

## Premature ovarian failure in women with juvenile idiopathic arthritis (JIA)

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**Key words:** Juvenile arthritis, premature ovarian failure, long term, follow up.

### ABSTRACT

**Objective.** To examine the effect of longstanding juvenile idiopathic arthritis (JIA) on menstrual irregularity and the incidence of premature ovarian failure in women.

**Methods.** Women with longstanding JIA who had abnormal or absent menstrual cycles had their circulating levels of gonadotrophins measured to check for the presence of ovarian failure. Disease demographics and subsets, function, age at onset of menstrual irregularity, previous medical intervention, concurrent diseases and history of pregnancy/delivery were documented.

**Results.** 177/187 (95%) of female adults with JIA who were identified and contacted, participated in the study. The average age at review was 35.4 years (19-78) with average disease duration of 28.7 years. 47.4% of all patients had clinically active arthritis. 44.6% of all patients had severe disability (HAQ score > 1.5). Six patients had premature ovarian failure unrelated to medication use, comprising 3.4% of the females in the study, compared to an expected incidence of 1% in the general population ( $p < 0.01$ ). In addition, three (1.7%) of these had onset of symptoms before age 30, compared to an expected incidence of 0.1% in the general population ( $p < 0.01$ ). The average maternal age at first delivery in women with JIA (27.2 years) was higher than the general population (23.5 years).

**Conclusion.** Idiopathic premature ovarian failure was more commonly found in individuals with juvenile idiopathic arthritis. In addition a small number of patients had iatrogenic premature ovarian failure related to chlorambucil use.

### Introduction

Premature ovarian failure (POF) is a condition characterized by amenorrhoea, infertility, oestrogen deficiency and elevated levels of circulating gonadotrophins in women under the age of 40 years. In the general population it affects 1% of women by the age of 40 years, and 0.1% by age 30 years (1).

Up to 32% of patients with POF have an associated autoimmune disorder (2)

including: rheumatoid arthritis, hypoparathyroidism, hypoadrenalism, myasthenia gravis, pernicious anaemia, Graves' disease, insulin dependant diabetes mellitus, Addison's disease and hypothyroidism, with hypothyroidism being the most common (2). Circulating antibodies to ovarian and other tissue have been found in up to a third of these women, but the tests are not well standardised, correlate poorly with ovarian histology and are highly variable (3). There remains a lack of consensus on ovary specific antibodies as a marker for ovarian autoimmunity (4). The gold standard for detecting immune ovarian destruction remains invasive ovarian biopsy, which shows lymphoplasmal cellular infiltrate around steroid-producing cells.

There is no published data on whether POF occurs in adults with JIA. David *et al.* (5) noted that 6/23 women with JIA treated with chlorambucil had ovarian failure. Østensen *et al.* (6) reported that compared to healthy controls, there was a significant increase in gynaecological diseases in women with JIA including: menstrual disturbance, pelvic inflammatory disease and ovarian disease.

There have been isolated reports of NSAID therapy causing female infertility (7,8). The likely mechanism is thought to be COX-2 inhibition causing luteinised unruptured follicle (LUF) syndrome, an anovulatory condition characterised by clinical signs of ovulation in the absence of follicular rupture and ovum release. LUF syndrome does not appear to alter luteinising hormone (LH)/ follicle stimulating hormone (FSH) levels, although the urinary pregnanediol:creatinine ratio is reduced post LH peak in the menstrual cycle.

### Patients and methods

Female patients with JIA over the age of 18 years were identified, who were either still attending clinics or had continuing contact with Wexham Park Hospital, a tertiary referral paediatric rheumatology centre. Patients were identified on a computerised database, by manually searching patient lists and by reviewing patient notes. Local ethics committee approval was obtained. Pa-

tients eligible for study entry were sent letters describing the aims and requirements of the study and were asked to return a signed consent form. Non-responders were sent a second study letter and subsequently contacted by telephone to ensure that their contact address was correct.

Patients were assessed individually by interview and clinical examination. Subsequently a full review of the patient's clinical notes was performed. All patients were assigned to a JIA subtype using the World Health Organisation / International League Against Rheumatism (ILAR) classification (9).

