"Ovarian macrocysts and gonadotrope-ovarian axis disruption in premenopausal women receiving mitotane for adrenocortical carcinoma or Cushing's disease"

Salenave, Sylvie ; Bernard, Valérie ; Do Cao, Christine ; Guignat, Laurence ; Bachelot, Anne ; Leboullieux, Sophie ; Droumaguet, Céline ; Bry-Gauillard, Hélène ; Pierre, Peggy ; Crinière, Lise ; Santulli, Pietro ; Touraine, Philippe ; Chanson, Philippe ; Schlumberger, Martin ; Maiter, Dominique ; Baudin, Eric ; Young, Jacques

ABSTRACT

Context: Mitotane is an adrenolytic and anticortisolic drug used in adrenocortical carcinoma (ACC), Cushing's disease (CD), and ectopic ACTH syndrome. Its effects on the ovaries are unknown. Objective: To evaluate the ovarian and gonadotrope effects of mitotane therapy in premenopausal women. Patients: We studied 21 premenopausal women (ACC: n=13; CD: n=8; median age 33 years, range 18-45 years) receiving mitotane at a median initial dose of 3 g/day (range 1.5-6 g/day). Methods: Gynecological history was collected and ovarian ultrasound was performed. Four women also underwent ovarian CT or magnetic resonance imaging. Serum gonadotropin, estradiol (E<sub>2</sub>), androgens, sex hormone-binding globulin (SHBG), and circulating mitotane levels were determined at diagnosis and during mitotane therapy. Results: In the women included, ovarian macrocysts (bilateral in 51%) were detected after a median 11 months (range: 3-36) of mitotane exposure. The median number of macrocysts per woman was two (range: 1-4) and the median diameter of the largest cysts was 50 mm (range: 26-90). Menstrual irregularities and/or pelvic pain were present in 15 out of 21 women at macrocyst diagnosis. In two women, the macrocysts were revealed by complications (ovarian torsion and hemorrhagic macrocyst rupture) that required surgery. Mitotane therapy was associated with a significant decrease in androstenedione and testosterone levels and a significant increase in LH levels. Serum FSH and E<sub>2</sub> levels were also increased, and SHBG levels rose markedly.

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Ovarian macrocysts and gonadotrope–ovarian axis disruption in premenopausal women receiving mitotane for adrenocortical carcinoma or Cushing’s disease

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*(S Salenave and V Bernard contributed equally to this work and should be considered as first authors)

Abstract

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Conclusions: Mitotane therapy causes significant morphological and ovarian/gonadotrope hormonal abnormalities in premenopausal women. Follicular thecal steroid synthesis appears to be specifically altered and the subsequent increase in gonadotropins might explain the development of macrocysts. The mechanisms underlying these adverse effects, whose exact prevalence in this population still needs to be determined, are discussed.

Introduction

Mitotane (o,p’DDD) is an adrenolytic drug widely used to treat adrenocortical malignancies (1, 2). It is also used as anticortisolic agent in adrenocorticotropic hormone (ACTH)-dependent Cushing’s syndrome associated with pituitary corticotrophic adenomas (3, 4, 5, 6) or with ectopic ACTH secretion (5). Although this treatment has been used for decades, the mechanisms of its action on adrenal steroidogenic cells are only beginning to be elucidated (7). One unresolved question is whether the inhibitory effect of this drug on steroidogenesis is specific to the adrenal cortex or also concerns other steroidogenic glands such as the gonads. Some recent studies suggest that the testicles may be affected (8), but the ovarian effects of mitotane have not yet been studied, despite the fact that Cushing’s disease (CD) and adrenocortical carcinomas (ACCs) are more common in women and can occur before the menopause. In this study, we describe for the first time the ovarian hormonal and gonadotropic impact of mitotane in 21 premenopausal patients. We also report and discuss the unexpected occurrence of ovarian macrocysts in the women studied.

