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RESEARCH ARTICLE

COMPARATIVE STUDY ON HORMONAL ABNORMALITIES IN INFERTILE WOMAN

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ABSTRACT

The human female reproductive system is one of the most complicated system and is influenced by a number of hormones secreted by both the pituitary gland and the ovaries. The normal reproductive system in females is characterized by the monthly menstural cycle. Any abnormality in the secretion of any of the female reproductive hormones will result in improper menstrual cycle or infertility.

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INTRODUCTION

The menstural cycle consists of two phases of parallel events – follicular and luteal phase in the ovaries and proliferative and secretory phase within the endometrium.

Ovary – Follicular phase During the first few days of the menstrual cycle, FSH and LH are secreted by the anterior pituitary. FSH is involved in the development of primary follicles by increasing the number of granulosa layers. The spindle cells of ovary interstitium adhere on the outer layer of granulosa cells and form the theca. Theca has two coverings-theca externa and theca interna. Theca externa forms a capsule on developing follicle. Theca interna becomes secretory and secretes estrogen and progesterone (Gougeon *et al*., 1994). Once the proliferation gets completed the granulosa secretes follicular fluid containing high concentration of estrogen. Accumulation of follicular fluid results in the formation of centrum (Ferin *et al*., 1993). Accelerated growth of primary follicle results in formation of vesicular follicles. Estrogen in follicular fluid results in increased number of FSH receptors in granulosa cells making it more sensitive to FSH. FSH and estrogen combines to promote LH receptors, thus leading to LH stimulation (Filicori *et al*., 1986).

Luteal phase

Shortly before ovulation a small area in the center of the follicular capsule protrudes to form stigma. Stigma ruptures to release the ovum. FSH and LH act synergistically for the final growth of the follicle (Sherman *et al*., 1976). LH is responsible for the release and rupture of the stigma and release of ovum from the follicle. Thus without the pre ovulatory surge of LH, ovulation will not take place. LH also plays an important role in converting the granulosa cells into progesterone and estrogen secreting cells (lutein cells). This process is termed as Luteinization (Guyton, 2006). If pregnancy does not occur, the lutein cells (corpus luteum) gets transferred into corpus albicans which gets degenerated after 12 days i.e. at the 26th day of the menstrual cycle which is followed by the onset of the next ovarian cycle (Bishop *et al*., 2010).

Uterus – Proliferative phase

During the follicular phase, the ovary secretes increasing quantities of estrogen causing rapid proliferation of stromal and epithelial cells in the uterus. This results in completion of re-epithelialized endometrial surface within 4 to 7 days (Taylor *et al*., 1995).

Secretory phase

Luteal phase in ovary and secretory phase in uterus occurs simultaneously. Increased levels of progesterone and estrogen released during the luteal phase in the ovary results in the secretory function of the uterine endometrial cells. This causes accumulation of glycogen, lipid, blood vessels and increased endometrial thickness to receive the fertilized ovum (Bishop *et al*., 2010). If ovum is not fertilized, the luteal cells transform

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into corpus albicans and ceases to produce progesterone and estrogen resulting in the desquamation of the endometrium (Klein *et al*., 1996). This is once again followed by increase in levels of FSH and LH of anterior pituitary gland and the cycle continues.

Role of hormones in reproductive system

FSH & LH

Gonadotropin – releasing hormone (GnRH) is a decapeptide pulsatile produced by neurons with cell bodies primarily in the arcuate nucleus of the hypothalamus (Plant *et al*., 1978). The gonadotropins FSH and LH are produced by the anterior pituitary gonodotroph cells and are responsible for ovarian follicular stimulation. Structurally, there is great similarity between FSH and LH. They are both glycoproteins that share identical β subunits and differ only in the structure of their β subunits, which confer receptor specificity (Muderris and Oner, 2012).

FSH plays a central role in the control of oogenesis, follicle development and gametogenesis. Thus, an increase in FSH level leads to follicle maturation and proliferation of granulosa cells. The increase of insulin level stimulates the sensitivity of granulosa cells to release FSH, resulting in the growth of follicle cysts and regulation of steroidogenesis in the ovary.

