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Slow Follicular Growth Rate Contributes to Longer Follicular Phases in Adolescents

Although it is accepted knowledge that irregular menstrual cycle lengths are commonly experienced by adolescent females, little is known about the mechanisms that cause the irregularities. Of particular interest is the rate of follicular growth, follicular dynamics, and the length of the follicular phase in this population. Researchers from the Federal University of Mato Grosso, Brazil, recently conducted a study for the purpose of verifying the prevalence of long follicular phases among healthy adolescents and to correlate the phase lengths with endocrine patterns and follicular growth rates.[1]

The participants for this study were 55 healthy (sexually active) female adolescents between the ages of 14 and 19 (mean age 16.9) who attended a Adolescent Clinic for the purpose of obtaining birth control. The participants received daily ovarian ultrasound measurements (of follicular growth) from day 2 to 5 of their menstrual cycle until ovulation was confirmed through visual collapse of the dominant follicle. In addition, blood was drawn from days 2 to 5 of the menstrual cycle to determine FSH, LH, and estradiol (E2) levels.

The researchers found that the menstrual cycle ranged from 25 to 35 days (with a mean of 29.5 days, SD = 1.6). The follicular phase length was a mean of 16 days, SD = 0.5 days. Twenty–five of the participants had follicular phase lengths greater than 16 days. There was a mild inverse correlation (r = -0.464) between FSH levels and follicular phase length, but there was no significant correlation between follicular phase length and LH and basal E2 levels. The researchers did find a faster speed of follicular growth among the adolescents with follicular phases 16 days or less compared to those with follicular phases greater than 16 days, i.e., 1.33 mm/day vs. 0.88 mm/day. The researchers concluded that long follicular phase lengths were common among adolescents and are probably a result of slow follicular growth.

Comments: Natural family planning (NFP) and fertility awareness (FA) teachers involved with adolescents can expect menstrual cycle length variability among their adolescent clients. According to this study the variability most likely is a result of the variation in rate of follicular growth. I would point out, however, that this was a rather small study with only 55 participants. A recent study by this author also found a mean of 16 days for follicular length among 141 healthy women with a mean age of 29. So this small cohort of adolescents did not display variability much different than a larger population of healthy women.

1. Cabral ZAF, de Medeiros SF. **Follicular growth pattern in normal-cycling Brazilian adolescents.** Fertility and Sterility, 2007; Epub ahead of print.

2. Fehring R, Schneider M, Raviele K. **Variability in the phases of the menstrual cycle.** JOGNN, 2006;35:376384.

Time to Pregnancy Shortened by Focused Intercourse (Theoretically)

Couples in the United States and other Western nations are delaying marriage and starting a family (i.e., having children) for the purpose of developing careers and stabilizing relationships. The risk of delaying childbirth to an older age is a diminished fertility and the expensive of infertility diagnosis and treatment. There is some evidence that focused intercourse during the six day fertile phase of the menstrual cycle will aid in a quicker time to pregnancy and avoidance of infertility care. However, what is not known is what are the optimal patterns of frequency and timing of intercourse to achieve a pregnancy. Research statisticians from Italy and the United States sought to determine -- based on an existing data set of menstrual cycles and utilizing Baysian analysis -- the optimal timing and frequency of intercourse to achieve a pregnancy.[1]

The data set included information from 193 women who were taught a mucus only (Billings) method of natural family planning. These women produced 2,755 menstrual cycles of data and 177 pregnancies. However, of these 193 women, 191 produced 2,536 complete data cycles and of these 191 women 132 of them achieved 161 clinical pregnancies. The median length of the cycles in the data set was 28 days with a range of 18 to 76 days. The menstrual cycle data included acts of intercourse and cervical mucus secretions descriptions. The investigators rated the cervical mucus descriptions on a scale from 1 to 4, with 1 = no mucus, dry sensation to 4 = slippery, wet, stretchy, clear mucus. The mean age of the 2,536 women participants was 29.95 years and their male partners 32.64. Each woman produced a mean of 13.28 cycles of data.

The researchers developed multiple scenarios of intercourse patterns with or without mucus during the middle most fertile days of the menstrual cycle (i.e., days 6–25) and during the estimated highest probability of fertility (i.e., days 13-17). They discovered that when intercourse is focused only on those days and not outside of days 6-25, the highest probability of pregnancy was with intercourse on each day from days 6–25 (i.e., 20 acts of intercourse) that yielded a cycle probability of conception = 0.687and 3 cycles of trying to achieve a 90% pregnancy rate. Couples who focused intercourse on the high rated fertile mucus (i.e., a number 4 rating) during days 13–17 of the menstrual cycle, the cycle probability of conception decreases to 0.347, with a mean intercourse rate of 2.42 days. With this scenario, the number of cycles to achieve a 90% pregnancy rate would take an average of 15 cycles.

Of interest, if the couples have intercourse (on average) every other day (no matter of the mucus rating) and focus on days 10-18 of the menstrual cycle, the cycle probability of conception only drops slightly to 0.647 and increases one additional cycle to pregnancy (i.e., 4 cycles) to achieve a 90% pregnancy rate.

