Natural Family Planning
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In this issue

Natural Family Planning

Self-detected Cervical Mucus Peak Symptom Determined to be Accurate and Practical Means of Ovulation Detection

Ultrasound detection of the day of ovulation (US-DO) is considered by many to be the "gold standard" of ovulation detection. Correlating other methods of ovulation detection with US-DO is a means of determining the accuracy and validity of those methods. Reliable, accurate, easy to determine and practical natural markers of ovulation detection are important for couples using natural family planning (NFP) to either achieve or avoid pregnancy and for the accurate timing of menstrual cycle procedures, tests and medications. Researchers from Claude Bernard University in Lyon, France collected one of the largest data sets (of menstrual cycles) that included US-DO and with self-detected cervical mucus peak day and basal body temperature readings. The data set was generated by 107 normally cycling women (aged 19 to 45) from 8 NFP clinics in France, Germany and Spain.(1) The women produced 326 cycles of data that included daily measurements of urinary luteinising hormone (LH), follicle stimulating hormone (FSH), estrone-3-glucuronide and pregnanediol-3α-glucuronide, and transvaginal ultrasound examination of the ovaries. Outcome measures for the study were how indices of ovulation varied from the LH expected day of ovulation (LH-DO) and the US-DO.

Ultrasound evidence of ovulation was verified in 283 out of the 326 cycles in the data set. In 28 of the cycles the US-DO was not detected because the ultrasound test of ovulation was performed too late or the participant did not attend the screening session. The following are the summation of results for three available self-detected indirect measures of ovulation, i.e., LH peak, BBT shift, and cervical mucus peak, in relation to plus or minus one day of the US-DO.

LH Peak

The urinary LH estimated day of ovulation was considered by the authors to be (on average) an equivalent of the US-DO. However, they determined that the initial rise of the LH surge rather than the peak of the surge was more efficient in estimating the day of ovulation. The initial rise of urinary LH was detected in 77% of the cycles plus or minus one day of the US-DO, whereas the LH peak was detected in 67% of the cycles. The authors estimated that taken together the initial rise and peak in LH would be an

accurate indicator of ovulation in about 90% of regular length and long cycles. They also stated that the LH test is relatively cheap and practicable for home testing. The initial rise in LH was found in 273 of the 283 US-DO cycles (96.5%) and the LH peak in 272 of the 283 cycles (96.1%).

Basal Body Temperature (BBT)

The BBT nadir and the BBT rise were judged not to be reliable estimates of the day of ovulation because they preceded or followed the US-DO by more than two days in nearly 13% of the cycles and plus or minus one day of the LH expected day of ovulation in 23% of the cycles. The authors indicated that a 6.8 to 9.5% error rate was inherent in the use of the BBT nadir or rise in estimating the day of ovulation. The BBT rise was detected in 277 of the 283 US-DO cycles (97.9%) and the BBT nadir in 100% of the cycles.

Cervical Mucus Peak Symptom

The peak symptom of self-detected cervical mucus fell plus or minus one day of the US-DO in nearly 75% of the cycles and plus or minus one day of the LH estimated day of ovulation in nearly 70% of the cycles. The authors concluded that the self-detection of the peak in cervical mucus was superior to BBT in detecting ovulation and indicated that the cervical mucus peak symptom may be conveniently used at home for "moderately rigorous or easy family planning." The peak symptom of cervical mucus was only detected in 215 of the 283 US-DO cycles (76%).

The authors concluded that the study "established clearly the high correlation between LH expected day of ovulation and the US-DO" and that their findings "confirm the interesting role of the cervical mucus peak symptom" in predicting ovulation.

Comments

I was not convinced that findings of this study were clear or convincing. First, these findings only apply to healthy regularly cycling women. The study criteria eliminated those with abnormal cycles (e.g., polycystic ovary disease), women who were post-partum or breastfeeding and those who used hormonal contraception in the past 3 months. Yet women who fit these criteria are commonly found in NFP service programs. Secondly the authors mention that the ultrasound detected day of ovulation can be subjective, yet they give no indication for the reliability or accuracy of the US-DO at the eight NFP clinics, nor say whether inter-rater reliability was used or attempted.

The fact that the researchers found a BBT nadir in 100% of the US-DO cycles is amazing, since previous literature indicated that this could be found in only 10-40% of cycles. It is also interesting that the authors rated cervical mucus peak day as superior over BBT rise, even though the cervical mucus peak was detected in only 76% of the US-DO cycles versus 97.9% for the BBT rise. The authors gave the definition of cervical mucus peak as the last day of clear, stretchy and/or lubricative mucus discharge. This definition is the same as the Creighton Model and that found in the research literature. The definition of the estimated day of ovulation for the LH surge was somewhat non-traditional, since most literature would indicate that the day of ovulation was about 24 hours after the LH surge in the urine, not the day of the surge. And most people would realize that the BBT shift is essentially a post-ovulatory event. Finally, with regard to the LH testing used in the study, readers should keep in mind that one of the authors worked for the Quidel Corporation that manufactures LH detection kits. This could be perceived as a conflict of interest or a source of potential bias in conducting, analyzing and reporting the results. (*RJF*)

1. Ecochard, R., Boehringer, H., Rabilloud, M. and Marret, H., **Chronological aspects of ultrasonic, hormonal, and other indirect indices of ovulation**, *British Journal of Obstetrics and Gynecology* 108 (2001): 822-829.

