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Original Studies

Usefulness of Monitoring Fertility from Menarche

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Abstract. The concept of the ovarian cycle as a continuum considers that all types of ovarian activity encountered during the reproductive life are responses to different environmental conditions in order to ensure the health of the woman. During the normal ovulatory cycle, a series of sequential events have to occur in a highly synchronized manner. Fertility awareness is useful in helping women to identify the different stages of their reproductive life cycle. Fertility awareness is also a valuable tool in helping women to identify gynecological disorders. Persistence of irregularities within the mucus patterns and the menstrual cycle should be of concern to women presenting with these problems. These irregularities may be due to obstetrical, endocrine, gynecological or iatrogenic disorders. Insight into early pregnancy complications, ovulatory dysfunction and pelvic inflammatory disease can be ascertained from abnormalities within the menstrual cycle and mucus pattern. Thus, fertility awareness will also enable the recognition and early treatment of several metabolic, endocrine and infectious diseases.

Key Words. Fertility awareness—Ovarian cycle—Menstrual cycle—Women's health

Introduction

Fertility is a transient biological state that depends on the fertility potential of the couple. During a woman's lifetime, the ovary will go through different states of hormonal secretion and ovulation. The concept of the ovarian cycle as a continuum considers that all types of ovarian activity encountered during the reproductive life are normal responses to different environmental conditions in order to ensure the health of the mother and child. The ovarian continuum begins at fertilization, when the zygote starts its development. Approximately 2 months after fertilization occurs, the future oogonia, called primordial germ cells at this moment, 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.[1]

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. The luteinizing hormone (LH) peak must follow the estrogen peak for ovulation to occur,[2] but there are a series of sequential events that must occur in a highly synchronized manner. During the first 2 years after menarche, occasional anovulatory cycles may occur. However, subsequently, a healthy ovary will exhibit regular monthly ovulations, characterized by a 25 to 36 day cycle.[3] The ovulatory cycles are normally only interrupted by pregnancies and breastfeeding. Normal ovulatory activity and fertility are restored following pregnancy and lactation; however, stress or excessive exercise may result in chronic ovulatory dysfunction which requires therapy. Abnormality in cycles such as anovulation or short luteal phases frequently occurs as menopause approaches. This is an expected part of a woman's reproductive life cycle.

With the use of instruments such as the ovarian monitor, which measures the urinary excretion of

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estrone glucuronide (E1G) and pregnanediol glucuronide (PdG), important metabolites of the two ovarian hormones, estradiol and progesterone, it has been possible to identify hormonal variations during different periods of a woman's life and to correlate these changes with her cervical mucus patterns.[4–6]

Events in the Normal Ovulatory Cycle

(1) Rising follicle-stimulating hormone (FSH) levels that cause follicular recruitment.[7]
(2) Follicular development that causes an increase in estradiol levels.[8,9]
(3) Increasing estradiol levels, 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.[10–14]
(4) Follicular dominance.[15]
(5) Estrogen together with inhibin shuts off FSH while the dominant follicle continues to grow.[16]
(6) Estrogen secreted by the dominant follicle feeds back negatively on the hypothalamo- pituitary axis.[17,18]
(7) The pituitary LH rises to LH peak and luteinization of the follicle is initiated. The ovum is released from the follicle (the ovum has a limited life span, 12 to 24 hours).[18]
(8) 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.[17,19]
(9) This pattern of LH secretion aids the formation of a normal corpus luteum and an adequate luteal phase of the menstrual cycle.[9,17,19]
(10) The corpus luteum produces progesterone and estrogen.[9,20]
(11) Progesterone changes the endometrium to the secretory type. It also affects the cervical mucus, converting it from estrogenic 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.[13,21,22]
(12) Estrogen and progesterone levels return to early follicular phase levels approximately 14 days after the initial formation of the corpus luteum.[7,23]
(13) This drop in sex hormone levels releases the suppression of FSH and LH and a new cycle commences.[7,24]
(14) Throughout the cycle the hypothalamus continues to produce gonadotropin-releasing hormone (GnRH) and secretes it continuously in a pulsatile fashion.[25,26]

Throughout life, the ovarian continuum may present different phases as documented by studies carried out with the ovarian monitor.[9]

