Women and Health

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ACADEMIC PRESS
A Harcourt Science and Technology Company

San Diego San Francisco New York Boston London Sydney Tokyo

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Women's Fecundability and Factors Affecting It

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I. Introduction

World population first exceeded a billion people in the early 1800s and it took approximately a century for the next billion increase. In 1999, our population exceeds six billion. Another billion increase is projected in just over a decade [1]. The rapid increase results from high fertility populations where average numbers of live births typically range from five to eight [2]. Other parts of the world have undergone demographic transition in association with industrialization and hover at or below replacement reproductive rates. The transition from high fertility to low fertility is influenced by complex social changes thought to be unrelated to basic biological capacity to reproduce.

Reproduction is a relatively rare event for women in industrialized countries. Only 6.5% of US women of reproductive age (15–44) gave birth in 1995 [3], and one out of six women aged 40–45 have never had a child [4]. Although most girls grow up assuming that they will be able to have children when and if they choose to do so, an estimated 10–15% of live births require more than a year to conceive [5], suggesting that these couples may be experiencing some fertility problems.

This chapter focuses on variability in biological capacity to reproduce. How variable are different populations? What accounts for variability among women within a population? Do women with abundant food have greater capacity for reproduction?

Terminology for describing fertility and fertility problems is not uniform across disciplines. We will follow Leridon [6]. *Fertility* refers to number of live births, a focus of demographic research. *Fecundity* denotes the biological capacity to reproduce, a focus of medical research. Fecundity is inherently difficult to measure; it requires successful interaction of several complex biological processes. Women may be fecund but choose to contracept and not demonstrate fertility. Conversely, they can be fertile despite impaired fecundity by utilizing specialized infertility treatments such as *in vitro* fertilization. *Fecundability*, the probability of conceiving in a given time interval, provides a measurement tool for the study of fecundity. It usually is measured as the probability of conceiving in any given menstrual cycle (or month) among couples who are sexually active and doing nothing to prevent pregnancy. The probability of conceiving is a function of the fecundity of the male and female partners but also varies with frequency and timing of sexual intercourse. As for any probability, it cannot be assessed for an individual couple but must be estimated for a group. If human conceptions could be identified at time of fertilization, we could measure *total fecundability*. Instead, most data provide estimates of *effective fecundability* (the probability of conceiving a pregnancy that survives to birth) or *apparent fecundability* (the probability of having a clinically recognizable conception).

This chapter explores the variability among couples in their ability to conceive, as measured by fecundability. Unless specifically stated otherwise, fecundability will refer to apparent fecundability, the probability of conceiving a clinically recognized pregnancy in any given menstrual cycle (or month). The broader questions about social and economic determinants of fertility and family size are beyond our scope. We start by summarizing fecundability estimates from both contracepting and noncontracepting populations. We then consider the major biological processes required for successful pregnancy and begin to quantify how failure of these processes contributes to reducing fecundability. The largest section summarizes research on factors affecting women's fecundability. Finally, we propose directions for future research.

II. Estimates of Fecundability

The majority of estimates of fecundability come from natural fertility populations (populations in which contraception is not used to limit family size). Today, natural fertility is most likely to be found among rural populations of developing countries and among conservative religious sects such as the Hutterites and Amish of North America [7,8]. There are possible theoretical as well as practical advantages to studying natural fertility populations. Natural fertility is thought to be the reproductive pattern of the vast majority of our evolutionary past, so natural fertility populations may be particularly suitable for exploring the evolved mechanisms that underlie differences in female fecundability [9,10]. Practically, the lack of contraceptive use can simplify data collection. Waiting-time data for calculating fecundability estimates can be conveniently collected for first birth intervals (time from entry into a sexual union, *e.g.*, marriage, to the date of first conception, imputed from date of live birth). When sexual union begins at marriage, existing marriage and birth records can be used to estimate fecundability retrospectively.

Wood *et al.*'s study of the Pennsylvania Amish provides one of the best examples of first birth interval studies [11]. They used the carefully-kept marriage and birth records of the Amish community to establish waiting times. Nearly all women married before age 30, so a fecundability estimate was calculated for women aged 18–29. The estimated effective fecundability for the study sample of 271 women was 0.25 (the probability of becoming pregnant in any given menstrual cycle was 25%). Similar methods were used in Taiwanese and Sri Lankan samples where effective fecundability varied from 0.16 to 0.30 for 25–29 year olds [11]. Prior estimates of fecundability (based on clinically recognized conceptions) in the first birth interval were summarized by Wood [12]. Populations were from the US, Taiwan, Peru, Brazil,

Mexico, France (including historical data), Tunis, and Quebec. Fecundability estimates ranged from 0.14 to 0.31, with corresponding conception waits of 10 months to 5.2 months.

Estimates of fecundability at the time of marriage often are limited to young women and tend to be elevated by high coital frequencies commonly seen with the onset of marriage [13,14]. Few studies have provided fecundability estimates for women across the reproductive life span because they require accurate information on the length of lactational amenorrhea. Studies in contracepting populations require added information on birth control usage. These concerns can be addressed best with prospective studies in which individual women are followed to collect accurate waiting-time data.

John *et al.* [15,16] conducted the first prospective study of fecundability in a natural fertility population, the rural Bangladesh of Matlab Thana. Family planning in this population was minimal. Women were sought for interviews once a month. Nonetheless, absences of the women from home on their interview days resulted in gaps of two to four months in the records. A sample of 403 married women aged 14–49 participated. Fecundability was 0.19 for nonbreastfeeding women and less than 0.07 for breastfeeding women. However, even with the prospectively-collected data, concern about accuracy of postpartum amenorrhea information led Leridon [14] to question these fecundability estimates.

Strassmann and Warner [10] studied the waiting time to conception in a Dogon village of 460 people in Mali, West Africa. The total fertility rate of the postreproductive women in this village was 8.6 births, and none of the women in any cohort reported that they had ever used contraception. During menses Dogon women spend five nights sleeping at a menstrual hut, which made it possible to monitor female reproductive status prospectively without interviews. By censusing the women present at the menstrual huts in the study village every night for two years, Strassmann and Warner were able to prospectively monitor the time from a woman's first postpartum menstruation to the onset of her last menstruation before a subsequent pregnancy. Urinary steroid hormone profiles for 93 women in two villages showed that, over a 10 week period, women in the principal study village went to the menstrual huts during 87.5% of all menses and did not go to the huts at other times [17]. Thus, menstrual hut visitation provided a reasonably reliable indication of menstruation.

The Dogon sample included 50 women aged 15–41 with prospectively observed conception waits. Fecundability was estimated at 0.11 with covariates assigned mean values for the population (covariates included age, time since marriage, gravidity, and lactation). This fecundability estimate corresponds to a conception wait of 8.3 months.

In contracepting populations prospective studies that can enroll women at the time they stop using contraception in order to conceive provide the most accurate waiting-time data. Though such studies have been done, none were done primarily to measure fecundability and none present fecundability estimates based on statistical modelling of the entire distribution of waiting times. However, first cycle conception rates provide a good estimate of mean fecundability for a population (described in Leridon [6]), and these data have been published. We describe three prospective studies that reported these data.

Tietze [18] reported data on 611 US women who had their IUDs removed in order to become pregnant. Ages ranged from 17 to 42, with median age of about 25. The apparent fecundability (estimated by first cycle conception rates for clinically recognized pregnancies) was 0.33. Most of the women had been pregnant before, so this estimate represents fecundability for couples of proven fertility. If women with no prior pregnancies had been included, the estimate of mean fecundability probably would have been lower.

The second study, the North Carolina Early Pregnancy Study, enrolled 221 volunteers at the time they began trying to conceive [19]. Follow-up continued for six months or through the eighth gestational week for those conceiving during the study. Women ranged in age from 21 to 42, with 80% between the ages of 26 and 35; 35% were nulligravid. The apparent fecundability was 0.24 (estimated by first cycle conception rates for clinically recognized pregnancies). This is probably a low estimate because some women stopped contraception well into their first cycle, so the opportunity to become pregnant during that first cycle was reduced for these women. On the other hand, women with known fertility problems were excluded from participation, so we would expect this factor to bias the estimate upward.

The third study [20], conducted in Denmark, enrolled 411 couples at the time they began trying to conceive a first pregnancy. Couples were recruited from four trade unions: metal workers, office workers, nurses, and daycare workers. Most participants (92%) were in their twenties. Couples were followed until clinically pregnant or through six menstrual cycles, whichever came first. Fecundability as estimated by the first cycle conception rate for clinical pregnancies was 0.16.

