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8-1-2009

Current Medical Research Winter 2007/Spring 2008

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Accepted version. *The Linacre Quarterly*, Vol. 76, No. 3 (August 1, 2009): 315-346. DOI. © 2009
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Current Medical Research Winter 2007/Spring 2008

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End-Expiratory CO₂ Pressure as a Measure for the Beginning of the Fertile Phase of the Menstrual Cycle

There are few self-detected natural biological indicators for estimating the beginning of the fertile phase of the menstrual cycle for use in natural family planning. The current measures include the first observation or sensation of cervical mucus, the self-measure of the estrogen rise in the urine with an electronic fertility monitor, and/or some type of calendar based formula. However, it has been known for many years that a woman's respiration changes during the phases of the menstrual cycle. A research team from Austria and Germany used this knowledge to determine if a woman's end-expiratory carbon dioxide (CO₂) pressure levels could be used as a self-measure for the beginning of the fertile phase (D. Hadziomerovic, K.T. Moeller, P. Lict, A. Hein, S. Veitenhansel, M. Kusmitsch, and L. Wildt, "The Biphasic Pattern of End-Expiratory Carbon Dioxide Pressure: A Method for Identification of the Fertile Phase of the Menstrual Cycle," *Fertility and Sterility* 90 [2007] 731–736). If the CO₂ end-pressure was effective in estimating the fertile phase, the researchers intended to develop a simple instrument for self-measuring end-tidal carbon dioxide production.

The participants for this study were 160 women (18–48 years old) with a history of regular menstrual cycles between 24–32 days in length. They produced 195 menstrual cycles in which end-expiratory pressure levels were measured once daily. Serum levels of estrogen, progesterone, and luteinizing hormone (LH) were measured from day 10 of the menstrual cycle until the LH surge was observed. Partial pressure of CO₂ was measured by an infrared spectrometry device that was connected to a side stream end-expiratory air collection device (i.e., a capnometer). An ovulatory cycle for this study was defined as a rise in serum levels of estrogen followed by an LH surge or progesterone levels above 10 ng/mL. Of the 195 menstrual cycles, 150 were ovulatory.

The theory behind the carbon-dioxide levels as a measure of the beginning of the fertile phase is that the human respiratory center is sensitive to increases in estrogen or progesterone. The researchers found that there was a significant mean decrease in carbon dioxide levels (i.e., 5–9 mm Hg) about 1–5 days before the LH surge. They did not find a significant decrease in carbon dioxide pressure levels in the non-ovulatory cycles. They also discovered that administering estrogen or progesterone alone to women who had chemically suppressed ovaries also showed a decrease in carbon dioxide pressure. The authors concluded that a capnometer might be used in natural family planning as a means of estimating the beginning of the fertile phase along with another measure such as the urinary LH surge to estimate ovulation. They also indicated that a simple self-measure capnometer device has yet to be perfected.

Comments: Obviously measures of end-expiratory carbon dioxide as a marker for the beginning of the fertile phase is exploratory at this time. However, the Austrian/German researcher team did find that there was no circadian rhythm aspects to that measure—i.e., the measure could be taken any time during the day—unlike urinary LH and basal body temperature. If a simple, accurate, and easy to use capnometer could be developed, this would be another tool to be used in NFP. The capnometer monitor—unlike measures of urinary estrogen and LH—would not require the use of expensive test strips.

Method Discontinuation Due to Dissatisfaction Found to Be Low among Fertility Awareness Users Compared to Users of Hormonal Contraceptives

Unintended pregnancies are a major health problem in the United States. Approximately 50% of all pregnancies in the U.S. are unintended, and many of these pregnancies are aborted. Most of these unintended pregnancies are due to discontinuation of contraceptive methods; and, in turn, discontinuation is often due to dissatisfaction with use of these methods. Researchers from the Office of Population Research at Princeton University, therefore, sought to determine the reasons for (and percentage of) discontinuations among U.S. women using reversible methods of contraception (C. Moreau, K. Cleland, and J. Trussell, “Contraceptive Discontinuation Attributed to Method Dissatisfaction in the United States,” *Contraception* 76 [2007]: 172–173).

The Princeton researchers utilized the Cycle 6 (2002) data set from the National Survey of Family Growth (NSFG). This data set involved 7,643 women participants between 15–44 years of age. The NSFG is a periodic national population-based survey of U.S. women selected through probability statistical methods to obtain representative samples. The women are interviewed in person about their contraceptive and reproductive history with an average of 85 minutes per interview. The NSFG had an 80% response rate. Of the 7,643 women, 6,724 used a reversible method of contraception

sometime during their reproductive life span. Of these women, 33% used fewer than 3 different reversible methods, 50% used 3–4 different methods, and the remaining 17% used more than 4 methods.

The researchers found that users of the cervical cap and diaphragm had the highest (un-weighted) percentage (51.6%) of discontinuation due to dissatisfaction, with users of the sponge in second place at 47.6%. Users of the long acting contraceptives DepoProvera and Norplant had a 42% discontinuation rate due to dissatisfaction, and users of oral contraceptives were associated with a 29% risk of discontinuation. However, users of fertility awareness methods had only a 14.6% discontinuation risk. The lowest rate of discontinuation (11%) was among users of the male condom. Among the users of the Pill, Norplant, and Depo-Provera, the most frequent reasons for discontinuation were side effects, menstrual cycle disorders, and method failure.

The most frequent reasons that women provided for discontinuation of the male condom included partner dissatisfaction, decreased sexual pleasure, and messiness of use. The authors suggested better contraceptive counseling might help improve satisfaction and continuation. However, the counseling should be based on a better understanding as to why women discontinue contraceptive methods.

Comments: No matter how the contraceptive method is packaged and marketed and how women are counseled on why they should not discontinue a method of contraception, if the method causes discomforting side effects, menstrual cycle disorders, is messy to use, or interferes with sexual pleasure, there will still be high rates of discontinuation. The “ever use” percentage of fertility awareness users listed in this study was 17.9%, compared with 84.5% ever users of the pill and 57.5% users of withdrawal. Fertility awareness was not defined, but probably included self-devised calendar methods and the more modern mucus- and temperature-based methods. It would be of benefit to understand better why users of fertility awareness methods discontinue their use.

Method Failure Most Frequent Reason for Discontinuing Periodic Abstinence Methods among Brazilian Women

Researchers utilized a 1996 population-based data set of 12,612 Brazilian women between the ages of 15–49 (selected through a 2-stage, random-selection method) to analyze reasons for contraceptive dissatisfaction (I.C. Leite and N. Gupta, “Assessing Regional Differences in Contraceptive Discontinuation, Failure and Switching in Brazil,” *Reproductive Health* 4 [2007]). The data set contained variables on contraceptive use and discontinuation ascertained through retrospective survey methods. Researchers were interested in reasons for discontinuation of reversible methods of contraception and expressed a concern about the high rate of unintended pregnancy in that country. Furthermore, unintended pregnancy tended to occur during the time period of discontinuing and switching to another method of contraception. Greater than 50% of the women who use contraceptive methods in Brazil use sterilization (either female 49% or male 3%) as a method of family planning. Only 4% of Brazilian women list periodic abstinence as a method of family planning.

The researcher found that “method failure” was the most frequent reason (17%) why women discontinue periodic abstinence methods in Brazil. The most frequent reason given for abandoning use of the Pill (11.8%) and injectable hormones (27.4%) was because of side effects and health. The most frequent reason for discontinuing the condom (5.1%) was method failure. The researchers calculated a

12-month cumulative failure rate for the various contraceptive methods and found a 22.7% failure rate for traditional methods (that included periodic abstinence and withdrawal), a 6.5% failure rate for the Pill, and 9.1% for the condom. However, the abandonment rate for the Pill was 13.4% and for injectable contraception 17%, whereas for the traditional methods only 3.7%. The highest continuation rate was found among Pill users at 64%, followed by condom users at 46%, and then traditional methods at 44%. There was a greater rate of abandonment, switching, and failure rates among the less educated younger women. The researchers felt there was a need for increased access to a greater range of contraceptive methods.

Comments: Since the fertility rate (2.1) among the more wealthy and educated Brazilian women is much lower than among the poor and less educated, and since the failure rates are also lower among the more educated, maybe the Brazilian government would do better to concentrate its efforts on better education and economic opportunities for the poor. Perhaps more efforts should be made to increase access to a greater variety of choices of modern fertility awareness based methods, especially for the poor that cannot afford the Pill or injectables.

Study Finds 7.7% Failure Rate among French Fertility Awareness Users

French researchers recently conducted a retrospective population-based study to determine method-specific contraceptive failure rates among women participants in a French national database (C. Moreau, J. Trussell, G. Rodriguez, N. Bajos, and J. Bouyer, "Contraceptive Failure in France: Results from a Population-Based Survey," *Human Reproduction* 22 [2007]: 2422–2427). A stimulus for the study was the concern that 1 of 3 pregnancies among French women is unintended, and, of these, 65% occur while on some form of contraception. The database was from the population-based cohort 2000 Cocon Study. This study involved a representative sample of 1,689 women aged 18–44 years who were randomly selected to answer a series of questions on their contraceptive and reproductive history, i.e., the time from first intercourse to the date of the interview. The sample was over-represented by women who had had an abortion or an unintended pregnancy. Life table survival analysis (Kaplan-Meier) was used for data analysis.

The researchers discovered that the lowest first year failure rate of 1.1% was among IUD users, followed by a 2.4% failure rate among oral hormonal contraceptive pill users, then the male condom at 3.3%, 7.7% among fertility-awareness users, 10.1% among withdrawal users, and 21.7% among those using spermicides. They also found a 24-month failure rate of 4.3% among IUD users, 3.6% among Pill users, 7.8% with condom users, and 18.8% among fertility awareness users. The researchers mentioned that the contraceptive failure rates among French women are in the same order of effectiveness but significantly lower than those among U.S. women. They speculated on possible reasons for this difference, including underreporting of abortion and the fact that the U.S. data analysis includes all pregnancies regardless of intention. Furthermore, the French data set could be limited by recall bias and lack of data on sexual activity. The researchers concluded that comparative contraceptive failure rates between French and U.S. women suggest differences in contraceptive practices. They recommended further study of contraceptive failure rates and practices among different populations.

Comments: The "unintended" label given by the researchers to pregnancies was rather liberal since it included: a) not being planned at all, b) being planned later, and c) did not remember if she had

planned to become pregnant at that time. The types of fertility awareness methods listed in the study included 31.6% using “periodic abstinence” and 68.4% “safe period by temperature or Ogino.” This is confusing in that it is not clear what they mean by “periodic abstinence” other than maybe this was a self-determined guess by the woman of when she was fertile or not. Furthermore, it is surprising that there was not an inclusion of more modern fertility awareness methods, such as the ovulation method and/or the symptothermal methods. Another point to consider is whether this retrospective cohort population of women contraceptive users was representative of the entire female reproductive population, i.e., the authors did not attempt to insure or provide evidence for representation of their sample of women. Finally, it is worth noting that there is a need for population-based studies which delineate more specifically which NFP methods were used and their comparative effectiveness, as well as perhaps a need for more effective methods of NFP.

