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REVIEW ARTICLE

Cardioprotective function of progesterone: A new perspective

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ABSTRACT

Cardioprotective mechanism in females during reproductive phase is unclear. New perspective explains cardioprotective function of progesterone. Progesterone, the intermediary metabolic product in synthesis of steroid hormones, with t/2 of 30 min, stimulates respiratory center inducing respiratory alkalosis in turn lowers plasma ionic calcium. This results in decreased blood coagulability and cardiac contractility along with smooth muscle relaxation. Vascular smooth muscle relaxation, leading to generalized vasodilatation causes better tissue perfusion resulting in diminished erythropoietin, and erythrocyte count. This reduces blood viscosity and afterload on the heart. Cardiac contractility remains balanced due to opposing influences of decreased plasma ionic calcium and raised basal body temperature. On sudden withdrawal of progesterone, as during premenstrual, postpartum and postmenopausal periods, cardioprotective changes are reversed. The awareness helps to build better body buffer system, aiming to correct acid-base imbalance, during expected fluctuations of progesterone.

KEY WORDS: Respiratory Alkalosis; Muscle; Smooth; Vascular; Perimenopause; Progesterone; Vasodilation

INTRODUCTION

Many studies like Stamler et al., McGill and Stem, Weigensberg et al., Kushwaha et al., Stampfer et al., Sullivan et al., Grodstein et al., and Williams and Adams, Miyagawa et al.[1-9] showed a well-established fact that females have protection from hypertension and coronary heart diseases during the reproductive phase which disappears after menopause. The female sex hormones, i.e., estrogen and progesterone are thought to be responsible for the same. The exact mechanism of the cardioprotection remains unclear.[1-9]

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It may be noted that the daily production of progesterone in females, during early follicular stage of menstrual cycle, is 1.5 mg/day, i.e., 10 times more than in male (0.15 mg/day).[10] The fluctuations of progesterone production occur along with estrogen, both during nonpregnant (menstrual cycle) and pregnant stages. The daily production of progesterone is increased by 6 times in preovulatory stage and by 200 times at 36 weeks of pregnancy as compared to the early follicular stage (Figure 1).[10,11] The progesterone/estrogen ratio shows changes from 6 to 20 in different stages of female reproductive cycle (Figure 2).[10,11] More the ratio, relatively less is estrogen synthesis and more is the release of the intermediary product, i.e., progesterone.

Although the *in vitro* studies in animals by Murray et al.[12] failed to demonstrate any direct beneficial effect of these hormones on isolated cardiac muscle or smooth muscle, the *in vitro* studies by Ryan and Pellecchia, Gill et al., Lee

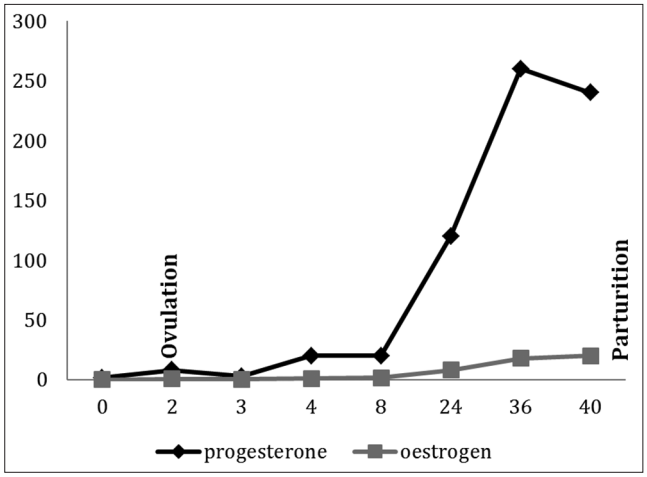

Figure 1: Daily production of progesterone and estrogen in different stages of pregnancy. Daily production of progesterone increased by 6 times in preovulatory stage and by 200 times at 36 weeks of pregnancy as compared to the early follicular stage[10,11]

