*In this issue*

**In Depth: Use of Natural Family Planning After Early Pregnancy Loss**

# Natural Family Planning

**What Are Modern Methods of Natural Family Planning?**

A series of articles recently appeared in the journal *Global Health: Science and Practice* addressing the issue as to whether or not fertility awareness methods (FAMs) were modern methods of family planning. The debate was stimulated by a commentary from members of the United States Agency for International Development's (USAID) Office of Population and Reproductive Health defending the opinion that FAMs were modern methods of family planning (Malarcher, Spieler, Fabic, Jordan, Starbird, and Kenon  2016A). The concern for this position came from recent publications that classified FAMs as traditional, along with the Rhythm Method and withdrawal, rather than modern methods of family planning. The USAID authors objected to this label for FAMs and described recent research and development of LAMS, i.e., the Lactational Amenorrhea Method (LAM), the Standard Days Method (SDM), and the Two Day Method (TDM). LAM is a breastfeeding protocol method, the SDM is a fixed calendar based method, and the TDM is a simple mucus based FAM system. All three methods are very simple to learn and teach. In addition, their effectiveness studies have been conducted in multiple developing countries. Much of the research in the development of these FAMs was funded by USAID.

The USAID authors provided criteria as to what they believe makes a contraceptive method modern.  These criteria are as follows:

- Effective at pregnancy prevention;
- Safe;
- Based on a sound understanding of reproductive biology;
- Include a defined protocol for correct use; and
- Have been tested in appropriately designed studies to assess effectiveness under various conditions.

The authors also mentioned a number of positive characteristics that modern FAMs provide, including:

- FAMs do not require clinical intervention, such as hormones, devices or procedures;
- FAMs are controlled by a woman and her partner;
- FAMs increase a woman's understanding of her fertility and biological processes;
- In the case of SDM and TDM, they provide the opportunity to facilitate pregnancy planning; and
- FAMs can be offered through a wide variety of channels, including settings completely outside the healthcare system.

The authors also pointed out that teaching FAMs to women provides the opportunity for fertility health teaching and discussing relationship dynamics with the woman user and her male partner. FAM providers often teach couples and not just the woman.

Soon after the article from the USAID, there was a rebuttal as to why FAMs are not modern methods of family planning (Austad, Chary, and Colom et al., 2016). These authors pointed out that the newer long acting reversible contraceptives (i.e., LARCs = hormonal implants and IUDs) are a lot more effective with typical use at around 99% compared to 85-88% with SDM or TDM. They also highlighted the World Health Organization ranking of contraceptive methods, which placed FAMs on the lower rung as a traditional method. They postulated that LARCs are a means to a rights-based approach since in the global system poor women need a secure method of family planning. They insist that a "secure method" is necessary due to the global need to lower abortion rates (even though research does not support this claim), and as a protective means to help manage violence against women (especially adolescents) who are at risk of becoming sex slaves and victims of rape. They also felt that the technical advances of LARCs overcome biology and enable couples to have sexual intercourse anytime they want. They said there is a need for health professionals to provide direction in the choice of contraceptive methods and that offering a less effective method is like a physician suggesting the use of a less effective medicine to treat illness.

The USAID authors then responded in another article by writing that family planning programs should be based on helping women choose the method that they want and not based on what the health provider or the health system wants (Malarcher, Fabic, Spieler, Starbird, and Kenon 2016B). They mentioned that there are many women and couples who would prefer to not have a medical or hormonal method. The responding authors also pointed out that the criteria for contraceptives having to "overcome biology" and "enable couples to have intercourse anytime" would require medical intervention. They then asserted that many women discontinue hormonal methods within six months of use due to dissatisfaction. They also provided a comparison of contraceptive methods and pointed out positive aspects of FAMs (e.g., they do not require surgical procedures, do not require use of powerful reproductive hormones, have both male and female control, and provide the woman user the ability to discontinue the method without needing a provider).

*Comments*

I agree that FAMs are modern in the sense that LAM, SDM, and TDM have been recently developed and have evidence for effectiveness among diverse populations. Unfortunately, contraceptive researchers, especially the LARC authors discussed above, typically define modern family planning methods as those that *overcome* human fertility. In that sense, FAM and NFP methods are "not modern" because they don't meet their requirements.

FAM and Natural Family Planning (NFP) methods are designed to work with and understand human biological fertility, not to overcome it. This approach is completely different from contraception which, by its very name, means to go against or overcome human biology. Family planning researchers begin this contraceptive mindset to manipulate and even suppress human fertility. They typically compare contraceptives to contraceptives.

FAMs, although a subset of Natural Family Planning (NFP), has typically included the option of using contraceptive methods (e.g., barriers such as condoms) during the estimated fertile phase of the menstrual cycle. That, of course is not NFP. As a method of family planning, FAM can be seen as unusual, even confusing to contraceptive researchers because it *combines* methods that are natural with artificial methods.

NFP educators and promoters understand that NFP methods are not contraceptive. NFP methodology does not try to overcome biology. Rather, NFP tries to understand and monitor reproductive biology and teaches couples how to live with their gift of fertility. NFP is authentic family planning. A discussion between NFP leaders and family planning researchers is needed to discern what methods of NFP are modern and by what criteria makes them modern.