Calendar Rhythm Users Often Make Incorrect Calculations of the Fertile Period

A multi-country focus group study was conducted recently to determine how couples actually use calendar methods, how they determine the fertile phase of the menstrual cycle, what behaviors they use during the fertile phase, and whether they are satisfied with natural methods of birth regulation.(1) The study was located in four countries (Hungary, Peru, the Philippines, and Sri Lanka) where a relatively high percentage of couples use natural methods of family planning. Each focus group consisted of 6-12 persons and a moderator familiar with group qualitative research techniques and experience in leading group discussions. The participants were men and women who avoided "unprotected" intercourse during certain days of the cycle to avoid pregnancy, were in stable relationships, were between the ages of 18-45, and who belonged to similar socioeconomic and cultural groups. The focus groups were conducted in community centers and lasted about 2 1/2 hours. In Sri Lanka, there were eight groups involving 32 men and 33 women; in Peru there were 13 groups with 41 men and 59 women; in the Philippines, eight groups were comprised of 27 men and 28

women; and in Hungary there were twenty groups with 13 men and 78 women. The majority of the Hungarian participants, unlike participants in the other countries, used primarily the Billings Ovulation method. The following is a summarization of the qualitative results.

Sources of information about natural methods

The men in the focus groups obtained information about natural methods from their wives or partners, friends, and older family members. The women obtained information from books, newspapers, health posts, friends and older family members.

Factors related to the identification of the fertile period

The participants in Peru, the Philippines, and Sri Lanka primarily used the calendar method, while those in Hungary used a mixture of natural methods including calendar, temperature, cervical self-examination and the Billings Ovulation Method. Participants in Peru and the Philippines did not apply the instructions for the Calendar Method consistently and the women in the Philippines often had a poor understanding of their menstrual cycle. For example one Philippine woman stated "A woman is fertile during the menstruation period. After menses she is no longer fertile." Only 26% of the ever users of the Calendar Method in the Philippines were able to correctly identify the fertile phase of the menstrual cycle.

The use of abstinence and alternatives during the fertile period

Most participants from each country reported the use of abstinence some time during the menstrual cycle to avoid pregnancy. However, participants in Peru, the Philippines and Sri Lanka reported the use of withdrawal, and those in Hungary and Peru commonly used condoms during the fertile time. Participants also reported the use of genital contact and "alternative sex" practices during the fertile period.

Perceptions of other contraceptives

All participants in all four countries reported that modern methods of contraception were available to them. Participants in all four countries also felt that oral contraceptives and the IUDs were unhealthy and dangerous to use or have some unacceptable side effects. Expense was viewed as a barrier to use of modern contraceptives in Hungary and Sri Lanka.

Acceptability of calendar methods

Participants in the Philippines and Sri Lanka, liked the calendar methods and found them effective, while those in Peru and Hungary disliked the natural methods because of their unreliability. Participants in every center felt that the methods were difficult to learn, understand and use. They also disliked coping with abstinence. However, they did appreciate the fact that the natural methods cost little, were safe and did not have negative side effects. Participants in three centers also felt that the autonomy of use and self-sufficiency were positive characteristics of the natural methods.

Suggested ways to improve calendar methods

In Hungary the participants called for the development of more reliable methods, in Sri Lanka participants were enthused about participation in NFP programs because they previously only had access to programs for modern contraceptive methods. In Peru, participants suggested the use of schoolteachers for promoting and teaching the use of the natural methods and in the Philippine participants asked for more counseling on alternative methods to be used during the fertile phase. All participants called for increased public knowledge, awareness and better public communication about calendar methods. They felt that credible persons in the mass media would be helpful. Credible and comprehensive counseling and support was also recommended.

Comments

The authors indicated that the participants in this study cannot be assumed to be representative of the population of Calendar Method users. However, the qualitative focus group approach does give a depth to the participant's responses and provides insights into their use of the methods. The authors also mentioned that many of the participants did not know how to use the Calendar Method and that the method could be more effective if the participants were taught how to use it and were given a better understanding of their menstrual cycles. Greater participation of the male in the use of the natural methods would also increase cooperation between the partners and efficiency of use. Helping couples to cope with abstinence during the fertile period-- coping methods that involve non-genital and non-contraceptive means in synch with Catholic sexual ethics--is also a need.

The authors also stated that "in every study center, clear negative attitudes toward modern contraceptives were expressed among persons who had much experience with them as well as those who had little experience. In all centers, modern contraceptives

were also clearly available." The authors then concluded that the survey findings challenge programs to both address these negative attitudes toward other methods and to enhance the effective use of natural methods. I agree that we need to enhance the effectiveness and ease of use of natural methods. We also need to address the use of contraceptives, not to promote them, but to point out that they are contrary to the nature of the human person and the true meaning of conjugal relationships. (*RJF*)

1. Research Group on Methods for the Natural Regulation of Fertility, **Periodic abstinence and calendar method use in Hungary, Peru, the Philippines, and Sri Lanka**, *Contraception*, 64 (2001): 209-215.

Standard Day Method Found to be Effective

Researchers from the Georgetown University Institute for Reproductive Health (IRH) recently reported on a multi-site effectiveness study of what they call the Standard Day Method (SDM) of family planning.(1) SDM is a simple to use and easy to teach natural method of family planning. The SDM is essentially a modified form of Calendar Rhythm that has a "fixed" number of days of fertility for each cycle – i.e., day 8 to 19. The method is intended for women who have regular cycles between 26 and 32 days in length. The SDM fixed day formula was "retrospectively" and theoretically tested with past data sets and reported in a previous study.(2) This study demonstrated that there was a very low probability of pregnancy outside of the projected 11-day period of fertility. The highest day of probability of pregnancy from an act of intercourse was only 0.007 during this extended window of fertility.