Hormonal Cycle Patterns

Throughout a woman's life, the ovarian continuum may present different phases or patterns depending on the presence or absence of ovulation. One pattern is characterized by an anovulatory ovarian activity; this type can be observed in two situations. The first type of anovulatory ovarian activity occurs when the FSH levels pass the threshold and stimulate a follicle to develop, but sufficient LH is not released or the resulting ovulatory mechanism does not operate. This is an important cause of long cycles. A second type is when the FSH levels rise above threshold, but not sufficiently to boost one follicle into dominance. A chronic situation develops in which follicles continue to grow and regress causing the estrogen levels to plateau. The effect of the raised but constant estrogen production is to develop an unstable endometrium that may bleed occasionally.[27]

Another different pattern of the continuum occurs when the estrogen levels rise to a peak resembling a preovulatory peak. LH is released but not in sufficient amounts to cause the follicle to rupture and ovulate. However, it is sufficient to cause a small amount of luteinization of the follicle with resultant low level of progesterone.[27] The ultrasound pattern will show the presence of a luteinized unruptured follicle.[28]

The ovarian continuum may also present as a deficient luteal phase. A cycle that presents a deficient luteal phase is one in which ovulation occurs, but the conditions during the luteal phase do not support an ongoing pregnancy. Thus, any cycle in which the progesterone levels fail to reach 10 μmole PdG/24 hours 7 days after ovulation has occurred or any cycle with a luteal phase length of 10 days or less could be regarded as "deficient."[9,28] Ovulation is always followed by menstrual bleeding, provided an endometrium capable of responding to the hormones is present and there is no human chorionic gonadotropin being produced.

Even in fertile ovulatory cycles the potential for conception varies with the timing of insemination, the groups of women studied, and the fertility potential of the male partner. Age also is an important factor to consider when analyzing fertility potential, as fertility decreases with age.

Cervical Mucus as a Determinant for Fertility

It has been shown that mucus quality is a better predictor of the possibility for conception than ovulation. Mucins are the main components of mucus.[29] To date a total of 20 distinct mucin genes have been identified.[30] Mucins are categorized into 3 groups on the basis of their structural properties such as transmembrane mucin (MUCs 1, 2, 3, 4, 12, 13, 15, 16, 17), gel-forming mucin (MUCs 2, 5AC, 5B, 6) and soluble mucin (MUCs 7, 9, 11, 14) and others that have not yet been categorized (MUCs 8, 10, 18, 19, and 20).[30] The four large gel-forming mucin genes are located on chromosome 11.p15.5.[31] Mucin 5B is the major gel-forming mucin expressed by the endocervical epithelium and its expression peaks at mid-cycle.[32,33] There is evidence of other mucins as well, such as MUC4, which are expressed in the ovulatory phase.[34]

Two main types of cervical mucus have been described: estrogenic and progestational. According to Odeblad's model, the estrogenic type can be subdivided into L, S, and P subtypes.[22,35,36] The L subtype is the most abundant type of mucus during the periovulatory period and the P subtype appears close to ovulation[37] (Figure 1). All mucins seem to diminish as progesterone levels increase in the blood.[38] During the luteal phase the progestational type (G) of mucus is dominantly present.

It has been demonstrated that fertility awareness can help women to identify the different stages of their reproductive life cycle.[35,39] Understanding the signs of fertility and infertility is important knowledge which should be available to every woman. Briefly, fertility awareness involves self detection of mucus at the vulva primarily by noting the progression from the basic infertile pattern of post-menstrual dryness to stickiness, wetness, and ultimate lubrication, the "peak day."[40,41] The woman who understands her own mucus pattern should be able to recognize changes in the normal ovulatory pattern and detect changes which may indicate a number of gynecological disorders.[35]

Questions arise as to when irregularities within the mucus patterns and the menstrual cycle should be considered abnormal and when the woman should be sufficiently concerned to consult a physician. Persistence of abnormal mucus patterns may herald reproductive system disorders. These may be due to serious metabolic or endocrine abnormalities or to other diseases, all of which need to be recognized. Menstrual disorders and alteration in the mucus pattern can be caused by obstetrical, endocrine, gynecological, or iatrogenic disorders.

