CASE REPORT

Atypical case of preterm ovarian hyperstimulation syndrome

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Accepted 7 February 2017

SUMMARY

Preterm ovarian hyperstimulation syndrome is a rare syndrome in which preterm infant girls have hypogastric, upper leg and labial swelling accompanied by elevated serum oestradiol levels and ovarian follicular cysts on ultrasound. Our case is an infant born at 23 weeks gestational age who at 30 weeks postconceptional age (PCA) developed elevated 17-hydroxyprogesterone on her newborn screen with associated clitoromegaly and a ventral groove on the inferior aspect of the erectile tissue. An initial pelvic ultrasound at 32 weeks PCA demonstrated a normal appearing uterus, but the ovaries were not visualised. At 39 weeks PCA, follicular ovarian cysts were noted bilaterally (31×26×21 mm on left and 38×25×36 mm on right). Without treatment, oestradiol and testosterone levels began normalising by 42 weeks PCA. After this point, the right ovarian cysts had resolved and the left ovarian cyst continued to diminish in size.

BACKGROUND

Activation of the hypothalamic–pituitary–gonadal (HPG) axis is a physiological process that occurs in the first month of life and it thought to be important for the development of reproductive functions.¹ Preterm ovarian hyperstimulation syndrome (POHS), however, was first described in 1985 by Sedin *et al* as a case series of four preterm female neonates (24–28 weeks postconceptional age (PCA)) reporting transient oedematous change of the perineal, lower abdomen and upper thigh. In these neonates, elevated serum oestradiol and gonadotropin levels and multiple ovarian cysts accompanied the oedematous changes by 36–39 weeks PCA.

In utero, oestrogen and testosterone are secreted from the placenta and inhibit fetal gonadotropin-releasing hormone (GnRH). At delivery, extraction of the placenta removes this inhibition resulting in secretion of leutenising hormone (LH) and follicle-stimulating hormone (FSH). It is thought that the preterm infant has an immature HPG axis with diminished sensitivity of negative feedback to LH/FSH from placental steroids. This subsequently leads to an increase in LH, FSH, testosterone, oestradiol and progesterone levels (figure 1).² This is in contrast to the iatrogenic ovarian hyperstimulation syndrome seen in women who have undergone supraphysiological ovarian stimulation with exogenous gonadotropins causing vasoactive peptides release from granulosa cells of the hyperstimulated ovaries.³ In these adult cases, the hyperstimulation is iatrogenic and does not result from a lack of response to the physiological

negative feedback of gonadotropins on pituitary hormone secretion.

CASE PRESENTATION

A female neonate was born by spontaneous vaginal delivery to a gravida nine para four mother aged 26 years at 23 weeks PCA. Antenatal serum screening was unremarkable. Her birth weight was 510 g (50th centile) and Apgar scores were 3, 5 and 7 at 1, 5 and 10 min, respectively. She had a prolonged stay in the neonatal intensive care unit (NICU) for 20 weeks due to extreme prematurity, and ongoing need for respiratory and feeding support. At 30 weeks PCA, it was noted that she had elevated 17-OH hydroxyprogesterone (41.4 nmol/L) on her newborn screen associated with clitoromegaly and a visible ventral groove on the inferior aspect of the erectile tissue. She had a normal appearing perineum, specifically a single vaginal opening, no fusion of labia and absence of palpable gonadal tissue. Owing to the clitoral enlargement and the clitoral structure with an apparent ventral groove, the assigned female sex was reconsidered. The ambiguity in appearance was sufficient for further workup of a disorder of sexual development and a discussion with the family regarding the potential aetiologies of virilisation of the infant.

INVESTIGATIONS

Further investigation revealed elevated testosterone (10.4 nmol/L), oestradiol (89 pmol/L) and DHEAS (17.4 µmol/L) (table 1). Karyotyping confirmed a 46XX chromosomal sex, therefore ruling out an undervirilised male, and partial androgen insensitivity. Congenital adrenal hyperplasia was ruled out after repeat 17-hydroxyprogesterone levels returned within the normal range (for XX), cortisol level was 180 pmol/L and normal adrenals were noted on ultrasound. At this point, additional blood work revealed elevation of FSH and LH levels at 40.4 and 36 IU/L, respectively.

The levels measured in our case throughout the clinical course in NICU. Hormone levels were measured with standard laboratory techniques and ultrasound with formal radiographer interpretation reports. No other abnormalities were detected on ultrasound.

At 39 weeks PCA, oestradiol levels rose to 1379 pmol/L and pelvic ultrasound demonstrated bilateral, large, thin-walled cysts on either side of the uterus. While findings were bilateral, figure 2 demonstrates the findings on the right ovary where each cyst contained at least one septate cyst. The uterus was reported as normal. Over the

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To cite: Durst MA, Wicklow B, Narvey M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-217517

Figure 1 Hypothalamus–pituitary–gonadal (HPG) axis. The physiological regulation of HPG axis. Secretion of oestradiol, progesterone and testosterone negatively feed back in short and long loop pathways.

Table 1 Serum hormone levels and ultrasound results

	30 weeks PCA	30+4 weeks PCA	32 weeks PCA	39 weeks PCA	41 weeks PCA	42 weeks PCA
17-hydroxy progesterone (nmol/L)	41.4	—	—	—	—	—
Oestradiol (pmol/L)	—	—	89	1379	1714	1068
Testosterone (nmol/L)	—	10.4	13	11	—	5.4
FSH (IU/L)	—	—	36	1.1	—	—
LH (IU/L)	—	—	40.4	2.7	—	—
DHEAS (μmol/L)	—	17.4	—	14.2	—	—
Cortisol (nmol/L)	—	180	—	—	—	—
US: Cyst L (mm)	No U/S	No U/S	Ovaries not visualised	31×26×21	20×15×12	No cysts
US: Cyst R (mm)	No U/S	No U/S	Ovaries not visualised	38×25×36	26×15×18	32×18×26

Figure 2 Ultrasound of the right ovary. Initial ovarian cyst findings at 39 weeks postconceptional age demonstrating large, thin-walled cysts including septate cysts. The uterus and bladder were normal. No free fluid was visualised in the pelvis.

course of the following 3 weeks, 9 weeks after initial symptom onset, oestradiol continued to rise (maximum 1714 pmol/L at 41 weeks PCA), while the ovarian cysts continued to diminish

(final ultrasound showed normalisation of the left ovary and a persisting, but diminishing right ovarian cysts of 32×18×26 mm).