The fecundability estimates presented here are highly variable (0.11 to 0.33), and variation exists both among the contracepting samples and among the natural fertility samples (Table 11.1). Some of this variation may have methodologic explanations. In natural fertility populations, accurate estimates depend on ascertainment of when a couple begins having sexual intercourse and when lactational amenorrhea ends. Reporting accuracy may vary with study design as well as with education and other characteristics of participants.

In contracepting populations, waiting times can be measured accurately in prospective studies of women stopping contraception in order to conceive, but these studies are based solely on women planning a pregnancy. This is a select group. Some women never attempt to conceive because they do not want children. Other women become pregnant even though they are not intending to. In the United States about half of pregnancies are unplanned [21]. Though nearly half of these unplanned pregnancies were to women not using contraception, the others were conceived during months when birth control had been used. This latter group of women might be expected to have high mean fecundability because they became pregnant while using some form of birth control around the time they conceived. Therefore, fecundability estimates based only on women trying to conceive are likely to be lower than true fecundability in the population. Given the methodologic issues and the limited number of studies, the degree to which populations differ in their true fecundability is not known.

Fecundability varies within populations as well. Regardless of the mean fecundability for the population and whether it is a

Table 11.1
Estimates of Fecundability in Selected Populations

References	Population	Design	N	Estimate	Estimation method
[11]	Amish, US natural fertility	Retrospective	271	0.25[a]	Model distribution of time from marriage to imputed conception
[11]	Taiwan, 1967 natural fertility	Retrospective	445	0.21[a] 25–29 year olds	Model distribution of time from marriage to imputed conception
[11]	Taiwan, 1973 natural fertility	Retrospective	471	0.30[a] 25–29 year olds	Model distribution of time from marriage to imputed conception
[11]	Sri Lanka, 1987 natural fertility	Retrospective	655	0.16[a] 25–29 year olds	Model distribution of time from marriage to imputed conception
[15,16]	Matlab Thana, Bangladesh natural fertility	Prospective	403	0.19[a] nonnursing	Model distribution of waiting times
[10]	Dogon, Mali natural fertility	Prospective	50	0.11[a]	Model distribution of waiting times
[18]	US women having IUDs removed to conceive	Prospective	611	0.33[b]	First cycle conception rate
[19]	North Carolina, US women stopping contraception to conceive	Prospective	211	0.24[b]	First cycle conception rate
[20]	Danish couples stopping contraception to attempt first pregnancy	Prospective	430	0.16[b]	First cycle conception rate

[a]Effective fecundability.
[b]Apparent fecundability.

natural fertility population or a contracepting population, nearly all studies show that some couples are more fecund than others. This heterogeneity is expressed in the gradual decrease in conception rates during successive months of trying. Using Tietze's data [18] as an example (Fig. 11.1), the conception rate in the first month of trying to conceive was 0.33, declining to 0.21 by month three and to 0.12 by month nine. This pattern is produced because the most fecund couples become pregnant quickly. Those still trying in the latter months are those couples who tend to have low fecundability. Identifying and quantifying the impact of factors that can account for this variability in fecundability is an active area of current research. Age and frequency of intercourse are obvious examples, but many other factors may also play a role.

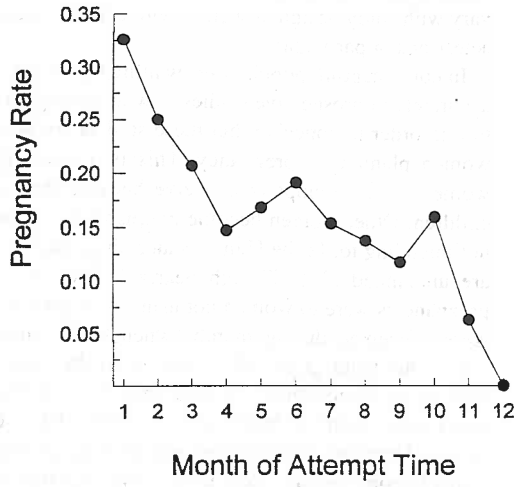

Fig. 11.1 Decline in fecundability seen in a population over months of attempt time. As the more fecund couples conceive and drop out of the pool of waiting couples, the sample becomes more and more selected for low fecundability couples. Data are from 611 women having IUDs removed in order to conceive [18].

III. Biological Processes Reflected in Measures of Fecundability

Figure 11.2 illustrates the reproductive failure or loss inherently measured in apparent and effective fecundability, using midrange estimates from the literature [21a]. For 100 women beginning the first menstrual cycle in which they attempt to conceive, 20–25% will start a viable pregnancy. The other 75 to 80 cycles represent some form of reproductive failure. The vast majority of women aged 25–39 who are not using hormonal contraceptives ovulate each cycle [22,23], so anovulation cannot account for much of this early reproductive failure. The rate of fertilization is unknown, but *in vitro* fertilization rates are high [24]. If sexual intercourse is timely, *in vivo* fertilization rates may also be high. There may be considerable loss prior to implantation, but no data are available.

Very early pregnancy testing can be used to estimate pregnancy loss after implantation, before normal clinical detection of pregnancy. Highly sensitive tests for the pregnancy hormone, human chorionic gonadotropin (hCG), can detect pregnancies around the time of implantation using daily first morning urine

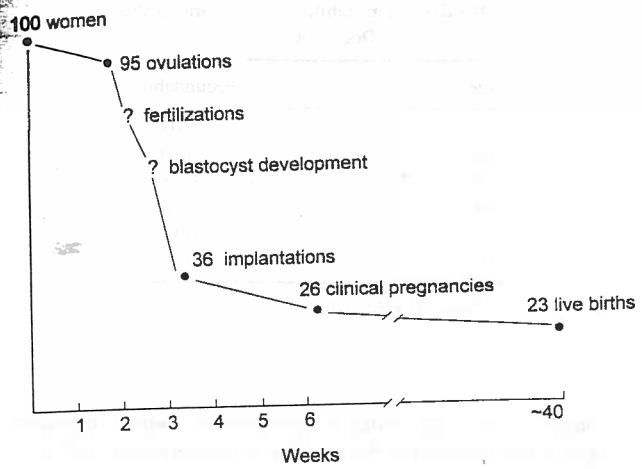

Fig. 11.2 Time line of reproductive failure. Of 100 sexually active women who start a noncontracepting menstrual cycle, approximately 95 will ovulate. An unknown number will have eggs fertilized and blastocysts develop. About 36 women will show urinary hCG evidence of pregnancy at around the time of implantation, but only about 26 of these pregnancies will survive long enough to be clinically detectable at about six weeks after the start of the last menstrual period. Compared to the earlier weeks, relatively little loss occurs after clinical detection. See text for references (figure adapted from Figure 1 in [21a]).

specimens from women trying to conceive. Early pregnancy losses can be identified by a rise and fall of hCG. The North Carolina Early Pregnancy Study, which used a very sensitive hCG assay, defined chemically detected pregnancies by hCG of 0.025 ng/ml or greater for at least 3 consecutive days, levels that exceeded those found in a group of women with tubal ligations [19]. In that study, 22% of chemically detected pregnancies were unrecognized clinically and another 2% were recognized clinically but lost within the same time period (*i.e.*, within six weeks of the start of the last menstrual period) [25]. Thus, very early postimplantation pregnancy loss was estimated to be 24%.

Two more studies tend to corroborate this estimate of early loss. Both followed somewhat similar protocols but used less sensitive assays for hCG (the North Carolina study used a polyclonal antibody to detect the intact molecule [26], and the antibody is no longer available). Bonde *et al.* [20] identified pregnancy by hCG $\geq$ 1 IU/L (0.076 ng/ml) in the first 10 days of the menstrual cycle following the conception cycle and reported a loss rate of 17%. Zinaman *et al.* [27] identified pregnancy by 3 consecutive days of hCG $>$ 0.15 ng/ml and reported a loss rate of 13%. If these two sets of criteria for detecting pregnancy are applied to the North Carolina data, the loss rates in that study would be 17% and 14%, respectively, suggesting that early loss rates in the three studies are remarkably similar.

Projecting these data onto the timeline of loss in Figure 11.2, we estimate that of the 100 women entering an attempt cycle, only 36 would have chemically detectable implantations. The combination of failure to fertilize, preimplantation loss, and loss at the time of implantation accounts for the majority of reproductive loss. By comparison, loss after clinical recognition is relatively small. Only about 3% of the original 100 cycles results in a clinically identified pregnancy that is lost spontaneously. This 3% represents a 10–15% spontaneous abortion rate [28,29] and a stillbirth rate (loss after 26 weeks) of less than 2% among clinical pregnancies [30].

Reproductive loss at the different stages involves alterations in diverse biological processes. Failure to ovulate can arise from impaired gamete production/maturation or from hormonal imbalance. Fertilization requires timely oocyte release, sexual intercourse, and transport of gametes through the female reproductive tract. Survival to clinical recognition requires successful blastocyst formation, uterine receptivity, and implantation. Failure in any of the biological processes will result in an apparent nonconceptive menstrual cycle. Factors that interfere with any of these biological processes will reduce fecundability.

