Nature and Grace in Women's Reproductive Health

Lecture given by
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The life of a new organism of the human species starts at the moment of fertilization. This is when the sperm and oocyte plasma membranes fuse. The ovarian continuum begins at fertilization, when the zygote starts its development.

Until now, a biological dogma has been that all sex differences in the brain arise from differences in the gonadal secretions. It has recently been demonstrated that the whole genome of males and females seems to be different; not only are the sexual chromosomes different, but also autosomes have a major role in sexual differentiation. For our purposes this will be very important to keep in mind, because during this lecture I would like to invite you to look at ourselves the way we were created. I would also like to invite you to look at the many instances by which this creation can be distorted.

Approximately 2 months after fertilization occurs, the future oogonia, called primordial germ cells at this time, leave the embryo and migrate to the vitelline sac in order to escape the process of cell differentiation. Some four weeks later these cells migrate to the region of the future ovary, the gonadal crest, and start their process of differentiation, forming millions of primordial follicles. At this time some 7 million primordial follicles are formed, most of which will undergo atresia. When the girl is born, 1 to 2 million follicles containing the oocytes remain. Of these, about 475 will complete folliculogenesis during ovulation.

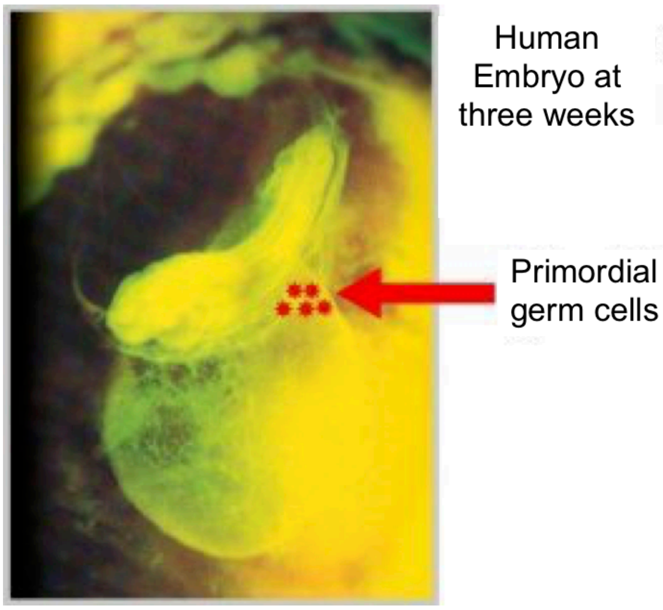

Figure 1. Human embryo at three weeks

The brain of the embryo is also developing. During pre natal and early neonatal development, there is a sensitive period for hormone dependent sexual differentiation.

There are also other periods of big hormonal changes during a woman's lifetime. One of these periods is puberty. Pubertal maturation of the hypothalamic–pituitary–gonadal (HPG) axis begins with activation of neurons that secrete gonadotrophin releasing hormone (GnRH).

GnRH is produced by thousands of neurons located in the hypothalamus and secreted in a pulsating fashion, by the so called GnRH pulse generator. The permissive signals that allow the initiation of puberty vary with sex. Girls have their pubertal development one year earlier than boys.

Puberty, viewed from the perspective of reproduction, could be considered as the process by which hormonal changes take place in order to permit the expulsion from the ovary of mature oocytes, thus allowing fertilization to take place. Follicular development, which lasts 85 days, has two phases: a gonadotrophin (GnRH) independent phase lasting 71 days and a gonadotrophin dependent phase that lasts 14 days. The menstrual cycle represents the gonadotrophin dependent phase of follicular development. GnRH pulses produce the Follicle Stimulating Hormone (FSH) that stimulates follicles with an antral cavity.

