An important scientific breakthrough of the 20th century, IVF helped open new horizons in medicine, such as pre-implantation genetic diagnosis and embryonic stem-cell therapy. A further contribution of assisted reproduction technology has been the better understanding of reproductive ageing. Data from IVF cycles suggest that there is a fixed time-interval between accelerated decline of fertility and the menopause. This leads to the hypothesis that a significant proportion of asymptomatic women in the early thirties may be at risk of early onset of subfertility. IVF provides a model for the development of ovarian reserve tests, some of which appear promising as potential screening tools for early ovarian ageing in the general population.

Key words: IVF/ovarian ageing/screening
thirties. Epidemiological studies have shown that 10% of women in the general population become menopausal by the age of 45 (Treloar, 1981; van Noord et al., 1997), and it is therefore estimated that 10% of women in the general population might be at risk. These women could have reduced fecundity which is otherwise unexplained (Scott et al., 1993; Hofmann et al., 1996; Leach et al., 1997). They could experience increased incidence of dizygotic twinning (Wyshak, 1975; Turner et al., 1994; Martin et al., 1997; Lambalk et al., 1998), increased incidence of aneuploidy (Nasseri et al., 1999; van Montfrans et al., 1999; Freeman et al., 2000; van Montfrans et al., 2002) and miscarriage (Trout and Seifer, 2000). They will also have a relatively poor response to ovarian stimulation. Assuming fixed time-differences between reproductive milestones, fertility will not be lost completely for 4 years, on average, following diagnosis. Menstrual cycles will continue to be regular, although relatively short, for 6–8 more years on average (Den Tonkelaar et al., 1998). Furthermore, these women might exhibit other physical and possibly mental and psychological signs compatible with accelerated general ageing (Dorland et al., 1998).

Screening for early ovarian ageing would probably be more effective in high-risk groups. Assuming that the same, mainly genetic, factors, which affect the time of menopause (Cramer et al., 1995; van Noord et al., 1997; Torgerson et al., 1997a; b; Snieder et al., 1998; Treloar et al., 1998; De Bruin et al., 2001; Te Velde and Pearson, 2002) will also determine all preceding reproductive milestones, a high-risk group for early ovarian ageing would include women with a family history of an early menopause. Other possible acquired factors may include: chemotherapy, radiotherapy, pelvic surgery (Lass et al., 1998; Tulandi et al., 2002), pelvic infections or tubal disease (Keay et al., 1998; Sharara, 1998), severe endometriosis (Barnhart et al., 2002), and heavy smoking (Augood et al., 1998). With regards to primary prevention, smoking, pelvic infection and surgical interventions may be avoidable. Screening for ‘early ovarian ageing’ in the early thirties could provide information to women, on which to base rational decisions about their fertility without risking involuntary childlessness. In the longer term advances in molecular reproductive biology and pharmacology may enable us to develop drugs or interventions that will delay the accelerated decline of ovarian reserve in some women.

An important contribution of assisted reproduction has been the development of tests for the assessment of the ovarian reserve. Among the tests already in use are basal biochemical markers, dynamic assays, biophysical tests, and ovarian biopsies. The driving force for the initial development of these tests was the desire to predict IVF outcome. However, some of them might be suitable as screening tools for early ovarian ageing in the general population. Small antral follicular counts (Broekmans et al., 1998; Bancsi et al., 2002) and new biochemical markers, such as antimüllerian hormone (De Vet et al., 2002), appear promising and warrant further evaluation. Ultimately, with developments in molecular genetics, it might become possible to construct ‘DNA fingerprints’ that will identify women with a genetic predisposition to ‘early ovarian ageing’ (Te Velde and Pearson, 2002).

In conclusion, on the basis of a fixed interval of 13 years between onset of accelerated decline of fertility (25 000 remaining follicles) and the menopause, it can be speculated that women who become menopausal by the age of 45 years, have experienced an accelerated decline of fertility around the age of 32. These women can be classified under a separate clinical entity, ‘early ovarian ageing’, which possibly affects 10% of the general population, and is potentially suitable for screening. IVF provides a model for the development of ovarian reserve tests; some of which could eventually enable us to detect early ovarian ageing in asymptomatic young women in the general population.

References