LH has several functions in the control of the developing follicle; in the early follicular phase low levels of LH induce a change in function of the theca interstitial cells from production of progesterone to that of androgen (Erickson *et al*., 1985). FSH then promotes the conversion of androgen to estradiol by the granulosa cells. Not only does LH initiate theca cell androgen production, but it is responsible for the completion of oocyte maturation, ovulation and for the conversion of pre ovulatory follicle into a corpus luteum.

Estradiol

Steroids with 18C are classified as follows a) Estrone (E1) is a dominant estrogen in prepubertal and postmenopausal periods. b) Estradiol (E2) is the most potent estrogen produced during the reproductive age. c) Estriol (E3) is the least potent estrogen produced in pregnancy and synthesized by maternal and fetal units together. Estrogen augments the release of LH and inhibits the release of FSH. Theory of ovarian steroidogenesis explains that estrogen biosynthesis requires the combined action of two gonadotropins (LH and FSH) on two cell types (theca and granulose cells) (Peters and Joint, 1980). The elevated LH level in turn stimulates androgen secretion by theca cells of the ovary, providing the precursors for continued oestrogen production in adipose tissue. In sum, ovarian steroidogenesis is dependent on the effects of LH and FSH acting independently on the theca cells and granulosa cells, respectively (Muderris and Oner, 2012). Long term acyclic estrogen exposure may lead to excessive endometrial growth, resulting initially in oligomennorhea interspersed with episodes of menorrhagia. During the reproductive period it is estrogen that is responsible for the follicular phase change in the uterus, with deficiency resulting in irregular and incomplete development of the endometrium (Waldstreicher *et al*., 1986). Patients with a day 3 estradiol greater than or equal to 80 pg/ml had a higher cancellation rate and achieved lower pregnancy rate (Leo *et al*., 1999). During the follicular phase- Early in the follicular phase, the ovary secretes very little estrogen. A rise in FSH however stimulates estrogen production. During the luteal phase- Estrogen levels peak 1 day before ovulation, at which a positive feedback mechanism results in an LH surge. In the absence of fertilization, a gradual decrease in the production of estrogen by the corpus luteum results in the shedding of the endometrium (Bishop *et al*., 2010).

Prolactin

Prolactin is structurally related to GH and human placenta lactogen. Considered as stress hormone, it has vital functions in relationship to reproduction. Clinical and experimental studies have suggested a close relationship between the Hypothalamic Pituitary-Thyroid axis (HPT) and the Hypothalamic Pituitary Ovarian axis (HPO) (Turankar *et al*., 2013). Prolactin inhibitory factor (PIF) was once considered a polypeptide hormone capable of inhibiting prolactin secretion; dopamine released during stress, however is the only neuroendocrine signal that inhibits prolactin. Any compound that affects dopaminergic activity in the median eminence of the hypothalamus will also alter prolactin secretion (Molitch, 1999). *Prolactin and Infertility* – Prolactin inhibits two hormones which are necessary for ovulation: the FSH and GnRH. Hyperprolactinaemia causes infertility because prolactin inhibits the GnRH secretion. When the GnRH secretion is low, the FSH and LH secretions are also low and so they do not stimulate the gamete production and the gonadal steroid synthesis. Tasneem (2011) stated that there was a higher prevalence of hyperprolactinemia, together with a greater propensity for thyroid disorders in infertile subjects as compared to those in females with normal fertility. This study stated that some of the women with high prolactin levels had been observed to have hypothyroidism which was characterized by high levels of serum TSH and low levels of T3 and T4. Lunenfeld *et al*. 1992 suspected that the patients with increased prolactin values were often hypothyroid while Cramer *et al*. 2003 reported high TSH levels contributing to low prolactin levels in women.

TSH

Hypothyroid women have a decreased clearance of androstenedione and estrone. Although LH/FSH levels are normal, blunted or delayed LH response to GnRH has been reported in some hypothyroid women and serum PRL levels may be increased due to increased hypothalamic Thyroid Releasing Hormone secretion (Krassas, 2000). In women of fertile age, hypothyroidism results in changes in cycle length and the amount of bleeding, probably due to estrogen break through bleeding secondary to anovulation. Defects in hemostasis factors (such as decreased levels of factors VII, VIII, IX and XI) that occur in hypothyroidism may further contribute to polymenorrhea and menorrhagia. Altered peripheral estrogen, metabolism, hyperprolactinemia, defects in hemostasis, and disturbances in GnRH secretion that result in an abnormal pulsatile release of LH are some of the main causes to explain the high frequency of infertility in hypothyroid women (Unuane *et al*., 2011).