The SDM was prospectively tested for its effectiveness in helping couples avoid pregnancy among 478 women from 5 different sites in three developing countries (the Philippines, Peru, and Guatemala). The participants were between 18-39 years old, had menstrual cycles between 26-32 days in length, and were willing to avoid intercourse for 12 consecutive days each cycle. Each study site had 5-10 trained health workers who instructed the participants in the SDM and who contacted them monthly for the length of the study. Participants were also asked to keep a calendar to record the beginning and end of their cycles, acts of intercourse, and any other method used to avoid pregnancy (e.g., condoms or withdrawal).

The SDM uses a colored bead necklace system (called CycleBeads) that indicate the beginning (a red bead) of the cycle, followed by 6 brown beads of infertility, then 12

days of fixed fertility (white beads) and then 13 more days of infertility (with brown beads). The CycleBead system also has a dark brown bead for day 27 that indicates to the user that if they start their menses before that date they should contact their "provider." If they reach the last bead (day 32) and still have not started their menses they were also asked to contact their provider. The marker beads helped the user to know whether they fell into the 26-32 day cycle length to which this CycleBead system applies. The rules for the CycleBead system are simple, i.e., "on brown bead days you can have intercourse with very low probability of pregnancy", and "on white bead days you can get pregnant. Avoid unprotected intercourse to prevent a pregnancy."

The 478 participants had a mean age of 29.4 years, most (90%) had at least a primary level education, 98.9% had children (mean 2.5), and almost 80% were Catholic. One third of the women were breastfeeding on admission to the study, but had at least three menstrual cycles since the last birth. Of the 478 women who entered the study, 46% completed 13 cycles of use. Most (28%) of the women who discontinued did so because they had 2 cycles out of the 26-32 day range.

The 478 women generated 4,035 cycles of data of which 92% had correct method use (i.e., no intercourse on the white bead fertile days of 8-19), 5% of the cycles had intercourse with condoms or withdrawal during the fertile phase, and 3% had intercourse during the fertile phase. Only 43 of the 478 women became pregnant with use of the CycleBead system. Of these 43, 15 conceived outside of the method defined fertile phase. Most (65%) of the pregnancies occurred in cycles in which the participant reported intercourse during the 8-19 day fertile phase. Using life table analysis the Georgetown University researchers were able to calculate a 1- year pregnancy rate of 4.8 (95%; CI 2.33-7.11) with perfect use and a pregnancy rate of 12 (88%; CI 8.74-15.33) with typical use of the method (that involved all cycles and all pregnancies).

The authors concluded that this study demonstrated that the SDM with use of the CycleBead system was an effective method of family planning that is comparable to the male condom and significantly better than other barrier methods. They also concluded that this method is acceptable to couples in a wide range of settings and would be a valuable addition to reproductive health providers and other community services programs.

Comments

Strengths of this prospective effectiveness study were that the researchers recommended guidelines for effectiveness studies and did not include data from cycles

that did not have any intercourse recorded. Further, they enrolled participants in the study when they first began using the system to avoid pregnancy (i.e., they did not have a learning phase with abstinence that typically occurs with NFP effectiveness studies). A potential limitation is that they relied on self-reporting of intercourse and the participants might have under-reported intercourse during the fertile phase. A caveat in interpreting the effectiveness of the SDM based on the study results is that there were monthly follow-ups and contacts of the participants by the health workers. This monthly contact might have increased the correct use of the method. It remains to be seen how effective this method would be without monthly in-person follow-ups.

The results of this study are similar to those of an earlier (2000) study using a fixed day method of fertility and a necklace bead system among the Mayan population in Guatemala.(3) The Guatemala study used a slightly more liberal formula for the fixed days of fertility than the SDM (i.e., day 9-19 instead of day 8-19) and resulted in a typical use pregnancy rate of 11%.

In the early 1980s, the JPH Corporation was selling (for $2) a "pure and simple" Fertility Finder. The Fertility Finder was a small credit card size card that provided the user a simple way of determining the fertile days of a cycle by month of the year. The card indicated that fertility begins on the 10th day of the woman's cycle and ends on the 18th day. The Fertility Finder was to be used for cycles in the 26-33 day range and was based on data from the University of London and reported in a 1969 issue of *Population Studies.*(4) However, there never was a prospective efficacy study of the Fertility Finder. I commend the researchers at Georgetown University Institute for Reproductive Health for doing a careful, well designed and systematic study of the SDM. A multi-site, prospective effectiveness study of a new method of family planning is a very difficult task. I look forward to further findings from this study. (*RJF*)

1. Arevalo, M., Jennings, V. and Sinai, I., **Efficacy of a new method of family planning: the Standard Day Method**, *Contraception* 65 (2002): 333-338.

2. Arevalo, M., Sinai, I. and Jennings, V., **A fixed formula to define the fertile window of the menstrual cycle as the basis of a simple method of Natural Family** Planning, *Contraception* 60 (1999): 357-60.

3. Burkhart, M. C., de Mazariegos, L., Salazar, S. and Lamprecht, V. M., **Effectiveness of a standard-rule method of calendar rhythm among Mayan couples in Guatemala**, *International Family Planning Perspectives* 26 (August, 2000): 131-136.