Early pregnancy complications such as bleeding or vaginal spotting can alert the woman who has recognized a previous fertile phase with a peak day, and can be identified or ruled out with the use of ultrasensitive pregnancy tests and pelvic ultrasound. Numerous studies have shown that 10–15% of couples suffer from a fertility disorder. These are mainly due to: (a) ovulatory dysfunction generally caused by hormonal disorders, and (b) inflammatory processes usually secondary to genital tract infections (GTI), mainly sexually transmitted diseases (STD). Ovulatory dysfunction is the most common disorder diagnosed in infertile couples (37%) and is predominantly associated with irregular menstrual cycles. Irregular cycles are present in 10% of women, but having an irregular cycle does not necessarily mean having an ovulatory dysfunction. We have been able to show according to cycle charting that 43% of women with irregular cycles present an ovulatory dysfunction, which can be characterized by the absence of ovulation or abnormal ovulatory activity, as seen in cycles with short or abnormal

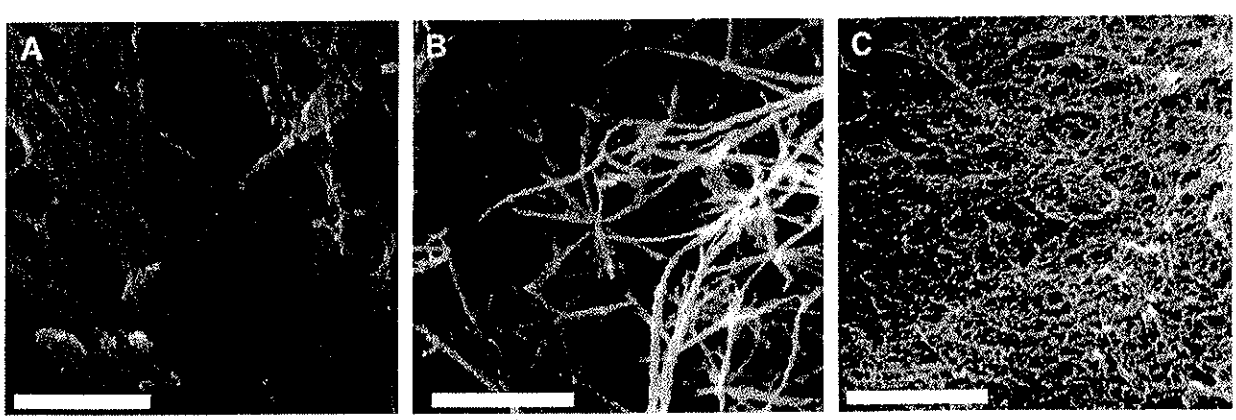

Fig. 1. Scanning electron-micrograph of cervical mucus types. Network-shaped mesh of estrogenic cervical mucus (type S) with spermatozoa migrating through it (A). In the estrogenic period type P mucus (B) appears close to ovulation. In the progestational period (C) the mucus is compact and impenetrable (type G). Bar = 10 μm.

luteal phases, while some of the rest have prolonged early infertile phases followed by a late, but normal ovulation. On the other hand, a young nulliparous woman with regular cycles, (i.e., cycle length between 25 and 36 days) may also present an ovulatory dysfunction identified by her understanding of the fertility pattern on her cycle chart.[3]

Endocrine disorders are the most common cause of ovulatory dysfunction.[42] They can be divided into hypothalamic, pituitary, or adrenal and/or ovarian, or general endocrine disorders.[34]

Hypothalamic disorders (e.g., anorexia nervosa) are characterized by long hypo-estrogenic cycles with the persistence of "dry" days (days with no mucus). Amenorrhea may be present. This condition is caused by a delay of the FSH levels to rise above threshold and thus initiate a new cycle. Unless the woman has permanent ovarian failure, such as having reached menopause, the situation eventually corrects itself. This condition is associated with long ovulatory or anovulatory cycles.

