Chapter 1

Subfertility – a logical approach

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The introductory point I would like to make is that the term "infertility" is no longer applicable and we should be referring to "subfertility". The Oxford Dictionary defines "infertility" as "not capable of producing offspring; barren". With the advances in treatment over the last three decades, the development of IVF, the use of intracytoplasmic sperm injection (ICSI), application of testicular biopsy, oocyte donation, sperm donation and surrogacy, there is no couple who cannot potentially conceive, so the term "infertility" should no longer be used. Therefore, this book is called the "Subfertility Handbook".

The probability of conception depends on the success rate of the particular treatment, and the number of cycles of treatment that a couple undertake. This has been applied to the "life-table" analysis of repeated treatment cycles by donor insemination [1], ovulation induction [2], and IVF [3]. The "life-table" concept, which takes into consideration what may happen to couples who have not yet had all their treatment cycles, suggests that if a couple keep trying, they should eventually all conceive. The concept of "if at first you don't succeed, try, try, try again" was proven by a report of a woman who successfully conceived after 37 cycles of IVF treatment (fresh and frozen) [4].

The investigation and treatment of a couple who have failed to conceive is like putting a jig-saw together. There are the three main fertility parameters (eggs, sperm, and tubes) (Figure 1.1), and if these are found to be relatively normal and the couple still does not conceive, we have what is termed "unexplained or idiopathic subfertility". If a problem is identified, then that should be corrected. The first factor is "are sufficient number of normal sperm placed in the right place at the right time"? As described in detail in Chapter 3 this requires determining that the timing of intercourse is appropriate and that penetration is adequate. The next step then is to assess sperm quality by semen analysis. If there is a significant male factor, there is only a small chance that an effective treatment to improve semen quality is available (Chapter 7), but fortunately it has been recognized for 25 years now that IVF has an important place in the treatment of male factor subfertility. Using standard IVF can be described as "taking the mountain to Mohammed", where many men have sufficient sperm to fertilize their partner's oocyte in vitro whereas they cannot do so naturally [5]. With the development of ICSI [6] men with very few sperm and even men with azoospermia can have a handful of sperm extracted and can now fertilize oocytes. The only men who cannot produce embryos are those with a total lack of sperm. Even this may be overcome in the future with haploidization of human cells [7] or the cloning of sperm cells.

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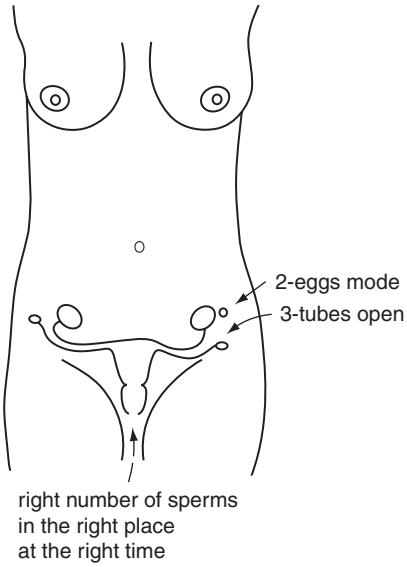

Figure 1.1 The three basic fertility parameters.

In the presence of potentially fertile semen, the next step to confirm is that ovulation is occurring, with regular ovulatory cycles of 25 to 32 days. Longer cycles or cycles with inadequate luteal phase should all be treated with the aim of producing regular cycles close to 28 days. Even in the presence of sub-normal semen it is worthwhile optimizing ovulation, which then may achieve a pregnancy. Many women who present with subfertility have polycystic ovarian syndrome (PCOS) with irregular or infrequent ovulation. There seems to be a tendency amongst some IVF specialists to treat these couples with IVF as a first line of treatment. In my opinion, this is over-treatment, and if there is a clear explanation for the inability to conceive, that is infrequent/inadequate ovulation, then initial treatment should be directed at the cause, and a course of ovulation induction should first be tried. If there is another recognized problem such as male factor or tubal disease then of course IVF is indicated as a first choice. Some of these couples will still fail to conceive after several ovulations, and then moving on to IVF is certainly indicated. How many cycles would depend on the woman's age, and the availability and affordability of treatment.