4. James, W. H., **The mathematics of the menstrual cycle**, *Population Studies* 22 (November, 1968): 409-413.

Personal Home Monitoring of Fertility Received Positive Evaluation

Acceptability of a method of family planning and in particular natural family planning is an important dimension to assess and evaluate. The developers of Persona (Unipath, Ltd.) a hand held urinary hormone monitoring device, were interested in the acceptability of this new technology for home fertility monitoring and as a means of naturally avoiding pregnancy. Researchers from the department of psychology at the University of Florida recently reported on the acceptability of the use of the Persona in a longitudinal study.(1) The authors of the study held the position that one method of family planning or NFP does not fit all. They wanted to find those couples who would be best suited for personal home monitoring using the Persona monitor, to determine to what extent participants would accept home monitoring of fertility, and how that acceptability might change over time.

Six hundred eighty English women participated in efficacy trials of the Persona monitor. The monitor measures metabolites of urinary estrogen and LH. It provides the user with a green light that indicates low fertility and a red light that indicates high fertility. The 680 participants were recruited through press advertising. They had to be willing to avoid pregnancy for at least 15 months and to be accepting of an unplanned pregnancy. The participants were between the ages of 18-45 years, had menstrual cycles between 23 and 35 days in length, were sexually active, had not used hormonal contraception for at least three menstrual cycles and had experienced at least three menstrual cycles after a pregnancy. The women were provided the Persona monitors without training and were asked to use them for 1 year.

Acceptability was conceptualized for this study as perception of accuracy and trust. Accuracy was measured on a 1-7 scale with 1= *inaccurate* and 7 = *accurate*. Perception of accuracy was asked of both the green light (infertile) and the red light (fertile) days that were provided by the home monitors. Trust in the monitor was evaluated with a 101 point scale with 0 = *no trust* and 100 = *complete trust*. The researchers also assessed contextual measures, i.e., women's education, number of children, and length of relationship as predictors of acceptability. Acceptability data were collected at the end of menstrual cycle 1, 3, 6, and 13. At cycle 1, there were 680 women participants, at cycle 3, 603 participants, at cycle 6, 480 participants, and by cycle 13, only 250 participants who provided data.

Acceptability - perceived accuracy: The mean perceived accuracy of the red (fertile) and green (infertile) light days ranged from 5.25 to 6.30 on a 7-point scale. On average the mean perceived accuracy was consistently higher for the green days than the red days. The authors indicated that people are usually more critical when they are told they cannot do something (i.e., have intercourse if they are avoiding pregnancy) then when they may proceed as desired. Based on paired *t*-test analysis, the participants perceived the accuracy of the red light days to be significantly higher at cycle 6 (M = 5.64) than at cycle 1 (M = 5.29) ($t = 3.71$, $p < 0.005$) and the accuracy of the green light days to be marginally statistically higher at cycle 6 (M = 6.09) than at cycle 1 (M = 5.95) ($t = 1.82$, $p = 0.07$). Therefore, perceived accuracy in home monitoring with the Persona monitor increased over time.

Acceptability – perceived trust

Overall trust in the Persona monitor was high. The mean trust scores ranged from 87.35 to 94.23 on a scale of 0-100. The mean trust scores also significantly increased from cycle 1 (M = 87.35) to cycle 6 (M = 91.74) ($t = 6.17$, $p < 0.005$). Therefore, trust in the use of the Persona for avoiding pregnancy also increased over time.

Acceptability – contextual variables: Based on regression analysis, the researchers determined that the number of years in relationship, the number of children, and the education level of the participants influenced trust over time. Those participants who lived with their partners longer reported significantly higher trust than those who lived with their partners for shorter periods ($t = 2.21$, $p < 0.03$). Those who had less education developed more trust in the monitor over time than those who had more education ($t = -1.98$, $p < 0.05$) and the more children the participants had the more they developed trust in the monitor ($t = 1.94$, $p = 0.05$). In addition, the less educated participants rated the monitor more accurate than the more educated and those in longer relationship rated the monitor more accurate than those in shorter relationships. Another finding was that women that did not have children or did not want any children and those women with an already large family (i.e., 4 or more children) were the least likely to be positive about the monitor or to report an increase in acceptability.

Comments

The authors concluded that the participants, in terms of initial acceptability of the Persona monitor, were very positive and that acceptability (i.e., perceived accuracy and trust) became more positive over time. Those women in stable unions, less education,

and 1-3 children rated the use of the monitor more positively and their ratings of acceptability increased over time. The authors speculated that those in new relationships were still in the discovery mode and in the process of reassuring themselves that the relationships will last. The authors did not indicate whether these relationships were marital unions or not. They also speculated that the more educated participants needed more evidence to be convinced of accuracy than those who were less educated – i.e., they reserved their judgments until more evidence of the monitors success in helping them to avoid was in.

The authors also felt that the women who had no children or wanted no children and those who had 4 or more children probably were more adamant in not wanting more children than those with 1-3 children. NFP experts have called these categories of users "limiters" and "spacers" respectively. The authors ended by saying that the use of personal hormone monitoring for avoiding pregnancy seems to be an attractive alternative for NFP especially for those with religious or personal preferences opposed to other forms of family planning.