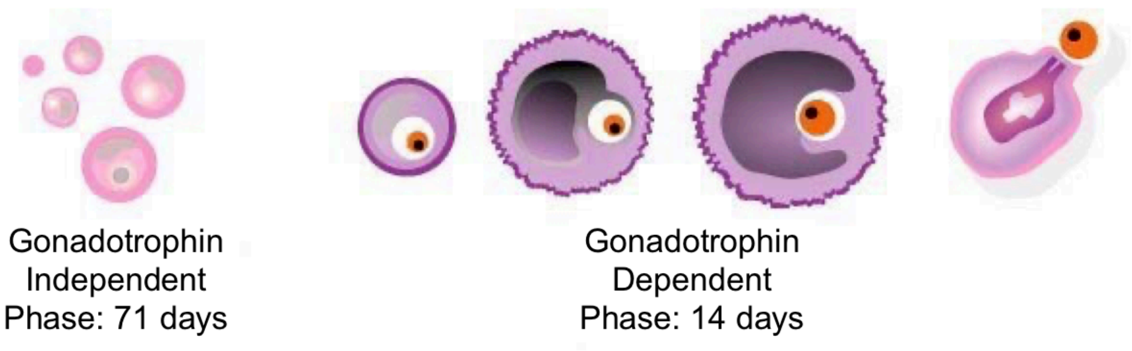

Figure 2. Main follicular development phases.

During the first 2 years after menarche, occasional anovulatory cycles may occur. These cycles may be longer or shorter; however, subsequently a healthy girl will exhibit regular monthly ovulations, characterized by a 25 to 36 day cycle. The data in Figure 3 shows that cycles get within this length after one or two years post menarche.

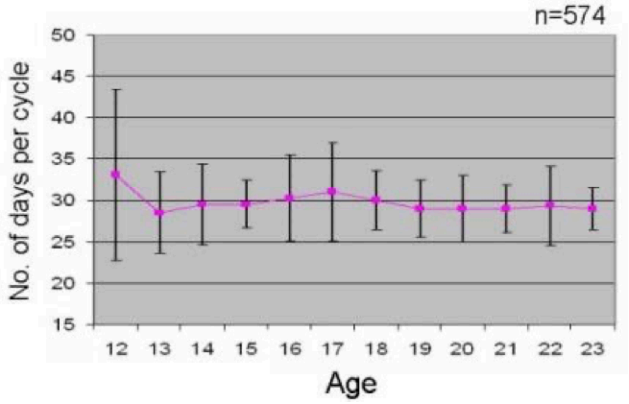

Figure 3. Variability of cycle by age.

Sometimes it is believed that it is normal to be irregular during teenage years. This is not a normal condition, but of course we all know it happens. Table 1 shows the classification of menstrual cycles.

Table 1 what is normal?

	Classification	**Number of Days**
Duration of cycle	Short	Cycle < 24
	Normal	24 ≤ Cycle ≤ 36
	Long	Cycle > 36
Ovulation Criteria	Ovulatory	9 ≤ Luteal phase ≤ 19
	Anovulatory	Luteal Phase < 9

Leptin is produced by adipocytes, the adipose tissue cells. Leptin is very important for pubertal development, and it signals when biological maturation has been completed. Leptin also influences the GnRH pulse generator. Obesity causes too much leptin to be circulating in the body thus masking the signal level to which the GnRH pulse generator normally responds. Poor diet and resulting obesity is becoming a cause of irregular cycles.

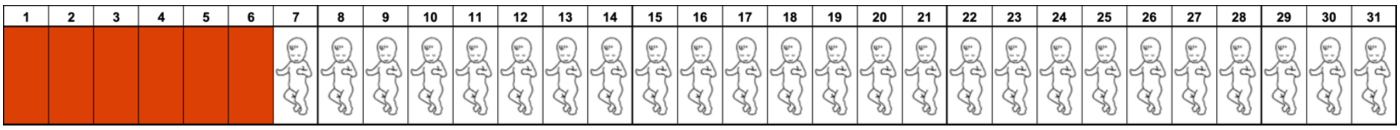

Figure 4. Cycle seen in obese girls caused by the overproduction of oestradiol as a result of a poor diet of fatty foods

The absence of leptin is also a cause of abnormal cycles. Figure 5 shows the chart of a girl with a dry pattern. This girl had an abnormal intake of water during the day. There is an absence of leptin so the GnRH pulse generator is not working. No follicles are being recruited.