The third part of the jig-saw is that the "tubes should be patent and normal". At what stage this should be undertaken and by which method is discussed fully in Chapter 4. What defines "tubal infertility" is harder to define. Bilateral tubal obstruction is clearly a barrier to conception, but does unilateral patency, peritubal adhesions, endometriosis, or abnormal "tortuous tubes" mean that there is a tubal factor? The treatment of these factors is described in Chapters 16 and 17. If after appropriate treatment and sufficient time a pregnancy has not been achieved, IVF is the fall-back treatment, and whether it is defined as "tubal" or "unexplained" subfertility is irrelevant.

If the three basic fertility parameters "sperm", "eggs" and "tubes" are adequate, and a pregnancy has still not been achieved, the subfertility is defined as "unexplained".

Explaining "unexplained" subfertility requires us to work through the potential steps required for a pregnancy to be conceived. Apart from three basic fertility factors, sperm, eggs

and tubes, there is the fourth "transport" factor, where sperm, oocytes and the subsequent embryo need to be transported. Once the sperm and oocytes are together, the fifth factor is that "fertilization" has to take place. IVF clearly has a role in overcoming transport problems, and also diagnoses whether the fertilization rate is within normal (>50%). In cases where fertilization appears to be the problem, subsequent cycles can be undertaken using ICSI, which usually overcomes the problem. Thus the most effective option to proceed to next if unexplained subfertility is diagnosed is IVF. Whether controlled ovarian hyperstimulation (COH) with intrauterine insemination (IUI) should be performed first, again depends on local facilities. This is described in Chapter 9. Whilst this does not totally overcome transport problems and gives no information on fertilization, it does sometimes result in pregnancies. The final sixth factor is "implantation". With IVF the embryo enters from a different perspective trans-cervically, but implantation is still a problem, with only one out of three transfers being successful.

In order to improve the investigation and treatment of subfertile couples in a busy gynecology clinic, a protocol using a flow chart was first developed in 1977 [8]. At that stage, many of the pathways ended in a question mark. With the development of IVF, the last option along any branch of the flow chart in 2010 is IVF, highlighting that IVF is the last option for whichever cause of subfertility the couple is experiencing.

Such a flow-chart, outlining a logical approach to managing subfertility, is shown in Figure 1.2.

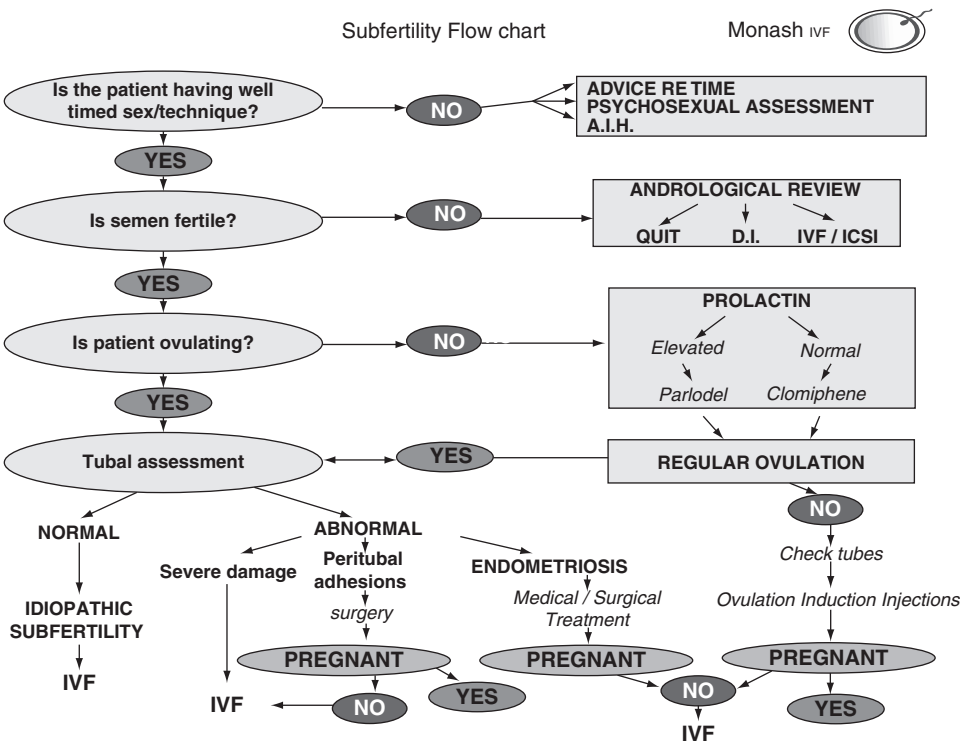

Figure 1.2 The subfertility investigation and treatment flow chart.