Long, anovulatory cycles are seen in athletes, and in this case they could be considered as a part of the continuum. These women frequently return to regular ovarian cyclic activity observed within 3 months of less strenuous physical exercise.[42] However, some of the young women in this category may further develop an anorectic state and despite discontinuation of strenuous physical activity will not return to normal cycles.[43]

Pituitary disorders (e.g. hyperprolactinemia) account for about 10% of ovarian dysfunction and are characterized either by amenorrhea or short cycles in which a short or abnormal luteal phase with premenstrual spotting can be observed. In vitro studies have shown impairment in steroidogenic activity of follicular cells under the influence of prolactin, which could explain, at least in part, the abnormal luteal phases commonly observed in the charts of women with hyperprolactinemia.[44] Galactorrhea may be also present. In women with hyperprolactinemia the interaction between neurological, endocrine, and immune systems must be taken into consideration.[45] These women may also present some immunologic alterations such as allergies. Stress may be an important factor associated with increased prolactin levels.[46]

Adrenal and ovarian abnormalities are the most frequent cause of ovarian dysfunction. The most common is the polycystic ovary syndrome (PCOS): an ovulatory dysfunction caused by hyperandrogenemia.[47] In these women, irregular cycles are usually present shortly after menarche.[48] Oligomenorrhea when present at 15 years of age has recently been shown to be the best predictor for PCOS.[49] These girls may present with acne and/or hirsutism as well as increased body weight and mood changes. Their cycles are characterized by a hyperestrogenic state where a continuous fertile type of mucus pattern (slippery, stringy, clear, mucus) is identified, or mucus patches (days of sticky or slippery mucus forming no progressive pattern to "peak") are present. Cycles can be ovulatory, with a long follicular phase, or anovulatory. When a young woman complains of menstrual abnormalities, teaching her to observe her fertility signs can be the first step to enable the clinician to rule out metabolic conditions such as hyperinsulinemia. Our studies have shown that in 82% of women who present with menstrual irregularities, an endocrine abnormality is present of which hyperandrogenemia is the most common (46% of cases).[3] It is important to note that an impaired insulin response to the oral glucose tolerance test is a commonly (50–80%) associated condition in these women. This requires treatment to prevent progression to type II diabetes mellitus.[50] Proper care, including diet, exercise, and medical treatment will restore normal cyclical ovarian activity. Women who know how to recognize their mucus symptoms will be able to follow the improvement of their endocrine abnormality.

Hypothyroidism is a less frequent (about 2%)[3] cause of ovarian dysfunction but it has to be considered along with hyperthyroidism. Different types of ovarian dysfunction can be observed in patients with thyroid disorders. Menorrhagia[50] is frequently associated with hypothyroidism. Although there is no specific pattern of ovarian activity associated with these endocrine abnormalities they should always be kept in mind and eliminated as a possible cause.

Women with ovulatory dysfunctions associated with irregular cycles and abnormal mucus patterns will not usually resume normal cycling spontaneously without appropriate treatment. Follow-up studies have shown that in the absence of treatment these conditions only worsen with time.[51,52]

Other conditions, such as premature ovarian failure, may also be a cause of fertility disorders presenting with irregular mucus patterns in response to fluctuating estrogen levels. These conditions are also observed in the perimenopausal period, where some cycles show an ovulatory pattern. As the condition worsens, anovulatory cycles will predominate.

In fertile women, naturally occurring midcycle cervical mucus studied with scanning electron microscopy shows an arrangement of parallel fibers oriented along the main axis of the mucus sample, probably corresponding to the S subtype.[12] Sperm transport may be facilitated by this normally occurring condition. At mid-cycle, cervical mucus is greater in quantity, has more mucin and less protein, and has higher water content than in the luteal phase.[13] This increase in the amount of mucin in the cervical canal, because of its hydrophilic character, probably functions to retain or hold water in place at the cell surface, keeping the cervical canal patent for sperm migration. The increase in water content of the mucin may protect the cervix. Pathogens or other toxins may be trapped by the mucin, thus preventing their entry into the uterus and Fallopian tubes.[31] Future research is needed to establish the ultrastructure and biochemical properties of mucus in different endocrine abnormalities. Also, the function of the specific mucins and mucus types remains to be determined as well as their possible alterations.