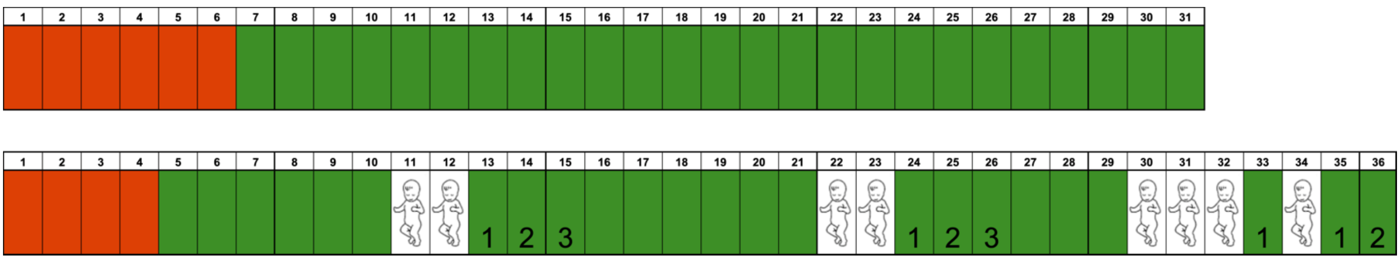

Figure 5. Anovulatory cycles that may be present in hypothalamic dysfunctions as seen in anorectic girls.

This is why during puberty and also later in life, obesity will interfere with the chronologically ordered events that have to take place in a highly synchronized manner during the normal menstrual cycle. Many obese girls may be very confused about their cycles, particularly when they are told cycles have to be regular and that a certain pattern will occur during the cycle. Obese girls will have high oestrogen levels produced by the adipocytes, so they may present a pattern of constant fertile type of mucus as shown in the chart of Figure 4.

Initial Events in the Normal Ovulatory Cycle (Figures 6, 7)

1. Rising follicle-stimulating hormone (FSH) levels that cause follicular recruitment.
2. Follicular development that causes an increase in oestradiol levels.
3. Increasing oestrogen (mostly oestradiol), secreted by maturing follicles, cause endometrium proliferation and an increase in the amount of mucus secreted by the cervical epithelium as well as change in the type of the mucus and the degree of the opening of the cervical os.
4. Follicular dominance.

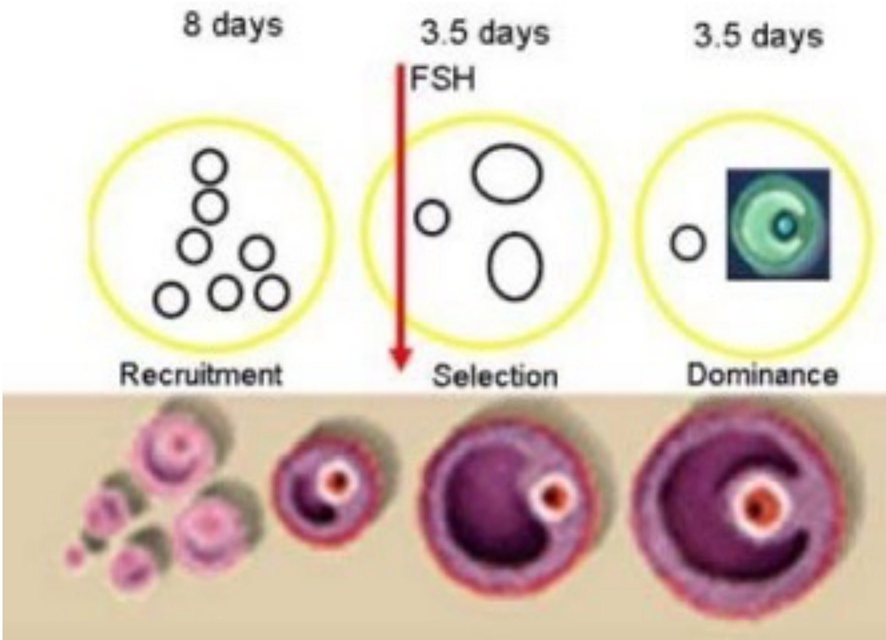

Figure 6. Events in the normal ovulatory cycle – stages of the follicular phase.