IV. Factors Affecting Fecundability

Factors affecting fecundability may operate through any of the biological pathways necessary for successful development of a conceptus. Frequency and timing of sexual intercourse is obviously important. Though fecundability clearly depends on effects on both male and female partners, we focus the remainder of the section on factors affecting female fecundity. Many factors have been identified, but the mechanisms by which they influence fecundability may not be known. Such factors include age, reproductive tract infections, previous methods of birth control, health-related behaviors such as cigarette smoking and exercise, and occupational exposures. Past exposures with long-term adverse effects may be as important as current conditions. Even a woman's exposures during her prenatal development could influence future fecundability by affecting her reproductive tract development and lifetime supply of ova.

A. Frequency and Timing of Sexual Intercourse

Sexual intercourse must occur close enough to the time when the egg is released from the ovary for fertilization to occur. Two studies provide detailed data on the length of the fertile window and day-specific estimates of conception probabilities relative to the day of ovulation. A third large study is in progress with preliminary results published. The first study enrolled 241 couples who used natural family planning [31]. The data were reanalyzed by Schwartz *et al.* [32] who reported a 7-day fertile window ending on day of basal body temperature rise, with highest probabilities of conception on the middle three days. A 6-day fertile window ending on estimated day of ovulation was reported by Wilcox *et al.* [33]. Pregnancies were identified by assay of daily urine specimens and included pregnancies that were lost very early. Conception probabilities for the last three days of the 6-day window were about twice those of the earlier three days. However, the conceptions occurring on the day of ovulation were at high risk of very early loss [34]. The probability of conceiving a surviving pregnancy was highest on the two days before ovulation (Fig. 11.3). This pattern is consistent with the earlier study [32] and preliminary data from the ongoing European Multicenter Study [35].

Couples who have frequent intercourse will be more likely to have sex on days when the probability of conception is high, and these couples should have higher fecundability. This is

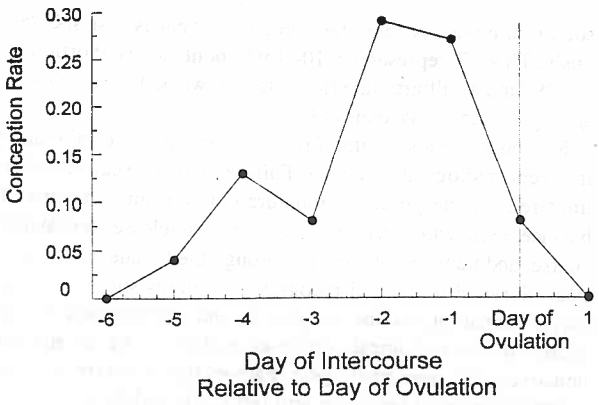

Fig. 11.3 The probability of clinical pregnancy following intercourse on a given day relative to ovulation. The estimated probability of conception is 0 outside of the 6-day window ending on the day of ovulation. Data are from the North Carolina Early Pregnancy Study (figure adapted from Figure 1 of [34]).

supported by data from natural fertility populations that show higher fecundability associated with recent marriage, an indirect measure of frequency of intercourse [10]. Higher fecundability also has been associated with frequent intercourse in studies based on interview data from women in the US [36,37]. Concern has been raised about possible adverse effects of too frequent intercourse (short abstinence time). Though a short abstinence time is associated with lower sperm count and sperm concentration [37a], even daily intercourse had no measureable adverse impact on fecundability in a study of couples with no known fertility problems [33,37b].

For couples having difficulty conceiving, purposeful timing of intercourse could be even more effective than increasing frequency, but some methods for timing intercourse are not optimal [38]. The basal body temperature shift comes too late. Urinary luteinizing hormone (LH) provides a signal close to ovulation [39], but gives no information about earlier fertile days. Couples using LH kits who wait for the urinary LH signal often will miss the two most fertile days. However, earlier days can be identified by cervical mucus characteristics [40]. Couples who have intercourse frequently after cervical mucus becomes receptive will tend to have intercourse on those days with the highest probabilities of conception.

B. Age

When age-specific fecundability data are available, women in their twenties usually show the highest fecundability. Table 11.2 shows this pattern in data from the Dogon. Effective fecundability had an inverse U-shaped relationship with the woman's age, peaking at 0.19 for ages 26–29 years [10]. The lower fecundability of adolescents is consistent with known menstrual cycle irregularities (including anovulation) in the years immediately following menarche [22,23]. The drop-off in fecundability with later ages is consistent with the decline in coital frequency usually found among older women [41]. However, women's fecundity also declines. A large French study of

Table 11.2
Effective Fecundability by Age among the Dogon of Mali

Age	Fecundability
15	0.03
20	0.10
25	0.18
30	0.18
35	0.11
40	0.03

Note. N = 50 [10].

women undergoing artificial insemination, whose husbands were sterile, found that the number of insemination cycles required for pregnancy increased with age [42]. Women in their twenties had the highest fecundability. It was somewhat lower for women in their early 30s, and those over 35 had a more marked reduction in fecundability. A similar study in the Netherlands has reported the same pattern [43].

The biological changes that underlie reduced fecundability in older women are not well understood. Several factors probably operate together. Ellison [44] summarizes three hormonal studies showing reduced levels of salivary progesterone in older cycling women. Others have considered the relative importance of egg quality and uterine receptivity [45]. Egg quality declines in older women, as demonstrated by higher pregnancy rates in older women having oocyte donation compared with other older women. However, the uterus also is implicated because among donor egg recipients, older women have lower pregnancy rates than younger women [45a]. Further research is needed to investigate other aspects of the reproductive process in older women. For example, do older women have fewer preovulatory days of fertile cervical mucus?

C. Lactation

Lactation suppresses ovulation and results in amenorrhea. Even after menses has resumed, breastfeeding appears to reduce fecundability. For example, in Assam, India, fecundability was 41% lower among cycling women who were breastfeeding compared to nonbreastfeeding women [46], and a strong effect also was seen in the Matlab of Bangladesh [15,16]. However, reproductive hormones are reported to return to normal cyclicity in the first couple of menstrual cycles after lactational amenorrhea [47,48], and fecundability also has been reported to rise rapidly during those first few menstrual cycles [47]. Thus, if women continue to breastfeed long after resumption of menses, this prolonged lactation may not reduce fecundability.

Leridon [14] points out how challenging it is to evaluate fecundability in postpartum women who nurse. Collecting sufficiently detailed time-dependent data on resumption of menses, nursing habits, and the inherently correlated factors of nutrition and health is very difficult. Small prospective studies in different ecologic settings that can collect detailed hormonal and nursing data along with information on sexual intercourse may

reveal more about lactation and subfecundity than large, less-detailed fecundability studies.

D. Pelvic Infection and Other Medical Conditions

Pelvic infections are a common cause of reduced fecundability and sterility [49]. Pathogens can ascend the female reproductive tract after vaginal entry and cause infection and subsequent scarring of the oviducts. Though tubal damage is the most studied sequelae of pelvic infections, chronic inflammation of the cervix and uterus might also reduce fecundability by interfering with gamete transport and implantation.

The sexually transmitted organisms, *Chlamydia trachomatis* and *Neisseria gonorrhoea* are the two widely recognized pathogens that cause pelvic inflammation [49]. Both are found throughout the world and are probably responsible for dramatically reduced fertility in sub-Saharan Africa [50]. In the United States, asymptomatic infection is thought to be even more common than diagnosed infection, and adverse effects on fecundability are not limited to symptomatic cases [49,51]. Trichomoniasis also has been associated with reduced fecundability [52].

Sexually transmitted pathogens may not be the only important microbes. A history of Cesarean-section [53] or a ruptured appendix [54] has been associated with reduced fecundability, and spread of infection to oviducts is a potential mechanism. Bacterial vaginosis and mycoplasmas also have been associated with pelvic disease [55,56]. It is not clear whether bacterial vaginosis directly reduces fecundability or predisposes the reproductive tract to infection by sexually transmitted organisms [57].

Other factors also may influence fecundability by affecting susceptibility to infection. The adverse effects on fertility associated with prior use of IUDs, especially the Dalkon Shield, is attributed to increased risk of pelvic infection [58,59]. On the other hand, the combination of barrier and chemical contraceptive methods (*e.g.*, diaphragm with spermicide) has been found to protect against tubal damage [60], presumably by reducing infection. Vaginal douching also may reduce fecundability by increasing susceptibility to infection [61]. Several studies show douching to be a risk factor for pelvic inflammatory disease (reviewed in Zhang *et al.* [62]), and supporting laboratory work shows that douching can reduce the prevalence of vaginal lactobacillus, a bacterium that protects against pathogens [63].

