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Current Medical Research: Summer–Fall 2009

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Current Medical Research Summer–Fall 2009

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Abstract

Note that the "Current Medical Research" feature focuses on issues relevant to natural family planning and the beginning of life. This piece is complemented by medical reviews published in The National Catholic Bioethics Quarterly, which focus more on other areas of general medical interest including end-of-life issues.—Ed.

Lifestyle Modification More Effective than Drugs in Treating Women with Polycystic Ovary Syndrome

About 5–10 percent of women of reproductive age are affected by polycystic ovary syndrome (PCOS), an endocrine pathology that interferes with the hypothalamic-ovarian axis of the menstrual cycle. Women who have this syndrome present with anovulatory menstrual cycles, androgen excess, clinical signs of hyper-androgenism (e.g., facial hair), and polycystic ovaries which are apparent on ultrasound. Many of these women also have insulin resistance. Treatment for this condition (especially for those seeking pregnancy) includes the use of clomiphene citrate (to promote the production of gonadotropin releasing hormone [GnRH]), metformin to treat the insulin resistance, and lifestyle modification that includes diet, exercise, and weight loss. There have been few studies comparing the relative efficacy of these treatments. Therefore, researchers set out to compare the efficacy of metformin, clomiphene

citrate (CC), metformin with clomiphene citrate, and lifestyle changes (M.A. Karimzadeh, and M. Javedani, "An Assessment of Lifestyle Modification versus Medical Treatment with Clomiphene Citrate, Metformin, and Clomiphene Citrate-Meformin in Patients with Polycystic Ovary Syndrome," *Fertility and Sterility* [2009]: article in press).

The participants for this study were 343 women who sought infertility services at the Infertility Research Center of Yasd Medical University, Iran. All of the women met the Rotterdam criteria for the diagnosis of PCOS, i.e., 1) chronic anovulation, 2) clinical or biochemical signs of hyper-androgenism, and 3) polycystic morphology as shown on serial ultrasound scans. The participants were randomized into a CC group (N=90) that received 100 mg of CC on days 3–7 of the menstrual cycle, a metformin group (N=90) that received a tailored approach of 500–1500 mg/day for 3–6 months, a metformin plus CC group (N=88), and a lifestyle group (N=75) that entailed a weight-loss diet and 30 minutes of exercise per day. All participants were assessed at initiation to the study and then eight months later for menstrual cycle changes, lipid levels, endocrine changes, waist circumference, and clinical pregnancy rates.

After eight months, the waist circumference, blood glucose levels, low density lipoprotein (LDL), testosterone, and sex hormone-binding globulin levels were significantly improved in the lifestyle group compared to the CC, metformin, and the CC plus metformin groups. Although there were no significant differences in the clinical pregnancy rates, the lifestyle group had a 20 percent pregnancy rate, the CC group 12.2 percent, the metformin group 14.4 percent, and the CC plus metformin group 14.8 percent, The researchers concluded that lifestyle modification significantly improved the lipid levels of the lifestyle group, and that lifestyle modification should be the first level of treatment for PCOS patients.

Comments: I agree with the authors of this study that lifestyle assessment changes should be a first-level treatment for women with PCOS. I would also recommend that monitoring the parameters of the menstrual cycle through charting natural indicators of fertility (i.e., basal body temperature and cervical mucus changes) would be helpful in diagnosing and in assessing the treatment of PCOS whether the treatment is lifestyle modification, medications, or a combination of both.

Menstrual Cycle Variability and Length Increases with Higher Levels of HbA1c among Adolescents with Type 1 Diabetes Mellitus

Longer length menstrual cycles and an increased incidence of menstrual irregularities have been associated with type 1 diabetes, heart disease, and polycystic ovary syndrome among adult women. It is known that adolescents have more variability in their menstrual cycles compared with older women. What is not well known is the influence of type 1 diabetes and the intensity of insulin control on menstrual cycle parameters among adolescents. Therefore, researchers from the School of Medicine at the University of Chile conducted a prospective study to determine the menstrual-cycle variability among adolescents with type 1 diabetes receiving at least three daily doses of insulin.[1]

The participants were 56 post-menarchal, adolescent girls with type 1 diabetes mellitus (average age 15.3) selected from three hospitals in Santiago, Chile. These 56 adolescents were matched with 56 controls (average age 14.7) based on gynecological age and body mass index. All participants were instructed in how to chart their menstrual diaries, were contacted with monthly reminders to complete

their diaries, and were provided educational activities at their school every two months. All participants charted in their diaries an average of four menstrual cycles.

In general, the researchers found that the adolescents with type 1 diabetes had longer and more variability in their menstrual cycle lengths compared with the controls, i.e., a mean of 48.0 days (SD = 38.9) for the adolescents with diabetes and a mean length of 32.0 (SD = 6.9) for the controls. They also found much higher rates of oligomenorrhea (58.9% versus 19.6%) and amenorrhea (10.7% versus 1.8%) among the adolescent diabetics compared to the controls. Furthermore, as the HbA1c levels increased, so did the length (and variability) of the menstrual cycles and the incidence of oligomenorrhea. For example, with HbA1c levels less than 7.6, the mean cycle length was 34.9 days (SD = 8.9), and the percentage of menstrual cycles with oligomenorrhea was 53.3 percent; with HbA1c levels between 7.6–8.9, the mean length was 48.6 days (SD = 17.8), and the percentage of cycles with oligomenorrhea was 72.2 percent; and with HbA1c levels greater than 9, the mean length was 57.0 days (SD = 52.3), and the percentage of oligomenorrhea was 54.5 percent. Based on regression analysis, as the HbA1c levels increased by one point, the menstrual cycle lengths increased by five days. The lengths of the menstrual cycles of adolescents with tight control of blood sugar levels resembled the parameters of the controls except for the incidence of oligomenorrhea.