Use of Passive Lactation Amenorrhea Method Related to Low Empowerment among Egyptian Women

Empowering women to make decisions about family planning and other health behaviors is important for the health of the woman and her family. An Egyptian researcher was interested in the association of the lactation amenorrhea method (LAM) and passive LAM on the empowerment of household decisions among Egyptian women with children below 6 months of age (M. Afifi, “Lactational Amenorrhea Method for Family Planning and Women Empowerment in Egypt,” *Singapore Medical Journal* 48 [2007]: 758–762). Passive LAM was defined as women who: a) satisfied all elements of LAM, b) did not report the use of another method of family planning, and c) did not report relying on prolonged breastfeeding as a method of family planning.

The author obtained data from the 2000 Egypt Demographic Health Survey which included 15,773 never married women. From that data set she selected women whose last born was less than three years of age, were currently married, were not sterilized, and were currently breastfeeding their children. There were 3,447 women who met those criteria, and, of these, 1,141 had children less than six months of age.

The researcher found that nearly 58% of the sample had children under six months of age and were exclusive breast-feeders, and, of these women, 70% had amenorrhea, i.e., they met the LAM criteria of: a) full or near full breastfeeding, b) post-partum amenorrhea, and c) an infant under 6 months of age. Most of the women (82%) who met the LAM criteria were passive LAM users. Almost 12% of the LAM users also used another method of contraception. The most frequent method among the entire sample was the IUD (33%). The researchers also found that empowerment in household decision making inversely predicted passive LAM along with increase in child age, i.e., the less empowered, the greater use of passive LAM. They concluded that women who had a low empowerment index in household decisions were more likely to use passive LAM. The passive use of LAM, however, might lead to discontinuation and unnecessary use of contraceptives. They felt that if women were provided knowledge of LAM, they would be more likely continue to use LAM and progress to use modern methods of contraception.

Comments: It should be added that increasing the knowledge of natural family planning and fertility awareness methods might empower the woman and her spouse. This type of empowerment might result in not needing to use hormonal or IUD methods of contraception. A recent study of LAM among

1,490 Mexican women found that the main reasons for accepting the use of LAM were “conviction following postpartum counseling” and “use of LAM initially before switching to another method of contraception” (M.G. Lopez-Martinez, G. Romero-Gutierrez, and A.L. De Leon, “Acceptance of Lactational Amenorrhea for Family Planning after Postpartum Counseling,” *European Journal of Contraception and Reproductive Health Care* 11 (2006): 297–301).

Fertility

Consuming Multivitamins (at Least Three per Week) Associated with Reduced Risk of Ovulatory Infertility

Infertility occurs among 1 of 6 couples over a reproductive lifetime, especially among couples in developed countries that are delaying childbearing to later in life. Use of IVF for treating infertility is extremely expensive and time consuming. Therefore, less expensive and less invasive methods of treatment or prevention are important. There is some evidence that the use of folate supplements aids in the ovarian response to FSH. Therefore, Harvard University researchers sought to determine the association of multivitamin supplementation on the incidence of ovulatory infertility (J.E. Chavarro, J.W. Rich-Edwards, B.A. Rosner, and W.C. Willett, “Use of Multivitamins, Intake of B Vitamins, and Risk of Ovulatory Infertility,” *Fertility and Sterility* 89 [2008]: 668–676).

The participants for this study were a subset of the Nurses’ Health Study (NHS) that began in 1989 with 116,671 female United States registered nurses between the ages of 24 to 42 years who were followed with a mailed questionnaire every 2 years. The questionnaire included information on dietary patterns, vitamin use, whether the respondents were unsuccessful in achieving pregnancy, and what caused the inability to conceive. The researchers identified 18,555 women without a history of infertility who tried to become pregnant or who became pregnant during the 8-year follow-up period of the study. In the 8-year follow-up period women who reported infertility caused by an ovulatory disorder were considered cases, and the remaining women were considered non-cases.

The researchers discovered that during the 8-year follow-up period of the NHS, there were 26,971 pregnancies and pregnancy attempts among 18,555 women. Of these pregnancy attempts, 3,430 reported infertility from any cause, and, of these, 438 reported ovulatory infertility. When adjusted for age and calendar time, multivitamin users had approximately a 1/3 lower risk of developing ovulatory infertility than nonusers ($p < 0.001$). The association of multivitamin use was dose dependent in that there was no difference in risk of infertility with those that consumed 2 or less multivitamins per week. The researchers estimated that 20% of ovulatory infertility could be avoided if women consumed 3 or more multivitamins per week. Specifically, the intake of folic acid, iron, vitamins B₁, B₂, and D attenuated the inverse association between multivitamins and ovulatory infertility. Furthermore, there was a strong inverse association between folic acid intake and ovulatory infertility. There was no interaction between use of multivitamins and age or presence of long menstrual cycles. However, multivitamin users were more likely to consume less alcohol and coffee, to smoke less, and to be physically active compared with nonusers of multivitamins. The authors concluded that the consumption of multivitamins at least 3 times per week was associated with a reduced risk of ovulatory infertility and that this association appeared to be partially mediated by folic acid.

Comments: NFP and fertility awareness method (FAM) teachers should recommend multivitamins that contain folic acid for those women who wish to attempt a pregnancy, particularly for those women who have long and irregular cycle patterns. Folic acid supplementation is already recommended for women wishing to become pregnant to prevent tubal defects. Therefore, the added effect of decreasing ovulatory infertility is a plus.

Supplementary Feeding Related to Resumption of Menstruation and Ovulation

The time after delivery of a child and before the onset of menstrual cycles is a difficult time for women (who wish to avoid pregnancy) because of the variability of return of menstruation and ovulation. The return of menstruation does not mean the return of ovulation. Furthermore, breastfeeding and supplementary feeding patterns confound this variability. Therefore, Chinese researchers studied the relationship of supplementary feeding after child birth to the return of menstruation and ovulation (W. Li and Y. Qiu, "Relation of Supplementary Feeding to Resumption of Menstruation and Ovulation in Lactating Postpartum Women," *Chinese Medical Journal* 120 [2007]:868–870).

The participants for this study were 101 primiparous lactating women from one province in China. Each participant monitored her basal body temperature every morning along with cervical mucus observations and completed a lactation history questionnaire. The participants were also monitored by ultrasonography, beginning at 6 weeks postpartum, to determine follicular development and to document ovulation.

Of these 101 women, 53 had ovarian follicles larger than 1.8 cm in diameter at the first measurement. The Chinese researchers found that those women with larger follicles (i.e., over 1.8 cm) began supplementary feeding earlier (a mean of 4 months; + 1.1 months). The first ovulation occurred at 110 days past delivery (mean 155; + 45 days), and the BBT was elevated 6–13 days afterwards. Of the 53 women, 23 (43.4%) had their first ovulation before their first menses. The other 30 had their first ovulation 8–172 days after the first documented menses—14 of which had their first ovulation after their second recorded menses and 3 after the third menses. They also found that the start of supplementary feeding positively correlated with the resumption of ovulation ($r=0.476$, $p<0.01$) and menstruation ($r=0.555$, $p<0.01$). The rate of ovulation within the first 6 months post-delivery was 1–5% among total breastfeeding mothers. The authors concluded that the starting time of supplementary feeding significantly affected the resumption of menstruation and ovulation. However, many other factors affect the resumption of menstrual cycles. They recommended that women prolong breastfeeding and postpone supplementary feeding to lengthen the time of amenorrhea.

Comments: I found it remarkable that the BBT shift (that confirmed ovulation) was 6–13 days after the ultrasound documented ovulation. Furthermore, ovulation occurred before the first menses in a considerable number of cases. This would negate the use of the BBT shift and menses as a viable marker for the return of ovulation and the resumption of intercourse.

Men with Excess Body Weight Are at Increased Risk for Infertility

Researchers from the National Institute of Environmental Health Sciences (NIEHS) recently investigated the influence of male obesity on infertility (R.H.N. Nguyen, A.J. Wilcox, R. Skjaervben, and D.D. Baird, "Men's Body Mass Index and Infertility," *Human Reproduction* 22 [2007]: 2488–2493). Obesity in the

United States (and worldwide) is increasing and is a risk related to many health problems. There have been few population-based studies to determine the influence of body mass and infertility among males, and there are no studies that examined coital frequency as a confounding factor. Therefore, NIEHS scientists conducted a study to determine the influence of being overweight, i.e., having a body mass index (BMI) of 25 or over, in association with infertility that included frequency of intercourse around the time of conception as a confounding variable.

This study was retrospective and population-based, utilizing data from the ongoing Norwegian Mother and Child Cohort Study (MoBa). The MoBa study aims to enroll 100,000 pregnant women from 52 hospitals and birthing centers throughout Norway. Available to the NIEHS researchers were 45,132 women participants, of whom 26,303 met the study criteria and included the women's reports of the man's height and weight. Of these women, 12 percent (3,113) were infertile. A BMI of > 25, calculated from the man's height and weight, was considered overweight, and a BMI > 30 was defined as obese.

The researchers found that infertility was significantly related to the man's BMI, with overweight men having a 19% increase in infertility (OR = 1.19: 95% CI = 1.03–1.37) and obese men having a 36% increase incidence of infertility (OR = 1.36: 95% CI = 1.12–1.62). When the odds ratios were adjusted for coital frequency, there was not much of a change in results with an OR of 1.20 for overweight men and an OR of 1.36 for obese men. The results did not change as well when adjusted for age and parity of the woman. The researchers speculated that the increase in infertility among obese men was due to a decrease in reproductive hormone levels and a decrease in sperm production. They also speculated that weight loss would improve their chances of conception.

Comments: Fertility awareness and NFP teachers working with couples who wish to achieve a pregnancy should assess the BMI levels of both the woman and her male partner. If either has a BMI over 25, weight loss might be recommended. It would be interesting to know if targeted intercourse during peak fertility as determined by fertility monitoring methods would increase the pregnancy rates or obtain the same results as found in this study?

Variability in LH Surge Found among Young Ovulatory Women

In order to better understand physiological pathology of the menstrual cycle, one must first know the physiological norms of the menstrual cycle. Monitoring the menstrual cycle for potential health concerns, such as heart disease, has been recommended by a number of authors and the American Pediatric Association. There is a need to learn more about the physiological norms of the menstrual cycle and their relationship to the health of the woman. Therefore, researchers from the New Jersey Medical School recently conducted a study to determine the patterns of the luteinizing hormone (LH) surge among normal ovulating young women as expressed in urinary outputs (S.J. Park, L.T. Goldsmith, J.H. Skurnick, A. Wojtczuk, and G. Weiss, "Characteristics of the Urinary Luteinizing Hormone Surge in Young Ovulatory Women," *Fertility and Sterility* 88 [2007]: 684–690).

The participants for this study were 46 volunteer women between the ages of 20–35 with menstrual cycles between 21–35 days in length. The participants collected a daily first void urine sample for one menstrual cycle (i.e., from the first day of menses through the entire menstrual cycle). The urine samples were assayed in a laboratory for LH, follicle stimulating hormone (FSH), estrone conjugate

(E1C), and pregnanediol-3-glucuronide (PDG). The E1C/PDG ratio was used to estimate the day of ovulation.

The results showed that of the 46 women 43 (93.5%) had an ovulatory cycle. The mean length of the menstrual cycles was 29 days (SD=4.0; Range 22–43 days), the mean follicular phase was 17.0 days (SD=3.6; Range 10–29), and the mean luteal phase length was 12.1 days (SD = 1.57; range 9–16 days). The researchers found that the LH surge varied in configuration with the onset being either rapid or gradual and the configuration being spiked, biphasic, or plateau in shape. They also discovered that the presence of an LH surge does not always result in an ovulation. They also found that the FSH rise or surge did not always coincide with an ovulatory event. However, when there was an E1C rise before the LH surge, there was always an ovulatory event.

