

Optimizing natural fertility

Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility

The American Society for Reproductive Medicine, Birmingham, Alabama

This Committee Opinion provides practitioners with suggestions for optimizing the likelihood of achieving pregnancy in couples attempting conception who have no evidence of infertility. (Fertil Steril® 2008;90:S1–6. ©2008 by American Society for Reproductive Medicine.)

Physicians may be asked to provide advice about sexual and lifestyle practices relating to procreation. Currently, there are no uniform counseling guidelines or evidence-based recommendations available. This document will provide practitioners with guidelines, based on a consensus of expert opinion, for counseling couples about how they might optimize the likelihood of achieving pregnancy when there is no history of or reason to question their potential fertility.

FERTILITY AND AGING

Fertility is defined as the capacity to produce offspring. Whereas the likelihood of conception remains relatively stable from cycle to cycle within individuals, it generally is highest in the first months of unprotected intercourse and declines gradually thereafter in the population as a whole (1). If no conception occurs within 3 months, monthly fecundability (the probability of pregnancy per month) decreases substantially among those who continue their efforts to conceive (1). Relative fertility is decreased by about half among women in their late 30s compared with women in their early 20s (2, 3).

Infertility is a disease, defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse (4). Earlier evaluation and treatment may be justified based on medical history and physical findings and is warranted after 6 months for women over age 35 years (4). Fertility varies among populations and declines with age in both men and women, but the effects of age are much more pronounced in women (2) (Fig. 1). Although semen parameters in men also decline detectably after 35 years of age, male fertility does not appear to decrease appreciable before approximately age 50 (3).

FREQUENCY OF INTERCOURSE

In some cases, physicians may need to explain the basics of the reproductive process. Information that, at least in theory, may help to define an optimal frequency of intercourse has emerged over the last decade. Whereas abstinence intervals greater than 5 days may adversely affect sperm counts, abstinence intervals as short as 2 days are associated with normal sperm densities (6). A widely held misperception is that frequent ejaculations decrease male fertility. A retrospective

study that analyzed almost 10,000 semen specimens observed that, in men with normal semen quality, sperm concentrations and motility remain normal, even with daily ejaculation (7). Surprisingly, in men with oligozoospermia, sperm concentration and motility may be highest with daily ejaculation (7). Abstinence intervals generally also do not appear to affect sperm morphology, as judged by “strict” criteria (8). However, after longer abstinence intervals of 10 days or more, semen parameters begin to deteriorate. Although studies of semen parameters provide useful quantitative data, those data may not predict accurately the functional integrity or capacity of sperm.

Although evidence suggests that daily intercourse may confer a slight advantage, specific recommendations regarding the frequency of intercourse may induce stress unnecessarily. In one study involving 221 presumably fertile couples planning to conceive, the highest cycle fecundability (37% per cycle) was associated with daily intercourse. Intercourse on alternate days yielded a comparable pregnancy rate per cycle (33%), but the likelihood for success decreased to 15% per cycle when intercourse occurred only once weekly (9). The stress associated with infertility can reduce sexual esteem, satisfaction, and the frequency of intercourse, and is aggravated further when the timing of intercourse is linked to a method for detecting ovulation or follows a strict schedule (10, 11). Couples should be informed that reproductive efficiency increases with the frequency of intercourse and is highest when intercourse occurs every 1 to 2 days but be advised that the optimal frequency of intercourse is best defined by their own preference within that context.

THE FERTILE WINDOW

For counseling purposes, the “fertile window” is best defined as the 6-day interval ending on the day of ovulation (9, 12). At least in theory, the viability and survivability of both oocytes and sperm should be maximal during that time. For clinical purposes, the interval of maximum fertility can be estimated by analysis of intermenstrual intervals, basal body temperature recordings, or cervical mucus scores.

