A case of early menopause

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This section is about the immediate management and investigation of an acute presentation in general practice. It is inspired by, but not based on, a real patient situation.

Jane is a 43-year-old woman who comes to see you for the first time. She requests a repeat script for a low-dose oral contraceptive pill (OCP). She tells you she has had an early menopause so she is not taking it for contraception. She wants to know more about whether this was the correct diagnosis.

What questions would you ask Jane at this point?

Answer: You should ask Jane about the early menopause, how it was diagnosed and what was happening with her periods at that time. When was her last normal period? An 'early menopause' is between 40 and 45 years of age. 'Premature menopause', using a standard definition, is under 40 years of age. Next you should ask her if she has any contraindications to the OCP. Has she any medical problems and is she taking any medications? Has she had hypertension, does she experience migraines, is there a personal or family history of clots in the leg or elsewhere in the body, is there a family history of breast cancer, early heart disease, stroke or diabetes, does she have any problems with her liver? If she has had children, did she have gestational hypertension or diabetes? Does she smoke? Does she know what her cholesterol level is?

Jane has no contraindications to taking the pill and has been taking it only for the past two years and six months. Her last normal period was at age 41 years. Her periods were irregular over the preceding year (with intervening gaps of up to several months). In that year she had about four periods and the GP told her she was in 'premature menopause'. She had some recurrent hot flushes and noted vaginal dryness with sexual intercourse. She had a blood test that apparently confirmed menopause and she was commenced on the OCP at that stage. What would you ask Jane next?

Answer: Did Jane's mother go through an early menopause? Has Jane had irregular periods before this at any stage in her life? If she has children, were there any problems conceiving or carrying pregnancies? Was an ultrasound examination of the uterus and ovaries done in the investigation of her secondary amenorrhoea?

Jane says she thinks her mother went through menopause earlier than normal at about the age of 44 years. Jane has two daughters and a P2G3 obstetric history. She was in her early 30s when she conceived and she had no problems with conception or her pregnancies, although she did have one early miscarriage. No pelvic ultrasound examination has been carried out since her last pregnancy. What is the definition of premature menopause?

Answer: Premature menopause in the absence of a medical cause is called 'premature ovarian insufficiency' (POI), previously called 'premature ovarian failure'. The diagnostic criteria are at least four months of amenorrhoea, a follicle stimulating hormone (FSH) level above 40 IU/L

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on two occasions at least a month apart, and the exclusion of secondary causes in a woman younger than 40 years (see the Box).

Natural menopause occurs between the ages of 45 and 55 years in most women. Complications of menopause, especially reduced bone density leading to the development of osteoporosis, are more frequently seen in women who reach menopause before the age of 45 years.

Has Jane gone through menopause?

Answer: The definition of menopause strictly includes no periods occurring for a year, so it is not certain that Jane has gone through menopause yet. Commencing the oral OCP when she did has made it impossible to say whether Jane has had an early menopause. It is likely that she was perimenopausal at age 41 years given the irregularity of her menstrual cycle at the time and her menopausal-type symptoms. The family history of early menopause is significant as this is associated with an increased risk of early or premature menopause.

What was the blood test that 'confirmed' Jane's early menopause? How accurate is this blood test?

Answer: The test was probably an isolated measurement of FSH levels. Level above 40 IU/L are likely to be due to ovarian insufficiency, with menopause being the most likely cause. This does not mean, however, that Jane has reached menopause yet. Periods may subsequently resume and the FSH level will drop if measured again that month. A raised FSH level indicates perimenopause or menopause as the cause of oligo- or amenorrhoea (especially if the level is over 40 IU/L), but there are other causes in younger women that need to be excluded. The FSH level is of no value if measured when a woman is taking the OCP (which needs to be stopped for at least a month before the blood test). The FSH level should be measured early in the cycle (in women who are having periods). The measurement should be repeated, along with measurement of serum oestradiol level, at least one month later if FSH level is abnormal.