Patients and methods

Patients

We retrospectively studied 21 women who received mitotane monotherapy between 2008 and 2013. Eight of them were treated for ACTH-dependent Cushing’s syndrome due to CD, while the remaining 13 women had ACC and received mitotane post-operatively for its antitumoral action as adjuvant therapy (Table 1). Six of these latter 13 women had hypercortisolism (elevated urinary free cortisol (UFC) and suppressed serum ACTH) at diagnosis, but were in remission after ACC surgery and before mitotane therapy. The diagnosis of CD was based on clinical phenotype, associated with elevated UFC excretion, a loss of the circadian plasma cortisol pattern, a lack of cortisol suppression in the overnight 1-mg dexamethasone suppression test, and not suppressed ACTH levels. CD was finally confirmed by inferior petrosal sinus sampling (IPSS) showing IPSS/peripheral blood ACTH ratio >3 after CRH stimulation (9). The ACC diagnosis was established by histological analysis after surgery and Weiss scores were comprised between 5 and 9.

Menopausal women and women receiving anti-gonadotrope treatment (oral contraceptives) that might complicate the interpretation of hormone assays were not eligible for the study. The baseline characteristics of the 21 patients are summarized in Table 1.

Mitotane therapy

In patients with CD, the median dose of mitotane (Lysodren 500 mg, HRA Pharma, Paris, France) was 2 g/day (range: 1.5–3.5) initially, and 1.5 g/day (0.5–3) at the diagnosis of ovarian cysts. The median doses were higher in patients with ACC: 4.5 g/day (3–6) initially and 2 g/day (1–3.5) at the diagnosis of ovarian cysts. Ovarian cysts were diagnosed after a median 11 months (range 3–36) of mitotane exposure (see below).

Hormonal evaluation

Pre- and post-treatment endocrine evaluations consisted of UFC and serum ACTH, DHEAS, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone, Δ4-androstenedione and sex hormone-binding globulin (SHBG) at baseline and at the moment of ovarian cyst diagnosis.

Assays

Various RIA and immunoradiometric assays were used in endocrine reference laboratories of referral centers to
measure, respectively, urinary cortisol, circulating DHEAS, E₂, total testosterone, Δ4-androstenedione, and serum ACTH, FSH, and LH. The characteristics of each hormone assay (assay method, limit of detection, and normal range) in each referral center are shown in Supplementary Table 1, see section on supplementary data given at the end of this article. Serum SHBG was measured with a solid-phase chemiluminescent immunometric assay (Immulite; Siemens Healthcare Diagnostic Products, Llanberis, UK) with a detection limit of 0.02 nmol/l. The intra- and interassay coefficient of variation (CV) values were 3.2 and 4.6% for a SHBG concentration of 56.4 nmol/l. Serum inhibin B levels were measured with a commercial ELISA (Serotec, Kidlington, Oxford, UK) with a detection limit of 6 pg/ml and inter- and intra-assay CV values of 13 and 6% respectively. Serum anti-Mullerian hormone (AMH) levels were assessed using the second-generation enzyme immunoassay AMH-EIA (ref. A16507) provided by Beckman Coulter Immunotech (Villepinte, France) according to the supplier’s instructions. Intra- and interassay CV values were <8.2 and 11.2%, respectively, and the functional sensitivity (i.e. the lowest concentration of AMH measured with an interassay CV <20%) was 0.8 pmol/l. Plasma mitotane concentrations were measured by HPLC after an overnight fast, as described previously (10). Intra-assay CV values were 20% at low values and 15% at high values.

**Morphological evaluation** Pelvic transabdominal and transvaginal ultrasound examinations were performed with 7.5-MHz probes by experienced gynecological radiologists. Four women also underwent ovarian CT or magnetic resonance imaging (MRI).

**Statistical analysis** All results are reported as individual values in the figures and as medians (range) in the tables and text. Baseline and on-treatment hormone concentrations were compared using the nonparametric Mann–Whitney U test or the Wilcoxon’s signed-rank (paired) test, as appropriate. GraphPad Prism software version 4 was used for all analyses. P values <0.05 were considered to denote significant differences.

