Review

Prolactinoma and estrogens: pregnancy, contraception and hormonal replacement therapy

Adénomes à prolactine et estrogènes : grossesse, contraception, traitement hormonal estroprogestatif

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Résumé

Le rôle stimulant des estrogènes sur la sécrétion de prolactine et sur la prolifération des cellules lactotropes est établi en physiologie, mais cet effet peut-il être élargi à un effet délétère des estrogènes sur les adénomes à prolactine ? L’objectif de cette revue est de faire le point actuel sur ce sujet chez la femme lors de la grossesse, la prise de contraception estroprogestative, et les traitements substitutifs hormonaux de ménopause. Les agonistes dopaminergiques permettent aux femmes qui souffrent d’un prolactinome de retrouver des cycles ovulatoires et d’être enceintes. Il n’existe aucune information péjorative concernant la tolérance des agonistes dopaminergiques au début de la grossesse, mais les informations manquent en ce qui concerne les traitements les plus récents comme la cabergoline et le quinagolide. Pour une femme présentant un microadénome la grossesse n’a en règle générale pas d’impact sur l’adénome, l’accouchement doit être normal et l’allaitement est autorisé. En ce qui concerne les macroprolactinomes, une évolution tumorale pendant la grossesse reste possible et la surveillance en milieu endocrinologique reste nécessaire. La contraception estroprogestative est le type de contraception actuellement le mieux toléré et la plus efficace. Elle a longtemps été contre-indiquée chez les patientes présentant un prolactinome. La reprise de la littérature reste très pauvre à ce sujet et n’apporte pas d’éléments péjoratifs tandis que l’expérience professionnelle incite à revoir cette attitude et à permettre aux femmes présentant un microprolactinome d’utiliser les pilules actuelles (avec une dose d’éthinylestradiol inférieure ou égale à 30 μg). Le problème le plus important à résoudre avec cette prescription qui masque les conséquences cliniques de l’hyperprolactinémie sera la négligence envers la pathologie hypophysaire que cela risque d’induire. Le problème du macroprolactinome est différent, la possibilité de prescription d’une pilule sera ici évaluée individuellement et son impact sur l’adénome sera très surveillé. La substitution estrogénique chez une patiente avec un hypogonadisme doit être tentée chez une patiente aux antécédents de prolactinome avec les précautions de suivi habituelles. Chez une femme ménopausée, si le traitement substitutif est souhaitable, un antécédent de microprolactinome ne doit pas le contre-indiquer.

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Abstract

The stimulatory role of estrogen on prolactin secretion and on proliferation of lactotropic cells is well established in terms of physiology but could this phenomenon be extended to include harmful effects of estrogens on prolactinoma? The aim of this review is to provide an up-to-date assessment of this subject with regard to pregnancy, use of contraceptive pills and postmenopausal hormone replacement therapy. Dopamine agonists allow women presenting prolactinoma to recover their ovulation cycles and become pregnant. There is no adverse data concerning the safety of dopamine agonists such as bromocriptine, if the woman is treated during the first trimester of pregnancy but there is little information regarding the most recent treatments such as cabergoline or quinagolide. In women with microadenomas, pregnancy generally has little impact on

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The relationship between estrogens and prolactin has been known for a long time, in physiology. The stimulatory role of estradiol on prolactin cell’s secretion by lactotropic cells and their subsequent growth is supported by numerous experimental and clinical data. Those experiments are the theoretical basis that has resulted for a long-standing fear from clinicians about hyperestrogenic contexts such as pregnancy as well as the use of contraceptive pills containing estrogens, and by analogy, all forms of replacement therapy containing estrogens in patients presenting prolactinoma. The aim of this review is to provide an up-to-date assessment of this question. This paper is part of the recent consensus of the French Endocrine Society (SFE) on prolactinomas.

1. Experimental data concerning the relationship between estrogens and prolactin

In the Fisher rat model (Fisher 344) an increased prolactin secretion may be induced together with the development of prolactinomas, by means of estrogen therapy [20]. These very particular animals constitute a model for the study of prolactinomas.