MATERIALS AND METHDOS

The hormonal investigation retrospective study was carried out with approved permission from the Research Centre's Ethics Committee at Prashanth Fertility Research Centre located in

Chetpet, Chennai, Tamil Nadu from August 2013 to April 2014. The inclusion criteria for the selection of cases were subjects who were referred by gynecologists for infertility investigation and in patients before IVF treatment; ranging in the age group from 20 to 48. The data were collected from 150 patients and grouped into infertile (n=143) and control (n=39). 5 milliliters of blood was collected during follicular phase 1-5 days (mostly second day of menstrual cycle) on a fasting by venipuncture and collected in vacutainers containing separating gel. The blood was allowed to clot and the serum was decanted and used for FSH, LH, Estradiol, Prolactin and TSH were estimated by ECLIA (Electro Chemi Luminesence Immuno Assay) using cobas e 411 analyser. Statistical analysis was done using Student's T –test and Pearson's correlation.

Table 1. Clinical Reference Values

FSH

Follicular cycle	1.1-9.5mIU/ml
Mid cycle	2.3-20.9mIU/ml
Luteal phase	0.8-7.5mIU/ml
Post Menopause	35-151mIU/ml

LH

Follicular cycle	1.9-12.5mIU/ml
Mid cycle	8.7-76.3mIU/ml
Luteal phase	0.5-16.9mIU/ml
Post menopause	8.2-40.8mIU/ml

Prolactin

Female non pregnant	upto30ng/ml
Pregnant	5-200ng/ml

Estradiol

Early follicle	20-150pg/ml
Late follicle	40-350pg/ml
Post menopause	<20mpg/ml

TSH

Normal range:0.4-7.0mIU/ml

RESULTS AND DISCUSSION

FSH assay was carried out in 51 infertile subjects out of which 44 (86.30%) were normal and 7 (13.70%) were having low FSH level. 20-35 age group had lower FSH than that of control sample this may result in improper development of follicle and thus affects fertility. The FSH concentrations in the infertile population showed significant difference compared to the control population (P <0.03). FSH begins to rise at the age of 35 with a marked increase beyond 40 years due to diminishing ovarian reserve (Kim *et al.*, 1997). The correlation of FSH and LH was found to be significant at 0.3972.

LH assay was carried out in 117 subjects out of which 62 (53%) were normal, 4 (3.40%) were high and 51 (43.60%) were having low LH level. The elevation of LH has been reported by Clifford *et al.* (1994), to be associated with an increased risk of infertility and cycle disturbance. The serum LH level was significantly elevated in the older group this finding may be related to the fact that earlier onset of FSH rise is associated with earlier accelerated dominant follicle development and ovulation in older anovulatory women (Klein *et al.*, 1996).

Prolactin assay was carried out in 103 subjects out of which 67 (65%) were normal, 36 (35%) were having high prolactin levels and low prolactin levels were not found in any of the subjects. Hyperprolactinemia may occur primarily as a result of normal body changes during stress, sleep, diseases affecting the hypothalamus and pituitary gland; disruption of the normal regulation of prolactin (Mancini *et al.*, 2008) decreases GnRH secretion, causing low FSH and LH secretion and thereby do not stimulate the gamete production and gonadal steroid synthesis. No significant correlation between prolactin and thyroid levels was found (- 0.028).

Estradiol level in normal women during the day 2-5 of the menstrual cycle is found to be 20-150 pg/ml, just before the onset of ovulation estradiol increases to its peak value 650-700pg/ml and drastically decreases during ovulation. In the samples of infertile women (all age groups) investigated in the present study has shown tremendous increase in the estradiol values (prior to the mid cycle LH surge) than the control. The elevated estradiol levels may be the result of androgen secretion by theca cells of the ovary, providing the precursors for continued estrogen production in adipose tissue (Muderris and Oner, 2012). Among 107 subjects 68 (64%) showed high levels and 8 (7%) were having low estradiol level.