The researchers speculated that hyperglycemia had a direct affect on the ovaries and worked by delaying oocyte maturation and increasing apoptosis. They concluded that efforts should be made to have good metabolic control with type 1 diabetic adolescent girls, and that researchers should evaluate the pathophysiology and develop treatment for oligomenorrhea.

Comments: The parameters of the menstrual cycle have been described by some physicians (and the American Academy of Pediatrics) as a fourth vital sign and have encouraged women, and in particular adolescent girls, to chart their menstrual-cycle parameters based on natural indicators of fertility.[2] The charting of fertility indicators can also be useful for health-care providers working with adolescents with diabetes to see how well their patients are in metabolic control. Health-care providers who find adolescent patients with very irregular menstrual cycles might want to assess blood sugar or HbA1c levels.

Focused Intercourse Determined to be More Efficient than Frequent Intercourse during Fertile Phase among Chinese Women

Since 1969, researchers have been determining day-specific probabilities of pregnancy during the fertile phase of the menstrual cycle based on timing of ovulation with basal body temperature changes, the peak in cervical mucus, or hormonal markers. These probabilities have been used to calculate time to pregnancy, efficacy of contraceptive methods, and, recently, efficacy of hormonal emergency contraception. Since these studies have been conducted with Western women, Chinese researchers wished to determine if there are differences in day-specific probabilities of pregnancy among a cohort of healthy Chinese women of reproductive age (X. Bilian et al., “Conception Probabilities at Different Days of Menstrual Cycle in Chinese Women,” *Fertility and Sterility* [July 6, 2009], article in press).

The participants for this study were healthy, married women between the ages of 18–35 with menstrual-cycle lengths between 25–35 days who attended 10 clinical centers in China. The husbands

of these women were healthy and have produced pregnancies with their wives. There were 861 women who met the eligibility criteria for the study. These women were asked to self-test their first morning urine with an LH test kit during every day of their calendar-estimated fertile window. The women participants also recorded their acts of intercourse for one to six menstrual cycles or until a pregnancy occurred. They were able to produce 2,177 menstrual cycles of data that had an LH surge (17.9% of the menstrual cycles that ended with a pregnancy did not have a detectable LH surge). In 498 of these menstrual cycles, there was only one act of intercourse recorded. There were 601 pregnancies during the course of the study. The researchers utilized the Barrett and Marshall technique of calculating probabilities of pregnancy during the five days before the estimated day of ovulation (i.e., the day of the LH surge = day 0) until one day after (i.e., days −5 to +1 = 7 days).

The day-specific probabilities of pregnancy from a single act of intercourse during day −5 to +1 were as follows; 0.216, 0.102, 0.236, 0.233, 0.388, 0.293, and 0.386. The probabilities of pregnancy during days −5 to +1 based on the menstrual cycles with one act of intercourse were as follows: 0.254, 0.271, 0.293, 0.365, 0.315, and 0.284. They recalculated the theoretical efficacy of emergency oral hormonal contraception based on this data and found a much higher efficacy (90.2%) compared to an earlier study that found a rate of 58.1 percent. A secondary finding was that there was no difference in the pregnancy rates with one act of intercourse during the fertile phase (0.309) versus the pregnancy rate with multiple acts of intercourse (0.326). The authors speculated that Chinese women are more fecund than Western women. The comparative day-specific probabilities of pregnancy from a study conducted in the United States for the four days prior to the estimated day of ovulation to one day after were 0.044, 0.10, 0.155, 0.148, 0.205, and 0.179 respectively (A.J. Wilcox, C.R. Weinberg, and D.D. Baird. "Timing of Sexual Intercourse in Relation to Ovulation—Effects on the Probability of Conception, Survival of the Pregnancies and Sex of the Baby," *New England Journal of Medicine* 333 [1995]: 1318–1321). Further studies are needed to determine cultural differences.

Comments: The day-specific probabilities of pregnancy with one act of intercourse has a similar pattern and rate from previous studies in that the rate increases the closer the act is to the estimated day of ovulation. However, it is difficult to compare the rates due to the varying acts of intercourse and to the method used to estimate the day of ovulation. The Chinese researchers felt that the use of urine LH testing was more accurate compared with other studies using basal body temperature or cervical-mucus peak. Of interest is that they found focusing intercourse during the fertile phase (i.e., with one act of intercourse) had similar rates compared to frequent acts of intercourse during the fertile phase. These results contradict current recommendations for optimizing fertility in order to achieve pregnancy (Practice Committee of the American Society for Reproductive Medicine, "Optimizing Natural Fertility," *Fertility and Sterility* 9 suppl. 3 [2008]: S1–S6). It should be noted that any use of a hormonal drug for emergency contraception that disrupts the implantation of a human embryo would be immoral.

Cervical Canal Width Correlates with Cervical Mucus Parameters

Infertility specialists recently determined whether the width of the cervical canal as determined through transvaginal ultrasound (TVUS) correlated with cervical mucus characteristics among women undergoing an infertility treatment or workup (I. Wolman, T.B. Gal, and A.J. Faffa, "Cervical Mucus Status Can Be Accurately Estimated by Transvaginal Ultrasound During Fertility Evaluation," *Fertility and Sterility* 92 [2009]: 1165–1167). One of the reasons for conducting this research is that when the

physician specialists provide ovulation stimulation medications (e.g., clomiphene citrate), they often track follicular development through TVUS and recommend optimal times for intercourse to achieve pregnancy.