The relationship between PRL secretion and estradiol is demonstrated by the ability to trigger a PRL secretion peak by means of prior administration of estrogen in the rat [28]. In molecular terms, PRL gene expression studies have demonstrated that estrogen administration, in cultured lactotropic cells, both in vivo and in vitro, results in an increased synthesis of PRL messenger-RNA followed by protein secretion [22]. This effect occurs at the transcriptional level [22] and is probably mediated by the estradiol receptor (ER), which is strongly expressed by normal and adenomatous lactotropic cells [37]. It involves estradiol response elements (ERE), as suggested by studies in murine GH3 lactotropic cell lines [11,12]. In addition to their stimulatory action on PRL secretion, estrogens thus increase mitotic activity, DNA synthesis and proliferation of lactotropic cells [21,36]. This effect is also probably mediated by ER alpha, as indicated by studies demonstrating inhibition by anti-estrogens of growth of a somatolactotropic cell line (GH3). Similarly, inactivation of wild-type ER by a dominant negative ER induces cell death and prevents the formation and development of tumors from the lactotropic GH4 cell line in nude mice [19].

One point that has not been fully elucidated concerns the mechanisms by which estrogens exert proliferative activity upon lactotropic cells. Some studies have investigated certain well-known natural targets such as neutralization by estrogens of antiproliferative dopamine signaling [1,27] as well as newer actors such as pituitary tumor transforming gene (PTTG) or fibroblast growth factor (FGF) [15], or even more recently, vasoactive intestinal polypeptide (VIP), mainly in Fisher 344 rats. In this study, the authors have demonstrated that the administration of VIP antagonists might partially neutralize the proliferative activity of estrogens, thereby suggesting an autocrine or paracrine role of this neuropeptide, which is also secreted by the pituitary [14].

Given the complexity of this process, which probably involves a number of signaling pathways, other researchers have taken a more global approach regarding estrogen-induced modification of gene expression involving a transcriptome study method [12]. Finally, a research team this year has adopted a novel comparative genomic approach in order to identify sensitivity predisposing to protumoral activity of estrogens, in Fisher 344 rats [38]. All of this research should help provide a better understanding of the mechanisms involved and allow identification of the agents involved in the proliferative effects of estrogens on lactotropic cell lines.

While estrogens may not be highly favorable to prolactinomas due to their proliferative effects, what is the relevance for clinical pathology? Can these results be readily extrapolated to a clinical human context?

2. Clinical data concerning the role of estrogens

There are differences between men and women in plasma prolactin levels and in women according to menstrual timing. Circulating prolactin levels are higher in post-pubertal women than in men.

During the menstrual cycle, blood prolactin levels increase but remain within normal limits, rising to a maximum of...
around 20 ng/ml during ovulation, i.e. when estradiol levels reach their peak.

During pregnancy, where hyperestrogenism is present, prolactin levels are multiplied 10-fold and the size of the pituitary increases (normal size up to 12 mm) as a result of lactotrophic cell hyperplasia [13,33].

The data regarding adenomas are more complex; PRL adenomas are seen more frequently in women, but are significantly smaller [9] than in men.

Drug-induced hyperestrogenia is occasionally performed in transsexual men and may be used as a clinical research model. In male receiving high doses of estrogens, blood prolactin levels increase and only rare cases of hypophysyal adenoma have been reported [17]. Furthermore, in patients previously receiving diethylstilbestrol treatment for prostate cancer, lactotrophic cell hyperplasia and hyperprolactinaemia have been observed [25].

While there is a clear relationship between estrogens, increased prolactin secretion and hyperplasia of normal lactotropic cells, a relationship between estrogens and the onset of prolactinomas or an increase in their volume is less obvious.

### 3. Pregnancy and prolactinomas

Since estrogens stimulate proliferation of prolactin cells, pregnancy, a situation involving physiological hyperestrogenism, involves a potential risk of growth of prolactinomas. The question of pregnancy-induced risk is extremely widespread in clinical settings since prolactinoma is often diagnosed as a result of failed resumption of menstruation following discontinuation of the contraceptive pill in a bid to become pregnant.

In patients wishing to become pregnant, dopamine agonists are the most common form of treatment. They are extremely effective and restore fertility in over 90% of cases. Transsphenoidal adenomectomy may also be considered before pregnancy, particularly in the event of resistance or intolerance to dopamine agonists, although this clinical setting has become extremely rare following the introduction of newer dopamine agonists.

