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Induction of lactation in a patient with complete androgen insensitivity syndrome

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Summary

With rising rates of adoption and surrogacy, induced lactation is likely to become increasingly relevant, allowing women who did not undergo pregnancy to breastfeed. We describe the case of a woman with complete androgen insensitivity syndrome (CAIS) on conventional oestrogen therapy who was expecting a child via surrogacy and who wished to breastfeed. The woman was commenced on supplementary oestrogen therapy, domperidone and breast stimulation by mechanical breast pump 8 weeks prior to the delivery of her child. Following delivery, the patient produced a small, unquantified amount of milk, allowing her to suckle the infant for a short period of time. Induced lactation is possible in chromosomally XY individuals. It has been most successful in cis-women and transwomen, both of whom have had progesterone/progestogen exposure to the breast. We suggest that the addition of a progestogen to our patient's treatment regimen, either as part of her original hormone therapy or part of the lactation induction program, would have improved her changes of establishing successful lactation.

Learning points

- Induced lactation is possible in chromosomally XY individuals with the use of pharmacological and non-pharmacological therapies.
- There are no standardised guidelines regarding the optimal regimen for induced lactation.
- Progesterone exposure to the breast is essential for ductal branching and alveolar maturation.
- In the published literature, induced lactation is more successful in transwomen and other XY individuals who have had prior progesterone exposure.
- The addition of progestogen to our patient's treatment regimen would have improved her chances of establishing successful lactation.

Background

Induced lactation is the process whereby a woman who has not recently been pregnant produces breast milk with the aid of pharmacological and/or non-pharmacological treatment. With rising rates of adoption and surrogacy, induced lactation is increasingly relevant, allowing women who did not undergo pregnancy to breastfeed. Breastfeeding has benefits to both the mother and infant. In addition to being a source of nutrition for the infant, it confers immunological, metabolic and psychosocial benefits including facilitating mother–child bonding.

Variable success rates for induced lactation are reported in the literature with various non-pharmacological and pharmacological protocols described. There are no clearly established guidelines for the optimal regimen for different circumstances. What is successful for 46XX women may not be

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successful for women with XY karyotype, either transwomen or those with disorders of sexual development. Three published case reports document induction of lactation in XY patients – two in transwomen and one in a woman with complete androgen insensitivity syndrome (CAIS) (1, 2, 3).

CAIS is an X-linked disorder characterised by complete resistance of the androgen receptor to testosterone, resulting in a female phenotype in individuals with XY chromosomes (4). We describe induced lactation in a woman with CAIS who was expecting a child via surrogacy.

Case presentation

Our patient presented at 18 years with primary amenorrhoea. She was 176.5 cm tall and weighed 65.7 kg. Breasts were Tanner stage 3 to 4, pubic hair stage 2 and axillary hair stage 1. She had normal external female genitalia. Biochemistry was as follows: luteinising hormone 23 U/L (1–10), follicle-stimulating hormone 13 U/L (1–10), oestradiol 140 pmol/L (75–700), progesterone <1.0 nmol/L, testosterone 24 nmol/L (<3.5) and sex hormone-binding globulin 45 nmol/L (30–90). Her karyotype was XY and genetic analysis found a stop codon mutation in the androgen receptor, leading to the loss of 44 amino acids. Pelvic ultrasound confirmed the lack of a uterus with a short blind end vagina. She had laparoscopic gonadectomy, with post-operative histology revealing two normal testes. Post-operatively she was treated, as by guidelines for the management of CAIS, with oestrogen therapy alone (5). For a short time, she had testosterone therapy, without perceived benefit for libido, and this was discontinued. At no stage did she have progestogen therapy.

At 32 years of age, oestradiol therapy was by subcutaneous oestradiol implants. She had married, and she and her husband had arranged a surrogacy pregnancy with donated ovum.

Investigation

Treatment

At 30 weeks gestation of the surrogate, she expressed a desire to breastfeed the baby. Eight weeks prior to delivery of the baby, the patient commenced domperidone 10 mg three times daily, and her oestrogen therapy was supplemented with an additional two actuations of oestradiol gel (Estrogel, Besins) daily. She used a breast pump for 5–10 min per breast two to four hourly whenever possible. On delivery of her child, transdermal oestradiol therapy was ceased and domperidone continued.

Outcome and follow-up

The patient produced a small, unquantified amount of milk allowing the infant to suckle for less than 4 weeks. However, this was not sufficient for effective long-term breastfeeding.

Discussion

The breast undergoes a lifetime of development in four main stages – embryogenesis, mammogenesis, lactogenesis and involution. Following menarche, mammogenesis is driven primarily by endocrine influences. Much of our understanding of hormonal influence on breast development and lactation comes from animal knock-out studies or breast cancer models (6). Oestrogen is essential for proliferation of breast tissue, particularly elongation of ducts into the mammary fat, whilst progesterone stimulates ductal, lobular and alveolar maturation and branching. These events occur during the normal follicular and luteal phase, respectively, of the menstrual cycle. Progesterone, in particular, completes ductal branching and alveolar proliferation, which is crucial for future successful lactation (7). Lactogenesis occurs during the second trimester of pregnancy, driven primarily by endocrine influences including oestradiol, progesterone, prolactin, placental lactogen and human chorionic gonadotrophin (8). Whilst these hormones are essential in supporting the pregnancy, they also prepare the breast for lactation. Experimentally, progesterone receptor knock-out models ($PR^{-/-}$) lack secondary duct branches and, in addition, absent alveolar development in response to pregnancy. High levels of progesterone and oestradiol inhibit milk production during pregnancy. Therefore, the delivery of the placenta at birth leading to a rapid fall in oestrogen and, particularly, progesterone allows initiation of lactation. Additionally, successful lactation requires ongoing nipple stimulation without which lactation cannot be sustained.