Intercourse is most likely to result in pregnancy when it occurs within the 3-day interval ending on the day of ovulation. In the earlier cited study involving 221 presumed fertile women, peak fecundability was observed when intercourse occurred within 2 days of ovulation (9) (Fig. 2). A second

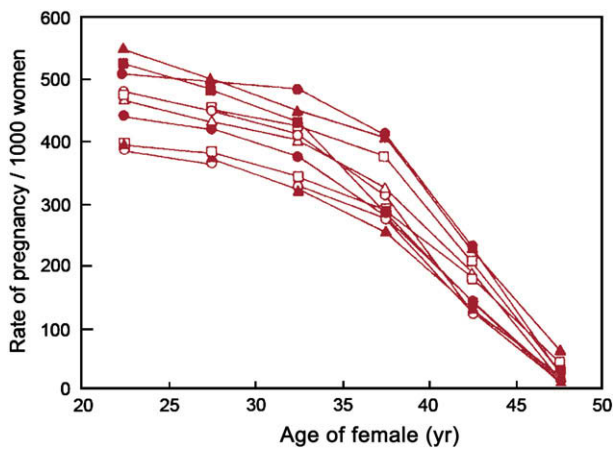
Committee Opinion

Received August 13, 2008; accepted August 14, 2008.

No reprints will be available.

FIGURE 1

Modified from Menken, Trussell, and Larsen (5). The 10 populations (in descending order at age 20 to 24) are Hutterites, marriages 1921–30 (solid triangles); Geneva bourgeoisie, husbands born 1600–49 (solid squares); Canada, marriages 1700–30 (solid circles); Normandy, marriages 1760–90 (open circles); Hutterites, marriages before 1921 (open squares); Tunis, marriages of Europeans 1840–59 (open triangles); Normandy, marriages 1674–1742 (solid circles); Norway, marriages 1874–76 (open squares); Iran, village marriages, 1940–50 (solid triangles); Geneva bourgeoisie, husbands born before 1600 (open circles).



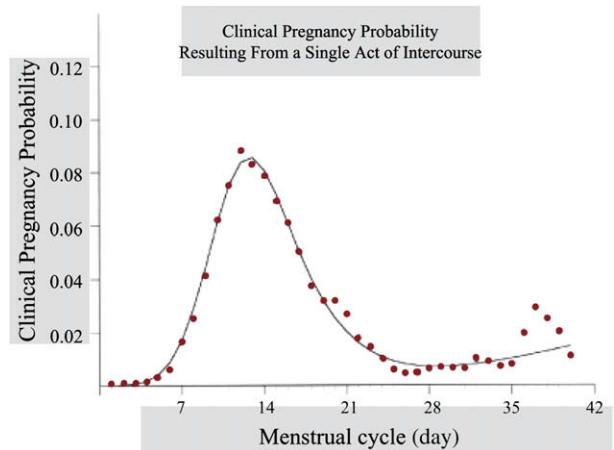
ASRM Practice Committee. *Optimizing natural fertility. Fertil Steril* 2008.

study involving 770 couples using natural family planning methods of contraception reached a similar conclusion regarding the relationship between the time of intercourse and likelihood of pregnancy (2). During the interval of observation, 647 couples had intercourse at least once during a 10-day “fertile” window, resulting in 433 pregnancies. The majority of pregnancies resulted from an episode of intercourse occurring within 6 days of ovulation, and cycle fecundability was highest when intercourse occurred within 2 days of ovulation. In a third family planning study, investigators combined data obtained from two cohorts, one using basal body temperature monitoring and the other using analysis of urinary estrogen/progesterone metabolites, to determine the likely time of ovulation; the likelihood of pregnancy was greatest when intercourse occurred within 2 days of ovulation and declined dramatically on the day of presumed ovulation (13).

Among women who described their menstrual cycles as “generally regular,” the likelihood of conception resulting from a single act of intercourse increases during the putative fertile window (14). The probability of clinical pregnancy increased from 3.2% on cycle day 8 to 9.4% by day 12, and decreased to less than 2% by cycle day 21. Whereas aging generally does not affect the size or shape

FIGURE 2

Probability of pregnancy with a single act of intercourse. Modified from Wilcox, Dunson, Weinberg, Trussell, and Day Baird (14).



ASRM Practice Committee. *Optimizing natural fertility. Fertil Steril* 2008.

