Chapter

Scientific Evidences Supporting the Activation of the Renin-Angiotensin-Aldosterone System during Estral Cycle and Pregnancy in Mares

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Abstract

In women and laboratory animals, local and circulating components of the renin-angiotensin-aldosterone system (RAAS) are related to specific reproductive functions that occur during the estrous cycle, such as folliculogenesis, ovulation, corpus luteum development, and steroidogenesis. Also, in pregnant females of these species, maternal cardiovascular and renal systems undergo intense modifications, with the aim of matching the increased energy requirements of the fetus and fetoplacental unit. Some of these changes can be the origin, and others the consequence of a new endocrine environment. The fetus and the placenta induce endocrine changes, with modifications in the protein, lipid, carbohydrate, and mineral metabolism, together with simultaneous cardiovascular changes derived from the uterine growth and its content. The participation of RAAS during this period is of vital importance to regulate these cardiovascular, hemodynamic, hematological, and metabolic adjustments imposed by pregnancy because they will have a direct influence on the correct development and viability of the fetus. In mares, our research team has been investigating the changes of RAAS in mares during the estral cycle and during pregnancy, and these results are presented in the current chapter, comparing with the data previously reported for women and laboratory animals.

Keywords: estrous cycle, mare, pregnancy, renin, angiotensin, aldosterone

1. Introduction

In nonpregnant females of various species, the components of the renin-angiotensin-aldosterone system (RAAS), i.e., prorenin, renin, angiotensin II (ANG-II), and aldosterone, are expressed in the tissues of reproductive organs, mainly the uterus and ovaries. These hormones have direct physiological relationships with specific reproductive functions, including folliculogenesis, oocyte maturation, ovulation, follicular atresia, corpus luteum development and luteolysis, steroidogenesis, angiogenesis, and expression of certain vasoactive substances [1–8].

A great body of literature has confirmed an increase in plasma activity of renin (PRA) and plasma concentrations of ANG-II and aldosterone in women during the

luteal compared to the follicular period of the estrous cycle [9–19]. The primary source of renin and aldosterone is progesterone (P4) secreted by the corpus luteum. The elevated P4 concentrations during the luteal period lead to increased renal plasma flow, glomerular filtration rate, and natriuresis. This natriuretic effect stimulates in a compensatory way the synthesis and release of renin, ANG-II, and aldosterone [10–12, 15, 16, 20–23]. However, these results do not agree with those described by Szmuilowicz et al. [19], who suggested that the synthesis of aldosterone might be independent of renin and ANG-II at the ovarian level. Another physiological event that happens during the estrous cycle of the women is the preovulatory increase of renin [14, 24], ANG-II [25], and aldosterone [10, 12, 25, 26].

Similar results to those described in women have been reported in laboratory animals [27–30]. A potential physiological mechanism related to these changes is the stimulatory effect exerted by estrogens (E2) on the synthesis of angiotensinogen [31]. Additional mechanisms could be the hemodynamic and renal blood flow variations, changes in Na concentrations at the macula densa in the kidney, alterations in local sympathetic activity, and release of corticotropin or adrenocorticotrophic hormone (ACTH). All of these mechanisms act as regulatory factors for aldosterone synthesis [17, 19, 32, 33].

During pregnancy, circulating and tissular RAASs interact closely in order to achieve a successful outcome of the pregnancy. The local RAASs involved in pregnancy are mainly located at the ovaries, uterus (both at the placenta and decidua), and intrarenal level. The nonrenal local RAAS systems have pivotal functions in the implantation and in the placentation as well as in the development of the uteroplacental and umbilical placental circulations. In addition, they contribute directly to the circulating RAAS of the pregnant female, determining in part the normal functionality of the cardiovascular and renal systems [34].

In this review, we summarize the state of the art of the current knowledge of the RAAS in reproductive mares. We provide comparative profiling of the hormones of this system with other species, mainly with women and laboratory animals. The results of our own investigations performed during the last 10 years have demonstrated that an activation of the RAAS happens around ovulation and during pregnancy in the reproductive mare, even though significant differences with the reports made for women and laboratory animals have been found.

2. Changes in the renin-angiotensin-aldosterone system during the estral cycle

2.1 A brief review of the estral cycle in the mare

An exhaustive review of the estral cycle of the mare and the neuroendocrine mechanisms associated has been published recently [35]. Briefly, the mean length of a mare's estral cycle is 21 ± 3 days. The cycle is divided into two physiological periods: the estrous or follicular period and the diestrus or luteal period. The duration of the follicular period is approximately 6 days, but it can take 4–10 days depending on the mare. The luteal period has a duration of 15 days, ranging between 12 and 18 days. Ovulation can occur at any time during the follicular period, although it usually occurs 24–48 h before the end of this period. During the estral cycle, physiological changes in mares include follicular development, selection of the dominant follicle, release of the oocyte from follicle, formation of the corpus luteum, and production of P4. These physiological events are controlled by gonadotropin-releasing hormone (GnRH) that stimulates the hypophysis to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These hormones control the development of

the follicle and stimulate the secretion of E2 from the follicle to induce ovulation and corpus luteum establishment and development [35, 36].

2.2 Changes in the renin-angiotensin-aldosterone system during the luteal period

Most researchers have documented that aldosterone concentrations rise between 2 and 4 times during the luteal period [11, 37]. Presumably, this increase mirrors the increase experienced by ANG-II concentrations. However, this supposition has not always been supporting, and as a consequence, later it was suggested that the changes in ANG-II might be attributed to other ways independent of the RAAS [19]. Although this hypothesis is currently the most defended in the literature, some authors would not be able to confirm it [32, 38].

A variety of studies have shown that the relationship between PRA and aldosterone from the middle to the end of the luteal period can be adjusted to a linear model [9, 10, 16, 22, 37, 39, 40]. The researches performed in women with luteal insufficiency have helped to clarify complex issues, such as the involvement of the sex hormones in the modifications of the different RAAS components during the different period of the estral cycle. In this sense, several early investigations compared the concentrations of angiotensinogen, aldosterone, gonadotropins, ovarian steroids, and PRA in women with ovulatory cycles and in women with luteal insufficiency. While in physiological estral cycles the peak of PRA was closely related to the increase in aldosterone, in women with anovulatory cycles, these temporal relationships between renin and aldosterone or PRA and aldosterone were not found [9, 10, 41]. Subsequently, it was hypothesized that once the corpus luteum reaches functional maturity, it acts as the primary source of renin and aldosterone. Thereby, there was an explanation for the direct relationship between P4 and other compounds derived from the corpus luteum and the RAAS in physiological estral cycles, but not in women with ovulatory failure, because these women show a significant decrease in P4 concentrations [18, 21, 42].

