

# Diabetes insipidus in a patient with PCOS treated with Depo-Provera

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## Summary

Depot medroxyprogesterone acetate, also known as Depo-Provera, is a progesterone-only contraceptive that is administered by injection to patients every three months. We describe the case of a 19-year-old female who was diagnosed with central diabetes insipidus following the administration of the contraceptive injection Depo-Provera. The patient was diagnosed with polycystic ovarian syndrome at age 16 and was originally prescribed oral contraceptives to restore menstrual regularity. Three years later, Depo-Provera was substituted for convenience, and symptoms of polyuria and polydipsia appeared one month after initiating the progesterone-only regimen. We are proposing that central diabetes insipidus may be a possible adverse effect of Depo-Provera in women with polycystic ovarian syndrome who receive the progesterone-only contraception, due to the interference of their arginine vasopressin mechanism through the alteration of estrogen levels. We review potential mechanisms through the presentation of previously completed research in polycystic ovarian syndrome.

## Learning points

- We propose that although rare, the decrease in estrogen that is experienced during the administration of Depo-Provera can interfere with arginine vasopressin release in patients with polycystic ovarian syndrome (PCOS).
- Increased awareness of possible lasting adverse effects on fluid balance with unopposed progesterone administration in PCOS is important, as this case of the development of diabetes insipidus suggests.
- Discussion of such potential side effects is important when considering contraceptive options for the regulation of menses in patients with PCOS.

## Background

Depot medroxyprogesterone acetate, also known as Depo-Provera (DMPA), is a progesterone-only contraceptive that is administered by injection to patients every 3 months. In 1960, DMPA was approved by the FDA for use as a contraceptive. Studies have shown that progesterone antagonizes the stimulatory effect of estradiol (E<sub>2</sub>) on estrogen receptors. This has led to warnings about the possible risk of bone demineralization and increased risk of fractures with long-term use. In terms of fluid balance, studies in postmenopausal women have shown that estrogen administration generates an arginine vasopressin

(AVP) response leading to fluid retention. Interference with this estrogen action on AVP may then promote polyuria.

## Case presentation

A 19-year-old female reported experiencing symptoms of dry mouth, polydipsia, polyuria, and nocturia that disrupted her work schedule which began one month after receiving her first DMPA injection in July 2019. She was administered the injection by her gynecologist in July 2019 for contraception and symptoms of oligomenorrhea. Although the urinalysis



performed by her primary care physician was unremarkable, she was treated empirically with three different courses of antibiotics without relief of symptoms. Again, she was later referred to her gynecologist who performed an ultrasound of the bladder and pelvis. An ultrasound of the thyroid was also performed. There were no abnormalities reported from any of these screening measures. With no suspicion of cranial diabetes insipidus from damage to the hypothalamus or pituitary gland, an MRI was not completed. The patient was gravida 0 and achieved menarche at age 10. The patient reported that her menses were always irregular which prompted her to start on oral contraceptives at age 16 to regulate her cycles. The patient was on birth control pills for three years, when at the age of 19, she had amenorrhea upon her discontinuation of oral contraceptives. Following this series of events, the diagnosis of polycystic ovarian syndrome (PCOS) was made. Following the diagnosis in June 2019, her first Depo progesterone injection was administered. Her physical examination was unremarkable. The patient was normotensive with a BMI of 26.6. Laboratory tests revealed the following values: glucose 87 mg/dL, HbA1c 4.8%, serum sodium 139 mmol/L, serum potassium 3.8 mmol/L, eGFR 90 mL/min, and calcium 9.0 mg/dL.

## Investigation

Following her symptoms of dry mouth, polydipsia, polyuria, and nocturia, a 24-h urine volume water deprivation test was completed by the patient. The results were a serum osmolality of 303 mOsm/kg and urine osmolality of 54 mOsm/kg. With a urine osmolality being <400 mOsm/kg and with a raised serum osmolality, it indicated an inability the patient had to concentrate her urine in the absence of renal tubular disease. This confirmed that the patient was experiencing a diagnosis of central diabetes insipidus.

## Treatment

Following a water deprivation test that was suggestive of central diabetes insipidus, the patient's symptoms were reversed with a desmopressin (DDAVP) injection of 4 µg/mL, resulting in a urine osmolality of 564 mOsm/kg. The patient was then prescribed the intranasal form of vasopressin, DDAVP 0.1 mg/mL (5 mL). She was instructed to continue administration at home every 12–24 h.