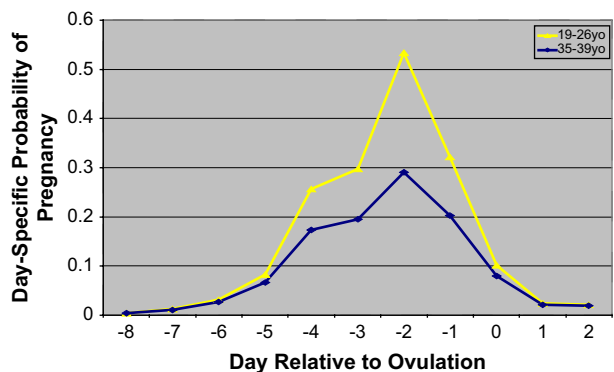
of the fertile window, the likelihood of success decreases with increasing age (Fig. 3), and cycle fecundability increases with the frequency of intercourse (15). Because accurately predicting ovulation can be challenging with any available method, the likelihood of conception can be maximized by increasing the frequency of intercourse beginning soon after cessation of menses in women having regular menstrual cycles.

MONITORING OVULATION

The time of peak fertility can vary considerably, even among women who have regular cycles. Women who monitor their cycles, tracking changes in cervical mucus, libido, pain, or mood, are able to predict ovulation accurately no more than

FIGURE 3

Probability of pregnancy by cycle day, involving recurrent intercourse, by age. Data from Stanford and Dunson 2007 (15).



ASRM Practice Committee. *Optimizing natural fertility. Fertil Steril* 2008.

50% of the time (16). Although there is no substantial evidence that monitoring by this or other methods increases cycle fecundability, a common public perception is that the timing of intercourse is crucial and should therefore be determined by applying some form of technology. That perception has contributed much to the popularity of various methods to determine or predict the time of ovulation.

Cervical mucus (vaginal secretions at the introitus) provides an inexpensive and private index of when ovulation may be expected. The estimated probability of conception, in relation to the characteristics of cervical/vaginal secretions, is shown in Figure 4. The probability is highest when mucus is slippery and clear (17), but such mucus is by no means a prerequisite for pregnancy to occur.

The volume of cervical mucus increases with plasma estrogen concentrations over the 5 to 6 days preceding ovulation and reaches its peak within 2 to 3 days of ovulation (18). A retrospective cohort study involving 1681 cycles observed that pregnancy rates were highest (approximately 38%) when intercourse occurred on the day of peak mucus (day “0”), and appreciably lower (approximately 15% to 20%) on the day before or after the peak (19). A prospective study including 2832 cycles observed that changes in cervical mucus characteristics correlate closely with basal body temperature and predict the time of peak fertility more accurately than a menstrual calendar (20, 21).

Ovulation detection devices, including kits for monitoring urinary luteinizing hormone (LH) excretion and electronic monitors, are promoted widely as tools that can help couples to determine their “fertile time.” There is some evidence to suggest that LH detection kits may decrease the time to conception (22). Although numerous studies have validated the accuracy of methods for detecting the midcycle urinary LH

surge (23–25), ovulation may occur anytime within the 2 days thereafter (26, 27), and false-positive test results occur in approximately 7% of cycles (28). Although urinary LH monitoring may help to reduce the time to conception in couples having infrequent intercourse by choice or circumstance, one large study found that changes in cervical mucus across the fertile interval predict the day-specific probabilities of conception as well or better than basal body temperature or urinary LH monitoring (29).

COITAL PRACTICES

Postcoital routines may become ritualized for couples trying to conceive. Although many women think that remaining supine for an interval after intercourse facilitates sperm transport and prevents leakage of semen from the vagina, the belief has no scientific foundation.

Studies in which labeled particles were placed in the posterior vaginal fornix at varying times of the cycle observed their transport into the fallopian tubes within as little as 2 minutes during the follicular phase (30). It is interesting that the particles were observed only into the tube adjacent to the ovary containing the dominant follicle and not in the contralateral tube. The number of transported particles increased with size of the dominant follicle and after administration of oxytocin, given to simulate the increase in oxytocin observed in women during intercourse and orgasm.

There is no evidence that coital position affects fecundability. Sperm can be found in the cervical canal seconds after ejaculation, regardless of coital position (31). Although female orgasm may promote sperm transport, there is no known relationship between orgasm and fertility. There also is no convincing evidence to indicate any relationship between specific coital practices and infant gender.