Several other medical conditions in women are associated with reduced fecundability, the most common being thyroid disease [64], endometriosis [65], polycystic ovary syndrome [66], and uterine fibroids [67]. Shared HLA-DR serotypes between male and female partners also may reduce fecundability [68].

E. Nutrition and Exercise

A woman's nutritional status and energy balance are expected to influence fecundability [69], but data are limited. Extreme cases of malnutrition, as in anorexia, result in anovulation and amenorrhea [70]. Similarly, intense physical training, as for ballet dancers or marathon runners, can result in anovulation and amenorrhea [71].

Effects on fecundability of more moderate nutrient deficits or exercise regimens are unclear, but menstrual cycle hormones are known to be affected. Bullen *et al.* [72] reported reduced luteal progesterone levels in untrained women after starting an exercise program. Salivary progesterone data from four separate studies (Boston, Poland, Zaire, and Nepal) showed similar patterns associated with energetic stress (reviewed by Ellison [44]). The Boston women were on a voluntary exercise program, the Polish women did seasonal agricultural work with no mechanized farm equipment, and the women in Zaire and Nepal belonged to subsistence populations with highly seasonal food resources. The latter two populations also were known to have seasonal changes in birth rates consistent with low fecundability in seasons of high energetic stress.

Despite hormonal evidence, actual links between hormones and fecundability in these populations have not been demonstrated. Higher luteal progesterone is associated with higher fecundability in some, but not all, of the few available studies, and these were all conducted in the US (summarized in Baird *et al.*, [73]).

John *et al.* initiated a study in Bangladesh designed to assess fecundability changes with chronic undernutrition [15,16]. They measured women's height and collected weight data monthly to determine changes in body mass. However, this measure of nutrition had no significant effect on fecundability. The nonsignificant results led the investigators to conclude that seasonality of conceptions in Bangladesh may have more to do with changes in coital frequency than to changes in nutrition. Physiologic studies in laboratory animals suggest that sexual behavior may be more sensitive than ovarian function to increased energetic demand [74].

Nutritional balance is more than just getting enough calories. Body fat may not be the best marker; specific nutrients may be more important. This is supported by findings from a clinical trial of folate supplementation designed to evaluate the vitamin's effects on birth defects. After randomization, the folate-supplemented group had significantly higher pregnancy rates [75]. These findings suggest the need for investigation of more nutritional markers when studying fecundability.

F. Obesity and Body Weight Distribution

Obese women tend to take longer to conceive than women of normal weight [76–78], probably because of endocrine imbalances (reviewed in Harlow and Ephross [79]). A history of obesity in adolescence is associated with reduced fecundity regardless of adult body mass [78,80]. The distribution of fat in the body also has been found to be associated with fecundability [81]. A 0.1 unit increase in waist-hip ratio (*e.g.*, the difference between a 26-inch waist and a 30-inch waist for women with 36-inch hips) was associated with a 30% decrease in fecundability. Women with higher waist-hip ratios have been reported to have low pH of the endocervical mucus and higher androgen levels [82].

To what extent elevated androgen levels and subclinical polycystic ovarian disease may be an underlying mechanism for obesity-related subfecundity is unknown. A 13-year follow-up study of adolescent girls showed that androgen levels tended to track over time (*i.e.*, higher adolescent levels were predictive of higher levels later in life) [83]. Furthermore, those with high androgen levels were less likely to have become pregnant during the 13-year follow-up, and this could not be explained by

other factors such as differences in sexual behavior or use of oral contraceptives. Further longitudinal research on androgen levels, the relationship with fecundability, and early-life factors that might cause elevation in androgen levels is needed.

G. Oral Contraceptives and Other Medication

Oral contraceptives were introduced in the 1960s, and by 1970 Wolfers [84] had shown that pill users had a temporary reduction in fertility during the first few months after discontinuing pill use. The effect appears to be mediated by endocrine effects [85]. The short-term subfecundity was substantiated by Harlap and Baras [86] who found a 30% reduction in the first month after discontinuation. The temporary reduction is followed by cycles during which pill users appear to have higher fecundability than the other women still attempting pregnancy. The effect was more marked in older women who had used the pill for longer durations. Pill users did not show more long conception waits (>12 months). The absence of long-term adverse fecundity effects of pill use has been substantiated in the Nurses Health Study [87]. A recent study also found temporary subfecundity after stopping the pill [20], suggesting that this effect occurs even with the new low-dose medication.

Little research has been done to evaluate effects of other common medications. This is a difficult area of research because women who take a medication have some underlying condition that might account for any observed decrease in fecundability. A case-control study of self-reported prescription medication use and ovulatory infertility found associations with thyroid preparations, antidepressants, tranquilizers, and asthma medication [88], but no adjustments could be made for underlying disease.

Laboratory animal evidence suggests that analgesic medications such as aspirin, indomethacin, and the nonsteroidal anti-inflammatory drugs like ibuprofen may reduce fecundability, but human evidence is still very limited. These drugs block prostaglandin production by inhibiting the cyclooxygenase enzymes. The reproductive function of these enzymes has been studied in knockout mice that lack the gene for one or the other of the two cyclooxygenase enzymes, COX-I or COX-II. COX-II appears to be necessary for implantation and also for release of the egg from the ovary during ovulation [89]. Thus, the cyclooxygenase inhibiting drugs might be expected to result in reduced fecundability in women. Small experimental studies of egg release measured by ultrasound show retention of eggs in women given indomethacin [90,91]. Ibuprofen has not been studied, but may show similar adverse effects when taken around the time of ovulation.

H. Prenatal Factors

A woman's lifetime supply of eggs is produced during fetal life, peaking at around six months gestation [66]. Prenatal exposures might reduce fecundability during adulthood by limiting egg numbers or affecting egg quality. Prenatal exposures can also affect reproductive tract development. Diethylstilbestrol (DES) provides the best documented example in humans. Prenatally exposed women are at higher risk for many reproductive problems, including reduced fecundability [92].

Reduced fecundability associated with reduced oocyte numbers has been demonstrated in laboratory animals exposed prenatally to benzo(a)pyrene, a component of cigarette smoke [93]. In women, prenatal exposure to cigarette smoke has been linked to reduced fecundability in one study [94], but not in others [95,96].

Repositories of data (and sometimes serum samples) from past studies of large cohorts of pregnant women present resources for research on prenatal effects on fecundability (*e.g.*, the California Child Health and Development Study and the Collaborative Perinatal Study). The daughters born to the participants are now adults whose fecundability can be studied [96]. Data on prenatal exposures are available from interviews conducted with their mothers during pregnancy.

I. Lifestyle Factors

Cigarette smoking was first linked with reduced fecundability in a Danish study in 1983 [97], and the relationship was investigated in several studies during the subsequent decade with most studies finding adverse effects (reviewed by Baird [98]). The association has been most convincingly confirmed in a multicenter study based on data from nine areas in Europe [99]. The researchers reported that nulliparous women smoking >10 cigarettes/day had significantly reduced fecundability. Results were fairly consistent across study populations, making it quite unlikely that the effect could be explained by bias.

Alcohol drinking also was linked to reduced fecundability in the 1983 Danish study [97]. Though very heavy drinking has clear adverse effects on fecundability [100,101], studies of moderate alcohol consumption have shown little consistency [102]. However, a report from the Danish prospective study of fecundability found adverse effects of even moderate alcohol consumption (1–5 drinks/week) [102a]. This study collected detailed data on alcoholic beverage consumption during each menstrual cycle of trying, thus providing more accurate data than were available in any of the previous studies. It may be that prior studies failed to find effects because of excessive misclassification of alcohol intake.

Caffeine and reduced fecundability was first reported in 1988 [103] for a subset of study participants who presumably provided the best data on caffeine intake. Results from further studies have been inconsistent, showing adverse, positive, and no measurable effect (reviewed in Dlugosz and Bracken [104] and Jensen *et al.* [105]). Furthermore, adverse caffeine effects are often found only in subgroups of study populations. For example, Olsen [106] found an effect only for smokers with very high caffeine intake, whereas Stanton and Gray [107] found an association only in nonsmokers. Results from the European Study of Infertility and Subfecundity, with data from five locations, show a small reduction in fecundability (10% reduction) only at very high caffeine levels, the effect being somewhat stronger in smokers [108]. A prospective study with cycle-specific caffeine data showed a weak (nonsignificant) decrease in fecundability only in nonsmokers [105]. The effect that is reported also is not consistent across various types of caffeinated beverages [109]. Because coffee drinking is related to other health-related behaviors like smoking and stress, the small effects seen in most studies could be explained by poorly measured associations with

other factors. At this point, no clear conclusions can be drawn. An intervention study with detailed prospectively recorded caffeine data may be the only way to clarify the issue.