P4 seems to be directly related to the luteal synthesis of aldosterone [15, 18, 21, 42]. Certain mechanisms dependent on P4, such as increased plasma flow, renal glomerular filtration rate, and Na and Cl excretion, result in natriuresis [16]. The initial natriuresis induced by P4 stimulates in a compensatory way the secretion of renin, ANG-II, and aldosterone [9–11, 20, 37]. The experimental administration of P4 results in natriuresis, which is followed by peaks of aldosterone secretion, aldosterone urinary excretion (AUE), and Na retention [11, 43]. Although PRA, ANG-II, and aldosterone increase after the administration of P4, the rises do not occur simultaneously [43]. These results have been explained in base of the competence between P4 and aldosterone for the mineralocorticoid receptor [12, 44, 45]. In physiological cycles, endogenously secreted P4 exerts a mild anti-aldosterone effect, avoiding an excessive retention of Na and water during the luteal period [46].

The E2 and P4 peaks during the luteal period lead to increases of PRA and ANG-II 2–3 times and also increases of AUE [17, 19]. However, the increase of E2 that happens during the first half of the estral cycle does not result in substantially raised PRA and AUE. Perhaps these events are mediated by the expression of aldosterone receptor protein and angiotensinogen in the absence of changes in ANG-II [46–48]. The lack of correlation between aldosterone and E2, as well as the lack of stimulation of aldosterone production in in vitro cultures of glomerulosa cells, could be other findings that might exclude E2 from the synthesis of aldosterone during the luteal period [19].

However, there are additional mechanisms involved in the synthesis of aldosterone independently of the P4 concentrations, such as the uptake of proteins and Na in the diet [49, 50] or a peripheral vasodilation [16]. It is difficult to interpret these

findings without considering the intake of Na, since this electrolyte determines primarily the production of aldosterone via RAAS [49]. However, many previous studies did not control or did not report Na concentrations, which is a limiting factor in the proper interpretation of the results. More recently, Szmuilowicz et al. [19] showed that circulating and urinary levels of aldosterone increase significantly during the luteal period in response to the infusion of ANG-II in women with high Na concentrations. In these situations, positive correlations between P4 and aldosterone have been found, without parallel changes in PRA and ANG-II. On the contrary, in women with low Na concentrations, these interrelationships do not occur, even though the restriction of Na in the diet is a powerful stimulus for the activation of RAAS [49]. In Na-restricted diets, PRA and aldosterone respond independently between each other, and therefore, the absence of modifications in PRA and ANG-II could rule out that the increase in aldosterone is modulated via RAAS activation during the luteal period.

Another mechanism that has been related to the synthesis of renin and aldosterone during the luteal period is the release of angiotensinogen and prorenin. However, the studies conducted in this field have provided contradictory results. The expression of angiotensinogen is regulated transcriptionally by E2 [31], and consequently, the administration of different ovarian stimulation treatments in women increases the concentrations of E2 and renin [15]. Therefore, the activation of the RAAS during the luteal period could be partially related to the increased synthesis of angiotensinogen [21] or be a direct consequence of the vasodilatory effects of E2 [51]. However, early studies have not revealed variations in angiotensinogen during the luteal period of physiological estral cycles [10, 52, 53]. The combined use of E2 and P4 during the luteal period in ovariectomized rats resulted in increases in PRA without significant simultaneous changes in angiotensinogen [54]. The lack of a significant relationship between PRA and angiotensinogen might rule out E2 as a cause of the modifications in renin concentrations, despite its involvement in the secretion of aldosterone [10, 53, 55].

Although the main source of circulating active renin is the kidney, the ovaries appear to be the source of the cyclic increase of prorenin during the estral cycle [14, 56]. In fact, the release of LH triggers an increase of three times the concentrations of prorenin, remaining elevated during the first half of the luteal period, even though the decrease in P4 at the end of the luteal period reduces simultaneously the prorenin levels [18, 21, 42, 56].

2.3 Changes in the renin-angiotensin-aldosterone system during the follicular period

Preovulatory increases of angiotensinogen, prorenin, PRA, renin, ANG-II, and aldosterone have been reported in women [11, 14, 25, 26] and laboratory animals [29]. According to other authors, the increase in aldosterone concentrations appears to be transient [11], or it is not constant in all cycles [37].

The origin of the preovulatory aldosterone peak is unknown, but it has been speculated that the increase in E2 could exert a stimulatory effect on angiotensinogen in the liver, and this, in turn, increases PRA and aldosterone [52, 53, 55]. Other researches, on the contrary, failed to find any relationship between angiotensinogen, PRA, and aldosterone in physiological cycles [11, 17, 19, 57], ruling out some type of significant influence of endogenous E2 on PRA and AUE during the periovulatory period [9, 10, 41]. Despite these contradictory results, the hypothesis that the increase in angiotensinogen is the cause of PRA and aldosterone peaks is still commonly accepted.

A transient peak of prorenin has been described simultaneously with the elevation of gonadotropins, mainly LH, toward the moment of the ovulation. It has been

speculated that this prorenin peak will be responsible later for the increase of active renin [58]. However, prorenin and LH are not always related to active renin [14, 15], because the most striking effects of this precursor appear toward the middle of the luteal period [18, 21, 42].

Because ACTH is one the main regulators of aldosterone secretion, the preovulatory peak of PRA might be related to the stimulatory effect of E2 on the adrenal gland and to the increase of the 17α-P4-enzyme, which also shows a preovulatory peak. This enzyme catalyzes the conversion of pregnenolone into 17-α-hydroxypregnenolone, which is a precursor of the sexual steroids [59]. However, although an experimental infusion of ACTH triggers an elevation in PRA [60], the absence of changes in cortisol (CORT) concentrations in physiological cycles could refute these hypotheses [17, 19, 32]. Other factors, including hemodynamic changes in renal blood flow, local sympathetic activity, and variation in Na concentrations at the macula densa level, have also been associated with the preovulatory peak of renin and aldosterone [33, 61].