The fact that 430 women participants discontinued the use of the monitor by the 13th cycle is also an indication of acceptability. Some wished to achieve a pregnancy. I wondered how many of participants were in marital relationships and how many were not. I would think that a marriage would provide more stability to a relationship and thus yield more trust. The fact that the participants were not instructed in the use of the monitor or provided any NFP fertility teaching did result in an unbiased group of participants. It would be interesting to repeat such a study within the context of an NFP program that includes an introduction and follow-up. It is commendable that this was a longitudinal study. Persona users were followed and assessed over time and on the variables of trust and accuracy. Longitudinal studies like this need to be conducted on the current methods of NFP and especially in comparing different methods of NFP. It is especially important to compare psychological variables among the different systems of NFP. NFP researchers also need to determine which NFP methods are more acceptable to specific types of users. As the University of Florida researchers indicated, the choice of a family planning method is not a simple matter and there is no single method of family planning that is best for everyone. (*RJF*)

1. Severy, L. H., Klein, C. T. and McNulty, J., **Acceptability of personal hormone monitoring for contraception: longitudinal and contextual variables**, *The Journal of Social Psychology* 142 (2002): 87-96.

Menstrual Cycle

Researchers Find Hormonal Variability Among Normal Menstrual Cycles

Researchers at the University of Chile Center for Natural Family Planning (Santiago, Chile) conducted a prospective case series study of 25 women in order to evaluate hormone profiles of normal menstrual cycles.(1) All 25 were experienced NFP users (i.e., they monitored cervical-vaginal fluid and basal body temperature), aged 24-37 years (mean age 30 years), had regular menstrual cycles of 25 to 35 days in length in the previous 6 cycles, and had not used any hormonal contraception in the previous 6 cycles. They collected early morning urine samples each day of the cycle for 3 or more cycles and generated 78 complete cycles of data. The early morning urine samples were frozen and analyzed by the University researchers for estrone glucuronide, LH, and pregnanediol glucuronide through noncompetitive radio-immunoassay methods.

The 78 cycles in the data set had a mean length of 28 days (range 23-35 days), with a follicular phase mean length of 16 days (range 11-24 days), and a mean luteal phase length of 13 days (range 10-17 days). Although the 78 cycles produced a classic mean hormonal value curve for the 3 hormones measured, only 23% of the cycles in the data set presented hormonal profiles similar to that classic curve. In 69% of cycles, the estrone glucuronide curve was similar to the mean curve and in 44% of the cycles the LH curve was similar to the mean curve. The estrone and LH peaks were not always easy to determine, some lasted more than one day or fluctuated with double or small peaks. The researchers found pre-peak estrone glucuronide surges, and pre and post-peak LH surges. The pregnanediol glucuronide, however, increased more clearly and in only 6% of the cycles did the pergnanediol fluctuate by more than one day.

The authors concluded that normal menstrual cycle hormonal profiles often differ from the classic mean hormonal curves. They also suggested that the addition of adding pregnanediol glucuronide would make ovulation detection kits based on urinary estrone and LH more reliable.

Comments

This study had some limitations in that there was no concurrent verification of the estimated day of ovulation through serial sonographic measurement of the developing follicle. Nor did the researchers validate the urinary hormone levels with blood levels. The urinary measures, with home collection, freezing, thawing, dilutions and timing

could have resulted in some of the variability in the findings. The results do show that even with healthy women, with regular menstrual cycles, there can be a lot of hormonal variability between cycles. This means that one cycle of hormonal data does not predict what the next cycle will look like. (*RJF*)

1. Alliende, M. E., **Mean versus individual hormonal profiles in the menstrual cycle**, *Fertility and Sterility* 78 (July, 2002): 90-95.

Progesterone Levels Found to be Adequate Among Women With Polycystic Ovaries

Researchers from the Department of Reproductive Science and Medicine at the Imperial College of Medicine (London, England) recently reported a study that investigated the frequency of ovulation and patterns of luteal phase progesterone secretion among women with polycystic ovaries (PCO) and who reported having regular cycles. Participants for the study were recruited from a single out-patient clinic and placed into one of three groups: 1) women (N=10; mean age 34) who presented with infertility, who reported to have regular cycles (i.e., cycles that varied less than 4 days in consecutive cycles) and who had PCO confirmed by ultrasound; 2) women (N=10; mean age 34) who presented with infertility, had regular cycles, and normal ovaries, and 3) a control group of women (N=6; mean age 33) with regular cycles, normal ovaries and proven fertility. The participants collected early morning urine samples from day 10 of their cycles until the next menses. The samples were analyzed by the researchers for pregnanediol-3-glucuronide (P-3-G). The PCO participants produced 29 cycles of data, the infertile normal ovaries group 30 cycles, and the participants with normal fertility 19 cycles of data.

The researchers found that the length of the cycles from each group varied considerably more than expected. The PCO group had a mean cycle length of 28 days (range 23-47 days), the infertile group with normal ovaries had a mean cycle length of 26 days (range 21-36 days), and the normal fertility group's mean cycle length was 27 days (range 25-38 days). The PCO women and the infertile normal ovary women had a higher proportion of short cycles with 6 out of 30 cycles for the PCO group and 5 out of 30 cycles for the infertile group lasting less than 25 days in length. Comparison of mean P-3-G levels among the three groups revealed that the early luteal phase values were significantly higher in the women with normal fertility but that there were no significant differences in progesterone levels in the late luteal phase. The researchers found that there was greater variability in the P-3-G levels among the PCO and infertile normal-

ovary group than with the women with normal ovaries and normal fertility. They concluded that women with PCO did not have more variability of cycle length than women with normal fertility and normal ovaries but they did have significantly lower levels of progesterone in the early luteal phase. They indicated that this lower level might contribute to a delay in conception among women with PCO.

Comments: According to the authors of this study, approximately 20% of women in the normal population have PCO. However, their study suggested "that in the majority of patients, impaired fertility in ovulatory women with PCO is not primarily due to inadequate progesterone production."