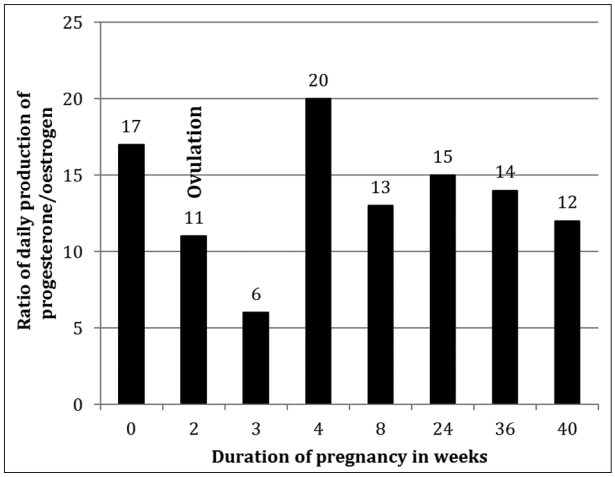

Figure 2: Ratio of daily production of progesterone/estrogen in different stages of pregnancy. Progesterone/estrogen ratio shows changes from 6 to 20 in different stages of female reproductive cycle. More the ratio, relatively less is estrogen synthesis and more is the release of intermediary product, i.e., progesterone[10,11]

et al. on smooth muscle in animals pretreated with these hormones, demonstrated better effects such as vascular endothelialization and smooth muscle relaxation with progesterone on estrogen-primed cells, than with estrogen or progesterone used individually.[13-15]

As per the textbooks of physiology like Guyton and Halll,[11] Kim et al.,[16] Hall,[17] Kim et al.,[18] Kim et al.,[19] the mitotic stimulating effect of estrogen in humans is well established and observed in Oocyte, granulosa cells, and theca cells during the maturation of graffian follicle; in luteal cells, during the development of corpus luteum; in stratum functionale layer of endometrium during menstrual cycle; in syncitio trophoblast cells of placenta during pregnancy; in alveolar cells of breast glands; with local estrogen hormone treatment on atrophic mucosa of vagina and nose: With estrogen treatment angiogenesis is favored and carcinogenicity is increased.[11,16-19]

Progesterone, along with direct stimulatory effect on respiratory center resulting in respiratory alkalosis, supports the estrogen-primed cell proliferation with following well-established observations such as associated hyperemia of ovaries; tortuous blood vessels in stratum functionale layer of endometrium; highly vascular corpus luteum; highly vascular placenta; and ½°C rise in basal body temperature (BBT) in postovulatory phase. It may be noted that inspite of universal acceptance of ½°C rise in BBT in postovulatory phase with noncalorigenic function of progesterone, i.e., unchanged oxygen utilization, and basal metabolic rate (BMR) by Telleria et al.,[20] Guyton and Hall,[11] Kim et al.,[16] Hall,[17] Kim et al.,[18] and Kim et al.,[19] the relation of increased BBT to generalized vasodilatation due to progesterone-induced decreased plasma ionic calcium remains ignored.

METHODOLOGY

This review was prepared based on the papers published in PubMed, Google Scholar, indexed journals and standard physiology, and pharmacology textbooks.

New Perspective

Cardioprotection as a function of progesterone hormone - A new perspective.

The new perspective theory concentrates on the direct stimulatory action of progesterone on respiratory center, with t/2 of 30 min. Details of mechanism are as follows (Figure 3).