Austad, K., A. Chary, A. Colom, R. Barillas, D. Luna, C. Menjívar, B. Metz, A. Petrocy, A. Ruch, and P. Rohloff. 2016. **Fertility awareness methods are not modern contraceptives: defining contraception to reflect our priorities**. *Global Health: Science Practice* 27;4 (2): 342-345.

Malarcher, S., J. Spieler, M. S. Fabic, S. Jordan, E. H. Starbird, and C. Kenon. 2016A. **Fertility awareness methods: distinctive modern contraceptives**. *Global Health: Science and Practice* 25;4 (1): 13-15.

Malarcher, S., M. S. Fabic, J. Spieler, E. H. Starbird, C. Kenon, S. Jordan. 2016B. **Response to Austad: Offering a range of methods, including fertility awareness methods, facilitates method choice**. *Global Health: Science and Practice* 27;4 (2): 346-349.

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**Effectiveness of Extended Use of an Online Natural Family Planning Program Using a Fertility Monitor**

*Reviewed by Kathleen Raviele, M.D.*

This is the twelfth paper published in peer-reviewed medical literature since 2007 by the investigators of the Marquette Method of Natural Family Planning (NFP). This study's goal was to test the long-term (24 months) effectiveness of the online version of this method. This was a prospective study involving 663 non-breastfeeding women, a subset of 1,530 participants. Enrollees signed up online through an online discussion forum for NFP healthcare professionals and by word of mouth. Participants used the website charting system for the online Marquette

Method after enrollment in the study. A pilot study on the effectiveness of teaching this program online to avoid pregnancy was published in 2011 and was followed by a randomized comparison study in 2015 comparing the use of an electronic hormonal fertility monitor with cervical mucus observations. The pilot study demonstrated the online program to be as effective as teaching in person and the second study showed the monitor with an algorithm was more effective at avoiding pregnancy than use of cervical mucus observations.

The website (http://nfp.marquette.edu) provides the woman and couple with all the information they need to use the method, as well as charting which automatically calculates the fertile window. Participants could use the fertility monitor alone, with an algorithm, cervical mucus observations alone, or mucus plus the monitor. For the study, nurses were available for questions, registrants had access to an online discussion forum, and a bioethicist and obstetrician gynecologist knowledgeable about NFP were available for questions. Especially helpful is a one-page Quick Start instruction that allows the couple to begin using the method immediately as long as the first day of the last period is known. Because the fertile window is automatically calculated, there is no learning curve for the couple's interpretation of the chart. If a pregnancy occurred, an online pregnancy evaluation was completed and evaluated by two NFP teachers.

Participants in the study were primarily Catholic (93%), college graduates (93%) and Euro-American (85%) from all 50 states and 5 foreign countries. Pregnancy rates were calculated based on survival analysis (Kaplan-Meier). Correct use unintended pregnancy was determined if there were no act of intercourse recorded on the chart during the fertile window. The rate was calculated based on 100 women per 12 and 24 cycles of use. The typical or total use unintended pregnancy rate was calculated with all charted cycles, both correct cycles of use and incorrect or inconsistent cycles of use.

The study with a total of 1,530 participants resulted in a gross correct use unintended pregnancy rate of 2.5 per 100 users at 12 cycles of use and 3.4 per 100 users at 24 cycles of use. The typical pregnancy rate was 12.6 per 100 users at 12 cycles and 23.8 users at 24 months per 100 users of the method. The correct use unintended pregnancy rate for the 663 non-breastfeeding women, of whom 9.9% had cycles longer than 35 days, was 1.6 per 100 women at both 12 and 24 months of use. They found that the electronic fertility monitor, using an algorithm for the beginning of the fertile window, had the lowest unintended pregnancy rate when comparing it with the observation of cervical mucus alone, and also with the use of the monitor plus cervical mucus identifying the beginning of the fertile window. The typical unintended pregnancy rate was 2 per 100 at 12 months for the monitor alone group and 6 at 24 months; for the mucus only group it was 19 at 24 months and for the mucus and monitor group it was 18 at 24 months. The number of cycles in the study was 1,681 for the monitor only subgroup, 481 for the mucus only subgroup and 3,086 for the monitor and mucus subgroup. This study showed that an online teaching program is effective in transmitting the basic information and providing a guide for the couple to understand their fertility immediately upon beginning to chart NFP.

*Comments*

The main limitations of the study are: the expense of purchasing the monitor; the ongoing purchase of supplies: couple motivation to avoid pregnancy for 24 months; and the need for nurses to monitor the site daily. That said, this study demonstrates that without personal interaction and extensive time spent teaching a method of NFP, the online teaching program is highly effective both in the short-term and the long-term, particularly using an electronic monitor that measures a woman's estrone and LH levels, with an algorithm.

Other NFP methods have online programs to a certain extent, but they have not studied whether the teaching model is effective. So much of the hindrance in spreading the good news about modern methods of NFP has been the lack of availability of teachers, especially in more rural areas of the country and throughout the world. This program has made that possible for anyone with a computer and the Internet. The program is available in Spanish and English.

The world is moving rapidly forward technologically and the NFP programs have to keep up or they will be deemed old-fashioned and out of date. The better we can identify the exact day of ovulation by hormonal measurements and confirm ovulation has occurred, the more acceptable NFP will be to young couples today. When women come to my medical office and I ask to see their charts, they open their phones where they are charting on some menstrual app. As an aside, the Marquette Institute of NFP has just developed an app for the Smartphone called *Marquette Fertility* available for free through iTunes and Google Android.  *KMR*

Fehring, R. J. and M. Schneider. 2016. **Effectiveness of a natural family planning service program**. *MCN, The American Journal of Maternal Child Nursing* 42 (1): 43-48.

