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Negative Feed Back Regulation of Oestrogen & Vasodilatory Function of Progesterone Responsible for Preovulatory Gonadotropin Surge [LH Surge] - A Hypothesis.

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ABSTRACT

At present there are many universal observations related to GnRH pulse & Gonadotropins surge in female. The explanation regarding the possible cause of preovulatory LH surge is not clear. An effort is made to explain this, with help of multiple experimental & human study observations as follows

First peak of oestrogen occurring 24hrs prior to ovulation ⇒ Inhibition of GnRH at Hypothalamus. ⇒ ↓FSH +↓ LH [from gonadotropes of pituitary] ⇒ ↓ Oestrogen [from Theca interna cells] ⇒ Regain of GnRH secretory pulse after 15hrs. ⇒ 3½ times increased secretion of gonadotropins as preovulatory surge . This surge has decreased ratio of LH : total gonadotropins

In conclusion "preovulatory gonadotropins' surge" is better word used than "preovulatory LH surge". There is one gonadotropin surge with one pulse of GnRH with LH content of 67% in follicular, 57% in preovulatory & 90% in luteal phases. Increase in LH content in luteal phase is due to vasodilatory effect of progesterone causing better hypothalamo – hypophyseal portal circulation, providing better nutrition supply of aminoacids [AA] favouring conversion of FSH to LH. The β subunit of FSH with addition of 3 AA. gets converted to LH i.e. 112 AA in FSH & 115 AA in LH.

Inspite of removal of inhibitory effect of 2nd peak of oestrogen on GnRH, Gonadotropins' surge does not occur. This may be due to generalized vasoconstriction caused by sudden withdrawal of progesterone, resulting in poor nutrition of secretory cells of hypothalamus & pituitary.

Keywords-*Estrogens, Gonadotropin –Releasing Hormone, Gonadotropins, LH surge, Ovulation, Progesterone*

Discussion

At present there are many universal observations related to GnRH pulse & Gonadotropins surge in female. The explanation regarding the possible cause of preovulatory LH surge is not clear. The conclusions of our theory are derived with the help of already existing multiple experimental & human observations.

Our postulated theory is based on following concepts –

1. Pulsatile secretion of GnRH by Hypothalamus causes pulsatile secretion of Gonadotropins [FSH & LH] [1] -[6]
2. Each GnRH pulse cause one Gonadotropin surge. [1] –[6]
3. GnRH , a polypeptide with 10 AA ,enters Hypothalamo – Hypophyseal [HH] portal circulation. The small amount of GnRH secreted, is biologically active to stimulate Gonadotropes of Pituitary, which then enters the general circulation ,gets diluted & become untraceable. So GnRH pulses are traced by Gonadotropin surges. [6]
4. The secretion of gonadotropins like FSH & LH by Gonadotropes are always observed as surges which may be due to sudden release of stored hormones in secretory granules. During each surge LH peaks more than FSH. LH disappears more quickly from general circulation as it's t½ is shorter [60min] than that of FSH [170 min] making the FSH levels apparently more [2]

   So it will be more appropriate if each surge is considered with the amount of total gonadotropins & LH content in percentage of total secretion. We have made effort to analyse the published data available in textbooks in relation to GnRH pulse rate , Total gonadotropin secretion & it's LH content in % and ovarian harmone production rate in different phases of menstruation. [Table no. 1] [1],[7],[8]
5. Gonadotrope cells secrete gonadotropins which are glycoproteins. Confusion exists regarding synthesis & secretion of FSH and LH. [9]

   We postulate that in the synthesis of Gonadotropins, FSH is precursor of LH. The observation of more LH content [90%] in midluteal phase as compared to a lesser LH content [67%] in early follicular phase, is probably because of the availability of more nutrients to Gonadotropes, due to the vasodilatory effect of progesterone on HH portal circulation.

Progesterone action is based on it's respiratory center stimulating effect causing a comparative alkalosis in body, leading to decreased ionic Ca^{2+} resulting smooth muscle relaxation . The smooth muscle relaxation more so vascular smooth muscle relaxation is fundamental cause of many observations during normal menstrual cycle. The vasodilatory effect of progesterone is dependent on it's blood concentration.[10]- [20]The gradual daily increase in progesterone production during luteal phase causes gradual increase in LH secretion probably meeting nutritional demand of gonadotropes.

Our postulated theory

[A] Preovulatory gonadotropin's surge following 1st peak of oestrogen during follicular phase.

