

## DEBATE—CONTINUED

### Definition and prevalence of subfertility and infertility

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**A common definition of sub- and infertility is very important for the appropriate management of infertility. Subfertility generally describes any form of reduced fertility with prolonged time of unwanted non-conception. Infertility may be used synonymously with sterility with only sporadically occurring spontaneous pregnancies. The major factor affecting the individual spontaneous pregnancy prospect is the time of unwanted non-conception which determines the grading of subfertility. Most of the pregnancies occur in the first six cycles with intercourse in the fertile phase (80%). After that, serious subfertility must be assumed in every second couple (10%) although—after 12 unsuccessful cycles—untreated live birth rates among them will reach nearly 55% in the next 36 months. Thereafter (48 months), ~5% of the couples are definitive infertile with a nearly zero chance of becoming spontaneously pregnant in the future. With age, cumulative probabilities of conception decline because heterogeneity in fecundity increases due to a higher proportion of infertile couples. In truly fertile couples cumulative probabilities of conception are probably age independent. Under appropriate circumstances a basic infertility work-up after six unsuccessful cycles with fertility-focused intercourse will identify couples with significant infertility problems to avoid both infertility under- and over-treatment, regardless of age: Couples with a reasonably good prognosis (e.g. unexplained infertility) may be encouraged to wait because even with treatment they do not have a better chance of conceiving. The others may benefit from an early resort to assisted reproduction treatment.**

*Key words:* definition of subfertility/fertility awareness/management of infertility/prevalence of infertility/time to pregnancy

#### Introduction

Terminology in reproductive medicine is indeed confusing and misleading (Habbema *et al.*, 2004). We therefore appreciate the current debate initiated by Habbema *et al.* very much. Firstly, the familiar term subfertility should not be completely abandoned, which may lead to greater rather than less confusion, but rather it should be used generally to name any form or grade of reduced fertility in couples unsuccessfully trying to conceive (Jenkins *et al.*, 2004). A balanced management of reduced fertility requires appropriate timing of infertility investigations and appropriate timing of starting treatment to avoid both over- and under-treatment (Brosens *et al.*, 2004). It is a general problem of epidemiological research in reproductive medicine that the definition of subfertility and its prevalence in the general population interact (Marchbanks *et al.*, 1989). Therefore, time-to-pregnancy estimations [TTP, cumulative probabilities of conception (CPC)] are of fundamental importance to find suitable thresholds to determine the prevalence of grades of subfertility. These thresholds may be used as the major indicator for timing

routine infertility investigations and starting treatment in the case of poor prognosis. This is important because increasingly couples soon seek advice about infertility care (Olsen *et al.*, 1996) with the danger of false-positive test results and following unnecessary over-treatment, as pointed out by Balasch (2000), which may expose women unnecessarily to medical complications and unnecessary expense (Van Voorhis and Syrop, 2000). On the other hand, late interventions may represent infertility under-treatment.

#### Time to pregnancy

Infertility (clinical definition) is currently defined as 1 year of unwanted non-conception with unprotected intercourse in the fertile phase of the menstrual cycles (Evers, 2002). Two new prospective studies (Gnoth *et al.*, 2003; Wang *et al.*, 2003) on TTP show that human fertility is probably higher than has previously been estimated (Juul *et al.*, 1999, 2000; Jensen *et al.*, 2001). These previous studies only recorded TTP retrospectively among pregnant women using

questionnaires to measure, for example, couple fertility, by assessing exposures related to semen quality, age or environment. Their study design does not estimate real fecundity. This is because infertile couples were excluded (Jensen *et al.*, 2000). Therefore, effects on the proportion of truly infertile couples (Baird *et al.*, 1986), which are of major importance, cannot be assessed. Another disadvantage is the possible inaccuracy because, at long-term recall, TTP may sometimes only be roughly estimated by the couples filling in the questionnaire.