The researchers concluded that the patterns of LH surges are variable and that the FSH rise is not essential for ovulation. However, they also confirmed that the E1C rise was critical for the initiation of the LH surge.

Comments: I found it interesting that the LH surge has many different patterns. This is not surprising, since there is a lot of variability in follicular development and resultant hormonal production. Of interest is that the LH surge or rise (as defined in this study) actually occurred on average over 7.6 days, (i.e., from the first rise from baseline readings until the LH surge returned to baseline). Furthermore, not all LH surges resulted in ovulation. As the author stated, this has clinical implications for women who use LH ovulation detection kits to time intercourse for achieving a pregnancy. Based on this information, those women who use a hormonal monitor to detect the rise of estrogen before the LH surge would have a better chance at achieving pregnancy by using menstrual cycles that indicate both the estrogen rise and LH surge. I also wonder if some of the LH test kits miss the LH surge in the biphasic LH cycles, where the LH peak is only around 28 mIU/mg.

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 change during the menstrual cycle in response to estrogen and progesterone. Human cervical mucus is primarily composed of mucins and glycosylated 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 (F. Flori, F. Secciani, A. Capone, E. Paccagnini, S. Caruso, M.G. Ricci, and R. Focarelli, "Menstrual Cycle-Related Sialidase Activity of the Female Cervical Mucus Is Associated with Exosome-Like Vesicles," *Fertility and Sterility* 88 [2007]: 1212–1219).

The researchers obtained 158 women volunteers between the ages of 17 and 45 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., days 5–11 were 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 provides some good basic biological science of the nature and function of cervical mucus during the menstrual cycle. It would be interesting 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.

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 microbe-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-microbial activity of cervical mucus has been established, few anti-microbial factors have been identified and purified. Therefore, Chinese scientists sought to identify new anti-bacterial molecules in human cervical mucus (L. Ming, P. Xiaoling, L. Yan, L. Wang, W. Qi, Y. Xiyong, W. Boyao, and H. Ning, “Purification of Antimicrobial Factors from Human Cervical Mucus,” *Human Reproduction* 22 [2007]: 1810–1815).

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-microbial 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 nucleosomal binding 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.

Women Unaware of Risks and Complications in Delaying Childbearing

Women in Western developed countries are increasingly delaying childbearing to a later age due to career development. Many of these women may be unaware of the potential maternal and fetal complications among older women. Researchers from Aberdeen University sought to determine women's awareness related to issues (social and medical) to delayed childbearing (A. Maheshwari, M. Porter, A. Shetty, and S. Bhattacharya, "Women's Awareness and Perceptions of Delay in Childbearing," *Fertility and Sterility* 90 [2008]: 1036–1042). The researchers were also interested in whether there was awareness of the limitations of artificial reproductive therapies among two groups of women: 1) women who were unsuccessful in achieving a pregnancy and were currently seeking infertility treatments, and 2) women who were currently pregnant.

The participants for the study were 772 women who were approached at the Aberdeen University Maternity Hospital, 8 of which refused to participate. There were 382 in each group, i.e., the infertility and the pregnant groups of women. They were all administered a 32-item questionnaire that ascertained their awareness of the limitations of infertility treatments, age limits for access to fertility treatment, and tests for the prediction of fertility.

The researchers found a higher portion of women in the sub-fertile group who sought pregnancy after age 30 compared to the pregnant group. There was a higher portion of women in the sub-fertile group that used contraception in the past compared to the pregnant group. Most of the women in both the sub-fertile group (85%) and the pregnant group (77%) thought that IVF treatments could overcome the effects of age even though they knew that fertility decreased with age. Most women in both groups (86% and 85%) were aware that delaying childbearing increased the risk for a child with trisomy 21. The authors concluded that most women they surveyed were aware of the risks of delaying childbirth to a later age, but were misinformed erroneously that IVF would reverse the effects of age.

Comments: Of interest, among the sub-fertile women in this study, over 80% felt that fertility decreases considerably among women between the ages of 30–39; however, about 40% felt that IVF would be able to reverse the effects of aging. Most of the women in both groups (>75%) felt that first-time motherhood after the age of 55 was unacceptable. One of the implications that this study has for NFP/FA teachers is that they probably will be seeing more older women seeking pregnancy for the first time. The NFP teachers need to be honest about the chances for achieving pregnancy with normal intercourse and with IVF treatments.

Contraception

Flip Chart Contraceptive Counseling Fails to Decrease Contraceptive Discontinuation

Contraceptive discontinuation is considered a major reproductive problem since there is a relatively high rate of unintended pregnancies during this period. Furthermore, there is a very high rate (> 50%) of discontinuation of hormonal contraception within the first year of use. Studies have recommended decreasing contraceptive discontinuation within improved contraceptive counseling that includes help

in contraceptive decision making and honesty in regards to side effects—and how to manage the side effects. In order to standardize a mechanism for better contraceptive counseling, a contraceptive counseling tool (flip chart) was developed through Johns Hopkins University. The flipchart counseling tool has simplified information about contraceptive methods, contraceptive decision making, contraceptive side effects, and contraceptive benefits and risks. Researchers recently tested the effects of using the contraceptive flipchart on contraceptive continuation among clients who seek contraception through Nicaraguan health department clinics (D.S. Chin-Quee, B. Janowitz, and C. Otterness, “Counseling Tools Alone Do Not Improve Method Continuation: Further Evidence from the Decision-Making Tool for Family Planning Clients and Providers in Nicaragua,” *Contraception* 76 [2007]: 377–382).

The researchers used a quasi-experimental design in which they determined prospectively which Nicaraguan clinics would provide the flip chart counseling intervention and which clinics would be considered control clinics. In the 41 experimental clinics, the contraceptive flip-chart counseling system was used by all trained counselors on first-time family-planning clients for 3–5 months. The first-time family-planning clients in the 24 control clinics received standard care. There were a total of 1,633 users at the clinical sites.

After 3–5 months of intervention, the researchers found that there was no difference in contraceptive use rate, with the experimental group at 80% and the control group 86%. In fact the control group had a higher injectable contraceptive use rate than the experimental group. However, those exposed to the flip chart expressed that they had a better counseling experience. The authors concluded that there is sufficient evidence that contraceptive counseling (with or without flip charts) does not increase contraceptive use rates. They felt that newer strategies need to be developed.

Comments: The authors admitted that, although they had control clinics, there might have been some crossover in use of the charts system and/or that there was some good contraceptive counseling in the control clinics. Furthermore, the flip chart was not always used in the experimental clinics. The researchers speculated that there are other factors that influence discontinuation of contraceptive methods, including side effects and lack of support from the husband. It should be pointed out that no matter how much counseling there is if women experience negative side effects, like unusual bleeding, they are not going to continue—nor should the health professional expect them to. A similar flip-chart counseling system could be developed and tested on NFP methods to help with NFP decision making.

Studies Show Mixed Results on the Post-Fertilization Effects of Levonorgestrel (Plan B) Emergency Contraception

Two recent studies in two prominent journals (*Fertility and Sterility* and *Human Reproduction*) investigated whether there are potential post-fertilization effects of levonorgestrel-only emergency contraception (EC) (R.T. Mikolajczyk and J.B. Stanford, “Levonorgestrel Emergency Contraception: A Joint Analysis of Effectiveness and Mechanism of Action,” *Fertility and Sterility* 88 (2007): 565–571; P.G.L. Latlikumar, S. Lalitkumar, C.X. Meng, A. Stavreus-Evers, F. Hambiliki, U. Bentin Ley, and K. Gemzell-Danielsson, “Mifepristone, but Not Levonorgestrel, Inhibits Human Blastocyst Attachment to an in Vitro Endometrial Three-Dimensional Cell Culture Model,” *Human Reproduction* 22 [2007]: 3031–3037). This topic is of importance to health professionals, potential users, and health-care facilities in which religious or ethical codes prohibit the use or prescription of drugs that produce an early

pregnancy loss. Some states in the United States have mandated the use of EC for rape victims in all hospital emergency rooms. So the answer to the question of whether or not levonorgestrel EC causes an early abortion is of importance.

The first study utilized a theoretical approach to determining whether there might be a post-fertilization mechanism of levonogestrel-only EC (Mikolajczyk et al., “Levonorgestrel Emergency Contraception”). The authors did this by estimating the efficacy rates of using EC to avoid pregnancy for up to 72 hours post-intercourse based on known day-specific probabilities of pregnancy and a follicular growth model. They determined that with a disruption of ovulation alone, the potential efficacy of EC was from 49% (with no delay in taking the drug) to 8% (taking the drug with a 72-hour delay). However, based on their models, with complete disruption of ovulation as the only mechanism, the potential effectiveness of avoiding pregnancy was from 90% (with immediate use) to a low of 16% (with a 72-hour delay). They concluded that the gap in efficacy rates between what is reported in the literature and what they modeled might either be explained by an overestimation of efficacy or by some type of post-fertilization effect.

The second study involved the use of an in vitro model with a culture model of the early luteal phase of the human endometrium (Latlikumar et al., “Mifepristone, but Not Levonorgestrel”). The researchers used 46 embryos donated from an IVF clinic, of which 14 were cultured with levonorgestrel, 15 with another anti-progesterone drug mifepristone, and the remaining 17 embryos served as controls. They found that none of the embryos that were cultured with mifepristone (a known abortion drug) demonstrated endometrial attachment, while 6 of the 14 levonorgestrel embryos attached as well as 10 of the 17 control embryos. There was no difference in the rate of attachment between the control and levonorgestrel-cultured embryos. The authors concluded that mifepristone inhibits embryo/blastocyst attachment but that levonorgestrel does not impair the attachment of human embryos as determined by the in vitro endometrial environment.

Comments: While there is no statistically significant difference in these implantation rates, it might be worth noting that the implantation rate of the controls (59%) is higher than that in the levonorgestrel group (43%). With additional testing this could become significant, but would require quite a large number of embryos to be killed in this experiment (~200 in each group) in order to have enough statistical power to detect differences—the killing of any embryos is morally unacceptable.

Of the two studies, the in vitro endometrial attachment construct study has more direct evidence and coincides with the results from other recent studies that showed no post-fertilization effect with the administration of levonorgestrel. However, as the “potential for a changes in the endometrium (which reduce the likelihood of implantation)” is noted in the prescribing information for levonorgestrel (e.g., see “Seasonique,” <http://www.seasonique.com/docs/prescribing-information.pdf>), women should be presented with the knowledge that Plan B has a potential post-fertilization effect. In addition, levonorgestrel is associated with “increased risk of several serious conditions including venous and arterial thrombotic and thromboembolic events (such as myocardial infarction, thromboembolism, and stroke), hepatic neoplasia, gallbladder disease, and hypertension” (ibid., 9). Therefore, if levonorgestrel is to be used, and if indeed it does not have a post-fertilization effect, it would seem prudent to first screen women to see if ovulation has occurred prior to administration of Plan B, and only administer Plan B to those who have not as yet ovulated, as is commonly the case in rape protocols for some Catholic hospitals. This would serve to minimize the risk of side effects to the women while still

permitting use when conception has not yet occurred. Both sets of researchers from these studies recommended further research into the matter.

