Low 11-deoxycortisol to cortisol conversion reflects extra-adrenal factors in the majority of women with normo-gonadotrophic normo-estrogenic infertility

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BACKGROUND: Women with normogonadotrophic normo-estrogenic oligomenorrhoea often disclose a variety of clinical symptoms. Many of these individuals are obese with features of pseudo-hypercortisolism. In the current study, 11-deoxycortisol and cortisol concentrations were determined in this group and compared with ovulatory controls. METHODS AND RESULTS: Twenty-six women with clomiphene citrate-resistant infertility, 12 lean and 11 obese ovulatory controls were studied. Women with infertility had the highest 11-deoxycortisol concentrations (mean \( \pm SD \): 4.1 \( \pm \) 1.5 ng/ml) compared with obese and lean controls (3.1 \( \pm \) 1.4 and 2.4 \( \pm \) 0.9 ng/ml) \( (P < 0.01) \), but similar morning cortisol concentrations (0.47 \( \pm \) 0.15, 0.45 \( \pm \) 0.16 and 0.47 \( \pm \) 0.18 nmol/l). Baseline 11-deoxycortisol/cortisol ratios (>90th percentile of ovulatory controls) were elevated in 23/26 infertile women (88%), and in 3/26 women (12%) after adrenocorticotrophic hormone (ACTH) stimulation. Three out of six lean infertile women had elevated baseline 11-deoxycortisol/cortisol ratios, but none of these women had elevated ratios after ACTH stimulation. Stepwise regression analysis, after exclusion of testosterone, revealed significant correlations between the groups (lean controls, obese controls, infertility) and ACTH-stimulated 11-deoxycortisol/cortisol ratio \( (P < 0.05) \), but not with fasting glucose, insulin, cortisol, 11-deoxycortisol and baseline 11-deoxycortisol/cortisol ratios. CONCLUSIONS: Congenital adrenal hyperplasia was not observed in the majority of infertile women. The data indicate that extra-adrenal factors were involved in most of the infertility syndromes that were studied.

Key words: cortisol/11-deoxycortisol/extra-adrenal factors

Introduction

Irregular menstrual cycles and associated ovulation dysfunction harbour a series of heterogeneous clinical entities that are frequently associated with hypertension, dyslipidaemia, hyperandrogenism, hirsutism, obesity and insulin resistance. Many women share three features that are generally accepted for the diagnosis polycystic ovary syndrome (PCOS): (i) oligomenorrhoea, (ii) clinical or biochemical evidence of androgen excess, and (iii) the exclusion of other endocrine disturbances (Lobo, 1995). Moreover, obesity and associated insulin resistance are observed in >50% of these women (Legro et al., 1998).

For overweight women, the first step in improving ovulation rates is to encourage weight reduction (Bates and Whitworth, 1982; Pasquali et al., 1989). Notably, insulin-sensitizing agents can also promote ovulation, thereby reducing circulating androgen concentrations (Dunaif et al., 1996; Ehrmann et al., 1997a,b; Nestler et al., 1998). Both elevated androgens as well as abnormal regulation of the hypothalamic–pituitary–adrenal (HPA) axis and elevated cortisol clearance rates have previously been reported in obese women (Strain et al., 1980, 1982). By contrast, women with Cushing’s syndrome commonly present with irregular menstrual bleedings, and ovarian morphology similar to that of PCOS (Kaltsas et al., 2000).

In a previously reported study, several isolated or combined enzyme deficiencies were reported in a third of women with irregular cycles with a substantial number of subjects exhibiting a diminished 11β-hydroxylase activity, suggestive for mild forms of congenital adrenal hyperplasia (CAH) (Eldar Geva et al., 1990). In the current study, we analysed the calculated 11-deoxycortisol/cortisol ratios, indicative for 11β-hydroxylase activity, in women with normo-gonadotrophic, normo-estrogenic oligomenorrhoea and clomiphene citrate-resistant infertility, compared with lean and obese ovulatory controls. Infertility is commonly observed in obese women who frequently cope with clinical features of pseudo-hypercortisolism, even though their morning serum cortisol concentrations are normal or even low, but their 24 h free urinary cortisol excretion usually is normal or even high, meaning that
although cortisol production in adipose tissue is high the clearance rate is also increased (Prelevic et al., 1993).