The authors also concluded, based on their findings (with a significant number of short and long cycles), that normal cycle length should be considered to be between 21 and 35 days. I would caution that this conclusion is based on 78 cycles of data, of which only 19 were from women of normal fertility. (*RJF*)

1. Joseph-Horn, R., Mason, H., Batty, S. et al., **Luteal phase progesterone excretion in ovulatory women with polycystic ovaries**, *Human Reproduction*. 17 (2002): 1459-1463.

Contraception

Noncompliance and a Novel Method of Contraception

Researchers at the University of Edinburgh Center for Reproductive Biology designed a prospective cohort study to determine and compare the incidence of non-compliance as measured by use of a home fertility monitor with self-reported compliance while using a new method of contraception. The "new" method of contraception was the use of a single dose of mifepristone. Mifepristone (RU-486) is a synthetic steroid that blocks receptors for progesterone and prevents pregnancy by blocking nidation.

Thirty-two sexually active women (age range 18-39 years) were provided a home use fertility monitor that detected estrone-3-glucuronide and LH. They were also given a monthly dose of 200 mg of mifepristone. The fertility monitor automatically records when a urine test is made and can be downloaded by the researcher into a computer for analysis. The participants were asked to take the mifepreistone on day LH+2, or, the first day of the "high" reading on the monitor plus 2 days. The researchers found that the women participants failed to perform 24.2% of the required tests in the 162 cycles that were analyzed. They also failed to make a test in 42% of what was called the critical

time of the cycle (i.e., the day an LH was likely to occur to the day it actually occurred by history) while they reported missing only 14.8% of the required tests. Poor compliance was found among younger women and women who used a method of contraception other than mifepristone. The authors concluded that the use of the microelectronic fertility monitor helped to improve understanding of compliance with contraception.

Comments

This research study shows that reported compliance with behaviors that are necessary for family planning are not necessarily the same as the actual behaviors. People tend to want to report to health professionals and others in authority (e.g., NFP teachers) the behavior the health professional wants to hear. However, this tendency will also be modified by the trust developed by the health professional and the client. The researchers called for the development of "no-fault" approaches to client non-compliance behavior rather than impose upon them a protocol or prescription.

Please note that the use of mifepristone as described in their research protocol does not prevent conception as is implied by the authors of the study. Mifepristone prevents pregnancy by preventing the implantation of the developing embryo, in other words, this is an early abortion drug. (*RJF*)

1. Hapangama, D. K., Glasier, A. F. and Baird, D. T., **Noncompliance among a group of women using a novel method of contraception**, *Fertility and Sterility* 76 (2001): 1196-1201.

Under the Microscope

Oral Contraceptives, Hormone Replacement Therapy, Breastfeeding and the Risk of Breast Cancer

Three studies that reported on the risk of breast cancer in 3 highly respected medical journals recently received wide media coverage. (1-3) One study showed there was no significant risk of breast cancer among users of oral contraceptives. (1) Another study was halted because of the increased risk of using a combined form of estrogen plus progestin for hormonal replacement. (2) The third study showed that both breast feeding and childbearing significantly lowered the risk of breast cancer. (3) These three studies are briefly reviewed below.

Breast Cancer and Oral Contraceptives

A pooled analysis of 54 studies on the relative risk of breast cancer among women who were currently using oral contraceptives was reported in a 1996 article in the medical journal *Lancet*.(4) The study showed a 24% increased risk of breast cancer among users and former users of oral contraceptives as compared to women who never used oral contraceptives. However, many of the studies in this article are old and the data was pooled – i.e., came from many studies. New evidence was needed to validate this risk and to determine if it existed among the large numbers of women who took oral contraceptives at an early age and are now reaching the age in which breast cancer is the highest. Therefore, a research group that was coordinated through the Centers for Disease Control and Prevention conducted what is called the National Institute of Child Health and Human Development Women's Contraceptive and Reproductive Experiences (Women's CARE) Study to determine if the use of oral contraceptives was a risk factor for breast cancer in women who were 35 to 64 years old.

The study was a large population-based case control investigation that enrolled eligible women participants from centers in Atlanta, Detroit, Philadelphia, Los Angeles, and Seattle. Participants were 35 to 64 years old and had an initial diagnosis of invasive breast cancer between 1994 and 1998. A total of 5,982 eligible women were selected and 76% (4575) were interviewed. The control group consisted of women who did not have a diagnosis of invasive breast cancer. They were selected from the same geographic location as the breast cancer group by use of a random digit dialing process and were matched (on age and race) with the breast cancer group. Of the 5,956 eligible controls selected, 79% (4682) were included in the study. All of the participants were interviewed to determine if they used or had used oral contraceptives in the past, the type of oral contraceptive used, length of use, and multiple demographics.

Results

Seventy–seven percent of the breast cancer group and 79% of the control group participants had used some type of oral contraceptive. The relative risk of breast cancer among women who ever had used oral contraceptives as compared to those women who had never used oral contraceptives was 0.9 (95% CI, 0.8 to 1.0)- i.e., there essentially was no demonstrated risk. The relative risk of breast cancer was 1.0 (95% CI; 0.8 – 1.3) for women who were currently using oral contraceptives and 0.9 (95% CI; 0.8 to 1.0) for those who previously had used oral contraceptives, i.e., again no risk. The risk of breast cancer did not increase with longer periods of use or with higher dose formulation of estrogen. The researchers also did not find an increased risk with initiation of oral

contraceptives at a young age, duration of use before the first term pregnancy, or among those who had a family history of breast cancer.