This book provides a comprehensive approach to each of the possible factors that act as a barrier to conception.

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Chapter 2

Pre-pregnancy counseling and treatment

Vicki Nisenblat and Robert J. Norman

Preconception care is an essential component of preventive health care that seeks to promote the health of a woman and her partner before pregnancy. Preconception care is defined as "interventions that aim to identify and modify biomedical, behavioral and social risks to a woman's health or pregnancy outcome through prevention and management" [1]. Its main goals are to optimize fertility and to maximize health outcomes for parents and their future children.

Lifestyle behaviors and environmental influences have significant impact on fertility at least in one partner. According to a Center for Disease Control and Prevention report, more than a third of pregnancies are complicated by maternal health issues, 11% of women smoke and 10% drink alcohol during the pregnancy, 69% do not take folate supplements, 31% are obese, 3% take medications that are known teratogens [1]. There is clear evidence that preconception interventions for women with chronic diseases, poor reproductive history and adverse lifestyle behaviors may lead to improved fertility and pregnancy outcomes [1–4].

Preconception counseling should be provided early. Given that most women do not recognize that they are pregnant until well after their "missed period", they are unaware of their pregnancy during the most vulnerable period for the fetus and many issues related to maternal and fetal health are addressed too late. Infertility clinics serve an excellent modality for providing a preconception evaluation, in particular because the pregnancy is planned and timing of conception can be delayed in order to improve the woman's health and to create a more favorable environment for future fetuses.

Medical, genetic and reproductive health conditions should be addressed. Preconception assessment includes risk variables pertaining to age, nutritional status, lifestyle, psychosocial factors, medical, reproductive and family history in both partners. Strategies to improve peri-conceptional health include healthy weight achievement, cessation of smoking, alcohol and illicit drug use, folate supplementation, immunizations, optimizing chronic disease control, genetic counseling, dental care and psychological support. Review of coital practices and education for optimizing of natural fertility may be beneficial before further extensive evaluations and treatments are undertaken.

Age

Relative fertility is decreased by half in women in their late 30s compared with women in their early 20s. Several large observational studies reported longer periods taken to conceive following increase in maternal age, with significant decline in natural pregnancy rate after 35

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years [5]. The success of infertility treatments accordingly reduces with age. IVF cannot reverse the effect of age on fertility, and live birth following IVF diminishes by 2% for each year of female age. The live birth rate is about 26–40% per IVF cycle in women less than 35 years old and declines to about 6% per cycle in women over age 40 [6,7]. Cumulative live birth after 2–3 IVF cycles approaches 50–60% for women under 35 years old with gradual decrease to about 30% after age of 40. The incidence of spontaneous miscarriages and genetic abnormalities substantially increases with maternal age both in spontaneous and treatment-associated pregnancies. The risk of chromosomal abnormalities for women delivering at age 20 is 1:526, but for women delivering at 45 is 1:21. Pregnancies of women aged 35 and older are more often complicated by preeclampsia, gestational diabetes, placental abruption, fetal malposition, intrauterine growth restriction and stillbirth. This can be partially attributed to underlying health problems increasing with age; however, maternal age itself is a strong independent factor for increase in pregnancy risks. Advanced paternal age is associated with an appreciable decline in male fertility, increased risk of genetic mutations and possibly autism-related disorders, mainly after the age of 45–50 [5].

- An increased risk for experiencing infertility later in life should be an important part of routine preconception counseling in women and men. Theoretic benefits of conception sooner rather than later should be discussed. Evaluations and treatments for infertility, usually postponed for after the first year of natural attempts, are justified after 6 months in women over 35 years old. Evaluations for medical comorbidities and discussion of genetic antepartum screening have to be addressed in the advanced age group. No specific guidelines recommend an otherwise different management approach based solely on age-related risks.