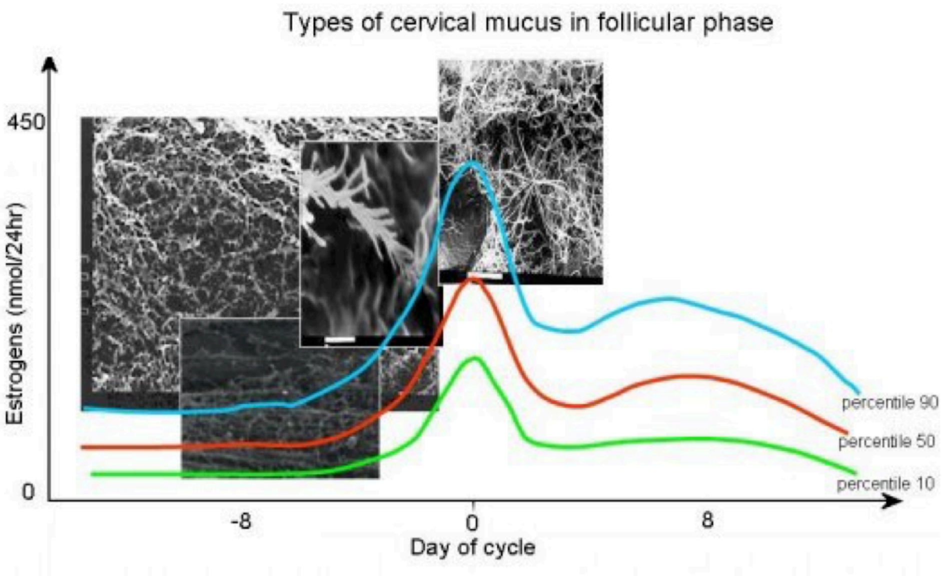

Figure 7. Normal range of ovarian hormones and the types of cervical mucus in the follicular phase.

In polycystic ovarian syndrome (PCOS) the ovaries, together with the adrenals produce too much testosterone. The problem with this overproduction is that the follicular development goes wrong. Granulosa cells can't manage the testosterone production so that follicles grow but they stay there. With so many follicles developing, oestradiol levels are present in considerable amounts so the mucus is always there. However in 85 to 90% of cases ovulation can occur sometime during the woman's life (see Figure 8).

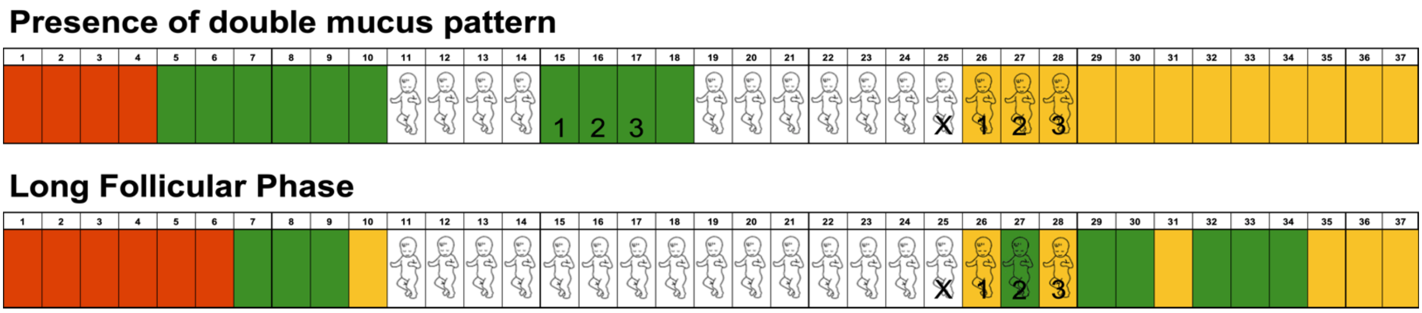

Figure 8. Cycles occurring with polycystic ovary.

Women suffering from PCOS notice their cervical mucus to be sticky and find it less elastic and hydrated than the cervical mucus of the fertile period. Among these women, alterations in the levels of sex steroid hormones would account for the stickiness of the cervical mucus as well as for the crystallization patterns found; in fact, it has been observed that, of all the physical properties of cervical mucus, crystallization is the most sensitive to changes at sex hormone levels. Other studies have shown that the chemical composition and ultrastructure of the cervical mucus depends on an interrelation between the levels of oestradiol and progesterone during the menstrual cycle.