The participants in this study were women who sought infertility assessment and treatment at one large medical facility. There were 101 women participants of which 23 were in a natural cycle group, 56 were in a clomiphene treatment group, and 23 were being treated with menotropins for ovulation induction. All of the women had TVUS performed and cervical mucus samples taken at the same time. The width of the cervical canal was measured at the widest section and gauged from inner to inner border. The cervical mucus was rated independently and graded from 1–3 as to amount, quality, and stretchability (i.e., spinnbarkeit), with 3 being the better quality cervical mucus. They discovered that mucus-rating scores were a mean of 6.1 for the natural-cycle group, 6.8 for the clomiphene group, and 4.9 for the menotropin group. They also found that the width of the cervical canal correlated well with the cervical mucus scores, i.e., the mean width was 1.0 mm for scant amounts of cervical mucus, 2.9 mm for abundant amounts, 0.8 mm for poor quality, and 1.8 for good quality cervical mucus. They calculated that using a score of 5 for the cervical mucus ratings was a good standard, since, when the scores were 5 or less, the canal width was a mean of 0.9 mm; when 5 or more, it was 2.1 mm, and with a score of 5, 0.97 mm. Therefore, they speculated that the endocervical canal width of 1 mm could serve as a cutoff score for favorable and unfavorable cervical mucus and the vaginal environment for fertilization. They promoted the use of TVUS results in measuring the width of the cervical canal as an easy way of indirectly measuring the cervical mucus and optimal environment for spermatozoa and possible fertilization.

Comments: From the standpoint of natural family planning, it would be just as easy to teach the woman infertility patient how to monitor the amount and quality of her cervical mucus. This would empower the woman, and she would have the ability to monitor future menstrual cycles. One of the positive aspects of this article was the description of the important functions that cervical mucus and the cervix play in fertility and the health of the woman, i.e., receptive environment for sperm, a reservoir for sperm, a defense against the hostile acidic vaginal environment, providing for the energy demands of the sperm, and filtering out abnormal and dismotile sperm. The authors also described the cyclic nature of cervical mucus and changes to the cervix in response to cycling estrogen and progesterone levels.

Prayer is Most Used Alternative Therapy for Infertility Patients

Approximately one in six couples of reproductive age suffers from the experience of infertility. The task of trying to conceive and failing over and over can be stressful, depressing, and frustrating. Couples who try to achieve pregnancy and are unsuccessful often seek interventions and information on infertility from sources other than their primary care providers. The Internet is one of the primary sources of information besides family members and friends. These sources frequently recommend alternative therapies in addition to traditional medical care. A group of infertility specialists noticed that many of their patients utilized alternative therapies and decided to conduct a more formal study to discover the extent and type of alternative therapy used by infertility patients (J. Schaffir, A. McGee, and E. Kennard, “Use of Nonmedical Treatments by Infertility Patients,” *Journal of Reproductive Medicine* 7 [2009]: 1–7).

The infertility specialists managed a large Midwestern infertility clinic that was located in the department of obstetrics and gynecology at the Ohio State University College of Medicine. They developed a questionnaire that contained questions on the types and frequency of alternative practices their patients utilized while seeking infertility care. They administered this questionnaire to 133 patients over a six-month period, which represented 12.5 percent of the 1,063 patients that they served. They discovered that the most frequent alternative method utilized was religious interventions (33.8%), i.e., personal prayer and intercessory prayer. The next most frequent alternative interventions were changes in sexual practices (28.6%) (i.e., more frequent intercourse, focused intercourse during the fertile phase, or positional practices) and dietary changes (21.8%) (i.e., diet types, weight loss, vitamins, herbal supplements). They also found that the younger patients (i.e., mean age of 33.2 versus 35.6, $p< 0.01$) were more likely to utilize alternative therapies. When asked to provide the reason for utilizing an alternative therapy, the most frequent response was "no harm in trying." Other frequent responses were "to try everything out of desperation," "to alleviate stress of treatment," and "to gain control over the process." The authors cautioned that infertility patients should be questioned as to what alternative therapies they utilize and to discourage those that could be harmful or that have no evidence base (e.g., herbal therapies).

Comments: The authors did point out the limitations of this study including the validity of some of the questions in the survey tool (e.g., lack of clarity as to what is an "alternative" therapy), and the potential bias of the respondents (i.e., there was a low response rate, and those that responded might have been those who were using an alternative therapy). Certainly many of these alternative therapies could be suggested and encouraged by health-care professionals involved in working with infertile couples—for example, the use of prayer (as a way of keeping life in perspective and as a source of hope), focused intercourse during the fertile phase (as identified with the use of natural family planning methods), and proper dietary practices.

Serious Infection Rates Fall with New Medical Abortion Protocol

Prior to March of 2006, the oral abortion drug mifepristone was followed up within 48 hours by the vaginal administration of misoprostol within the established protocol for Planned Parenthood clinics nationwide. However, the rates of serious infections with this protocol were higher than those in Europe, and some deaths were reported. After March of 2006, the protocols were changed not only to have misoprostol delivered either orally or buccally, but also to have either a follow-up assessment for infection risk or the prophylactic administration of a broad spectrum antibiotic. Researchers from Planned Parenthood or its affiliates, therefore, were interested in whether there was a significant decrease in serious infections rates with the initiation of the new protocol (M. Fjerstad et al., "Rates of Serious Infection after Changes in Regimens for Medical Abortions," *New England Journal of Medicine* 361 [2009]: 145–151).

This was a retrospective comparison study that involved 78 Planned Parenthood affiliates and 227,823 women who met the criteria of the study and underwent their medical abortion protocols. All serious infections were reported through the standardized Planned Parenthood protocols and auditing system. They found that the serious-infection rate decreased by 73 percent with the administration of buccal misoprostol (i.e., from 0.93 infections per 1000 abortions to 0.25 infections per 1000 abortions) and by another 73 percent with the provision of prophylactic antibiotics (i.e., to 0.06 infections per 1000 abortions)—a total decline of 93 percent in total infection rates. Therefore, the standard protocol for

the Planned Parenthood system of buccal administration of the abortion follow-up drug and the use of prophylactic antibiotics was recommended.

Comments: It is good to know that the serious-infection rates have declined, and that there were no reports of deaths. However, every developing baby was killed in this study through the use of this medical protocol. What is relevant is to know that at least one-third of all first-term abortions in the Planned Parenthood system are through the use of medicines. Medical abortion protocols such as this will facilitate the likelihood that these abortion medications will be prescribed by non-physician providers, such as certified nurse midwives and advanced practice nurse practitioners. This study was not a randomized prospective clinical trial but the numbers involved and the low infection rates are convincing.

