



IMPACT OF THREE PERIOVULATORY PROGESTERONE FLUCTUATIONS IN OVULATION AND TUBAL SUCTION OF RELEASED OVUM: A NEW PERSPECTIVE.

Physiology

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ABSTRACT

New perceptive theory concentrates on progesterone [PR] [$t/2=30\text{min}$] respiratory center stimulation causing respiratory alkalosis, low plasma ionic calcium, smooth-muscle relaxation, generalized vasodilatation. Impact of three perioovulatory PR fluctuations on ovulation is highlighted. First preovulatory PR spurt fluctuation is due to PR accumulation as intermediary product in estrogen [ER] synthesis during negative feedback effect of 1st ER peak and is responsible for hypothalamo – hypophyseal vasodilatation producing preovulatory gonadotropins' surge, augments PR synthesis through explosive dominant follicular proliferation. Resultant elevated intrafollicular pressure compressing dilated thecal vessels causes follicular wall ischemia, prevents follicular PR absorption into circulation producing 2nd PR withdrawal fluctuation. PR withdrawal induced follicular vascular wall contraction augments intrafollicular pressure squeezing antral fluid and ovum out through stigma i.e. weakened follicular wall. It manifests as Mittelschmerz and endometrial spotting. 3rd postovulatory PR fluctuation due to peritoneal antral fluid PR absorption causes relaxation of already spastically contracted uterus facilitating tubal ovum suction.

KEYWORDS:

Calcium, Ovulation, Progesterone, Suction, Vasodilation

INTRODUCTION-

In reproductive phase of woman, during each menstrual cycle, one oocyte from one of the two ovaries matures and gets released i.e. ovulation. It is well accepted that Hypothalamo – hypophysio – ovarian axis works in coordination and brings ovulation. The pulsatile secretion of Hypothalamic GnRH, with resultant pulsatile gonadotropins' secretion of Anterior Pituitary i.e. Follicular stimulating hormone (FSH) and Luteinizing hormone (LH), is responsible for nourishment & maturation of graafian follicle. A surge of Gonadotropins occurring 9hrs before ovulation, is essential for ovulation. [1-4]

At present, ovulation is thought to be an inflammatory process due to hypoxic microenvironment which triggers formation of prostaglandins [PG], proteolytic enzymes etc. But this hypoxic microenvironment does not lead to complete ischaemia of follicle [1-20]. Despite many studies [5- 20] trying to establish relation between LH, PR, PG and genetic expression during ovulation, confusion still persists.

The lacuna in understanding is probably due to failure of direct demonstrable effect of PR on isolated smooth muscle in vitro studies. The direct respiratory centre stimulatory action of PR [$t/2$ 30min] causes respiratory alkalosis with resultant diminution in plasma calcium ions leading to smooth muscle relaxation including vascular muscle effecting in generalized vasodilatation. So till today the possible role of PR induced vasodilatation on mechanism of preovulatory gonadotropins' surge and ovulation is not thought of. Recently Dharwadkar et al [2014, 2015 and 2017] explains the details of the vasodilatory function of PR and its role in cardio protection and preovulatory gonadotropins' surge [21-23]. In the present article, the role of PR- induced vasodilation in Hypothalamus, Hypophysis, Graafian follicular wall and their influence in pulsatile secretions, related to mechanism of ovulation is discussed.

METHODOLOGY

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

New perspective –

Ovulation as a vasodilatory function of Progesterone – A new perspective

New perspective theory concentrates on PR [$t/2$ 30 minutes] induced respiratory alkalosis, low plasma ionic calcium and vascular smooth-muscle relaxation leading to generalized vasodilatation. Vasodilatation occurs simultaneously at Hypothalamus, hypophysis and graafian follicular wall due to PR and vice versa i.e. vasoconstriction on its withdrawal. [fig no 1 & 2]. Production of PR, an intermediary product, is amplified during block in Estrogen [ER] synthesis by follicular cells under pulsatile gonadotropins' influence.