The researchers also analyzed intercourse scenarios with not only intercourse during the middle of the cycle (i.e., days 6–25) but also with $1/7^{th}$ of the acts of intercourse outside of that range. Interesting, according to the data set, this increases the probability of pregnancy. For example, if the couples have intercourse every other day (i.e., a mean of

9 days of intercourse between days 10-18), and have 1/7th of intercourse outside of that range then the cycle probability of pregnancy is 0.654 and a 90% pregnancy rate within 3 cycles of trying.

The authors concluded that focusing intercourse on days of high fertile mucus (i.e., 4-rated mucus) would be useful for couples to shorten their time to pregnancy and not require a high frequency of intercourse. They also admitted that just using a calendar method and having intercourse on average every other day (during the estimated fertile window) and occasionally outside of the fertile window are sufficient. In this case mucus identification does not add to the efficiency of achieving pregnancy.

Comments: The intercourse scenarios presented in this study are theoretical and need to be tested in actual life and in particular with randomized control trials – for example comparing calendar based intercourse patterns versus high fertile mucus focused intercourse patterns. It seems, based on this theoretical data, that intercourse every other day during the estimated fertile phase of the cycle has very high probability of efficiently achieving a pregnancy. This article was very similar to a recent article by the same authors – that focused on the statistical models used for this study.[2]

I wonder if an externally observed mucus data base is the best to determine efficient intercourse patterns to achieve pregnancy. One of the reasons for my skepticism of this type of data set is that cervical mucus is not very efficient or accurate in estimating the fertile window. Based on the data presented in this article, the mean number of days of 2-4 rated mucus was 18.92 days for women between the ages of 20–26 and ranged from 15–19 days for all women in the data set. Since the mean length of the cycles was 28 days, this means that on average more than half the days had mucus rated days and on average, cervical mucus overestimates the fertile window by a factor of 3.

1. Scarpa B, Dunson DB, Giacchi E. **Baysian selection of optimal rules for timing intercourse to conceive by using calendar and mucus**. *Fertility and Sterility*, 2007: E-pub ahead of print.

2. Scarpa B, Dunson DB. **Bayesian methods for searching for optimal rules for timing intercourse to achieve pregnancy**. *Statistics In Medicine*, 2007;26:1920-1936.

Anti-Mullerian Hormone found to be best Predictor of Menopausal Transition

The years leading up to menopause can be a difficult time for women using natural methods of fertility regulation due to the variability of the menstrual cycles, increased anovulatory cycles, and increased menopausal symptoms. So too, are the decisions to be made in regards to use of supplementary hormones. In 2001, experts on the physiological changes of the menstrual cycle developed what is called the "Stages of Reproductive Aging Workshop" and the STRAW model of menopausal transition. The STRAW has 5 stages leading up to the final menstrual period, the early, peak and late reproductive phases (i.e., phases -5 to -3), the early and late menopausal transition (i.e., stages -2 and -

1). These stages are primarily based on the increased variability in the menstrual cycles and increased levels of FSH. Researchers from the University of Sidney, Australia, were interested in determining and clarifying the endocrine changes during the stages of menopause transition as identified by the STRAW model.

To do so, the researchers measured key hormones during the menstrual cycle of 77 women recruited through community advertisement. The women volunteers included 21 between the ages of 21 to 35 and 56 between the ages of 45 to 55. The older cohort of women were categorized based on the last 3 stages of the STRAW Model, i.e., stage -3, the late reproductive age but regular menstrual cycle lengths (LRA); stage -2, early menopausal transition with variability in menstrual cycle lengths greater than 7 days (EMT); and stage -1, the late menopause transition with at least one menstrual cycle interval lasting 60 days or more (LMT). The women collected menstrual cycle diaries that included first morning basal body temperatures for 3-6 months. Researchers collected blood samples three times a week through the first 7 days of the next menstrual cycle. The blood samples were analyzed for FSH, LH, estradiol (E^2), progesterione (P), inhibin A (INHS) inhibin B (INHB) and anit-Mullerian Hormone (AMH).

Of the 93 subjects, 77 women contributed data for the study, and 21 were classified as mid-reproductive age (MRA), 16 in the LRA stage; 17 in EMT, and 23 in LMT. They found that ovulatory cycle lengths were shorter in the LRA group compared to the MRA and EMT group but luteal phases were similar in all four groups. They discovered that FSH, LH and E2 levels increased with the progression of the STRAW stages and mean P levels decreased. Inhibin levels also decreased steadily across the STRAW stages but were undetectable in the anovulatory and long ovulatory cycles. The AMH decreased steadily and markedly across the stages of menopause transition. The researchers felt that the marked changes in AMH might be a good marker of indicating and predicting menstrual cycle stage changes. However, they indicated that large cohorts of women would be needed to verify these findings.

Comments: I would recommend that the changes in AMH would also have to prove to be more precise in predicting menopause transitions than normal menstrual cycle variability and natural biological markers of fertility. For example, is the AMH changes better predictors than the criterion of having menstrual cycle length variability greater than 7 days and having menstrual cycle lengths greater than or equal to 60 days? These changes could be found among women who use natural methods of fertility regulation or those women who just monitor the lengths of their menstrual cycles. I would think use of natural methods of fertility monitoring would be a less expensive means of monitoring menopausal transitions compared to having blood work to measure AMH levels.