Oestradiol levels are reduced to basal levels at times of anovulation (such as menopause) but are also normally reduced early in the cycle. They do not predict menopause but indicate anovulation (hence levels are reduced before an egg is developing during each monthly cycle).

The antimullerian hormone (AMH) test is an indication of ovarian reserve. Women in their early 40s usually have reduced ovarian reserve and hence a reduced AMH level. However, the test is not usually undertaken unless it is part of an infertility work up because other tests are cheaper and more reliable, and perimenopause/menopause is usually a clinical diagnosis not requiring investigation if taking place in the normal age range. It is better to rely on the history along with the FSH and oestradiol levels. A high AMH level in women in their 40s is associated with polycystic ovarian syndrome.

What would you advise Jane regarding the 'early' menopause? Should Jane have any further investigations?

Answer: Certain investigations may be carried out while Jane continues taking the OCP. You should discuss with Jane whether she would like to see if she is menopausal or not; this would involve ceasing the OCP and seeing whether her periods resume over the next year (see the diagnostic criteria for POI described earlier). This may help to guide treatment, and this information would also be beneficial to Jane's daughters, as both POI and early menopause are often hereditary. If Jane does have this condition, her daughters should be advised not to delay childbearing unnecessarily. Women who have POI before the age of 30 years should have chromosomal studies arranged for chromosomal abnormalities (most commonly Turner's syndrome, XXY and fragile X syndrome).

If Jane has an FSH level above 40 IU/L while not taking the OCP and when amenorrhoeic this is supportive evidence of early menopause. If Jane's periods resume and are still very irregular, this FSH level is less supportive, even when measured early in the cycle, as it will be more variable. Jane should use an appropriate contraceptive method, such as a barrier method, if needed while she is not taking the OCP in case she commences spontaneous ovulation and falls pregnant before her first period, and for contraception afterwards. Jane should have a transvaginal pelvic ultrasound examination to

Differential diagnoses of secondary amenorrhoea

- Gonadal hormonal causes: pregnancy, missed abortion, hormone therapy, polycystic ovarian syndrome, hormonally active ovarian cysts and dysgerminomas
- Hypothalamic amenorrhoea: especially anorexia, bulimia, any cause of significant weight loss, significant amount of exercise, serious medical or surgical conditions that are ongoing
- Autoimmune conditions: especially thyroid disease, polyglandular autoimmune syndromes, Addison's disease
- Pituitary dysfunction: prolactinomas
- Psychiatric: severe anxiety and depression
- Genetic abnormalities: ovarian dysgenesis, Turner's syndrome, fragile X syndrome, XXY, isolated LH and FSH receptor defects
- Iatrogenic: chemotherapy, radiotherapy and pelvic surgery
- Infections: cytomegalovirus, mumps

Practice points

- The diagnostic criteria of premature ovarian insufficiency (POI) in a woman under the age of 40 years who has gone through menarche are: at least four months of amenorrhoea, an FSH level above 40 IU/L on two occasions at least a month apart, and the exclusion of secondary causes.
- It is of no value to test FSH level or oestradiol levels when a patient is taking the oral contraceptive pill (OCP).
- It is not necessary to test these hormones routinely just to assess whether a woman is menopausal if she is in the menopausal age group – this is a clinical diagnosis.
- Secondary causes of amenorrhoea should be excluded in patients with early/premature menopause. Ideally an ultrasound examination should be carried out at least two months after ceasing the OCP (or at the end of a period) if interpreting the uterine lining thickness.
- POI and early menopause are often hereditary, and the daughters of patients with the condition should be made aware of this in relation to fertility.
- The recommendation is that women who experience premature menopause or POI take some form of sex hormone replacement therapy until at least the average age of menopause at 51 years as they are at increased risk of premature osteoporosis and cardiovascular disease. The low-dose combined OCP is often recommended in younger women. Routine monitoring for breast cancer in women taking hormone replacement therapy is indicated.