Wang *et al.* (2003) prospectively observed 518 newly married Chinese textile workers (20–34 years of age) trying to conceive. They recorded vaginal bleeding, sexual intercourse and collected daily first-morning urine specimens for up to 1 year or until a clinical pregnancy was achieved. Survival curves (Kaplan and Meier, 1958) were calculated for proportion of conceptions over number of menstrual cycles. In their cohort of women, ~50% became clinically pregnant in the first two cycles and >90% in the first six cycles. They found that the monthly fecundity varied between 30 and 35%.

In this journal we reported on 346 women using natural family planning methods to conceive (Gnoth *et al.*, 2003). They were observed from their first cycle of trying to conceive onwards. Only cycles with intercourse in the fertile phase were included. Pregnancy was assessed by either ultrasound, positive pregnancy test or a luteal phase >18 days. In both latter cases, only later-confirmed clinical pregnancies (live birth, ectopic implantation or clinical abortion) were included in the analyses. Kaplan–Meier survival analyses (cumulative probabilities of conception, CPC) were carried out for the whole group and separately for those who finally conceived (truly fertile couples). A total of 310 pregnancies occurred among 346 women in a maximum of 29 cycles of observation with a mean of 3.56 and SD of 4.03 for a total of 1208 cycles observed. Only the data of 340 out of 346 women could be included in the analysis because for six women out of those who finally conceived TTP was inaccurate because some cycles were completely missed. Estimated CPC for the total group (340 women included) at one, three, six and 12 cycle(s) were 38, 68, 81 and 92% respectively. For those who finally conceived (truly fertile couples, 304 women included), the respective pregnancy rates were 42, 75, 88 and 98%. Most couples conceived within six cycles of timed intercourse. Thereafter we have to assume slight or serious subfertility in every second couple. As expected, CPC declined with age because heterogeneity in fecundity increases. In the subgroup of truly fertile couples, CPC was statistically age independent (as judged by the Wilcoxon test) because of high homogeneity even with advancing age.

Both studies underline the positive effect of timed intercourse on pregnancy probabilities for women, using their fertility potential optimally. This was recently also emphasized by Stanford *et al.* (2002). Vulvar mucus observations seem to be an effective tool in self-assessment of peak fertility in the menstrual cycles and seem to be superior to the relative timing of intercourse to ovulation (Bigelow *et al.*, 2004). A current prospective study comparing clinical pregnancy

rates in intrauterine insemination cycles with either cycle monitoring by ultrasound and LH or exclusively vulvar mucus observation should further evaluate its effectiveness.

In this journal a very important prospective study was published on the long-term follow-up of subfertile couples with a history of >1 year of unprotected intercourse and no treatment thereafter (Snick *et al.*, 1997). They found that couples with a history of 1 year unwanted non-conception still have a cumulative live birth rate of 52.5% at 36 months. The cumulative live birth rate was highest in couples with unexplained infertility and low for severe male, tubal and ovulation defects. Prognostic factors related to higher cumulative pregnancy rates were duration of infertility <24 months, a previous pregnancy in the same partnership and a female age <30 years (multiplication factors of 1.4–1.5). Gleicher *et al.* (1996) reported a cumulative pregnancy rate of 19.9% after 12 months in a subfertile population with unwanted non-conception of ≥1 year's duration with a total of 9079 inactive treatment months of observation. In an important multicentre study Collins *et al.* (1995) observed among 2198 couples with unwanted non-conception of >1 year (18364 untreated months of observations on 873 untreated couples, combined with observations before the first treatment among 1325 later treated couples with 9761 untreated months before the first treatment) a cumulative rate of conceptions leading to live birth of 14.3% at 12 months. Interestingly, ~20 years ago Hull *et al.* (1985) published similar results.

## Discussion

Wait or act? We completely agree with Brosens *et al.* (2004) that timing of investigation (acting) in couples unsuccessfully trying to conceive has to receive much more attention to find a balanced management of subfertility avoiding both over- and under-treatment. Although methods for exploring female and male subfertility are becoming less invasive and probably more accurate, there is still the danger of false-positive test results and following unnecessary over-treatment as pointed out by Balasch (2000). This is of increasing importance as more and more couples soon seek advice about infertility care (Olsen *et al.*, 1996) resulting in increasing numbers of assisted reproductive treatment cycle(s) being requested by well-informed patients so that IVF could become first line treatment (Karande *et al.*, 1999), bringing possible early success with all its attendant risks and high costs. It is sometimes very difficult to persuade patients with infertility problems to wait unless they are informed in detail about their prognosis, the proposed pattern of investigation and treatment and also alternative ways of becoming parents (Schmidt *et al.*, 1995; Schmidt, 1998).

