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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Premature ovarian failure 3 years after menarche in a 16-year-old girl following human papillomavirus vaccination

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Summary

Premature ovarian failure in a well adolescent is a rare event. Its occurrence raises important questions about causation, which may signal other systemic concerns. This patient presented with amenorrhoea after identifying a change from her regular cycle to irregular and scant periods following vaccinations against human papillomavirus. She declined the oral contraceptives initially prescribed for amenorrhoea. The diagnostic tasks were to determine the reason for her secondary amenorrhoea and then to investigate for possible causes of the premature ovarian failure identified. Although the cause is unknown in 90% of cases, the remaining chief identifiable causes of this condition were excluded. Premature ovarian failure was then notified as a possible adverse event following this vaccination. The young woman was counselled regarding preservation of bone density, reproductive implications and relevant follow-up. This event could hold potential implications for population health and prompts further inquiry.

BACKGROUND

Since secondary amenorrhoea and its causes may have great significance for a woman's future health, investigation of such presentations is warranted and is best addressed prior to potential masking by the oral contraceptives (OC). Subsequent diagnosis of premature ovarian failure, as in this young woman, will significantly affect her future health management. The occurrence of premature ovarian failure, previously known as premature menopause, in mid-teen years is extremely rare. The annual incidence of premature ovarian failure has been reported as 10/100 000 person-years between the ages of 15 and 29 years.[1] The cause of ovarian failure before age 40 years remains unknown in up to 90% of cases.[2] After diagnosis, evaluation for autoimmune disorder, genetic defect and exposure to ovarian toxins is important for counselling, surveillance for associated illnesses, for treatment and to further our understanding of the pattern of disease prevalence of premature ovarian insufficiency.

Recent data presented to the European Society of Human Reproduction and Embryology Conference in Stockholm in 2011[3] suggest that unexplained premature ovarian failure may have a current incidence sixfold greater than previously thought.

The unexplained occurrence of premature ovarian failure may reflect specific toxins or certain genotypes which currently available genetic examinations are not adequate to explore. Premature ovarian failure developing here, however, after human papillomavirus (HPV) vaccination prompted inquiry concerning ovarian histology of vaccinated rats at intervals of postvaccination. There was no record obtainable of these histological ovarian assessments. It also raised suggestions that long-term follow-up studies of natural cycles and fertility of vaccinated women should be considered.

CASE PRESENTATION

A 16-year-old girl presented with a history of 5 months amenorrhoea, preceded by approximately 12 months oligomenorrhoea. Menarche had occurred at the age of 13 in 2007 with initially light periods which became heavier and developed a regular monthly pattern over the following 12 months.

Early in 2009 menses became irregular. In early 2010 they became scant and occurred infrequently, two or more months apart. Menstrual periods ceased in January 2011. Following the development of amenorrhoea, the patient experienced hot flushes. She identified that an alteration in the menstrual pattern had started following HPV vaccination.

On first presentation to her local doctor she was prescribed the OC for amenorrhoea after exclusion of pregnancy. She elected not to take the contraceptive pill at that time and sought further opinion regarding her continuing amenorrhoea.

There was no past or present history of significant other illness, stressors or surgery, no known exposure to radiation or toxins and no other medications were being taken during or preceding this time. She was a non-smoker. There was no known family history of genetic abnormalities, premature menopause or of autoimmune disease. There were no abnormal findings on clinical examination; her weight was 56 kg, and body mass index was 22.6. The absence of a clinical basis for amenorrhoea prompted more evaluation.

INVESTIGATIONS

Further assessment revealed a normal full blood count, and normal renal, liver and thyroid function. Prolactin level and androgen profile were also within normal limits.

Follicle stimulating hormone (FSH) was raised at 108 U/l (menopausal range is 20–140 U/l); luteinising hormone was 31 U/l, (menopausal range is 10–65 U/l); estradiol was low at 63 pmol/l (normal follicular phase range is greater than 110, menopausal range is 40–200 pmol/l). Progesterone was low at 1.1 nmol/l (menopausal range is less than 2.2 nmol/l). Anti-Mullerian hormone was low at less than 1.0 pmol/l (levels below 14 pmol/l suggest failing ovulatory reserve). Serology was consistent with known previous mumps vaccination.

Karyotype was established as 46 XX. No ovarian antibodies were detected, and there were no adrenal antibodies. Thyroid peroxidase antibodies were 2 IU/ml and thyroglobulin antibodies were 44 IU/ml (levels up to 100 IU/ml can occur in normal subjects). Galactosaemia screen was negative (Gal-1-P uridyl transferase-RC was 0.42 U/g haemoglobin, the normal range is 0.26–0.52). Fragile X (Cytosine-Guanine-Guanine) n Repeats 28 was normal (normal range is less than 50). Pelvic ultrasound was normal.