## Outcome and follow-up

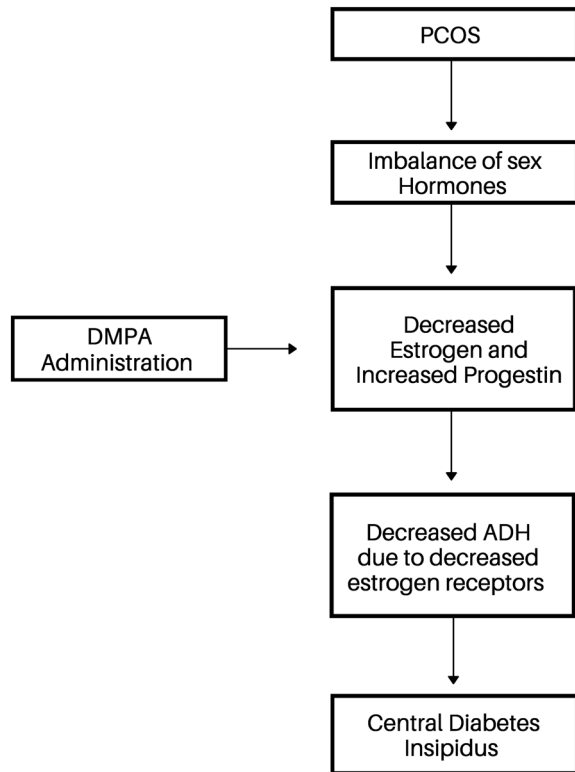
Following her diagnosis of central diabetes insipidus and initial DMPA injection in 2019, the patient has not received another DMPA injection. She was started on the

treatment of DDAVP 0.1 mg/mL (5 mL), which resolved all her symptoms. Her symptoms have since continued to remain resolved since starting her treatment and she continues the same DDAVP daily administration without reported complaints.

## Discussion

Osmoreceptors and baroreceptors have various influences, one being the release of arginine vasopressin (AVP), an important hormone in human water homeostasis. AVP is controlled by various factors relating to plasma osmotic pressure, and volume status. Receptors for estrogen and progesterone are found in nonreproductive tissue involved in fluid regulation, such as the hypothalamus. Circulating AVP is influenced by ovarian steroid blood levels and various studies have shown changes in AVP concentration during the normal menstrual cycle in women since baseline plasma-osmolality and sodium are decreased in high estrogen states, due to a resetting of the osmoreceptors for thirst and AVP release. PCOS is characterized by hyperandrogenism, menstrual disturbance, anovulation, infertility, and obesity, with most experts considering hyperandrogenism to be the main characteristic. Several theories aim to explain the manifestations of PCOS such as (i) a primary enzymatic default in ovarian and/or adrenal steroidogenesis; (ii) an impairment in gonadotropin-releasing hormone (GnRH) secretion that promotes luteal hormone (LH) secretion; or (iii) alterations in insulin actions that lead to insulin resistance with compensatory hyperinsulinemia (1). Clinical signs of PCOS often include elevated LH and GnRH levels, while FSH levels are less influenced. We believe that since individuals with PCOS experience an imbalance in estrogen and progesterone, the effects on body fluid regulation may be aggravated by DMPA administration, as depicted in Fig. 1.

To identify the effect of different concentrations of estrogen on diurnal urine regulation, volunteers in one study were administered estrogen twice during the follicular phase (low progesterone). The study showed a difference in plasma osmolality between the mid-follicular (low estrogen) and the preovulatory phase (high estrogen). Plasma sodium and packed cell volume changed in parallel with plasma osmolality, suggesting a small increase in plasma volume due to high endogenous estrogen. Exogenous estrogen unopposed to progesterone increased the basal concentration of vasopressin, whereas progesterone in combination with estrogen lowered basal AVP concentration. Progesterone was therefore shown to antagonize the stimulatory effect of E<sub>2</sub> on vasopressin secretion (2).



**Figure 1**

The endocrine etiologies of polycystic ovarian syndrome (PCOS) often lead to an imbalance of sex hormones, such as estrogen. The decrease in estrogen levels can affect antidiuretic hormone (ADH) levels, ultimately resulting in the effects and symptoms of dehydration. With the additional administration of Depo-Provera (DMPA), ovulation is successfully suppressed, resulting in high progestin and low estrogen levels. With lower levels of estrogen, lower levels of ADH can follow, resulting in a possible diagnosis of central diabetes insipidus.