Under the influence of gonadotropins, the theca cells are the source of circulating oestrogens during the follicular phase. The 1st peak of oestrogen [at production rate of 0.70mg/day] observed 24 hrs before ovulation, causes negative feedback INHIBITION of GnRH pulse, inturn inhibiting gonadotropin secretion. There is sudden decrease in the circulating levels of oestrogen which removes the inhibition on GnRH secretion within 15hrs [900min]. This triggers a preovulatory surge of Gonadotropins which is 3 ½ times more than that produced during other phases [1]–[4].

The flowplan-

1. Negative feedback inhibition of 1st peak of oestrogen [occurring 24hrs prior to ovulation] ⇒
2. Inhibition of GnRH at Hypothalamus. ⇒
3. ↓FSH +↓ LH [from gonadotropes at pituitary] ⇒
4. ↓ Oestrogen [from Theca interna cells] ⇒
5. Regain of GnRH secretory pulse after 15hrs. ⇒
6. 3½ times increased secretion of gonadotropins as preovulatory surge . This surge has decreased ratio of LH : total gonadotropins i.e. 57% compared to 67% of follicular phase & 90% of luteal phase.

B] Absence of similar gonadotropins' surge following 2nd peak of oestrogen during luteal phase.

[Note – The 2nd peak of oestrogen occurs on 9th postovulatory day, even with less concentration than 1st peak it can produce inhibition of GnRH secretion as the bioavailability of oestrogen is increased with maximum vasodilatory effect of progesterone.]

The flowplan-

1. Second peak of oestrogen occurring on 9th postovulatory day ⇒
2. Inhibition of GnRH at Hypothalamus. ⇒
3. ↓FSH +↓ LH [from gonadotropes of pituitary] ⇒
4. ↓ Oestrogen + ↓Progesterone [from Luteal cells] ⇒
5. ↓ Progesterone ⇒ ↓ respiratory center stimulation ⇒ Hypoventilation ⇒ acute respiratory acidosis ⇒ ↑ ionic Ca^{2+} ⇒ smooth muscle contraction i.e. vasoconstriction ⇒
6. Due to sudden generalized vasoconstriction + vasoconstriction of HH portal circulation ⇒
7. ↓ nutrition to both hypothalamus & pituitary. ⇒
8. Both Regain of GnRH secretory pulse & regain of Gonadotropes secretory function becomes less efficient due to ⇒ ↓ nutrition to respective secretory cells
9. Abscence of Gonadotropin surge inspite of removal of inhibitory effect of 2nd peak of oestrogen on GnRH.

C] Gonadotropins' surge can be explained as follows in other physiological & pathological condition as follows.

I. LH surges in perimenopausal woman. - may be due to less responsive ovary i.e. maturing graffian follicle which might be producing less oestrogen & more progesterone.

II. LH surges in bilateral ovariectomized young woman – may be due to additive effect of normal gonadotropins surge as both hormones are not utilized in the body with no production of oestrogen & progesterone.

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Table 1 – Details of GnRH, Gonadotropins & ovarian hormones in different phases of menstrual cycle.

	Early Follicular	24 hrs Preovulatory phase		Luteal
		15hrs preovulatory	9 hrs preovulatory Gonadotropins' surge	
GnRH [pulses/24hrs]	15	0	?	8
GnRH pulse interval [in min]	90 min	900 min		180min
Max FSH [mIU/ml] /GnRH pulse	6	0	30	2
Max LH [mIU/ml] /GnRH pulse	12	0	40	20
Total gonadotropins [mIU/ml]/GnRH pulse	18		70	22
LH/Total gonadotropins[%]	67%		57%	90%
Progesterone production [mg/day]	1.5	8		29
Oestrogen production[mg/day]	0.10	0.70 to >0.50		0.50

CONCLUSION

In conclusion "preovulatory gonadotropins' surge" is better word used than "preovulatory LH surge". There is one gonadotropin surge with one pulse of GnRH with LH content of 67% in follicular, 57% in preovulatory & 90% in luteal phases. Increase in LH content in luteal phase is due to vasodilatory effect of progesterone causing better hypothalamo – hypophyseal portal circulation, providing better nutrition supply of aminoacids [AA] favouring conversion of FSH to LH. The β subunit of FSH with addition of 3 AA. gets converted to LH i.e. 112 AA in FSH to 115 AA in LH.

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