The women in the study were asked whether they had a regular monthly menstruation rhythm. In those patients without regular menstruation, circulating levels of gonadotrophins were measured if the presence of menopause had not previously been confirmed. The patient's age, age at first delivery and/or abortion and the patient's age at the onset of menstrual irregularity or absence were recorded. Previous medication use and concurrent diseases including Turner's syndrome were also documented. The incidence of POF in the study group was compared to that described by Coulam *et al.* (1) rather than a control group, because of the large numbers of controls required to reliably predict such an uncommon occurrence in the general population.

Non-parametric Spearman correlation was used to assess any correlations between independent variables. Chi squared analysis was used to assess any significant differences between incidences described in the study population, compared to the expected incidences in the general population.

## Results

Of 187 women identified with long standing JIA, 177 (94.6%) attended for an interview, clinical examination and notes review. 40 patients (22.5%) were reviewed either in their local hospital or at home. The mean patient age was 35.4 years (range 19-78, S.D. = 11.1). The mean age at disease onset was 7.1 years (range 0.8-15.9, S.D. = 4.2). The mean disease duration was 28.7 years (range 8-73, S.D. = 10.8). Less than 3%

of patients had a disease duration below 10 years and 9% below 15 years. 47.4% of all patients had clinically active arthritis. 44.6% of all patients had severe disability (HAQ score > 1.5). The frequency of individuals in each JIA subset was: systemic onset 18.2%, oligoarticular 7.4%, extended oligoarticular 26.1%, rheumatoid factor negative polyarticular 19.9%, rheumatoid factor positive polyarticular 18.2%, enthesitis related 4.5% and psoriatic 5.1%.

53/177 (30%) of all women had been pregnant and 44/177 (24.9%) had delivered live offspring. The average age at the end of pregnancy (abortion or delivery) was 26.8 years (range 18.3-41.5 years S.D.= 4.1) and the average age at the time of delivery of a live child was 27.2 years (range 20-41.5 years S.D.= 4.3). The average age at first delivery in the general UK population is 23.5 years (10), that is significantly lower ( $p < 0.02$ ) than the study population.

37/177 (20.9%) female patients were found to be either amenorrhoeic or having significant menstrual irregularity as shown in Figure 1. The gonadotrophin levels in 10 patients (5.7%) indicated that they did not have ovarian failure, with LH/FSH levels within normal menstrual cycle range. Two further patients were known to have Turner's syndrome (1.1%), which has a recognised association with JIA (11). Of the remaining 25 patients who were menopausal, 9 (5.1%) became amenorrhoeic before the age of 40. There was no significant correlation between either amenorrhoea or POF and JIA subset.

3/9 of the patients with POF had been treated with chlorambucil (2 for JIA related amyloidosis and one for disease activity control). Chlorambucil was prescribed for a total of 9 patients in the study group. In those with iatrogenic POF it had been prescribed for a period of 1.1 years from age 15, 2.7 years from age 9 and 16.1 years from age 10. The use of DMARDs in the remaining 6 patients included penicillamine, sulphasalazine, azathioprine and gold, but there was no evidence of the use of alkylating agents that could cause iatrogenic premature menopause. Two patients with idiopathic premature ovarian failure had an additional autoimmune disease (hyperthyroidism and alopecia).

The six patients with premature ovarian failure unrelated to medication use comprised 3.4% of the females in the study, compared to an expected incidence of 1% (1) in the general population ( $p < 0.01$ ). In addition, three (1.7%) of these had onset of symptoms before age 30, compared to an expected incidence of 0.1% in the general population ( $p < 0.01$ ).

Although there was a correlation between premature ovarian failure and duration of NSAID treatment at review ( $p < 0.05$ ), the subgroup with POF were on average 6.8 years older than the study group, bringing the significance of this finding into question. Duration of NSAID treatment at review was not found to be a predictive variable in a stepwise multiple regression analysis for early menopause, with age being the only predictor of 38.9% of the variance in early menopause ( $p < 0.005$ ).

