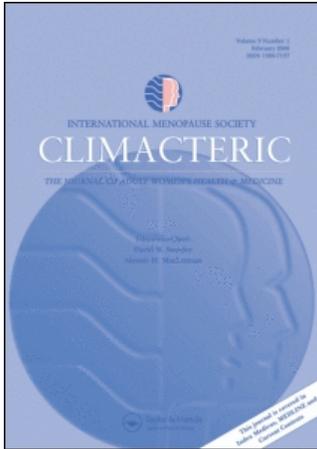


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## Editorial

# Premature ovarian failure: a growing concern

Nick Panay and Anna Fenton

EDITORS-IN-CHIEF

Premature ovarian failure (POF) has been estimated to affect about 1% of women younger than 40 years, 0.1% under 30 and 0.01% of women under the age of 20. However, as the cure rates of cancers in childhood and young women continue to improve, it is likely that the incidence of prematurely menopausal women will rise rapidly<sup>1</sup>. The recent adverse media reports on hormone replacement therapy (HRT) could not have come at a worse time. We live in an era when the naturally menopausal population is growing, but of even greater concern is the impact that the reporting of data from the Women's Health Initiative (WHI) study and the Million Women Study (MWS) has had on the growing population of young women who have suffered premature ovarian failure. Data suggest that 37% of women with POF considered stopping HRT because of breast cancer fears following the original WHI/MWS reports and only 44% were aware that the reports did not apply to their age group<sup>2</sup>.

In the past, the focus of medical care has been on improvement of survival rates. Very little attention has been given to the maintenance of quality of life in the short term and to the avoidance of the long-term sequelae of a premature menopause. One of the main reasons for this has been the bias of economic expenditure and medical endeavor to the prolongation of life (e.g. cancer treatments) rather than towards optimizing quality of life in cancer survivors. Should this trend continue, we are in danger of creating a population of young women who have been given back the gift of life but left without the physical and/or psychological zest to live it to its full<sup>3</sup>.

We need urgently to determine the scale of the problem, initially by the trawling of data from all

clinics that manage women with POF. The data will undoubtedly demonstrate extreme variations in management and deficiencies will emerge. Armed with this information, departments of health can then be petitioned to provide appropriate funding for the setting up of multidisciplinary units for the management of the particular psychological and physical needs of women with POF. Of even more concern are the young women who are not attending recognized clinics and are essentially 'lost to follow up'. The reality is that we will never know the true scale of the problem.

POF is a difficult diagnosis for women to accept, and a carefully planned and sensitive approach is required when informing patients of the diagnosis. In a recent study, 71% of women with spontaneous POF were unsatisfied with the manner in which they were informed by their clinician<sup>4</sup>. As a minimum, the initial investigation of patients presenting with erratic periods, for which pregnancy should be excluded, should include measurement of serum follicle stimulating hormone (FSH), estradiol and thyroid hormones. If the FSH level is in the menopausal range, the test should be repeated before the diagnosis is made, as levels can fluctuate. It is particularly concerning that, in a recent study, 50% of women with amenorrhea had to consult three physicians before any sort of testing of ovarian reserve was performed<sup>5</sup>. Evaluation of other hormones of ovarian origin, such as inhibin B and anti-mullerian hormone, improves the predictive value of ovarian reserve testing but is not indicated on a routine basis. In the long term, the polygenic inheritance of risk for spontaneous POF will be unravelled and banks of genes will be tested to give an individual her precise risk of suffering POF<sup>6</sup>.

A dedicated multidisciplinary clinic, separate from the routine menopause clinic, will provide ample time and the appropriate professionals to meet the needs of these emotionally traumatized patients. Counselling at this stage should include explanation that remission and spontaneous pregnancy can still occur in women with spontaneous or medical POF. Specific areas of management include the provision of counselling support, diet and nutrition supplement advice, hormone replacement therapy (HRT), and reproductive health care, including contraception and fertility issues.

Young women with spontaneous POF have pathologically low estrogen levels compared to their peers with normal ovarian function. HRT is therefore required to control vasomotor symptoms, minimize risks of cardiovascular disease<sup>7</sup>, osteoporosis<sup>8</sup> and possibly Alzheimer's disease, as well as maintain sexual function. The results of the Women's Health Initiative reanalysis and other studies show a clear trend towards benefit for cardiovascular disease and all-cause mortality in the youngest cohort<sup>9,10</sup>. By extrapolation, it is possible that the benefits would be even greater for women who have undergone an earlier menopause.

Since spontaneous ovarian activity can occasionally resume, consideration should be given to appropriate contraception in women not wishing to fall pregnant. Although standard oral contraceptive pills are sometimes prescribed, they contain synthetic steroid hormones at a greater dose than is required for physiological replacement and so may not be ideal. Low-dose combined pills may be used to provide estrogen replacement and contraception, but may be less effective than HRT in the prevention of osteoporosis and cardiovascular disease<sup>11</sup>. The levonorgestrel intrauterine system may also be offered to those who choose HRT and require contraception.

HRT in POF patients simply replaces ovarian hormones that should normally be produced at this age. It is of paramount importance that the patients understand this in view of the recent press on HRT. Logically, the aim should be to replace hormones as close to physiological levels as possible; therapy should generally continue at least until the estimated age of natural menopause (on average 51 years). In our experience, the choice of HRT regimen and the route of administration vary widely among patients. In the

absence of good, long-term, randomized prospective data, treatment should be individualized according to choice and risk factors. Where low sexual desire and tiredness are a problem, testosterone replacement may well be of benefit, especially in surgically menopausal women. There is an urgent need for large-scale, long-term, randomized prospective studies to determine the optimal routes and regimens of HRT in this group of women. Outcome measures should include short-term quality-of-life measures, vasomotor, urogenital and psychosexual symptoms and the long-term effect on cardiovascular, skeletal and cognitive health.

Women with POF are not necessarily sterile unless surgically menopausal and, in up to 50% of these women, some ovarian activity may return. For this reason, we share the view of others that POF would be better termed premature ovarian dysfunction (POD)<sup>12</sup>. This also avoids use of the emotive term 'failure'. There is, however, less than a 5% chance of spontaneous conception and, in our database of over 200 POF sufferers, 90% were nulliparous at time of diagnosis<sup>13</sup>. Women for whom fertility is an issue should be informed that assisted conception by *in vitro* fertilization, using donor oocytes or embryos, is the only realistic option at present. However, the use of genetically foreign oocytes is not acceptable to all POF sufferers. In one audit, only 50% of POF patients would consider oocyte donation. Adoption should be discussed as another family-building option. Advances in the technology of *in vitro* maturation of oocytes derived from stem cells and of ovarian tissue cryopreservation will provide other options in the future.

Young women with POF have unique needs that require special attention. There is an urgent need to determine the scale of the problem, particularly after iatrogenically induced menopause, and to develop evidence-based guidelines based on solid research in order to optimize the care of this group of women. It is clear from recent editorials<sup>14</sup>, review articles<sup>15</sup> and international meetings that a diverse group of specialists have an interest in this field. It is now time for these specialists to convene a study group, ideally under the auspices of the International Menopause Society, in order to identify and involve all relevant stakeholders, develop National/International databases and to propose future research projects, particularly to determine optimum therapeutic regimens.

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