In **PCOS** regular observation shows hyper secretion of LH (Balen and Jacobs, 1991); but among the 5 women who clinically appeared to have PCOS that were taken for the study showed hormonal levels that do not exceed the normal level. This may be due to the fact that assay based on monoclonal antibodies do not allow the various glycosylated form of LH sometimes found in PCOS to be detected and this may account for some of the differences seen between polyclonal and monoclonal assays. This possibly also accounts for the extremely low levels of LH found in small proportions of PCOS (Milsom *et al.*, 2003). This may be the reason for confirmation of PCOS through ultrasound diagnosis and not through hormonal test.

Menopause

Fertility declines sharply after the age of 37 and therefore fertility is significantly halved if the female partner is 35 years or more (Tietz, 2006). After the age of 35, follicle-stimulating hormone (FSH) levels begin to increase together with a subtle decrease in inhibin B without simultaneous changes in estradiol (E2). Moreover, a steady gradual decline with age has been observed in serum androgens. Finally, the number of antral follicles assessed during the early follicular phase has recently been shown to decrease with advanced age (Helen *et al.*, 2001). FSH levels are often elevated for 2-3 years before menses ceases because of ovarian resistance to gonadotropins during menopause. The increased insulin level is thought to have a direct effect on the ovaries; causing disturbances in normal hormone output and follicular development. With the approach of natural menopause and the beginning of ovarian failure of any cause, serum FSH level increases.

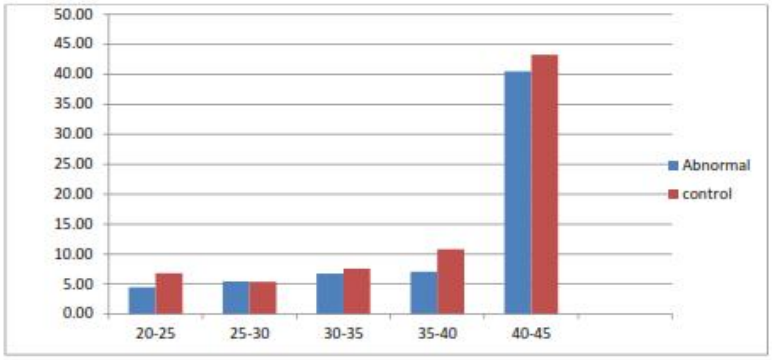

Fig.1. Differences between younger (20-35 years) and older (35-45 years) infertile and control samples during follicular phase of the menstrual cycle in Follicle stimulating hormone (FSH)

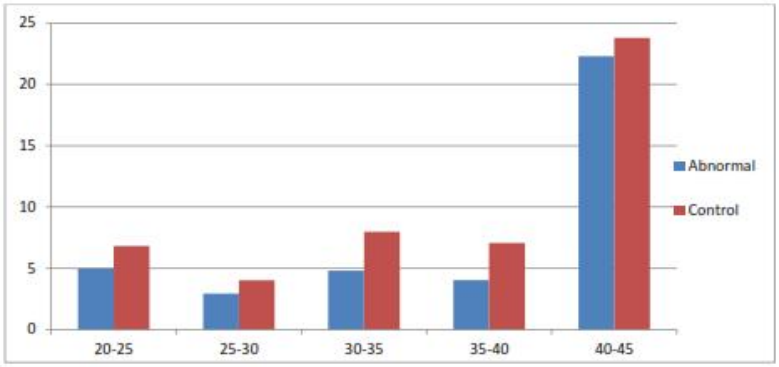

Fig. 2. Difference between younger (20-35 years) and older (35-45 years) infertile and control samples during follicular phase of the menstrual cycle in Leutinizing hormone (LH)