Post-Fertilization Effects Influence Women's Choice of Family Planning Methods

Providing information about the mechanisms of action of family planning methods by health providers is important for the decision-making process of potential users. One of the concerns is whether family-planning methods act post-fertilization and cause early embryo loss. Spanish researchers recently surveyed 755 potentially fertile women in order to determine their attitudes towards post-fertilization effects of family-planning methods (J. De Irala, C. Lopez del Burgo, C. Lopez de Fez, J. Arredondo, R.T. Mikolajczyk, and J. Stanford, "Women's Attitudes towards Mechanisms of Action of Family Planning Methods: Survey in Primary Health Centres in Pamplona, Spain," *BMC Women's Health* 7 [2007]: 1–10).

The 775 female participants were between the ages of 18–49 and were approached by health providers at 10 primary health centers in Pamplona, Spain. They were asked to complete a 30-item questionnaire about family-planning methods, mechanisms of action, and medical and surgical abortion. Of the 755, the researchers were able to obtain 581 (80%) usable questionnaires.

The researchers found that almost half of the respondents (46.3%) believed that life begins at fertilization, and most (58.7%) felt it was important to distinguish between natural embryo loss and those caused by family-planning methods. A majority of respondents (57%) would not use a family-planning method that sometimes works after implantation of the embryo, and a large minority (39.4%) would not use a family-planning method that sometimes works after fertilization but before implantation. The researchers realized that the respondents (who were mostly well educated Catholic women) did not represent the entire population of Spanish women and recommended further studies with other populations. The authors concluded that the results emphasize that full information about the mechanisms of action for family-planning methods is important for many women.

Comments: Since some bioethicists claim that NFP methods are a cause of early embryo loss due to aging gametes, it would be interesting to know if those Spanish women would consider NFP a natural cause. The researchers also asked an open-ended question as to what are the most important characteristics in choosing a method of family planning. The three highest rated responses were: 1) efficacy (76%), 2) convenience and ease of use (53.4%), and 3) absence of side effects (28.6%). Although most of the respondents listed their religion as Catholic, there was a low level of religiosity among the participants based on church attendance and self-reported importance of religion.

Oral Hormonal Contraceptive Use Increases Estrogen Receptors in Vulvar Vestibular Mucosa

Swedish researchers sought to determine the effects of combined oral contraceptive (COC) use on the sex steroidal receptors in vulvar vestibular mucosa in healthy women (U. Johannesson, L. Sahlin, B. Masironi, E. Rylander, and N. Bohm-Starke, "Steroid Receptor Expression in the Vulvar Vestibular Mucosa—Effects of Oral Contraceptives and Menstrual Cycle," *Contraception* 76 [2007]: 319–325). The background reason for conducting this study was that this area of research has few studies, and these same researchers recently found morphological changes in vulvar vestibular mucosa during COC use.

Furthermore, the Swedish researchers believe that there is some connection between COC use and vestibular pain during intercourse.

The researchers recruited 45 healthy sexually active subjects of which 20 (mean age 23.7) were on COCs for a minimum of one year (actual use ranged from 2–15 years) and 25 control women (mean age 25.6 years) who used non-hormonal means of contraception. A vestibular punch biopsy was obtained on the 7–11th day after the beginning of the menstrual cycle in all subjects. Serum samples for estradiol and progesterone levels were drawn to determine the phases of the menstrual cycle. Tissue from the punch biopsies were subjected to immunohistochemistry analysis for sex steroid receptors. Five of the control women were determined not to have ovulated during the test cycle and were not included in the analysis.

The researchers found that there were significantly more beta-type estrogen receptors in the vulvar vestibular tissue of the COC users compared to the controls ($p < 0.024$). They also found a greater abundance of progesterone receptors in the vulvar tissue during the follicular phase than in the luteal phase ($p < 0.01$) among the non-COC users. They did not find any significant differences in the abundance of progesterone, androgen, or glucocorticoid receptors between the two groups. However, the researchers did point out a limitation in the small number of participants in each group. They concluded that the results indicated a hormonal influence on the steroid receptor expression by ethinyl estradiol as well as by progestins. They believed that the hormones in the COCs not only effect the expression of the estrogen receptors but the morphology of the vestibular mucosa as well.

Comments: The Swedish researchers indicated that the clinical implication for the findings was unknown. However, they have proposed that COCs make the vestibular tissue more sensitive and that this is a possible reason why COC users report more sexual pain compared to non-users. It would be interesting to know if the increase in estrogen receptors also occurs in the cervical endometrial tissue and is one reason why there is an increase of cervical mucus found in post-COC users who switch to a mucus-based method of fertility awareness.

Return of Menses Occurs Rapidly after Use of Continuous Oral Contraception

Traditional oral hormonal contraception produces an artificial menses every 28 days due to the withdrawal of exogenous hormones with the use of hormone-free placebo pills or by a Pill-free interval. Recently, continuous oral hormonal contraception has been introduced that reduces the frequency of artificially induced menses. There is some concern that use of continuous hormonal contraception might delay the return of menses and ovulation. Therefore, researchers conducted a study to determine the effect that prolonged use of continuous hormonal contraception has on the return to fertility—with spontaneous menses as the marker of fertility return (R. Davis, R. Kroll, B. Soltes, N. Zhang, G.S. Grubb, and G.D. Constantine, “Occurrence of Menses or Pregnancy after Cessation of a Continuous Oral Contraceptive,” *Fertility and Sterility* 89 [2008]: 1059–1063).

The participants for this study were 198 women who were a subset of the 2,134 subjects (with regular menstrual cycles of 21–35 days) who participated in a phase-3 efficacy and safety trial of daily continuous oral levonogestrel (LNG) 90 µg/ethinyl E₂ (EE) 20 µg (trade name Lybrel) and who completed at least 6 months of use. Most (81.8%) of the 198 subjects had completed 12 months of Lybrel with a mean duration before enrollment of 349 days. Of the 198 participants, 187 completed

the study. Of these, 185 (98.9%) returned to spontaneous menses or became pregnant within 90 days of stopping LNG/EE. Of the two subjects that did not experience a return of menses within 90 days, one did so at 124 days and the other approximately 2 months after the completion of the study. The median time to return of menses was 32 days. Furthermore, the researchers found that the length of amenorrhea (i.e., length of use of LNG/EE) was unrelated to the time to return of menses. The authors concluded that the inhibition of menses with continuous use of LNG/EE was readily and quickly reversible.

Comments: NFP/FA teachers who have women coming off of continuous LNG/EE (Lybrel) to achieve a pregnancy or to use natural methods for avoiding pregnancy can assure them that menses (and presumably ovulation) will most likely return within 1–3 months. However, these results apply only to those women who previously had regular-length menstrual cycles.

Menstrual Cycle

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 to verify the prevalence of long follicular phases among healthy adolescents and to correlate the phase lengths with endocrine patterns and follicular growth rates (Z.A.F. Cabral and S.F. de Medeiros, "Follicular Growth Pattern in Normal-Cycling Brazilian Adolescents," *Fertility and Sterility* 88 [2007]: 1625–1631).

The participants for this study were 55 healthy and sexually active female adolescents between the ages of 14 and 19 (mean age 16.9) who attended an adolescent clinic for the purpose of obtaining birth control. The participants received daily ovarian ultrasound measurements (of follicular growth) from days 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 is most likely a result of the variation in rate of follicular growth. It should be pointed 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 (R. Fehring, M. Schneider, and K. Raviele, "Variability in the Phases of the Menstrual Cycle," *Journal of Obstetric, Gynecologic, and Neonatal Nursing* 35 [2006]: 376–384). So this small cohort of adolescents did not display variability much different than a larger population of healthy women.

Time to Pregnancy Shortened by Focused Intercourse (Theoretically)

Couples in the United States and other Western nations are delaying marriage and postponing starting a family (i.e., having children) for the purpose of developing careers and stabilizing relationships. Delaying childbirth to an older age brings with it the risk of a diminished fertility and the expense 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 are the optimal patterns of frequency and timing of intercourse to achieve pregnancy. Research statisticians from Italy and the United States sought to determine—based on an existing data set of menstrual cycles and utilizing Bayesian analysis—the optimal timing and frequency of intercourse to achieve a pregnancy (B. Scarpa, D.B. Dunson, and E. Giacchi, "Bayesian Selection of Optimal Rules for Timing Intercourse to Conceive by Using Calendar and Mucus," *Fertility and Sterility* 88 [2007]: 915–924).

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). This pattern of daily intercourse yielded a cycle probability of conception = 0.687. This pattern also resulted in only 3 cycles of trying to achieve a 90% pregnancy rate. For couples who focused intercourse on the high-rated fertile mucus (i.e., a number 4 rating) 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.

Interestingly, if the couples have intercourse (on average) every other day (regardless of the mucus rating) and focus on days 10–18 of the menstrual cycle, the cycle probability of conception drops only 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 not only with intercourse during the middle of the cycle (i.e., days 6–25) but also with 1/7th of the acts of intercourse outside of that range. 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 the acts of intercourse outside of that range, 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. With this scenario, 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 (B. Scarpa and D.B. Dunson, “Bayesian Methods for Searching for Optimal Rules for Timing Intercourse to Achieve Pregnancy,” *Statistics in Medicine* 26 [2007]: 1920–1936).

It would be interesting to know if an externally observed mucus database is the best to determine efficient intercourse patterns to achieve pregnancy. One of the reasons for 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- to 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.

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 family planning due to the variability of the menstrual cycles, increased anovulatory cycles, and increased menopausal symptoms. Also difficult at this time, 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, i.e., phases –5 to –3 are the early, peak, and late reproductive phases, and stages –2 to –1 are the early and late menopausal transition phases. These stages are primarily based on the increased variability in the menstrual cycles and increased levels of FSH. Researchers from the University of Sydney, Australia, were interested in determining and clarifying the endocrine changes during the stages of menopause transition as identified by the STRAW model (G.E. Hale, X. Zhao, C.L. Hughes, H.G. Burger, D.M. Robertson, and I.S. Fraser, “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* 92 [2007]: 3060–3067).

To do so, the researchers measured key hormones during the menstrual cycles 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 (E₂), progesterone (P), inhibin A (INHS), inhibin B (INHB), and anti-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: From a natural methods perspective, researchers should have to provide evidence that the changes in AMH are more precise in predicting menopause transitions than normal menstrual-cycle variability and natural biological markers of fertility. For example, are 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. Natural methods of fertility monitoring would be a less expensive means of monitoring menopausal transitions compared to having blood work to measure AMH levels.

In Depth Stress and Menstrual Cycle Variability

Stress is a common experience in modern Western cultures. For women using fertility awareness based (FAB) methods of family planning, the effect of stress on the menstrual cycle is of concern. In particular the concern is whether stress causes menstrual-cycle variability, suppression or delay in ovulation, and disruption in the biological signs of fertility. When women are under stress, the impression is that FAB methods are more difficult to use because of menstrual cycle variability and confusing biological indicators of fertility.

