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Mild hyperprolactinemia in a couple: What impact on fertility?

Dominique Maiter

Service d'Endocrinologie et Nutrition, UCLouvain Cliniques Universitaires Saint-Luc, avenue Hippocrate 10, 1200 Bruxelles, Belgium

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ABSTRACT

Mild-to-moderate hyperprolactinemia is a frequent finding in young women presenting with infertility. Prolactin (PRL) concentration should be determined accurately, whether or not the patient has other symptoms suggestive of excess PRL such as galactorrhea or menstrual cycle disorder. After confirmation of persistent hyperprolactinemia on a second blood sample (avoiding conditions known to raise prolactin) and exclusion of macroprolactinemia, prolactinoma and other identifiable non-tumoral causes of hyperprolactinemia must be ruled out. Mildly elevated PRL levels may cause luteal insufficiency in cycling women and are associated with recurrent miscarriage. Any confirmed hyperprolactinemia should be treated in a woman who wishes or fails to become pregnant. Preference is given to cabergoline at the lowest possible dose that normalizes PRL, restoring fertility in the vast majority of cases.

Evidence is much less robust in men, in whom PRL concentrations are less prone to increase and the reproductive system is less sensitive to the negative effects of hyperprolactinemia. Nevertheless, chronic and significant hyperprolactinemia in men may impair fertility or cause infertility (with or without hypogonadism) and must be treated, as in women. However, more clinical studies are clearly needed concerning male reproductive function.

The significance of mild but persistent hyperprolactinemia in either member of a couple incidentally discovered during assisted reproductive technology (ART) procedures is unclear, and future evidence-based studies are needed to determine whether normalizing prolactin can improve ART outcome.

1. Introduction

Infertility is defined as the inability for a couple to conceive after 12 months' regular intercourse without contraception, or the inability to carry a child to term. This is a frequent problem in Western countries: 10% to 15% of couples have difficulty conceiving (primary infertility) or obtaining the desired number of children (secondary infertility). About 35% of causes of infertility concern the woman, 30% the man, 20% both and 15% are unknown. In 2017, 940,503 cycles of assisted reproductive technology were undertaken in Europe, resulting in 198,215 births, accounting for about 5% of all births that year [1].

2. Effects of prolactin on the reproductive axis in men and women

High prolactin (PRL) concentrations negatively affect the gonadotropic axis in both men and women, at multiple levels and independently of the cause [2]. The main effect is to suppress pulsatile gonadotropin releasing hormone (GnRH) secretion through inhibition of hypothalamic kisspeptin neurons and possibly other GnRH afferent neurons [3–5]. PRL also directly suppresses pituitary LH and FSH secretion and the positive feedback of estradiol on mid-cycle gonadotropin release. These effects commonly disrupt ovulatory cycles in young women, from short luteal phase with persistent cycles in moderate hyperprolactinemia [6] to overt hypogonadism and the well-known symptoms of oligomenorrhea or amenorrhea when PRL remains elevated [2,7].

PRL also modulates the reproductive axis peripherally, although much less in humans than in rodents [8]. PRL receptors are present in human ovarian granulosa cells and in-vitro experiments showed that, while low-concentration PRL is required for normal progesterone production by human ovarian tissue, an excessive amount directly suppresses baseline and gonadotropin-stimulated progesterone and estrogen synthesis [9–13]. Regularly cycling women with mild or transient hyperprolactinemia show low plasma progesterone concentration and deficient luteal phase, impairing endometrium development and causing failure of embryo implantation [6,14]. These peripheral effects of excess PRL are important, as they may impact the outcome of in-vitro fertilization (IVF) (see below).

E-mail address: dominique.maiter@uclouvain.be

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Prolactin is also directly synthesized in the human decidualized endometrium at end of cycle and in the myometrium, where it directly stimulates smooth-cell proliferation by an autocrine/paracrine mechanism, although its precise role here remains to be deciphered [13,15]. Interestingly, serum PRL levels were also found to be significantly higher in infertile patients with endometriosis stage III/IV than in those without endometriosis, and a PRL threshold of 20.1 μg/l significantly discriminates between patients with and without severe endometriosis [16]. Thus, a mild hyperprolactinemia can also be a biomarker of endometriosis-related infertility, and studies are underway to assess dopamine agonist (DA) treatment in infertile women with endometriotic lesions (see [13] for review).

Hyperprolactinemic men also show infertility and signs of hypogonadism such as loss of libido and erectile dysfunction, although suppression of the male gonadotropic axis occurs only at a much higher PRL level and not systematically: 25–40% of men with prolactinoma still have normal or only marginally decreased testosterone levels and conserved spermatogenesis [17–19]. However, when they are treated with DAs and PRL is restored to normal, their testosterone levels increase further, and hypogonadism symptoms and semen quality improve [20]. In vitro, direct negative effects of high PRL concentrations on Leydig cells were reported in rodents [21], but not so far in humans, although PRL receptors (PRL-R) are present in the human testis.

