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Resumption of ovulatory menstrual cycles in a postmenopausal woman

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Introduction

Menopause is the complete cessation of menses, defined as 12 months of amenorrhoea (Greendale et al, 1999). Throughout the reproductive years, there is a steady depletion in the number of ovarian follicles, with the highest number being during fetal life; the depletion of this finite follicular pool drives menopause (Burger, 2006). As the number of follicles decreases, so does production of oestradiol and inhibin, subsequently increasing levels of follicle-stimulating hormone and luteinising hormone until follicular exhaustion occurs (Burger, 2006).

It is well documented that post-menopausal ovaries are inactive, although hormone production still occurs (Burger, 2006). This case reports the resumption of multiple ovulatory cycles in a patient previously considered postmenopausal.

Discussion

A literature search reveals only one case report of the resumption of ovulation postmenopause (Seungdamrong and Weiss, 2007). This described a 57-year-old, with no significant past

Case report

A 51-year-old woman, parity 1, with a body mass index 22 kg/m^2, presented to the gynaecology clinic in October 2020 with postmenopausal bleeding, referred by primary care under the suspected cancer pathway. She had experienced two episodes of per vaginum bleeding, 28 days apart, lasting for 4–5 days, accompanied by breast tenderness and pelvic pain. She reported no postcoital bleeding, bladder or bowel symptoms.

She reported having regular menses throughout life, with menarche at the age of 12 years. Her last menstrual period was 4 years before presentation, at 46 years of age. In the UK, menopause is a clinical diagnosis and can be made without laboratory tests in those over 45 years old (National Institute for Health and Care Excellence, 2015).

She had a Mirena coil inserted in 2017 as hormone replacement therapy for symptomatic relief. She had a medical history of hypothyroidism treated with levothyroxine. Surgically, she had an elective caesarean section in 2003 and an open appendicectomy. Her last smear test (2019) was normal.

On review in clinic, speculum examination revealed a normal cervix. Outpatient hysteroscopy revealed a small anterior wall polyp and the Mirena coil in situ. Pipelle endometrial biopsy showed normal endometrium with no atypia or malignancy. She underwent a Myosure polypectomy and replacement of the Mirena coil 1 week later; the resulting histology was benign.

A subsequent transvaginal ultrasound showed an anteverted uterus and two normal ovaries with follicles bilaterally, indicating ovulatory cycles. There was an incidental finding of an intramural fibroid measuring 30x25x28 mm. No adnexal masses were seen.

Magnetic resonance imaging of the pelvis showed a 7 mm right ovarian haemorrhagic cyst, haemosiderin deposition in both ovaries, and evidence of burnt-out adenomyosis in the uterus. There were no other significant findings.

Laboratory hormone results (Table 1) showed that her oestradiol levels in 2016 were consistent with menopause, and 5 years later, levels were consistent with ovulation. Day 8 serum follicle-stimulating hormone levels in 2020 were consistent with the follicular phase of an ovulatory menstrual cycle. Other hormone markers were within normal ranges.

She noticed the same pattern of bleeding in the following months and was discharged back to primary care with resumption of menstrual periods.

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Table 1. Laboratory results		
Date	**Marker**	**Value (normal range)***
February 2016	Oestradiol	<55 pmol/litre (<118 pmol/litre – normal range postmenopause)
	Progesterone	0.9 nmol/litre (<4.4 nmol/litre – normal range postmenopause)
November 2020	Day 8 follicle-stimulating hormone	3.4 IU/litre (1–9 IU/litre – normal range for follicular phase)
September 2020	CA125	21 kU/litre (0–35 kU/litre)
January 2021	Oestradiol	816 pmol/litre (235–1309 pmol/litre – normal range for ovulatory phase)
	Progesterone	<1 nmol/litre (<5.0 nmol/litre – normal range for follicular phase)
	Cortisol (10 am)	396 nmol/litre (119–618 nmol/litre)
	Prolactin	207 IU/ml (59–619 IU/ml)
	Testosterone	1.0 nmol/litre (0.7–2.8 nmol/litre)

**reference ranges from South Tees NHS Trust Pathology Tests (https://www.southtees.nhs.uk/services/pathology/)*

medical history, who experienced a single ovulation 3 years postmenopause. Five weeks later, oestradiol and progesterone returned to postmenopausal levels. Although similar, this case reported only a single ovulation, whereas the present case describes the resumption of multiple ovulatory cycles.

Another report described a 53-year-old woman who, after 32 years of oestrogen-deficient amenorrhoea secondary to anorexia nervosa, experienced resumption of menses after returning to a healthy body mass index (Gentile et al, 2011). It was reported 4 years later that regular menses continued in this woman, indicating the possibility of ovulatory resumption in women in their fifties.

Much of the literature surrounding resumption of menses is related to anorexia nervosa or athletes, highlighting the impact of lifestyle factors including diet, body weight, physical activity and stress on the hypothalamic–pituitary–gonadal axis. If energy reserves are unable to meet requirements, secretion of gonadotropin-releasing hormone decreases in the hypothalamus, leading to functional hypothalamic amenorrhoea causing reduced levels of luteinising hormone and follicle-stimulating hormone, and a subsequent hypo-oestrogenic state (Huhmann, 2020).

It is possible that the 4-year period of amenorrhoea in this patient could have been misdiagnosed as menopause because of her age. Lifestyle changes could have precipitated functional hypothalamic amenorrhoea, with resumption of menses years later. However, the patient reported no significant lifestyle changes to support this.

A study of patients with idiopathic premature ovarian insufficiency found that 23% showed features of spontaneous ovarian resumption (Bachelot et al, 2017). Owing to her age at last menstrual period and a history of regular menses, this patient was given a clinical diagnosis of menopause rather than premature ovarian insufficiency. However, as the underlying mechanisms are analogous, resumption of ovarian cycles postmenopause could be possible if follicular exhaustion has not fully occurred or if the person is in a state of ovarian insufficiency rather than true menopause.

It may be assumed that further unreported cases of ovulatory cycle resumption have occurred in postmenopausal women. This case questions existing knowledge regarding ovarian senescence, the sensitivity of the hypothalamic–pituitary–gonadal axis in menopause, and how resumption of ovulatory cycles may be possible after menopause.

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Learning points

- Resumption of ovulatory cycles may be possible after onset of menopause, especially if follicular exhaustion has not yet occurred.
- Any postmenopausal bleeding requires full investigation including hysteroscopy and endometrial biopsy, full blood hormone profile and imaging.
- States of primary ovarian insufficiency are analogous to menopause and the diagnoses can be confused in a woman over the age of 45 years.
- The hypothalamic–pituitary–gonadal axis is very sensitive to lifestyle factors, and this should be explored in depth when history taking.

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