The respiratory center stimulation results in hyperventilation and excess wash out of carbon dioxide (CO_2). This leads to decreased arterial CO_2 pressure (PCO_2) resulting in respiratory alkalosis. Alkalosis favors a combination of plasma proteins with calcium ions, lowering the plasma ionic calcium. Decreased plasma calcium ions cause diminished blood coagulability, reduced cardiac contractility, and smooth muscle relaxation including the vascular smooth muscle, which are very sensitive to extracellular fluid (ECF) calcium ions. The vascular smooth muscle relaxation leads to generalized vasodilatation, better tissue perfusion, and adequate O_2 supply. This lowers erythropoietin production, and erythrocyte count causing reduction of blood viscosity. The generalized vasodilatation and reduced blood viscosity decreases cardiac afterload by reducing peripheral resistance. The generalized vasodilatory function of progesterone is responsible for the ½°C rise in BBT in postovulatory phase. However, cardiac contractility remains balanced due to opposing influences of decreased plasma calcium ions and ½°C rise in BBT. Reversal of these beneficial effects occurs during postparturition period and after menopause. The

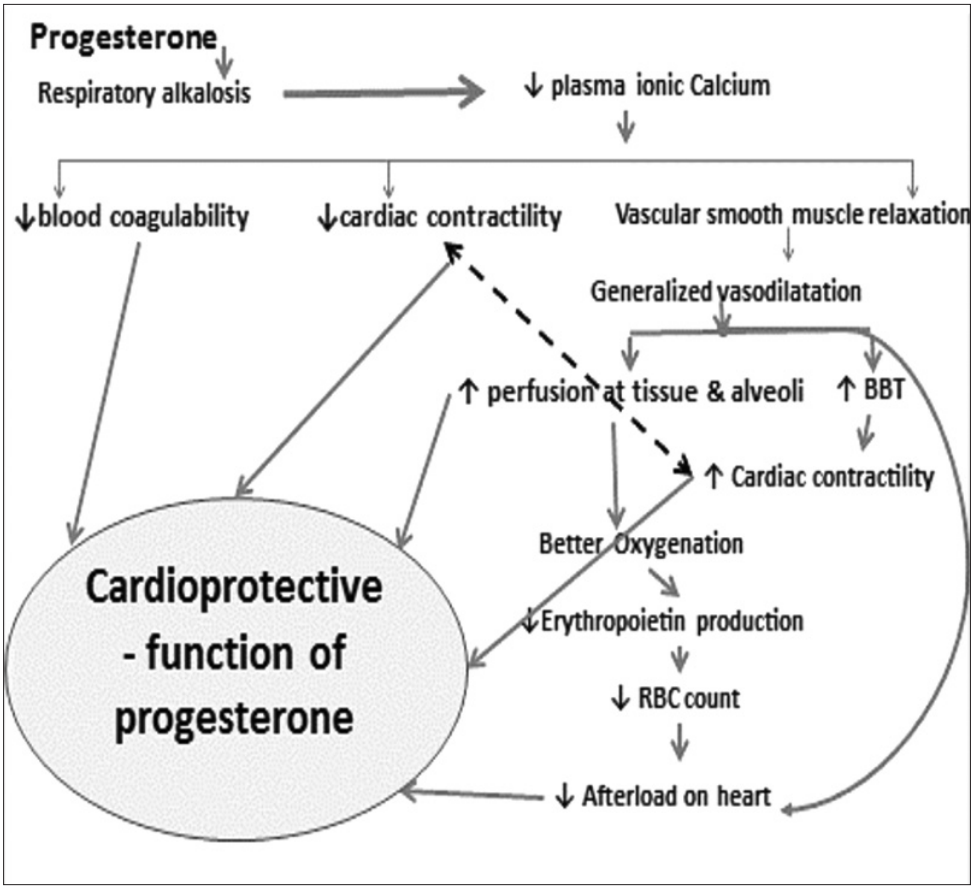

Figure 3: Postulated mechanism of cardioprotection by progesterone. Progesterone-induced respiratory alkalosis decreases plasma ionic calcium causing generalized vasodilatation**.** Cardiac contractility remains balanced due to opposing influences of decreased plasma ionic calcium and raised basal body temperature as shown in dashed line. Diminished blood coagulability, balanced cardiac contractility, reduced cardiac afterload due to vasodilatation and low erythrocyte count, and better tissue perfusion inclusive of heart, lungs, and kidney result in cardioprotection

vulnerability to thromboembolism increases in postpartum period due to the sudden release of plasma Calcium ions as a result of withdrawal of progesterone. Symptoms during perimenopausal period can be attributed to exaggerated fluctuations of progesterone (an intermediary product in the synthesis of estrogen) levels, i.e., night sweats to generalized vasodilatation (low plasma calcium ions), and hot flushes to sudden release of plasma calcium ions (a sensation similar to feeling of warmth felt during intravenous injection of calcium).