Psychological stress has been associated with infertility problems, but because psychological stress has been measured after fertility problems are recognized, it may well be a result, rather than a cause, of reduced fecundability [110]. One prospective study measured psychological stress before couples had ever tried to conceive [111]. They reported reduced fecundability in stressed women whose menstrual cycles were long, but not in the majority of stressed women, and suggested those with long cycles may represent women who were particularly susceptible to stress. An intervention study designed to evaluate the effects of a stress-reduction program for infertility patients is now being conducted in the United States. Only more prospective studies can provide meaningful information on this important issue.

J. Occupational Exposures

The discovery of reduced fertility and sterility in males exposed to the fumigant dibromochloropropane [112] focused attention on occupational effects on fecundability. The initial search was directed at male exposure and its effects on semen characteristics, but subsequent studies have included or even focused on occupational effects on females. The first was a Danish study that examined a broad range of occupations and chemical and physical exposures in both men and women [113]. In the 1990s came reports of adverse effects for women associated with nitrous oxide [37], video display terminals [114], mercury vapor [115], and pharmacists working with antibiotics [116] (see reviews in Gold and Tomich [117] and Baird *et al.* [118]). Other studies have implicated employment as a hairdresser [119], shift work [120,121], employment requiring high energy demand or long hours [122,123], pesticides [124,125], lead [126], and solvents [125,127–129].

However, other studies find little evidence for occupational exposures adversely affecting women's fecundability (*e.g.*, Spinelli *et al.* [130]), and results for specific exposures often show apparently differing results. The lack of consistent findings is not surprising. Unless a study is focused on a group of exposed women, the number of women with a given occupational exposure often will be too few to estimate effects. Also, exposures usually have been assessed by self report of past employment situations so that exposure levels may not be comparable across studies. Future studies will need to focus more on enrolling large numbers of exposed women and quantifying exposure more precisely.

V. Summary and Directions for Future Research

The description of fecundability began with demographers and has only recently been addressed by epidemiologists and anthropologists. The available data suggest that fecundability may vary widely among populations. Differences between natural fertility populations and contracepting populations appear to be much smaller than variability within each group. Some differences in fecundability probably reflect different study designs and methodology, but known determinants of fecundability also differ among populations. No study has systematically tried to compare fecundability estimates among populations by adjusting for differences in age, frequency of intercourse, and prevalence of *Chlamydia* and gonorrhea.

Methodology for anthropologic and epidemiologic investigation of fecundability is still being developed, and issues of validity and bias have been addressed [21a,131–134]. Prospective studies can provide accurate waiting-time data but involve select populations with limited generalizability. Retrospective studies also have their own methodologic challenges. Though research supports the general validity of recalled time-to-pregnancy data [135,136], studies based on recall data involve pregnancy attempts that began at various times in the past. Variation over time in family planning practices, desired family size, and prevalence of exposures can be difficult to adjust for in such studies.

Concern has been raised about whether fecundity has declined with the possible increase of reproductive toxicants in the environment [137,138]. However, fecundability in developing countries shows increases over time [139]. Given the current limitations in methodology, it is easier to study the effects on fecundability of specific exposures than to compare fecundability over time.

Perhaps the most efficient research strategy is to incorporate multiple approaches. Studies of fecundability in the general population (such as the European Infertility and Subfecundity Studies) can provide data on prevalent lifestyle factors like cigarette smoking and can provide insight into methodologic issues of measurement and selection bias. Any exposure that is only experienced by a small portion of the population (which includes most occupational exposures) must be studied in specially identified groups known to have high prevalence of exposure (*e.g.*, selection of microelectronics workers for study of glycol ethers).

Combining fecundability studies with laboratory research designed to elucidate possible biological mechanisms can be very helpful. For example, data showing adverse effects of vaginal douching on fecundability are very limited, but laboratory data showing that douching can shift the vaginal ecology toward pathogen susceptibility makes the fecundability data more persuasive. Similarly, if folate supplementation were found to enhance follicular growth, support more rapid midcycle luteinization, or reduce very early pregnancy loss, the limited data on fecundability effects would be more convincing. Future research that involves collaboration among biologists, toxicologists, epidemiologists, and anthropologists is likely to have the most impact.

Acknowledgments

We thank Robert McConnaughey for graphical displays, Andrew Rowland and Allen Wilcox who provided useful comments on an earlier draft of the manuscript, and NIEHS library staff who assisted in locating literature.

References

1. Famighette, R., ed. (1996). "The World Almanac and Book of Facts, 1997." World Almanac Books, Mahwah, NJ.
2. Wood, J. (1994). "Dynamics of Human Reproduction: Biology, Biometry, Demography." de Gruyter, New York.
3. Abma, J., Chandra, A., Mosher, W., Peterson, L., and Piccinino, L. (1997). Fertility, family planning, and women's health: New