In broodmares, Satué et al. [62] evaluated the changes in circulating RAAS components around ovulation, considering the 5 days before ovulation (from day 5 to day 1), the day of the ovulation (day 0), and the 5 days immediately after ovulation (from day 1 to day 5). A summary of the main endocrine changes, including those of the RAAS, is presented in **Figure 1**.

A progressive increase in plasma renin concentrations was found before ovulation, peaking at the day of the ovulation [62] (**Figure 2**). The increase in plasma renin before ovulation in other species, as has been previously attributed to the release of LH or to the stimulating effect of human chorionic gonadotropin (hCG) [24]. Another plausible explanation for this rise in plasma renin before ovulation was the increase in E2 concentrations, since a positive correlation between both variables has been found in mares ($r = 0.744$) [62] (**Figure 3**). These results in mares agree with the data provided by Sealy et al. [15] in women with ovarian stimulation, in whom significant simultaneous increases in renin and E2 were detected. Another explanation for the rise in renin concentrations in the mares could be a mild hypovolemia associated with the presence of interstitial fluid in

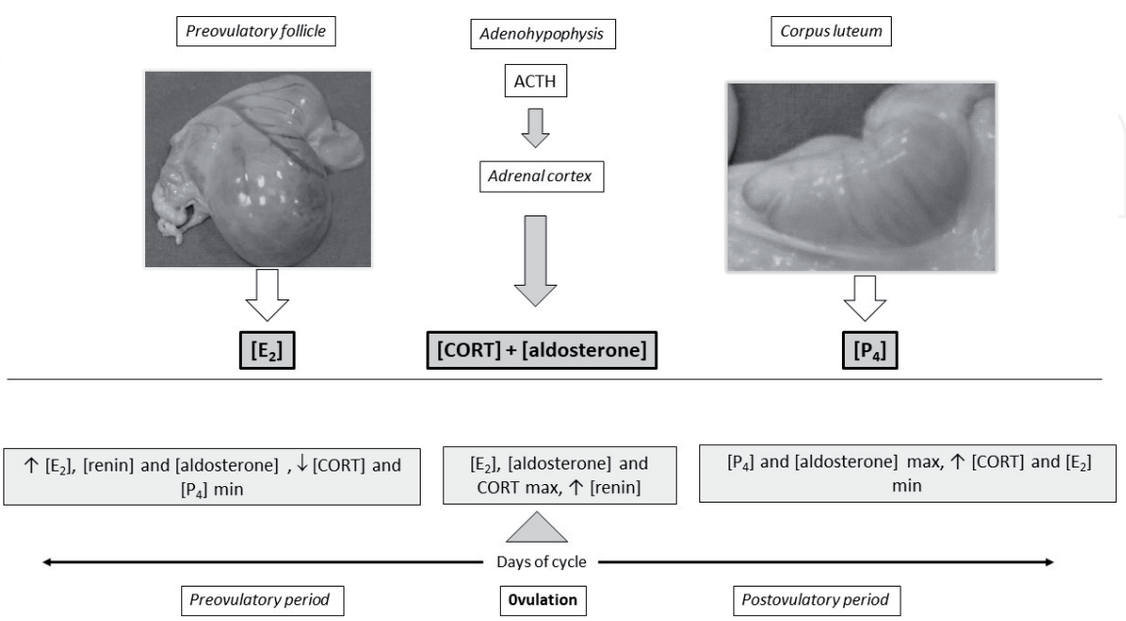

Figure 1.
Representative scheme of the hormonal changes that occur in the mare during the 5 days before ovulation (preovulatory period), the day of the ovulation, and the last first 5 days after ovulation (postovulatory period) (ACTH, adrenocorticotrophic hormone; E2, estrogens; CORT, cortisol; P4, progesterone).

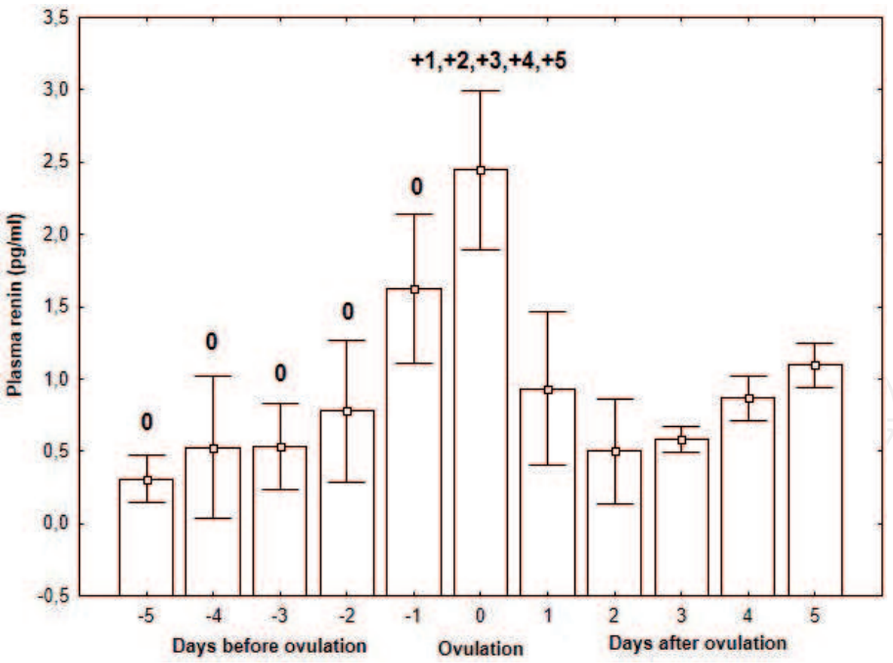

Figure 2.
Plasma renin concentrations during the 5 days before ovulation, the day of the ovulation, and the first 5 days after ovulation in mares (numbers indicate the days between which significant differences were found at $p < 0.05$).

