

Hyperprolactinaemia and galactorrhoea with combined oral contraceptive pill use

A refresher

Kay Rui Choy, Audris Wong

CASE

A woman aged 24 years with no past pregnancies presented with a nine-month history of bilateral nipple discharge during the week after her period, which was associated with occasional severe headaches without visual disturbance. She was otherwise well with no medical history and only on 500 µg norethisterone–35 µg ethinyloestradiol combined oral contraceptive pill (COCP), which she had started six months prior to the onset of symptoms. A pregnancy test was negative, and there were no signs of bilateral breast tissue infection. No abnormalities were detected during the breast examination. Her repeated blood tests showed hyperprolactinaemia (1210 mIU/L and 855 mIU/L) with a normal macroprolactin level. No prolactinomas were detected with magnetic resonance imaging (MRI) of the brain. A trial of lifestyle modifications, such as reducing nipple stimulation for six months, was found to be ineffective. The patient's serum thyroid function test showed subclinical hypothyroidism with a raised thyroid stimulating hormone (TSH) level of 13.5 mIU/L and normal T4 levels. Further investigations identified raised levels of thyroid peroxidase antibodies, but normal levels of TSH receptor antibodies.

A trial of thyroxine was found to be ineffective, but after switching to a 150 µg

levonorgestrel–30 µg ethinyloestradiol COCP on shared decision-making, the patient's galactorrhoea resolved. However, mild hyperprolactinaemia (604 mIU/L) persisted.

QUESTION 1

What is galactorrhoea and what causes it?

QUESTION 2

What is COCP-induced galactorrhoea?

QUESTION 3

What is the association between hypothyroidism and galactorrhoea?

QUESTION 4

What is the most likely cause of the galactorrhoea in this clinical scenario? What should be considered in the differential diagnosis?

QUESTION 5

What investigations should be performed?

QUESTION 6

What are the treatment options?

ANSWER 1

Galactorrhoea is a milk-like discharge from the nipples when the patient is neither pregnant nor breastfeeding. It happens when abnormally high levels of serum prolactin stimulate the lactotroph cells in the mammillary glands of the breast, resulting in galactorrhoea.¹ Prolactin secretion is regulated by stimulatory

or inhibitory hormones produced in the hypothalamus. Stimulatory hormones include thyrotropin-releasing hormone (TRH) and epidermal growth factor, while inhibitory hormones include dopamine and gamma-aminobutyric acid.²

Physiological causes include pregnancy, stress and nipple stimulation. Pathological causes of hyperprolactinaemia are due to anti-dopaminergic medications, such as antipsychotics. In the absence of these medications, pituitary tumours account for approximately 50% of hyperprolactinaemia cases.² Additionally, subclinical hypothyroidism has been found to be associated with hyperprolactinaemia.³

ANSWER 2

The incidence of COCP-associated galactorrhoea is unclear due to lack of recent data on newer agents. Literature from the 1980s suggest that 10–19% of women on a COCP experience galactorrhoea,^{1,4} with up to 30% experiencing hyperprolactinaemia.⁵ Some studies have found that COCPs use can increase serum prolactin levels,^{1,4} whereas other studies do not show any effect on prolactin levels.⁶ Galactorrhoea is usually seen in COCPs containing high oestrogen doses (35 µg),⁶ and is most apparent in the week of the placebo pills.⁴ In recent newer contraceptives with lower oestrogen doses, this is rarely observed.⁶ The proposed mechanism is the stimulatory effect of oestrogen and progesterone on prolactin secretion and the oestrogen-induced

proliferation of lactotroph in the anterior pituitary gland.⁷

The prevalence of pituitary tumours can be as high as one in 865, and up to 66.2% of these are prolactinomas, which are 10 times more common in females.⁸ The stimulatory effect on pituitary lactotrophs could trigger the formation of prolactinomas.⁹ However, Coulam et al found no significant association between COCP use and prolactinomas.¹⁰

ANSWER 3

In primary hypothyroidism, such as Hashimoto's thyroiditis, there is an increase in serum TRH levels, which stimulates hyperprolactinaemia, as well as TSH secretion.³ Reduced metabolic clearance in patients is also believed to contribute to high serum prolactin levels.¹¹ Therefore, it is always good practice to correct abnormalities in thyroid biochemistry in women with galactorrhoea to see if symptoms resolve. Referral to an endocrinologist might be also warranted.

ANSWER 4

The most likely diagnosis in this scenario is a COCP-induced galactorrhoea, after excluding other possible differential diagnoses including pregnancy, intracranial lesions (ie pituitary prolactinoma), breast pathology, idiopathic galactorrhoea and drug-induced hyperprolactinaemia.