data from the 1995 National Survey of Family Growth. National Center for Health Statistics. *Vital Health Stat.* **23**(19), 1–114.
4. National Center for Health Statistics (1997). "Health and Injury Chartbook." U.S. National Center for Health Statistics, Hyattsville, MD.
5. Greenhall, E., and Vessey, M. (1990). The prevalence of subfertility: A review of the current confusion and a report of two new studies. *Fertil. Steril.* **54,** 978–983.
6. Leridon, H. (1977). "Human Fertility: The Basic Components." University of Chicago Press, Chicago.
7. Campbell, K. L., and Wood, J. W. (1988). Fertility in traditional societies. *In* "Natural Human Fertility: Social and Biological Determinants" (P. Diggory, M. Potts, and S. Teper, eds.), pp. 39–69. Macmillan, London.
8. Wood, J. (1990). Fertility in anthropological populations. *Ann. Rev. Anthropol.* **19,** 211–242.
9. Strassmann, B. I. (1997). The biology of menstruation in *Homo sapiens:* Total lifetime menses, fecundity, and nonsynchrony in a natural fertility population. *Curr. Anthropol.* **38,** 123–129.
10. Strassmann, B. I., and Warner, J. (1998). Predictors of fecundability and conception waits among the Dogon of Mali. *Am. J. Phys. Anthropol.* **105,** 167–184.
11. Wood, J. W., Holman, D. J., Yashin, A. I., Peterson, R. J., Weinstein, M., and Chang, M.-C. (1994). A multistate model of fecundability and sterility. *Demography* **31,** 403–426.
12. Wood, J. W. (1989). Fecundity and natural fertility in humans. *Oxford Rev. Reprod. Biol.* **11,** 61–109.
13. Goldman, N., Westoff, C. F., and Paul, L. E. (1985). Estimation of fecundability from survey data. *Stud. Fam. Plann.* **16,** 252–259.
14. Leridon, H. (1993). Fecundability and postpartum sterility: An insuperable interaction? *In* "Biomedical and Demographic Determinants of Reproduction" (R. Gray, H. Leridon, and A. Spira, eds.), pp. 345–358. Clarendon Press, Oxford.
15. John, A. M., Menken, J. A., and Chowdhury, A. K. M. A. (1987). The effects of breastfeeding and nutrition on fecundability in rural Bangladesh: A hazards-model analysis. *Popul. Stud.* **41,** 433–446.
16. John, A. M. (1988). Lactation and the waiting time to conception: An application of hazard models. *Hum. Biol.* **60,** 873–888.
17. Strassmann, B. I. (1996). Menstrual hut visits by Dogon women: A hormonal test distinguishes deceit from honest signaling. *Behav. Ecol.* **7,** 304–315.
18. Tietze, C. (1968). Fertility after discontinuation of intrauterine and oral contraception. *Int. J. Fertil.* **13,** 385–389.
19. Wilcox, A. J., Weinberg, C. R., O'Connor, J. F., Baird, D. D., Schlatterer, J. P., Canfield, R. E., Armstrong, E. G., and Nisula, B. C. (1988). Incidence of early loss of pregnancy. *N. Engl. J. Med.* **319,** 189–194.
20. Bonde, J. P. E., Hjollund, N. H. I., Jensen, T. K., Ernst, E., Kolstad, H., Henriksen, T. B., Giwercman, A., Skakkebaek, N. E., Andersson, A.-M., and Olsen, J. (1998). A follow-up study of environmental and biologic determinants of fertility among 430 Danish first-pregnancy planners: Design and methods. *Reprod. Toxicol.* **12,** 19–27.
21. Henshaw, S. K. (1998). Unintended pregnancy in the United States. *Fam. Plann. Perspect.* **30,** 24–29, 46.
21a. Baird, D. D., Wilcox, A. J., and Weinberg, C. R. (1986). Use of time to pregnancy to study environmental exposures. *Am. J. Epidemiol.* **124,** 470–480.
22. Doring, G. K. (1969). The incidence of anovular cycles in women. *J. Reprod. Fertil. Suppl.* **6,** 77–81.
23. Metcalf, M. G. (1983). Incidence of ovulation from the menarche to the menopause: Observations of 622 New Zealand women. *N. Z. Med. J.* **96,** 645–648.
24. Edwards, R. G. (1985). Current status of human conception *in vitro. Proc. R. Soc. London, Ser. B* **223,** 417–448.
25. Weinberg, C. R., Hertz-Picciotto, I., Baird, D. D., and Wilcox, A. J. (1992). Efficiency and bias in studies of early pregnancy loss. *Epidemiology* **3,** 17–22.
26. Armstrong, E. G., Ehrlich, P. H., Birken, S. *et al.* (1984). Use of a highly sensitive and specific immunoradiometric assay for detection of human chorionic gonadotropin in urine of normal, nonpregnant, and pregnant individuals. *J. Clin. Endocrinol. Metab.* **59,** 867–874.
27. Zinaman, M. J., O'Connor, J., Clegg, E. D., Selevan, S. G., and Brown, C. C. (1996). Estimates of human fertility and pregnancy loss. *Fertil. Steril.* **65,** 503–509.
28. Harlap, S., Shiono, P. H., and Ramcharan, S. (1980). A life table of spontaneous abortions and the effects of age, parity and other variables. *In* "Human Embryonic and Fetal Death" (I. H. Porter and E. B. Hook, eds.), pp. 145–164. Academic Press, New York.
29. Goldhaber, M. K., and Fireman, B. H. (1991). The fetal life table revisited: Spontaneous abortion rates in three Kaiser Permanente cohorts. *Epidemiology* **2,** 33–39.
30. Feldman, G. B. (1992). Prospective risk of stillbirth. *Obstetr. Gynecol.* **79,** 547–553.
31. Barrett, J. C., and Marshall, J. (1969). The risk of conception on different days of the menstrual cycle. *Popul. Stud.* **23,** 455–461.
32. Schwartz, D., MacDonald, P. D. M., and Heuchel, V. (1980). Fecundability, coital frequency and the viability of ova. *Popul. Stud.* **34,** 397–400.
33. Wilcox, A. J., Weinberg, C. R., and Baird, D. D. (1995). Timing of sexual intercourse in relation to ovulation: Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N. Engl. J. Med.* **333,** 1517–1521.
34. Wilcox, A. J., Weinberg, C. R., and Baird, D. D. (1998). Postovulatory ageing of the human oocyte and embryo failure. *Hum. Reprod.* **13,** 394–397.
35. Masarotto, G., and Romualdi, C. (1997). Probability of conception on different days of the menstrual cycle: An ongoing exercise. *Adv. Contraception* **13,** 105–115.
36. Baird, D. D., and Wilcox, A. J. (1985). Cigarette smoking associated with delayed conception. *J. Am. Med. Assoc.* **253,** 2979–2983.
37. Rowland, A. S., Baird, D. D., Weinberg, C. R., Shore, D. L., Shy, C. M., and Wilcox, A. J. (1992). Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. *N. Engl. J. Med.* **327,** 993–997.
37a. Blackwell, J. M., and Zaneveld, L. J. D. (1992). Effect of abstinence on sperm acrosin, hypoosmotic swelling, and other semen variables. *Fertil. Steril.* **58,** 798–802.
37b. Zhou, H., and Weinberg, C. R. (1996). Modeling conception as an aggregated Bernoulli outcome with latent variables via the EM algorithm. *Biometrics* **52,** 945–954.
38. Agarwal, S. K., and Haney, A. F. (1994). Does recommending timed intercourse really help the infertile couple? *Obstet. Gynecol.* **84,** 307–310.
39. Collins, W. P., Branch, C. M., Collins, P. O., and Sallam, H. M. (1983). Biochemical indices of the fertile period in women. *Int. J. Fertil.* **26,** 196–202.
40. Katz, D. F., Slade, D. A., and Nakajima, S. T. (1997). Analysis of pre-ovulatory changes in cervical mucus hydration and sperm penetrability. *Adv. Contraception* **13,** 143–151.
41. Frank, O., Bianchi, P. G., and Campana, A. (1994). The end of fertility: Age, fecundity and fecundability in women. *J. Biosoc. Sci.* **26,** 349–368.
42. Federation CECOS, Schwartz, D., and Mayaux, M. J. (1982). Female fecundity as a function of age. *N. Engl. J. Med.* **306,** 404–406.
43. Van Noord-Zaadstra, B. M., Looman, C. W. N., Alsbach, H., Habbema, J. D. F., te Velde, E. R., and Karbaat, J. (1991). Delay-

