Investigation of the infertile couple: when is the appropriate time to explore female infertility?

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While the appropriate method for the investigation of female infertility continues to be debated, the timing of the investigation has received less attention. The current approach is time-consuming, and paradoxically may lead to overtreatment as well as undertreatment. Recent findings on fecundity and the conception window in humans have important implications for the timing of the investigation of female infertility. The findings support the view that fertility-oriented intercourse may have a major impact in reducing the time to pregnancy. Procedures for the investigation of female infertility are becoming less invasive and more accurate, while the therapies for infertility are more effective. It is proposed that under appropriate circumstances female infertility should be investigated after 6 months of fertility-oriented intercourse.

Key words: endometriosis/infertility exploration/natural family planning/time to pregnancy

Introduction

The optimal approach in the management of female infertility requires that the timing and method of the routine investigation are beneficial for the couple by avoiding both under- and overtreatment. Unfortunately, infertility is a disorder in which the diagnosis and consequently reliable treatments are frequently unduly and excessively delayed.

The duration of infertility, or time to conception, has been used as a major factor for timing routine exploration and starting treatment. It has been assumed that the longer the interval, the lower is the probability of conception, and therefore investigations are usually not started before 1 year of infertility. On the other hand, a prolonged duration of infertility has also been proposed as an indication to use assisted reproductive technology (ART), even without routine investigation of the female infertility. Therefore, a delayed diagnosis may paradoxically favour both under- and overconsumption of ART.

Recent prospective studies on fecundity have shown that human beings may be more fertile than has previously been estimated. In view of the new data on fecundity and the conception window, and the availability of more accurate diagnostic tools and effective treatments such as surgery and ART, our current approach in the routine exploration of female infertility needs to be revisited.

Time to pregnancy

Subfertility is defined as 1 year of unprotected intercourse without conception. This definition is based on the estimation that in normal couples the fecundity, or the chance to achieve a pregnancy within one cycle, is 20% (Evers, 2002). On this basis it is assumed that ~85% of women should be pregnant within 1 year and that 10–15% of couples are subfertile. Previous studies on time to pregnancy are, however, mostly retrospective, and are therefore exposed to bias.

Recent prospective population-based studies have demonstrated that the time to clinical pregnancy in most women is not more than 6 months. Wang et al. (2003) investigated in China a population-based cohort of newly married textile workers with an age range between 20 and 34 years who intended to conceive. They found that the monthly fecundity varied between 30% and 35%, and 50% were pregnant within two cycles and 88% within 6 months. Of the 971 women who were eligible, 518 (53%) were included in the study. The reasons for excluding 453 women were, in 75% of cases, related to violation of the strict study protocol of recording intercourse and collecting daily early morning urine sample, and the exclusions apparently did not give rise to a selected group of couples with higher or lower fertility. The study also included, in addition to clinical pregnancy, conception rate and early pregnancy loss. The authors found no negative correlation between early pregnancy loss and the time to clinical pregnancy, which led to the conclusion that early pregnancy loss can be regarded as a positive indicator that the stages of reproduction leading to implantation are intact. Obviously, caution is needed before generalizing the results of this population-based cohort study in China to other populations.
A large prospective European study was carried out based on users of natural family planning methods trying to achieve a pregnancy (Gnoth et al., 2003). The authors prospectively studied 346 unselected women who used natural family planning methods to conceive from their first cycle onward. They made optimal use of their fertility potential by timing intercourse according to vulvar mucus symptoms to identify the peak days of fertility. The estimated cumulative probabilities of conception for the total group at 1, 3, 6 and 12 months were respectively 38, 68, 81 and 92%. The authors estimated that after 6 months, 50% of the remaining couples were subfertile or infertile.

It can be concluded from both prospective studies that ~50% of healthy women become clinically pregnant during the first two cycles, and between 80 and 90% during the first 6 months. These results provide a more optimistic figure of the normal monthly fecundity than previous retrospective studies. While these cohort studies may not be representative for a general population, they indicate that under appropriate circumstances, most couples are likely to conceive early, and the question of subfertility can be raised after 6 months of unprotected intercourse without conception.

### Timing of fertility-oriented intercourse

Among healthy women trying to conceive, nearly all pregnancies can be attributed to intercourse during a 6-day period ending on the day of ovulation, with a probability varying from 0.10 when intercourse occurred 5 days before ovulation to 0.33 when it occurred on the day of ovulation itself (Wilcox et al., 1995). Using standardized vulvar observations of vaginal mucus discharge, Stanford et al. (2003) found that the duration of the fertile window with a probability >0.05 is 6 days for normal fertile women and 3 days for subfertile couples. The highest probability of pregnancy occurred on the peak day of vulvar mucus, and is 0.38 for normally fertile couples and 0.14 for subfertile couples. The probability of pregnancy was >0.05 for normally fertile couples from 3 days before to 2 days after the peak, and for subfertile couples from 1 day before to 1 day after the peak. To maximize the likelihood of conception, intercourse should occur on the days with optimal mucus quality, as observed in vaginal discharge, regardless of the exact timing relative to ovulation (Bigelow et al., 2004).