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# Fertility

**Optimizing Natural Fertility**

The Practice Committee of the American Society of Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility recently (2017) published an article that provides guidelines for helping couples with no known fertility problems achieve pregnancy. The findings and recommendations are based on multiple evidence based studies in each area. The following is a summarization of their recommendations and findings.

**Age and Fertility**

- A woman's fertility is more affected by age than for a male.
- A woman in her 30s is about 50% less fertile than when in her 20s.
- A man's fertility does not decrease significantly until in his 50s.

- Most couples (80%), will achieve pregnancy by 6 months of trying.
- A woman's fertility decreases significantly by age 35.
- Earlier assessment and treatment is warranted for a woman who is 35 and has not achieved pregnancy by 6 months of trying.

**Frequency of Intercourse**

- Everyday intercourse yields the greatest probability of pregnancy.
- Every other day intercourse is a close second choice of frequency.
- Every other day is the best for semen quality and quantity.
- Abstinence longer than ten days is detrimental to sperm/semen quality.
- Having intercourse 2-3 times a week is adequate.
- Couples need to establish their own intercourse patterns and reduce the stress of having to "perform."

**The Fertile Window**

- Theoretically the biological fertile window of the menstrual cycle is 6 days, the day of ovulation and the five preceding days.
- Generally the most fertile days of the biological fertile window are the two days before the day of ovulation.
- The days of the fertile window within the menstrual cycle varies from cycle to cycle.
- Frequent intercourse was recommended for assuring that the biological fertile window is not missed.

**Monitoring Ovulation**

- Only 50% of women are able to correctly predict ovulation and the fertile window by monitoring natural fertility symptoms, i.e., cervical mucus changes.
- There is a high probability of pregnancy on peak mucus days.
- For some women use of ovulation predictor kits, i.e., luteinizing hormone monitoring may be helpful.

**Coital Practices**

- There is no evidence that coital practices or coital positions enhances fertility, e.g., remaining quiet on back after intercourse.
- Sperm will be within the cervical canal within seconds during peak fertility and in the fallopian tubes within minutes after an act of intercourse.
- The mature ovarian follicle enhances speed of sperm transport to the side of the mature follicle.
- Some vaginal lubricants decrease fertility based on their effect on sperm.

- It is prudent to use lubricants (when needed) that do not affect fertility (e.g., mineral oil, canola oil, or hydroxyethylcellulose-based lubricants, PreSeed) that have no impact on sperm health.

**Diet and Life Style Factors**

- Other than being very thin or obese as factors that decrease fertility, there is little evidence for dietary patterns that enhance fertility.
- Women attempting pregnancy should be taking a folic acid supplement (at least 400 mcg daily) to reduce risk of neuro tubal defect.
- Smoking reduces fertility by enhancing follicle depletion and is related to an increased risk of miscarriage.
- Evidence for risk of drinking alcohol is mixed, but it is recommended that when attempting pregnancy, no more than two drinks per day should be consumed. When pregnant no alcohol should be consumed.
- One to two cups of coffee per day before or during pregnancy has no detrimental effect on fertility. Some evidence suggests that high levels of consumption of coffee (i.e., greater than five cups per day) decreases fertility.
- Marijuana and other recreational drugs should be avoided as they have a detrimental effect on the developing fetus.
- Environmental pollutants and toxins should be avoided.

*Comments*

I generally agree with the committee's recommendations, but I think that it misses a very important area and, that is, the role in protecting natural fertility. There is no mention of risky sexual practices such as early sexual debut and multiple sexual partners that can lead to obtaining a sexually transmitted disease and damaging fertility. Furthermore, although frequent intercourse (i.e., 2-3 times per week) will provide acts of intercourse during the 6 day fertile window, focusing intercourse on the 2-3 most fertile days requires fertility monitoring. The authors do not mention some randomized studies that found focused intercourse was helpful in achieving pregnancy and decreased the time to pregnancy (Robison, Wakelin, and Ellis 2007; Tiplady, Hones, Campbell, Johnson, and Ledger 2013).

Robinson, J. E., M. Wakelin, and J. E. Ellis. 2007. **Increased pregnancy rate with use of the Clearblue Easy Fertility Monitor**. *Fertility and Sterility* 87 (2): 329-334.

Practice Committee of the American Society for Reproductive Medicine. 2017. **Optimizing natural fertility: A committee opinion**. *Fertility and Sterility*. Published Ahead of Print.

Tiplady, S., G. Jones, M. Campbell, S. Johnson, and W. Ledger. 2013. **Home ovulation tests and stress in women trying to conceive: a randomized controlled trial**. *Human Reproduction* 28 (1): 138-151.