Some vaginal lubricants may decrease fertility, based on their observed effects on sperm survival in vitro. Whereas commercially available water-based lubricants (e.g., Astroglide®, KY Jelly®, and Touch®) inhibit sperm motility in vitro by 60% to 100% within 60 minutes of incubation, canola oil has no similar detrimental effect (32). KY Jelly, olive oil, and saliva diluted to concentrations even as low as 6.25% adversely affect sperm motility and velocity, but mineral oil has no such effect (32–34). Hydroxyethylcellulose-based lubricants such as Pre-Seed® (INGfertility, Valleyford, WA) also have no demonstrable adverse impact on semen parameters (35). Although there is no evidence to indicate that use of any vaginal lubricant decreases fertility, it seems prudent to recommend mineral oil, canola oil, or hydroxyethylcellulose-based lubricants when they are needed.

DIET AND LIFESTYLE

Diet

Fertility rates clearly are decreased in women who are either very thin or obese, but data regarding the effects of normal variations in diet on fertility in ovulatory women are few (Table 1) (36). Whereas a healthy lifestyle may help to

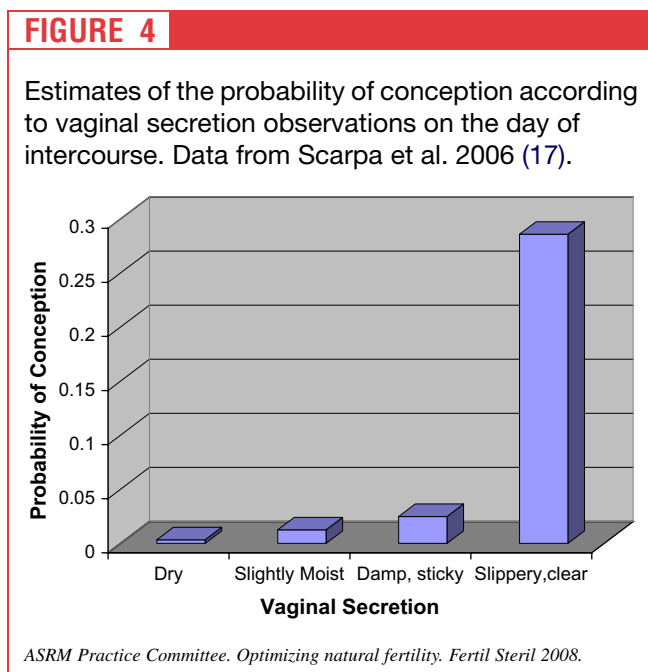


TABLE 1**Lifestyle factors that may impact fertility.**

Factor	Impact on fertility	Study
Obesity (BMI >35)	Time to conception increased two-fold	Hassan and Killick, 2004 (72)
Underweight (BMI <19)	Time to conception increased four-fold	Hassan and Killick, 2004 (72)
Smoking	RR of infertility increased 60%	Clark et al., 1998 (37)
Alcohol (>2 drinks/day)	RR of infertility increased 60%	Eggert et al., 2004 (48)
Caffeine (>250 mg/day)	Fecundability decreased 45%	Wilcox et al., 1988 (53)
Illicit drugs	RR of infertility increased 70%	Mueller et al., 1990 (59)
Toxins, solvents	RR of infertility increased 40%	Hruska et al., 2000 (62)

Note: BMI = body mass index; RR = relative risk.

ASRM Practice Committee. *Optimizing natural fertility. Fertil Steril* 2008.

improve fertility for women with ovulatory dysfunction (37), there is little evidence that dietary variations such as vegetarian diets, low-fat diets, vitamin-enriched diets, antioxidants, or herbal remedies improve fertility or affect infant gender. Elevated blood mercury levels from heavy seafood consumption have been associated with infertility (38). Women attempting to conceive should be advised to take a folic acid supplement (at least 400 μg daily) to reduce the risk for neural tube defects (39).

Smoking

Smoking has substantial adverse effects on fertility. A large meta-analysis comparing 10,928 smoking women with 19,128 nonsmoking women found that smoking women were significantly more likely to be infertile (odds ratio [OR] 1.60; 95% confidence interval [CI], 1.34–1.91) (40). The observation that menopause occurs, on average, one to four years earlier in smoking women than in nonsmoking women suggests that smoking accelerates the rate of follicular depletion (41, 42). Smoking also is associated with an increased risk of miscarriage, in both naturally conceived pregnancies and those resulting from assisted reproductive technologies (42, 43). Although decreases in sperm density, motility, and abnormalities in sperm morphology have been observed in men who smoke, available data do not demonstrate conclusively that smoking decreases male fertility (44–46). The effects of smoking on fertility in men and women and the mechanisms that may explain its adverse impact are discussed at length in a separate Practice Committee report (47).

