From William McK. Jeffries
SAFE USES OF CORTISOL

Chapter 5

GONADAL DYSFUNCTION AND INFERTILITY

The beneficial effects of physiologic dosages of cortisone acetate and cortisol in patients with congenital adrenal hyperplasia led to their being tried in women with ovarian dysfunction, hirsutism, and acne, since this combination of abnormalities occurred in both types of conditions. The dosages of glucocorticoids initially administered were relatively large, in the range of the full replacement dosages employed in congenital adrenal hyperplasia. Improvement occurred, but the possibility of adrenocortical suppression and impairment of resistance to stress from such doses was disturbing, so progressively smaller doses were tried, and we were pleased to find that impressive improvement occurred from physiologic dosages of 5 mg four times daily or even 2.5 mg four times daily, provided treatment was continued for a sufficient length of time.[1] It was therefore postulated that such cases might represent variants of the adrenogenital syndrome, viz., mild disorders of adrenal steroid metabolism characterized by excessive production of adrenal androgen and estrogen in sufficient quantities to interfere with ovarian function.

At that time, assessment of adrenal steroid production was limited clinically to measurements of urinary excretion of 17-ketosteroids (17-KS) and 17-hydroxycorticosteroids (17-OHST), resulting in indirect estimates at best, since levels of urinary metabolites might be affected by steroid metabolism in the liver and peripheral tissues, by blood levels of steroid-binding proteins, or by renal function, as well as by changes in rate or pattern of steroid production by the adrenals.

Responses of urinary excretion of 17-KS and 17-OHST of these patients to a standard stimulus with ACTH were usually consistent with normal adrenal responsiveness, but when urinary 17-KS were fractionated, excretion of dehydroepiandrosterone (DHEA), androsterone (A), and etiocholanolone (E) frequently showed much greater variation than that of women with regular ovulatory cycles.[2]

Later, when plasma levels of cortisol, testosterone, DHEA-sulfate, estrogen, and FSH could be measured, it was found that some women with gonadal dysfunction that could be corrected by subreplacement dosages of cortisone acetate or cortisol had poor responsiveness to ACTH indicative of low adrenal reserve, some had elevated levels of free (or unbound) testosterone or of DHEA-sulfate, and some had elevated or low levels of estrogen and low or normal levels of FSH. Those with elevated plasma free testosterone had associated acne and hirsutism, but urinary 17-KS excretion might be within normal limits. On the other hand, some women with acne and/or hirsutism might have normal plasma testosterone with elevated urinary 17-ketosteroids, indicating the production of an excess of androgen other than testosterone, usually DHEA. Women with elevated levels of estrogen usually had metropathia hemorrhagica.

After subreplacement dosages of glucocorticoids were found to correct ovarian dysfunction in this type of patient, studies were undertaken to determine the effects of small doses of cortisone acetate on fluid and electrolyte excretion as well as urinary steroid levels.[3] It was found that small changes in urinary sodium and potassium excretion did occur but that these changes were corrected within eight days even though the steroid was continued (see Fig. 2). It was also noted that a new, stable level of urinary steroid excretion did not occur until approximately ten to fourteen days after these small doses were initiated. It was further found that these small doses did not interfere with the adrenals' ability to respond to a standard dose of ACTH[3] (Fig. 5).

The concept of a close functional relationship between the ovaries and the adrenals is not new. The steroid-forming tissues of the gonads and adrenal cortices have a common embryonic origin, and these glands share many enzymatic steps in the production of their steroid hormones. The changes in adrenocortical activity that occur at puberty and the menopause further suggest a close association between these two pairs of glands. The well-known effects of stress upon the function of both of these pairs of glands could be due to simultaneous independent effects or to a sequential effect wherein the effect of stress upon one pair of glands, e.g., the adrenals, in turn affected the function of the other pair of glands. Clinical observations that patients with disorders of adrenocortical function, such as adrenal insufficiency (Addison's disease), hyperfunction (Cushing's syndrome), or dysfunction (congenital adre-