Vulvar mucus observation is likely to become an essential part in the conservative management of patients attempting pregnancy. If the patient is fertile and able to observe vulvar mucus changes, she is highly likely to conceive by fertility-oriented intercourse within a period of 6 months. In case where conception does not occur after 6 months or where the woman is unable to detect mucus changes, she can be advised at an early stage to undergo infertility investigation. In cases of unexplained infertility, the early start of intrauterine insemination is in line with the recommendation of a progression from low-tech to high-tech treatment (Collins, 2003). The approach is likely to shorten the currently recommended waiting period of 2 or 3 years before intrauterine insemination is attempted and, in case of failure, the time before IVF is attempted.

### The age factor

The age factor is important, as the day-specific probability of conception declines with age. Dunson et al. (2002) found that women’s fertility begins to decline in the late 20s, with a substantial decrease by the late 30s, and that also, when other factors are corrected for, there is a decrease in male fertility from 30 years of age onwards. Gnoth et al. (2003) found that with age, the decline of fertility may not be gradual in women, and that the cumulative probabilities of conception decline because the heterogeneity in fecundity increases due to a higher proportion of infertile couples.

In older couples, some argue that laparoscopy can be omitted from the infertility work-up when the hysterosalpingography is normal and there is no abnormal contributing history, and, as a consequence, the cost of fertility treatment is reduced without compromising success rates (Fatum et al., 2002). Balasch (2000) argued that in relatively older women an evaluation would find more diseases known to cause infertility, such as pelvic adhesions and endometriosis. However, two studies aimed at determining infertility factors in women of advanced reproductive age concluded that there is no unique pattern of infertility diagnosis in such patients (Balasch et al., 1992; Miller et al., 1999). This supports the view that the routine investigation of infertility should not differ based on the age of the patient. Karande et al. (1999) found, in a prospective randomized trial, that a higher pregnancy rate with lower costs is achieved with a traditional treatment algorithm than with IVF-embryo transfer as first-line therapy.

Women should be informed that the chance of a live birth following IVF treatment varies with age, and that the chance of a live birth is significantly decreased after the age of 35 years, and is <10% after the age of 40 years. On the other hand, after surgical treatment, as shown in well-selected cases of tubal infertility with absence of tubal mucosa damage, such as tubal sterilization, the results may be surprisingly good in women >40 years of age (Trimbos-Kemper, 1990). Therefore, a delay in the investigation in older patients may be more unfavourable for subsequent ART than surgical treatment.

### Role of endometriosis

A recent retrospective study of infertile women undergoing laparoscopy found that the time to natural conception differs significantly between women with unexplained infertility and infertile women with minimal or mild endometriosis (Akande et al., 2004). In that study, a group of 192 fully investigated infertile couples were followed up for up to 3 years following laparoscopy. No surgical therapy was undertaken to treat the endometriosis found at that time. The authors found that the likelihood of pregnancy was significantly reduced in infertile women with minimal or mild endometriosis compared with those infertile women with a normal pelvis. In a previous
study the Canadian Collaborative Group on endometriosis found that the fecundity rates were lower in women with minimal or mild endometriosis (18.2%) than in unexplained infertility (23.7%), but the difference did not reach statistical significance (Bérube et al., 1998). Several reasons may explain the difference between the two studies, such as the exclusion of patients with subtle, although active, lesions of endometriosis and the short duration of follow-up of only 6 months in the Canadian study.

The view that the diagnosis and treatment of minor endometriosis in an early stage of subfertility is beneficial is supported by the results of the Canadian Collaborative Group on endometriosis (Marcoux et al., 1997). In a study of 341 infertile patients with minimal and mild endometriosis who were randomized to laparoscopic ablation or expectant management, the authors found that laparoscopic ablation of minimal or mild endometriosis doubled the cumulative fecundity rate after a follow-up period of 36 weeks: 30.7% in the treatment group versus 17.7% in the no treatment group. A second Italian study could neither reject or confirm this observation. The study included 101 infertile patients, but demonstrated no difference in fecundity rates after a follow-up period of 1 year (Parazzini, 1999). A recent review combined the results of these two randomized controlled trials into a meta-analysis and showed that surgical treatment is more favourable than expectant management (odds ratio for pregnancy 1.7; 95% confidence interval 1.1–2.5) (Olive and Pritts, 2002).

