of hypertension (systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg) and proteinuria (≥300 mg in 24h) after 20 weeks of gestation. Other potential clinical manifestations are placental alterations, cerebral ischemia, liver abnormalities, cardiac hypertrophy and impaired vascular reactivity, although they are not seen in all preeclamptic women [88]. Patients with severe preeclampsia can also develop pulmonary oedema, haemolysis, elevated liver enzymes and low platelets syndrome, severe central nervous system symptoms, renal failure and intrauterine growth restriction [89].

Several factors have been involved in the development of preeclampsia, such as placental abnormalities, oxidative stress, endothelial dysfunction, inflammation and immunity, but none

have been clearly proven [86]. Preventive therapies such as antioxidants have not demonstrated any beneficial effects while calcium supplementation only helps patients with calcium depletion [90, 91]. Therefore, physicians usually try to control the progression of the disease using antihypertensive therapies, such as methyldopa (an α-adrenergic agonist), labetalol (an α- and β-blocker) and nifedipine (a calcium channel antagonist), which are considered relatively safe for the foetus. On the contrary, other drugs, such as RAS inhibitors, which are teratogenic and diuretic, are not compatible with regards to the hypovolemic state associated with preeclampsia. As such, they are not recommended for the treatment of this disease [92]. Ultimately, premature delivery of the foetus is the only effective treatment available, which can be problematic if the development of the foetus, has not sufficiently progressed.

4.4.2. Preeclampsia and RAS

Dysregulation of the RAS has been observed in preeclampsia compared to women with healthy pregnancies [6, 93, 94]. In particular, contrarily to normal pregnancy, preeclamptic women suffer from a hypovolemic hypertension (as mentioned above) characterized by a reduction in plasma renin, Ang I, and Ang II levels [70]. However, PE is characterized by a heightened sensitivity to vasoconstrictors when compared to normal pregnancy [6] partly due to an upregulation of the Ang II type 1 receptors [93], which would contribute to the increased blood pressure associated with this condition. Moreover, recent human studies revealed that both plasma Ang-(1-7) and Ang II are increased in normal pregnancy but decreased in preeclampsia [70]. However, the analysis of the Ang-(1-7)/Ang II ratio demonstrates that there is a greater decrease in Ang-(1-7) relatively to Ang II levels in preeclamptic [70], tipping the vasopressive balance towards increased vasoconstriction in pathological pregnancies. In addition, many epidemiological studies have suggested a relation between alleles of the RAS and PE [95]. For instance, women carrying specific polymorphisms of ACE [96] or Ang [97–99] genes have been reported to have an increased PE risk. Interestingly, these alleles are associated with an increase in systemic RAS [100].

In contrast, patients with preeclampsia have also been reported to have an increased Ang II content and AT1R expression in maternal decidua and in the placenta itself. Brosnihan's group also found in placental chorionic villi from human preeclamptic pregnancies an increase in Ang II and AT1R while Ang-(1-7) was not elevated and the Mas-R was significantly decreased [44]. They proposed that this increased Ang II effect in the chorionic villi could produce a decrease in foetal blood flow, and thus contribute to a reduction in foetal oxygen and nutrients as well as to the development of the intra-uterine growth restriction observed in these pregnancies. The same group showed that the placental increase in Ang-(1-7) content observed during normal pregnancy was reduced in a rat model of PE (the reduced uterine perfusion pressure model), although this was not accompanied by a concomitant decrease in ACE2 [101]. Moreover, we have demonstrated that R^+A^+ mice, an animal model of preeclampsia, have increased AT1Rand decreased Mas-R protein in both placenta and aorta, a condition expected to decrease angiotensin-(1-7) effects in favour of angiotensin II effects [102]. The importance of different RAS components in the development of preeclampsia will be further discussed below.

4.4.3. Prorenin and prorenin receptor ((P)RR) and preeclampsia

Expression of the (P)RR has been shown to be localized to the syncytiotrophoblasts both in normotensive and preeclamptic pregnant women [103]. Placental prorenin and (P)RR levels as well as the circulating soluble form of (P)RR (s(P)RR) were shown to be significantly higher in preeclamptic compared to normotensive pregnant women [104]. Moreover, placental (P)RR expression positively correlates with systolic blood pressure only in preeclamptic women. The concomitant modulations of prorenin and (P)RR in preeclamptic women reinforce the idea that an increase in RAS local activation could promote the elevation of blood pressure in this pathology. However, the implication of an increase in s(P)RR in the development of preeclampsia is still misunderstood.