In the present study we tested the hypothesis that changes in cortisol metabolism of infertile women are more related to extra-adrenal factors than to adrenocorticotrophic hormone (ACTH)-driven steroidogenesis. Our study objective was to determine 11-deoxycortisol/cortisol ratios before and after ACTH stimulation, thereby differentiating CAH (11β-hydroxylase deficiency) from extra-adrenal factors.

Materials and methods

Study patients and ovulatory controls

The current study included 26 normo-gonadotrophic, normo-estrogenic, oligomenorrheic women, consecutively referred by the hospital IVF programme for endocrine analysis. All women had a history of oligomenorrhea defined if cycle lengths of >42 days were reported (Committee of the Dutch Fertility Society, 1996). They were healthy and displayed no endocrine disorders such as prolanctoma, hypo- or hyperthyroidism, diabetes mellitus and hypogonadotropic hypogonadism. The possible presence of CAH was unknown at the time of inclusion. Patients were classified as being clomiphene citrate resistant if, despite taking 150 mg clomiphene citrate from day 3 to time of inclusion. Patients were classified as being clomiphene citrate hypo- or hyperthyroidism, diabetes mellitus and hypogonadotrophic healthy and displayed no endocrine disorders such as prolactinoma, 17α-hydroxylase, and/or sonographic signs of ovulation were lacking. Twelve lean day 7 of the menstrual cycle, progesterone did not rise to >15 nmol/l, and/or sonographic signs of ovulation were lacking. Twelve lean women [body mass index (BMI) <25 km/m²] and 11 obese women (BMI >25 km/m²), with proven regular and ovulatory cycles and with children of their own, served as the control group. Serum progesterone values of >35 nmol/l in the luteal phase of their cycle (blood samples were drawn by day 5 and 8 after ovulation) were measured in these two groups. In all participants of the study, baseline blood sampling was performed either during the follicular phase of the menstrual cycle or at random, when the last menstrual bleeding had occurred >3 months prior to inclusion in the study. At least 30 min before blood samples were taken, an indwelling catheter was inserted. All blood samples were drawn between 0800 and 0900, following 12 h of fasting.

The Medical Ethical Committee of Hospital Reinier de Graaf Groep approved the study. Both patients and controls gave their informed consent for participation in the study.

Methods

Hormone assessments were determined by commercially available assays. Hormones and steroid precursors were analysed in one assay, except for 17α-hydroxyprogrenenolone (17OH-preg). The latter steroid was assayed by additional runs for reasons of validation. Three experienced laboratory technicians performed all assays. All precursors were assayed at baseline and at 30 min after an ACTH bolus i.v. (250 μg synthetic α₃₄-2₅-ACTH (Cortrosyn®)).

Fasting insulin, reference values: <20 mIU/l (enzyme-linked immunoassay, EIA; IMX-Abbott Laboratories, USA), cortisol, reference values: <0.73 μmol/l between 0800 and 0900; total testosterone, reference values: <3.1 nmol/l before menopause. All these hormones were measured using IMA (Immublitz; DPC, Los Angeles, CA, USA). The reference value for fasting glucose was <6.0 mmol/l.