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## Contraception

**Nurses' Health Study Provides Risks and Benefits of Exogenous Reproductive Hormone Use**

The Nurses' Health Study (NHS) was initiated in the early 1970s for the purpose of determining the long-term effects of the use of hormonal contraception among women between 30 and 55 years old. The participants were 230,000 married professional registered nurses. However, by 1983 there were fewer than 500 participants and the data set lost power. In 1984, the Nurses' Health Study II (NHSII) was initiated with younger women between 24 to 44 years old. This new study (besides obtaining more participants) recognized that women were now being prescribed hormonal contraception earlier and there were many newer and lower dose formulations of the synthetic estrogens and progestins in the hormonal pill – over 220 different preparations. Furthermore, women were also being prescribed reproductive hormones for peri-menopause and menopausal symptoms. The NHSII also included new questions about diet and lifestyle. This current study is an extensive review of NHS and NHSII studies for the purpose of understanding the complex relationship between exogenous hormones (oral contraceptive and postmenopausal hormones) and health outcomes in women and in particular cardiovascular disease and cancer (Bhupathiraju, Grodstein, Stampfer, Willett, Hu, and Manson 2016). The authors performed a narrative review of the publications of the NHS and NHSII from 1976 to 2016. The following are findings from their review.

1) Cardiovascular Disease

Current use of OCs is associated with a higher risk of cardiovascular disease (CVD) especially among women with other risk factors like smoking and hypertension. Among young healthy women who are not smoking, the risk of CVD is small enough that use of hormonal contraception remains an option for family planning.

*Comments*

The authors do not say that the studies under review which provide risk data, show that current hormonal contraception users have an 80% higher risk of hypertension and myocardio infarction (MI) and two times the risk of pulmonary embolism. Note, that one study showed a 19 times increase in the relative risk of MI among smokers with hypertension. The authors seemed to dismiss these findings, since the CV disease factors are due to thrombolytic mechanisms and not atherosclerosis and that the risk decreases soon after discontinuation of the hormonal contraceptives. I would also add that many of these young women are on the hormonal contraceptives for a longer time than in the past.

2) Cancer

The NHS studies on the risk of cancer for users of hormonal contraception is mixed. The studies show a greater risk of breast cancer and skin melanoma but a lower risk of ovarian and colorectal cancer.

*Comments*

One NHS study showed a 50% higher risk of invasive breast cancer with current use of OCs, and Triphasics OC users had 3 times the risk of breast cancer compared to women who were not on hormonal contraception. Current hormonal oral contraceptive use showed a 2 times the risk factor for melanoma. In addition, when on the hormonal pill for 10 years or more there is more than a 3 times the risk factor for melanoma compared with women who are not on hormonal contraception. According to the CDC the rates of cancer among women (as of June 2016) are 124 per 100,000 women for breast cancer, 52 per 100,000 for lung cancer, and 37 per 100,000 for colorectal cancer. Ovarian cancer is the 9th most common cancer among women. Invasive melanoma is projected to be the sixth most common cancer for women (34,940 cases) in 2017. See more at: https://www.aad.org/media/stats/conditions/skin-cancer#sthash.5mPaAdRP.dpuf There are far more women being diagnosed with breast and skin cancer compared with ovarian and colorectal cancer. Furthermore, the lower risk identified in the NHS was non-significant at about 16% for ovarian cancer and a lower risk with a greater than 10 years of use of hormonal oral contraception at about 38%.

*Use of Hormones Therapy (HT) among Peri-menopausal Women*

The NHS has been tracking the effects of HT among menopausal women for the past four decades. The following are some of the updated findings.

1) Cardiovascular Disease

Based on the notion that estrogen was protective of heart disease in younger women the early NHS showed an approximate 70% decrease in coronary heart disease and non-fatal myocardio infarction. However, following the Women's Health Initiative, randomized control studies had to be stopped before completion since there were significant increases in stroke and other health problems. The supposed reason for the difference in the studies is that the NHS had younger menopausal women than the Women's Health Initiative studies. Subsequent NHSs showed a higher risk of stroke with current use of estrogen alone or combined with progestins. Another more recent NHS study showed a 2 times the risk of stroke with current use of HT.

2) Cancer

The Nurses Health Studies show that current use of HT has a significant increased risk for breast cancer and that this risk increases with longer use. Long term use of HT also showed an increase risk for ovarian cancer and endometrial cancer.

3) Other Health Problems

Interestingly, other analysis of data from the NHS showed that past and current use of HT is associated with higher rates of cognitive decline in older women, ulcerative colitis, systemic lupus erythematosus, urinary incontinence, gastroesophageal reflux disease, and a lower risk of gout and hip fractures (but only among women with low levels of physical activity).

Based on these findings the authors did not recommend use of HT for managing or preventing chronic health problems, i.e., cardiovascular disease, cancer, and other health problems. They did say that use of HT might be used for treating menopausal symptoms, like hot flashes in younger women. More studies are needed to determine subgroups of women in which HT might be a benefit, for example finding out if younger women who are closer to menopause onset have a more favorable risk-benefit profile than do older women from use of hormone therapy for relief of vasomotor symptoms.

*Comments*

Although a large number of women are included in these studies, the results and findings are not necessarily population based and generalizable. The women in the NHS are professional nurses and thus have a higher degree of health knowledge, education, and less ethnic diversity than women in the US population. Another NHS was initiated in 2010 (i.e., NHS III) with the goal of making this phase of the NHS more diverse; it includes not only professional nurses but also LPNs and male professional nurses.

Although the authors would not recommend use of HT for treating or preventing chronic health problems among menopausal women (except for maybe menopausal symptoms among younger or newly menopausal women), they do not seem to have much concern about use of reproductive hormones for family planning purposes nor about the length of use of these reproductive hormones. I would like to see studies that look at health practices, like exercise, diet, weight loss, sleep patterns, vitamins, etc., on menopausal symptoms in comparison with risky hormones.