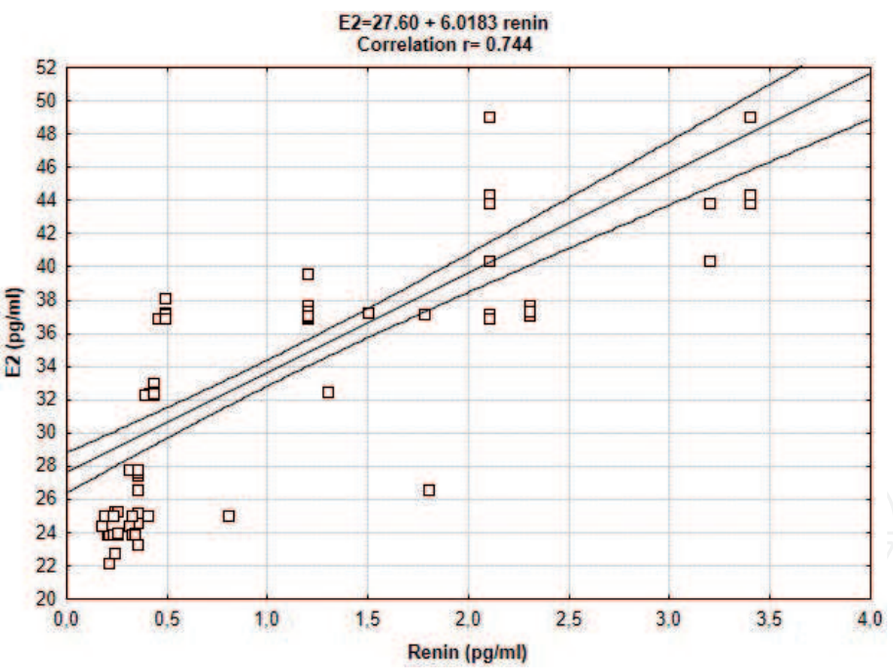

Figure 3.
Significant positive correlations between plasma estrogens (E2) and renin concentrations in mares before ovulation ($r = 0.744$).

abdominal cavity during ovulation. Even though changes in Na and Cl concentrations at the renal juxtaglomerular apparatus significantly influence the release of renin [63], the correlations between renin and these electrolytes appear to be low in mares before ovulation [62]. In the same way, Roussel et al. [64] described cyclic patterns of plasma Na and aldosterone concentrations in cow, but without significant correlations with the components of the RAAS.

After ovulation, a sharp decrease in plasma renin concentrations was detected in mares (**Figure 2**). Similar changes have been reported in women [17]. Ounis-Skali et al.

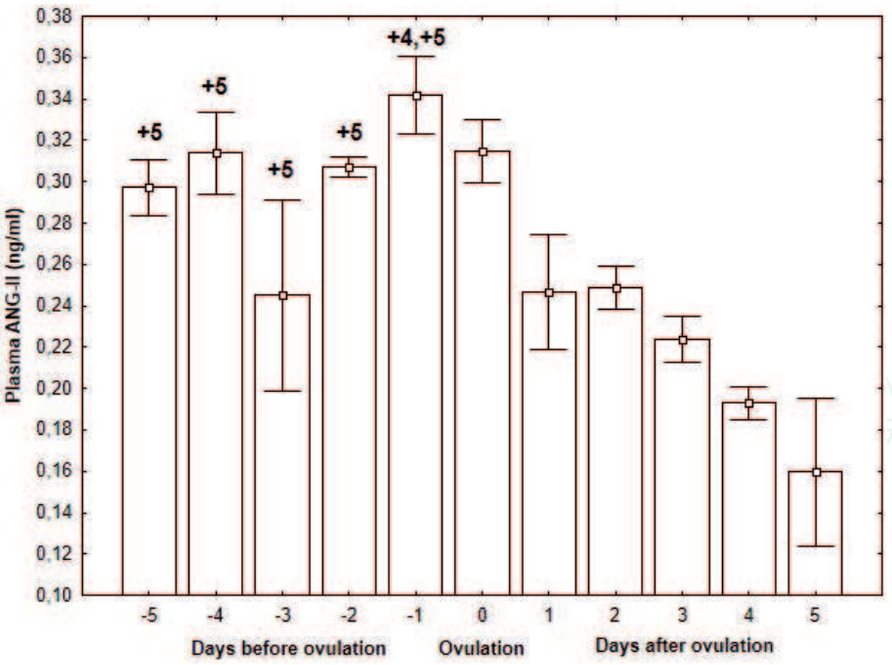

Figure 4.
Plasma angiotensin-II concentrations during the 5 days before ovulation, the day of the ovulation, and the first 5 days after ovulation in mares (numbers indicate the days between which significant differences were found at $p < 0.05$).

[18] attributed these results to the release of renin from the corpus luteum, reflecting a direct relationship between P4 and renin after ovulation, and similar hypotheses might be extrapolable to the mare. Two studies performed by our research team demonstrated low correlations between P4 and renin, suggesting other factors different from P4 might be considered in order to explain the non-significant trend toward an increase in renin concentrations during the first days after ovulation [65, 66].

Plasma ANG-II concentrations did not show significant variations before ovulation, but it experienced a sharp and progressive decrease after ovulation [62] (**Figure 4**). On the contrary, significant increases in ANG-II have been previously observed in sows [11] and in rats [29] before ovulation. ANG-II concentrations in women after ovulation were almost the double of the values found before ovulation [17–19]. This increase in women was attributed to the modulation of the flow in the ovarian blood vessels during oocyte maturation [15]. The reason why ANG-II concentrations decrease in the mares after ovulation, which is an opposite change to this described for women and laboratory animals, is not currently known.

Plasma aldosterone concentrations increased progressively from the fifth day before ovulation until the day of the ovulation. After this moment, aldosterone concentrations did not change and persisted to be significantly higher than before ovulation [62] (**Figure 5**). Because an increase in renin was also found the day of the ovulation in mares and ANG-II was higher during the 5 days before ovulation, it was speculated that the increased renin was the starting point to activate RAAS, resulting in increased aldosterone concentrations. This hypothesis was proven when the correlations between hormones before and after ovulation were assessed (**Figure 6**). A positive significant correlation ($r = 0.756$) was found between renin and aldosterone concentrations before ovulation. Surprisingly, ANG-II and aldosterone concentrations did not present a significant correlation before ovulation (**Figure 6**). These data might indicate a dissociation between ANG-II and aldosterone before ovulation in the mare. In this case, the synthesis of aldosterone might have occurred in addition via other pathways independent from the activation of the RAAS [62].