Women presenting with polycystic ovary are often prescribed oral contraceptive pills. Previously they may have experienced irregular cycles, bleeding a lot, or suffering long cycles. The pill gives them regularity and can reduce acne. Unwelcome effects are bad mood, and weight gain. Diet and exercise are recommended to compensate. The role of insulin is overlooked.

Insulin transports blood sugar into muscles, the liver and also the neurons. If there is resistance to this transport function, then too much insulin is produced by the pancreas in order to normalize sugar blood levels. However, insulin also acts upon the ovarian follicles. Too much insulin causes lots of follicles to grow all together. Thus, insulin imbalance gives the appearance of PCO. Half of the women with PCO will have insulin resistance. The problem with oral contraceptives is that the oestradiol present in the pill will worsen this condition; it will make the pancreas produce even more insulin.

Thus, women presenting with this condition have to be aware that taking the pill will normalize cycle length but will worsen any insulin resistant condition. Many of these women will also be obese and insulin will also increase the androgens, so obesity is going to be in the form of an apple. Obese women that present with a pear like shape are less likely to be insulin resistant (see Figure 9).

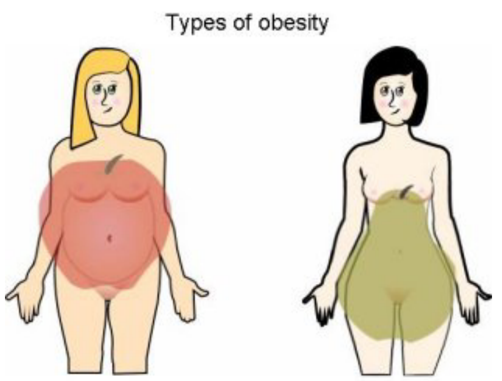

Figure 9. Obesity caused by increased androgens results in apple shaped obesity.

Subsequent Events in the Normal Ovulatory Cycle (see Figure 10)

5. Oestrogen together with inhibin shuts off FSH while the dominant follicle continues to grow.
6. Oestrogen secreted by the dominant follicle feeds back negatively on the hypothalamic-pituitary axis and then changes to a positive feedback.
7. The pituitary LH necessary to rupture the dominant follicle rises to an LH peak and luteinization of the follicle is initiated.
8. Progesterone starts to rise before ovulation occurs. This pre-ovulatory rise determines the LH peak.
9. The ovum is released from the follicle (the ovum has a limited life span, 12 to 24 hours).
10. With the initiation of follicular luteinization, secretion of progesterone commences in the follicle. This initial rise in progesterone maintains the plateau of LH during the LH peak. Its effect is important for the occurrence of the Peak day of the cervical mucus symptom.
11. This pattern of LH secretion aids the formation of a normal corpus luteum and an adequate luteal phase of the menstrual cycle.
12. The corpus luteum produces progesterone and oestrogen.
13. Progesterone changes the endometrium to the secretory type. It also affects the cervical mucus, converting it from oestrogenic to progestational type, which is not suitable for sperm transport through the cervix. If fertilization has not occurred, the corpus luteum begins to regress after 6–7 days.
14. Oestrogen and progesterone levels return to early follicular phase levels approximately 14 days after the initial formation of the corpus luteum.
15. This drop in sex hormone levels releases the suppression of FSH and LH and a new cycle commences.