The decision to treat depends on the spontaneous pregnancy prospect and whether the treatment has proven effectiveness (Collins and Van Steirteghem, 2004) at low risks of the methods involved. Three major factors affect the spontaneous probability of conception: time of unwanted non-conception, age of the female partner (Hunault *et al.*, 2004) and the cause of subfertility (Snick *et al.*, 1997). Before referral to a specialized centre for reproductive medicine or

**Table I.** Definition and prevalence of subfertility and infertility

Time	Prevalence/grading	Chances to conceive spontaneously in the future
After six unsuccessful cycles	About 20% at least slightly subfertile couples	50% of these couples will conceive spontaneously in the next six cycles, the remaining are moderately subfertile [Equivalent to slightly reduced fertility (Habbema <i>et al.</i> , 2004)]
After 12 unsuccessful cycles (former clinical definition of infertility)	About 10% at least moderately or seriously subfertile couples	50% of these couples will conceive spontaneously in the next 36 months, the remaining are nearly complete infertile [Equivalent to moderately/seriously reduced fertility, (Habbema <i>et al.</i> , 2004)]
After 48 months	About 5% nearly complete infertile couples	Couples with only sporadic spontaneous conceptions [Equivalent to sterile couple (Habbema <i>et al.</i> , 2004)]

at the first consultation because of infertility problems, we (normally) only have the time of unwanted non-conception and the age of the women, on which we base our primary decision to act and to explore for causes of subfertility (with the risk of false-positive results) and then perhaps to start treatment. Or we encourage to wait.

In general, cumulative probabilities of conception decline with age but because of increasing heterogeneity in fecundity with age, the effects mainly depend on individual factors (Dunson *et al.*, 2002; te Velde and Pearson, 2002; Gnoth *et al.*, 2003; Dunson *et al.*, 2004) and may only be judged after a first infertility exploration.

Therefore, the duration of unwanted non-conception remains as the main factor indicating timing of investigation in case of a subfertility problem and it mainly defines the grades of subfertility and determines prevalence estimations. Based on the cited prospective TTP studies, we propose a simple, easy and memorable three-step grading for all day clinical use (Table I).

It can be concluded from the cited prospective studies that the question of subfertility must be raised after six cycles of unprotected intercourse without conception—regardless of age because most of the women <30 years of age should have conceived (Gnoth *et al.*, 2003) and for women after the age of 35 years—if treatment (e.g. IVF) will be necessary—the chance of a live birth will decrease rapidly. We recently proposed this threshold for timing the first infertility investigation in selected groups of couples after six cycles with fertility-focused intercourse (Gnoth *et al.*, 2003; Brosens *et al.*, 2004) to avoid over- as well as under-treatment. Thereafter, a prognostic statement (Hunault *et al.*, 2004) and a detailed grading (0–4, ranging from normal fertility with a  $\geq 60\%$  chance of spontaneous conception within the following year to complete infertility with a nearly zero chance (Habbema *et al.*, 2004) is possible. In cases with a good prognosis (especially unexplained infertility) the couples should be encouraged to wait because they have a similar probability of achieving a pregnancy with and without treatment (Stolwijk *et al.*, 1996, 2000). Self-monitoring of the menstrual cycle to identify peak fertility by vulvar or cervical mucus observation ('fertility awareness') may be all that is necessary in that time and can strongly be recommended to improve pregnancy prospects (Gnoth *et al.*, 2002; Stanford *et al.*, 2002). In cases with bad prognosis (e.g. tubal pathology or severe male factor infertility) immediate assisted reproductive

treatment should be discussed because they are superior to any expectant regime (Evers *et al.*, 1998).

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