There are 3 perioovulatory fluctuations of PR. First fluctuation is as “preovulatory PR spurt” occurring 24hrs before ovulation. Second fluctuation is as “PR withdrawal” during dominant follicular wall compression occurring 8hrs after gonadotropins' surge and ½ hrs before release of ovum i.e. ovulation. Third postovulatory fluctuation is as “sudden increase in circulatory PR” due to peritoneal absorption of PR from antral fluid.

The preovulatory spurt of PR controls the negative feedback inhibition of 1st peak of ER on GnRH pulse for 15 hrs as compared to follicular GnRH pulse inhibition for 3hrs by increasing ER bioavailability at vasodilated hypothalamus. During GnRH inhibition, the vasodilated hypophysis synthesises and stores 4-5 times more gonadotropins. And on GnRH pulse regain, they are released as preovulatory gonadotropins' surge [9 hrs before ovulation]. The Gonadotropins' surge causes augmented synthesis of ovarian hormones from dominant follicle for duration of 8½ hrs. before ovulation The ovarian hormones, i.e. ER with its local mitotic stimulating effect and PR with its vasodilatory effect, result in explosive proliferation of follicular cells, increased antral fluid formation, angiogenesis and vasodilatation of thecal blood vessels.

The new perspective explains as follows: The compression of dilated thecal blood vessels of dominant follicle, by explosive increase in intrafollicular pressure, leads to ischaemic necrosis of follicular wall, with stigma formation at ovarian surface. The same mechanism also blocks absorption of follicular antral PR into general circulation. The resultant sudden PR withdrawal [$t/2=$ 30 min] from general circulation causes thecal vascular smooth-muscle contraction as an unit squeezing ovum, granulosa cells and antral fluid out through stigma within 30 minutes.

There is rapid absorption of PR contained in this extruded antral fluid from the pelvic peritoneal surface resulting in increased levels of PR in general circulation during the immediate postovulatory period. It leads

to relaxation of uterus which was in the state of spasmodic contraction during ovulation owing to transient PR-withdrawal. This uterine relaxation acts as suction pump and aids in the capillary tube suction effect of fallopian tube causing aspiration of the released ovum into latter.

Peritoneal PR absorption also triggers Luteal phase changes like corpus haemorrhagicum and corpus luteum formation, raised Basal Body Temperature [BBT], reduced GnRH pulse rate, increased LH/total gonadotropins and PR/ER ratio. The PR vasodilatory function triggering luteal phase changes can be explained as follows.

There is high ER content of Theca and Granulosa cells of dominant follicle at the time of ovulation. The ER by its local mitotic stimulating action helps in angiogenesis of ruptured follicle results in the formation of highly vascularized corpus luteum which is also supported by vasodilatory effect of PR. The vasodilatory effect of PR at Hypothalamus reduces the GnRH pulse rate which is basically decided by the pulsatile ER negative feedback by augmenting its bioavailability. Reduced GnRH pulse rate along with PR induced hypophyseal vasodilatation allows sufficient duration and necessary nutritional supply i.e. extra 3 AA addition to β chain of FSH for conversion to LH [90%]. During luteal phase each gonadotropins pulse with 90% LH content, stimulates ER production by luteal cells. As the t/2 of LH [70min] is three times less than FSH t/2 [180 min], the highly vascular corpus luteum produces proportionately more PR/ER [60:1] as compared to follicular phase PR/ER ratio of 10:1 i.e. release of more intermediary product PR due to longer block in ER synthesis. Thus in conclusion during luteal phase, vasodilatory effect of PR facilitate proportionately more production of LH from pituitary and shorter t/2 of LH facilitate more production of PR from the highly vascular corpus luteum.

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 vasodilatory role of PR in ovulatory mechanism definitely helps for the better management in assisted reproductive clinical practice.

Though studies detected presence of PR hormone receptors, Telleria et al. study reports PR action without presence of specific receptor^[24]. We postulate the respiratory center stimulating action of PR itself is responsible for all the associated actions based on our belief of existence of ER primed PR receptors probably only in respiratory centers irrespective of the existence of such receptors in other peripheral organs.