DIFFERENTIAL DIAGNOSIS

The presence of menopausal gonadotrophin levels in association with over 3 months of amenorrhoea or oligomenorrhoea before age 40 years defines premature ovarian failure. Following an elevated FSH level it was next confirmed that this young woman's anti-Mullerian hormone demonstrated no measurable ovarian reserve. The exclusion of genetic causes such as Turner's syndrome, Fragile X and galactosaemia was necessary together with investigation for other endocrine or autoimmune disorders.

New South Wales Health has confirmed that three Quadrivalent Human Papillomavirus (types 6, 11, 16 and 18) Recombinant Vaccinations were administered to the client in the high-school vaccination programme in February, May and August 2008.

TREATMENT

This young woman was referred for specialist gynaecological review and management. She was advised of the need for adequate calcium, vitamin D, exercise and hormone replacement for bone density preservation. Implications for future childbearing and the need for periodic review were discussed. Hormone replacement was started in the form of the OC to treat menopausal symptoms as she approached matriculation studies. Plans were outlined for future follow-up of these issues together with monitoring side effects and complications of the contraceptive pill.

OUTCOME AND FOLLOW-UP

Baseline bone mineral density (BMD) was assessed, but standard references ranges for BMD do not extend to this patient's young age, so special reference ranges were used. These suggested femoral neck BMD of 0766 g/cm^2 to be in the low range for age, height and weight, and lumbar spine BMD of 0.903 g/cm^2 to be normal for height and weight but lower than the expected range for age. Interval reassessment is planned.

Premature ovarian failure has been notified as a possible adverse event to the Therapeutic Goods Administration of Australia (reference no. 285383) and to the company which produces this vaccine and to the sponsor.

Each 0.5 ml dose of the quadrivalent human papillomavirus virus-like particle vaccine (HPV VLP vaccine) contains proteins of HPV types 6, 11, 16 and 18; 225 mcg of aluminium (as amorphous aluminium hydroxyphosphate sulphate adjuvant); 9.56 mg of sodium chloride; 0.78 mg of L-histidine; 50 mcg of polysorbate 80; 35 mcg of borax and water.

It is not known whether this event of premature ovarian failure is linked to the quadrivalent HPV vaccine. More detailed information concerning rat ovarian histology and ongoing fecundity post-HPV vaccination was sought from the Therapeutic Goods Administration (TGA). Although the TGA's Australian Public Assessment Report for Human Papillomavirus Quadrivalent Vaccine, February 2011, does report on the histology of vaccinated rat testes and epididymides,[4] no histological report has been available for vaccinated rat ovaries.

The TGA subsequently agreed to a freedom of information application in the public interest (FOI 001-1112) requesting documented rat ovarian histology post-quadrivalent HPV vaccination that may have been performed by the sponsor and forwarded to the TGA. However, a histological report of the ovaries of vaccinated rats remained unavailable beyond a numbering of the corpora lutea present at postweaning euthanasia following the first litter (Extract Study no. TT#03-703-0(CTD Module 4, volumes 1–3) summary for non-clinical study report 'Intramuscular developmental toxicity and immunogenicity study in rats with postweaning evaluation').

DISCUSSION

Since there can be many causes of secondary amenorrhoea, from physiological to constitutional, systemic and failure of the hypothalamic–pituitary–ovarian axis, determining the aetiology requires broad considerations. In this woman it required exclusion of metabolic, other endocrine, autoimmune and genetic disorders.

Results consistent with premature ovarian insufficiency in a 16-year-old girl have significant consequences for her future health and for her prospects of motherhood.

Had this young woman taken the OC as prescribed for correction of her oligomenorrhoea/amenorrhoea, her diagnosis of premature ovarian insufficiency may not have been determined for perhaps some years. The possibility of its link to an adverse pharmaceutical event might also have been lost.

Anecdotal evidence from an informal discussion with high-school students suggests that one in three girls of this age is taking an OC for reasons of cycle control, acne management or for contraception. Given the prevalence of OC usage in this age group, combined with the possibility of initial OC prescription for the management of oligomenorrhoea (presumably to reduce associated anxiety, re-establish a 'normal' cycle and to protect bone mass, etc), conditions affecting menstrual function in this age group will be undetected and undiagnosed. Menstrual abnormalities and particularly ovarian insufficiency at this time may therefore be under-reported as possible adverse events following vaccination or other medication.

In addition, as the Australian sponsor of this vaccine has stated after notification: 'the postmarket reporting of adverse events is voluntary and from a population of uncertain size, and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure'.

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Learning points

- It is suggested that oligomenorrhoea and amenorrhoea even in young women be investigated prior to the start of the oral contraceptives.
- It is also suggested that development of oligomenorrhoea or amenorrhoea after establishment of regular menses be considered for notification as possible adverse events where they follow vaccination or medication.
- Assessment of vaccinated rat ovarian histology at intervals after vaccination is relevant and appropriate.
- Since there may potentially be a group for whom this vaccine is contraindicated, and since the occurrence of this event may possibly represent broader public health implications, it is also suggested that long-term follow-up of ovarian function in a cohort of vaccinated girls and women be undertaken.

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Competing interests None.

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