ing childbearing: Effect of age on fecundity and outcome of pregnancy. *Br. Med. J.* **302,** 1361–1365.
44. Ellison, P. T. (1994). Salivary steroids and natural variation in human ovarian function. *Ann. N. Y. Acad. Sci.* **709,** 287–298.
45. Pellicer, A., Simon, C., and Remohi, J. (1995). Effects of aging on the female reproductive system. *Hum. Reprod.* **10**(Suppl. 2), 77–83.
45a. Meldrum, D. R. (1993). Female reproductive aging—ovarian and uterine factors. *Fertil. Steril.* **59,** 1–5.
46. Singh, K. K., Suchindran, C. M., and Singh, K. (1993). Effects of breast feeding after resumption of menstruation on waiting time to next conception. *Hum. Biol.* **65,** 71–86.
47. Diaz, S., Miranda, P., Cardenas, H., Salvatierra, A. M., Brandeis, A., and Croxatto, H. B. (1992). *Fertil. Steril.* **58,** 498–503.
48. Campbell, O. M. R., and Gray, R. H. (1993). Characteristics and determinants of postpartum ovarian function in women in the United States. *Am. J. Obstet. Gynecol.* **169,** 55–60.
49. Cates, W., Jr., Wasserheit, J. N., and Marchbanks, P. A. (1994). Pelvic inflammatory disease and tubal infertility: The preventable conditions. *Ann. N. Y. Acad. Sci.* **709,** 179–195.
50. Cates, W., Farley, T. M. M., and Rowe, P. J. (1985). Worldwide patterns of infertility: Is Africa different? *Lancet* **2,** 596–598.
51. Cates, W., Jr., Joesoef, M. R., and Goldman, M. B. (1993). Atypical pelvic inflammatory disease: Can we identify clinical predictors? *Am. J. Obstet. Gynecol.* **169,** 341–346.
52. Grodstein, F., Goldman, M. B., and Cramer, D. W. (1993). Relation of tubal infertility to history of sexually transmitted diseases. *Am. J. Epidemiol.* **137,** 577–584.
53. Hemminki, E., Graubard, B. I., Hoffman, H. J., Mosher, W. D., and Fetterly, K. (1985). Cesarean section and subsequent fertility: Results from the 1982 National Survey of Family Growth. *Fertil. Steril.* **43,** 520–528.
54. Mueller, B. A., Daling, J. R., Moore D. E., Weiss, N. S., Spadoni, L. R., Stadel, B. V., and Soules, M. R. (1986). Appendectomy and the risk of tubal infertility. *N. Engl. J. Med.* **315,** 1506–1508.
55. Sweet, R. L. (1995). Role of bacterial vaginosis in pelvic inflammatory disease. *Clin. Infect. Dis.* **20**(Suppl. 2), S271–S275.
56. Koch, A., Bilina, A., Teodorowicz, L., and Stary, A. (1997). *Mycoplasma hominis* and *Ureaplasma urealyticum* in patients with sexually transmitted diseases. *Wien. Klin. Wochenschr.* **109,** 584–589.
57. Hill, G. B. (1993). The microbiology of bacterial vaginosis. *Am. J. Obstet. Gynecol.* **169,** 450–454.
58. Daling, J. R., Weiss, N. S., Metch, B. J., Chow, W. H., Soderström, R. M., Moore, D. E., Spadoni, L. R., and Stadel, B. V. (1985). Primary tubal infertility in relation to the use of an intrauterine device. *N. Engl. J. Med.* **312,** 937–941.
59. Cramer, D. W., Schiff, I., Schoenbaum, S. C., Gibson, M. Belisle, S., Albrecht, B., Stillman, R. J., Berger, M. J., Wilson, E., Stadel, B. V., and Seibel, M. (1985). Tubal infertility and the intrauterine device. *N. Engl. J. Med.* **312,** 941–947.
60. Cramer, D. W., Goldman, M. B., Schiff, I., Belisle, S., Albrecht, B., Stadel, B., Gibson, M., Wilson, E., Stillman, R., and Thompson, I. (1987). The relationship of tubal infertility to barrier method and oral contraceptive use. *J. Am. Med. Assoc.* **257,** 2446–2450.
61. Baird, D. D., Weinberg, C. R., Voigt, L. F., and Daling, J. R. (1996). Vaginal douching and reduced fertility. *Am. J. Public Health* **86,** 844–850.
62. Zhang, J., Thomas, A. G., and Leybovich, E. (1997). Vaginal douching and adverse health effects: A meta-analysis. *Am. J. Public Health* **87,** 1207–1211.
63. Hillier, S. L. (1991). The vagina as an ecosystem. *9th Int. Meet. Int. Soc. STD Res.*, Banff, Alberta, Canada, 1991.
64. Koutras, D. A. (1997). Disturbances of menstruation in thyroid disease. *Ann. N. Y. Acad. Sci.* **816,** 280–284.
65. Moen, M. H., and Schei, B. (1997). Epidemiology of endometriosis in a Norwegian county. *Acta Obstet. Gynecol. Scand.* **76,** 559–562.
66. Speroff, L., Glass, R. H., and Kase, N. G., eds. (1994). "Clinical Gynecologic Endocrinology and Infertility," 5th ed. Williams & Wilkins, Baltimore, MD.
67. Farhi, J., Ashkenazi, J., Feldberg, D., Dicker, D., Orvieto, R., and Ben-Rafael, Z. (1995). Effect of uterine leiomyomata on the results of in-vitro fertilization treatment. *Hum. Reprod.* **10,** 2576–2578.
68. Ober, C., Elias, S., Kostyu, D. D., and Hauck, W. W. (1992). Decreased fecundability in Hutterite couples sharing HLA-DR. *Am. J. Hum. Genet.* **50,** 6–14.
69. Warren, M. P. (1983). Effects of undernutrition on reproductive function in the human. *Endocr. Rev.* **4,** 363–377.
70. Copeland, P. M., Sacks, N. R., and Herzog, D. B. (1995). Longitudinal follow-up of amenorrhea in eating disorders. *Psychosom. Med.* **57,** 121–126.
71. Henley, K., and Vaitukaitis, J. L. (1988). Exercise-induced menstrual dysfunction. *Ann. Rev. Med.* **39,** 443–451.
72. Bullen, B. A., Skrinar, G. S., Beitins, I. Z., von Mering, G., Turnbull, B. A., and McArthur, J. W. (1985). Induction of menstrual disorders by strenuous exercise in untrained women. *N. Engl. J. Med.* **312,** 1349–1353.
73. Baird, D. D., Wilcox, A. J., Weinberg, C. R., Kamel, F., McConnaughey, D. R., Musey, P. I., and Collins, D. C. (1997). Preimplantation hormonal differences between the conception and non-conception menstrual cycles of 32 normal women. *Hum. Reprod.* **12,** 2607–2613.
74. Wade, G. N., Schneider, J. E., and Li, H-Y. (1996). Control of fertility by metabolic cues. *Am. J. Physiol.* **270,** E1–E19.
75. Czeizel, A. E., Dudas, I., and Metneki, J. (1994). Pregnancy outcomes in a randomised controlled trial of periconceptional multivitamin supplementation: Final report. *Arch. Gynecol. Obstet.* **255,** 131–139.
76. Green, B. B., Weiss, N. S., and Daling, J. R. (1988). Risk of ovulatory infertility in relation to body weight. *Fertil. Steril.* **50,** 721–726.
77. Grodstein, F., Goldman M. B., and Cramer, D. W. (1994). Body mass index and ovulatory infertility. *Epidemiology* **5,** 247–250.
78. Lake, J. K., Power, C., and Cole, T. J. (1997). Women's reproductive health: The role of body mass index in early and adult life. *Int. J. Obes. Relat. Metab. Disord.* **21,** 432–438.
79. Harlow, S. D., and Ephross, S. A. (1995). Epidemiology of menstruation and its relevance to women's health. *Epidemiol. Rev.* **17,** 265–286.
80. Rich-Edwards, J. W., Goldman, M. B., Willett, W. C., Hunter, D. J., Stampfer, M. J., Colditz, G. A., and Manson, J. E. (1994). Adolescent body mass index and infertility caused by ovulatory disorder. *Am. J. Obstet. Gynecol.* **171,** 171–177.
81. Zaadstra, B. M., Seidell, J. C., Van Noord, P. A. H., te Velde, E. R., Habbema, J. D. F., Vrieswijk, B., and Karbaat, J. (1993). Fat and female fecundity: Prospective study of effect of body fat distribution on conception rates. *Br. Med. J.* **306,** 484–487.
82. Jenkins, J. M., Brook, P. F., Sargeant, S., and Cooke, I. D. (1995). Endocervical mucus pH is inversely related to serum androgen levels and waist to hip ratio. *Fertil. Steril.* **63,** 1005–1008.
83. Apter, D., and Vihko, R. (1990). Endocrine determinants of fertility: Serum androgen concentrations during follow-up of adolescents into the third decade of life. *J. Clin. Endocrinol. Metab.* **71,** 970–974.
84. Wolfers, D. (1970). The probability of conception after discontinuance of oral contraceptives: A note on "Oral contraception, coital frequency, and the time required to conceive" by Westoff, Bumpass, and Ryder. *Soc. Biol.* **17,** 57.