3. Infertility in women with mild hyperprolactinemia

Due to the known adverse effects of prolactin on the female gonadotropic axis, infertility is a frequent problem, occurring in 50-80% of cases of young women with a moderate-to-severe hyperprolactinemia, depending on series and etiology [2]. The exact prevalence of fertility disorder is, however, not known in mild hyperprolactinemia (i.e., PRL consistently elevated but below 2-fold the upper limit of normal), or in "occult" hyperprolactinemia (i.e., transient hyperprolactinemia occurring for only a few days during the cycle or only a few hours during the day), although it has been suggested that a DA may restore normal fertility [14,22].

On the other hand, several studies reported variable but significant prevalence (7-20%) of hyperprolactinemia in women seeking medical advice for primary or secondary infertility. In a study of 8,500 infertile couples by the World Health Organization (WHO), hyperprolactinemia accounted for about 7% of female causes [23]. About the same rate (5.6%) was found by Souter and colleagues in a group of 1,328 infertile women with persistent menses and no galactorrhea [24]; PRL concentrations were only mildly elevated (32 ± 13 μg/L), and the overall prevalence of hyperprolactinemia did not differ according to the cause of infertility or the presence or absence of menstrual irregularity. This prevalence is 10-fold higher than the prevalence of all-cause hyperprolactinemia in the general population matched for age and gender [25], and 100-fold higher than the prevalence of prolactinoma [26], suggesting that PRL should be measured in all women with infertility, whether or not they have other symptoms suggestive of PRL elevation or pituitary adenoma. On the other hand, when other symptoms such as oligomenorrhea or amenorrhea and/or galactorrhea are present, prevalence is much higher. Thus, in a compilation of 367 symptomatic women with infertility, up to one-third showed hyperprolactinemia [2,27].

In these populations, all etiologies of hyperprolactinemia may be found, and prolactinoma is by no means the most frequent. In 590 unselected women undergoing ART in our center in 2010, 70 (12%) had a mild-to-moderate PRL elevation (range 21–89 μg/L) on first hormonal evaluation, while only half had confirmed hyperprolactinemia on a second control and only a minority ($n = 6$) had a diagnosis of prolactinoma (D. Maiter, personal data). Physiological causes such as stress, exercise, a recent protein-rich meal, ovulation or naturally occurring hormonal pulse are likely responsible for frequent mild PRL elevation not confirmed on subsequent fasting assay. Measuring PRL from an indwelling cannula after prolonged rest avoids overdiagnosis by removing stress as a confounding factor, and should be considered when repeated fasting PRL values remain mildly elevated (25–55 μg/L) [28]. Finally, macroprolactinemia (related to multimeric complexes of several PRL molecules) should always be ruled out, as it may represent 15–30% of all hyperprolactinemic serum, depending on the type of assay used [29],

When true mild-to-moderate hyperprolactinemia is confirmed on several occasions, pituitary MRI is usually advised to rule out PRL-secreting pituitary tumor or other hypothalamic-pituitary abnormality. This issue is still a matter of debate, as the probability of finding a significant pituitary abnormality is rather low in this population (20%) and must be balanced against the incidence of pituitary incidentaloma (10%). Prevalence seems largely independent of absolute PRL level (within this range of mild-to-moderate increase) [24] and no clear minimal PRL cut-off has so far been established as for performing pituitary imaging or not. A baseline evaluation of the other pituitary hormonal axes may prove useful, as central hypothyroidism, for example, increases the likelihood of finding a hypothalamic-pituitary disease such as sellar or perisellar tumor, empty sella or pituitary stalk disorder.

In addition to microprolactinoma, the main pathological causes of mild-to-moderate hyperprolactinemia in young women comprise:

- drug-induced hyperprolactinemia, involving most neuroleptics and anti-emetic agents, tricyclic antidepressants and, to a lesser extent, selective serotonin reuptake inhibitors, antihistaminic (H2) agents, opiates, monoamine oxidase inhibitors and some anti-hypertensive drugs such as verapamil, alpha-methyl-dopa and reserpine. In most cases, PRL levels remain below 100 μg/L, but metoclopramide, risperidone and derivates and phenothiazines can lead to PRL levels exceeding 200 μg/l [7];
- primary hypothyroidism, which must always be ruled out before any pregnancy;
- polycystic ovary syndrome, although a direct link with hyperprolactinemia is still controversial [30];
- idiopathic hyperprolactinemia.