Increased Rates of Breast Cancer Associated with Induced Abortion among Turkish Women

Breast cancer rates in Turkey have increased over the past decades as it increases its economic status and living standards. Taking on the lifestyles of women from more developed countries might have contributed to this trend. Researchers in Turkey wished to discover what risk factors and characteristics were related to the increase in breast-cancer rates among Turkish women (V. Ozmen et al., "Breast Cancer Risk Factors in Turkish Women—A University Hospital Based Nested Case Control Study," *World Journal of Surgical Oncology* 7 [2009]: 1–5).

A case control study of women between the ages of 18–70 who were diagnosed with breast cancer was conducted at a university-based clinic in the largest city in Turkey (i.e., Istanbul). These women with breast cancer were compared to women who had attended clinics at the same hospital, and who were free of any chronic disease. There were 2,167 women who served as non-cancer case controls, and 1,492 who were diagnosed with breast cancer. All women in the study were administered a 25-item demographic and lifestyle questionnaire. The researchers found that age greater than 50, age at first birth greater than 35, BMI greater than 25 kg/m^2, first-degree family member with history of breast cancer, and induced abortion were related to an increased risk for breast cancer. However, education over 13 years, spontaneous abortion, cigarette smoking, breast-feeding, nulliparity, hormone replacement therapy, and oral-contraceptive use were related to a decreased rate of breast cancer. Multivartiate logistic regression showed that age (> 50), induced abortion, and oral contraceptive use (negatively) were associated with breast cancer risk as independent factors. The authors concluded that age and induced abortion were related to an increased risk of breast cancer, but that oral contraceptive use was not. They recommended further studies to determine if these risks are actual because some are contradicted by evidence in the current scientific literature, for example cigarette use.

Comments: The results of this study need to be taken with caution, because they only infer association and not cause and effect. Furthermore, the results of the study could be a consequence of bias in selection of the participants, since they were all taken from patients who attended one university-based hospital in an urban area, i.e., sicker people might be seeking these types of medical services. Furthermore, some risks, like hormone replacement therapy, have been found in randomized control trials to increase the risk for breast cancer. It is of interest that the authors stated the increased risk of breast cancer with abortion was also found in a majority of studies they reviewed in the literature.

Increased Risk for Breast Cancer Found among Cohort of Women with Prior use of Oral Contraception

The Mayo Breast Clinic (Rochester, Minnesota) opened in 1993. Since then, physicians at the clinic have seen thousands of women who have concerns about their breasts. Women who attend the clinic fill out a history form that includes modifiable risks (e.g., smoking, high-fat diets, hormonal therapy) and non-modifiable risks (e.g., age, age at menarche and menopause, pregnancies, family history of breast cancer). Researchers at the Mayo Clinic were interested in determining if modifiable risk factors—and, in particular, smoking—were predictive of breast cancer among a cohort of women who attend the breast clinic (I.T. Croghan et al., "The Role of Smoking in Breast Cancer Development: An Analysis of a Mayo Clinic Cohort," *Breast Journal* 15 [2009]: 489–495). The authors pointed out that approximately 13 percent of women born in the United States will eventually develop breast cancer.

The participants for the study were all women who attended the breast clinic from 1993 through November of 2003 and did not have a current diagnosis of breast cancer, i.e., 8,927 patients. Of these patients, 8,097 met the inclusion criteria for the study. Of these patients, 1,225 were diagnosed with breast cancer within one year of completing the risk-factor survey, and 6,872 were cancer free. To be included in the smoking risk-factor group, the participant had to indicate that she had smoked at least 100 cigarettes in her lifetime. The breast-cancer group was somewhat older (a mean of 58 years versus 54) but had significantly more pregnancies (2.9 versus 2.7). The researchers discovered (with the use of logistic regression analysis) that smoking, older age, the use of the birth-control pill for longer than 11 years, and use of exogenous hormones (i.e., post-menopausal hormone therapy) were predictive of breast cancer. The odds ratio (OR) for smoking was 1.25 ($p = 0.004$), for older age 1.02 ($p < 0.001$), for birth-control pill use greater than 11 years 2.10 ($p = < 0.001$) and hormone therapy 1.81 ($p < 0.001$). The authors discussed only the results of the smoking risk factor at length and mentioned that the risk was similar to previous studies. They concluded that with this cohort of Mayo Breast Clinic patients smoking was a predictive risk for breast cancer, but that more research is needed to confirm these results.

Comments: It is of interest that in the regression model they employed, use of oral hormonal contraception for 11 years or more was by far the greatest risk factor of breast cancer. It is also of interest that the authors did not comment on this risk in their discussion, even though their main interest was on smoking risk. The main author (Croghan) is part of the Mayo Clinic Nicotine Research Program.

Oral Contraceptive Use is Associated with Fivefold Increased Risk of Venous Thrombosis

The risk of deep venous thrombosis has been associated with the use of oral hormonal contraception soon after the birth-control pill was introduced for public use in the early 1960s. Over the years the dose of estrogen in the birth-control pill has decreased, and different types of progestins or progestogens have been added. The various combinations of estrogens and progestogens over the years that have been used in the combined birth-control pill are called "generations." The first generation of the birth-control pill contained the progestogen lynestrenol (which is seldom used today), the second generation used primarily the progestogen levonorgestrel, and the third generation