Evaluation of evidence and related discussion of progesterone [PR] hormone respiratory center stimulation leading to Respiratory Alkalosis, decreased plasma Calcium ions, smooth muscle relaxation including vascular smooth muscle with resultant generalized vasodilatation

It is discussed in detail by Dharwadkar et al in “A Comparative Study of breath holding time as an Index of Central Ventilatory Response in young Healthy Adults of both Sexes” [2014]^[21], “Negative Feed Back Regulation of Estrogen & Vasodilatory Function of Progesterone Responsible for Preovulatory Gonadotropin Surge [LH Surge] - A Hypothesis”, [2015]^[22] “Cardioprotective function of Progesterone – A new perspective.” [2017]^[23]

Evaluation of pulsatile GnRH causing release of pulsatile gonadotropins secretion

It is observed that pulsatile GnRH causes release of Gonadotropins from anterior pituitary, where as continuous infusion causes complete inhibition of Gonadotropins^[1-4]. The study observation by Marshall JC, Kelch RO: Gonadotropin-releasing hormone: Role of pulsatile secretion in the regulation of reproduction. N Engl J Med 1986; 315:1459 as cited in Figure 22.20 of Ganong's review of Medical Physiology^[1] and data from Wilson RC, Kesner JS, Kaufman JM et al: central electrophysiologic correlates of pulsatile luteinizing hormone secretion. Neuroendocrinology 39:256, 1984 as cited in figure 96-9 of Guyton and Hall Textbook of medical physiology^[4] shows Gonadotropins secretion as pulsatile with each GnRH pulse, supports new

perspective idea that “GnRH pulse stimulates the release but not the synthesis of gonadotropins from anterior pituitary”.

Evaluation of evidence for the role of PR vasodilatory effect on luteal phase changes like decreased GnRH pulse rate along with enhanced ratio of LH/total gonadotropins and PR/ER secretion.

The luteal phase shows decreased GnRH pulse rate of 8/day along with 90% LH/total gonadotropins ratio secretion and PR/ER ratio of 200 as compared to follicular phase GnRH pulse rate of 15/day with LH/total gonadotropins ratio of 60% and PR/ER ratio of 5 [fig 22.20]^[1].

New perspective explanation for the above observation is as follows–

The vasodilatory effect of PR at Hypothalamus, by enhancing bioavailability of ER, reduces the GnRH pulse rate which is basically decided by the pulsatile ER negative feedback. Reduced GnRH pulse rate along with PR induced hypophyseal vasodilatation allows sufficient duration and necessary nutrition supply i.e. by adding extra 3 AA to β chain of FSH converting it to LH [90%]. Thus during luteal phase each gonadotropins pulse with 90% LH content, stimulates ER production of luteal cells. Reduced gonadotropins pulse rate and reduced t/2 of LH [70 minutes] as compared to FSH t/2 [120 min.], causes longer block in ER synthesis facilitate release of proportionately more PR as intermediary product from the highly vascular corpus luteum.

In conclusion, during luteal phase, vasodilatory effect of PR at hypothalamo –hypophyseal portal circulation reduces GnRH and Gonadotropins pulse rate facilitating enhanced LH synthesis from pituitary. Reduced Gonadotropins pulse rate and shorter t/2 of LH, prolongs the break in ER synthesis, facilitating release of more PR, an intermediary product during ER synthesis from corpus luteum.

Evidence for the follicular vascular wall compression of dominant follicle.

- Pre-ovulation pain or Mittelschmerz can appear suddenly and usually subsides within hours. In some women, the mittelschmerz is localized enough so that they can tell which of their two ovaries provided the egg in a given month. “Mittelschmerz” a German word meaning “middle pain” is a medical word for “ovulation pain” or “midcycle pain”. About 20% of women experience mittelschmerz, some every cycle, some intermittently.^[25-28]

At present, ovulation is thought to be an inflammatory process due to hypoxic microenvironment which triggers formation of prostaglandins [PG], proteolytic enzymes etc. ruling out possibility of complete ischaemia of follicle.^[1-28] The cause responsible for this inflammatory process, hypoxic microenvironment remains elusive till today.