According to the manufacturer’s instructions, blood samples assayed for 17OH-preg (ng/ml) were prepared with an ethyl acetate/hexane extraction and column chromatography. The final analysis was done with a solid-phase ¹H radioimmunoassay (ICN Pharmaceuticals, Costa Mesa, CA, USA). The entire procedure had a maximal intra- and inter-assay coefficient of variation (CV) of 10.3 and 15.0% respectively. Mean ± SD values in 24 ovulatory controls before and after ACTH stimulation were 4.5 ± 4.7 and 9.7 ± 4.7 ng/ml. 17α-Hydroxyprogesterone (17OH-prog; nmol/l) was determined with a solid-phase ¹²⁵I radioimmunoassay (DPC) with maximal intra- and inter-assay CV of 5.6 and 5.7% respectively. Values in ovulatory controls were 6.2 ± 3.9 and 10.9 ± 3.7 nmol/l before and after ACTH stimulation respectively. 11-Deoxycortisol (ng/ml) was determined with a solid-phase ¹²⁵I double antibody radioimmunoassay (ICN Pharmaceuticals) with a maximal intra- and inter-assay CV of 5.9 and 13.7% respectively. Values in ovulatory controls before and after ACTH stimulation were 2.8 ± 1.2 and 4.3 ± 1.4 ng/ml.

Steroid ‘precursor-to-product ratios’

Three enzyme activities were indirectly analysed by calculating precursor-to-product ratios; these were (i) 3β-hydroxy-Δ₅-steroid dehydrogenase (17OH-preg/17OH-prog), (ii) 21α-hydroxylase (17OH-preg/11-deoxycortisol) and (iii) 11β-hydroxylase (11-deoxy-cortisol/cortisol). Normal laboratory reference ranges of these ratios before and after the ACTH bolus were obtained from the control group, which consisted of both lean and obese ovulatory women. Ratios higher than the 90th percentile values in the controls were considered indicative of abnormal steroidogenesis. ACTH-stimulated ratios higher than the 90th percentile of values in the controls were diagnostic for late onset CAH. The reference values obtained from the current study were 1.2 (basal) and 11.1 (after ACTH) for 3β-hydroxy-Δ₅-steroid dehydrogenase, 3.5 (basal) and 7.9 (after ACTH) for 21α-hydroxylase, and 8.3 (basal) and 18.1 (after ACTH) for 11β-hydroxylase.

Statistical analysis

Hormone and steroid levels from the lean ovulatory, obese ovulatory and infertile groups were compared using analysis of variance. Comparisons per group of basal and post-ACTH values were performed using paired Student’s t-tests. Correlations between groups and physical variables such as BMI, fasting glucose and insulin, testosterone, 11-deoxycortisol, cortisol and the calculated precursor-to-product ratio were analysed using stepwise regression analysis. P < 0.05 was considered statistically significant.

Results

Demographic characteristics and endocrine data are shown in Table I. Age was not different across groups. BMI was also not statistically different between women in the infertile group compared with obese controls. Total testosterone levels, however, were highest in the group of infertile women, ~2-fold compared with obese and 4-fold higher compared with lean controls. Insulin levels were also elevated in the infertile group, but only significantly higher compared with levels in lean controls. Glucose levels were lowest in the lean ovulatory controls.

Precursor-to-product ratios

None of the women with infertility had abnormal 21α-hydroxylase activities (17OH-prog/11-deoxycortisol); all baseline ratios were less than the reference value of 3.4, and all ACTH ratios were <3.9. Four women (4/26) had elevated 17OH-preg/17OH-prog ratios, i.e. a baseline value >1.2. One of these women with a BMI of 34.0 kg/m² had CAH (3β-hydroxy-Δ₅-steroid dehydrogenase deficiency) presenting with a basal value of 2.3 and of 12.8 after ACTH (reference value of
The ACTH-stimulated 17OH-preg/17OH-prog ratios of the three other women remained <12.8.

