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Sex hormone replacement in ovarian failure – new treatment concepts

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Premature ovarian failure is associated with decreased bone mass and fractures, and an increased risk of premature death from cardiovascular disease. There is also fertility compromise associated not only with the loss of ovarian function but, in those with pre-pubertal POF, inadequate uterine morphology. A wide variety of hormone replacement regimes are reported, but there is no clear evidence of best practice. Hormone replacement therapy (HRT) and the combined oral contraceptive pill (COCP) will suppress menopausal symptoms; however neither is designed to achieve physiological replacement of oestrogen and progesterone. There is evidence that physiological sex steroid replacement is superior to standard hormone replacement, in improving uterine volume as well as an improved blood pressure profile and bone mineral density. Sex steroid replacement therapy is long-term in these women, and therefore it is essential that the risk benefit ratio is optimal to maximise longer term health.

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Introduction

Premature ovarian failure (POF) occurs in 1 in 100 women under the age of 40, and in 90% of women the aetiology will be undetermined [1]. Secondary failure is becoming more important as survival following treatment for malignancy improves [2]. Sex steroid hormone replacement until the average age of natural menopause is advised, particularly for maintenance of bone mass [3]. Cardiovascular risk must also be considered, and in women with pre-pubertal ovarian failure, optimal uterine development is vital to future fertility prospects. A wide variety of sex steroid replacement regimes are reported, but there is no clear evidence of best practice. There is evidence demonstrating improvements in uterine morphology with physiological sex steroid replacement (pSSR) when compared to standard replacement regimes [4] and data are emerging revealing potential differences in cardiovascular risk and bone protection [5,6].

Premature ovarian failure (POF)

POF occurs as a result of the loss of normally functioning ovaries. This may be as a result of dysfunctional ovarian follicles or a decline in primordial follicles. The difference, however, is academic, as to distinguish between the two would require ovarian biopsy, and even in the absence of follicles on biopsy, pregnancy has occurred [7].

POF is also referred to as premature menopause, and naturally occurring menopause occurs as a result of decreasing numbers of primordial follicles available for recruitment, with subsequent decreased production of ovarian sex steroid hormones, resulting in loss of the normal hypothalamic, pituitary, gonadal feedback loop. Women become oligomenorrhoeic and eventually amenorrhoeic. The terminology surrounding POF has met with some debate, as neither POF nor premature menopause is accurate. Both convey that the process is irreversible, which in some, it is not. Up to 50% of young women with spontaneous POF experience intermittent and unpredictable ovarian function [8], although there is only a 5–10% chance of spontaneous conception [9]. Additionally, the term premature ovarian failure conveys that the woman has failed in some way and may be considered offensive. Premature ovarian insufficiency (POI) is increasingly used, as this describes impaired ovarian function on a continuum [10], which may be transient or progressive, rather than defining a specific endpoint, however, consensus is yet to be reached. For the purpose of this paper, we will use the term POF.

Aetiology

POF occurs in 1 in 100 women under the age of 40 [11], 1 in 1000 women under the age of 30, and 1 in 10 000 women under the age of 20 and it can be primary or secondary [12]. Primary POF may occur in women at any age, and can present as primary or secondary amenorrhoea. Secondary POF is becoming more important as survival improves following treatment for malignancy through surgery, chemotherapy and radiotherapy.

Causes of POF are shown in Table 1 [7].

Table 1
Causes of POF [12]. Reproduced with permission from Elsevier.

Primary
Chromosome abnormalities (X chromosome; Down Syndrome)
FSH receptor gene polymorphism and inhibin B mutation
Enzyme deficiencies (Galactosaemia; 17α-hydroxylase deficiency)
Autoimmune disease
Secondary
Chemotherapy and radiotherapy
Bilateral oophorectomy or surgical menopause
Hysterectomy without oophorectomy/uterine artery embolisation
Infection e.g. mumps