- The new perceptive highlights that the compression of vasodilated follicular wall of dominant follicle due to explosive increase in intrafollicular pressure under the influence of preovulatory Gonadotropins surge results in the ischaemic necrosis of follicular wall triggering formation of prostaglandins [PG], proteolytic enzymes etc leading to stigma formation at ovarian surface and is responsible for Pre-ovulation pain or Mittelschmerz pain.
- The sudden PR withdrawal due to blockade of PR [t/2=30min] entry from follicle into the circulation, reverses respiratory alkalosis to acute respiratory acidosis leading to smooth muscle contraction. Follicular vascular wall contraction as a unit is responsible for the squeezing effect on follicular contents through already weakened wall i.e. stigma within 30 minutes of its formation and is also responsible for Mittelschmerz pain. The associated endometrial vasospasm causes endometrial spotting and myometrial spasm prepares uterus as suction pump for sucking the released ovum.

One of the Evidences for postovulatory peritoneal antral PR absorption as 3rd acute periovulatory fluctuations is uterine suction pump

It is well observed phenomenon that immediately after release of ovum one can actually see a slow fluid current flowing toward the ostium^[4]. This can be explained as follows.

- There is rapid postovulatory peritoneal PR absorption from the extruded antral fluid which triggers ovum suction into fallopian tubes as follows. The capillary tube suction effect of fallopian tubes is aided by uterus which acts as suction pump i.e. uterine spasmodic contraction due to PR withdrawal during ovulation is followed by uterine relaxation due to postovulatory peritoneal PR absorption

In conclusion there are *three periovulatory fluctuations of PR in general circulation* i.e.

- Preovulatory spurt of PR for 24hrs before ovulation
- Ovulatory time PR withdrawal for ½ hrs due to dominant graffian follicular vascular compression resulting in Ovulation and
- Post-ovulatory spurt of PR due to peritoneal PR absorption from extruded antral fluid immediately after peritoneal release of ovum.

Simultaneous action of Progesterone[PR] on ovary and uterus is due to rich vascular anastomosis between them [fig 3] : Preovulatory PR withdrawal due to follicular wall compression, inducing vascular wall contraction results in ovulation, uterine vasospasm [spotting], myometrial spasm. Postovulatory PR due to peritoneal antral fluid absorption, inducing myometrial relaxation facilitates suction of ovum.

Evidence for the peritoneal PR absorption –

- Peritoneal PR absorption is responsible for suction of released ovum into fallopian tubes immediately after ovulation. Myometrial relaxation aids the capillary suction of fallopian tubes.
- Peritoneal PR absorption is responsible for triggering “Luteal phase changes” like corpus haemorrhagicum formation, raised BBT, reduced GnRH pulserate, increased LH/ total gonadotropins and PR/ER ratio. The role of vasodilatory function of PR in luteal phase can be explained as follows. There is high estrogen content of Theca and Granulosa cells of dominant follicle at the time of ovulation. The ER by its local mitosis stimulating action helps in angiogenesis of ruptured follicle supported by vasodilatory effect of PR results in the formation of highly vascularized corpus luteum. The vasodilatory effect of PR at Hypothalamus reduces the GnRH pulserate which is basically decided by the pulsatile ER negative feedback by augmenting its bioavailability. Reduced GnRH pulserate along with PR induced hypophyseal vasodilatation allows sufficient duration and necessary nutrition supply i.e. extra 3 AA addition to b chain of FSH for conversion to LH [90%]. During luteal phase each gonadotropins pulse with 90% LH content, stimulates ER production of luteal cells. As the t/2 of LH [70min] is three times less than FSH t/2 [180 min], the highly vascular corpus luteum produces proportionately more PR/ER [60] as compared to follicular phase PR/ER ratio of 10 i.e. release of more intermediary product PR due to longer block in ER synthesis.

Thus in conclusion, during luteal phase, vasodilatory effect of PR facilitate proportionately more production of LH from pituitary and shorter t/2 of LH facilitate more production of PR from the highly vascular corpus luteum.