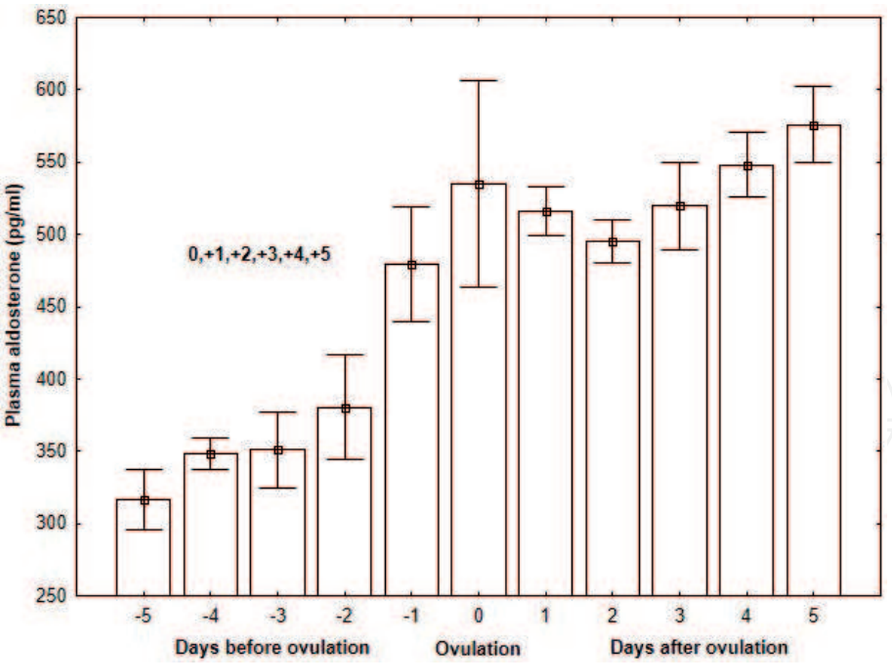

Figure 5.
Plasma aldosterone concentrations during the 5 days before ovulation, the day of the ovulation, and the first 5 days after ovulation in mares (numbers indicate the days between which significant differences were found at $p < 0.05$).

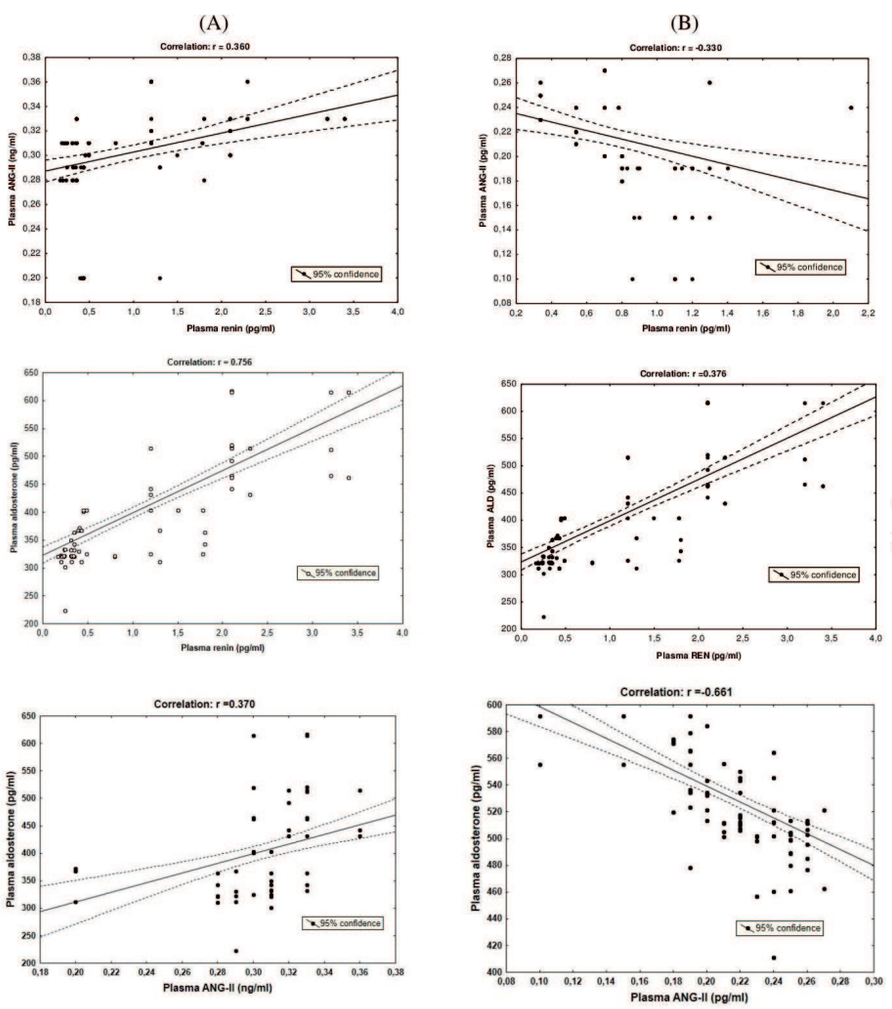

Figure 6.
Correlations between the three main components of the renin-angiotensin-aldosterone system in mares before (A) and after ovulation (B).