Alcohol

The effect of alcohol on female fertility has not been clearly established. Whereas some studies have concluded that alcohol has a detrimental effect, others have suggested that alcohol may enhance fertility. A prospective survey of 7393 women in Stockholm observed that the risk of infertility was significantly increased (relative risk [RR] 1.59; 95% CI, 1.09–2.31) among women who consumed two alcoholic drinks/day, and decreased (RR 0.64; 95% CI, 0.46–0.90) for those who consumed less than one drink per day (48).

In contrast, data obtained by self-report from 29,844 pregnant Danish women have suggested that time to conception was shorter for women who drink wine than for women who consume no alcohol (49). A study involving 1769 Italian women found no relationship between alcohol consumption and fertility (50).

Higher levels of alcohol consumption (≥ 2 drinks/day) probably are best avoided when attempting pregnancy, but there is no evidence to indicate that more moderate alcohol consumption adversely affects fertility. Of course, alcohol consumption should cease altogether during pregnancy because alcohol has well-documented detrimental effects on fetal development and no “safe” level of alcohol consumption has been established (51).

Caffeine

High levels of caffeine consumption (>5 cups of coffee/day or its equivalent; 500 mg) have been associated with decreased fertility (OR 1.45; 95% CI, 1.03–2.04) (52). During pregnancy, caffeine consumption over 200 to 300 mg/day may increase risk for miscarriage (53–55) but does not affect risk for congenital anomalies (56). In one trial involving 1207 women who were randomly assigned to drink decaffeinated versus caffeinated coffee (at least 3 cups/day) during pregnancy, there were no observed differences between the two groups in gestational age at delivery or in infant weight, length, head circumference, or abdominal circumference (57). Overall, moderate caffeine consumption (one to two cups of coffee per day or its equivalent) before or during pregnancy has no apparent adverse effects on fertility or pregnancy outcomes.

Other Considerations

The effects of marijuana and other recreational drugs are difficult to determine because their use is illegal. Nevertheless, such drug use generally should be discouraged for both men and women, particularly because they have well-documented harmful effects on the developing fetus (58). One study found that the prevalence of infertility was increased in ovulatory

women who reported using marijuana (RR 1.7, CI 95%, 1.0–3.0) (59).

A literature review concluded that sauna bathing does not decrease female fertility and is safe during uncomplicated pregnancy (60). In normal men, recommendations for behavioral modifications aimed at controlling or decreasing exposure of the testicles to sources of heat are unjustified (61).

Fecundability may be decreased in women exposed to certain toxins and solvents such as those used in the dry cleaning and printing industries, and men exposed to heavy metals may be more likely to have abnormal semen parameters (62).

Pesticide exposure may be a concern for agricultural workers because the risk of infertility appears increased for women who mix and apply herbicides (OR 2.7; 95 % CI, 1.9–3.8) (63). In men, exposure to agricultural pesticides had a detrimental impact on semen parameters in one study (64), but not in another (65). However, animal studies have demonstrated clearly that environmental exposures can have important reproductive consequences (66–70).

Although evidence is limited, exposure to lead and industrial microwaves is probably best avoided or minimized (71). Prescription drug use should be carefully controlled and must be managed on an individual basis.

SUMMARY AND RECOMMENDATIONS

- Frequent intercourse (every 1 to 2 days) yields the highest pregnancy rates, but results achieved with less frequent intercourse (two to three times per week) are nearly equivalent.
- The “fertile window” spans the 6-day interval ending on the day of ovulation and correlates with the volume and character of cervical mucus.
- Specific coital timing or position and resting supine after intercourse have no significant impact on fertility.
- Time to conception increases with age. For women over age 35 years, consultation with a reproductive specialist should be considered after 6 months of unsuccessful efforts to conceive.
- For women having regular menstrual cycles, frequent intercourse beginning soon after cessation of menses can help to maximize fecundability.
- Devices designed to determine or predict the time of ovulation may be useful for couples who have infrequent intercourse.
- Moderate alcohol or caffeine consumption (one to two drinks per day) has no demonstrable adverse effect on fertility.
- Smoking, higher levels of alcohol consumption (>2 drinks per day), recreational drugs, and use of most commercially available vaginal lubricants should be discouraged for couples trying to conceive.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine and the Society for Reproductive Endocrinology and Infertility as a service to their

members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. This report was approved by the Board of Directors of the American Society for Reproductive Medicine and by the Board of the Society for Reproductive Endocrinology and Infertility.

