

The paradox of declining fertility but increasing twinning rates with advancing maternal age

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BACKGROUND: Advancing female age is associated with declining fertility potential due to decreasing numbers and quality of oocytes but also with a distinct increase in dizygotic twinning rates, a phenomenon that has never been explained. **METHOD:** An analysis of follicle development was made in 959 spontaneous ovulatory cycles of 507 women. **RESULTS:** Multiple ovarian follicular development (>1 follicle >14 mm) and, by implication, multiple rather than single ovulations occurred in 105 women whose mean age (36.1 versus 34.6 years) and mean basal FSH concentrations (10.3 versus 7.7 IU/l) were significantly greater than those with monofollicular development ($P < 0.01$). The prevalence of multifollicular development increased with age. **CONCLUSIONS:** Dizygotic twinning must be associated with the development of >1 large follicle, which we found to be a significantly more frequent occurrence in older women. It is hypothesized that the response of pituitary release of FSH to the decreased negative feedback induced by impending ovarian failure often ‘overshoots’, causing multiple follicular development. In the presence of two good-quality oocytes, a twin pregnancy may result.

Key words: advanced maternal age/dizygotic twins/fertility/follicle development

Introduction

Heredity and fertility treatments are well-defined factors associated with dizygotic multiple pregnancies. A history of multiple pregnancies in first-degree relatives is strongly associated with an increased risk of dizygotic twin pregnancies (Hemon *et al.*, 1981; Parazzini *et al.*, 1996). Ovulation inducing or stimulating agents and assisted reproductive technologies since their inception have had a massive influence on the increase in multiple pregnancy rates (Derom *et al.*, 1993; Westergaard *et al.*, 1997). Intriguingly, advanced maternal age has also been documented as a factor influencing the incidence of spontaneous dizygotic multiple pregnancies (Bortolus *et al.*, 1999). In studies performed before the inception of ARTs and controlling for parity, twinning rates were found to increase by 300% between the ages of 15 and 37 years (Bulmer, 1970). This increase is particularly prominent in the maternal age group of 35–39 (Bortolus *et al.*, 1999). No scientifically based explanation for this phenomenon has been forthcoming. It is all the more fascinating as it occurs, paradoxically, in the age group when fertility potential starts to decline rapidly.

As dizygotic twin pregnancies must be aetiologically linked with multiple follicular growth and double ovulations, we examined the prevalence of multiple follicular growth according to maternal age in natural ovulatory cycles.

FSH concentrations rise with increasing age. We have, therefore, also looked at the relation between FSH concentrations and the incidence of multiple follicular growth.

Subjects and methods

An analysis of follicular growth in natural ovulatory cycles was made from the cycles of 507 women in the age range of 24–41 years. All were undergoing intrauterine insemination in an unstimulated cycle for either unexplained infertility or a mild male factor infertility during 1995–2003. In each patient, we used data from an ultrasound examination of follicle number and size, when this was performed within 24 h before ovulation. The statistical unit of analysis has been the patient. As we believe that having multiple follicle growth is probably not a constant phenomenon and could differ from cycle to cycle, we decided to look into more cycles of a patient if possible. For the analysis, we utilized a maximum of three consecutive cycles with a mean of 1.9 ± 0.9 SD cycles per patient, a total of 959 cycles. Among the various age categories, there was no difference in number of women who contributed with one, two or three cycles ($P = 0.2$, linear-by-linear association). Multiple follicle growth was defined as two or more follicles over 14 mm in diameter on this day. We compared the number of patients with multiple follicle growth in one or more cycle in three age groups: under 30 years ($n = 61$), 30–35 years ($n = 212$) and over 35 years ($n = 234$). An examination of basal serum FSH concentrations was available on the third day of the menstrual cycle in 281 of the subjects.

Statistical analysis was performed using SPSS 11.0 for Windows. The difference in age between the group of women with monofollicular growth and those with multifollicular growth was measured by the independent samples *t*-test. The means of the basal FSH levels were measured by the independent samples *t*-test. Age-dependent relations were tested by linear-by-linear association. Two-sided *P*-values <0.05 were considered to indicate statistical significance.