To investigate the effects of estrogen on the body water regulation system, a study conducted by Stachenfeld in 2008 administered oral contraceptives to young women and then evaluated their responses to progressive, exercise-induced dehydration and a subsequent rehydration period (3). Combined oral contraceptive agents delivered pharmacological levels of estrogens that exhibited 6–10 times the estrogenic activity provided by endogenous, circulating estrogens. In contrast, progestin-only pills, comparative to the DMPA injection, and the unopposed progestin tended to downregulate estrogen receptors (3). This investigation suggested that the shift in osmoregulation was due to the estrogen component of oral contraceptive pills. Stachenfeld also demonstrated that administered oral contraceptive pills containing  $E_2$  were found to lower the osmotic threshold for AVP and thirst stimulation during hypertonic saline infusion and dehydration, leading to a lower osmotic operating point for body fluid regulation (3). These results were similar

to those found during the luteal phase, when estrogen is lowest, suggesting that  $E_2$  has a primary effect on body fluid regulation during oral contraceptive administration.

DMPA being medroxyprogesterone acetate causes ovulation to be inhibited, thus eliminating a rise in estrogen. Since estrogen influences the response of these target tissues to AVP, its decreased levels during DMPA administration could promote concerns in some patients suffering from PCOS (4).  $E_2$  is produced by the dominant ovarian follicle during the monthly menstrual cycle and is the most potent natural estrogen in comparison to Estrone ( $E_1$ ), which is the dominant form of estrogen during menopause (5). Since the pioneering work of Sar and Stumpf, using autoradiographic analysis of  $E_2$  binding sites in the rodent brain, it is known that AVP neurons in the supraoptic and paraventricular nuclei are direct targets of  $E_2$  (6).  $E_2$  signals through either estrogen receptor alpha ( $ER\alpha$ ) or beta ( $ER\beta$ ) to activate several estrogen-responsive genes (7). In humans,  $ER\beta$  inhibits, whereas  $ER\alpha$  stimulates ADH neuronal activity (4).

The decrease in the osmotic threshold for AVP secretion observed during the luteal phase of the menstrual cycle is consistent with  $ER\alpha$ -mediated increases in the sensitivity of the osmoreceptors. Since ovulation is prevented through the administration of DMPA,  $E_2$  levels are decreased (7). In addition, estrogen secretion in PCOS women is characterized by chronic secretion without the cyclic pattern that accompanies an ovulatory cycle. Serum  $E_2$  levels may vary in PCOS but are usually in the mid-follicular phase range of 60–90 pg/mL. In contrast, serum levels of  $E_1$  are usually greater than those of  $E_2$  which is the reverse of the  $E_1:E_2$  ratio seen in women with normal cycles. This abnormality is due to enhanced peripheral aromatization of androgens to estrogens in extra-glandular tissues in the presence of androgen excess (8).

In comparison to estrogen, fewer studies have examined the regulatory role of androgen on hypothalamic-pituitary-adrenal (HPA) function. The altered hormone levels experienced with PCOS can lead to an increase in GnRH, stimulating the ovarian thecal cells, and later producing excess androgens. A previous study showed that testosterone implanted into the medial preoptic area of male rats post gonadectomy decreases median eminence vasopressin concentrations compared to controls. This data suggest that androgens inhibit HPA function through androgen-receptor-mediated central mechanisms (9). In 1979, Skowsky, Swan, and Smith reported that an increase in plasma vasopressin (pVP) 2 weeks after male rats were castrated was reversed by testosterone administration (4). The opposite however occurred in females, as estrogen



treatment of ovariectomized rats increased pVP leading to the conclusion that androgens inhibit and estrogen stimulates vasopressin release (4).

Lastly, insulin resistance, occurring in 70–95% of obese people with PCOS and 30–75% of lean people with PCOS, can also indirectly decrease the levels of AVP (10). Chronically elevated insulin sends signals to the ovaries to increase androgen production, leading to an increase in abdominal fat. Abdominal adiposity promotes inflammation and worsens insulin resistance, thereby perpetuating a vicious cycle, and impairing ovulation. How insulin dysregulation originates in this syndrome is not fully understood but is likely related to impaired insulin signaling and/or receptor function leading to increased insulin secretion and decreased hepatic insulin clearance.

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#### Declaration of interest

The authors declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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#### Funding

This case study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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#### Patient consent

Written informed consent for publication of their clinical details was obtained from the patient to participate in this case study.

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#### Author contribution statement

AM: Conceived the project, took the primary role in data acquisition, analysis, interpretation writing the manuscript, and publication of the

project. NM: revised the project, involved in interpretation and manuscript preparation. Both authors revised the final draft of the manuscript.

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Received in final form 14 October 2022

Accepted 11 November 2022