Menstrual disorders and alteration in the mucus pattern can also be caused by gynecologic disorders such as anatomical abnormalities, neoplasia, or inflammatory diseases. The second most frequent cause of fertility disorders are inflammatory processes, usually secondary to GTI, which predominantly have their origin in STD. Microbial mucin degrading enzymes are associated with sexually transmitted infections and are produced by the offending micro organisms. These enzymes will alter the mutually beneficial cohabitation that normally exists between commensals such as Lactobacillus, which use glycogen as an energy source and contribute to normal mucin turnover by the production of mucin degrading enzymes such as sialidase. Mucin molecules would be partly or completely degraded by the microbial enzymes. These molecules dictate the rheological properties which determine the amount and viscosity of the mucus, so these properties will change in response to enzymes produced by microbial organisms in the genital tract.[51]

A woman who knows her own mucus pattern in times of health will be able to recognize a GTI early. These will usually cause a continuous discharge whose characteristics will depend upon the etiologic agent causing the infection. In general, an ovulatory pattern is identifiable alongside the continuous discharge. Symptomatic infections (itching and a characteristic discharge) are usually caused by fungi, bacteria, or parasites. *Chlamydia trachomatis* infections, with an incidence of 13% in infertile couples and often associated with tubal pathology, may be asymptomatic or present with continuous vulvar moistness and variable degrees of pelvic pain.[53] This infection may also show a mucopurulent discharge associated with the mucus discharge. The recognition of this infection and timely treatment may prevent fertility disorders. It has been shown that these infections provoke pelvic inflammatory processes and are associated with spontaneous abortions. Recent studies have shown that the mesh spacing between mucin fibers is large enough for small viruses such as human papilloma virus, associated with cervical neoplasia, to diffuse unhindered through mucus.[54] Bacterial vaginosis-related bacteria, *Mycoplasma homini*, *Trichomonas vaginalis*, and *Gardnerella vaginalis* among others, must also be considered when unusual mucus patterns or menstrual irregularities occur. In this situation, both members of the couple should be treated in order to restore the healthy condition.

Fertility disorders may also be iatrogenic, caused by contraceptive pills or by hormonal therapy. Women discontinuing steroidal contraception may present cycles with short luteal phases, absence of a well-defined mucus pattern indicating anovulation, poor mucus response due to damaged cervical epithelium and/or a poor menstrual flow due to alterations of the endometrium.[55] Major cycle disturbances lasting for up to seven cycles (cycle length $>$ 35 days or luteal phase $<$ 10 days, monophasic basal body temperature or anovulatory cycles) occur in women after discontinuation of oral contraception. They also have lower monthly conception rates during the first 3 months off the pill, and a somewhat lower percentage from the fourth to the tenth month after discontinuation of the pill.[56–58]

In conclusion, although usually used for fertility awareness, cycle charting provides women with information about their cycle pattern and ovarian function. Klaus and Martin[41] showed that ethnically and socioeconomically diverse perimenarchal girls can be taught to recognize their cervical mucus patterns and distinguish anovulatory from ovulatory cycles.[44] Menstrual irregularities and/or ovarian dysfunction may reflect several systemic or reproductive disorders. Recent studies have shown that the menstrual cycle pattern during the first years after menarche is a better predictor for ovulatory dysfunction in adulthood than androgen or LH concentrations.[49] This and other previously conducted studies support the evidence that conditions such as hyperandrogenic ovulatory dysfunction in the adult female have their origin in adolescence. Most of these conditions are not self-limited disorders and will worsen during adulthood.[59] These studies suggest that if young women were taught how to chart their cycles they could be able to detect menstrual irregularities and ovarian dysfunction early in life. This finding could alert women to seek medical advice early which could be crucial for the prevention of disorders such as type II diabetes.

Furthermore, sex education programs that include training in fertility awareness have an impact in prevention of unintended adolescent pregnancy.[59] These programs have shown retardation of sexual initiation and discontinuation of sexual activity among sexually active adolescents, which is important for prevention of STD and pregnancies.[60–62]

Teaching fertility awareness to young women involves an effort that may be useful for every women throughout her life.

Summary

Knowledge about fertility awareness acquired by self observation of cervical mucus patterns at the vulva is an invaluable tool for women desiring to achieve and maintain a healthy reproductive system. The identification of medical and environmental causes of abnormal menstrual cycle patterns may provide clues to the causes of the most frequent fertility disorders. Early diagnosis of these alterations, as can be achieved through fertility awareness, will not only improve fertility disorders, but may help in the diagnosis and treatment of other pathologies such as metabolic and endocrine disorders, anatomical alterations, pelvic inflammatory diseases or even neoplasia. Mucus as well as the menstrual cycle patterns are important components of the clinical decision-making process.

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