(which came available in the 1980s) used either desogestrel or gestodine. Recently (mid-1990s to early 2000s), other progestogens have been added in this so-called third generation of the birth-control pill, i.e., cyproterone acetate and drospirenone. (The birth-control pills with these progestins are known as Yaz and Yasmin in the United States and are the number one selling brands of birth-control pills.) The combined birth-control pill that has cyrpoterone acetate or drospirenone became widely used because of the use of these drugs for treating acne vulgar-is and mild hirsutism. However, numerous studies have shown an increased risk of venous thrombosis with the combined pill that contains cyproterone acetate (but other studies have shown mixed results). Furthermore, there are only a few studies that have investigated the risk of thrombosis with the newer combined pill that contains the progestin drospirenone. Based on the mixed studies in previous studies and the lack of studies specifically on drospirenone, researchers from the Netherlands conducted a large case control study to determine the influence of various types of oral birth-control pills (i.e., doses of estrogen and type of progestin) on the risk of deep vein thrombosis (DVT) (A. Van Hylckama Vliegt et al., "The Venous Thrombotic Risk of Oral Contraceptives, Effects of Oestrogen Dose and Progestogen Type: Results of the MEGA Case-Control Study," *British Medical Journal* 339 [2009]: h2921).

The participants for this study came mainly from a larger study that enrolled patients who were less than 70 years of age and had a deep vein thrombosis diagnoses at one of the participating clinics in the Netherlands. This larger parent study was called the "multiple environmental and genetic assessment of risk factors for venous thrombosis study" or MEGA. From this study they enrolled 1,524 female patients who were aged 18–50 and experienced deep vein thrombosis. Their controls were 712 of their male partners and 1,048 female controls that they obtained through a randomized dialing process, which resulted in a total of 1,760 controls. All participants filled out a standardized questionnaire about risk factors of deep vein thrombosis, pregnancy, and use of hormonal contraception. The mean age of the cases was 37.1 and the controls 37.4.

The relative risk of having a deep vein thrombosis with current use of oral contraceptives was fivefold (i.e., incidence in contraceptive users per 10,000 person years) (95% confident interval, 4.2–5.8). However, the risk increased from 3.7 at an age less than 30 to 13.3 at 40–50 years of age. The relative risk for the three highest combined hormonal contraceptives, based on the type of progestin, was 7.3 for Desogestrel, 6.8 for Cyrpoterone acetate, and 6.3 for Drosirenone (all third generation-type birth-control pills). Levonorgestrel had the lowest risk at 1.6. As expected, those birth-control pills with the highest dose of ethnytestradiol (i.e., 50 μg) had the highest rate of deep vein thrombosis—but only 4.4 percent of users had this type of dose. The lowest rate was among those that had 20 μg of ethinylestradiol, with 11.2 percent of users. The authors concluded that the birth-control pills with the lowest risk of thrombosis are those that contain the progestin levonorgestrel and low levels of estradiol but, that overall, current available oral contraceptives were a major contributing factor to deep vein thrombosis among women.

Comments: It would worthwhile to see a case control study like the one described above with women who have never used hormonal contraception. Although many of the control group (N=637) were not currently using hormonal contraception, many were the partners of the deep vein thrombosis cases, and some of the women controls had previously used hormonal contraception.

An article in a recent issue of *The New York Times Magazine* mentioned that for the manufacturer of the Yaz-type birth-control pill—which is the number one money-making drug for the company with

worldwide sales of $ 1.8 billion—is now being sued with multiple law suits (N. Singer, "Health Concerns over Popular Contraceptives," *New York Times*, September 26, 2010). A medical apologist (paid by Bayer) mentioned in the article that the rate of increased risk with desgogne is minimal. However, with over 100 million women using birth-control pills worldwide, this small risk projects to many women.

Serum Zinc Levels Lower in Women Using Hormonal Contraception

Deficiencies in trace metals such as zinc and selenium have been linked to neurodegenerative disease, cardiovascular disease, and to an increased risk for cancer. Selenium has been suspected as a protective factor against breast cancer. Previous research has indicated that the levels of zinc and selenium have been altered in users of estrogen-progesterone type hormonal contraceptives. Therefore, researchers in Iran sought to determine the effect of the hormonal (low dose) contraceptive pill on the selenium and zinc status of healthy women (S. Rallah, F.V. Sani, and M. Firoozrai, "Effect of Contraceptive Pill on the Selenium and Zinc Status of Healthy Subjects," *Contraception* 80 [2009]: 40–43).

Participants were 50 women not using hormonal contraceptives and experiencing regular menstrual cycles and another 50 women who were on low-dose estrogen progesterone-type oral contraceptives for a minimum of three cycles. Blood samples were taken between 9:00 a.m. and 11:00 a.m. from all participants and analyzed for selenium and zinc levels. The researchers found that there was a significant decrease in zinc levels among the contraceptive group compared to the normal controls, i.e., 76.84 mcg/dL for the contraceptive group compared with 81.61 mcg/dL for the controls ($t = 3.66$, $p < 01$). They also found lower levels of selenium among the contraceptive group (69.94 mcg/dL) compared to the controls (70.35 mcg/dL), but the differences did not reach significance ($t=0.935$, $p = 0.081$). Length of time on the hormonal contraceptive was not a factor in decreased zinc or selenium levels beyond three months of use. Although the researchers admitted that the physiological implications for alterations in zinc levels are unknown, they suggested that the dietary requirements for women on contraceptives be increased.

Comment: Although the results of this study are interesting, they need to be understood within the weakness of the study design. First of all, there was no mention of how the participants were selected, or whether the participants were matched on important confounding variables. In other words, the differences found might have occurred due to selection bias. Furthermore, the researchers did not reveal any power analysis to determine the number of participants needed to reach statistical significance. We also do not know if the decreased zinc or selenium levels have any clinical significance. It is of interest that the introduction of hormonal contraception was recent in the country of Iran, so there is a greater opportunity to determine differences among women who have never used these methods.

Under the Microscope

The Breast-Feeding Transition and Natural Family Planning

Among women who breast-feed their infants, the time from the birth of a baby until the resumption of regular ovulatory menstrual cycles is known as the breastfeeding transition. This transition is often the most difficult time for women (and couples) who wish to use natural methods of family planning (NFP).