**Results**

**Menstrual status and pelvic symptoms** We observed a high frequency of menstrual disorders at baseline in women with ACC and CD (14/21 patients, Table 1 and Supplemental Fig. 1A, see section on supplementary data given at the end of this article) (present in 14/21 patients at baseline) (11). At the time of diagnosis of ovarian cysts, 15 out of 21 patients had

<table>
<thead>
<tr>
<th>Normal range in EFP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ4-androstenedione (ng/ml)</td>
<td>0.4–2.0b</td>
</tr>
<tr>
<td>Testosterone (ng/ml)</td>
<td>0.2–0.6b</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>34–100b</td>
</tr>
<tr>
<td>LH (IU/l)</td>
<td>2.6–9.5b</td>
</tr>
<tr>
<td>FSH (IU/l)</td>
<td>3.2–10b</td>
</tr>
</tbody>
</table>

EFP, early follicular phase.

*Median (range).

Lower and upper limits of normal range indicated are the mean of values obtained with the different assays used in the reference centers (see also Supplementary Table 1).

### Table 1

Clinical and hormonal characteristics of women with Cushing’s disease (CD) or adrenocortical carcinoma (ACC) before mitotane therapy. To convert the values for testosterone in ng/ml to nanomoles/l, multiply by 3.467 and to ng/dl multiply by 100. To convert the values for Δ4-androstenedione in ng/ml to nanomoles/l, multiply by 3.492 and to ng/dl multiply by 100. To convert the values for estradiol to picomoles per liter, multiply by 3.671.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 (18–45)a</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29 (17–47)a</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>CD: 8/21 (38%); hypercortisolism (8/8)</td>
</tr>
<tr>
<td></td>
<td>ACC: 13/21 (62%); hypercortisolism (6/13)</td>
</tr>
<tr>
<td>Menstrual cycles</td>
<td>Regular: 6/21 (29%)</td>
</tr>
<tr>
<td></td>
<td>Amenorrhea: 7/21 (33%)</td>
</tr>
<tr>
<td></td>
<td>Oligomenorrhea: 7/21 (33%)</td>
</tr>
<tr>
<td></td>
<td>Uterus ablation: 1/21 (5%)</td>
</tr>
</tbody>
</table>

Δ4-androstenedione (ng/ml) 2.4 (0.6–12.4)a 0.4–2.0b
Testosterone (ng/ml) 0.8 (0.1–6.2)a 0.2–0.6b
Estradiol (pg/ml) 31.5 (2–56)a 34–100b
LH (IU/l) 3.0 (0.05–17)a 2.6–9.5b
FSH (IU/l) 4.6 (0.1–14)a 3.2–10b

EFP, early follicular phase.

*Median (range).

Lower and upper limits of normal range indicated are the mean of values obtained with the different assays used in the reference centers (see also Supplementary Table 1).
menstrual disorders (Supplemental Fig. 1B). However, symptoms at diagnosis of ovarian cysts were bleeding (four patients) and pelvic pain (four other patients), neither of which was reported to be present in any patient at baseline (see below).

Discovery of ovarian cysts in women with CD and ACC receiving mitotane

In the 21 patients studied herein, ovarian macrocysts (>1 cm in diameter) were detected after a median 11 months of mitotane exposure (range 3–36 months). The circumstances of cyst discovery were variable. In 14 patients (67%), the diagnosis was made during pelvic ultrasound examination performed for either pelvic pain (n=4), or abnormal bleeding (n=4), or oligo/amenorrhea (n=6). The sonographic aspects of six representative patients are shown in Fig. 1. In four patients (19%), pelvic ultrasound was performed after cyst discovery by CT or MRI performed to monitor their adrenal malignant disease. Figure 2 shows the typical aspect of the ovarian cysts in these patients on CT (Fig. 2A, B, and C) and MRI (Fig. 2D). The remaining three patients (14%) were examined routinely by pelvic ultrasound, following the discovery of this complication in the previous patients. Supplementary Fig. 2, see section on supplementary data given at the end of this article, shows the sonographic aspect before and after mitotane exposure in a representative patient.