The authors concluded that for women between the ages of 35 to 64 years, current or former use of oral contraceptives was not associated with an increased risk of invasive breast cancer. They also emphasized that their study provided strong evidence that former oral contraceptive use does not increase the risk of breast cancer later in life when the incidence of breast cancer is the highest.

Analysis

I first heard about this study listening to the evening news. The announcer excitingly stated that this was "the definitive" study on the risk of breast cancer and the use of oral contraceptives. After reading the study, I was not at all convinced that this was the definitive study, or that there was little or no risk of breast cancer among current and ever users of oral contraceptives. The following are my reasons for not being convinced that the authors produced the definitive results.

One of the most obvious flaws in the study is that the comparison group of women without the diagnosis of breast cancer is not from the same pool of subjects that the breast cancer group came from. Although the researchers tried to match the participants (on race and age) though a randomized case-control method, in my opinion they did not reach that goal. The women participants in the invasive cancer group compared to the case control group women differed significantly on 7 different variables, including age at menopause, age at first term pregnancy, number of term pregnancies, family history of breast cancer, and current or past use of hormone replacement therapy. All of these variables could influence the rate of invasive breast cancer. Furthermore, the researchers did not measure use or duration of breastfeeding among the participants. As will be seen in the third study reviewed below, breastfeeding can significantly reduce relative risk for breast cancer.

The researchers did not use a strong design to detect the comparable rates of breast cancer. Instead of investigating the differences in the rate of invasive breast cancer between groups of women who never used oral contraceptives versus women who did use oral contraceptives prospectively, they looked at the rates between those women who had invasive breast cancer and those who did not retrospectively (i.e., from past history). Both groups had a similar rate of use or non-use of oral contraceptives. Previous studies that detected an increased rate of breast cancer among oral contraceptive users did so by comparing women who never used oral contraceptive with those that had a history of

use.(4) The researchers of this study admit that while they had a 65% response rate with the control group of non-invasive cancer participants, they do not know how these women differed from those who responded and thus could be a potential source of bias. Finally, much of the data collected was from recall. The researchers did not validate the use or non-use of contraception nor the type or amounts or lengths of use. Recall data could and often is a source of error.

Hormonal Replacement and Breast Cancer

A study that received even more press than the oral contraceptive study was the Women's Health Initiative's (WHI) randomized control trial of estrogen plus progestin in healthy postmenopausal women. This study received cover story status in both the July 14-20th, 2002 *Newsweek* and *Time* magazines. The study deserved cover story status because of the magnitude of the findings and because the prospective randomized control group design is one of the strongest research designs that can be used to detect differences and cause and effect.

This study was sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health and involved the recruitment of 373,002 women with intact uteruses between the ages of 50 and 79 from 40 participating clinical centers throughout the United States. Of these women, 18,845 provided consent and reported no hysterectomy, but 2,237 women were excluded due to compliance risks (e.g., alcoholism, dementia) and serious health risks. The remaining 16,608 women participants were randomized into a placebo group (N= 8,102) or a treatment group that received a daily dose of 0.625 of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate. The participants were enrolled in the study from 1993 through 1998. The objective of the study was to examine the effect of estrogen plus progestin on the prevention of heart disease and hip fractures, and any associated change in risk for breast and colon cancer.

The initial intent of the research group was to continue the study until 2005, but the study was halted on May 31, 2002 due to the increased risk of breast cancer. The specific findings for the estrogen plus progestine group compared to the placebo group include:

- A 41 percent increase in strokes
- A 29 percent increase in heart attacks
- A doubling of rates of venous thromboembolism
- A 22 percent increase in total cardiovascular disease

- A 26 percent increase in breast cancer
- A 37 percent reduction in cases of colorectal cancer
- A one-third reduction in hip fracture rates
- A 24 percent reduction in total fractures
- No difference in total mortality

According to Jacques Rossouw, MD (the acting director of the WHI), these results translate into a relatively small risk for the individual woman (http://www.nlm.nih.gov/databases/alerts/estrogen_progestin.html). For example, during a 1 year period, among 10,000 postmenopausal women with an intact uterus who are taking daily estrogen plus progestin, 8 more will have invasive breast cancer, 7 more will have a heart attack, 8 more will have a stroke, and 18 more will have blood clots than a similar group of women who do not take hormone replacements. However, he also indicated that with approximately 6 million women taking estrogen plus progestin replacements across the United States, this could add up to tens of thousands of serious health cases in a one year period.

The authors of this study concluded that the risks of taking estrogen plus progestins as replacement therapy among healthy women with uteruses for an average of 5.2 years exceeded the benefits. Furthermore, the risks of taking these hormonal replacements is not consistent with the requirements for a viable intervention for main prevention of primary disease. The results indicate that this therapy should not be initiated or continued for primary prevention of coronary heart disease.

Analysis: The authors reported that the results of this study do not necessarily apply to lower dosages of these drugs, or to other formulations of estrogen and progestin, nor to other routes of administration of these hormones, e.g., through a transdermal patch. They also mention that this study could not distinguish the effects of estrogen from progestin. The results only apply to the combination of the two. There is a concomitant study that the WHI group is conducting with 10,739 women who had a hysterectomy to determine if oral estrogen (alone) will prevent coronary heart disease. The authors did mention that the relatively high rate of discontinuation in the treatment group (42%) and a cross over to active treatment in the placebo group (10.7%) are a limitation to the study. They mentioned that the result of this limitation may underestimate the magnitude of both the adverse effects on coronary heart disease and invasive breast cancer.