Evaluation of New Perception

The new perceptive theory visualizes the already accepted universal observations with a new outlook trying to interpret the mechanism connecting the different segments of observations. We strongly believe that the theory requires acceptance of new idea as a whole rather than demanding any further proof for it and the awareness of mechanism definitely helps for the better cardioprotection.

Although studies detected the presence of progesterone hormone receptors, Telleria et al. study report progesterone action without the presence of specific receptor.[20] We believe in the estrogen-primed progesterone receptors in respiratory center, but remain silent about progesterone receptors in peripheral organs, as we postulate the respiratory center stimulating action itself is responsible for all the associated actions.

Evaluation of Evidence and Discussion Related to Direct Respiratory Center Stimulatory Action of Progesterone Hormone and it's Relation to Respiratory Alkalosis

Two separate neural mechanisms regulate respiration. One is responsible for voluntary control and the other for automatic control. The voluntary system is located in the cerebral cortex and sends impulses to the respiratory motor neurons through the corticospinal tracts. The automatic system is driven by a group of pacemaker cells in the medulla. Impulses from these cells activate motor neurons in the cervical and thoracic spinal cord that innervate inspiratory muscles.[10,11,16-19]

The nervous system normally adjusts the rate of alveolar ventilation almost exactly to the demands of the body so that the oxygen pressure and PCO_2 in the arterial blood are hardly altered

even during heavy exercise and most other types of respiratory stress. The respiratory center is under the direct influence of the arterial concentration of CO_2 and hydrogen ions. A change in blood CO_2 concentration, therefore, has a potent acute effect on controlling respiratory drive, but only a weak chronic effect after a few days adaptation due to renal handling.[11,17,19]

For more than a century, the influence of sex hormones on breathing is studied. The studies by Hasselbach and Gammeltoft.[21,22] reported that women have decreased alveolar PCO_2 and lowered arterial PCO_2 during pregnancy. Later studies by Griffith et al.[23] described cyclic fluctuations in ventilation during the normal menstrual cycle that ceased with menopause. In the ensuing years, considerable data have accumulated showing that throughout life estrogen, progesterone, and testosterone can influence respiratory function in animals and humans as shown by Telleria et al.,[20] Dempsey et al.,[24] Tatsumi et al.,[25] Pequignot et al.,[26] Jones et al.,[27] Behan et al.,[28-30] Lebrun et al.,[31] and Richardson et al.[32]

Animal and human studies by Lysons and Antonio,[33] Skatrud et al.,[34] DA Bayliss et al.[35,36] proved that administration of synthetic progesterone alone or in combination with conjugated estrogen, consistently increases both resting and exercise MV(VE) with attendant reductions in $PaCO_2$, positron emission tomography CO_2, (end-tidal), $PCSFCO_2$ (cerebrospinal fluid). Progesterone increased the sensitivity of respiratory center to CO_2, resulting in increased tidal volume and minute ventilation (MV) as immediate effect.

Animal and human experiments in both male and female by Lysons and Antonio,[33] Zwillich,[37] Schoene et al.,[38] Gougoux et al.,[39] and Tatsumi et al.[40] proved that female sex hormones sensitize respiratory center by increasing the respiratory rate (RR) as immediate effect. The RR is restored back to normal by renal handling of acid-base balance as discussed by Weinberger et al., Haramati and Nienhuis, Hudson et al., Greenberger and Patterson, Effros and Swenson, Seifter.[41-46] On the other hand, respiratory frequency, O_2 consumption, CO_2 production, and body temperature were not affected. The arterial pH increased slightly, with a concomitant decrease in plasma (HCO_3^-). Dharwadkar et al. (2014)[47] observed decreased breath holding time (BHT) in young females compared to young males of same age concluding that BHT along with RR can be a simple measure for sensitivity of central ventilatory response. In conclusion, the mechanism of progesterone-induced increased sensitivity of respiratory center due to estrogen-primed progesterone receptors in respiratory center results in respiratory alkalosis.