The relationships between the diameter of the predominant follicle and the hormones of the RAAS have also been investigated in mares [62] (**Figure 7**). A significant positive correlation was found between renin and aldosterone concentrations and the diameter of the follicle before ovulation in the mares (r = 0.742 and 0.804, respectively) [62] (**Figure 7**). In other species, RAAS regulates the development and growth of the antral follicles. Receptors AT1 and AT2 for ANG-II have been found in the granulosa cells of the antral follicles and in the primordial primary and secondary follicles of sows [67]. Administration of an ANG-II inhibitor in cows avoided the growth of the predominant follicle and also induced a reduction in the concentrations of E2 [68, 69]. In the same way, in women subjected to ovarian stimulation with

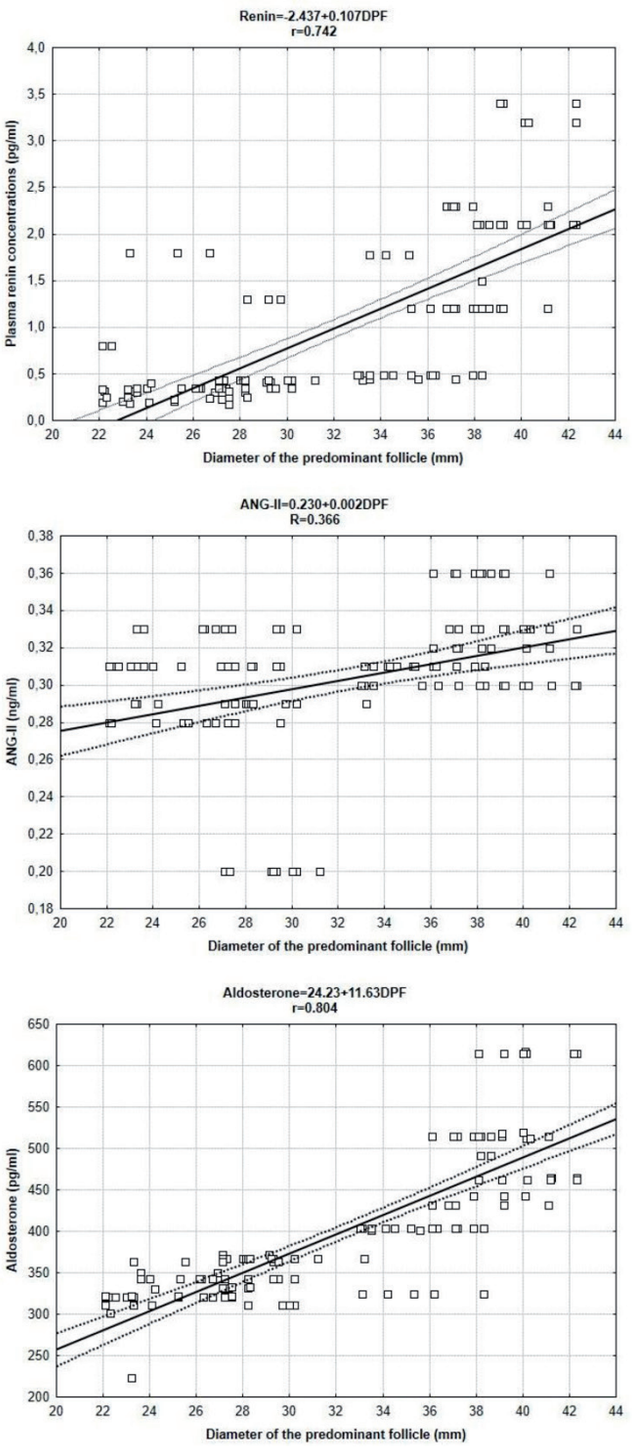

Figure 7.
Correlations between the diameter of the predominant follicle (DPF) and the concentrations of renin, angiotensin II, and aldosterone before ovulation in mares.

human menopausal gonadotropin (HMG), concentrations of ANG-II were positively correlated with E2 and the diameter of the predominant follicle [70]. In our research in mares, however, correlations between the diameter of the predominant follicle and ANG-II were very low (r = 0.366), despite the significant correlations between this diameter and the concentrations of renin and aldosterone [62] (**Figure 7**). Our results might suggest that circulating ANG-II concentrations do not exert a transcendental effect on the development of the ovarian follicle or, alternatively, some antagonist peptides of the ANG-II might be produced before ovulation in mares [65, 66].

3. Changes in the renin-angiotensin-aldosterone system during the pregnancy

Plasma concentrations of prorenin increase by 5–10 times during the first 10 weeks of pregnancy in women. This increase is simultaneous with the increase in hCG and after, both decreased until the moment of the delivery. Although prorenin is mainly synthesized in the renal juxtaglomerular cells, there are other extrarenal sources, such as the ovary, follicular fluid, and placenta [71]. The prorenin concentrations also increase when the LH concentrations peak at the moment of the ovulation [71, 72]. The combined administration of LH and FSH causes a 390% increase in plasma prorenin, while hCG increases above 1000% [13, 73]. An early study speculated that prorenin could act as a hormone with functions independent of the active renin [13]. Until now, to the authors' best knowledge, the prorenin concentration in plasma/serum has not been quantified in mares.

A substantial increase in the circulating concentrations of angiotensinogen has also been documented during the first weeks of pregnancy in women [74]. Angiotensinogen concentrations remain elevated throughout pregnancy, peaking at term. In sheep, a bimodal pattern of secretion of this hormone has been described, with a first peak at the beginning of the pregnancy, concomitant with the period of the maximum placental growth. The second peak occurs at term, suggesting an association between plasma angiotensinogen and fetal growth [75].

The increased synthesis of angiotensinogen has been attributed to the stimulating effect of E2 at hepatic level [16, 17, 76]. However, the relationships between angiotensinogen and E2 are not always positive [77]. In nonpregnant women undergoing estrogen treatments, angiotensinogen and ANG-II increased in blood, whereas renin concentrations tended to decrease because of the negative feedback exercised by angiotensinogen [76]. However, the angiotensinogen concentrations have not been measured in mares yet.

The total concentration of circulating renin, both its active and inactive forms, increases during pregnancy in women. However, the contribution of the physiologically inactive renin to the total renin is greater than that of the active renin [78]. During the first third period of the pregnancy, renin concentrations increased between 2 and 4 times above baseline [79, 80]. After it reaches a plateau, around the fifth month of pregnancy and after that, the concentrations remained unchanged until the end of the pregnancy [81], being the main reason involved in the rise of PRA during the first and second thirds of the pregnancy, respectively [11, 80, 82–84]. Toward the end of the pregnancy, the renin concentration decreases intensely [78]. Even though the increased renin release contributes greatly to the ANG-II synthesis, the renin concentrations could decrease because of a negative feedback mechanism [15, 85].