Bhupathiraju, S. N., F. Grodstein, M. J. Stampfer, W. C. Willett, F. B. Hu, and J. E. Manson. 2016. **Exogenous hormone use: Oral contraceptives, postmenopausal hormone therapy, and health outcomes in the Nurses' Health Study**. *American Journal of Public Health* 106 (9): 1631-1637.

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# <u>Pregnancy</u>

**Sex Education Programs Found Not to Reduce STDs and Pregnancy Among Adolescents**

An evidence-based analysis of the effects of school-based sexual and reproductive health programs on sexually transmitted infections and pregnancy among adolescents was recently published as a Chochrane review (Mason-Jones, Sinclair, Mathews, Kagee, Hillman, and Lombard 2016). The need for the review was based on the critique that such programs are widely used but evaluations of them are usually based on measuring knowledge and self-reported behaviors (e.g., sexual activity) rather than more objective and relevant measures such as pregnancy and sexually transmitted infections (STIs). The evidence-based review was conducted with an extensive search of online medical search engines, clinical trial registries, and conference presentations. The search included only reports of randomized controlled trials (RCTs) that evaluated school-based sexual education programs. Two review authors independently assessed studies for inclusion and were able to identify eight RCTs that enrolled 55,157 participants. Five trials were conducted in Africa, one in Latin America, and two in Europe (England and Scotland). There were no reports that met the inclusion criteria from the United States. There were six trials that evaluated school-based educational interventions, two trials that evaluated incentive-based programs to promote school attendance, and one trial that evaluated free school uniforms as an intervention.

None of the school-based sexual education programs had a positive effect on the prevalence of HIV, or other STIs (herpes simplex virus prevalence: or syphilis prevalence) and none had any apparent effect on the number of young women who were pregnant. In the two trials that evaluated incentive-based programs to promote school attendance, there was no effect on HIV prevalence. However, in comparison with the controls, the prevalence of herpes simplex virus infection was lower in young adolescent women who received a monthly cash incentive to stay in school (RR 0.30, 95% CI 0.11 to 0.85), but not in young people given free school uniforms. Furthermore, the number of young women who were pregnant at the end of the trial was lower among those who received incentives (RR 0.76, 95% CI 0.58 to 0.99) compared to the controls. The study that evaluated free school uniforms also included a trial arm in which participants received both uniforms and a program of sexual and reproductive education. In this trial arm herpes simplex virus infection was reduced (RR 0.82, 95% CI 0.68 to 0.99) but no effect was detected for HIV or pregnancy.

The authors concluded that little evidence exists that educational curriculum-based programs were effective in improving sexual and reproductive health outcomes for adolescents. However, incentive-based interventions that focus on keeping young people in secondary school may reduce adolescent pregnancy but further trials are needed to confirm this. The authors then

jumped to the conclusion that there is a need to provide contraceptive and condom choices to adolescents, and that schools may be a good place in which to provide these services.

*Comments*

I commend the authors that sought studies that had more objective and relevant outcomes of STDs and pregnancy rather than knowledge for evaluating sexual education programs. I was surprised that there were none conducted in the United States that utilized RCTs. The authors did not analyze the mode of delivery and content of the sexual education programs, e.g. if the programs were contraceptive-based or chastity-based. As such, this begs the question as to whether the sexual education programs in question actually promote the notion that sexual activity outside of marriage is normative and that what is required for "safe sex" is the knowledge of contraception to prevent pregnancy and use of condoms to prevent STDs. The authors reveal their bias in that case when they recommended sexual education programs provide contraceptive and condom choices. This, of course is a problem since it ultimately directs adolescents to accept contraception and sex outside of marriage as normative.

Mason-Jones, A. J., D. Sinclair, C. Mathews, A. Kagee, A. Hillman, and C. Lombard. 2016. **School-based interventions for preventing HIV, sexually transmitted infections, and pregnancy in adolescents**. Cochrane Data Base of Systematic Reviews. First published: 8 November 2016; Editorial Group: Cochrane Infectious Diseases Group.

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**Synthetic Progestogen Supplementation Found Effective for Treating Recurrent Miscarriage**

Approximately 1-2% of women seeking pregnancy will experience a miscarriage. Most miscarriages are due to chromosomal defects of the embryo, especially among older reproductive age women. However, when a woman experiences two or more miscarriages, while attempting pregnancy, treatment is recommended. One other possible reason for miscarriage is a poor ovulatory event and the lack of progesterone production and, as a result, lack of a healthy endometrium for implantation of a human embryo.  Supplementary progesterone, both synthetic progestogens and natural progesterone (P), have been utilized in a number of studies with mixed results. So too, different levels of progesterone and methods of administration have been utilized as treatments for repeated miscarriages of unknown cause. Researchers, therefore, conducted a systematic review of studies that investigated supplemental progesterone treatment for repeated miscarriage and conducted a meta-analysis to investigate whether treatment with progestogens in the first trimester of pregnancy would decrease the incidence of miscarriage in women with a history of unexplained recurrent miscarriage (Saccone, Schoen, Franasiak, Scott, and Berghella 2017).