Twenty-three out of 26 infertile women (88%) had a low 11-deoxycortisol to cortisol conversion (11-deoxycortisol/cortisol), i.e. a baseline value >8.1 (reference value). Three of these women (BMI: 38.0, 35.0 and 44.1 kg/m²) had CAH (11β-hydroxylase deficiency) exhibiting elevated ACTH-stimulated 11-deoxycortisol/cortisol ratios (35.7, 32.1 and 18.3) (reference value after ACTH: >18.1). From the infertile group, six women (23%) were lean (e.g. BMI <25 kg/m²) and 20 (77%) were considered to be obese (e.g. BMI >25 kg/m²). Of the lean women with infertility, three had mildly increased basal 11-deoxycortisol/cortisol ratios (35.7, 32.1 and 18.3) (reference value after ACTH: >18.1). The ACTH-stimulated 17OH-preg/17OH-prog ratios was seen as the sole significant step (P < 0.01). A similar picture emerged between groups (including obese ovulatory and infertile women) of the three groups. Baseline 11-deoxycortisol concentrations were elevated in the infertile group, and increased significantly after ACTH stimulation (Table I). Finally, basal 11-deoxycortisol/cortisol ratios were significantly higher in the infertile group. Although this ratio remained unchanged after ACTH stimulation, these levels were still significantly higher than those in either of the ovulatory control groups.

**Interrelationships**

Following stepwise regression analysis between groups (lean ovulatory, obese ovulatory and infertile women) of the variables fasting glucose and insulin, testosterone, cortisol, 11-deoxycortisol and its ratio, the only significant relationship that existed (the only step of the regression analysis) was that of fasting glucose and insulin. None of these variables showed a relationship with ACTH-stimulated deoxycortisol/cortisol ratios than the reference value of 18.1. All 20 infertile obese women had increased basal 11-deoxycortisol/cortisol ratios but only three of them had increased deoxycortisol/cortisol ratios after ACTH (18.3, 32.0 and 35.9).

As demonstrated in Table II, baseline and ACTH-stimulated morning cortisol concentrations were similar among the three groups. Baseline 11-deoxycortisol concentrations were elevated in the infertile group, and increased significantly after ACTH stimulation (Table I). Finally, basal 11-deoxycortisol/cortisol ratios were significantly higher in the infertile group. Although this ratio remained unchanged after ACTH stimulation, these levels were still significantly higher than those in either of the ovulatory control groups.

### Table I. Demographics and laboratory measurements in infertile women and in obese and lean ovulatory controls

<table>
<thead>
<tr>
<th></th>
<th>Infertile controls (n = 26)</th>
<th>Obese controls (n = 11)</th>
<th>Lean controls (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>33 ± 5 (25–44)</td>
<td>34 ± 5 (25–40)</td>
<td>33 ± 4 (27–38)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31 ± 7 (20–46)</td>
<td>36 ± 7 (27–51)</td>
<td>21 ± 4 (19–24)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Testosterone (nmol/l)</td>
<td>3.5 ± 0.9 a (0.9–6.8)</td>
<td>1.4 ± 0.8 (0.6–2.9)</td>
<td>0.9 ± 0.3 (0.01–1.3)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>5.3 ± 0.9 (4.2–7.5)</td>
<td>5.3 ± 0.6 (4.4–6.1)</td>
<td>4.1 ± 0.4 a (3.6–4.9)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Insulin (IU/l)</td>
<td>22 ± 10 (4–78)</td>
<td>15 ± 11 (5–41)</td>
<td>4 ± 1 a (2–5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>17OH-Pregnenolone (ng/ml)</td>
<td>2.6 ± 1.9 (0.9–8.6)</td>
<td>4.4 ± 5.3 (0.4–16.7)</td>
<td>4.5 ± 14.5 (0.3–13.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Basal</td>
<td></td>
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</tr>
<tr>
<td>17OH-Progesterone (nmol/l)</td>
<td>10.4 ± 6.1 (4.4–34.6)</td>
<td>9.9 ± 4.5 (3.5–18.6)</td>
<td>9.5 ± 5.0 (4.2–19.4)</td>
<td>NS</td>
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<tr>
<td>Basal</td>
<td></td>
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<tr>
<td>11-Deoxycortisol (ng/ml)</td>
<td>4.0 ± 2.0 (1.3–8.9)</td>
<td>6.4 ± 4.1 (1.6–13.2)</td>
<td>6.0 ± 3.9 (1.2–12.9)</td>
<td>NS</td>
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<tr>
<td>Basal</td>
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<tr>
<td>Stimulated</td>
<td>10.1 ± 3.8 (3.8–18.2)</td>
<td>11.3 ± 1.8 (7.3–13.6)</td>
<td>10.6 ± 4.9 (4.6–22.9)</td>
<td>NS</td>
</tr>
<tr>
<td>11-Deoxycortisol (ng/ml)</td>
<td>4.1 ± 1.5 (1.7–8.4)</td>
<td>3.1 ± 1.4 (1.3–6.4)</td>
<td>2.4 ± 0.9 a (1.2–4.2)</td>
<td>&lt; 0.01</td>
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<tr>
<td>Basal</td>
<td></td>
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<tr>
<td>Stimulated</td>
<td>9.0 ± 5.0 a (3.4–25.7)</td>
<td>5.1 ± 1.5 (3.2–8.2)</td>
<td>3.6 ± 0.9 (2.2–5.2)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range).