REFERENCES

1. Gnath C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G. Time to pregnancy: results of the German prospective study and impact on the management of infertility. *Hum Reprod* 2003;18:1959–66.
2. Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. *BMJ* 1985;290:1697–700.
3. Dunson DB, Baird DD, Colombo B. Increased infertility with age in men and women. *Am J Obstet Gynecol* 2004;103:51–6.
4. Practice Committee of the American Society for Reproductive Medicine. Definitions of infertility and recurrent pregnancy loss. *Fertil Steril* 2008;89:1603.
5. Menken J, Trussell J, Larsen U. Age and infertility. *Science* 1986; 26(233):1389–94.
6. Elzanaty S, Malm J, Giwercman A. Duration of sexual abstinence: epididymal and accessory sex gland secretions and their relationship to sperm motility. *Hum Reprod* 2005;20:221–5.
7. Levitas E, Lunenfeld E, Weiss N, Friger M, Har-Vardi I, Koifman A, et al. Relationship between the duration of sexual abstinence and semen quality: analysis of 9,489 semen samples. *Fertil Steril* 2005;83:1680–6.
8. Check JH, Epstein R, Long R. Effect of time interval between ejaculations on semen parameters. *Arch Androl* 1995;27:93–5.
9. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation—effects on the probability of conception, survival of the pregnancy, and sex of the baby. *New Engl J Med* 1995;333:1517–21.
10. Lenzi A, Lombardo F, Salacone P, Gandini L, Jannini EA. Stress, sexual dysfunctions, and male infertility. *J Endocrinol Invest* 2003;26:72–6.
11. Andrews FM, Abbey A, Halman LJ. Is fertility-problem stress different? The dynamics of stress in fertile and infertile couples. *Fertil Steril* 1992;57:1247–53.
12. Brosens I, Gordts S, Puttemans P, Campo R, Gordts S, Brosens J. Managing infertility with fertility-awareness methods. *Sex Reprod Menopause* 2006;4:13–6.
13. Dunson DB, Baird DD, Wilcox AJ, Weinberg CR. Day-specific probabilities of clinical pregnancy based on two studies with imperfect measures of ovulation. *Hum Reprod* 1999;14:1835–9.
14. Wilcox AJ, Dunson DB, Weinberg CR, Trussell J, Day Baird D. Likelihood of conception with a single act of intercourse: providing benchmark rates for assessment of post-coital contraceptives. *Contraception* 2001;63:211–5.
15. Stanford JB, Dunson DB. Effects of sexual intercourse patterns in time to pregnancy studies. *Am J Epidemiol* 2007;165:1088–95.
16. Sievert LL, Dubois CA. Validating signals of ovulation: do women who think they know, really know? *Am J Hum Biol* 2005;17:310–20.
17. Scarpa B, Dunson DB, Colombo B. Cervical mucus secretions on the day of intercourse: an accurate marker of highly fertile days. *Eur J Obstet Gynaecol Reprod Biol* 2006;125:72–8.
18. Leader LR, Russell T, Stenning B. The use of Clearplan home ovulation detection kits in unexplained and male factor infertility. *Aust NZ J Obstet Gynaecol* 1992;32:158–60.
19. Stanford JB, White GL, Hatasaka H. Timing intercourse to achieve pregnancy: current evidence. *Obstet Gynecol* 2002;100:1333–41.
20. Stanford JB, Smith KR, Dunson DB. Vulvar mucus observations and the probability of pregnancy. *Obstet Gynecol* 2003;101:1285–93.
21. Dunson DB, Sinai I, Colombo B. The relationship between cervical secretions and the daily probabilities of pregnancy: effectiveness of the TwoDay Algorithm. *Hum Reprod* 2001;16:2278–82.
22. Robinson JE, Wakelin M, Ellis JE. Increased pregnancy rate with use of the Clearblue Easy fertility monitor. *Fertil Steril* 2007;87:329–34.