As such, artificial induction of lactation requires mimicking the aforementioned hormonal changes associated with breast development and pregnancy via pharmacological methods (9). High levels of prolactin via the use of a galactagogue and concurrent nipple stimulation are required. Carzola-Ortiz *et al.* reviewed 24 articles describing lactation induction in couples expecting via surrogacy or adoption (10). Various protocols were utilised, all describing the use of mechanical stimulation with variable utilisation of pharmacological treatment (hormonal therapy and galactagogues). The success of inducing lactation was variable and influenced mostly

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by the individual's previous pregnancy or breastfeeding experience and the frequency of breast stimulation. Metoclopramide and domperidone are readily available galactagogues, although it is not known which is superior. Herbal galactagogues have been demonstrated to be ineffective (9). Finally, the cornerstone of induction of lactation relies upon nipple stimulation, commonly achieved via mechanical breast pumps (9). Specialist lactation health professionals can provide crucial ongoing support, advice and counselling regarding breast pumping and breastfeeding techniques (10). At present, optimal dose and duration of pharmacotherapy and nipple stimulation frequency are not known. However, earlier commencement is likely to aid in success.

To our knowledge, only three case reports in the literature describe lactation induction in individuals chromosomally XY – one in a woman with CAIS and two in transwomen. LeCain *et al.* reported partially successful lactation induction in a woman with CAIS expecting a child through surrogacy (3). Lactation was induced with a combination of topical oestrogen, oral domperidone, fenugreek, milk thistle and mechanical breast stimulation 4 weeks prior to the delivery of the child. The woman subsequently went on to produce an 'unquantified but small amount' of milk, allowing her to partially breastfeed her infant for 1 month.

Conversely, in XY transwomen Reisman and Goldstein described successful lactation induction in a transgender woman on conventional cross-sex oestrogen-based hormone therapy who wished to breastfeed her adopted infant (1). She had a progressively escalating regimen of high dose oestradiol, progesterone, domperidone and nipple stimulation three months prior to delivery. On delivery, she stopped all treatment apart from a low dose oestradiol patch. She subsequently produced breast milk allowing her to exclusively breastfeed for 6 weeks. More recently, Wamboldt et al described induced lactation in a transgender woman who had been maintained on oestrogen and progesterone as part of her cross-hormone therapy (2). Four months prior to initiation of pharmacological therapy, she began mechanical stimulation of her breasts, and had already noted production of droplets of breast milk. To induce lactation, domperidone was initiated and her progesterone therapy doubled. Four weeks post initiation of this regimen, the woman described subsequently produced a maximum of 150 mL of breast milk a day for approximately 8 weeks.

Transwomen and CAIS women are exposed to a different hormonal milieu as part of their sex hormone therapy. Transwomen are usually exposed to both oestrogen and progestogen therapy, the latter to suppress endogenous testosterone production, at least until orchidectomy (11). However, in this population, breast development is usually suboptimal as a result of early androgen exposure, with most transwomen developing only Tanner stage 2–3 breasts (12). Nevertheless, in the two case reports of lactation induction in transwomen, successful lactation was achieved.

On the other hand, treatment guidelines for CAIS women recommend oestrogen therapy alone, with possible addition of testosterone but not progestogen. Our patient and the patient reported by LeCain achieved less success with adequate lactation than that reported in the transwomen. Although there is currently little evidence confirming the benefit of progesterone in promoting breast development and lactation in the XY population, with knowledge of the physiology of breast development, in conjunction with our patient's outcome and that described by LeCain utilising only oestrogen therapy, compared to the outcomes described by Reisman and Goldsman and Wamboldt et al where progestogen therapy was part of transhormone therapy, it does raise the probability that progestogens should play a crucial role in successful lactation induction in XY women. Our patient received only 8 weeks of preparatory therapy after she, herself, expressed an interest in breastfeeding. We acknowledge that this is likely suboptimal. Ideally, clinicians could discuss the possibility of breastfeeding with their XY patients at the beginning of the surrogate pregnancy or at the beginning of the surrogacy arrangements in order to allow a longer lead time to lactation for appropriate hormonal therapy.

Since surrogacy is becoming more available in reproductive units worldwide, it is important that regimens for induction of lactation be adapted for XY women particularly women with CAIS or other disorders of sexual development. Since progesterone is crucial for ductal branching, lobular formation, and alveolar maturation, we postulate that the use of progestogens in lactation induction in this group of women is essential. We therefore recommend the addition of progestogen to hormone therapy, commencing ideally at the time when a surrogate birth is being planned in order to successfully prepare the breast for future lactation.

Declaration of interest
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Author contribution statement
BGAS was involved in the management of the patient. KV drafted and edited the manuscript. BGAS contributed to the editing of the manuscript. Both authors have read and approved the final version of the manuscript.

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