Likewise, it is a time when women who use NFP often get pregnant without intending to. This is a problem because spacing of births is healthier for the mother and baby, and because there can be serious reasons for not having a pregnancy soon after childbirth.[1]

In general, the breastfeeding transition includes the immediate postpartum anovulatory amenorrhea phase, the ovulatory-pre-menses phase, the first menses and irregular menstrual-cycle phase, and, finally, the resumption of regular-length menstrual cycles. Although there is decreased fertility during these phases, this is a difficult time to estimate fertility because: 1) there are no menstrual markers in the pre-menstrual phases, 2) the traditional markers of fertility (i.e., cervical mucus and basal body temperature changes) do not always coincide with hormonal indicators of fertility, 3) women often ovulate before their first menses, 4) hormonal indicators are in disassociation with follicular development, and 5) the first three to six menstrual cycles are very irregular in length and with the time of ovulation.

The purpose of this short review is to determine the state of the art of NFP for the breastfeeding transition. This review will provide a brief description of the physiology of breastfeeding and the suppression of fertility, discuss the use of lactational amenorrhea as a method of family planning, describe how current NFP methods recommend monitoring fertility during the breastfeeding transition, and summarize efficacy research on the use of NFP methods during the transition.

Physiology of Breast-Feeding

The hormone prolactin is the major hormone responsible for the production of milk in the breasts. Prolactin levels increase throughout pregnancy and (in breastfeeding women) remain elevated for 4–6 weeks postpartum.[2] After 4–6 weeks, prolactin levels fall to non-pregnant levels, but breastfeeding will cause spikes in prolactin for about two more months. The major mechanism for prolactin-induced milk production is stimulation of the breast nipple through suckling. Suckling and the stimulation of milk release is known as the milk ejection or “letdown” reflex. The milk letdown can be a mechanical response, but it can also be caused by the psychological preparation for nursing. Suckling stimulates the release of prolactin that in turn stimulates oxytocin release from the posterior pituitary gland. Oxytocin stimulates the duct cells in the breast to contract and express milk.

Prolactin is also the major hormone responsible for the suppression of ovulation during breastfeeding. Prolactin inhibits the production of gonadotropin releasing hormone (GnRH) from the hypothalamus. GnRH in turn modulates follicle stimulating hormone (FSH) and luteinizing hormone (LH) so that production of these hormones are decreased, and follicular development and estrogen production ceases in the ovaries and ovulation is suppressed. The frequency of suckling and the duration of suckling by the baby influence the effectiveness and length of ovulation suppression. In some tribes in Africa, the frequency of suckling causes the suppression of ovulation for an average of 44 months.[3] The duration and frequency of breastfeeding are also the important variables behind what is called the lactational amenorrhea method of child spacing, known by the acronym “LAM.”

Amenorrhea is the absence of having a menses or “period” due to the suppression of ovulation. If a mother does not breast-feed her infant, fertility returns quickly—within 9–13 weeks. Prolactin production decreases with less frequent breastfeeding and suckling. This occurs usually when the baby does not feed during the night and with the introduction of solid foods. Stress, anxiety, and illness also

can be factors in the reduction of prolactin production and the suppression of ovulation. Obviously, stress, anxiety, and reduced suckling time are normal for the postpartum period and thus contribute to the difficulty in monitoring fertility during the breastfeeding transition. However, for some women who use total breastfeeding in the early postpartum time period (i.e., the first six months), this period can be a relatively easy time for the use of natural methods. This is so because the breastfeeding woman can learn her signs of fertility and not have to fear an unintended pregnancy.

Breast-Feeding and the LAM Protocol

In 1988, world experts on breastfeeding met in Bellagio, Italy, and (after a review of the available research) concluded that there is less than a 2 percent pregnancy rate within the first 6 months of lactational amenorrhea if women are fully or nearly fully breastfeeding and have not experienced a menstrual bleed. In the last ten years there have been a number of studies that have re-confirmed the lactational amenorrhea method (LAM) protocol including a large prospective multinational study supported by the World Health Organization (WHO) to determine the relationship between breastfeeding practices and lactational amenorrhea and to test the Bellagio consensus.[4] A total of 4,118 women who were breastfeeding were enrolled in the WHO study from 5 developing and 2 developed countries. The cumulative pregnancy rate for all the women who were still breastfeeding and amenorrheic at 6 months was 0.8 percent and at 12 months 4.4 percent. The differences in pregnancy rates between fully breastfeeding and partially breastfeeding women were not statistically significant at either the 6- or 12-month time period. The WHO task force concluded that the lactational amenorrhea method is a viable method for postpartum family planning.

What is usually not emphasized along with the three main LAM criteria (i.e., amenorrheic, total breastfeeding, and within 6 months postpartum) is that there should also be no long intervals between breastfeeding, and that night breast-feeds are important. Variation from these criteria can increase the pregnancy rate. For example, a recent prospective study conducted among 170 urban, middle-class, Chilean women separated from their infants by work resulted in a 6-month pregnancy rate of 5.2 percent with the use of LAM.[5] Although the women were monitored on a monthly basis and were taught how to express their milk manually, the pregnancy rate was higher than the pregnancy rate in those women who did not work. Of interest in the Chilean study is that only 28.2 percent of the study participants met the LAM criteria at 6 months. This is about half the level found in the non-working participants in previous studies on LAM. The authors concluded that women using LAM should be informed that separation from the infant might increase their risk of pregnancy.

Since 1988 there have been at least ten studies conducted with women from over 10 countries that have confirmed the LAM protocol.[6] In fact, the studies show that LAM when followed properly might be more effective than 2 percent, and be robust to some changes (such as the introduction of solid foods) as long as the woman continues the frequency and length of breastfeeding. Furthermore, the suppression of ovulation seems to extend up to a year with an increased pregnancy rate of only 5 percent. However, in the United States the portion of childbearing women who had ever breast-fed is only around 50 percent. Whereas in Japan and in developing countries more than 90 percent of childbearing women breast-feed their infants. At this time, it might be unrealistic for women in today's modern society to return to childbearing and breastfeeding patterns that were characteristic a century ago.