The median number of cysts per patient on ultrasound was two (range 1–4). Out of 21 patients, 11 (52%) had bilateral cysts. The median size of the largest cysts was 50 mm (range 26–90). The cysts were complicated in two cases (women with ACC), by adnexal torsion in one case and by hemorrhagic cyst rupture in the other case, requiring emergency surgery. Four patients with particularly large cysts underwent ovarian cystectomy for diagnostic purposes.

In order to ascertain that ovarian macrocysts were related not merely to hypercortisolism or ACC, but also to mitotane therapy, we evaluated their frequency in patients treated with mitotane when compared with women with Cushing’s syndrome or ACC but not receiving this drug. In 36 premenopausal women suffering from untreated CD and having had an ovarian ultrasound, none had ovarian macrocysts. This was also the case in seven women with ACTH-independent Cushing’s syndrome, whereas in 24 women with ACC not receiving mitotane, ovarian macrocysts were detected in two. This comparison (See also Supplementary Table 2, see section on supplementary data given at the end of this article) indicated that the frequency of ovarian macrocysts was significantly higher in women receiving mitotane (P<0.001), strongly suggesting the causal relationship between mitotane...
therapy and the appearance of macrocysts. Finally, we were able to evaluate the fate of cysts in two patients with CD who have stopped mitotane after their effective removal of adrenocorticotropic pituitary adenoma. In both patients, we observed a regression of ovarian cysts by means of ultrasound scanning performed 3–4 months after discontinuation of mitotane.

Mitotane levels and hormonal status at the time of macrocyst discovery

Mitotane ► Median mitotane concentrations at cyst diagnosis were 11 mg/l (8.6–24) in patients with CD and 14.3 mg/l (5–20.5) in patients with ACC.

Hormonal status ► Adrenal function ► Median (range) 24 h UFC and serum DHEAS levels were reduced much significantly during treatment with mitotane (12), respectively, from 224 (25–2579) to 27.5 (0–136) μg/24 h (P<0.001) and from 1758 (608–14 550) to 40 (0–65) ng/ml (P<0.001).

Changes in ovarian and gonadotrope functions ► Changes from baseline in individual total testosterone, Δ4 androstenedione, and LH levels are shown in Fig. 3. Circulating levels of the two androgens (median; range) fell markedly during mitotane therapy: testosterone from 0.77 (0.1–6.2) to 0.15 (0–0.72) ng/ml (P<0.001, Fig. 3A) and Δ4 androstenedione from 2.35 (0.57–12.38) to 0.69 (0.11–1.8) ng/ml (P<0.001, Fig. 3B). This was accompanied by a very significant increase in circulating LH: from 3.0 (0.2–17) to 16 (3.6–30.6) IU/l (P<0.001, Fig. 3C).

Figure 4 shows changes in individual total E2, FSH, and SHBG levels. The median (range) total E2 level increased significantly during mitotane treatment, from 31.5 (2–56) to 96.5 (45–385) pg/ml (P<0.001, Fig. 4A), as did the FSH level, from 4.6 (0.2–14) to 5.35 (2.7–15) IU/l (P<0.05, Fig. 4B). A significant increase in SHBG levels (12) was noted during mitotane therapy (from 36.5 (15–65) to 256.5 (151–506) nmol/l, P<0.001, Fig. 4C).

In three patients (33–45 years) with CD, we measured circulating AMH and inhibin B before and during treatment with mitotane. Basal serum AMH levels, measured in three patients (33–45 years) with CD, were 12, 3, and 6 pmol/l and were, respectively, at 14, 8, and 12 pmol/l during mitotane therapy (normal range in women aged 32–42 years: 7.7–36.2). In these three patients, basal serum inhibin B levels were 21, 11, and 20 pg/ml and, respectively, 39, 18, and 4 pg/ml during mitotane therapy (normal range in women aged 32–42 years: 38–96 pg/ml).