Breast Cancer and Breastfeeding

The Collaborative Group on Hormonal Factors in Breast Cancer (from the United Kingdom) recently reported a study that can shed further light on the development of breast cancer and the increasing rates of this cancer in developing countries. The United Kingdom Cancer Research group wanted to determine the contribution that breastfeeding had on the protective effect against breast cancer. They also intended to differentiate this effect (if any) from the known protective effect that childbearing has on breast cancer. The UK research group collected individual data from 47 epidemiological studies on breast cancer and breastfeeding from 30 different countries. These studies resulted in a data set of 50,302 women with breast cancer and a control group of 96,973 women without the disease. Among the women with breast cancer the average age at diagnosis was 50.1 years. The breast cancer group on average had fewer births than the control (2.2 *vs* 2.6), a greater portion never had children (16% vs 14%), and a lesser portion of the breast cancer group had never breastfed (71% vs 79%). One of the objectives of the study was to differentiate the relative protective effect of breastfeeding as opposed to childbearing.

Breast cancer in relation to childbearing in women who never breastfed

There were 12,214 (29%) women in the breast cancer group and 16,900 (21%) control cases that had never breastfed. The results showed that the younger a woman began childbearing the lower was the relative risk for breast cancer. The relative risk declined by about 3% for every year younger a woman was when her first child was born. The relative risk also decreased with the number of births that a woman had at a rate of 7% per birth.

Breast cancer in relation to breastfeeding

The relative risk of breast cancer declined with increasing parity in women who had ever breastfed. The relative risk of breast cancer declined by 3.4% for each child that was breastfed. Furthermore, the relative risk of breast cancer declined with the increasing duration of breastfeeding. The relative risk declined by 4.5% with 12 months of breastfeeding.

The authors calculated that the incidence of breast cancer in developing countries could be reduced by 42% solely by breastfeeding and increasing the duration of breastfeeding. In the United States (which has one of the highest rates of breast cancer) the portion of childbearing women who had ever breastfed is only around 50%. Whereas

in Japan and in developing countries more than 90% of childbearing women breastfeed their infants. The authors also estimated that the incidence of breast cancer could be reduced by half if women in developed countries had the average number of children and duration of breastfeeding that was prevalent in developing countries until recently.

Analysis

The authors admitted that the reporting of the duration of breastfeeding is not precise with women having a tendency to round up to the nearest 6 months. They felt, however, that this would lead to an underestimation of the true protective effect of breastfeeding. The authors also said out that there was no differentiation between exclusive breastfeeding and breastfeeding with supplements. They recommended that future studies measure the length of breastfeeding with more precision and differentiate between total breastfeeding and breastfeeding with supplements. The authors are aware that it might be unrealistic for women in today's modern society to return to childbearing and breastfeeding patterns that were characteristic a century ago.

Overall analysis of the three studies on breast cancer risk

Of the three studies reviewed by far the best is the hormone replacement study that utilized a randomized treatment versus control group (placebo) design. That study had a prospective design, a large group of subjects and was able to detect significant differences and relative risk. The breastfeeding study, by pooling individual data from many studies was able to have a very large data set that allowed the researchers to determine relative risk and show that there is a good likelihood that the increased incidence of breast cancer in modern developed countries is likely a result of decreasing parity, delayed child birth, and lack of breastfeeding. I believe that the jury is still out on the relative risk of oral contraceptive use and breast cancer. I found the weakest of the three studies to be the NEJM study on the risk of breast cancer and oral contraception. I do not see how the authors can claim that they had matched the two groups of participants when they differed significantly on 7 different variables. The authors also failed to determine breastfeeding patterns and the history of abortion. One has to wonder why the WHI researchers were able to find an increased risk of breast cancer among women who use a combination of estrogen and progestins for hormonal replacement, but the Women's CARE study researchers were not able to find an increased risk when higher levels of estrogen and progestins are used for contraception. Nobody seems to provide an explanation for this contradiction or to even mention that there is a contradiction.

The Kaiser Daily Reproductive Report (3/26/2002) recently reported a study in which 103,027 women between the ages of 30 and 49 were followed by researchers for the development of breast cancer from 1991-1992 to December, 1999. They found that women who reported using oral contraceptives at some time during that period of time had a 26% greater risk of developing breast cancer than women who never used birth control pills. The risk increased to 58% for women who used oral contraceptives for the duration of the study. This study, unlike the Women's CARE study was prospective (over time) and compared users of oral contraception with non-users. This was a much stronger designed study (than the NEJM oral contraceptive use and risk for breast cancer study) and as a result yielded increased risk with use of oral contraceptives. I am looking forward to seeing the study reported in a peer reviewed journal so that it can receive further scrutiny and coverage.

1. Marchbanks, P. A., McDonald, J. A. and Wilson, H. G. et al., **Oral contraceptives and the risk of breast cancer**, *The New England Journal of Medicine* 346 (2002): 2025-2032.

2. Writing Group for the Women's Health Initiative, **Risks and benefits of estrogen plus progestin in healthy postmenopausal women**, *Journal of the American Medical Association*, 288 (2002): 321-333.

3. Collaborative Group on Hormonal Factors in Breast Cancer, **Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease**, *Lancet* 360 (2002): 187-195.

4. Collaborative Group on Hormonal Factors in Breast Center, **Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies**, *Lancet* 347 (1996): 1713-27.