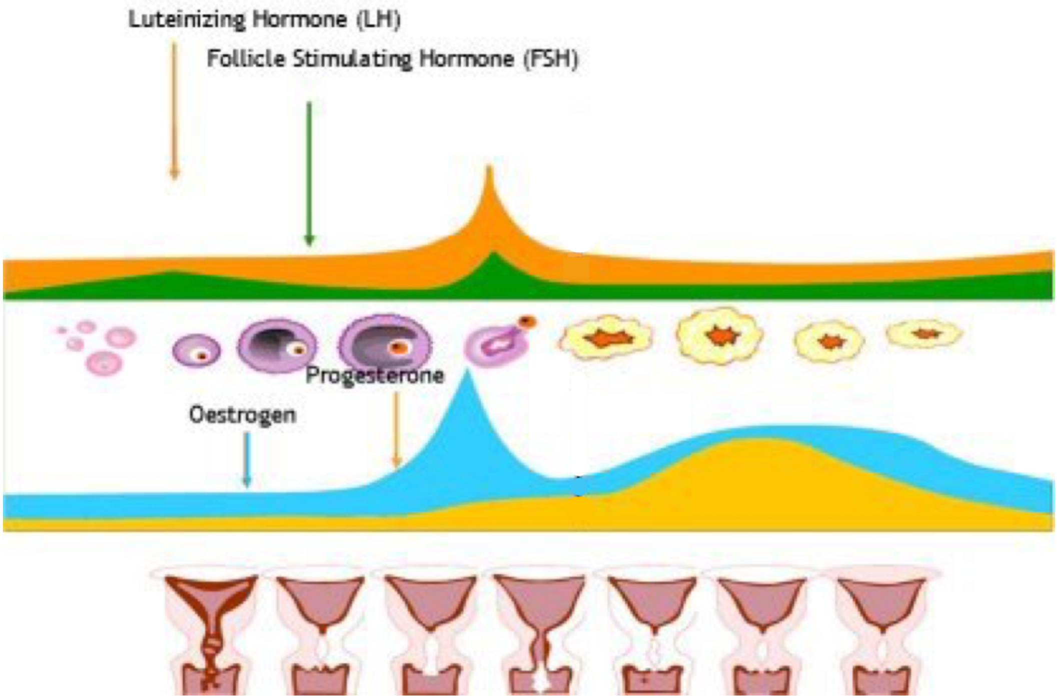

Figure 10. Events in the ovulatory cycle

(Levonorgestrel, the so-called emergency contraceptive, disrupts the LH peak ensuring that the luteal phase won’t be adequate and if for any reason there is an embryo around, implantation will be altered as the luteal phase will be insufficient. Monkeys do not have the same pattern during the periovulatory period as humans, so experiments with levonorgestrel done in monkeys do not necessarily translate to the human experience.)

Other abnormalities that can be observed are cycles presenting with short luteal phases as seen in Figure 11. Short luteal phases can be caused by high prolactin levels coming from the pituitary gland (Figure 11). These women often refer having allergies - the women cannot use common earrings, only gold ones. They are often prescribed oral contraceptives.

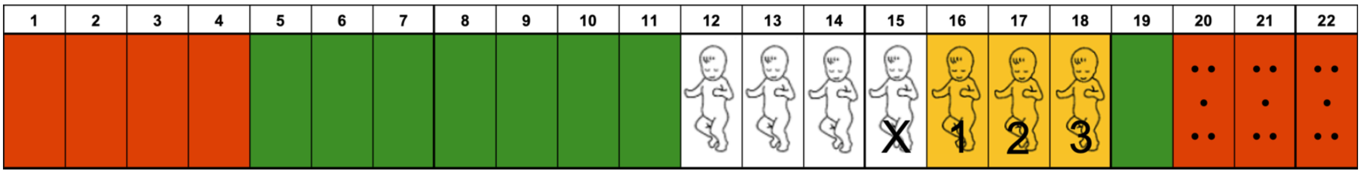

Figure 11. Short luteal phases can be present in women with prolactin levels.

We have described a series of events taking place in the woman. I now ask you to stop for a moment and think in terms of creation: “God created man in his image...male and female he created them”. Following this narrative in the Book of Genesis, we observe that the definitive creation of man, after Adam wakes up from the Torpor (which is a term used in the sacred scripture when extraordinary events are to take place), consists of the unity of two beings. This means that from the beginning of this loving act of creation there is a pre-determined union between man and woman.

You may think from this deviation that I have confused my papers at this conference. No! I would like to share with you some very recent data that we have just published in Andrologia that will give insight into biological fundamentals for further discovering this pre-determined union.

A pre-ovulatory rise in progesterone has been shown to occur. All of us know that this pre-ovulatory rise is very important for the occurrence of the Peak day for the woman. Now we will take a look at the sperm.