Social and medical scientists have accumulated many studies to show that as stress events accumulate during a calendar year (or longer), the more likely the person will experience a stress-related illness.¹

Researchers have developed a list of events from death of a spouse at the top to a minor parking ticket at the bottom, with marriage is ranked as the number two stressor just below death of a spouse. The more life changes and the higher on the list are the life changes that an individual experiences, the more likely she will experience stress-related health problems. Anecdotally, NFP teachers often comment that the menstrual cycle during the week of the marriage event is extremely variable as a result of the stress of the marriage and marriage preparations.

The research evidence on the effects of stress on the menstrual cycle is mixed.² A study conducted with women from India showed that women who worked in physical-type jobs, such as farm or craft work, had significantly longer cycles than women who worked in sedentary jobs, such as clerical work.³ Another study among U.S. and Italian nurses found that there was a significant relationship between the perceived stress of their jobs and longer and monophasic cycles.⁴ However, the Italian nurses who worked with rotating shifts compared to fixed shifts had significantly shorter menstrual cycles and shorter luteal phases determined by the basal body shift as the proxy indicator for ovulation.

Two recent studies indicated that the experience of stress was related to shorter menstrual cycles.⁵ One study was conducted with 276 healthy, premenstrual U.S. women.⁶ The researchers found that those women in “stressful jobs” had more than twice the risk of having shorter menstrual cycles than those women in non-stressful jobs. However, there was no relationship between the participants’ *perceived* stress and menstrual-cycle variability. Another study showed that there was no relationship between menstrual-cycle length and accumulation of stressful life events over a calendar year among 206 healthy U.S. women.⁷ However, women with increased stress levels over a 2-year period had significantly shorter menstrual cycles compared to women with less stress.

Two other studies found no relationship between measures of stress and variability of the parameters of the menstrual cycle.⁸ One study measured urinary stress hormones (adrenaline, noradrenaline, and cortisol levels) and a psychological measure of mood states among 34 healthy menstruating women.⁹ Neither the psychological measure of stress nor the urinary stress hormones correlated with menstrual-cycle variability. Of interest was that the psychological measure of stress through perceived mood states did not correlate with the urinary measures of the stress hormones. Finally, a recent two-part study of both ovarian hormones and stress hormones found no differences in stress hormone levels or ovarian hormonal levels between 95 female students taking the medical school entrance exam (the stressor) and 27 female controls.¹⁰ The researchers also found no differences in pre- and post-entrance exam test stress hormone levels within the medical school entrance exam group.

Therefore, the evidence of stress effects on the menstrual cycle is not conclusive. Part of the reason for the mixed results is the mixed means of measuring stress (mentally and physically) and measuring menstrual-cycle changes. Furthermore, there is no consistent meaning of “stress” whether the stress is chronic or acute, and how much stress is being experienced—and whether the stress was physical or psychological. In order to have a better idea of how stress affects the menstrual cycle, there needs to be a more standardized means of measuring stress and menstrual-cycle parameters.

Researchers at Marquette University recently analyzed the effects of stress on the menstrual cycle by analyzing the effect marriage has on the menstrual cycle. As mentioned previously, marriage is considered a very high level life-experience stressor. They measured the length of the menstrual cycle and the length of the luteal and follicular phases among 13 women during the pre-wedding menstrual

cycle, the wedding menstrual cycle, and the next two post-wedding menstrual cycles. The 13 women were between the ages of 20 and 37 (mean age 26.5, SD=5.28), and all 13 had regular cycle lengths. Repeated measure analysis indicated that there was a significant change in the length of the menstrual cycle from the pre-to the two menstrual cycles post the wedding cycle. Post hoc statistical testing indicated that the pre-wedding menstrual cycle length and the last menstrual cycle length (from the wedding cycle) were significantly shorter than the menstrual cycle experienced during the wedding month. See [table 1](#) below.

Table 1
Menstrual-Cycle Parameters Pre- and Post-Wedding Day (N=13)

Parameter	Pre-Wedding	Wedding Cycle	Post-Wedding	Last Cycle
Length	30.1 (SD=4.2)	27.8 (SD=3.6)	28.5 (SD=3.3)	30.0 (SD=4.4)
Follicular	16.7 (SD=3.7)	15.1 (SD=3.4)	16.1 (SD=3.3)	17.2 (SD=4.5)
Luteal	13.4 (SD=2.4)	12.8 (SD=1.9)	12.4 (SD=3.4)	12.7 (SD=1.8)

Although there was no significant change in the length of the follicular phase (as indicated by the day of the peak day of cervical mucus) and the length of the luteal phase, [table 1](#) results do show that the peak day was almost (on average) two days earlier during the wedding cycle than the pre-wedding and last cycles. The power to detect changes was low since there were only 13 participants in this analysis. Therefore, the data suggest that stress has the effect of shortening the menstrual cycle mostly due to a short follicular phase. This would indicate that rather than suppressing ovulation, stress actually stimulates ovulation to occur earlier. The stress hormones might be stimulating the reproductive hormones. These results coincide with the two studies mentioned above that provided evidence that stress shortens the menstrual cycle.

Table 1
Normative Statistical Parameters of the Menstrual Cycle

Parameter	Mean	SD	95% CI	Individual Variance
Total cycle length	27.7	2.4	25–32 days	0.8–5 days
Follicular phase length	14.7	2.4	10–20 days	1.0–13 days
Luteal phase length	13.2	2.0	9–17 days	0.3–9 days
Day of implantation	24.6	3.1	20–30 days	NA

Fertility awareness methods and NFP method textbooks generally report that stress will lengthen the menstrual cycle and/or delay or suppress ovulation.¹¹ According to T. Weschler, stress will lengthen the menstrual cycle and either delay or suppress ovulation.¹² Weschler and others also indicated that the cervical mucus sign will be diminished or that there will be a buildup, tapering off, and then another buildup of cervical mucus during a stress cycle.¹³ Some methods call this a double peak.¹⁴ The double peak in the mucus buildup supposedly indicates a suppression and delay in ovulation. E. Clubb and J. Knight also wrote that if stress is severe enough, ovulation will be completely suppressed.¹⁵ Several of the texts mentioned that, besides the double-peak phenomenon, the basal body temperature shift will be delayed for up to one week.¹⁶ Several of the texts provided example charts with delayed ovulation, double buildup of mucus, and longer menstrual-cycle lengths. One even mentioned the wedding cycle

and provided an example of the menstrual cycle recorded during the wedding month.¹⁷ None of the textbooks provided evidence of the effects of stress other than anecdotal cases.

A number of reproductive physiological texts concur with the NFP/FA textbooks that stress will cause a hypothalamic response possibly leading to anovulation and amenorrhea.¹⁸ This happens with high-intensity runners or women who participate in a high-intensity-type sport activity. However, the amenorrhea (and anovulation) is usually not due to the running or high intensity of the sport but to having insufficient nutritional energy to make up for the deficit.¹⁹

In summary, the effects of chronic and acute stress on the menstrual cycle are mixed. Generally, they will include a decrease in the length of the cycle and the follicular phase. However, if the stress is acute enough, ovulation will be suppressed. One of the big indicators of how the menstrual cycle will react is the energy factor—does the body have enough energy to sustain ovulation. Most women's bodies do, especially if they maintain an adequate diet, moderate exercise, and appropriate amounts of sleep and rest. However, if you have young women who are avid runners or who are trying to starve themselves into a smaller-sized wedding dress, ovulation might be delayed and suppressed. As always, a balanced lifestyle of moderate exercise, appropriate diet that meets the energy requirements of the body, rest and sleep, and good mental outlook will help to moderate stress and the effects it will have on the menstrual cycle. Monitoring the normal parameters of the menstrual cycle through NFP can also be a way of monitoring a healthy lifestyle.

Current Medical Research Summer/Fall 2008

Richard J. Fehring, Ph.D., R.N.

Self-Assessment of Cervical Pupil Sign as a Possible New Natural Family Planning Method

It is well known among natural family planning (NFP) and fertility-awareness method (FAM) teachers that the cervical opening (i.e., cervical os) softens and opens during the peak of fertility, and then closes and tightens soon after ovulation. Users of the symptothermal method of NFP are taught to feel for this opening of the cervical os by the insertion of clean fingers into the vagina and to estimate “blindly” the cervical opening. Researchers from Belgium recently conducted a study to determine if women could accurately measure the fertile phase of the menstrual cycle by the self-use of a lighted vaginal speculum called the Femiscope (I. Brosens, P. Hernalsteen, A. Devos, B. Cloke, and J.J. Brosens, “Self-Assessment of the Cervical Pupil Sign as a New Fertility-Awareness Method,” *Fertility and Sterility* 91 [2009]: 937–939).

Twenty volunteer women between the ages of 21–44 with regular-length menstrual cycles participated in the study. Of these 20 women, 7 were nulliparous, and 13 had one or more vaginal births. All of the women had previous experience with NFP methods. These women were taught how to self-assess their cervical os by use of the Femiscope on a daily basis from day 8–18 of their menstrual cycles. They were instructed to rate the cervical opening from 1–3, with 1 = less than 1 mm, 2 = 1 to 3 mm, and 3 = greater than 3 mm. The 3 rating was considered the “pupil” sign. The women volunteers also self-assessed their cervical mucus on a 1–6 rating scale and measured their daily basal body temperature (BBT). The BBT shift in temperature was used to verify the estimated day of ovulation. These women

produced 58 menstrual cycles of data over a 6-month time period (2–3 cycles per woman). All 58 of the menstrual cycles showed a BBT shift and a 9–14 day luteal phase.

However, in only 38 (63%) of the menstrual cycles did the self-observation of the cervical opening define the fertile phase, and in only 36 (62%) of the menstrual cycles did the self-observed cervical mucus sign correlate with the fertile phase. The length of the fertile phase by the pupil sign was between 1–11 days (mean 3.1) and by the cervical mucus observations 2–8 days (mean 4.8 days). The researchers determined that the fertile phase by the pupil sign was significantly shorter and more consistent than when estimated by the cervical mucus sign. The authors concluded that the self-assessment of the cervical pupil sign was feasible when used to estimate the fertile phase of the menstrual cycle. They also concluded that the self-assessment of the cervical os and the pupil sign needs further investigation.

Comment: Insertion of a plastic speculum to view the cervical opening is invasive. Ten of the 20 volunteer women in the study reported some pain and discomfort with this method. The researchers will need to show how the use of the Femiscope and the self-assessed pupil sign is an advantage over the other traditional, natural, biological indicators, such as using BBT and measuring urinary reproductive hormones. Furthermore, future studies should include more objective measures of ovulation, such as LH levels or serial ultrasound of the developing follicle, to correlate with the pupil sign.

Menstrual Cycle Length Found to Correlate with Reduced Ovarian Reserve and Pregnancy Outcome

It is well known that fertility decreases with age, and that this decrease is largely due to reduced ovarian reserve, i.e., a decreased follicle/oocyte pool in the ovary. It is also known that mean menstrual-cycle length gradually decreases from a maximum length for women in their 20s to a low when in their late 40s. The last 2 years before menopause is a time when the menstrual-cycle length and menstrual-cycle length variability increases dramatically. Based on this information, researchers from Sweden wished to determine if menstrual-cycle length could be used to predict ovarian reserve (T.B. Brodin, R. Bergh, L. Berglund, N. Hadziosmanovic, and J. Holte, “Menstrual Cycle Length Is an Age-Independent Marker of Female Fertility: Results from 6,271 Treatment Cycles of in Vitro Fertilization,” *Fertility and Sterility* 90 [2008]: 1656–1661).