The investigators utilized the Cochrane review process and sought only peer reviewed published studies that utilized randomized control trials (RCTs) in an extensive search of multiple electronic databases. Through this process they identified 16 RCTs that compared some type of progesterone supplementation in the first trimester of pregnancy with a control of either a placebo or no treatment among women with a history of repeated miscarriage. The primary outcome variable was the incidence of miscarriage but they also recorded if there were any significant negative side effects such as premature birth or fetal anomaly. Only ten of the studies were of good quality with adequate numbers of participants and detailed enough for statistical comparisons. The ten remaining studies used all types of progestogens, including natural P and synthetic progestins.  Two of the studies used natural P, and the remaining, some form of progestin. The researchers found with the pooled data that women with a history of unexplained recurrent miscarriage and who received supplemental progestogens in the first trimester had a lower risk of recurrent miscarriage (RR 0.72, 95% CI 0.53-0.97) and higher live birth rate (RR 1.07, 95% CI 1.02-1.15) compared with those who did not. No statistically significant differences were found in the other secondary outcomes, including preterm birth, neonatal mortality and fetal genital abnormalities.

The authors concluded that there is evidence that supplemental progestogens may reduce incidence of recurrent miscarriages but that synthetic progestogens, and not natural P, were associated with a lower risk of recurrent miscarriage. The authors did not feel there was enough evidence to recommend route, dose, or timing of the progesterone supplements. They did call for further comparison studies to do so.

*Comments*

A recent study provided some evidence towards defining, route, dose and timing of a P supplement (Stephenson, McQueen, Winter, and Kliman 2017). Researchers tested the effectiveness of a luteal start vaginal micronized P among women with recurrent pregnancy loss. They used the vaginal route and a dose of 100-200 mg of a micronized P starting 3 days after the LH surge, i.e., what they called the luteal start. They also were able to use a biological marker of endometrial development based on levels of glandular epithelial nuclear cyclin E (nCyclineE) found in endometrial cells. A high level of nCyclinE expression (i.e., >20%) in endometrial glands is associated with infertility.  Their study involved 116 women with a history of recurrent pregnancy loss of which (n = 59) had elevated nCyclinE and (n = 57) had normal nCyclinE. They found that pregnancy rates in the 59 women with elevated nCyclinE significantly improved after intervention: 6% (16/255) in prior pregnancies versus 69% (57/83) in subsequent pregnancies. Pregnancy success in subsequent pregnancies was higher in women prescribed vaginal micronized P compared with controls: 68% (86/126) versus 51% (19/37); odds ratio = 2.1 (95% confidence interval, 1.0-4.4). They concluded that use of luteal start vaginal micronized P was associated with improved pregnancy success in a strictly defined cohort of women with RPL.

A limitation of this study, besides being only observational, the researchers used day 13 of the menstrual cycle as a proxy measure of the LH surge. However, the LH surge and day of ovulation can vary as much as seven days in normally cycling women. This study would not have met the criteria for the progesterone supplement review.

Saccone, G., C. Schoen, J. M. Franasiak, R. T. Scott, Jr., and V. Berghella. 2017. **Supplementation with progestogens in the first trimester of pregnancy to prevent miscarriage in women with unexplained recurrent miscarriage: a systematic review and meta-analysis of randomized, controlled trials**. *Fertility and Sterility* 107 (2): 430-438.

Stephenson, M. D., D. McQueen, M. Winter, H. J. Kliman. 2017. **Luteal start vaginal micronized progesterone improves pregnancy success in women with recurrent pregnancy loss**. *Fertility and Sterility* 107 (3): 684-690.

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**Low Dose Aspirin Improved Pregnancy Rates Among Women with Low Grade Inflammation**

Researchers recently compared the effectiveness of daily low dose aspirin (LDA, 81 mg/day) versus placebo in time to pregnancy and pregnancy rates among women with recurrent pregnancy loss (Schisterman, Mumford and Schliep et al. 2015). The participants were 1,128 women recruited from medical centers across the United States who had 1 to 2 confirmed pregnancy losses and randomized into a daily LDA (N = 615) group or a group that received a placebo (N = 613). The researchers found no significant differences in 6-month pregnancy rates between the two groups. They did find a significant increase of fecundity of 28% among the LDA group who had only one miscarriage of less than 20 weeks pregnancy in the past year compared to the placebo group who also had only one miscarriage of 20 weeks or less. The researchers concluded that the findings indicated daily use of LDA preconception does not significantly shorten time to pregnancy with any history of pregnancy loss. They did suggest that since LDA is inexpensive and relatively well-tolerated that its use might be recommended among women with specific types of pregnancy loss but that generalized use is not recommended until further studies are conducted. This research group also reported on a previous study with the same participants and groups but the major outcome was live birth rates (Schisterman, Silver, and Lesher et al. 2014). Like the current study they found no significant difference in live birth rates between the LDA and the placebo groups, but did find that LDA significantly aided the birth rate of the subset of women with one miscarriage of less than 20 weeks in the past year.

Based on the theoretical pathophysiological mechanisms that inflammation contributes to recurrent pregnancy loss, another group of researchers used the same women participants and a secondary analysis of the data to determine the effects of daily preconception use of LDA on pregnancy loss, live birth rates, and inflammation during pregnancy (Sjaarda, Radin, and Silver

et al. 2017). They compared confirmed pregnancy, live birth, and pregnancy loss between the LDA group and the placebo group but also on three levels of C-reactive protein (CRP), i.e., low: <0.70 mg/L; mid: 0.70-<1.95 mg/L; and high: $\geq$1.95 mg/L. CRP is a reflection of systemic inflammation.