85. Rice-Wray, E., Correu, S., Gorodovsky, J., Esquivel, J., and Goldzieher, J. W. (1967). Return of ovulation after discontinuance of oral contraceptives. *Fertil. Steril.* **18,** 212–218.
86. Harlap, S., and Baras, M. (1984). Conception-waits in fertile women after stopping oral contraceptives. *Int. J. Fertil.* **29,** 73–80.
87. Chasan-Taber, L., Willett, W. C., Stampfer, M. J., Spiegelman, D., Rosner, B. A., Hunter, D. J., Colditz, G. A., and Manson, J. E. (1997). Oral contraceptives and ovulatory causes of delayed fertility. *Am. J. Epidemiol.* **146,** 258–265.
88. Grodstein, F., Goldman M. B., Ryan, L., and Cramer, D. W. (1993). Self-reported use of pharmaceuticals and primary ovulatory infertility. *Epidemiology* **4,** 151–156.
89. Lim, H., Paria, B. C., Das, S. K., Dinchuk, J. E., Langenbach, R., Trzaskos, J. M., and Dey, S. K. (1997). Multiple female reproductive failures in cyclooxygenase 2-deficient mice. *Cell (Cambridge, Mass.)* **91,** 197–208.
90. Athanasiou, S., Crayford, T. J. B., Bourne, T. H., Hagström, H.-G., Khalid, A., Campbell, S., Okokon, E. V., and Collins, W. P. (1996). Effects of indomethacin on follicular structure, vascularity, and function over the periovulatory period in women. *Fertil. Steril.* **65,** 556–560.
91. Killick, S., and Elstein, M. (1987). Pharmacologic production of luteinized unruptured follicles by prostaglandin synthetase inhibitors. *Fertil. Steril.* **47,** 773–777.
92. Senekjian, E. K., Potkul, R. K., Frey, K., and Herbst, A. L. (1988). Infertility among daughters either exposed or not exposed to diethylstilbestrol. *Am. J. Obstet. Gynecol.* **158,** 493–498.
93. MacKenzie, K. M., and Angevine, D. M. (1981). Infertility in mice exposed in utero to benzo(a)pyrene. *Biol. Reprod.* **24,** 183–191.
94. Weinberg, C. R., Wilcox, A. J., and Baird D. D. (1989). Reduced fecundability in women with prenatal exposure to cigarette smoking. *Am. J. Epidemiol.* **129,** 1072–1078.
95. Baird, D. D., and Wilcox, A. J. (1986). Future fertility after prenatal exposure to cigarette smoke. *Fertil. Steril.* **46,** 368–372.
96. Schwingl, P. (1992). Prenatal smoking exposure in relation to female adult fecundability. Doctoral Dissertation, University of North Carolina, Chapel Hill.
97. Olsen, J., Rachootin, P., Schiodt, A. V., and Damsbo, N. (1983). Tobacco use, alcohol consumption and infertility. *Int. J. Epidemiol.* **12,** 179–184.
98. Baird, D. D. (1992). Evidence for reduced fecundity in female smokers. *In* "Effects of Smoking on the Fetus, Neonate, and Child," pp. 5–22. Oxford University Press, Oxford.
99. Bolumar, F., Olsen, J., Boldsen, J., and the European Study Group on Infertility and Subfecundity (1996). Smoking reduces fecundity: A European multicenter study on infertility and subfecundity. *Am. J. Epidemiol.* **143,** 578–587.
100. Wilsnack, S. C., Klassen, A. D., and Wilsnack, R. W. (1984). Drinking and reproductive dysfunction among women in a 1981 national survey. *Alcohol.: Clin. Exp. Res.* **8,** 451–458.
101. Mello, N. K., Mendelson, J. H., King, N. W., Bree, M. P., Skupny, A., and Ellingboe, J. (1988). Alcohol self-administration by female macaque monkeys: A model for study of alcohol dependence, hyperprolactinemia and amenorrhea. *J. Stud. Alcohol* **49,** 551–560.
102. Olsen, J., Bolumar, F., Boldsen, J., Bisanti, L., and the European Study Group on Infertility and Subfecundity (1997). Does moderate alcohol intake reduce fecundability? A European multicenter study on infertility and subfecundity. *Alcohol.: Clin. Exp. Res.* **21,** 206–212.
102a. Jensen, T. K., Hjollund, N. H. I., Henriksen, T. B., Scheike, T., Kolsad, H., Giwercman, A., Ernst, E., Bonde, J. P., Skakkebaek, N. E., and Olsen, J. (1998). Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. *Br. Med. J.* **317,** 505–510.
103. Wilcox, A. J., Weinberg, C. R., and Baird, D. D. (1988). Caffeinated beverages and decreased fertility. *Lancet* **2,** 1453–1456.
104. Dlugosz, L., and Bracken, M. B. (1992). Reproductive effects of caffeine: A review and theoretical analysis. *Epidemiol. Rev.* **14,** 83–100.
105. Jensen, T. K., Henriksen, T. B., Hjollund, N. H. I., Scheike, T., Kolstad, H., Giwercman, A., Ernst, E., Bonde, J. P., Skakkebaek, N. E., and Olsen, J. (1998). Caffeine intake and fecundability: A follow-up study among 430 Danish couples planning their first pregnancy. *Reprod. Toxicol.* **12,** 289–295.
106. Olsen, J. (1991). Cigarette smoking, tea and coffee drinking, and subfecundity. *Am. J. Epidemiol.* **133,** 734–739.
107. Stanton, C. K., and Gray, R. H. (1995). Effects of caffeine consumption on delayed conception. *Am. J. Epidemiol.* **142,** 1322–1329.
108. Bolumar, F., Olsen, J., Rebagliato, M., Bisanti, L., and the European Study Group on Infertility and Subfecundity (1997). Caffeine intake and delayed conception: A European Multicenter Study on Infertility and Subfecundity. *Am. J. Epidemiol.* **145,** 324–334.
109. Wilcox, A. J., and Weinberg, C. R. (1991). Tea and fertility (letter). *Lancet* **337,** 1159–1160.
110. Edelmann, R. J., Connolly, K. J., Cooke, I. D., and Robson, J. (1991). Psychogenic infertility: Some findings. *J. Psychosom. Obstet. Gynecol.* **12,** 163–168.
111. Henriksen, T. B. (1999). General psychosocial and work-related stress and reduced fertility. *Scand. J. Work Environ. Health* **25** (Suppl. 1): 38–39.
112. Whorton, D., Krauss, R. M., Marshall, S., and Milby, T. H. (1977). Infertility in male pesticide workers. *Lancet* **2,** 1259–1261.
113. Rachootin, P., and Olsen, J. (1983). The risk of infertility and delayed conception associated with exposures in the Danish workplace. *J. Occup. Med.* **25,** 394–402.
114. Brandt, L. P. A., and Nielsen, C. V. (1992). Fecundity and the use of video display terminals. *Scand. J. Work Environ. Health* **18,** 298–301.
115. Rowland, A. S., Baird, D. D., Weinberg, C. R., Shore, D. L., Shy, C. M., and Wilcox, A. J. (1994). The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occup. Environ. Med.* **51,** 28–34.
116. Schaumburg, I., and Olsen J. (1989). Time to pregnancy among Danish phamacy assistants. *Scand. J. Work Environ. Health* **15,** 222–226.
117. Gold, E. B., and Tomich, E. (1994). Occupational hazards to fertility and pregnancy outcome. *Occup. Med.: State Art Rev.* **9,** 435–469.
118. Baird, D. D., Rowland, A. S., and Weinberg, C. R. (1994). Relative fecundability as an outcome measure in epidemiologic studies of infertility. *Infertil. Reprod. Med. Clin. North Am.* **5,** 309–320.
119. Kersemaekers, W. M., Roeleveld, N., and Zielhuis, G. A. (1997). Reproductive disorders among hairdressers. *Epidemiology* **8,** 396–401.
120. Bisanti, L., Olsen, J., Basso, O., Thonneau, P., Karmaus, W., and The European Study Group on Infertility and Subfecundity (1996). Shift work and subfecundity: A European multicenter study. *J. Occup. Environ. Med.* **38,** 352–358.
121. Ahlborg, G., Jr., Axelsson, G., and Bodin, L. (1996). Shift work, nitrous oxide exposure and subfertility among Swedish midwives. *Int. J. Epidemiol.* **25,** 783–790.
122. Florack, E. I. M., Zielhuis, G. A., and Rolland, R. (1994). The influence of occupational physical activity on the menstrual cycle and fecundability. *Epidemiology* **5,** 14–18.
123. Tuntiseranee, P., Olsen, J., Geater, A., and Kor-anantakul, O. (1998). Are long working hours and shiftwork risk factors for subfecundity? A study among couples from southern Thailand. *Occup. Environ. Med.* **55,** 99–105.

124. Abell, A., Juul, S., and Bonde, J. P. (1997). Time to pregnancy in female greenhouse workers. *Int. Symp. Environ., Lifestyle, Fertil.*, Aarhus, Denmark, 1997.
125. Smith, E. M., Hammonds-Ehlers, M., Clark, M. K., Kirchner, H. L., and Fuortes, L. (1997). Occupational exposures and risk of female infertility. *J. Occup. Environ. Med.* **39,** 138–147.
126. Sallmen, M., Anttila, A., Lindbohm, M.-L., Kyyronen, P., Taskinen, H., and Hemminki, K. (1995). Time to pregnancy among women occupationally exposed to lead. *J. Occup. Environ. Med.* **37,** 931–934.
127. Sallmen, M., Lindbohm, M.-L., Kyyronen, P., Nykyri, E., Anttila, A., and Taskinen, H. (1995). Reduced fertility among women exposed to organic solvents. *Am. J. Ind. Med.* **27,** 699–713.
128. Correa, A., Gray, R. H., Cohen, R., Rothman, N, Shah, F., Seacat, H., and Corn, M. (1996). Ethylene glycol ethers and risks of spontaneous abortion and subfertility. *Am. J. Epidemiol.* **143,** 707–717.
129. Eskenazi, B., Gold, E. B., Samuels, S. J., Wight, S., Lasley, B. L., Hammond, S. K., O'Neill-Rasor, M., and Schenker, M. B. (1995). Prospective assessment of fecundability of female semiconductor workers. *Am. J. Ind. Med.* **28,** 817–831.
130. Spinelli, A., Figa-Talamanca, I., and Osborn, J. (1997). Time to pregnancy and occupation in a group of Italian women. *Int. J. Epidemiol.* **26,** 601–609.
131. Olsen, J., and Skov, T. (1993). Design options and methodological fallacies in the studies of reproductive failures. *Environ. Health Perspect.* **101**(Suppl. 2), 145–152.
132. Baird, D. D., Weinberg, C. R., Schwingl, P., and Wilcox, A. J. (1994). Selection bias associated with contraceptive practice in time-to-pregnancy studies. *Ann. N. Y. Acad. Sci.* **709,** 156–164.
133. Weinberg, C. R., Baird, D. D., and Rowland, A. S. (1993). Pitfalls inherent in retrospective time-to-event studies: The example of time to pregnancy. *Stat. Med.* **12,** 867–879.
134. Weinberg, C. R., Baird, D. D., and Wilcox, A. J. (1994). Sources of bias in studies of time to pregnancy. *Stat. Med.* **13,** 671–681.
135. Zielhuis, G. A., Hulscher, M. E. J. L., and Florack, E. I. M. (1992). Validity and reliability of a questionnaire on fecundability. *Int. J. Epidemiol.* **21,** 1151–1156.
136. Joffe M., Villard, L., Li, Z., Plowman, R., and Vessey, M. (1995). A time to pregnancy questionnaire designed for long-term recall: Validity in Oxford, England. *J. Epidemiol. Commun. Health* **49,** 314–349.
137. Feichtinger, W. (1991). Environmental factors and fertility. *Hum. Reprod.* **6,** 1170–1175.
138. Olsen, J. (1994). Is human fecundity declining—and does occupational exposures play a role in such a decline if it exists? *Scand. J. Work Environ. Health* **20** (Spec. Issue), 72–77.
139. Kallan, J., and Udry, J. R. (1986). The determinants of effective fecundability based on the first birth interval. *Demography* **23,** 53–66.