Comparisons of age, body mass index (BMI), testosterone, glucose, and insulin between groups. Women were categorized as lean if their BMI was <25 kg/m² and obese if >25 kg/m². Values are mean ± SD. aSignificantly (P < 0.05) lower and bsignificantly higher values compared with groups without symbols.

NS = not significant.

### Table II. Comparisons of morning cortisol levels and 11-deoxycortisol/cortisol ratios in infertile women and ovulatory controls

<table>
<thead>
<tr>
<th></th>
<th>Infertile women (n = 26)</th>
<th>Obese controls (n = 11)</th>
<th>Lean controls (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (μmol/l)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>0.48 ± 0.17</td>
<td>0.45 ± 0.16</td>
<td>0.47 ± 0.18</td>
<td>NS</td>
</tr>
<tr>
<td>ACTH stimulation</td>
<td>0.72 ± 0.22</td>
<td>0.73 ± 0.1</td>
<td>0.77 ± 0.14</td>
<td>NS</td>
</tr>
<tr>
<td>11-Deoxycortisol/cortisol</td>
<td>9.9 ± 4.8 a</td>
<td>6.9 ± 1.6</td>
<td>5.2 ± 0.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Baseline</td>
<td>12.7 ± 7.2 a</td>
<td>7.0 ± 2.2</td>
<td>4.7 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ACTH stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SD.

aSignificantly higher values compared to groups without symbols.

ACTH = adrenocorticotropic hormones.

NS = not significant.
including only the lean and obese ovulatory groups in the analysis revealed two significant relationships, for fasting glucose levels ($P < 0.01$) and baseline 11-deoxycortisol/cortisol ratios ($P < 0.05$).

**Discussion**

Lean and obese ovulatory women, and women with normo-gonadotrophic, normo-estrogenic oligomenorrhoea, were compared in the current study. All infertile women were resistant to clomiphene citrate therapy and none of them disclosed general endocrine disorders. The most interesting finding was that the majority (88%) of women in the infertile group displayed elevated 11-deoxycortisol/cortisol ratios without further increase after ACTH. These findings argue against co-existent CAH and support the idea that extra-adrenal factors are involved, possibly the increase of cortisol clearance. On the contrary, infertility and 11-deoxycortisol/cortisol ratios were stronger correlated after ACTH stimulation compared with baseline values, which indicated some involvement of adrenal steroidogenesis.

Clinical features of pseudohypercortisolism even with low morning cortisol concentrations have been reported in obese individuals (Björntorp and Rosmond, 2000). Based on the current observations, we questioned whether the abnormalities of cortisol metabolism that were observed should be ascribed to a mild form of CAH and/or to the concomitant state of an obesity-related metabolic disorder. Notably, it appeared that 11-deoxycortisol/cortisol ratios were highest in the infertile group.