Lifestyle

Weight

More than half of the general population in developed countries is overweight and more than a third is obese [8]. Obesity (BMI $\geq 30\,kg/m^2$) is associated with increased risk of diabetes mellitus, hypertension, heart disease, osteoarthritis, respiratory impairment, sleep apnea and certain types of cancer. Being underweight (BMI $\leq 18\,kg/m^2$) is prevalent among women with eating disorders or who undertake strenuous exercise, and poses significant health risks related to nutrient deficiencies, cardiac arrhythmias, low bone mass and excess death. Both obesity and being underweight are associated with a decline in natural fertility, mainly through chronic anovulation. A lower fecundity is also present even in ovulating obese women and may be partly attributed to hyperinsulinemia [2]. In the Nurses' Health Study, a cohort of 116 678 women, an increase in BMI resulted in a higher risk of infertility with relative risk of 3.7 [95% CI 2.0–3.7] for BMI ≥ 30 [9]. The rate of infertility in obese women increases by 4% per each kg/m^2 BMI [10]. Obesity significantly reduces the success of fertility treatments, associated with half the chance of pregnancy rate after IVF treatment compared with normal-weight individuals. The combination of reduced responsiveness to stimulation protocols, higher cycle cancellation rate, reduced embryo quality and impaired implantation are responsible for poorer outcomes in obese patients. This is particularly prominent in abdominal adiposity; pregnancy rate decreases by 30% per cycle for each 0.1 increase in waist/hip ratio. Obesity has been also linked to increased rates of early pregnancy loss, gestational diabetes, hypertensive disease in pregnancy, large for gestational age infants

and higher rate of operative deliveries. Low pre-pregnancy weight increases risks for preterm birth and low birth weight both associated with significant neonatal morbidity. An increase in birth defects has been reported in association with abnormal maternal weight, including gastroschisis in underweight and neural tube or cardiac malformations in obese women [3].

In men obesity relates to impaired sexual function, abnormalities in sperm count and higher DNA fragmentation index, particularly for BMI ≥ 35 kg/m^2. The pathogenetic mechanisms may include increased testicular temperature due to fat deposition and a decrease in circulating testosterone due to sleep apnea, hyperinsulinemia and dysregulation of the hypothalamo-pituitary axis by increased estrogen.

Achievement of healthy weight reduces metabolic risks, increases chances for conception and improves pregnancy outcomes. Guidelines for obesity management recommend an initial weight loss of at least 5–10% and maintaining a reduction in weight of 10–20% with waist circumference of less than 88 cm [8,10]. Even mild weight loss results in favorable reproductive results; however, severely obese women should reduce their BMI at least to 35 kg/m^2 before conception to minimize associated risks. Weight loss in men results in normalizing of hormonal profile, but there are limited data on the extent that weight loss in infertile men effectively restores fertility. The primary managing strategies for weight reduction and maintenance include lifestyle modifications through either diet or exercise or both. Overall lowering caloric intake is more important for weight reduction than the actual composition of diet. Dietary treatment is better tolerated if designed for gradual weight loss and tailored on an individual basis considering personal eating habits. Pharmacological treatment with weight-reduction drugs and bariatric surgery are reserved for patients who fail to achieve the established weight loss goals with lifestyle changes or whose BMI exceeds 40 kg/m^2. In BMI exceeding 50 kg/m^2, bariatric surgery is recommended as a first-line option. Stress reduction and elevation of self esteem have been found to contribute to the success of weight-loss programs. Several studies on multifactorial lifestyle interventions, which incorporated diet, exercise and behavioral therapy and were provided by a multidisciplinary team, showed beneficial metabolic and reproductive effect [2].

- All women should be counseled about risks to their health and future pregnancies, including infertility in regard to their BMI. The worldwide standard of care in obese women of reproductive age is advice on weight loss prior to conception. Obese women should be advised that it will take longer to conceive and weight loss is likely to increase their chances for conception. Women with BMI ≥ 25 kg/m^2 should be offered life-modifying strategies based on decrease in caloric intake and increase in physical activity, preferably within structured weight-loss programs. Women with BMI ≤ 19 kg/m^2 should be assessed for eating disorders and referred to a specialist in the field and/or to a nutrition specialist.

Nutritional composition

There is little evidence that dietary variations, including vitamin-enriched, herbal remedies, vegetarian or low-fat diets, improve fertility [3]. The safety of many of the dietary supplements in pregnancy has not been established, while most data available are gained from case reports, retrospective or animal studies. A balanced diet usually addresses most of daily nutritional requirements.