The presence of normal levels of thyroid hormones and TSH receptor antibodies with raised TSH and thyroid peroxidase antibodies indicate subclinical Hashimoto's thyroiditis. It is reasonable to have this corrected to see if the hyperprolactinaemia resolves. Given that there was no improvement after using thyroxine, it is unlikely that subclinical hypothyroidism is the main cause of the galactorrhoea. The patient tested negative on a pregnancy test and is not on any other medications (including complementary and alternative medicines), except for the norethisterone-ethinylestradiol COCP. Intracranial pathology was also ruled out with the MRI scan of the brain. Given that the galactorrhoea only started after the commencement of COCPs,

idiopathic galactorrhoea is less likely than COCP-induced galactorrhoea. Although the association between nipple stimulation and hyperprolactinaemia is established, the recommended duration for reduced stimulation to be effective is unclear.⁶

ANSWER 5

Serum prolactin levels should be measured after fasting, but can be measured at any time of the day.⁶ A single raised prolactin level should always be repeated. A difficult venepuncture can cause a false-positive result; however, persistently raised prolactin levels warrant investigation. To confirm galactorrhoea, the nipple discharge should be collected and tested for fat globules.

ANSWER 6

COCP cessation should eventually result in long-term galactorrhoea improvement if it is related to the COCP. However, despite this, it has been reported that COCP discontinuation could stimulate hyperprolactinaemia and induce galactorrhoea.¹ Symptom resolution might be temporary given the raised serum prolactin level and the continued stimulation of prolactin secretion from the patient's levonorgestrel-ethinylestradiol COCP.¹² Contraceptives without oestrogen, such as progesterone-only pills, should be considered. It is important that the patient is part of their management and to educate the patient on other possible adverse effects of hyperprolactinaemia, such as infertility, sexual dysfunction and osteoporosis.

Key points

- High oestrogen COCPs can result in hyperprolactinaemia and galactorrhoea. Switching to a lower-dose COCP or a progesterone-only pill is a reasonable option to consider.
- It is important to perform two confirmatory testings of prolactin level, including a request for macroprolactin.
- Thyroid dysfunction-induced hyperprolactinaemia should resolve with thyroxine use.

Authors

Kay Rui Choy MD, Resident Medical Officer, Gold Coast University Hospital, Southport, Qld; Lecturer, Griffith University School of Medicine, Southport, Qld
Audris Wong FRANZCOG, MRCOG, MRCPI, Obstetrics and Gynaecology Staff Specialist, Gold Coast University Hospital, Southport, Qld
Competing interests: None.
Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Correspondence to:

KayRui.Choy@health.qld.gov.au

References

1. Holtz G. Galactorrhea in oral contraceptive users. *J Reprod Med* 1982;27(4):210-12.
2. Majumdar A, Mangal NS. Hyperprolactinemia. *J Hum Reprod Sci* 2013;6(3):168-75. doi: 10.4103/0974-1208.121400.
3. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000;160(4):526-34. doi: 10.1001/archinte.160.4.526.
4. Sakiyama R, Quan M. Galactorrhea and hyperprolactinemia. *Obstet Gynecol Surv* 1983;38(12):689-700. doi: 10.1097/00006254-198312000-00001.
5. Reyniak JV, Wenof M, Aubert JM, Stangel JJ. Incidence of hyperprolactinemia during oral contraceptive therapy. *Obstet Gynecol* 1980;55(1):8-11.
6. Samperi I, Lithgow K, Karavitaki N. Hyperprolactinaemia. *J Clin Med* 2019;8(12):2203. doi: 10.3390/jcm8122203.
7. Badawy SZ, Rebscher F, Kohn L, Wolfe H, Oates RP, Moses A. The relation between oral contraceptive use and subsequent development of hyperprolactinemia. *Fertil Steril* 1981;36(4):464-67.
8. Vroonen L, Daly AF, Beckers A. Epidemiology and management challenges in prolactinomas. *Neuroendocrinology* 2019;109:20-27. doi: 10.1159/000497746.
9. Sherman BM, Harris CE, Schlechte J, et al. Pathogenesis of prolactin-secreting pituitary adenomas. *Lancet* 1978;2(8098):1019-21. doi: 10.1016/s0140-6736(78)92339-5.
10. Coulam CB, Annegers JF, Abboud CF, Laws ER Jr, Kurland LT. Pituitary adenoma and oral contraceptives: A case-control study. *Fertil Steril* 1979;31(1):25-28. doi: 10.1016/s0015-0282(16)43754-4.
11. Tolis G. Prolactin: Physiology and pathology. *Hosp Pract* 1980;15(2):85-95. doi: 10.1080/21548331.1980.11946556.
12. Mishell DR Jr, Kletzky OA, Brenner PF, Roy S, Nicoloff J. The effect of contraceptive steroids on hypothalamic-pituitary function. *Am J Obstet Gynecol* 1977;128(1):60-74. doi: 10.1016/0002-9378(77)90295-2.

correspondence ajgp@racgp.org.au