#### 3.1. Since dopamine agonists are frequently used in order to restore ovulation, in women seeking a pregnancy, what are the actual data concerning fetal safety of these drugs?

**Which dopamine agonist should now be preferred in order to induce ovulation?**

There is now a choice between several older dopamine agonists, from the well-tried and tested bromocriptine (Parlodiel® 2.5 and 10 mg) to the more recent and better-tolerated cabergoline. Bromocriptine has a very long history of use and a number of publications authorize its use, even though no medical authorization (MA) has been granted as such. In most reported cases, treatment was administered for the first 4 weeks of pregnancy [4]. The overall results are reported in Table 1, after Molitch [23]. The overall results are reported in Table 1, after Molitch [23].

#### Table 1

<table>
<thead>
<tr>
<th>Effects</th>
<th>Bromocriptine</th>
<th>Normal population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>6239</td>
<td>100.0</td>
</tr>
<tr>
<td>Miscarriage</td>
<td>620</td>
<td>9.9</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>31</td>
<td>0.5</td>
</tr>
<tr>
<td>Births</td>
<td>4139</td>
<td>100.0</td>
</tr>
<tr>
<td>At term (&gt;38 WA)</td>
<td>3620</td>
<td>87.5</td>
</tr>
<tr>
<td>Pre-term (&lt;38 WA)</td>
<td>519</td>
<td>12.5</td>
</tr>
<tr>
<td>Pregnanacies</td>
<td>5120</td>
<td>100.0</td>
</tr>
<tr>
<td>Monofetal</td>
<td>5031</td>
<td>9.3</td>
</tr>
<tr>
<td>Multiple</td>
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<td>1.7</td>
</tr>
<tr>
<td>Newborn</td>
<td>5213</td>
<td>100.0</td>
</tr>
<tr>
<td>Normal</td>
<td>5030</td>
<td>96.5</td>
</tr>
<tr>
<td>With malformations</td>
<td>93</td>
<td>1.8</td>
</tr>
</tbody>
</table>

no more complications than those seen in the general untreated population. The levels of fetal malformations are identical.

Regarding cabergoline, which currently is often favored as first-line treatment due to its remarkable safety profile, as it induces less orthostatic hypotension, less nausea as well as a once-weekly administration, a total of 300 cases have been described in reassuring publications. So far, no reports of teratogenicity have been reported. While this study population is low and certainly does not fully reflect current use of the drug, it provides reassurance for patients becoming pregnant while on this treatment [5,31,32,41]. Furthermore, it also allows patients to continue such treatment if it is advantageous in terms of safety and efficacy.

In order to determine whether cabergoline may widely be prescribed in cases of infertility, more cases and greater experience are required. A study is set to begin soon in France collecting all cases and events occurring both during pregnancy and in the ensuing years, following pregnancies initiated while the mother was on cabergoline.

The data for quinagolide are also reassuring [3,26] but are as yet insufficient to allow meaningful analysis (167 cases). Once again, reassurance should be given to women becoming pregnant while taking this drug. However, its use is not recommended during the pre-conception period unless it provides improved efficacy and safety. Pharmacovigilance reporting should be recommended.

#### 3.2. Pregnancy and tumor risk

##### 3.2.1. Microprolactinomas

The analysis of the literature recently carried out by Molitch [24] comprises data from 363 pregnancies. The conclusions are extremely reassuring since only 1.4% of these women experienced symptomatic increases in prolactinoma’s size during pregnancy. No instances of worsening requiring surgery were reported. Within this highly reassuring context, patients should not be “over-treated” or “over-medicated”. It is thus currently recommended that dopamine agonist treatment should be dis-
continued as soon as the diagnosis of pregnancy is performed. Patients and their treating doctors should be informed of warning signs potentially suggestive of the development of a prolactinoma (particularly headaches). One should remember some rare clinical histories of extensive clinical development of microprolactinomas during pregnancy. Therefore, women should be advised and gynecologists should carefully follow-up such patients. Prolactin assays during pregnancy serves no useful purpose since the normal physiological increase makes any interpretation of changing levels complex. In normal pregnant women, the serum prolactin level reaches 200–300 ng/ml. Similarly, systematic imaging or MRI scans are not useful. However, patients should be seen as soon as they present an increased or unusual headache or visual disturbances. In such cases, an MRI without gadolinium injection should be requested.