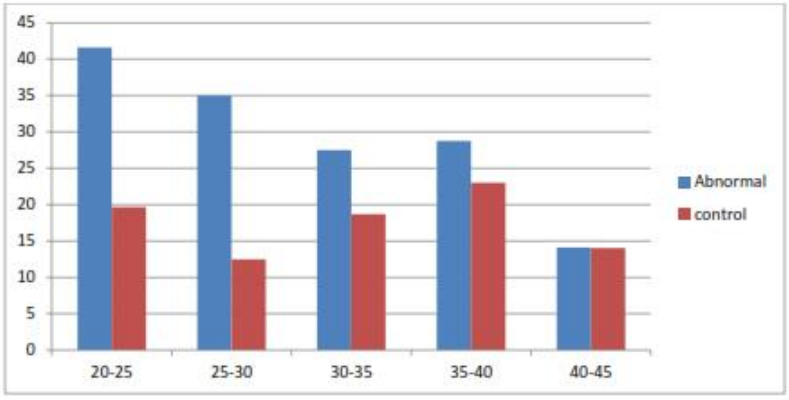

Fig. 3. Differences between younger (20-35 years) and older (35-45 years) infertile and control samples during follicular phase of the menstrual cycle in Prolactin

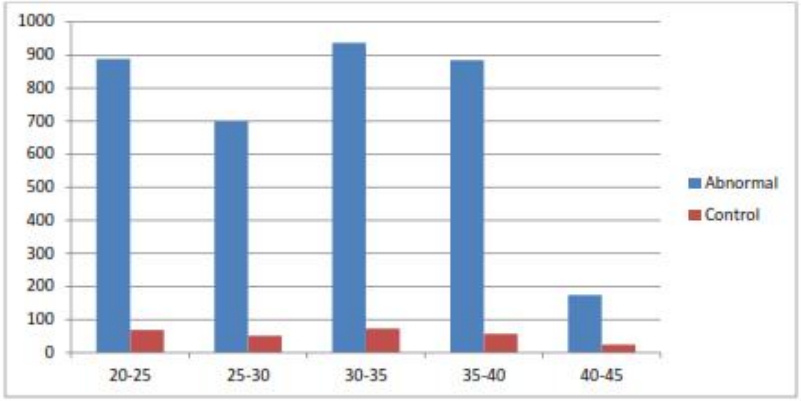

Fig. 4. Differences between younger (20-35 years) and older (35-45 years) infertile and control samples during follicular phase of the menstrual cycle Estradiol (E.2)

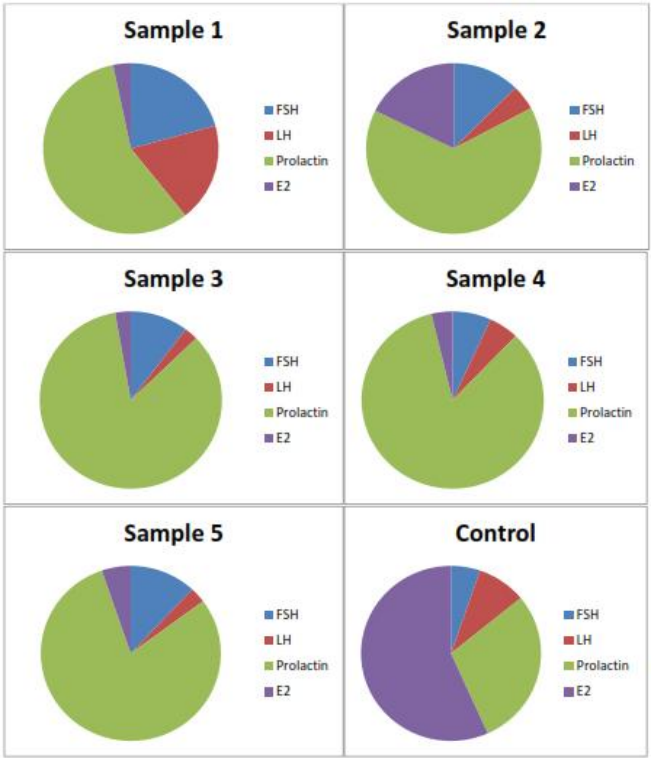

Fig. 5. Polycystic Ovarian syndrome

The overview of the present study reveals that the female reproductive hormones play an important role in maintaining the fertility in females. However, various other environmental factors also have a role to play. Hence in maintaining a healthy reproductive system, one has to be aware of the factors affecting the menstrual cycle and the need for a life style change in order to prevent the complications associated.

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REFERENCES

Balen, AH. and Jacobs, HS. 1991. Gonadotrophin surge attenuating factor: a missing link in the control of LH secretion. *Clin Endocrinol*, 35:399-402.