While it is generally accepted that moderate and severe endometriosis affects fertility and requires surgical treatment, it is frequently overlooked in the discussion that without endoscopy no staging of endometriosis can be performed. For example, in the absence of endoscopy there is no reliable technique to diagnose the presence and extent of endometriotic adhesions or the presence of ovarian endometriomas when the diameter not > 2 cm.

In a recent meta-analysis of IVF outcome for patients with endometriosis, Barnhart et al. (2002) recommended that patients with endometriosis of any stage should be referred for early aggressive infertility treatment, including IVF, to increase chances of conception. It remains an unfortunate fact that the diagnosis of endometriosis is still unduly delayed in many patients with infertility (Dmowski et al., 1997).

Other factors delaying the time to pregnancy

It is likely that in a population with a high prevalence of modern contraceptive techniques, the time to pregnancy will be prolonged. Previous use of hormonal contraception results in a modest, but significant, increase in the time to pregnancy that is dependent on the duration of use (Hassan and Killick, 2004). The negative effect of previous combined oral contraceptive use on subsequent fertility is probably due to transient persistance of ovarian suppression or anovulation, particularly in susceptible women. Long-term users of oral contraceptives are also unlikely to have developed experience in vulvar mucus observations to identify the peak day of fertility when they change from contraception to reproduction. In this respect, the prospective studies on fecundity indicate the importance of individualizing the infertility management and taking advantage of vulvar mucus observations for reducing the time to pregnancy. The use of an intrauterine device has also been reported to be associated with conception delay. After short-time use the delay may be explained by the events for which intrauterine device use was prematurely discontinued, while long-term use in nulliparous women recently also appeared to be associated with an increased risk of fertility impairment (Doll et al., 2001).

The results of treatments with a large effect size also show an early high pregnancy rate when no other infertility factors are present. Braat et al. (1991) found, in patients treated for anovulation with intravenous GnRH, a cumulative pregnancy rate of 78% at 6 months, and in the presence of additional infertility factors a cumulative pregnancy rate of 60%.

In a retrospective study of ovulation induction, Capelo et al. (2003) found significant pelvic pathology in one-third of the patients failing to conceive after four ovulatory cycles of clomiphene citrate, and concluded that early endoscopic diagnosis of such pathology would have allowed the couple to proceed directly to IVF.

Oliveira et al. (2003) found a high incidence of pathological findings on hysteroscopy in patients with repeated failures of IVF-embryo transfer despite transfer of good-quality embryos. Relevant therapeutic interventions before the third cycle significantly improved clinical pregnancy and implantation rates in comparison with a control group.

In a retrospective study of 495 patients, Tanahatoe et al. (2003) found that laparoscopy after an hysterosalpingogram and before intrauterine insemination altered the treatment decision in 25% of the patients.

First-line investigation of female infertility

Previous studies have indicated that the optimal management of infertility requires an early and accurate evaluation of the reproductive tract, including uterine cavity, tubal patency and tubo-ovarian structures. It is no surprise that at present hysterosalpingography is challenged by more complete ultrasound- or endoscopy-based approaches (Kelly et al., 2001; Gordts et al., 2002). Transvaginal hydrosonography is increasingly used for evaluation of the uterine cavity, but its accuracy in testing tubal patency and detecting pelvic pathology remains to be established. Transvaginal hydrolaparoscopy is a minimally invasive technique that, in combination with minihysteroscopy, permits in patients without obvious pelvic pathology to test tubal patency by the chromoperturbation test, and to detect, biopsy and treat uterine and tubo-ovarian pathology. However, it remains to be proven whether the use of any of the new techniques are cost effective and whether the interventions are effective in improving pregnancy rates.

Conclusions

The assumptions on which the current definition of human subfertility is based have not been confirmed by prospective studies, and therefore the current definition of subfertility as 1 year of unprotected intercourse without conception can be
challenged as valid for all populations. In selected groups of patients it seems justifiable to investigate female as well as male fertility after 6–12 months of subfertility. Several factors, in addition to age, can affect the fecundity in a normal population, such as previous contraceptive use and the presence of unsuspected uterine and pelvic pathology. Recent studies indicate that in women attempting pregnancy, the use of vulvar mucus symptoms for timing intercourse on the peak day can be strongly recommended. In these women, the timing of fertility investigation after 1 year of infertility can be questioned. Postponing the investigation in these women can be regarded as undertreatment when the couple is affected by a disorder or a combination of disorders for which an effective treatment, such as surgery or ART, may exist. The prolonged waiting period without diagnosis and appropriate counseling is frequently a source of frustration and overtreatment.

There is a need to use a more accurate first-line technique than hysterosalpingography for the early investigation of female infertility. It remains to be assessed whether the use of new ultrasound- or endoscopy-based techniques is cost effective and whether the diagnosis related to such interventions results in improved pregnancy rates.

References


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