The synthesis of renin, in addition to renal juxtaglomerular cells, can also be carried out in other extrarenal tissues, as the uterus. This organ is the priority organ of renin synthesis during pregnancy, leading to the so-called hyperreninemia of the

pregnancy [80, 86]. The renin at the level of the fetal membranes and the uterus is found predominantly in the form of prorenin, and although it is supposed that it can be released into the maternal circulation, the degree of contribution to the maternal circulating levels is unknown. Both active renin and inactive renin have been identified in the uterus, placenta, and myometrium in women and in some laboratory animals [87]. Despite this, amniotic fluid seems to be the main source of renin produced by the chorionic cells during pregnancy [74].

The placenta appears to be the major source for the conversion of angiotensin I into ANG-II, since the prorenin, active renin, angiotensin converting enzyme (ACE), and ANG-II have been identified in the chorion and in the placenta [88]. The physiological roles of these components have not been completely clarified, but it has been speculated that they might participate in the regulation of the blood flow [89–92].

The increase in renin concentrations during pregnancy has also been attributed to the loss of electrolytes as a consequence of the increase in the glomerular filtration rate as well as of the secretion of P4, due to the antagonic effects of the hormone on aldosterone, because P4 induces natriuresis [74, 76, 93]. On the other hand, the positive influence of E2 on the synthesis of angiotensinogen has also been considered a plausible reason for the renin peak during pregnancy [76]. Surprisingly, it is possible to find increased renin concentrations without a simultaneous increase of ANG-II concentrations. In addition, the sequestration of Na and water at the uterus might be another triggering factor for the release of renin during pregnancy, as documented in pregnant bitches [94].

In pregnant mares, Satué et al. [95] described a significant increase in the renin from the seventh month of pregnancy (**Figure 8**). In pregnant women, as stated before, the increase in renin concentrations occurs earlier than in the pregnant mares [79, 80, 84]. At present, it is unknown if the origin of these differences is the different animal species or it could be due to the influence of other physiological factors. In the mare, ANG-II concentrations did not vary significantly during pregnancy (**Figure 9**), despite the changes in renin concentrations (**Figure 8**). These data might suggest that there is a dissociation between renin and ANG-II during pregnancy in the mares. In pregnant women, it has been shown that the increase in

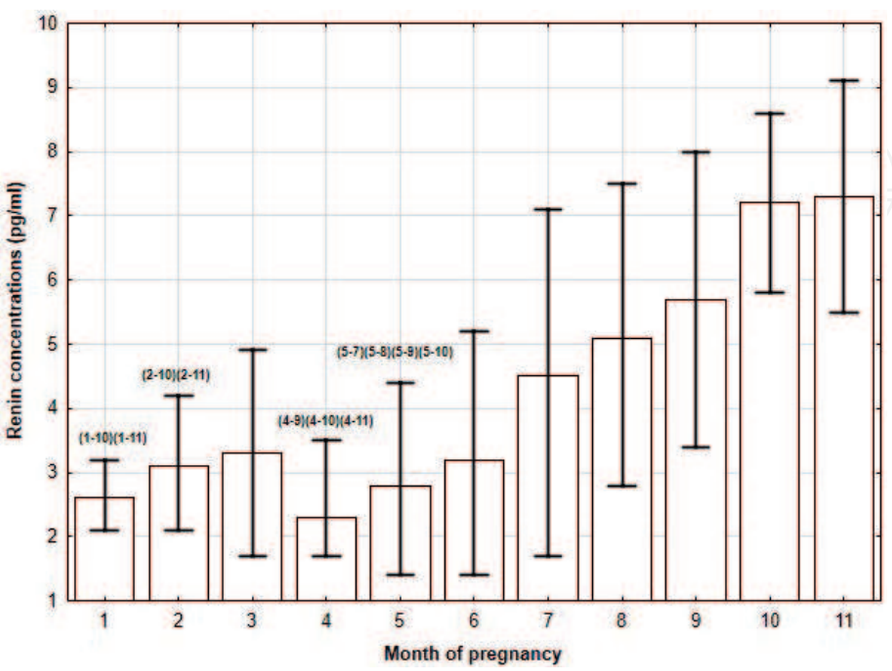

Figure 8.
Mean (maximum and minimum indicated in bars) concentrations of renin in mares during pregnancy (significant differences between months indicated with numbers at $p < 0.05$).

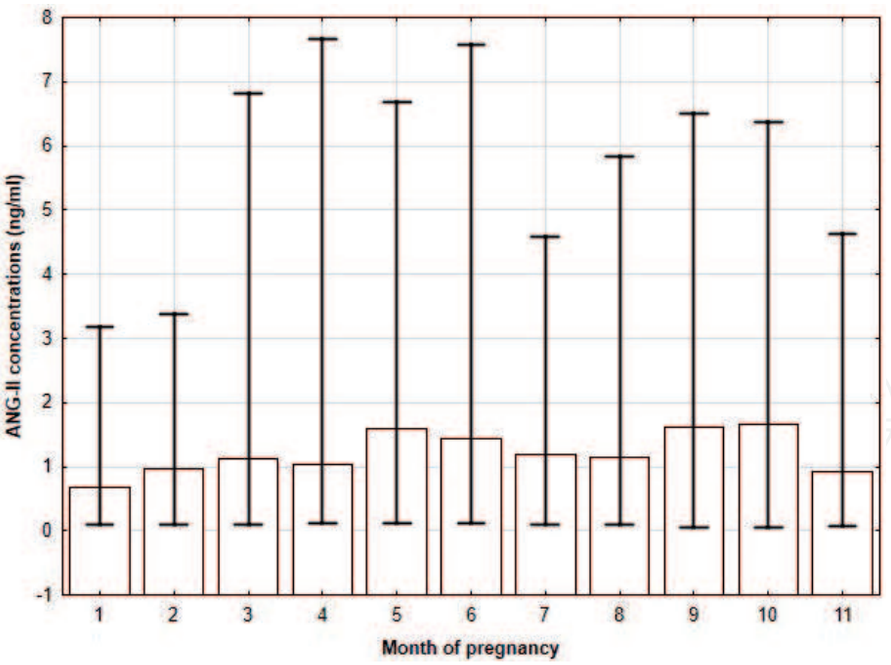

Figure 9.
Mean (maximum and minimum indicated in bars) concentrations of angiotensin II in mares during pregnancy.

ANG-II exerts a negative feedback effect on renin secretion [74, 85, 96]. In addition, it has been proposed that the peak of renin during pregnancy is in part associated with the release of estrogens, which act on the production of angiotensinogen in the liver [15, 76, 97]. Moreover, Satué et al. [98] found a dissociation between renin and E2, in agreement with previous results described for pregnant women [77, 99].