Conclusion –

In conclusion the new perspective theory highlights the role of PR induced smooth muscle relaxation in the mechanism of ovulation i.e. release of mature ovum into the peritoneal cavity. Circulatory PR [t/2 30min.] by inducing respiratory alkalosis with resultant decreased plasma ionic calcium causes smooth muscle relaxation including vascular smooth muscle effects in generalized vasodilatation and vice versa on its withdrawal. Preovulatory spurt of PR responsible for preovulatory surge of Gonadotropins, influences the explosive proliferation of dominant graffian follicle leads to increased intrafollicular pressure compressing the vascular follicular wall. The resultant ischaemic necrosis of follicular wall forms stigma on ovarian surface in 8 ½ hrs of preovulatory surge. The vascular compression induced block in absorption of PR from follicle into circulation, causes sudden decline of PR from circulation resulting in acute respiratory acidosis and smooth muscle contraction. Contraction of dominant follicular vascular smooth muscle as one unit causes in squeezing of antral fluid and ovum through already weakened wall i.e. stigma. The PR withdrawal at the same time causes endometrial vasospasm and myometrial contraction resulting in spotting. Postovulatory peritoneal PR absorption from antral fluid reverses uterine changes. The

postovulatory Myometrial relaxation makes uterus to function as suction pump for the released ovum. Thus the acute fluctuations of PR and the rich vascular anastomosis between ovary and uterus assures a controlled force and speed for the release of ovum at fimbrial end of fallopian tube and its immediate suction into the fallopian tube.

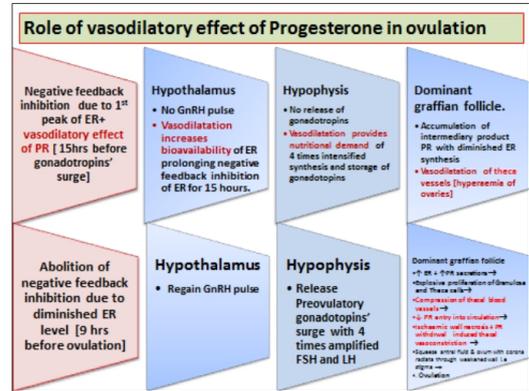


Figure 1: Role of vasodilatory effect of preovulatory spurt of Progesterone [PR] on Hypothalamo – hypophysio- ovarian axis during ovulation. PR- induced vasodilatation, prolongs the negative feedback effect of Estrogen [ER] for 15hrs, resulting in a 4 times augmented Gonadotropins surge, which occurs 9hrs preovulatory, leads to ovulation.

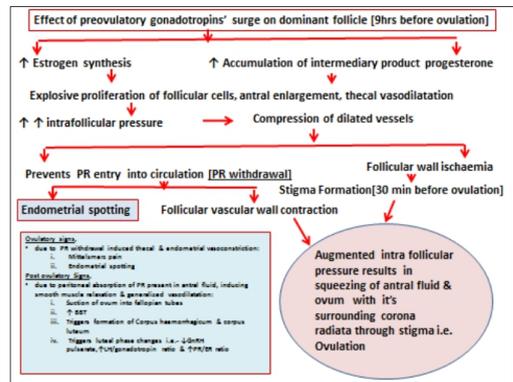


Figure 2 – Effect of preovulatory gonadotropins' surge on dominant follicle results in compression of dilated thecal blood vessels, follicular wall ischaemia and prevention of Progesterone [PR] entry into circulation. Sudden PR withdrawal results in, vascular wall contraction squeezing antral fluid & ovum through stigma [Ovulation], uterine vasospasm [endometrial spotting] and myometrial spasm.

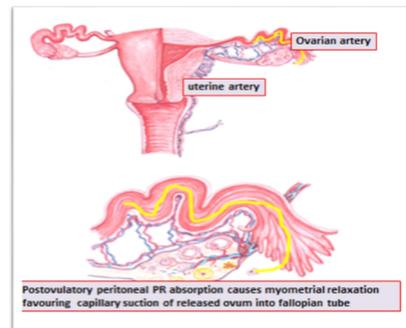


Figure 3 – Simultaneous action of Progesterone[PR] on ovary and uterus due to rich vascular anastomosis between them: Preovulatory PR withdrawal due to follicular wall compression, inducing vascular wall contraction results in ovulation, uterine vasospasm [spotting], myometrial spasm. Postovulatory PR due to peritoneal antral fluid absorption, inducing myometrial relaxation facilitates suction of ovum.

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