The participants for the study were women seeking IVF treatments for infertility. The researchers recorded the self-recalled menstrual-cycle length. Some of the women participants had menstrual-cycle diaries, others did not. The outcomes were pregnancy, delivery rates following IVF treatment, and follicular stimulating hormone (FSH) levels. The data was taken from 6,721 IVF treatment cycles.

As with past studies, the researchers found that increasing age was associated with decreasing mean menstrual-cycle length. However, they also found that pregnancy and delivery rates also correlated positively with increasing menstrual-cycle length. For example, they found that the pregnancy rate was almost double for women with mean menstrual-cycle lengths greater than 34 days compared with women with mean menstrual-cycle lengths shorter than 26 days. The researchers also found that menstrual-cycle length was associated with FSH stimulation and embryo quality. They concluded that

menstrual-cycle length was associated with positive IVF outcomes regardless of age, and that menstrual-cycle length could possibly be used as a simple marker of ovarian reserve.

Comments: Although the results seem clear, there are several concerns with the study. The first is the use of recall data for menstrual-cycle length. Although there is some correlation with recall, some studies have shown that there is a considerable amount of error in recall of menstrual-cycle length. The second problem is that the researchers used only women with infertility problems. A stronger study would have involved women with regular fertility seeking pregnancy who tracked their cycle length prospectively, i.e., women using NFP or fertility-awareness methods. In addition, the immorality of IVF makes the conduct of this study unacceptable. However, these results do provide another reason for women to monitor menstrual cycles, i.e., to be aware of ovarian reserve to better assess their ability to become pregnant using natural methods.

12-Month Typical-Use Failure Rate of Fertility-Awareness-Based Methods Estimated to Be 25 Percent

Researchers from the Alan Guttmacher Institute and Princeton University recently analyzed the data from the 2002 (Cycle 6) National Survey of Family Growth (NSFG) to determine contraceptive failure rates of the most commonly used methods of family planning in the United States (K. Kost, S. Singh, B. Vaughan, J. Trussell, and A. Bankole, "Estimates of Contraceptive Failure from the 2002 National Survey of Family Growth," *Contraception* 77 [2002]: 10–21). They also compared the 2002 data with the 1995 NSFG data to determine trends in contraceptive failure among these methods. A rationale for analyzing this data was that contraceptive failure is the biggest cause of unintended pregnancy and, as a result, higher abortion rates. Another reason is that the U.S. Department of Health and Human Services has stated a goal of reducing the unintended pregnancy rate as a result of contraceptive failure from the estimated 13% in 1995 to 7% in the year 2010.

The NSFGs are periodic population-based surveys conducted by the National Center for Health Statistics on women between the ages of 15–44. The 2002 NSFG composed a sample of 7,643 women. The methods of family planning that the researchers analyzed were the five most commonly used methods in the U.S. These methods are injectable contraceptives, oral contraceptives (i.e., the Pill), the male condom, withdrawal, and fertility-awareness-based (FAB) methods (that included calendar, mucus, temperature, periodic abstinence, and natural family planning). The researchers used life-table analysis to determine typical-use failure rates at 3, 6, and 12 months of use. They also used a statistical technique to correct for under-reporting of abortion. Typical use unintended pregnancy rates includes imperfect or inconsistent use of the methods.

The 12-month probability of failure for the five contraceptive methods (when corrected for the underreporting of abortions) were as follows: 6.7% for injectables, 8.7% for the pill, 17.4% for male condom, 18.4% for withdrawal, and 25.3% for FAB methods. The overall total unintended pregnancy rate for all methods combined was 12.4%. In contrast the 1995 NSFG unintended pregnancy rates were as follows: 5.4 % for injectable, 8.8% for the pill, 17.8% for male condom, 28.4 % for withdrawal, and 22.6% for FAB methods. The overall unintended pregnancy rate was 14.9%. Although not statistically significant, the unintended pregnancy rate for FAB methods was 2.7% higher in 2002 than in 1995.

Other findings of interest were: 1) women aged 30 and older were less likely to experience unintended pregnancies; 2) non-Hispanic black women were the most likely sub-group race to experience unintended pregnancies; 3) the unintended pregnancy rate among poor women below the poverty level remained high in 2002, i.e., at a 19.9% level; and 4) co-habiting women have the highest risk of having unintended pregnancies, 9.5% in 2002.

The authors concluded that there was no clear improvement in contraceptive failure rates from 1995–2002, and that failure rates were particularly high for condom, withdrawal, and FAB methods.

Comments: The failure rates for FAB methods are somewhat skewed in that they include not only the more modern methods of mucus and temperature monitoring, but also “self-devised” calendar or counting methods. These self-devised methods would most likely be used by the highest risk groups (e.g., poor, single, sexually active adolescent women), and, thus, these methods would have increased failure rates. It would be good to see a comparison of the 1995 to 2002 data with the “true” natural family planning methods that include self-observations of markers of fertility among married women. However, the number of users in this category would probably be too low for analysis purposes.

Normative Statistical Parameters of the Menstrual Cycle

Knowing the normal parameters of the menstrual cycle is important for health professionals, so that they can recognize abnormal patterns that might signal significant health problems, such as polycystic ovarian disease. So too, natural family planning teachers should be knowledgeable of normal parameters so they are able to counsel their clients and alert them to what is abnormal or irregular. Most studies conducted on the parameters of the menstrual cycle have included women with abnormal menstrual cycles. Researchers from the University of New Mexico recently conducted a study with only healthy women participants with non-hormonal contraceptive menstrual cycles (L.A. Cole, D.G. Ladner, and F.W. Byrn, “The Normal Variabilities of the Menstrual Cycle,” *Fertility and Sterility* 91 [2009]: 522–527). These researchers also eliminated any menstrual cycles that were abnormal from their calculation, i.e., menstrual cycles that were longer than 40 days. The purpose of their study was to define the normative statistical parameters of the menstrual cycle, i.e., the length of the follicular, ovulatory, and luteal phases, as well as the timing of implantation.

The participants for this study were 184 healthy women volunteers between the ages of 18–36 years. Of these 184 participants, 17 were eliminated due to unusual cycle lengths or abnormal hormonal levels. The participants had their daily urine collected for laboratory determinations of the peak reading in LH and hCG levels. The length of the follicular phase of the menstrual cycle was defined as the first day of menses until and including the day of the highest LH reading. The participants produced 408 normal non-contraceptive menstrual cycles and 111 menstrual cycles that ended in a pregnancy.

The mean, standard deviation (SD), and the 95% confident interval of the statistical parameters of the menstrual cycle, including total length, follicular phase length, ovulation phase, luteal phase, and day of implantation as determined in this study are shown in [table 1](#). The day of implantation was determined from the 111 cycles that resulted in a pregnancy. The first detectable hCG reading was considered the day of implantation. The range of the 95% confident interval (CI) can be considered the ranges of normality. The estimated range of the day of implantation could also be interpreted as 5–14 days after the estimated day of ovulation. The finding that implantation can occur as early as day 4

after the day of ovulation is different than has been previously reported in the literature. The authors concluded that the results provided by this study could be used as guidelines for differentiating normal and problem menstrual cycles.

Comments: The results from this study can be used as normative parameters of the menstrual cycle. When women have menstrual cycles outside of these lengths, the health professional, NFP provider, or the individual woman should have some concern. Only women who have been tracking the length and the estimated day of ovulation with some type of NFP method would have knowledge of these parameters.

Follicular Growth during Lactational Amenorrhea Found to Be Greater than During Normal Ovulatory Menstrual Cycle

Lactational amenorrhea (LA) is considered to be a time of ovarian quiescence due to the suppression of ovarian hormones by the suckling mechanism that produces prolactin. Included in this quiescent period are not only low levels of estradiol and progesterone but also follicular growth. It is thought that elevated levels of prolactin make follicles less responsive to the actions of FSH and LH. However, very little is known about the biological mechanisms that take place during LA and the anovulation that is associated with breastfeeding. Therefore, researchers from Chile and Argentina decided to conduct a longitudinal study of LA in order to describe the steroidal and follicular dynamics that occur during breastfeeding and the subsequent ovulatory menstrual cycles (.V. Velasquez, R.V. Trigo, S. Creus, S. Campo, and H.B. Croxatto, "Pituitary-Ovarian Axis during Lactational Amenorrhoea. I. Longitudinal Assessment of Follicular Growth, Gonadotrophins, Sex Steroid and Inhibin Levels before and after Recovery of Menstrual Cyclicity," *Human Reproduction* 21 [2006]: 909–915).

The participants for this study were 22 healthy nursing mothers (between the ages of 18–23) that were accessed in a maternity ward within 2 days after a normal vaginal singleton delivery. All of these women were instructed to (and agreed to) exclusively breast-feed their baby for the first 6 months post-partum. At the 60th day post-partum these women had ultrasound exams of their ovaries and blood samples taken twice a week for 4 consecutive weeks. When their menstrual cycles resumed, vaginal ultrasound examinations and blood samples were drawn on days 1–4 (which was labeled the early follicular phase, EFP) and days 7–10 (which was labeled the mid follicular phase, MFP) of the second and third menstrual cycle post-partum. The blood samples were assayed for FSH, LH, prolactin, estradiol, progesterone, inhibin A, inhibin B, and Pro-alpha C levels. Of the 22 participants, 10 entered and completed the study.

The results showed that the number and diameter of the follicles were significantly greater during LA compared to the EFP or the MFP. Estradiol levels were similar during LA, EFP, and MFP. In comparison to the EFP and the MFP phases of the menstrual cycle, LA is associated with higher prolactin levels, normal or slightly elevated steroidal gonadotrophins (LH and FSH), and increased number and size of follicles, without an increase in estradiol, inhibin B, and Pro-alpha C. The authors concluded that during LA there is a profound dissociation between follicular growth and follicular endocrine activity.

Comments: The more that is learned about the mechanisms of how breastfeeding suppresses ovarian activity, the more likely it will be to provide better instructions for monitoring fertility during this transition from amenorrhea to ovulatory menstrual cycles. One criticism of this study is that the MFP

was actually in the later stages of the follicular phase. In this study the MFP was days 7–10, but, there is evidence that ovulation is delayed in the first 3 or more post-partum menstrual cycles. If the authors measured the follicular sizes from days 10–16, they likely would have found they were greater.

Web-Based Patient Education Intervention Found Beneficial for Women Experiencing Infertility

The medical and technical aspects of infertility tests and treatments can be psychologically challenging for couples with infertility problems. There are few support systems to help patients cope with the psychological aspects of infertility treatment. In today's world, many people pursue medical information and advice from online Internet-based programs. However, there have been few studies that have investigated the effectiveness of these online programs. Therefore, infertility researchers sought to develop and test the effectiveness of a brief Web-based education and support system for female infertility patients (T.M. Cousineau, T.C. Green, E. Corsini, A. Seibring, M.T. Showstack, L. Applegarth, M. Davidson, and M. Perloe, "Online Psychoeducational Support for Infertile Women: A Randomized Controlled Trial," *Human Reproduction* 23 (2008): 554–566). They built an online program called the Infertility Source program that included information on fertility, reproductive anatomy and physiology, cognitive behavioral skills, and stress management techniques. They hypothesized that those women who were exposed to an online Infertility Source program would demonstrate a reduction in infertility-related stress and an improvement in infertility self-efficacy.