1. Hale GE, Zhao X, Hughes CL, Burger HG, Robertson DM, Fraser IS. **Endocrine features of menstrual cycles in middle and late reproductive age and the menopausal transition classified according to the Staging of Reproductive Aging Workshop (STRAW) staging system**. *Journal of Clinical Endocrine Metabolism*, 2007: E-publ ahead of print.

Sialidase Activity of Female Cervical Mucus Highest in Ovulatory Phase

It is well known by natural family planning and fertility awareness teachers that the rheological properties of cervical mucus changes during the menstrual cycle in response to estrogen and progesterone. Human cervical mucus is primarily composed of mucins and glcosylated proteins secreted by the epithelial cells in the endocervical canal and vaginal mucosa. However, it has been speculated that the changing rheological properties of cervical mucus are not due to the protein structures of the mucins but rather to their carbohydrate components and in particular the oligosaccharide moieties of mucins, i.e., sialic acid (a nine carbon sugar). It is also thought that sialic acid-modifying enzymes, such as sialidases are important for proper development of physiological functions of sperm, e.g., sperm capacitation and sperm progression in the female genital tract. Most studies on the presence of sialic acid and sialidase activity do not take into account the timing of the women's menstrual cycle. Therefore, researchers from the University of Siena, Italy conducted a study to describe the endogenous sialidase activity in cervical mucus during the phases of the menstrual cycle and during pregnancy.

The researchers obtained 158 women volunteers between the ages of 17 and 45 years of age and collected cervical mucus samples (with sterile cotton swabs) during a gynecological exam. The samples were classified as to when during the menstrual cycle the samples were collected, i.e., from day 5-11 was considered the pre-ovulatory phase, days 12 – 16 the ovulatory phase, and days 17 – 29 the post-ovulatory phase. They also collected samples from 150 women during weeks 27 – 39 of pregnancy. The cervical mucus samples were assayed for sialidase activity, centrifuged, and observed under an electron microscope.

The researchers found that sialidase activity reached a maximum during the ovulatory phase of the menstrual cycle. They also found significant sialidase activity in the cervical mucus of pregnant women. When the sialidase was observed under electron microscope they saw membrane vesicle structures that they speculated might facilitate intercellular communication before and after fertilization. The researchers concluded that female cervical mucus contains endogenous sialidase that increases during the fertile phase of the menstrual cycle – which helps to change the rheological properties of cervical mucus which serves to facilitate sperm progression.

Comments: This study provided some good basic biological science of the nature and function of cervical mucus during the menstrual cycle. I would like to see a more precise indication for the timing of the samples during the menstrual cycle – either through LH testing or other natural biological indicators of ovulation like BBT and/or self-observed peak in cervical mucus.

1. Flori F, Secciani F, Cpone A, paccagnini E, Caruso S, Ricci MG, Focarelli R. **Menstrual cycle-related sialidase activity of the female cervical mucus is associated with exosome-like vesicles**. *Fertility and Sterility*, 2007, Epub ahead of print.

Two New Antimicrobial Factors found in Human Cervical Mucus

Infections in the female genital track are known to be deleterious for fertility, for the fetus, and for maintaining a pregnancy. The vagina is a microb-rich environment but the uterine environment is sterile. Cervical mucus serves as a filtering and anti-microbial host defense system between the vagina and uterus. Although the anti-microbrial activity of cervical mucus has been established, few anti-microbrial factors have been identified and purified. Therefore, Chinese scientists sought out to identify new anti-bacterial molecules in human cervical mucus.

The participants for this study were 8 healthy volunteer women between the ages of 24-35 (mean age 26) with a parity of 1 and at least one year after the delivery of their child. A specimen of cervical mucus was obtained by a 1 ml syringe from the cervix of each volunteer 3-4 days after menstruation. The samples were chemically analyzed for anti-microbrial proteins.

The researchers found that the cervical mucus was a viscous hydrogel weighing between 0.15 and 0.30 g, with a median pH of 7.2, range 6.4-8.0. The researchers were able to discover two anti-microbial effectors (i.e., antibacterial peptides): 1) a high-mobility group nucleosomalbinding domain (HMG N2) and 2) a secretory leukocyte peptidase inhibitor (SLPI). They concluded that these two anti-microbials serve as and constitute part of the cervix immune surveillance and defense system against pathogens in the human reproductive system.

Comments: NFP and FA teachers need to be aware of and understand the female reproductive system, especially those components that involve biological markers of fertility such as cervical mucus. It would be good to have further studies to examine the makeup of anti-microbials in cervical mucus during the different states of the menstrual cycle and in particular during the fertile phase.

Ming L, Xiaoling P, Yan L, Wang L, Qi W, Xiyong Y, Boyao W, Ning H. **Purification of antimicrobial factors from human cervical mucus.** *Human Reproduction,* 2007;22(7):1810-1815.