Under these circumstances, there are no special problems regarding delivery, and breast-feeding is authorized, particularly since discontinuation of dopamine agonists during pregnancy will make lactation possible. This approach in women with microprolactinomas is recommended in other countries, particularly in Great Britain [8] and the United States [34].

Following delivery, the situation should be reassessed, at least 2 months after delivery or after stopping lactation. Hyperprolactinemia can in fact resolve, with different rates being reported in the literature, reaching 11 to 35% of cases (35% for Bricaire et al. [2], 29% for Crosignani et al. [7], 11% in a personal long-term series). A 50% reduction in prolactin serum level was noted in 50% of patients with hyperprolactinemia in a small study involving 58 patients [30]. Spontaneous resumption of menstruation can also occur as well as the return of normal menstrual cycles (subsequent relapse of hyperprolactinemia is a possibility). In other cases, treatment with dopamine agonists is resumed to restore ovulation. Control MRIs scans are recommended 2 months after the end of lactation in order to assess any morphological changes in the adenoma.

### 3.2.2. Macroprolactinomas

Here the clinical situation is different since development of macroprolactinomas during pregnancy is not rare [24]. The analysis reported by Molitch, based on 84 cases reported in the literature, showed that macroprolactinoma developed during pregnancy in 26.2% of women when they had not been treated with surgery or radiotherapy. On the other hand, macroprolactinomas increased in size only in 3% of women when they had been pretreated with dopamine agonists (based on 67 cases). In 4 out of 19 cases, symptoms required surgery during pregnancy, while the remainder of patients responding to resumption of bromocriptine.

We must therefore carefully consider all the circumstances in which growth of the adenoma could endanger the optic chiasm. This type of tumor must be brought under control even before the women starts a pregnancy. Drug treatments may be considered as such agents are effective with regards, not only to hormonal prolactin levels but also to tumor size. A pregnancy should be authorized only when the threat to the chiasm is avoided. Therefore, repeated MRI scans may be required. Surgery may be necessary in very few cases before authorizing the pregnancy. But, one should remember that it is often incomplete and does not necessarily prevent pregnancy-induced development of residual adenoma. Before patients attempt to become pregnant, it is thus necessary to ensure that the tumor has regressed and no longer presents a threat to the chiasm. It is only at this condition that pregnancy may be authorized.

This prior monitoring requires discussing contraception with the patient upon diagnosis of PRL macroadenoma as well as when medical treatment is started. Mechanical and nonhormonal means of contraception should be preferred when possible, until pregnancis allowed.

Monitoring during pregnancy should be extremely strict and relies mainly on outpatients’ visit: screening for headaches, visual field examination every 2 months, occasional MRI without injection, preferably after the first trimester of pregnancy. Prolactin assays may be useful in the event of an increase in adenoma’s size in order to assess development of the latter since any increase in lesion’s size could also be due to apoplexy rather than tumor progression. With macroadenomas there is in theory less risk of confusion between values obtained for patients during pregnancy and normal physiological increased values.

There is no consensus on the use of dopamine agonists during pregnancy. If the adenoma is away from the chiasm or comprises a “small macroadenoma,” an approach may be recommended similar to that described for microadenomas, namely discontinuation of dopamine agonists upon diagnosis of pregnancy, clinical monitoring ± morphological examinations. If the adenoma is still fairly large or if the macroadeno- noma previously threatened the chiasm, the dopamine agonist, in this case bromocriptine, may readily be monitored throughout the entire pregnancy. No teratogenic effects have been reported to date with use of this substance during pregnancy, but the number of women on treatment reported in the literature is lower than 150 [4,18,26,29,32]. Some precaution is required during the first trimester of pregnancy, as the patient might vomit. In such cases, dopamine agonists may be poorly absorbed. It is advisable to inform patients to take their treatment again if vomiting occurs within 2 hours of bromocriptine intake.

There is no evaluation of the targets needed when patients take dopamine agonist: is it low prolactin levels or levels within the high physiological limits associated with pregnancy. The treatment’s goal is mainly to maintain the tumor away from the chiasm.