The researchers utilized a randomized control trial design in which 190 women, who were at least 21 years old with a diagnosis of infertility, were randomized into a group that was exposed to the online Infertility Source program and a group that served as a control and were told that they were in a study to determine how couples cope with infertility. The outcomes that were assessed were infertility distress, infertility self-efficacy, decisional conflict, marital cohesion, and coping style. The researchers found that those women who were exposed to the online Infertility Source program had significant improvement in the area of social concerns related to infertility and felt more informed about medical decisions in which they were involved. Those women who were exposed to the Web site for 60 minutes or more experienced a significant decrease in global stress and increased self-efficacy. The researchers concluded that an online infertility support program can have beneficial psychological effects and can be a cost effective resource for fertility practices.

Comments: The participants in this study received one hundred dollars for participating and filling out the study questionnaires. Having a financial incentive could be a con-founder for the results of the study in that without the incentive we do not know how effective the Web site is or how many women would use it. This study also points out the importance of being exposed to the intervention, i.e., the information on the Web site. The study showed that the more exposure to the Web site, the better the outcome. Web site information for fertility and infertility are convenient and accessible. This was the first study to determine the efficacy of an online infertility support and educational system. Similar studies are needed to assess the benefits of online charting and information for natural family planning purposes.

Quality of Infertility Information on the World Wide Web Rated Poor

The Internet has increasingly become the source of information for people seeking health information and advice. A recent study showed that up to 80% of people in the United Kingdom (UK) who are connected to the Internet have used the World Wide Web (WWW) as a source of health information (J.V. Marriott, P. Stec, T. El-Toukhy, Y. Khalaf, P. Braude, and A. Coomarasamy, "Infertility Information on the World Wide Web: A Cross-Sectional Survey of Quality of Infertility Information on the Internet in the UK," *Human Reproduction* 23 [2008]: 1520–1525). The use of the Internet as a source of information includes people seeking information on infertility. There are many Web sites dedicated to information on infertility. However, there has never been a study to assess the quality of these web sites. Therefore, researchers from the UK conducted a study to determine the quality of information on infertility available on the Web.

The researchers performed a Google search with the word "infertility" and then assessed and classified the first 107 usable and relevant Web sites that were produced by the search. The Web sites were classified as either: 1) National Health Service (NHS) managed and funded, 2) private assisted-reproductive-technology (ART) clinic Web site, 3) non-ART treatment providing, 4) commercial information providing, 5) non-profit making information site, and 6) patient forum sites. The quality of the Web site was assessed by 3 key features: credibility, accuracy, and navigability. Credibility was assessed by 6 criteria, accuracy by 3, and navigability by 6, for a total of 15 criteria that were either present or not (see criteria listed below). The researchers summed and averaged the criteria for all 107 sites. Therefore, the maximum score for credibility and navigability was 642 and for accuracy 321.

The researchers found that the total scores for all types of infertility web sites were low. The lowest rated feature was accuracy in which a total of only 50 points out of 321 (16%) were tallied. The highest rated feature was navigability with 60% or 387 points out of 642, and then credibility with 275 of the 642 points (43%) tallied. The highest rated sub-criteria was having fully functional internal and external links with 90% of the sites receiving a score. The NHS ART clinic sites rated higher overall than the private ART clinic sites and the commercial and non-profit information sites. The authors concluded that the quality of Internet information sources for infertility is variable, but generally poor.

Comment: The authors also recommended that individual clinicians rate and assess the quality of Web sites before recommending them to their patients. The same recommendation should be made for natural-family-planning and fertility-awareness teachers. The criteria for each of the three key Web features are listed below for use in assessment:

Credibility:

- 1) Authorship—names of authors are clearly displayed
- 2) Currency—either date of last amended or copyright date
- 3) Legal disclaimer—legal statement disclaiming responsibility for the information presented or what users choose to do with the information
- 4) Review process—information provided about a review board
- 5) Funding or sponsorship—information concerning the source of the organization funding
- 6) Absence of advertising or financial incentives

Accuracy:

- 1) Claims supported by valid evidence or professional body guidelines
- 2) Clearly defined success rates
- 3) Display of accurate references

Navigability:

- 1) Functional internal and external links
- 2) Viewer is not directed to unintended sites
- 3) Active feedback mechanism with e-mail based contact
- 4) Frequently asked question (FAQ) page
- 5) A site map
- 6) Internal search engine

Discontinuation Rates of Fertility-Awareness Methods Found to Be High Compared to Other Family Planning Methods

Women of child-bearing years often discontinue methods of contraception for many reasons (other than seeking to achieve pregnancy) and switch to another method that they believe will fit their lifestyle better, be more effective, have less side effects, or maybe be easier to use. The transition from one method to another, however, is a time when women often become unintentionally pregnant. Researchers from the Guttmacher Institute in collaboration with Professor James Trussell at Princeton University recently analyzed data from the 2002 National Survey of Family Growth (NSFG) to determine the discontinuation rates of the Pill, injectable, male condom, withdrawal, and fertility-awareness based methods of family planning (B. Vaughan, J. Trussell, K. Kost, S. Singh, and R. Jones, "Discontinuation and Resumption of Contraception Use: Results from the 2002 National Survey of Family Growth. *Contraception* 78 [2008]: 271–283). They analyzed the 2002 NSFG data and adjusted the results based on the underreporting of abortion.

The 2002 NSFG is a population survey conducted on a periodic basis by the National Center for Health Statistics. The 2002 NSFG involved 7,643 women between the ages of 15–44. The participants in the NSFG were interviewed in person by inputting data into a laptop computer. The researchers discovered that the discontinuation rate for method-related reasons within the first year was as follows, 57% for the male condom, 54% for withdrawal, 53% for fertility-awareness based methods, 44% for injectables, and the lowest was 33% for the Pill. The researchers also found that although these women abandon a method of contraception, 72% will resume another method of contraception within the initial month of exposure. The researchers did not analyze the reasons for the discontinuation of fertility-awareness-based methods. The researchers did find for all methods that teenagers and those cohabitating are more likely to abandon contraceptive methods compared to non-teenage married women.

Comments: Although the discontinuation rates are fairly high with fertility-awareness-based methods (according to the NSFG 2002 data), one should keep in mind that included in these methods are self-

devised calendar methods. If the researchers analyzed only those women who were married and were using a more modern method of NFP, such as temperature or cervical mucus methods, they most likely would find a much lower discontinuation rate. Furthermore, in a recent study involving the same data from the 2002 NSFG, researchers found that there was a very low discontinuation rate with fertility-awareness-based methods due to dissatisfaction, i.e., only 14.6% for ever-users of fertility-awareness methods, compared with much higher rates for the diaphragm or cervical cap (52%), long acting hormonal methods (42%) or oral contraceptives (29%) (C. Moreau, K. Cleland, and J. Trussell, "Contraceptive Discontinuation Attributed to Method Dissatisfaction in the United States, *Contraception* 76 [2007]: 267–272). The failure of the authors to include a discussion in their paper of the relatively low discontinuation rate due to dissatisfaction with fertility-awareness-based methods may indicate a bias against these methods by the authors.

Increased Breast Tissue Proliferation Found with Combined Oral Contraceptives

There are many health benefits for women taking combined oral contraceptives (COCs), but there are health risks as well, such as thrombosis, that could lead to a stroke or myocardial infarction. Another health risk is breast cancer, in particular for young women who are on COCs for a long time before discontinuing or becoming pregnant. Researchers from Stanford University and the Federal University of Brazil recently conducted a study to investigate further the possible influence of COCs on breast tissue (i.e., mammary epithelial cells) during one cycle of use (D.G. Narvaiza, A.H. Navarrete, R. Falzoni, C.M. Maier, and A.C.P. Nazario, "Effect of Combined Oral Contraceptives on Breast Epithelial Proliferation in Young Women, *Breast Journal* 14 [2008]: 460–465). The proliferation of normal breast epithelium is most extensive during the natural luteal phase of the menstrual cycle.

The researchers enrolled 82 volunteer patients who were undergoing excision of a fibroadenoma. The 82 women, who were between the ages of 14–36 with normal length menstrual cycles and who never used COCs, were randomized into either a treatment group that received one cycle of COCs (containing ethinyl estradiol and levonorgestrel) or a control group that had a normal spontaneous menstrual cycle. Serum progesterone levels were taken to document suppression of endogenous progesterone secretions with the COC participants and to determine the phases of the menstrual cycle with the control group members. All participants had mammary tissue biopsied throughout the menstrual cycle. There were no statistical differences in age of menarche, number of pregnancies, parity, and lactational history.

The researchers found a greater proliferation index in the COC group compared to the normal cycling control. They also found greater proliferation in the COC cycles during the first week of the pseudo-menstrual cycle. The researchers speculated that this alteration in the pattern of proliferative activity may explain some of the increased risk of breast cancer associated with COC use.

Comment: Epithelial cell proliferation in normal (non-COC) menstrual cycle occurs in the luteal phase, when both estrogen and progesterone levels are high. This suggests that there is a synergistic mechanism. The fact that this takes place early in the menstrual cycle and continues throughout the use of COCs might explain some of the possible carcinogenic effects of COCs. The researchers made it clear that this study needs to be replicated in order to validate these findings.

Induced Abortion Reported Not to Be Associated with Breast-Cancer Risk

Past retrospective and case-controlled studies have shown an association between induced abortion and the risk of breast cancer. Authors of these studies have speculated that the increase was due to a number of reasons, i.e., the loss of the protective effect of pregnancy against breast cancer, the stimulation of the growing breast tissue by pregnancy hormones, and the stopping of breast-cell differentiation at the time of abortion. With a full-term pregnancy, breast tissue is allowed to differentiate and mature, and is not, therefore, susceptible to carcinogenic effects. Large recent prospective studies have not found the association between abortion and breast cancer and have not supported these hypothetical mechanisms.

Researchers recently conducted a large prospective cohort study to see if an association existed between early induced abortions and breast cancer (K.D. Henderson, J. Sullivan-Halley, P. Reynolds, P. Horn-Ross, C.A. Clarke, E.T. Chang, S. Nuehausen, G. Ursin, and L. Bernstein, "Incomplete Pregnancy Is Not Associated with Breast Cancer Risk: the California Teachers Study," *Contraception* 77 [2008]: 391–396). They also investigated the association between miscarriage and breast cancer. The study population consisted of women who responded to the California Teachers Study (CTS). The CTS involved 133,479 current, recent, and retired female public-school teachers and administrators who completed the CTS survey. The CTS survey included items about pregnancy, pregnancy outcomes, abortion, and miscarriage. The final number of women for the study was 109,893 due to a reduction of participants who did not meet the criteria for the study. The number of incident breast-cancer cases reported by this group and validated by the California cancer registry was 3,324. Of these participants, approximately 19% reported miscarriages, and 19% reported abortions. However, the results did not show any significant association between breast cancer and induced abortion, nor did it show an association between miscarriage and breast cancer when compared with nulliparous or parous women. The authors concluded that this study provided strong evidence that there is no relationship between any means of incomplete pregnancy and breast-cancer risk among nulliparous and parous women. The study results are supported by two other recent large prospective cohort studies, i.e., one involved the 105,716 women in the Nurses' Health Study and the other 267,361 women recruited from 20 centers and 9 European countries (K.B. Michels, F. Xue, G.A. Colditz, and W.C. Willett, "Induced and Spontaneous Abortion and Incidence of Breast Cancer among Young Women," *Archives of Internal Medicine* 167 (2007): 814–820; G.K. Reeves, S.W. Kan, T. Key, et. al., "Breast Cancer Risk in Relation to Abortion: Results from the EPIC Study," *International Journal of Cancer* 119 [2006]: 1741–1745). Both studies concluded that neither induced abortion nor spontaneous abortion was associated with the incidence of breast cancer. However, the European study found a slightly higher risk among those with 2 or more spontaneous abortions.

