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# Reproductive characteristics of women diagnosed with premature ovarian insufficiency




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**Abstract** In this retrospective cohort study ( $n = 479$ ), the proportion of women with premature ovarian insufficiency (POI) who conceived was assessed, the reproductive characteristics of women with POI who had previously been pregnant or had never been pregnant compared, and the interval between last conception and the menopause in women with POI who had become pregnant assessed. Time to pregnancy and maternal age at first childbirth were compared between women with POI and population-based controls ( $n = 2304$ ). Women with POI who had previously been pregnant ( $n = 249$  [52%]) experienced menopause at a later age compared with controls (35.0 years: interquartile range [IQR] 32.0–37.5 versus 30.0 years [IQR 23.0–35.0];  $P < 0.001$ ). The median interval between last conception and menopause in the former group was 4.0 years (IQR 1.0–8.0). Time to pregnancy did not differ between women with POI and controls. Women with POI were younger at first childbirth compared with controls (27.3 years [IQR 23.4–30.5] versus 29.2 years [26.4–32.0];  $P < 0.001$ ). The reproductive capacity of young women with POI is comparable to women in the general population, up until a given age; thereafter a rapid loss of the potential to conceive occurs. 

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**KEYWORDS:** menopause, POI, reproductive characteristics, time to pregnancy

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## Introduction

Women with premature ovarian insufficiency (POI) experience menopause before 40 years of age (Coulam et al., 1986). This condition affects about 1% of women, and is associated with multiple health problems, such as infertility, osteoporosis, cardiovascular disease and decreased well-being (Roeters van Lennepe et al., 2014; Uygur et al., 2005; van der Stege et al., 2008). It is considered a multifactorial, heterogeneous condition, for which the exact underlying cause remains unclear in most affected women (Bachelot et al., 2009). Various genetic causes have been identified, and associations with autoimmune diseases and environmental factors, such as smoking, have been described (Hoek et al., 1997; van Asselt et al., 2004; Voorhuis et al., 2014).

Extremely low success rates have been reported with various infertility interventions in women with POI (De Vos et al., 2010; Hsueh et al., 2015). To date, little information is available concerning the reproductive characteristics of women diagnosed with POI during their preceding reproductive life (Bachelot et al., 2009; Janse et al., 2010).

On the basis of data from general population studies, it is thought that, for a given woman, a fixed time interval exists between the various reproductive phases, i.e. the onset of subfertility, infertility and the subsequent age at menopause (Broekmans et al., 2009; te Velde and Pearson, 2002). Menopause generally occurs around the age of 51 years, with an age range extending between 40 and 60 years (Treloar et al., 1967). Historical studies carried out in populations with unrestricted reproduction show a mean age at last childbirth of 41 years, suggesting that the end of natural fertility occurs about a decade before natural menopause (Menken et al., 1986; Wood, 1989). If decreasing reproductive capacity with advancing age in women is indeed caused by a gradual decrease in both the quantity and quality of the oocytes, it is plausible that an early age at menopause is preceded by an early age at infertility (Broekmans et al., 2009).

Whether the above mentioned association between fertility loss and age at menopause is similar in women diagnosed with POI is unknown. Therefore, the present descriptive study aimed to illustrate the reproductive characteristics in a large cohort of well-phenotyped women with POI. Of particular focus was the proportion of women with POI who were able to conceive, with analysis of the following: possible differences between women with POI who had previously been pregnant or those who had never been pregnant; the interval between last conception and menopause in women with POI who had achieved a pregnancy; and its possible association with spontaneous miscarriage. Finally, potential differences in the required time to establish a pregnancy and age at first childbirth were compared between women with POI and controls from a general fertile population.

## Materials and methods

### Study population

In 2005, a multicentre study was initiated in the Netherlands in which women with hypergonadotropic hypogonadism were systematically screened. The screening procedure

of this study has been detailed previously (Janse et al., 2010). In short, women consulted their gynaecologist for various reasons, such as menstrual cycle disturbances, fertility problems or climacteric complaints. Women were diagnosed with premature ovarian insufficiency (POI) if they had experienced a secondary amenorrhoea of at least 4 months before the age of 40 years with accompanying FSH levels above 40 IU/L. The standardized clinical evaluation of women with POI consisted of a questionnaire covering medical, reproductive and family issues, and blood pressure measurement, waist-hip circumference, height and weight. A transvaginal ultrasound was carried out to assess endometrial thickness and antral follicle count. A blood sample was taken to evaluate hormonal and metabolic status, and to screen for the presence of circulating autoantibodies (antithyroid peroxidase, antiadrenal, antiparietal and anti-zona pellucida antibodies). Genetic testing consisted of karyotyping and determination of number of cytosine-guanine-guanine repeats to screen for fragile-X mental retardation gene 1 (*FMR1*) premutation carriership, defined as a cytosine-guanine-guanine repeat length between 55 and 200 repeats. Bone mineral density was measured with a dual-energy x-ray absorptiometry scan.

### Study parameters

For this study, women with spontaneous POI were included, thus excluding women who experienced iatrogenic premature menopause, resulting from bilateral oophorectomy and chemo-radiation therapy, for example. Furthermore, women with overt genetic anomalies, such as karyotype aberrations and proven *FMR1* gene premutation carriers, were excluded from the analyses. For the analyses of reproductive and obstetric characteristics obtained, women with POI who conceived through oocyte donation treatment were excluded.

The primary study population was divided into women with POI who had previously been pregnant or those who had never been pregnant. The following reproductive characteristics were compared between the two groups: ethnicity, smoking status, age at menarche, age at secondary amenorrhoea, years between secondary amenorrhoea and clinical evaluation, menstrual cycle pattern before secondary amenorrhoea, serum FSH and oestradiol levels, antral follicle count and prevalence of circulating autoantibodies.

As the primary study provided limited detailed pregnancy information, an additional questionnaire was sent out to all women with POI who had previously been pregnant. Because of ethical objections about the potential emotional burden, women with POI who had never been pregnant were not questioned about details concerning unsuccessful pregnancy attempts. The additional questionnaire focused on alterations in menstrual cycle pattern throughout life, oral contraceptive use, awareness of potential future fertility problems, early menopause, or both, desired family size, number of pregnancies, methods of conception, pregnancy outcomes and complications, time to pregnancy (TTP) in months, age at childbirth, age at menopause and the interval between last spontaneous conception and menopause. Spontaneously conceived pregnancies were defined as those pregnancies established without the use of any infertility treatment. Fertility treatment comprises all available infertility treatment; however, women who conceived through oocyte

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