Bishop, ML. Edward, P. *et al.* 2010. Clinical Chemistry: Techniques, Principles, Correlations (6th Ed.); Publisher: Lippincott Williams & Wilkins, 477-492.

Clifford, K. *et al*. 1994. An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases. *Hum. Reprod*., 9:1328–1332.

Cramer, DW. *et al*. 2003. Serum prolactin and TSH in an in vitro fertilization population: is there a link between fertilization and thyroid function? J Assist Reprod. 20:210.

Erickson, GF. *et al*. 1985. The ovarian androgen producing cells: a review of structural function relationships. *Endocrinol Rev*., 6:371-399.

Ferin, M. Jewelewicz, R. and Warren, M. 1993. The menstrual cycle: physiology, reproductive disorders and infertility. New York: Oxford University Press.

Filicori, M. 1986. Characterization of the physiological pattern of episodic gonadotropin secretion throughout the human menstrual cycle. *J Clin EndocrinolMetab*., 62:1136-1144.

Gougeon, A. Ecochard, R. and Thalabard, J. 1994. Age-related changes of the population of human ovarian follicles: increase in the disappearance rate of nongrowing and early-growing follicles in aging women. Biol Reprod 50:653-663.

Guyton, AC. 2006. Textbook of Medical Physiology (5th ed.). Philadelphia: W.B. Saunders.

Helen, B. *et al*. 2001. Age-related differences in features associated with polycystic ovary syndrome in normogonadotrophic oligo- amenorrhoeic infertile women of reproductive years. *European J of Endocrinology*, 145:749-755.

Kim, YK. *et al*. 1997. Utility of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol and FSH:LH ratio in predicting reproductive age in normal women. *Human Reproduction*, 12(6):1152–1155.

Klein, N. *et al*. 1996. Ovarian follicular development and the follicular fluid hormones and growth factors in normal women of advanced reproductive age. *J Clin Endocrinol Metab*., 81:1946–1951.

Krassas, GE. 2000. Thyroid disease and female reproduction. *Fertil Steril*., 74(6):1063-70.

Lunenfeld, B. *et al*. 1992. Female Infertility. Classification of anovulatory states. Diagnosis and Treatment of Functional Infertility, 3 edn. Blackwell Wiss Verl, 26-33.

Mancini *et al*. 2008. Endocrinology and Metabolism Clinics of North America, 2008.

Milsom *et al*. 2003. LH levels in women with polycystic ovarian syndrome: have modern assays made them irrelevant? BJOG: *an Int J of Obstetrics and Gynaecology*, 110:760–764.

Molitch, M. 1999. Medical management of prolactinomas. *Endocrinol Metab Clin North Am*., 28: 143-169. Muderris, I. and Oner, G. 2012. Sex Hormones and Infertility, Sex Hormones, Prof.Raghvendra Dubey (Ed.), ISBN: 978-953-307-856-4.

Peters, H. and Joint, A. 1980. The Ovary: A Correlation of Structure and Function in Mammals. Berkeley, University of California Press.

Plant, TM. *et al*. 1978. The arcuate nucleus and the control of the gonadotropin and prolactin secretion in the female rhesus monkey. *Endocrinol*., 102:52-62.

Sherman, BM. *et al*. 1976. The menopausal transition: analysis of LH, FSH, estrogen and progesterone concentrations during menstrual cycle of older women. *J. Clin. Endocrinol Metab*., 42:629-636.

Tietz, 2006. Textbook of Clinical Chemistry and Molecular Diagnostics, 4th Edition, Elsevier Saunders Publishers, 2021-2027.

Turankar, S. *et al*. 2013. Hyperprolactinemia and its comparison with Hypothyroidism in primary infertile women. *J Clin Diagn Research*, 7(5): 794-796.

Unuane, D. *et al*. 2011. Endocrine disorders & female infertility; Best Practice & Research. *Clin Endocrinol & Metab*., 25:861–873.

Waldstreicher, J. *et al*. 1988. Hyperfunction of the hypothalamic-pituitary axis in women with polycystic ovarian desease; indirect evidence for partial gonadotroph desenitisation. *JCMB*, 165

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