Any confirmed true hyperprolactinemia should be treated in young women who wish to become pregnant, as it may cause infertility even with normal cycles. In some cases, the cause of excess PRL can be withdrawn or treated (drug-induced hyperprolactinemia, primary hypothyroidism). If this is not possible, low-dose DA must be initiated, and restores normal ovulatory pattern and fertility in most cases, in particular in non-tumoral hyperprolactinemia [26,31]. In a Belgian study of 244 women with idiopathic hyperprolactinemia or microprolactinoma treated with low-dose cabergoline, PRL was normalized in more than 90% of cases, and similar efficacy was reported by many other groups [7]. In a recent non-randomized Georgian study of 96 women with idiopathic hyperprolactinemia, aged 20–44 years, with infertility and/or history of recurrent pregnancy loss, treatment with bromocriptine normalized PRL after 2–5 months, restored ovulatory cycles within 3–7 months and allowed pregnancy in all cases within 3–17 months, with a very low rate of miscarriage (3.1%) [32].

To our knowledge, there are no data for an optimal PRL target range to improve fertility, but most women can become pregnant as soon as PRL is normalized. Following the recent guidelines of the European Society of Endocrinology, preference should now be

given to cabergoline over other DAs, as it has shown better efficacy and tolerability and a good safety profile in pregnant women [33,34].

4. Hyperprolactinemia and recurrent miscarriage

Hyperprolactinemia, or at least some PRL elevation, was found in about one-third of women with history of unexplained recurrent miscarriage: i.e., three or more consecutive spontaneous abortions at a stage where the embryo or fetus was incapable of surviving, generally within the first 20 weeks of gestation [22,35,36]. A causative role of high PRL was therefore suggested, via defective luteal phase support at implantation [37]. A systematic Cochrane analysis reviewed the effectiveness of DAs in preventing repeated miscarriage in women with idiopathic hyperprolactinemia [35]. There was only 1 randomized controlled trial, including a small number of women ($n = 46$) and with high risk of bias. This Japanese study showed that bromocriptine, at a dose of 2.5 to 5.0 mg/day until the 9th week of gestation, was effective in preventing miscarriage, with a risk ratio of 0.28 (CI 0.09–0.87), while birth and conception rates were not affected [22]. The Cochrane review concluded that there is currently insufficient evidence to evaluate the effectiveness of DAs in this setting, and that further high-quality research is needed [35]. Nevertheless, the French Clinical Practice Guidelines published in 2016 recommended including PRL assay in the work-up for women with recurrent miscarriage, with DA treatment in case of isolated hyperprolactinemia (grade B level of evidence) [38].

5. Hyperprolactinemia and in-vitro fertilization (IVF)

Whether women with mild hyperprolactinemia undergoing ART should be treated with a DA is currently unresolved. In IVF, oocyte maturation is induced by serial gonadotropin stimulation, and sufficient luteal phase support is usually guaranteed by progesterone administration. In a recent retrospective study of 340 untreated women undergoing IVF in our institution, mild-to-moderate hyperprolactinemia was found in 54 (16%) and confirmed in 16 (4.7%). Although there were no differences according to age, FSH level or the etiology of the couple's infertility, the pregnancy rate after the first IVF cycle tended to be lower in hyperprolactinemic women (8/54 vs. 67/286, $P = 0.108$) and the birth rate after the first cycle was significantly lower (4/54 vs. 50/286, $P = 0.042$). The final cumulative pregnancy rate was, however, not different between the two subgroups (D. Maiter and P. Laurent, unpublished data).

Discordant results were reported in other studies. In a recent large series of more than 3,000 patients with basal PRL level < 50 ng/mL undergoing IVF with intracytoplasmic sperm injection (ICSI) cycles for tubal or male factors, there were slightly more oocytes (9 vs. 8, $P = 0.013$) and embryos (6 vs. 5, $P = 0.015$) in patients with basal PRL > 16 μg/L, and prognosis for successful pregnancy improved with increasing basal PRL level [39]. However, macroprolactin was not excluded in this study, and the difference in median PRL levels between women giving live birth (16.25 μg/L) and those who did not (15.85 μg/L) was too slight to be of clinical significance. In another study of 135 women with transient or borderline hyperprolactinemia measured in the late follicular or mid-luteal phase of the cycle and undergoing IVF/ICSI, cumulative pregnancy rate did not differ according to cabergoline treatment [40]. Clearly, further studies are needed to clarify this issue, but for now there are no firm data to indicate that asymptomatic women with a mild/transient hyperprolactinemia found incidentally ahead of IVF/ICSI should be treated with a DA [39].