In previous studies, it has been demonstrated that obesity is related to several changes in the HPA axis. Obese individuals sometimes have low serum cortisol concentrations despite having an increase in cortisol production (Strain et al., 1980, 1982). Subtle alterations in cortisol responses were described in obese individuals after corticotrophin-releasing factor and ACTH stimulation as well as after very low dose dexamethasone suppression (Kopelman et al., 1988; Marin et al., 1992; Pasquali et al., 1993; Ljung et al., 1996; Rosmond et al., 1998). Finally, stress-related cortisol hyper-responders showed interactions with clinical features of the ‘metabolic syndrome’ (central obesity, hypertension, insulin resistance, and dyslipidaemia; Rosmond et al., 1998). Apart from these changes, obesity can also be related to an increase in cortisol production rate (Szenas and Pattee, 1959; Migeon et al., 1963; Prezio et al., 1964; Zelissen et al., 1991). Moreover, there is compelling evidence that cortisol is exposed to enzymatic transformation in peripheral target tissues, mostly in liver and visceral fat (Bujalska et al., 1997). One cortisol conversion system includes the peripheral 11β-hydroxysteroid-dehydrogenases (11β-HSD), metabolizing cortisol to the less active cortisone (Type 2 enzymes) or back to cortisol (Type 1 enzymes) (Bujalska et al., 1997; Seckl, 1997). Non-obese individuals with hypertension may have subtle adrenal 11β-hydroxylase or peripheral 11β-HSD Type 2 deficiencies, resulting in mild mineralocorticoid excess. Obese individuals, displaying features of ‘the metabolic syndrome’, have evidence of an altered peripheral handling of glucocorticoids through a reinforcement of peripheral 11β-HSD, Type 1. This enzyme system enhances the local production of cortisol, particularly in visceral adipose tissues (Rask et al., 2001, 2002). We speculate that the imbalance between cortisol and its precursor steroid (11-deoxycortisol), as observed in infertile women, mirrors an insufficient cortisol production in relation its high clearance rate. Local cortisol production in peripheral tissues (11β-HSD, Type 1 in visceral fat) may compensate this minute systemic low cortisol status.

The presence of defects in ovarian and adrenal steroidogenesis of women with infertility has been previously reported in the laboratory (Gilling-Smith et al., 1997) and in clinical studies (Gonzalez, 1997; Rosenfield, 1999). Notably, (patient) populations described in previous research are heterogeneous as a result of the inclusion of different clinical syndromes with infertility. In an effort to be consistent in the selection of patients, we only included women with normo-gonadotrophic normo-estrogenic oligomenorrhoea who were resistant against clomiphene citrate. It is widely believed that this infertile group embodies several different reproductive disorders. In daily practice, these women are commonly divided in two distinct subgroups: obese women with high fasting insulin concentrations and lean women with insulin levels which are adequately low (Meirow et al., 1995). Convincing arguments have been provided to support the concept that PCOS includes a phenotypic spectrum of metabolic disorders. Firstly, insulin resistance is also observed in lean women with PCOS (Dunaif et al., 1989). Secondly, lean and fat body mass calculations have shown that in lean women with PCOS, changes in fat distribution involved primarily an increase of visceral fat mass (Kirchengast and Huber, 2001). Finally, we have observed changes in cortisol metabolism mainly due to extra-adrenal factors in lean as well as obese women with infertility.

In conclusion, abnormal baseline 11-deoxycortisol/cortisol conversions were found in 88% of women with clomiphene citrate-resistant normo-gonadotrophic normo-estrogenic oligomenorrhoea. This abnormality disappeared almost completely after ACTH administration, thus excluding overt CAH and suggesting an alternative operational pathway in non-adrenal tissues. Further studies are needed to compare the effects of interventions such as dietary programmes or insulin-sensitizing agents, to investigate cortisol metabolism, and ultimately to improve ovulation and pregnancy rates for these women.

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**References**


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11-Deoxycortisol/cortisol ratios in infertility