NFP and Avoiding Pregnancy during the Breast-Feeding Transition

Most NFP systems, whether they are cervical mucus only methods or symptom-thermal methods (i.e., basal body temperature plus mucus monitoring), recommend that all women (whether breastfeeding or not) begin to observe and chart their signs of fertility as soon as the bleeding (lochia) dries up after the birth of their baby (which will occur from 22–34 days after the birth of the child or on average 27 days).[7] The temperature shift and the urinary LH surge will not be present during this time, since a woman is not ovulating. However, a woman should observe and chart her cervical mucus observations and, if she likes, her basal body temperature. Before the return of fertility, breastfeeding women usually observe long periods of dryness with occasional mucus days. Some women experience an unchanging pattern of a moist sensation or constant pattern of mucus. The temperature chart will show swings from high to low. Women who use NFP during breastfeeding are asked to be consistent in observing and charting fertility signs (mucus) and temperature (if desired), to have intercourse only at the end of dry days or on days of the basic infertile pattern of unchanging mucus, and to treat any day with a change from the basic infertile pattern of dryness or unchanging mucus and the three days after as fertile. It should also be noted that some symptom-thermal methods advocate the use of internal checks of the cervix to determine if the cervix is hard and closed or open and soft and secreting mucus.

When fertility returns (usually by the observation of the first menses), women are instructed as follows: 1) continue to have intercourse only at the end of the day on dry days (or a basic infertile pattern of unchanging mucus) before ovulation (some cervical-mucus only methods recommend having intercourse only every other day on dry days or during a basic infertile pattern); 2) before ovulation, to consider any day of mucus (or any change from the basic infertile pattern) and 3 days past as fertile; 3) if using temperature, to resume intercourse at the end of the third day of high temperatures above the cover line, i.e., the first three high temperatures over the previous six; 4) if using cervical mucus signs only, to continue to have intercourse at the end of the day on dry days only during the first cycle. In subsequent cycles, if the woman is confident that it is her peak day of cervical mucus, then intercourse may resume at the end of the fourth day past peak. All women are asked to be aware of variability in cycle length, the return of mucus, and possible short post-ovulatory phases. If they experience a continuous pattern of mucus and are confused about their fertility signs, they are asked to make an appointment with their NFP instructor. It will take about three menstrual cycles after cessation of breastfeeding for cycles to regulate back to normal.

Efficacy of NFP during the Breast-Feeding Transition

There are few studies that have investigated the efficacy of NFP methods during the breastfeeding transition. Australian researchers and NFP teachers reported a study in which they followed 55 postpartum, breastfeeding women for a mean of 7.8 months (i.e., a total of 36 years) to discern patterns of returning fertility.[8] The women observed their daily cervical mucus changes on a scale of −1 to +9 (with the higher number indicating more fertile mucus), and some measured their basal body temperature. Of these 55 women, 22 women achieved a pregnancy, 14 of which were unintended (i.e., about 14% of the breastfeeding women). Furthermore, they discovered that mucus symptoms often, i.e., 40 percent of the time, did not correlate with hormonal values of fertility. Estrogen levels were detected through 24-hour urine collection samples from the participants.

L. Hatherley investigated the efficacy of NFP among 251 postpartum women who were using NFP methods to avoid pregnancy, of which 205 were lactating.[9] After one full year postpartum, the researcher found 34 (16%) unintended pregnancies among the lactating group and two (5%) among the non-lactating women. In the NFP group 5.8 percent conceived within 9 months, and 11.1 percent within 12 months. He concluded that the variability of the menstrual cycles and the hormonal fluctuations during the postpartum period were not conducive to the use of NFP. He also stated that the hormonal changes and menstrual-cycle variability among the breastfeeding women were associated with confusion in the interpretation of cervical-mucus and basal body temperature signs. This, in turn, resulted in frustration, misapplication of the rules of the NFP method, and unplanned pregnancies. Other researchers investigating the efficacy of the ovulation method found that the pregnancy rates increased when ovulation resumed and when supplemental infant feeding was introduced. They also discovered that unintended pregnancy rates were higher when the users of the ovulation method adhered to the rules of the method. They speculated that use of NFP actually increased the unintended pregnancy rate.[10]

An NFP system practitioner and a physician-researcher investigated a subset of breastfeeding women who were using the Creighton Model ovulation method of NFP.[11] They discovered a net pregnancy rate of 24 percent and gross rate of 32 percent and that the pregnancy rate was higher than that found with the total study (i.e., a 17% pregnancy rate). They speculated that the higher rate might be due to a higher rate of achieving related behaviors among the breastfeeding group of women.

In summary, there are few studies that have investigated the efficacy of NFP methods during the breastfeeding transition. Researchers who have conducted studies have found a fairly high unintended pregnancy rate, and some believe that NFP might actually increase the unintended rate among those who follow the rules of the NFP methods. The reason that this might be so is that there is dissociation between the traditional natural indicators of fertility and actual fertility during the breastfeeding transition.

Disassociation of Fertility Symptoms

The Australian study, referred to above, had 55 breastfeeding women participants rate their cervical mucus from −1 to a +9 and collect daily 24-hour urine samples for estrogen levels.[12] The researchers discovered that the cervical mucus ratings did not correlate with the presumed fertility (i.e., estrogen rises) about 40 percent of the time. An Italian group of researchers followed 40 breastfeeding women through their first menstrual cycle postpartum with serial ultrasound.[13] The participants also charted their cervical mucus observations and basal body temperature. They found that eight of the women failed to record cervical mucus changes, 12 had cervical mucus constantly present, six had cervical mucus present greater than 20 days, and 14 had fertile mucus for 7–10 days. They concluded that cervical mucus monitoring was inaccurate in predicting postpartum fertility. They also found 28 of the 40 women had inadequate or no discernable temperature shift in ovulatory cycles.