23. Fehring RJ, Raviele K, Schneider M. A comparison of the fertile phase as determined by the Clearplan Easy Fertility Monitor and self-assessment of cervical mucus. *Contraception* 2004;69:9-14.
24. Nielsen MS, Barton SD, Hatasaka HH, Stanford JB. Comparison of several one-step home urinary luteinizing hormone detection test kits to Ov-Quick. *Fertil Steril* 2001;76:384-7.
25. Tanabe K, Susumu N, Hand K, Nishii K, Ishikawa I, Nozawa S. Prediction of the potentially fertile period by urinary hormone measurements using a new home-use monitor: comparison with laboratory hormone analyses. *Hum Reprod* 2001;16:1619-24.
26. Miller PB, Soules MR. The usefulness of a urinary LH kit for ovulation prediction during menstrual cycles of normal women. *Obstet Gynecol* 1996;87:13-7.
27. Pearlstone AC, Surrey ES. The temporal relation between the urine LH surge and sonographic evidence of ovulation: determinants and clinical significance. *Obstet Gynecol* 1994;83:184-8.
28. McGovern PG, Myers ER, Silva S, Coutifaris C, Carson SA, Legro RS, et al. Absence of secretory endometrium after false-positive home urine luteinizing hormone testing. *Fertil Steril* 2004;82:1273-7.
29. Bigelow JL, Dunson DB, Stanford JB, Ecochard R, Gnath C, Colombo B. Mucus observations in the fertile window: a better predictor of conception than timing of intercourse. *Hum Reprod* 2004;19:889-92.
30. Kunz G, Beil D, Deininger H, Wildt L, Leyendecker G. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum Reprod* 1996;11:627-32.
31. Settlage DS, Motoshima M, Tredway DR. Sperm transport from the external cervical as to the fallopian tubes in women: a time and quantitation study. *Fertil Steril* 1973;24:655-61.
32. Kutteh WH, Chao CH, Ritter JO, Byrd W. Vaginal lubricants for the infertile couple: effect on sperm activity. *Int J Fertil Menopausal Stud* 1996;41:400-4.
33. Anderson L, Lewis SE, McClure N. The effects of coital lubricants on sperm motility in vitro. *Hum Reprod* 1998;13:3351-6.
34. Tulandi T, Plouffe L Jr, McInnes RA. Effect of saliva on sperm motility and activity. *Fertil Steril* 1982;8:721-3.
35. Agarwal A, Deepinder F, Cocuzza M, Short RA, Evenson DP. Effect of vaginal lubricants on sperm motility and chromatin integrity: a prospective comparative study. *Fertil Steril* 2008;89:375-9.
36. Scott S, Duncan CJ. Nutrition, fertility and steady-state population dynamics in a pre-industrial community in Penrith, Northern England. *J Biosocial Sci* 1999;31:505-23.
37. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998;13:1502-5.
38. Choy CM, Lam CW, Cheung LT, Britton-Jones CM, Cheung LP, Haines CJ. Infertility, blood mercury concentrations and dietary seafood consumption: a case-control study. *BJOG* 2002;109:1121-5.
39. Lumley J, Watson L, Watson M, et al. Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *Cochrane Database Syst Rev* 2001;3:CD001056.
40. Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. *Hum Reprod* 1998;13:1532-9.
41. Mattison DR, Plowchalk DR, Meadows MJ, Miller MM, Malek A, London S. The effect of smoking on oogenesis, fertilization and implantation. *Semin Reprod Endocrinol* 1989;7:291-304.
42. Adena MA, Gallagher HG. Cigarette smoking and the age at menopause. *Ann Hum Biol* 1982;9:121-30.
43. Winter E, Wang J, Davies MJ, Norman R. Early pregnancy loss following assisted reproductive technology treatment. *Hum Reprod* 2002;17:3220-3.
44. Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, et al. Cocaine and tobacco use and the risk of spontaneous abortion. *New Engl J Med* 1999;340:333-9.
45. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. *Hum Reprod Update* 2000;6:122-31.
46. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. *Fertil Steril* 1986;46:545-66.