They found that the lowest pregnancy rates were among the high CRP group that received the placebo. The high level CRP that received daily LDA increased their pregnancy rates by 59% compared to 44% with the placebo group. The 59% pregnancy rate was similar to the pregnancy rates among the low and mid-range CRP groups. The researchers concluded that among women with high CRP and a history of pregnancy loss that daily use of LDA may increase pregnancy rates comparable with woman without inflammation.

*Comments*

Use of a diagnostic test for CRP helped to define the type of woman with recurrent pregnancy loss that would benefit with daily LDA. This is similar to the study that found that a diagnostic test for nCyclinE expression was helpful in defining the type of woman who would benefit with use of supplemental P also with recurrent pregnancy. Research studies like these are helpful in defining not only the route, dosage, and timing of treatment but also which women would benefit the most with these treatments for early pregnancy loss.

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# Under the Microscope

**Use of Natural Family Planning After Early Pregnancy Loss**

Early pregnancy loss can be defined as a loss of pregnancy within the first trimester of pregnancy or 13 weeks from the last menses (American Academy of Obstetrics and Gynecology 2015). Others define early pregnancy loss (also called miscarriage or spontaneous abortion) as a loss up to 20 weeks of pregnancy (Fritz and Speroff 2016). After 20 weeks, the loss of the baby is called stillbirth or a premature birth. When defined as loss of pregnancy within the first 12 weeks of pregnancy, the occurrence of early pregnancy loss (EPL) is from 30 – 60% of all pregnancies - with 30% being unrecognized clinical pregnancies happening before implantation. Most early pregnancy losses are due to chromosomal defects of the embryo, especially among older reproductive age women. There are, however, many other causes for EPL.

For the purpose of this review, EPL is defined as up to and including 12 weeks of pregnancy. It is within that time period, or soon after, that NFP providers will most likely be confronted in helping women cope with EPL. Natural family planning (NFP) can be useful in providing predictors of EPL and for the diagnosis and treatment of EPL. The NFP provider, however, is most often challenged in how to help the couples use NFP post EPL. NFP users want to know when or how long it takes for fertility to return post EPL, when to resume intercourse to avoid or achieve pregnancy post EPL, and when to start observing and charting signs of fertility after they have experienced an EPL.

*When Does Fertility Begin Post EPL?*

An indication for a return to fertility after an EPL is when a woman's human chorionic gonadotrophin (hCG) levels return to normal levels. hCG is the hormone that is produced by the human embryo after fertilization. It is the hormone that is measured in home urine pregnancy tests. And, hCG's continued rise indicates a healthy pregnancy (Heffner and Schust 2014). If the levels of hCG in the urine are less than 5mIU/ml, it means the test is negative for pregnancy. Most women can expect their levels to return to a non-pregnant range in about four to six weeks after an EPL. Health care providers commonly will monitor hCG levels after an EPL to ensure they return back to <5.0 IU/mL. The highest levels of hCG occur from 8 to 10 weeks of gestation, and thus, when an EPL occurs during that time period it may take longer for hCG levels to return to level and for fertility to return.

Generally speaking, it takes one to two full months for a woman to have her menstrual cycle return after experiencing a miscarriage. One study found on the basis of the endocrine data (i.e., daily urine measures of estrogen, LH, and progesterone) that among 18 women following an EPL, ovulation occurred in all 18 women in the cycle prior to first menses at a mean of 29 days post-partum (range 13-103 days) (Donnet, Howie, Marnie, Cooper, and Lewis 1990). They also found that the mean luteal phase length of 12.9 days in the first cycle was shorter than the

mean of 14.4 days in the second cycle. Another study found among 50 patients with pregnancy loss that the average time to the return of ovulation, as diagnosed by histological findings of the secretory endometrium, was 50 days (range 10 to 104 days) (Ratten 1970). These findings show that, although there is some disturbance of endocrine function in the first cycle after an EPL, the majority of women have a rapid return to ovulation and thus the early use of NFP or abstinence would be necessary for those wishing to avoid pregnancy.

*NFP Charting Evidence for Return of Fertility Post EPL*

Researchers at Marquette University are developing a data set of women with EPL and who chart their menstrual cycles in an online NFP charting system (Fehring and Schneider 2016; see example chart of an EPL in Figure 1). Chart data from 10 women with an EPL who used an electronic hormonal fertility monitor to observe their fertility, detect the LH surge, and the return of fertility, found that the average day of the first LH surge (and assumed ovulation) post EPL was 76.2 days (Range, 34 --119 days). The mean length of the first cycle post EPL was 33.9 days (Range, 28-42 days) with a luteal phase length of 11.9 days (Range, 4-19 days). The second menstrual cycle post EPL had an average length of 28.0 days (Range. 26-30 days) and with an average luteal phase of 12.3 days (Range, 9-14 days). It is obvious from this data that there is a lot of variability in the return of fertility post EPL. The data also shows that parameters of the menstrual cycle normalize quickly, i.e., by the second cycle post EPL. These parameters are similar to what Donnet, Howie, Marnie, Cooper, and Lewis (1990) found, in that the parameters of the menstrual cycle (i.e., length, and luteal phase length) normalize by the second cycle post EPL. Larger data sets of post EPL menstrual cycle charts however, need to be gathered and analyzed to have a clearer picture of this variable return to fertility and to determine what other factors affect this variability, such as how many weeks of pregnancy when the EPL occurred.