### 3.2.3. Breast-feeding and macroprolactinoma

Breast-feeding differs from pregnancy since there is no hyperestrogenism but rather hypoestrogenism due to hypogonadal hypogonadism due to reflex hyperprolactinoma.

Until now, breast-feeding has not been recommended and it was in fact often ruled out by continued use of bromocriptine. In the event of “small macroprolactinomas” when untreated
during pregnancy, breast-feeding can be discussed, on the basis of several cases in our own personal experience.

Evaluation of adenomas should be resumed post-partum by means of MRI as well as measurements of serum prolactin levels, given that remission is unusual. These tests are recommended 2 months after delivery.

In this section on prolactinomas and pregnancy, the analysis is based on older retrospective studies including few patients in relation to the number of patients actually concerned and levels of precision are consequently not high. However, the available data is sufficient to reassure patients, as most of them present a microadenoma. Great care is required for macroadeninomas, particularly the largest tumors, for which there is little available data in the literature (the macroadenoma group is highly heterogeneous). Pregnancy for these patients should only be allowed after assessment of the size of the adenoma. Close monitoring is essential; patients should be fully informed and their endocrinologists and obstetricians must work together in close collaboration during the entire pregnancy. Under these conditions, current results are excellent. Neurosurgery for macroadenomas during pregnancy has now become extremely rare.

4. Prolactinomas and contraception

What do we really know about the effects of hormonal contraceptives on prolactinomas, other than that they represent a relative contraindication under the standard recommendations? The question of prolactinomas and contraception is however extremely important since patients treated with dopamine agonists are very likely to recover previously diminished fertility extremely rapidly (patients must be informed of this recovery). It should also be noted that moderate hyperprolactinemia does not in itself prevent pregnancy.

First, we must recognize the extreme lack of studies. The few published are from the 1980s and lack of current relevance. However, post-marketing follow-up has provided no negative input on pills containing estrogen and adenomas, despite the fact that prescription of these drugs has become increasingly frequent. It should be noted that only studies concerning pills containing 35 μg or less of ethinyl estradiol are of current interest.

4.1. Can the use of modern steroid contraceptives favor the appearance of prolactinomas?

The study reported by Shy et al. [35] provided an answer more than 20 years ago. These authors showed in a retrospective small study that steroid contraceptives were used more frequently in women with hyperprolactinemia, than among a population of control women of the same age. However, if we analyze the indications for the “pill,” for contraception, identical numbers of cases were seen in the two groups, while for menstrual disorders, the indication was seen in a far higher number of hyperprolactinemic women. The obvious conclusion is that the “pill” was used in these women to treat pre-existing menstrual disorders, which were in all likelihood symptoms of pre-existing but undiagnosed hyperprolactinemia.

4.2. Do steroid contraceptives worsen pre-existing prolactinoma?

An answer to this question is provided by two studies, albeit in very small populations [6,39]. The authors used steroid pills for women presenting hyperprolactinemia associated with microadenoma, i.e. what is referred to as idiopathic hyperprolactinemia, without adding dopamine agonists. A follow-up of 2 years or more demonstrated stable or reduced prolactin levels with no changes in the size of the adenoma on medical images.

To our knowledge, there are no comparable studies in patients presenting macroadenoma but there have been isolated reports of either “poor tolerability” or, conversely, acceptable tolerability in the experience of clinicians. In the practice of the authors, dopamine agonists are not discontinued following prescription of steroid contraceptives.

4.3. What type of contraceptives should be proposed for women presenting prolactinoma, apart for an IUD?

Alternatives to estrogen–progestogen pills have long been indicated.

Microdose progestagen contraceptives. This type of “pill” exhibits good metabolic and vascular safety although these types of benefits are not the primary goal in women with prolactinomas. However, such contraception has a number of drawbacks: risk of contraceptive failure through imperfect compliance, risk of ectopic pregnancy, menstrual disorders and poor tolerability. This form of contraceptive may be proposed but the existence of prolactinoma is not in itself an indication.