4.4.4. AT1 receptors autoantibodies in preeclampsia

In recent years, a wealth of evidence has emerged supporting a role for AT1R autoantibodies (AT1-AA) in the development of preeclampsia. Studies have shown that these autoantibodies are elevated in patients with preeclampsia compared to normal pregnancies and have been shown to specifically stimulate Ang II type 1 receptors, suggesting that these autoantibodies may be involved in the development of preeclampsia [93, 105]. Studies in animal models of preeclampsia have shown that the hypoxia used to induce the disease (caused by the reduction in placental perfusion in pregnant rats) strongly stimulated AT1-AA production [106]. Moreover, infusion of AT1-AA from preeclamptic patients in normal pregnant animal was able to trigger hypertension through an increase in endothelin-1 expression, a potent vasoconstrictor [107]. *In vitro* and *in vivo* studies have demonstrated the binding of those autoantibodies to AT1R on different cell types [108]. In particular, AT1-AA binding at the surface of human trophoblastic cells cause an activation of NADPH oxidase, contributing to the rise in oxidative stress putatively involved in the development of preeclampsia [109]. In addition, activation of AT1R in this cell-type stimulates the release of PAI-1, resulting in decreased trophoblastic invasiveness causing a defect in placentation [110]. It was also observed that AT1-AA stimulates the release of sFlt-1 and s-Eng by the placenta which stimulates endothelial dysfunction [111, 112]. Overall, these results indicate that the vasoconstrictor angiotensin receptor signalling is a key pathway involved in the development of PE.

4.4.5. RAS and angiogenic factors in preeclampsia

A molecular hallmark of preeclampsia is a decrease in plasmatic angiogenic markers, free VEGF and placental growth factor (PlGF), along with an increase in the circulating levels of anti-angiogenic markers, soluble fms-like tyrosine-1 (sFlt-1, a soluble variant of the VEGF receptor) and soluble endoglin (sEng), compared to normal pregnancies [113–115]. The decrease in VEGF and PlGF would lead to the improper spiral artery remodelling which is associated with preeclampsia [116]. Moreover, hypoxia, through an increased expression of hypoxia-inducible factor 1 α (HIF-1α), stimulates the expression of sFlt-1, and therefore amplifies the hypoxic placental microenvironment [117, 118]. HIF-1α has also been shown

http://dx.doi.org/10.5772/66748

to upregulate the expression of both endothelin-1 and endoglin, a membrane-bound precursor of sEng [119, 120]. In addition, increased secretion of sEng has been measured from both chorionic villi from preeclamptic placenta and hypoxic trophoblastic cells [121]. The increase in endothelin-1 would promote the increase in blood pressure associated with preeclampsia, while the increase in sEng levels would prevent trophoblastic differentiation and invasion.

4.4.6. Beneficial effects of exercise training on preeclampsia could be through modulation of the RAS

While exercise training is well known for its health benefits in the general population, it has also been shown to improve pregnancy outcome during normal human gestation [122]. Moreover, there are data demonstrating that it can also reduce the prevalence of human pregnancy disorders such as gestational diabetes. There is also a significant body of evidence supporting the exercise training-induced reduction in risk of developing PE by 35% to 78% [123]. We have recently demonstrated that exercise training (mouse voluntary wheel running) before and during gestation significantly prevents the development of preeclampsia superimposed on chronic hypertension phenotypes in our mouse model of that disease [102]. We noted that the pregnant mice naturally reduce the duration and intensity of their exercise training throughout pregnancy and cease exercising 2–3 days prior to delivery, a phenomenon we call the graded intensity or GI-exercise training program. Indeed, this GI-exercise training program normalized the mouse preeclampsia phenotypes, and: (1) prevented the increase in blood pressure; (2) reduced the development of the proteinuria; (3) abolished the increase in placental mRNA and circulating levels of sFlt-1; and (4) prevented the development of the placental pathology characteristic of preeclampsia, and thus also prevented the associated foetal intra-uterine growth restriction phenotype. In support of this beneficial effect of the GI-exercise training program, we also observed similar benefits in a mouse model of preeclampsia (*hAGT*hREN model*; normotensive female mice which overexpress human angiotensinogen, bred with males that overexpress human renin) [124]. Interestingly, we found that these beneficial effects of exercise training in R^+A^+ mice were associated to a normalisation of AT1R and MasR in the placenta as well as an increase Mas receptor content in the aorta [102]. Hence, this could contribute to the prevention of the increase in blood pressure and the normalisation of placental development observed in this animal model.

5. Conclusion

In conclusion, the reproductive system's local RAS has been clearly shown to be implicated in fertility, reproduction and pregnancy. Moreover, dysregulation of the RAS has been associated with gestational pathologies, although more work is needed to clearly identify the molecular mechanisms involved. As such, the development of new therapies aiming at amplifying the vasodilating arm of the RAS could help in improving both maternal and foetal outcomes although caution needs to be taken given that RAS inhibitors have been shown to be teratogenic.

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