Results

Of the 507 women examined, 105 demonstrated the development of two or more follicles of >14 mm diameter in one or more cycles and 402 never had multiple follicular growth. The mean age of women with monofollicular growth was 34.6 years (± 4.5 SD) and 36.1 years (± 7.3 SD) for women with multiple follicle growth ($P = 0.009$). The prevalence of multiple follicular growth increased with age ($P < 0.05$) (Figure 1).

The basal FSH level increased with age in women with both monofollicular and multifollicular growth. In the whole group, basal FSH was higher in women with multifollicular growth (10.3 ± 8.7 IU/l SD) compared with monofollicular growth (7.7 ± 6.2 IU/l SD) ($P = 0.008$). In the age group 24–29 years, there was no difference in FSH concentrations between those with multifollicular and monofollicular growth, but as only 5 of 61 had multifollicular growth in this age group, any significant interpretation is not possible. In the age groups 30–34 (8.7 versus 6.2 IU/l) and 35–41 (11.5 versus 8.7 IU/l), the mean FSH concentrations were significantly higher in those with multifollicular growth ($P = 0.02$).

Discussion

This is the first documentation that progressive ageing is related to an increased prevalence of natural multiple follicle growth and that elevated FSH levels are associated with multiple follicle growth in natural cycles. Monofollicular growth takes place when a certain threshold in the concentration of FSH is only marginally exceeded (Schoemaker *et al.*, 1993). Multiple follicle growth induced during exogenous ovarian stimulation is associated

with FSH levels higher than the threshold or with levels exceeding the threshold for an extended time.

Seemingly paradoxical, female ageing is not only related to a decline in fecundity but also related to an increase in risk of multiple pregnancies. With increasing age, the size of the cohort of available follicles at the time of recruitment declines. Towards the end of the reproductive lifespan, the monthly cohort consists of only very few follicles.

Because of a decline in ovarian feedback capacity, in particular, due to lower levels of inhibin secretion allowing a pituitary more sensitive to GnRH, pulse amplitudes of FSH increase and FSH levels rise (Klein *et al.*, 1996; de Koning *et al.*, 2000) and overshoot the threshold (de Koning *et al.*, 2004). This will generally not lead to multiple pregnancies because of the low number of available follicles with less oocytes of high quality. However, if two or more follicles containing good-quality oocytes are available, then a multiple pregnancy is more likely (Lambalk, 2001).

The current findings strongly support the hypothesis that the well-documented increased prevalence of twin pregnancy in the fertile advanced age group is because of an increased tendency towards multiple follicular development. This, in turn, is associated with FSH concentrations induced by the negative feedback mechanism, which overshoot the threshold of ovarian follicle response in this age group.

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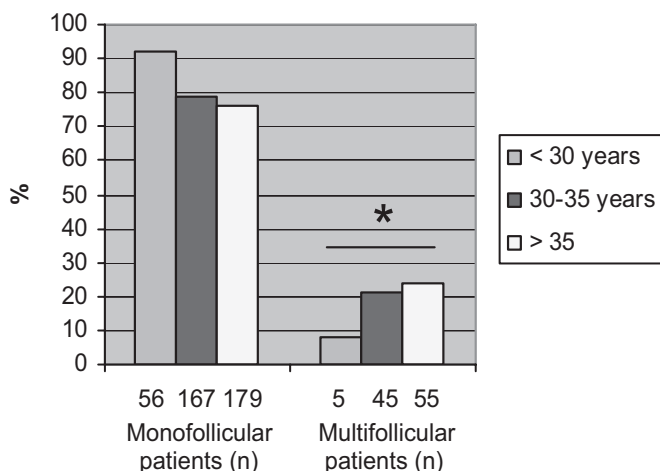


Figure 1. The occurrence of multiple follicular growth in natural ovulation cycles according to maternal age.

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