Discussion

Mitotane is widely used to treat malignant ACC and ACTH-dependent Cushing’s syndrome (1, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13). This drug, derived from DDT, acts through a dual mechanism involving both apoptosis of adrenal cortex cells and inhibition of adrenal steroid synthesis (4, 7). Some ancient studies performed in canine and bovine adrenals demonstrated that these effects could be related to a deleterious action on mitochondrial functions (14, 15, 16). More recently, Hescot et al. (7) showed that mitotane significantly reduced the activity of respiratory
chain complex 4, leading to mitochondrial fragmentation and cell death. Some crucial enzymes involved in steroid synthesis are located in mitochondria; this is notably the case of CYP11A (also called cholesterol side-chain cleavage (scc) or P450scc), the enzyme responsible for biosynthesis of pregnenolone, the common precursor of all adrenal, ovarian, and testicular steroids (17). However, biosynthesis of this steroid precursor requires prior translocation of cholesterol into the mitochondria by STAR protein (17). Mitotane might therefore, through its deleterious effect on mitochondria, inhibit gonadal steroidogenesis, in addition to its established effect on the adrenal cortex (4, 7). Evidence of an effect on testicular steroidogenesis has indeed been reported, thereby strengthening this hypothesis (8, 12). These authors showed a decrease in testosterone levels in men, associated with an increase in circulating LH levels, suggesting impaired Leydig cell steroidogenesis.

The aim of this study was to examine the ovarian effects of chronic mitotane administration in premenopausal women treated for ACC and CD. We found that mitotane frequently led to a drastic decline in testosterone and its immediate precursor Δ4-androstenedione. Before menopause, circulating testosterone is derived from androgenic precursors produced both by the reticulate region of the adrenal cortex and by the theca interna cells of large antral ovarian follicles (18). The decline in testosterone and Δ4-androstenedione observed and confirmed in this study during mitotane therapy could partly be explained by the decline in adrenal DHEAS described previously (12). However, the massive decline in Δ4-androstenedione and testosterone suggests that ovarian androgen biosynthesis ensured by cells of the theca interna may also be affected by mitotane. This hypothesis is supported by the very significant concomitant increase in circulating LH levels, which could be secondary to abolition of the negative feedback exerted by the ovaries. Similar rises in gonadotropin levels, and particularly LH levels, have indeed been described in situations in which ovarian androgen biosynthesis is affected by genetic disorders such as mutations in the LH receptor (19, 20, 21, 22, 23), STAR (24, 25, 26), or 17-hydroxylase (27, 28, 29). In addition, given the expected rise in serum SHBG induced by mitotane (12, 30), the androgen deficiency in our patients might even have been underestimated. However, we recognize that the intimate mechanism underlying the very significant increase in circulating LH levels was not demonstrated by our work and that further studies are needed to establish precisely as to why mitotane induces both a dramatic decrease in androgen levels and an increase in LH levels. We must stress that irrespective of the mechanisms possibly involved in the decline in circulating androgen levels we observed, this decrease could be useful, as it could prevent the onset of clinical signs of hyperandrogenism in women receiving this drug for hypercortisolism or ACC.

Mitotane also caused an increase in total E2, which, although statistically significant, was inconsistent. This might be explained, at least in part, by the rise in SHBG levels, which itself might be related to the hepatic estrogenic effect of mitotane (30). Indeed, SHBG carrier...
protein binds with high affinity to E2 and could thereby reduce the metabolic clearance of E2 and lead to its accumulation (31). This hypothesis is consistent with what was described in women with hyperthyroidism, which exhibits concomitant increases in SHBG, E2, and total FSH levels (32). It is also conceivable that the very large increase in SHBG levels could lead to a decrease in the bioactivity of circulating E2 (33) and to an increase in FSH levels by lifting the negative feedback effect of E2 on FSH production. The increase in E2 observed in this study is somewhat surprising, given the decline in androgen precursors. However, we cannot rule out the existence of residual ovarian androgen production by theca interna cells, followed by local metabolism to E2 by granulosa cells under the influence of aromatase induced by elevated FSH levels (34). Besides the possibilities suggested above, we cannot exclude a lack of specificity of E2 immunoassays used in the different participating centers that could also recognize other circulating steroids or their metabolites. To decide between these different hypotheses, we believe that it would be useful to assess E2 levels in premenopausal women taking mitotane using more specific techniques such as GCMS or LCMS.