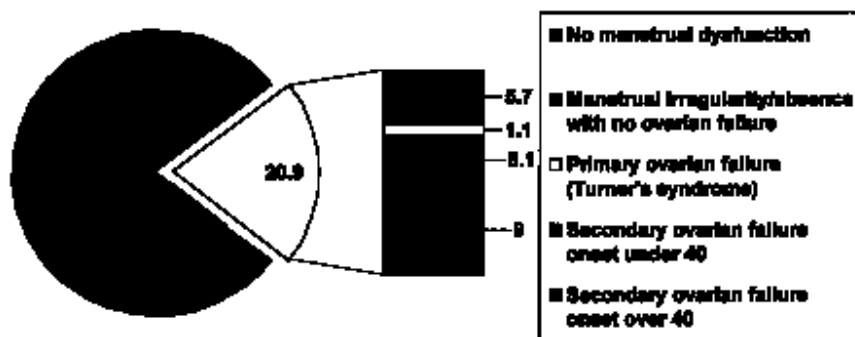


Fig. 1. Percentage of women with JIA with menstrual dysfunction.

This suggests that there is no real correlation between duration of NSAID treatment and early menopause.

### Discussion

The study group is not a true cohort and is skewed towards those patients with severe and persistent disease. However, they do represent those patients most likely to be encountered in an adult rheumatologists clinical practice.

Because premature menopause occurs in 1% of the general population below 40 years and 0.1% below 30 years, the size of a control group to reliably predict the incidence of POF becomes prohibitively large. Published data on general population incidence was therefore used to create a theoretical control group.

As previously described a significant proportion of women with JIA had menstrual disturbances (6). At the time of this study, 1.7% of women below 30 years of age and 3.4% of women below 40 years of age had POF. However, these figures should be assumed to be an underestimate, as 40/177 (22.5%) patients had not reached 30, and 106/177 (60%) patients had not reached 40. These patients still have the potential to develop ovarian failure and subsequently further increase the incidence described. In contrast to other autoimmune disorders, the increased risk of early ovarian failure is present throughout adult life, since by definition the onset of JIA is before an individual reaches adulthood.

Although premature ovarian failure has been described in other autoimmune conditions it has not been previously described in JIA. Early loss of ovarian function has both significant physical sequelae (amenorrhoea, breast atrophy, mucosal dryness, fatigue and loss of libido) and psychosocial sequelae (exclusion from 'motherhood', loss of self-esteem and poor body image).

There are significant implications for women with JIA in terms of when they should consider starting a family, as delay may put them at increased risk of infertility. This is of particular importance as the average maternal age at first delivery in the study group is 3.7 years higher than the general popula-

tion. A proportion of this increase in maternal age may be related to adults with JIA entering stable relationships (marriage or cohabitation) at an older age (12).

POF was previously considered to be irreversible and was described as premature menopause; however half of women with POF are now recognized to have intermittent ovarian function (13) and pregnancies do occur in POF (14). Patients have a 5-10% chance of spontaneous pregnancy and pregnancies have even been reported in women with no follicles observed on ovarian biopsy. Young women with POF sustain sex steroid deficiency for more years than naturally menopausal women, resulting in a significantly higher risk for osteoporosis (15) and cardiovascular disease (16) with an almost two-fold increase in mortality rate (17). The proportion of women 3/9 (33.3%) with POF related to chlorambucil therapy is comparable to other studies (5). There is some evidence from Koyama *et al.* (18) that younger women are more resistant to the ovarian effects of alkylating agents than older women. In some younger patients with iatrogenic POF, ovarian function may return. Recent reports of the preservation of fertility in women with SLE following treatment with chlorambucil or cyclophosphamide using concurrent gonadotrophin-releasing hormone agonist analogue (GnRH-a), to induce a temporary pre-pubertal hormonal milieu, suggests that the ovarian toxicity of chlorambucil may be able to be partially ameliorated (19).

Further study would be useful, prospectively assessing a group of individuals with JIA entering adulthood. This should include an assessment of whether ovarian autoantibody levels predict ovarian failure and whether the antibody levels change at the time of POF onset.

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