47. Practice Committee of the American Society for Reproductive Medicine. Smoking and infertility. *Fertil Steril* 2006;86:S172-7.
48. Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption of female fertility during an 18-year period. *Fertil Steril* 2004;81:379-83.
49. Tolstrup JS, Kjaer SK, Holst C, Sharif H, Munk C, Osler M, et al. Alcohol use as a predictor for infertility in a representative population of Danish women. *Acta Obstet Gynecol Scand* 2003;82:744-9.
50. Parazzini F, Chatenoud L, Di Cintio E, La Vecchia C, Benzi G, Fedele L. Alcohol consumption is not related to fertility in Italian women. *BMJ* 1999;318:397.
51. American Academy of Pediatrics. Committee on substance abuse in the United States, 1992-1998. Publication No. NCJ-190636. Washington, DC: Executive Office of the President, 2001.
52. Bolumar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. *Am J Epidemiol* 1997;15(145):324-34.
53. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. *Lancet* 1988;2:1453-6.
54. Signorello LB, McLaughlin JK. Maternal caffeine consumption and spontaneous abortion: a review of the epidemiologic evidence. *Epidemiology* 2004;15:229-39.
55. Kesmodel U, Wisborg K, Olsen SF, Henriksen TB, Secher NJ. Moderate alcohol intake in pregnancy and the risk of spontaneous abortion. *Alcohol* 2002;37:87-92.
56. Browne ML. Maternal exposure to caffeine and risk of congenital anomalies. *Epidemiology* 2006;17:324-31.
57. Bech BH, Obel C, Henriksen TB, Olsen J. Effect of reducing caffeine intake on birth weight and length of gestation: randomized controlled trial. *BMJ* 2007;334:409.
58. Addis A, Moretti ME, Ahmed Syed F, Einarson TR, Koren G. Fetal effects of cocaine: an updated meta-analysis. *Reprod Toxicol* 2001;15:341-69.
59. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. *Epidemiology* 1990;1:195-200.
60. Hannuksela ML, Ellahham S. Benefits and risks of sauna bathing. *Am J Med* 2001;110:118-26.
61. Jung A, Schuppe HC. Influence of genital heat stress on semen quality in humans. *Andrologia* 2007;39:203-15.
62. Hruska K, Furth P, Seifer D, Sharara F, Flaws J. Environmental factors in infertility. *Clin Obstet Gynecol* 2000;43:821-9.
63. Greenlee AR, Arbuckle TE, Chyou PH. Risk factors for female infertility in an agricultural region. *Epidemiology* 2003;14:429-36.
64. Swan SH. Semen quality in fertile US men in relation to geographical area and pesticide exposure. *Int J Androl* 2006;29:62-8.
65. Magnusdottir EV, Thorsteinsson T, Thorsteinsdottir S, Heimisdottir M, Olafsdottir K. Persistent organochlorides, sedentary occupation, obesity and human male subfertility. *Hum Reprod* 2005;20:208-15.
66. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;16:972-8.
67. Lee PC. Disruption of male reproductive tract development by administration of xenoestrogen, nonylphenol, to male newborn rats. *Endocrine* 1998;9:105-11.
68. Rune GM, DeSouza P, Krowke R, Merker HJ, Neubert D. Morphological and histochemical effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) on marmoset (*Callithrix jacchus*) testes. *Arch Androl* 1991;26:143-54.
69. Kyselova V, Peknicova J, Buckiova D, Boubelik M. Effects of p-nonylphenol and reseratrol on body and organ weight and in vivo fertility of outbred CD-1 mice. *Reprod Biol Endocrinol* 2003;30:1-10.
70. Poon R, Lecavalier P, Mueller R, Valli VE, Procter BG, Chu I. Subchronic oral toxicity of di-n-octyl phthalate and di(2-thylhexyl)phthalate in the rat. *Food Chem Toxicol* 1997;35:225-39.
71. Weyandt TB, Schrader SM, Turner TW, Simon SD. Semen analysis of military personnel associated with military duty assignments. *Reprod Toxicol* 1996;10:521-8.
72. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. *Fertil Steril* 2004;81:384-92.