On the contrary to the data found for ANG-II in mares [95], most of the investigations performed in women and laboratory animals showed that during pregnancy, circulating concentrations of ANG-II increased up to two and even three times from nonpregnant values [74, 78, 100, 101]. This increase in women appears from the beginning of the pregnancy, peaking at the seventh month and persisting to be elevated until the moment of the delivery [102].

Pregnant mares showed a marked increase in circulating aldosterone concentrations during pregnancy, with mean values that exceed almost 12 times the physiological reference range for healthy adult horses [103] (**Figure 10**). Similar results have been reported in pregnant women [74, 84, 104], bitches [105–107], and some species of laboratory animals [108]. In pregnant bitches, Robb et al. [94] and in rats, Brochu et al. [106] attributed the increase in aldosterone concentrations to a higher activity of the enzyme aldosterone-synthase and to an increased synthesis of mRNA in the cells of the zona glomerulosa, these cells being the only production site, without fetal and/or placental participation, on the contrary of what appears to happen in women [78].

In mares, our team has found lower aldosterone concentrations during the second month of pregnancy, compared to the fifth, sixth, and seventh months of pregnancy (**Figure 10**). The highest values were observed in the fifth month of pregnancy. In the eighth, ninth, and tenth months of pregnancy, aldosterone concentrations were significantly lower than the mean values found in the fifth month. In pregnant women, it has been speculated that the increased release of aldosterone would occur in an attempt to conserve Na and water to favor the expansion of the fetoplacental unit. In this way, the adequate supply of nutrients to the fetus, the maintenance of the ideal oxygen tension for fetal development, as well as the homeostasis and appropriate blood pressure between the mother and the fetus would be guaranteed [108, 109].

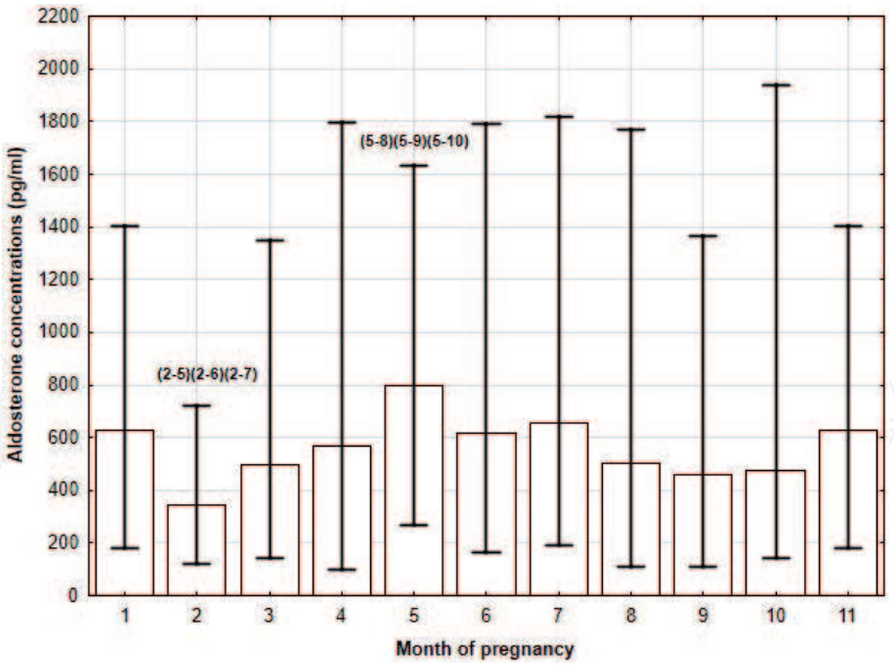

Figure 10.
Mean (maximum and minimum indicated in bars) concentrations of aldosterone in mares during pregnancy (significant differences between months indicated with numbers at $p < 0.05$).

Although the evolution of aldosterone concentrations during pregnancy is similar in women, laboratory animals, and mares, there are temporary differences in the moment in which the peaks of concentrations are reached. In women and laboratory animals, the maximum increase in aldosterone appears in the second third of pregnancy, followed by a decrease in the third period of pregnancy. In the mare, on the contrary, as shown in **Figure 10**, the maximum concentrations were found in the fifth month.

The increase in aldosterone during pregnancy in women has been attributed, firstly, to the increase in the sensitivity of the cells of the adrenal gland to the increased synthesis and release of renin [74, 110] and, secondly, to the increase in ANG-II concentrations, a finding that has been associated with an increase in placental lactogen [74]. In women, it is known that placental lactogen plays a regulatory role in metabolic homeostasis, triggering an increase in ANG-II receptors during the second period of the pregnancy [111, 112]. It has also been speculated in women that the increase in the concentrations of aldosterone during pregnancy could be a decisive physiological event in order to prevent the massive natriuresis that could arise from an enhanced glomerular filtration rate. In these cases, aldosterone shows a physiological action opposite to the natriuretic effect of P4 at the level of the distal convoluted tubule, avoiding excessive loss of Na and allowing its gradual accumulation in the fetoplacental and in the extracellular maternal fluids [113]. However, the antagonism between both mineralocorticoids, i.e., aldosterone and P4, during pregnancy does not seem to be constant [114, 115].

4. Conclusions

Our results obtained in healthy reproductive mares demonstrated that there is an activation of the RAAS around the time of ovulation, as indicated by the increased plasma renin and aldosterone concentrations. After ovulation, the rapid decrease in plasma renin and ANG-II concentrations might indicate a modulation of the previously activated RAAS, even though plasma aldosterone concentrations increased during this period, suggesting a dissociation of the components of this system.

In the pregnant mare, there is also an increased activity of various components of the RAAS. Pregnant mares show a progressive increase in circulating renin, with fluctuating changes in aldosterone, peaking at fifth month of pregnancy and without significant changes in ANG-II. The reason for the apparent dissociation between the three main hormones of the RAAS at determined moments of the pregnancy remains unclear. The data obtained in pregnant mares regarding the RAAS seems to indicate that renin is a more intense stimulus for the increased synthesis of aldosterone than ANG-II.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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