*When to Start Achieving Pregnancy Post EPL*

There is also the question as to when couples should try for pregnancy after an early pregnancy loss. There is a wide divergence of opinion concerning the interval a woman should wait after a miscarriage before attempting a new pregnancy. Waiting a full two months, or for a complete and normal menstrual cycle (which generally takes about two months), ensures that the pregnancy hormone hCG has dipped to levels so low that it's undetectable. It also makes it more likely that the luteal phase will be long enough and the uterine lining has returned to normal, making it receptive to receive a future human embryo. There is a concern that women need to wait 3-4 months in order to reduce the risk of another miscarriage. One study found among 91 women post EPL that 19 women conceived within the first 12 weeks with no spontaneous abortions (miscarriages), and 18 pregnancies proceeded normally; 30 women conceived between 12 and 26 weeks, 29 pregnancies proceeded normally, and none miscarried; and 42 women conceived later than 26 weeks after the miscarriage, with 7 pregnancies terminated in miscarriage, and 30 proceeded normally (Rud and Klünder 1985). These authors found no reason

to advise women to postpone a new conception after an EPL. Another study investigated whether a longer pregnancy interval lowers the risk of repeat miscarriage and/or prematurity (Wyss, Biedermann, and Huch  1994). Results showed that there was no evidence to recommend a waiting period between an EPL and a subsequent pregnancy.  They found that the risk of another EPL was around 20% irrespective of interval duration. Prematurity too was not influenced by a waiting period after an EPL.  Finally, Davanzo, Hale, and Rahman (2012) found that the shorter the time following a miscarriage, the more likely the subsequent pregnancy is to result in a live birth. Hence, it seems reasonable to attempt conception soon after an uncomplicated miscarriage in otherwise healthy women depending on their desire.

 *Use of NFP Post EPL*

A common recommendation for use of NFP after miscarriage is to abstain from intercourse until the first menses, which will be in about four to six weeks after the miscarriage. Women NFP users may observe and chart signs of fertility until then. The body temperature most likely will be elevated for some time due to hCG levels but gradually return to baseline (Couple to Couple League 2007). Others recommend avoiding genital contact for four weeks while leaning to develop confidence in observing natural signs of fertility (i.e., cervical mucus changes) and to begin to have intercourse only at the end of the day on dry mucus days through the first menstrual cycle post miscarriage (Hilgers, Daly, Hilgers, and Prebil 1982). Another NFP text indicated to wait to have intercourse until the Symptom-Thermal rule has been met i.e., experiencing a significant temperature shift and waiting for three temps post the shift above the baseline (Fuller and Huetner 2000).There are no studies on the effectiveness of NFP methods in helping women/couples to avoid or achieve pregnancy post EPL.

A conservative approach to avoiding pregnancy after an EPL would be to wait until the woman has her first menses and then wait until they have established the end of the estimated fertile phase by use of the body temperature shift, the cervical mucus Peak day, or an LH surge. After the first menses they could also follow the instructions for using cervical mucus or urinary estrogen changes to estimate the beginning of the fertile phase and then follow normal instructions for avoiding pregnancy. Post EPL couples can be informed that it might take some time for the first ovulation and first menses to occur. They can also be instructed that the first menstrual cycle will most likely have a delay in ovulation and a shorter than normal luteal phase. The menstrual cycle should return to normal functioning by the second cycle post EPL.

For achieving pregnancy, the conservative approach would be to wait one full menstrual cycle before trying to achieve a pregnancy post EPL. This approach would help to begin achieving pregnancy when the menstrual cycle has normalized its hormonal patterns and the length of the luteal phase of the menstrual cycle. However, newer thinking and evidence is to advise the couple that they can decide when to achieve when they are ready psychologically and physically (Knight 2016).

In summary, the following represents current understanding about return of fertility post EPL and NFP use:

- The return of fertility post EPL is variable and can be as early as 13 days post EPL but as long as 100 days or more.
- The parameters of the menstrual cycle and in particular the luteal phase normalizes by the second menstrual cycle post EPL.
- There is no evidence that achieving pregnancy soon after EPL will result in another EPL.
- Couples who wish to achieve a pregnancy post EPL should try to achieve a pregnancy when they are physically and mentally ready.
- Effectiveness of using NFP post EPL to avoid pregnancy or achieve pregnancy is unknown.

The biggest challenge with the use of NFP post EPL is coping with the unknown time of abstinence during the wait for the first menses post EPL. This time period could be very short but also 100 days or more. One approach could be to use periodic hCG home urine pregnancy tests, and as long as they are positive, the couple would not have to worry about pregnancy. The level of hCG detection in home pregnancy tests is around 20-25 IU/mL, a level that would ensure that pregnancy is not possible. Another option is to use postpartum NFP protocols that various NFP providers have developed; however, most of these protocols are not very effective with postpartum breastfeeding women (Bouchard, Schneider, and Fehring 2013). More research on the variability of the return to fertility and the effects on the menstrual cycle is needed. There is also the need to test the effectiveness of NFP protocols post EPL as well.

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