THE RELATION OF ACID-BASE BALANCE TO PLASMA IONIC CALCIUM

A clinical case report by Dharwadkar et al.[48] reported the importance of total calcium versus ionic calcium in females. Diffusible ionic calcium is physiologically very active and forms 50% of the total plasma calcium. It is necessary for blood coagulation, muscle contraction, and nerve function, etc. Plasma proteins are more ionized when the pH is high, providing more protein anion to bind with calcium ions. It is established fact that alkalosis favors combination of plasma proteins with ionic calcium decreasing plasma ionic calcium and vice versa with acidosis releasing calcium ions.[16] Progesterone with its half-life of 30 min causes proportionate fluctuations of diffusible ionic calcium to its nondiffusible protein bound form, as an immediate effect. We further want to put forward the following two observational proofs for fluctuations of ionic calcium along with progesterone, which remains unexplained till today.

- Perimenopausal period is considered to be a comparative hypogonad state. It is associated with increased amplitude and frequency of luteinizing hormone (LH) surges.[16] Progesterone being the intermediary product of estrogen shows exaggerated fluctuations in its production along with LH surges. Hence, the mechanism of perimenopausal symptoms associated with LH surges which remained unexplained till today can be attributed to exaggerated fluctuations of progesterone., i.e., night sweats to generalized vasodilatation (due to low plasma calcium ions) and hot flushes to sudden release of plasma calcium ions similar as feeling of warmth felt during Intravenous injection of calcium as documented in Tripathi.[49]
- Immediately after delivery of young ones, there is curdling effect on boiling the cattle milk which gradually disappears in the next few days. It is probably due to acidic pH of milk secretion with the sudden release of ionic calcium, favoring the precipitation of milk proteins. This may be due to sudden reversal of alkalosis to acute acidosis after parturition on sudden withdrawal of progesterone.

THE RELATION OF DECREASED PLASMA IONIC CALCIUM TO GENERALIZED SMOOTH MUSCLE RELAXATION INCLUDING VASCULAR IS RESPONSIBLE FOR GENERALIZED VASODILATATION

Smooth muscle is divided into two types, i.e., multiunit smooth muscle and unitary (single unit) smooth muscle. In the multiunit smooth muscle, each fiber contract independent of others and their control is mainly through nerve signals. In unitary, smooth muscles hundreds to thousands of fibers contract together as a single unit and their control is mainly through non-nervous stimuli. The functional unity is due to the fibers arranged in sheets and cell membranes joined by many gap junctions through which ions can freely flow so that action potentials or simple ion flow without action

potentials can travel. Ryan and Pellecchia.[13] observed that local calcium perfusion reversed the progesterone pretreated gallbladder smooth muscle relaxation. Guyton and Hall documented that local diminished calcium ion concentration causes local vasodilatation.[11]

We want to highlight that, due to decreased ECF ionic calcium, the unitary smooth muscles of gastrointestinal tract, myometrium, and vascular smooth muscle show relaxation under the progesterone influence, in spite of variable degrees of both local and general nervous control. The generalized vascular smooth muscle relaxation thus leads to generalized vasodilatation.

Following are the Proofs for the Generalized Vasodilatation

There is universal acceptance of ½°C rise in BBT in postovulatory phase due to progesterone which is noncalorigenic, i.e., with no change in oxygen utilization and BMR. We want to highlight that generalized vasodilatation is the reason for increase in BBT, so increased BBT itself is the proof of generalized vasodilatation. We want to highlight that, the presence of vasodilatation in the estrogen-primed target organs such as hyperemia of ovaries, tortuous blood vessels in stratum functionale layer of endometrium, highly vascular corpus luteum, and highly vascular placenta are all a part of generalized vasodilatation. The tissue fluid retention observed during postovulatory (premenstrual) phase of menstruation and pregnancy proves the fact of increased vascular permeability and inturn supports the idea of generalized vasodilatation.