DIFFERENTIAL DIAGNOSIS

A number of differentials were considered when clitoromegaly was noted.

- Overvirilised XX
 - Congenital adrenal hyperplasia (21-hydroxylase or 11 β steroid dehydrogenase deficiency)
 - Gestational hyperandrogenism
- Undervirilised XY
 - Partial androgen insensitivity
 - 3-β hydroxysteroid dehydrogenase deficiency
 - 5-α reductase deficiency

TREATMENT

No treatment was undertaken.

OUTCOME AND FOLLOW-UP

Consultation with Pediatric Endocrinology expanded clinical investigations, which excluded many causes in the

Figure 3 Preterm ovarian hyperstimulation clinical course. Courtesy of Esen and Demirel.⁸ (A) Initial presentation with swelling of the external genitalia, clitoris and vulva as well as hypogastrium and upper thighs. (B) Six weeks later, considerable spontaneous swelling reduction. (C) Complete resolution by 14 weeks.

aforementioned diagnoses under consideration. An observational approach was taken, without initiating treatment, with serial measurements of hormone levels and ultrasounds over a period of several weeks. With naturally regressing ovarian cysts, normalising hormone levels, and reduction in swelling of the genitalia, the diagnosis was established as POHS (figure 3).

By 42 weeks PCA, the right ovary had normalised with no cyst detected, while the left ovarian cyst continued to diminish in size. Oestradiol and testosterone levels continued to normalise as well.

DISCUSSION

POHS has been previously characterised by four main features: (1) prematurity (24–31 weeks PCA), (2) swelling of the hypogastrium, upper leg and vulvar regions, (3) elevated oestradiol (80–5300) and gonadotropin levels between 35 and 39 weeks PCA and (4) ovarian follicular cysts (10–40 mm).⁴ Our case is unusual in that this is the first description of an infant born before 24 weeks presenting with symptoms and also, in contrast to all other reports findings, our case appeared earlier than previously described (onset at 30 weeks PCA) with a significantly elevated initial oestradiol level of 89 pmol/L. The timing of the presentation, the initial presentation of clitoromegaly without obvious hypogastric and labial swelling resulted in an exhaustive work up for a disorder of sexual development which did not initially include the ultrasound to look for ovarian cysts related to this syndrome.

Minipuberty is a normal finding as a result of gonadotropin inhibition discontinuing with placental separation; the HPG axis is activated and mildly elevated oestradiol with high FSH levels are noted in early months.^{5 6} Oedema is thought to be a result of excessive stimulation of LH/hCG receptors resulting in higher concentrations of LH or hCG together with stimulation of FSH receptors,⁵ but the precise pathophysiology remains greatly unknown.

Previous studies have described POHS as a self-limiting condition that resolves without treatment by 52 weeks PCA.⁷ Esen and Demirel⁸ described a patient with considerable reduction in swelling 6 weeks after presentation with complete resolution by 14 weeks. Twelve months after presentation, the infant remained well.⁸ Coexistence of functional ovarian cysts and genital swelling and the subsequent reduction in oedema as the cysts regress suggests that the cysts may contribute to the swelling. Subsequent normalisation of gonadotropins and increase in oestradiol as maturation of the gonadal steroid-dependent positive feedback and continuously increasing oestradiol suggests autonomous secretion.⁴

Starzyk *et al*⁴ published a case series of POHS with review of the literature. The median gestational age at delivery was 27 weeks with the onset of oedema at 38 weeks PCA. Treatment

of persistent swelling with medroxyprogesterone acetate did not shorten the duration of swelling. While surgical removal of these cysts have been described, further understanding of this condition has limited such practice to situations where the cysts are larger than 5 cm and at risk of rupture, torsion or haemorrhage.⁵ Clearly, such decisions should not be taken lightly, given the risk to future reproductive success and potential for surgical complications. Infants with POHS merit follow-up through puberty to monitor for the potential occurrence of polycystic ovarian syndrome, metabolic syndrome and reproductive dysfunction.⁵

Learning points

- Preterm ovarian hyperstimulation syndrome (POHS) can present with features suggestive of ambiguous genitalia, particularly in preterm newborn and must be considered as part of the differential diagnosis of ambiguous appearing genitalia as it is a self-limiting syndrome that does not require treatment unless at risk of torsion, haemorrhage or rupture.
- The onset of oedematous change may occur earlier than previously described and should prompt evaluation for POHS as part of a comprehensive workup for the patient with ambiguous genitalia.
- High oestradiol levels and ovarian cysts may confirm the diagnosis.
- Infants with POHS should be followed closely in infancy monitoring for regression of cysts and again in puberty for occurrence of polycystic ovarian syndrome, metabolic syndrome and reproductive dysfunction.

Acknowledgements The authors thank Children's Hospital Research Institute Manitoba for assistance in publication expenses.

Contributors MN identified and managed the case in the NICU. BW was consulted for management of the case as a paediatric endocrinologist. MD was involved in the latter part of patient's stay in the NICU as a resident. MN, BW and MD were involved in producing the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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