Supplementation of folic acid for women of reproductive age has been associated with clear success in reducing neural tube defects (NTD) in offspring by up to 70% [11].

Iron deficiency anemia increases risk for preterm birth, growth restriction in the fetus as well as poor maternal well-being. Inadequate maternal iodine levels can affect neurological development in the fetus. Despite iodine food fortification programs, iodine intake in women of reproductive age is insufficient in many areas worldwide. Maternal vitamin D deficiency is associated with rickets and convulsions in neonates and is common in individuals with dark skin or limited exposure to sun. Vegans and individuals with poor intestinal absorption or heavy alcohol consumption are more prone to other vitamin deficiencies.

Certain food products should be avoided due to potential harmful effects on the fetus [12]. Elevated blood mercury levels associated with heavy sea-food consumption have been linked to infertility and neurological impairment in offspring. Consumption of raw meat and fish carries a risk of toxoplasmosis. Unpasteurized milk product intake can be associated with the risk of *Listeria* infection.

- All women should be assessed for nutritional and caloric adequacy. Women should be asked about use of vitamins, minerals, herbs and other remedies and advised in light of evidence available. Intake of supplements in excess of recommended daily allowances or of unproven safety should be discouraged. All women of reproductive age should be advised to ingest 0.4 mg of folic acid or a folic-acid-containing multivitamin supplement and to consume a balanced healthy diet of folate-rich food. Women who have previously had a child with a NTD or take anti-epileptic drugs should take 4 mg folic acid a day. All women should be screened for iron-deficiency anemia. Screening for vitamin deficiencies should be provided to individuals at risk. Maintenance of adequate iodine intake prior to conception and in pregnancy should be encouraged (200–250 μg a day). Calcium supplements should be recommended if dietary sources are inadequate. Women considering conception should avoid fish high in methylmercury and soft cheeses, and eliminate contact with raw fish, poultry and meat.

Exercise

Regular physical activity modifies cardio-metabolic risk factors, improves body composition, and helps to reduce and control weight. Exercise also has a favorable impact on eating behaviors, bone health and general well-being. Although direct benefits of physical activity before conception on reproductive health are unclear, weight control and mood stability have clear indirect plausible beneficial effects. The combination of exercise with diet on weight reduction in obese adults is more beneficial than either diet or exercise as sole intervention. In obese anovulatory women an exercise training program for 20–24 weeks leads to significant improvement in free androgen index, restoration of menstrual cycles with increase in ovulation and pregnancy rates either as a single intervention or in combination with diet [2,3]. Physical activity and leanness in men have been associated with reduced risk for erectile dysfunction.

Current guidelines vary between a minimum of 30 min exercise at least three times a week to 30–90 min activity daily with strong agreement on continuity and adherence to a physical activity combined with healthy eating habits [3,10].

- Moderate-intensity physical activity, such as 30 minutes brisk walking on most days, or at least three times a week, should be recommended to all adults during the preconception period and beyond.

Smoking

Smoking leads to a significant risk of death from neoplastic, ischemic heart and cerebrovascular diseases. Deleterious effects on fertility are observed in active and passive smokers either through decreased ovarian function or adverse effect on sperm. According to the results of a large meta-analysis comparing 10 928 smoking with 19 128 non-smoking women, infertility was more common in smoking populations with odds ratio of 1.60 [95% CI 1.34–1.91] [13]. Smoking has been associated with significant delayed conception with odds ratio of 1.54 [95% CI 1.19–2.01] in active smokers and 1.14 [95% CI 0.92–1.45] in passive smokers compared to non-smokers [14]. Smokers have a higher risk of menstrual abnormalities, increased baseline FSH levels, lower pregnancy rates and earlier menopause. There is compelling evidence of a negative effect of smoking on IVF outcomes with decreased response to stimulation, significant decline in pregnancy and live birth rate and an increase in number of treatment cycles. It takes two times longer for smokers to achieve pregnancy with IVF; the risk of treatment failure increases with each year of smoking. Smoking in men has been associated with deterioration in all semen parameters and a higher rate of DNA damage in addition to exposure of their female partner to passive smoking. Smoking-related risks in pregnancy include preterm births, miscarriages, stillbirths, growth restriction, placental abruption and placenta previa [15].