The universal observation of occasional syncopal attacks during early pregnancy will support our theory of sudden generalized vasodilatation caused due to progesterone. Bayliss et al.[35] in their study of progesterone administration at high concentration by both routes i.e., intravenously or directly into the medulla oblongata in anesthetized and paralyzed male and female cats showed decreased phrenic nerve activity (used as indicator of respiratory center sensitivity) along with a substantial hypotension, may be in support of our theory of sudden generalized vasodilatation caused due to progesterone.[35]

THE RELATION OF DOSE-DEPENDENT PROGESTERONE-INDUCED GENERALIZED VASODILATATION WITH BETTER TISSUE PERFUSION, TO DECREASED ERYTHROCYTE COUNT BOTH IN NONPREGNANT AND PREGNANT STATE

Studies by Skatrud et al.[34] proved that arteria-venous difference of oxygen remains constant in a satisfactory limit during nonpregnant and different trimesters of pregnancy, i.e., the constant tissue oxygen extract even in the presence of decreased erythrocyte count.

We want to have a new outlook of "Role of dose-dependent progesterone-induced general vasodilatation with better tissue perfusion as the reason for decreased erythropoietin inturn decreased erythrocyte count" rather than the present accepted explanation of "Increased tissue fluid retention as the reason for decreased hematocrit value and reason for decreased erythrocyte count during pregnancy."

Progesterone-induced generalized vasodilatation by, decreasing velocity of blood in blood vessels, increasing lateral wall pressure, i.e., perfusion pressure (as per the Bernoulli's principle), and increasing vascular capillary permeability, leads to better gas exchange both at tissue and alveolar capillary membrane. It maintains normal tissue oxygen extraction level reducing erythropoietin production inturn erythrocyte count (Figure 1). It may be noted that more is the progesterone more will be the generalized vasodilatation; more is the generalized vasodilatation more will be reduction in erythrocyte count. In conclusion, reduction in erythrocyte is dose-dependent on progesterone.

Observational Proofs for Our Argument

In the absence of nutritional deficiency, as in Kim et al.,[16] the 10% decrease in erythrocyte count of adult female reverts back to comparable values of age-matched male after menopause and there is further decrease in erythrocyte count proportionate to progesterone level during pregnancy which reverts back to nonpregnant levels after parturition.

CONCLUSION

In conclusion, the new perspective theory is "A new outlook of cardio protection as a function of progesterone hormone-induced respiratoy alkalosis, decreased plasma ionic calcium and generalized vasodilatation." It explains the lack of cardioprotection in the absence of progesterone hormone in postpartal and postmenopausal women. During postpartum period, there is vulnerability to thromboembolism due to sudden plasma ionic calcium release on sudden withdrawal of progesterone, which sometimes may be fatal. In the absence of progesterone, the vulnerability of postmenopausal females to cardiovascular diseases is same as that of males. All the cardioprotective changes are reverted back resulting in respiratory acidosis, increased plasma ionic calcium thus augmenting the coagulability of blood with a vulnerability for thrombosis, i.e., intravascular clotting. The resultant generalized vasoconstriction diminishes tissue perfusion including coronary perfusion, elevates erythrocyte count, raises viscosity, and in turn amplifies the load on heart.

The awareness helps for better cardioprotection achieved with building up of better buffer system of the body, for

example, by deep breathing exercises, consumption of acidic type of foods (vitamin C), and by judicious use of HCO_3^- etc. In addition, further studies on the efficacy of buffer system as assessed by arterial blood gas analysis, in phases of anticipated fluctuations of progesterone, will support the new idea.

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