Comments: Although there was some speculation that the participants underreport-ed abortion, as is often found in studies with self-reporting of abortion, the rate of abortions reflects the number of abortions reported in a well-educated middle-class population. As a health professional or NFP teacher, although there is conflicting evidence regarding the link between abortion and breast cancer, it does not appear to be appropriate to suggest that there is a relationship between abortion and breast cancer to women at this time. For a different perspective, see Angela Lanfranchi, "Normal Breast Physiology: The Reasons Hormonal Contraceptives and Induced Abortion Increase Breast-Cancer Risk," in this issue.

Women Using Hormonal Contraceptives Report More Negative Well-Being Compared to Women with Natural Hormonal Menstrual Cycles

Little research has been conducted to determine the effects of hormonal contraception, and, in particular, injectable hormonal contraception (i.e., Depo-Provera), on the physical and psychological well-being of women. Injectable contraceptives, unlike oral hormonal contraception and natural menstrual cycles, do not have the cyclical variations of the hormones estrogen and progesterone. Therefore, women on the injectable contraceptive probably would not vary in their well-being as would women with variations in hormonal profiles. Researchers from the University of Hawaii conducted a study to determine if there were differences in well-being of women who used Depo-Provera injectable contraceptives compared to women with natural hormonal menstrual cycles, and with women on cyclical hormonal oral contraceptives (S.G. Brown, L.A. Morrison, L.M. Larkspur, A.L. March, and N. Nicolaisen, "Well-Being, Sleep, Exercise Patterns, and the Menstrual Cycle: A Comparison of Natural Hormones, Oral Contraceptives and Depo-Provera," *Women & Health* 47 [2008]: 105–121).

The participants for this study were 36 women, selected by convenience with flyers and short announcements at university events and courses. Most of the women participants were students from the researcher's university. Twelve of the women were using DepoProvera, 12 were using oral hormonal contraceptives, and 12 were using condoms or coitus-interruptus during intercourse and, thus, had synthetic hormone-free menstrual cycles. All of the participants were asked to complete a well-being questionnaire and monitor their sleep and exercise patterns on a daily basis for 3 menstrual cycles (or for three 28 day cycles for the women on Depro-Provera). The 36 women produced 108 menstrual cycles of data. The participants ranged in age from 18–36 years.

The researchers found that the women participants in the natural-hormone group reported significantly less negative well-being compared to women in the hormonal-contraceptive groups (i.e., the oral and injectable hormonal contraceptive participants). Furthermore, the women with natural, hormonal menstrual cycles and the women on cyclical, oral-hormonal contraception reported more positive well-being mid-cycle that was correlated with increased sleep. This variation in well-being was not reported with the DepoProvera group of women. The authors concluded that the use of DepoProvera interfered with the natural relationships between sleep, well-being, and cycle phases.

Comments: The results of this study must be taken with reservations, since the participants were selected by convenience and were not randomized into the three groups. Therefore, there could be other reasons for the differences in well-being found between the three groups. Furthermore, there were not enough participants in each group to have enough statistical power to elicit statistical differences on many of the variables. It was interesting that negative well-being (as measured by a multiple-item questionnaire that is utilized to diagnose premenstrual dysphoric disorder or PMS) was less among the natural, hormonal menstrual cycle group, since hormonal contraceptives are often used to treat that syndrome. It would be good to see a replication of this study with non-sexually active women in the natural hormonal group, since sexual relationships could be a confounding variable.

Under the Microscope

Breast-Feeding and Early Pregnancy Loss

William Saletan, a political columnist for the online Web site *Slate* (www.slate.com), recently wrote a letter to the secretary of the U.S. Department of Health and Human Services (Michael O. Leavitt) concerning the administration's proposal to eliminate financial aid to health-care institutions that violate the right of health-care providers who, for reasons of conscience, refuse to participate in abortion and the prescribing of potentially abortifacient contraceptive methods.¹ Throughout his letter, Saletan ostensibly supported the administration's proposal. Saletan stated in the letter that the government should not only protect health-care providers who refuse to participate in abortion, but also provide protection for employees that are involved in other potentially abortifacient activities, i.e., those employees that promote and teach breastfeeding, those who are involved with the manufacture or selling of coffee in any capacity, and those who are involved with promoting exercise. He provided studies and evidence that all three of these activities are potentially abortifacient. Obviously his proposed extension of the right to refusal for conscience purposes by health professionals to breastfeeding, coffee, and exercise was full of sarcasm and is a type of *reductio ad absurdum*.

The study he cited for evidence that breastfeeding can act as an abortifacient was conducted by a group of researchers (including NFP professional nurse teachers) at the Pontifical Catholic University of Chile.² The study involved a comparison of 49 fully breastfeeding post-partum women and 25 non-nursing women who had regular menstrual cycles. The researchers measured plasma estradiol (E) and progesterone (P) levels twice a week up to the second postpartum menses. They found that in the first post-partum menstrual cycles the luteal phase for the breastfeeding women was on average 9.2 days (SD=0.5) in length and for the non-nursing women 13.3 days (SD = 0.4). Since about one-fourth of the non-nursing women became pregnant during the study time period, but only 7% of the breastfeeding women, the authors speculated that the reason for such a difference was due to interference with implantation of the embryo associated with luteal phase defects.

Another study conducted by researchers from Johns Hopkins University concluded the same thing.³ They monitored 60 breastfeeding women from Baltimore and 41 from Manila (Philippines) by having them provide urine samples for E, P, LH, and human chorionic gonadotropin (HCG) on a daily basis. They found that 41% of the first ovulation cycles had luteal phase defects. They also found a 6% pregnancy rate in the first cycle after the first menses. In another study, an Australian research group analyzed the P levels of 89 breastfeeding women by daily salivary samples.⁴ They defined a deficient luteal phase when P levels were less than 40 pg/mL and a short luteal phase as a period of 11 days or less from ovulation to menstruation. They found only 32% of the women had adequate luteal phases after their first menstruation. Another earlier study by an Australian group found with 55 post-partum breastfeeding women that, after the first menses, 40% had anovulatory ovarian activity, 25% experienced ovulation but with short luteal phases, and 16% had normal ovulations with deficient luteal phases, i.e., luteal-phase lengths less than 11 days.⁵

It is clear from the evidence provided by the above studies that there are many (25–40%) deficient (hormonally) and short (by days) luteal phases in the first post-partum menstrual cycle. There also is evidence that the pregnancy rate of women during the first post-partum menstrual cycle is much lower than expected in normal cycling women, i.e., 6–7% compared to 25%. One possible explanation is that luteal phase defects cause a failure in implantation of the embryo. However, all of this evidence is

indirect. None of these studies compared the pregnancy rate or the luteal phase parameters with post-partum non-breastfeeding women. An earlier study from Ireland monitored the daily salivary E and P levels of 30 post-partum breastfeeding and non-breastfeeding women.⁶ As expected, they found that the return of first menstruation among the 20 breastfeeding women was much longer than the non-breastfeeding women, i.e., a mean of 127 days compared to 57 days. The researchers also found that 44% of the breastfeeding women and 40% of the non-breastfeeding women had abnormal luteal phases. There was no evidence for differences in the amount of luteal phase defects in the first menstrual cycle post-partum among the breastfeeding and non-breastfeeding women. In both groups 50–56% of the first cycles were anovulatory. Therefore, the luteal phase deficiency might not be due to breastfeeding but rather the hormonal readjustment that occurs during the post-partum time frame. Furthermore, the decreased pregnancy rates for post-partum breastfeeding women might largely be due to anovulatory menstrual cycles, i.e., menstrual cycles with no chance of fertilization.

Evidence from other recent studies also raises some questions about whether breastfeeding might cause a disruption in implantation due to luteal phase defects. A study, reviewed earlier in this publication, showed that among normal menstrual cycles, implantation (as determined by HCG levels) can occur as early as the fourth day post-partum.⁷ The researchers gave a normal range of 5–14 days for the luteal phase. The 11-day post-partum mean reported for breastfeeding cycles (i.e., as reported in the above studies) fit well into this range. O. Bukulmez and A. Arici questioned the wisdom of diagnosing a luteal phase defect and preferred to view it as an ovulatory defect.⁸ The authors point out that luteal phase defects are poorly defined and often diagnosed in women with proven fertility.

Even if breastfeeding caused luteal-phase deficiencies and impaired the implantation of human embryos, it is not the moral equivalent of the use of hormonal contraception to prevent pregnancy. Breast-feeding is done primarily for the intent of providing adequate nutrition for the neonate. Breast-feeding is natural and healthful for both the baby and the mother and is recommended, for at least one year, by the American Pediatric Association. Breast-feeding is better than artificial nutrition. Breast-feeding is a good and natural act for the purpose of a good end that also (at times) might result in the unintended death of embryos (although direct evidence for such an effect is lacking).

Hormonal contraception, on the other hand, is used for the purpose of suppressing a natural process (i.e., fertility) for the intended effect of avoiding pregnancy and having intercourse without any consequences. Even though breastfeeding could be viewed as an external hormonally suppressing process, the child's need for nutrition is not. The ingestion of steroidal hormones frustrates the natural fertility of the woman. Furthermore, the suppressing effect of breastfeeding diminishes as the baby grows and starts to utilize solid foods and liquids. The use of and need for hormonal contraception continues throughout the entire reproductive life of the woman.

A secondary reason for using hormonal contraception might be to enhance one's health or to treat a disease process. The hormones, however, might just as easily cause health problems, such as increased risk for blood clots, stroke, heart attack and breast cancer. Furthermore, the use of hormonal contraception prevents the integration of fertility within the marital act of intercourse. The intention of hormonal contraception is to frustrate this integration. Hormonal contraception is not a holistic but rather a non-integrative externally controlled act. Whereas breastfeeding diminishes fertility, especially in the first 6 months of use, the infertility that is established is not permanent and is more like the infertility that one experiences after menopause, i.e., it is a natural infertility. But probably the

biggest difference between hormonal contraception and breastfeeding is that contraception takes fertility and procreation out of the picture altogether. It makes the contracepting individual susceptible to being an object of sex rather than a person deserving of love and acceptance of who they are—not who they are minus their fertility.

To morally equate breastfeeding with hormonal contraception in causing early pregnancy loss is absurd. Saying that breastfeeding is a cause of early pregnancy loss and that health professionals should inform women of this process is tantamount to saying that we should warn women against living a virtuous life. No more would a health professional warn a woman about driving a car because she might get into an accident and kill a pedestrian. As Miller points out in his essay on contraception, contraception is contrary to reason itself, and so it is immoral.⁹ Breast-feeding is not contrary to reason and not contrary to the expectation that it is a good for a woman to nourish her child through breastfeeding. Saletan, in his opinion article, is trying to argue that it is absurd for health professionals to refuse to prescribe both the use of contraception and breastfeeding. However, his parallel absurdities do not logically work.

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