Review of: "Metoclopramide Test in Hyperprolactinemic Women With Polycystic Ovarian Syndrome: Old Wine Into New Bottles?"

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Dear Editor,

The retrospective study by Rodier et al. reviewed the utility of metoclopramide testing in patients with PCOS and hyperprolactinemia secondary to pituitary adenomas. Among 430 women, 179 patients diagnosed with polycystic ovarian syndrome (PCOS) were selected and separated into two groups: 21 patients with hyperprolactinemia and PCOS, and 158 patients with normoprolactinemia and PCOS. Demographics, clinical phenotypes, as well as hormones including testosterone, estradiol, and others were compared between the two groups. Among the PCOS and hyperprolactinemia group, five women had microprolactinomas with PRL levels >60 ng/mL. Metoclopramide testing was done in the hyperprolactinemia/PCOS group, which revealed less than 300% basal prolactin increase in patients with prolactinomas, whereas patients with other causes of hyperprolactinemia had greater than 300% basal prolactin increase in response to metoclopramide. Rodier et al. highlighted the potential benefit of using metoclopramide to differentiate causes of hyperprolactinemia, especially in comparison of microprolactinomas and other causes (1).

The exact mechanism of action of metoclopramide in relation to prolactin release is unclear. Metoclopramide's activity is localized to the pituitary gland and the hypothalamus as a D2 receptor antagonist (2). When metoclopramide binds to the D2 receptor, it promotes more prolactin release (2). In fact, animal studies show that metoclopramide stimulates the metabolic activity of pituitary lactotrophs as evidenced by increased nuclear volume (10). Metoclopramide causes prolactin level increase in all patients regardless of PCOS status (8-10). However, patients with normal prolactin levels are more sensitive to dopamine receptor blockade with metoclopramide compared to patients with hyperprolactinemia from a pituitary tumor (8). This distinction may help distinguish different etiologies of hyperprolactinemia (8).

There are no established protocols, so metoclopramide dosing, so its administration is based on the discretion of a researcher. For instance, in the Rodier et al study, patients were given IV metoclopramide 10 mg and prolactin levels were checked at 30 minutes and 60 minutes post injection. Vázquez-Matute et al. evaluated effects of oral metoclopramide, and prolactin levels were checked at 60 and 120 minutes (2). The onset of action for oral metoclopramide takes 30 to 60 minutes, while IV is 1 to 3 minutes. Therapeutic duration of action is 1 to 2 hours regardless of route. There are reports suggesting that metoclopramide reaches peak effect in approximately 120 minutes (2). Brandes et al. evaluated metoclopramide effects on prolactin levels in ten pregnant women in their second trimester compared to normal controls

and those with PCOS. In this study, IV metoclopramide at a dose of 10 mg was administered to all groups, and had a peak of 6.5-fold increase in prolactin within 15 minutes, with prolactin levels remaining elevated for up to 4 hours (14). Interestingly, the pituitary gland maintains its inhibitory control of prolactin (14).Although pregnant patients were not included in the Rodier et al. study, it highlights the robust regulatory mechanism for prolactin which does not change under the exogenous stimulus of a dopamine antagonist like metoclopramide (14).

PCOS and prolactinomas may have overlapping symptoms, such as oligomenorrhea or amenorrhea, weight gain, and insulin resistance, which makes the clinical presentation difficult to differentiate. Prolactin is not only released by the pituitary gland, but also secreted by other tissues, including the uterus, mammary glands, and adipose tissue (11). Additionally, besides dopamine, prolactin release may be stimulated by estradiol (1). Davoudi et al. reported increased estradiol levels in patients with hyperprolactinemia and reported higher levels of insulin resistance in hyperprolactinemia/PCOS patients compared with normoprolactinemia/PCOS patients (13). Although Rodier et al. did not report a significant difference in estradiol levels found between the PCOS patients with normal versus elevated prolactin levels, it would be interesting to evaluate the relationship of insulin resistance and hyperprolactinemia in patients with PCOS.

The pathogenesis of hyperprolactinemia in PCOS is likely hypothalamic with GnRH pulsatility leading to elevated LH levels (6). Barnes et al. studied the effects of low dose dopamine infusion (0.5 /xg/kg-min) in five PCOS patients and five non-PCOS patients, and found that the dopamine infusion led to reduced LH in subjects with PCOS (7). A relative dopamine deficiency may cause hypersecretion of prolactin and LH in patients with PCOS and hyperprolactinemia (7). LH response to metoclopramide stimulation, while may have been unchanged, was not addressed in Rodier et al (1).

Older guidelines suggest higher prolactin cut off ranges to be more than or equal to 250 ng/mL for a diagnosis of prolactinomas. However, Wright et al. highlighted that low levels between 55-94 ng/mL may also suggest prolactin secreting pituitary tumors (5). Given lower cut-offs, an established test to differentiate hyperprolactinemia due to pituitary tumors from other causes would be extremely valuable. Rodier et al. used a prolactin level less than or equal to 60 ng/mL as a cut off for metoclopramide testing. Perhaps adjusting the prolactin level cutoff to a lower value based on previous data may capture more microprolactinomas. It would also be interesting to study the role of metoclopramide testing in differentiating true prolactinomas from stalk effect and other causes of hyperprolactinemia. It is important to recognize that prolactin to tumor volume ratios are helpful in differentiating non-functioning pituitary adenomas from prolactinomas, thus lower prolactin cutoffs may be useful in the setting of stalk effect (5).

We applaud the authors for rekindling interest in metoclopramide testing to distinguish hyperprolactinemia secondary to two common entities, PCOS and prolactinomas. A detailed look into the effects of metoclopramide on prolactin driven insulin resistance and estrogen levels would have potentially added further understanding into the etiology of hyperprolactinemia in these diseases. We also suggest future studies with lower prolactin cut-offs to include true prolactinomas and perhaps extend use to evaluate other etiologies. Prolactin response to metoclopramide can be

variable, based on peak effect times, as well as relationships to weight, estrogen levels, and insulin resistance may play a factor in testing. Although metoclopramide testing may be a useful tool in the diagnosis of hyperprolactinemia in patients, more research is needed to assess its true utility.

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