High dose antigonadotropic progestogen contraceptives have long been and remain widely prescribed in practice, in France. The advantages of this form of treatment are good metabolic and vascular safety, which again are not the issues, better contraceptive safety than small dose progestogens, and an anti-PRL effect for nor-steroids. The drawbacks include absence of marketing authorization in this indication, fairly widespread induction of menstrual disorders and long-term hypoestrogenism. The effects of these contraceptives on the development of hyperprolactinemia have not been assessed. This treatment may be proposed but should be restricted to patients with poor tolerance to steroid contraceptives.

Steroid contraceptives containing estrogens are easier to use and better tolerated. In the literature, there are no strong arguments against their use. However, cautions are nevertheless required. Given that pregnancy, which results in very high plasma estradiol concentrations, is authorized in this population, prescription of steroid pills appears fairly risk-free. Use of these agents requires continued use of dopamine agonists, for several years at least.

Tolerability of estrogen–progestogens should be assessed by assay of serum prolactin levels before and 3 months after the
start of the pill. MRI should evaluate the size of the adenoma during the first year of their use in order to rule out any enhancement of tumor growth (opinion of the authors). Under the above conditions, this form of contraceptive may be proposed for women with prolactinoma, and monitoring should be tightened for large adenomas (in this area, there are only expert opinions, both for and against).

It should also be noted that in certain cases of resistance to dopamine agonists involving difficulty in restoring normal menstrual cycles, the “pill” is well tolerated [10] and provides an accurate treatment against hypoestrogenism in such patients, as well as ensuring contraception.

Care is required with long-term monitoring of these patients since estrogen–progestogen pills can mask signs of hyperprolactinemia, with women having normal periods and galactorrhea being rare. Use of such treatment without monitoring could thus result in an underlying disease being overlooked for and in order to avoid this situation, information must be given to patients and their doctors.

5. Estrogen–progestogen replacement hormonal therapy

This treatment is prescribed in different clinical circumstances. The first one is: patients with pituitary deficiency due to macroprolactinoma-induced compression. The second one is when surgery induced gonadotropic insufficiency (too aggressive); the third one is hormonal postmenopausal therapy.

Persistent gonadotropic insufficiency following correction of hyperprolactinemia affects 15% of women presenting macroadenoma (personal study). The associated risk factors are size of adenoma and aggressive treatments, particularly radiotherapy. This results in the usual complications of hypoestrogenism and should therefore be substituted by sequential estrogen–progestogen therapy or more simply with a “pill.” As well as previously described, the standard precautions must be taken: evaluation of prolactin secretion before and after the start of treatment, systematic measurement of adenoma’s size by MRI over the first year and continuation of dopamine agonist therapy. Under these conditions, these treatments, for which no publications exist in the literature, are very well tolerated (opinion of the authors).

At menopause, it is usual to discontinue dopamine agonists in patients presenting macroadenoma. Symptoms such as menstrual disorders are no longer a problem, ovulation is not a goal and hypoestrogenism inhibits galactorrhea.

However, HRT may be prescribed for patients with prolactinoma, for climacteric symptoms or for osteoporosis, which is far more common in hyperprolactinemic patients [16]. At the usual doses, no special caution appears necessary with this drug since it only prolongs pre-existing hormonal levels [40]. Continued use of a dopamine agonist is probably unnecessary in microprolactinoma patients. In patients with macroadenoma, continuation of hyperprolactinemia treatment depends upon tumor size. However, follow-up is essential beyond menopause as classic clinical symptoms of hyperprolactinemia disappear with ovarian activity.

In conclusion, the existing data as well as a professional experience allow us to better identify problems induced by estrogens in patients with prolactinomas. In microprolactinoma, steroid contraceptives containing estrogens may be prescribed. During pregnancy dopamine agonist therapy may be stopped and replaced by clinical monitoring alone. Breast-feeding is authorized and menopausal hormone therapy may be prescribed with concomitant discontinuation of dopamine agonists coupled with appropriate monitoring. For macroprolactinomas, particularly with large tumors reaching the optic chiasm, specialized management is necessary. Pregnancy, contraception and hormonal therapy for menopause require special cautions. There is a need for concomitant prescription of dopamine agonists and long-term follow-up of the hypophyseal tumor. However, further prospective studies including large numbers of patients are needed to evaluate these practices.

6. French version

A French version of this article is available at doi: 10.1016/j.ando.2007.03.009.

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