exclude an ovarian tumour and polycystic ovarian syndrome; ideally the ultrasound should be performed two months after ceasing the OCP to interpret the uterine lining thickness, but if Jane does not want to cease the OCP the ultrasound is still of value to assess the ovaries. Jane should also have measurement of her thyroid-stimulating hormone level and, if POI is diagnosed, testing for antithyroid antibodies as part of the work up for secondary amenorrhoea. A complete family and personal history (especially for autoimmune disease) and physical examination should eliminate or guide the need for further investigations.

If Jane ceases the OCP and her periods do not resume, she is at increased risk of osteoporosis. How is this best prevented?
Answer: Jane could commence hormone replacement therapy (HRT) or restart the OCP. The oestrogen in HRT (which is approximately the same as the level at ovulation) and in the low-dose OCP (which is approximately twice the level at ovulation) prevents bone loss that occurs around menopause, when the ovaries stop producing this hormone. If Jane spontaneously recommences ovulation, she is at risk of pregnancy if using HRT and may also have erratic bleeding as HRT does not suppress ovulation. Most doctors would suggest she restart the low-dose OCP as she has no contraindications to this and contraception is secure. Also, if her periods return and are irregular, her risk of osteoporosis is increased as there is decreased oestrogen secretion. If desired, she could skip the inactive tablets and avoid the withdrawal bleed for up to three months at a time. This would also provide her with continuous oestrogen, in contrast to taking the OCP with a withdrawal bleed. Combining levonorgestrel-releasing intrauterine device with the transdermal or oral oestrogen used in HRT is an alternative method.

Jane should have baseline bone densitometry (hip and spine) carried out and if her bone density is already abnormal (probably from the oligomenorrhoea at about 40 years of age) this should be repeated in the future. There is a Medicare rebate applicable if a woman is under 45 years of age and has had more than six months of amenorrhoea. If low bone density is present, Jane should ideally have other tests to help ensure there are no other reasons for low bone density. These tests include coeliac serology, serum calcium level, liver and kidney function tests, thyroid-stimulating hormone level (if not already measured), immunoelectrophoresis studies, and 25-OH vitamin D level. Calcium intake and 25-OH vitamin D levels should be optimised. If Jane has already developed marked osteopenia or osteoporosis, she should be referred to an endocrinologist for a further opinion and management.

Is there anything else that Jane needs to know about her health if she has POI?
Answer: Women with POI are also at increased risk of early onset cardiovascular disease and should have regular screening for hypertension. They should have baseline fasting serum cholesterol and blood glucose level if this has not been done recently. The frequency of further testing will depend on these results and the woman's personal medical and family history. They should be encouraged to do weight-bearing exercises, to keep within a healthy body weight range, and not to drink alcohol excessively or to smoke. Women with POI may also decrease their risk of premature cardiovascular and possible cognitive dysfunction by taking certain forms of sex hormone replacement. Routine monitoring for breast cancer in women with POI taking sex hormone replacement is indicated, which includes clinical examination and, in those aged over 40 years, consideration of mammography and possibly an ultrasound examination.

Outcome: Jane is keen to see whether her periods resume while she is not taking the OCP. If they do resume, she plans to restart the low-dose OCP after her second serial natural period. If she appears to be postmenopausal then she will decide whether to use a hormonal intrauterine device (as she is still concerned about possible pregnancy risk) and an oestrogen patch until age 50 years, or whether to restart the low-dose OCP. She understands the vascular complication rate is higher with use of the low-dose OCP, especially the nonandrogenic third-generation progestogens. If Jane develops symptoms of oestrogen deficiency (such as hot flushes), she may decide to start HRT immediately and use a barrier contraceptive method until she is sure she is through the menopause. She is yet to have the blood tests, bone densitometry and pelvic ultrasound. ET