6. Infertility in men with mild hyperprolactinemia

With the notable exception of prolactinoma (and particularly macroprolactinoma), hyperprolactinemia in men is a largely overlooked research area. Basically, most of the causes and effects of hyperprolactinemia observed in women can be observed in men. However, whatever the cause, hyperprolactinemia is much less frequent in males, as confirmed in a Scottish epidemiology study [25]. This can be partly explained by the fact that symptoms of male hypogonadism, such as loss of libido, erectile dysfunction, altered sperm features and infertility, gynecomastia or osteopenia, are often unrecognized for a long period of time, or attributed to other causes such as age, drugs or depression [18]. Galactorrhea is also less frequent in men, as it requires both a fall in testosterone level and excess estrogens, which is not the rule in case of male hyperprolactinemia. Moreover, for still unknown reasons, the male gonadotropic axis appears to be less sensitive to the effects of excess PRL, and even very high PRL concentrations in men with macroprolactinoma can still be compatible with normal testosterone concentration and fertility [17,18]. For example, in a study by Colao et al., semen quality was significantly impaired in fewer than 50% of men with a prolactinoma [19].

Overall, endocrine disorder (including hyperprolactinemia) is a rare etiology of infertility in men, accounting for only 2–4% of cases, whereas primary testicular defects in spermatogenesis are largely predominant (75%). Thus, it is not surprising (although still questionable) that some European guidelines do not include serum PRL assay in the work-up for male infertility [41]. Another difficulty lies in the fact that the degree of infertility is often relative, and men with endocrine disorders have subnormal semen parameters but are still capable of reproduction [42].

In a series of 65 men with prolactinoma (including 50 with a macroprolactinoma, half with concomitant hypopituitarism, and all with PRL >50 μg/L), 46 (71%) had testosterone deficiency and only 16 (25%) were referred for infertility (20]. Several cases of impaired semen quality were found in a subset of these patients: total sperm count $\leq 40 \times 10^6$/volume of ejaculate in 28 (43%), sperm forward progression < 25% in 46 (71%) and live spermatozoa count < 75% in 54 (83%). Importantly, the prevalence of impaired semen quality was similar in patients with macro- or micro-prolactinoma. In 43 of these patients not requiring testosterone or gonadotropin replacement, 24 months' treatment with cabergoline normalized PRL in all but 2 patients, restored normal testosterone levels in all, and significantly improved seminal fluid characteristics, which became similar to controls, except for live spermatozoa count and some fine characteristics of sperm kinetics [20].

Other non-tumoral causes of chronic hyperprolactinemia in men (more or less similar to those in women) may also be responsible for hypogonadism and infertility, but there are no robust data regarding the prevalence and severity of related gonadotropic axis defect or the effect of PRL normalization. It seems, however, wise to administer DA to any infertile male patient with significant persistent hyperprolactinemia, whether or not he is symptomatic or has a low testosterone level.

It remains unknown whether mild idiopathic hyperprolactinemia should be treated or not when found in the man at the first evaluation of an infertile couple. We reviewed data for 45 male patients with mild idiopathic hyperprolactinemia (16–51 μg/L) attending our infertility clinic for IVF and compared them with 45 age-matched controls with normal PRL concentrations seen during the same period. There was no difference in testosterone concentration, testicular volume, total sperm count, motility, vitality or proportion of abnormal forms (D. Maiter and C. Wyns, unpublished data). There was no significant difference in pregnancy rate after IVF (64 vs. 73%). These preliminary results do not argue for treating

hyperprolactinemia in such circumstances, but clearly need to be confirmed in larger future studies.

7. Conclusions

Mild-to-moderate hyperprolactinemia is a frequent finding in young women with infertility, and prolactin assay is warranted in these patients, whether or not they have other symptoms suggestive of excess PRL, such as galactorrhea or menstrual cycle disorder. After confirmation and exclusion of macroprolactinemia, prolactinoma and other non-tumoral causes of hyperprolactinemia must be ruled out. Any truly confirmed hyperprolactinemia should be treated in young women who wish to become pregnant, and preference should be given to cabergoline at the lowest dose that normalizes PRL. Normal fertility will then be restored in the vast majority of these women. There are also preliminary data indicating that mild or transient hyperprolactinemia may be a causal factor in women with history of recurrent miscarriage, and that DA treatment may be beneficial.

Data are much less robust in men, in whom PRL concentrations are less prone to increase and the reproductive axis is often less sensitive to the effects of hyperprolactinemia. Nevertheless, chronic significant hyperprolactinemia in men may impair fertility (with or without hypogonadism) and must be treated as in women. However, more clinical studies are clearly needed in this male reproductive area.

Incidental finding of mild basal hyperprolactinemia in a couple undergoing ART must first be confirmed by a second PRL determination, avoiding known factors (such as stress) that may transiently raise prolactin concentration. If hyperprolactinemia is confirmed, it is presently unknown whether it has any influence on the outcome of IVF and should be treated or not.

Disclosure of interest

The author declares that he has no competing interest and received no funding.

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