You may all be familiar with the sperm structure in that sperm cells have a head and tail. Over the head we find the acrosome which is a secretory granule that contains enzymes necessary for the sperm passage through the oocyte’s zona pellucida and cumulus cells. A synchronized acrosome reaction (AR) has to occur in order for the sperm to acquire the fertilizing ability.

We have recently shown that the menstrual cycle hormonal changes not only affect the events occurring in the ovary, but these changes also act upon the sperm. Specifically, during the fertile period high oestradiol levels are present in the cervical mucus, preventing the acrosome reaction. This is very important, because if the AR took place in the mucus, sperm would lose their fertilizing ability before getting in touch with the oocyte.

Once sperm leave the cervix, they go through the endometrial cavity and then into the fallopian tubes. If ovulation has occurred, follicular fluid is going to be present in the tube. Progesterone rises before ovulation, so the follicular fluid contains high concentrations of this hormone which is going to be present around the oocyte.

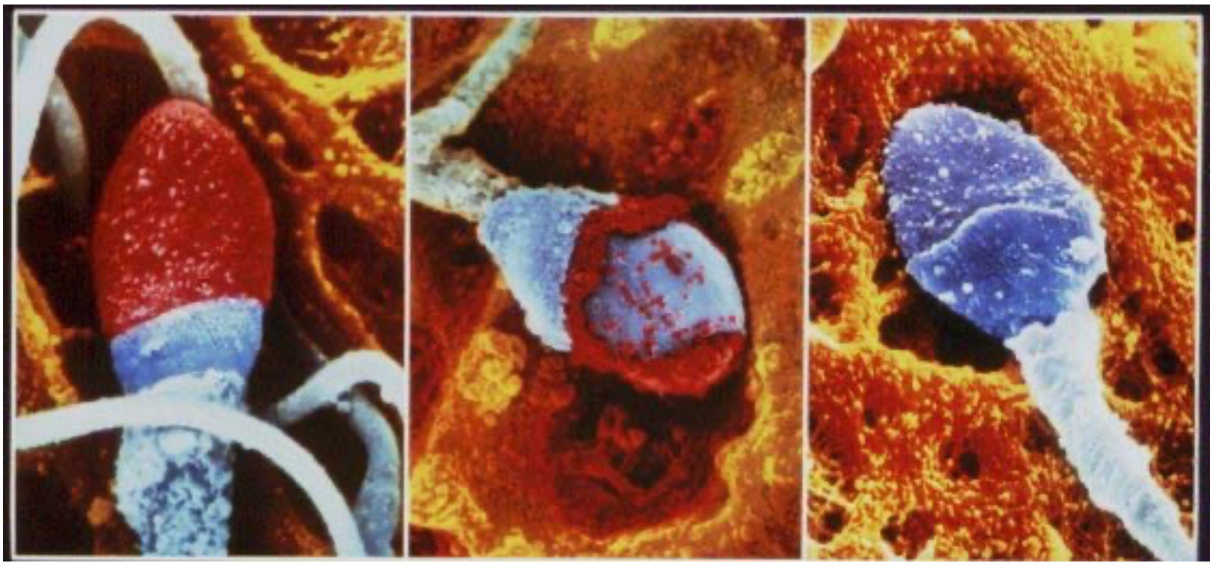

Figure 12. Acrosomic reaction

Progesterone induces the AR (Figure 12). So the hormonal changes that take place during the cycle, inhibit the AR when sperm are in the cervix and induce it when they reach the site of fertilization.

The union of man and woman denotes above all, the identity of human nature; duality. Every man and woman has a value in himself and herself, but woman is for man and man for the woman.

We suggest that the hormone variations that take place in vivo during the menstrual cycle could regulate in a non-genomic way the AR favouring the timely occurrence of this process.

The classic way in which steroidal hormones act in the cells is genomic action. Non-genomic action is a recently discovered way by which steroidal hormones can give their messages. Neurotransmitters usually act this way. For example, oestradiol can act upon receptors located in the plasma membrane of pancreatic B cells, which are responsible for insulin production. In this very rapid way, oestradiol directly induces the release of insulin from these cells. This is also the way oestradiol contained in oral contraceptives produces hyperinsulinemia.