In a small sample of breastfeeding women using the symptothermal method of NFP, researchers found that in the first ovulatory cycle, the basal body temperature shift was four days after the LH peak +1 day estimated day of ovulation.[14] In other studies, the first basal body temperature shift was from 6–13 days after the first ultrasound detected ovulation, and the symptoms overestimated the actual time of fertility, i.e., were not very specific.[15] This dissociation of the fertility symptoms of NFP from the

actual hormonal picture is perplexing. A recent study found that the follicular development during the amenorrhea phase of breastfeeding was actually larger than during the follicular phase in the first menstrual cycle.[16] The results showed that the number and diameter of the follicles were significantly greater during breastfeeding amenorrhea compared to the early and mid-follicular phase of regular menstrual cycles. They also found that estradiol levels were similar during lactation amenorrhea, the early follicular phase, and the mid-follicular phase. However, compared to regular menstrual cycles, lactational amenorrhea is associated with higher prolactin levels, normal or slightly elevated steroidal gonadotropins (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 lactational amenorrhea, there is a profound dissociation between follicular growth and follicular endocrine activity.

New Protocols for Using NFP during the Breast-Feeding Transition

A few fertility awareness and NFP researchers have been trying to develop better protocols for monitoring fertility during the breastfeeding transition. Researchers at the Georgetown University Institute for Reproductive Health applied the rules for both the Standard Days Method and the TwoDay Method, i.e., two newer NFP methods that have been developed at that institute, to breastfeeding menstrual-cycle charts that were available from another study that tracked the hormonal indicators of fertility and ovulation.[17] The Standard Days Method is for women who have menstrual cycles between 26 and 32 days in length and are able to avoid intercourse from day 8 through day 19 of the menstrual cycle, i.e., the standard days for avoiding for every cycle.[18] For the TwoDay Method, the woman simply asks herself whether she has observed cervical-vaginal secretions or not on the current day of observations and the day before; if she answers “no” to each question, she should consider herself in the infertile phase of the menstrual cycle.[19] The Standard Days Method is not usable during the pre-ovulatory phase of the breastfeeding transition, since there is no marker for the beginning of the menstrual cycle and when days 8–19 take place. When applied to the first two menstrual cycles after the first menses, the researchers found the probabilities of pregnancy too high for the Standard Days Method. However, the TwoDay Method seemed to provide adequate coverage of the estimated fertile phase to be a useful method of NFP during all phases of the breastfeeding transition.

Since J.B. Brown found that there was often a dissociation of the cervical mucus sign from the actual hormonal rises in estrogen during the breastfeeding transition, he recommended that some type of monitor be developed and used to measure the reproductive hormones during the breastfeeding transition.[20] Researchers from Marquette University developed a breastfeeding protocol based on an electronic hormonal fertility monitor that measures a threshold level of estrogen and LH in the urine.[21] The protocol requires the woman to monitor artificial 21-day “menstrual cycles” for the rise in estrogen and the eventual LH surge before the first ovulation. The reason for the 21-day length is that the monitor will ask for a test strip for 20 days in a row or until it detects the LH surge. By re-triggering the monitor, the woman user is able to constantly monitor her estrogen rises and the eventual LH surge during the pre-ovulatory transition phase. Marquette University and Saint Louis University researchers demonstrated that among 10 women users of the protocol, who also monitored their cervical mucus, the monitor would cut the estimated time of abstinence approximately in half. These researchers are now testing the effectiveness of this protocol for avoiding pregnancy among a cohort of 50–70 breastfeeding users.

Variability during the Breast-Feeding Transition

Understanding the dynamics and complexity of the breastfeeding transition will most likely help with designing natural methods of monitoring fertility. The breastfeeding transition is complex and extremely variable. Studies give a mean range of the first ovulation from 193–322 days (and actual range of 24–750 days) and a mean range of the first menses from 179–298 days (actual range 35–698 days).[22] About 33 percent of breastfeeding women will have their first ovulation before their first menses in the first three months postpartum, but this figure goes up to 87 percent after the first 12 months.[23] We also know that, after the first ovulation, the luteal phase will be short (i.e., less than 6 days) in about 60 percent of the cases.[24]

The first menstrual cycle after the first menses can last from less than 20 days to over 600 days with around 8 percent having cycle lengths greater than 55 days.[25] The second menstrual cycle also has extreme variability with a range of less than 20 days to over 400 days, and about 4 percent having lengths greater than 55 days. The third cycle postpartum approaches the norms of variability, with most in the 25–35 day range, and none over 55.

Summary

The breastfeeding transition is one of the most challenging situations for women wishing to use natural methods of family planning and for NFP teachers to guide these women through the transition. There is great variability in the length of lactational amenorrhea among breastfeeding women, in the percentage of ovulations that occur before the first menses, and in the lengths of the first three menstrual cycles postpartum. Besides the problem of variability, there is the problem that not many women in the U.S. meet the criteria for LAM. Only about 35 percent of U.S. women will continue to breast-feed until 6 months postpartum (according to data from cycle 6 of the National Survey of Family Growth) and, for those that do, the breastfeeding intensity and frequency is less than what is needed for suppression of ovulation.[26] The traditional natural signs of fertility with use of NFP methods (i.e., cervical mucus and basal body temperature) often do not coincide with actual fertility and often create undue abstinence. This dissociation of the natural signs of fertility and the hormonal landscape is documented in physiological studies. Furthermore, the few studies that we have on the efficacy of NFP methods during the breastfeeding transition show that they are ineffective or might actually increase the unintended pregnancy rate. Researchers from several universities in the United States are currently working on testing protocols of natural methods for use during the breastfeeding transition (i.e., Georgetown University, Saint Louis University, and Marquette University).

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