A drawback of our study is that we could only obtain measurements of circulating AMH and inhibin B in three women. However, the preliminary results reported in this study do not show a dramatic decline in AMH, and therefore do not suggest a decline in ovarian reserve, which is rather reassuring. However, prospective future research, including a significant number of patients, will be needed to actually assess the levels of these ovarian peptides in premenopausal women treated with mitotane.

The development of ovarian macrocysts, in our patients during mitotane therapy, was surprising as never reported before. This is all the more curious since this drug has been used for decades in ACC (1, 2, 12) and CD (3, 4, 5, 6), both of which are predominantly female diseases that can occur before menopause. How did this adverse effect go unnoticed until now? One possible explanation is that pelvic imaging is underused in these women, despite their frequent gynecological symptoms. Two-thirds of patients included in our study had pelvic symptoms during treatment with mitotane. Menstrual disorders such as oligomenorrhea and amenorrhea are difficult to assign to mitotane because of their frequency in women with hypercortisolism (11). Nevertheless, we believe that an interview focusing on bleeding and/or pelvic pain, which are frequent in this setting, could help to detect this adverse effect earlier. However, we recognize that systematic studies examining the prevalence of these latter gynecological signs both in women with Cushing’s syndrome and ACC, receiving mitotane or not, are still necessary to specify their predictive value for the presence of macrocysts.

Another drawback of our study is our inability to establish the exact prevalence of ovarian cysts in premenopausal women treated with mitotane. To define the prevalence of ovarian complication, prospective studies, in either women taking oral contraceptives or not, will be needed.

In two patients with CD, we observed regression of ovarian cysts by means of ultrasound scanning performed 3–4 months after discontinuation of mitotane. This favorable evolution seems to reinforce the imputability of mitotane in the development of cysts. But interestingly, it especially suggests that this side effect could be reversible, which is rather reassuring.

The mechanism of formation of these cysts is unclear. We can speculate that the increase in pituitary gonadotropins may play a role, as in the above-mentioned genetic diseases affecting ovarian steroidogenesis. Indeed, ovarian macrocysts are also observed in women (XX karyotype) with mutations of the LH receptor, STAR protein, or 17α-hydroxylase, which are associated with both a decrease in circulating androgen levels and an increase in gonadotropins (19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29). Mitotane might induce the formation of these macrocysts through a similar mechanism. If the gonadotropin elevation indeed plays a pivotal role in the development of these cysts, it might be possible to prevent them by inhibiting pituitary gonadotropin secretion in women treated with mitotane. The use of hormonal contraception recommended for patients treated with mitotane, by lowering circulating gonadotropins, could help prevent the occurrence of these cysts. Pending trials of such a preventive strategy, we believe, are unable to dictate specific recommendations that women treated with mitotane should receive regular ultrasound monitoring to detect ovarian cysts before the onset of complications such as bleeding and torsion, especially in those with gynecological symptoms such as pelvic pain or abnormal bleeding. In women with ACC undergoing routine imaging usually performed for evaluation of ACC, MRI or CT could be enough to detect macrocysts, provided that radiologists are aware of this complication and that the imagery properly explores the pelvic region.

Finally, in our study, we excluded postmenopausal women and therefore we cannot exclude the possibility that ovarian macrocysts may appear in this population.
A specific study will be necessary to assess the frequency of such an ovarian complication in these women.

In conclusion, we show in this study for the first time that ovarian and gonadotropin functions are markedly affected by mitotane in premenopausal women. This effect is accompanied by a dramatic decrease in androgen levels and an increase in gonadotropin levels, suggesting impairment of the theca interna, adding to the inhibition of adrenal androgen secretion. Ovarian macrocysts are a frequent adverse effect of mitotane and therefore warrant routine ovarian ultrasound screening to avoid complications.

References


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