- All couples should be counseled to avoid smoking and to eliminate exposure to passive smoking. Those who smoke should be offered smoking-cessation interventions based on behavioral and pharmacotherapy.

Alcohol

The maximum recommended alcohol consumption is no more than one standard drink per day for adult women and no more than two standard drinks per day for adult men [15]. In women alcohol has been associated with anovulation and impaired implantation. Reduced libido, impotence and abnormal sperm parameters have been linked with alcohol intake in men. However, the literature is controversial; dose–effect associations vary within reports and some studies failed to support an alcohol–infertility relationship. Alcohol intake in pregnancy is linked to risks of miscarriage, growth restriction and fetal alcohol syndrome. There is no established safe level of alcohol in pregnancy. Due to the deleterious effects on fetal development alcohol consumption in pregnancy should be discouraged. The Australian National Health and Medical Research Council recommend zero alcohol intake in pregnancy.

- All women should be assessed for alcohol use and advised of the risks to fertility and to the fetus. Women should be informed that there is no safe level of alcohol exposure in pregnancy. Interventions to reduce alcohol use should be delivered to the women who exceed recommended alcohol limits prior to conception.

Caffeine

The literature on the effects of caffeine on fertility and pregnancy remains confusing, mainly due to the lack of well-designed randomized controlled trials, individual differences in caffeine metabolism and difficulties in estimating caffeine consumption. Although caffeine has been associated with a decline in fertility, spontaneous abortions, growth restriction and stillbirth, after adjustment for various confounders there is little evidence to support an adverse effect of

mild to moderate caffeine consumption. Overall, caffeine consumption of 200–400 mg a day is not associated with negative impact on general or reproductive health. The safe level of caffeine intake in pregnancy remains unclear. It is prudent to recommend to women who are trying to conceive or who are pregnant that they reduce their caffeine intake to 100–200 mg per day, which is equivalent to less than two cups of coffee or 3–4 cups of tea per day [16].

- Caffeine consumption in the peri-conception period and pregnancy should be reduced to 100–200 mg a day.

Illicit drugs

Recreational drugs have been associated with reduced fertility and negative effect on pregnancy rate [15]. Marijuana leads to lower fertility and intellectual impairment in offspring. Abnormal sperm counts and sexual dysfunction have been demonstrated in heroin-addicted males. Cocaine use in pregnancy increases risk of prematurity, growth restriction, stillbirth and placental abruption. Anabolic steroids lead to suppression of hypothalamo-gonadal axis, erectile dysfunction and decreased sperm quality that last up to one year after the use is discontinued.

- Couples should be counseled on the risk of illicit drug use before and during the pregnancy. Pregnancy should be delayed until individuals are drug free.

Environmental pollutants

Exposure to pesticides, household glues, glycol ethers, heavy metals and solvents used in dry-cleaning or the printing industry has been associated with reduced fertility in both men and women [2,3].

- Those planning pregnancy should be questioned and counseled about reducing their peri-conceptional exposure to pollutants at home, in their community and at work.

Psychosocial stress

Growing evidence suggests that chronic psychosocial stress may disturb ability to conceive and successfully maintain pregnancy. Indirect effects of stress include depression, violence, higher risks of substance abuse, transient sexual dysfunction, lower compliance with pre-conception care and maternal suicide. Stress may directly suppress reproductive function via endocrine, immune and autonomic nervous systems. Higher stress levels in the preconception period have been linked to lower pregnancy and live birth rates and higher risk of miscarriage. The effects on pregnancy may include preterm birth, lower birth weight, lower Apgar scores and poor neurological performance in infants. In IVF patients, higher stress levels have been related to lower number of retrieved oocytes and lower implantation and pregnancy rates. Severe depression or significant acute stress in men may lead to decreased testosterone levels and impaired spermatogenesis [17]. Stress reduction and elevation of self esteem contribute to the success of lifestyle modifications, such as weight loss and stopping smoking. However, others have found no relationship between stress and stress-relieving interventions and reproductive outcomes.

- Screening for socioeconomic and psychosocial risks helps to identify women with depression, domestic violence or social instability. Exposure to stress should be limited before conception. Referral to appropriate resources can help to decrease stress and improve social support.