At the cervix, the oestradiol (E2) contained in the periovulatory cervical mucus has an inhibitory effect on the occurrence of the AR. Then, the distal third of the Fallopian tube presents high concentrations of progesterone (P4) coming from the follicular fluid, which would favour the AR at the moment of the encounter of the spermatozoon and the oocyte.

GABA is the chief inhibitory neurotransmitter in the central nervous system. The presence of GABA in the female reproductive tract has been identified. Thus, it could also play a significant role in the AR (Figure 13). These non-genomic pathway interactions of GABA, P4 and E2 might not be exclusive of the spermatozoon and be present in other cells as well. There is an interaction of hormones and neurotransmitters in regulating important processes occurring in our bodies.

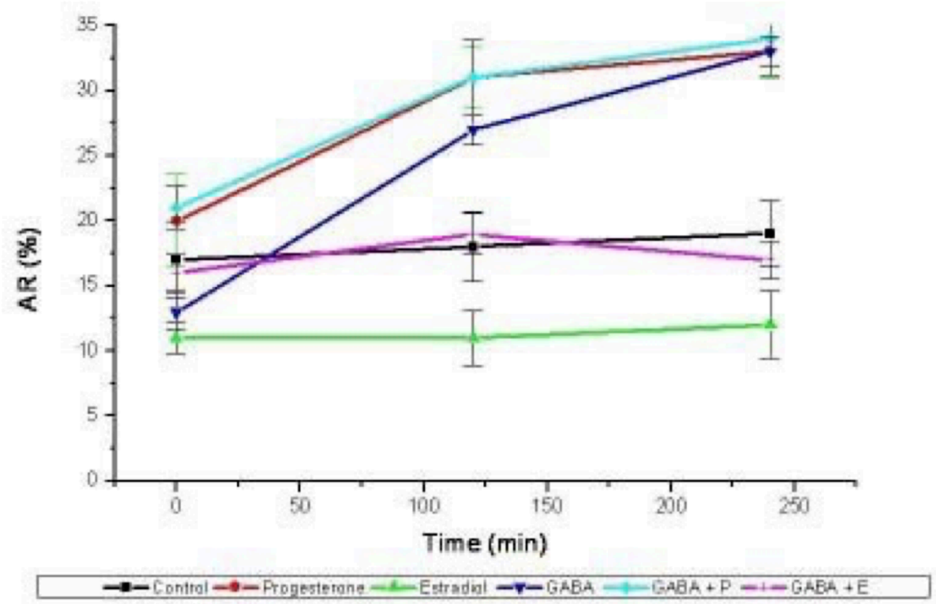

Figure 13. Effects of GABA, progesterone and oestradiol on human spermatozoa acrosome reaction.

During a woman's lifetime, there are periods of important physiological changes such as puberty and menopause. Puberty, viewed from the perspective of reproduction, could be considered as the process by which hormonal changes take place in order to permit the expulsion from the ovary of mature oocytes, thus allowing fertilization to take place. But we also know that adolescence is an important developmental period during which hormonal and physical changes take place that encompass not only reproductive maturation but also cognitive, emotional, and social maturation.
We have demonstrated how steroidal hormones can influence the occurrence of the human sperm acrosomic reaction. Surprisingly, the mammalian sperm and neuron appear to share many of many of these 'neuronal' receptors. Considering this evidence, it is then reasonable to think that hormonal changes taking place during puberty will influence not only the reproductive system but could also have an impact in brain development. Puberty and adolescence are intricately linked because the brain is a target organ for steroid hormones.

God created man in his image, male and female he created them. We were created with a pre-determined union, man for woman and woman for man. Recent studies such as the ones we have seen have shown us how the hormonal changes that take place during the cycle will have an effect upon the woman's reproductive cycle and also will have an important effect upon the sperm regulating mechanisms such as the acrosome reaction which is necessary for fertilization to occur.

It has also been shown that neurotransmitters act upon the reproductive system and that hormones act upon the nervous system. The brain as we will see in my next talk is a target organ for hormones.