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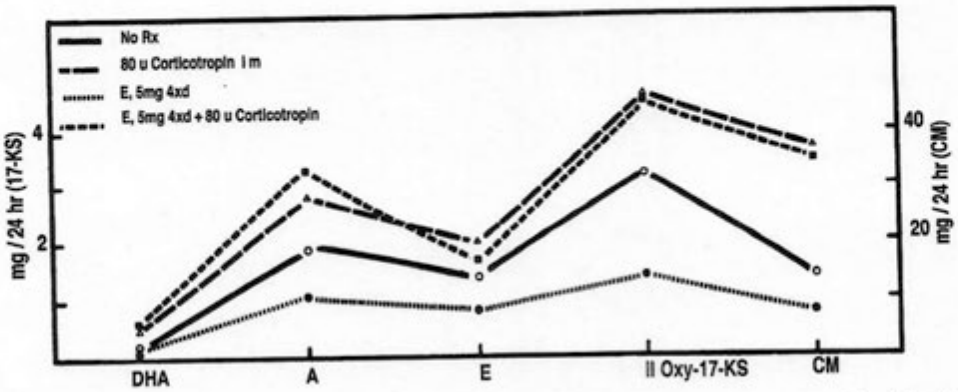

Figure 5. Effects of same dose of corticotropin (ACTH) administered to a 13 year old girl with probable rheumatoid arthritis upon urinary steroid fractions before treatment and while in a symptomatic remission on cortisone acetate (E), 5 mg four times daily (4 × d) (DHEA = dehydroepiandrosterone, A = androsterone, E = etiocholanolone, 11-oxy-17 KS = 11-oxygenated-17-ketosteroids, CM = cortisol metabolites). From William McK Jefferies, Low Dosage Glucocorticoid Therapy, *Archives of Internal Medicine, 119*:265–278. Copyright 1967, the American Medical Association. Reprinted by permission.

nal hyperplasia), had associated disorders of gonadal function were consistent with the concept of a close relationship between these glands. Furthermore, when cortisone was first tried in women with rheumatoid arthritis, interference with normal menstrual cycles was reported.[4,5]

In spite of such abundant suggestive evidence of a functional relationship between the gonads and adrenal cortices, this relationship has not been very intensively studied. Andrews[6] has summarized reports prior to 1976 relative to this relationship and pointed out the need for more work in this field. The work of Kitay and his associates[7,8] emphasizes the subtle nature but important potential of these relationships. They found that in castrated rats, estrogen replacement increases ACTH secretion and decreases adrenal responsiveness to ACTH, whereas androgen decreases ACTH and increases adrenal responsiveness to ACTH. They also reported that low doses of testosterone stimulate adrenal enzymatic and steroidogenic capacity, but large doses have inhibitory effects. Furthermore, testosterone may potentiate the action of ACTH.[9] The possible effects of adrenal progesterone upon gonadal function remain to be clarified.

Our observations in women with adrenal insufficiency reported in Chapter 4 also indicate the sensitive but potent interactions of these two

sets of glands. The occurrence of amenorrhea in these women, the restoration of normal menstrual cycles and fertility by administration of physiologic dosages of cortisone acetate or cortisol in cases of spontaneous deficiency, and the requirement for supplementary small doses of DHEA in the patient with total bilateral adrenalectomy exemplify this relationship.

Initially, treatment of ovarian dysfunction with small dosages of cortisone acetate or cortisol was restricted to patients with associated acne or hirsutism, but after observing the safety and beneficial effects of such therapy, it was decided to try similar dosages on patients who had ovarian dysfunction without hirsutism or acne. Many of these patients also experienced improvement in their clinical disorders.

Menstrual problems encountered included amenorrhea, either primary or secondary, but more often the latter, irregular menses, functional uterine bleeding, and luteal phase disorders. Women with ovarian dysfunction tend to have a high rate of infertility, and small doses of cortisone acetate or cortisol not only resulted in improvement of abnormal menstrual cycles but also in ability to conceive and to carry pregnancies normally to term. Effective dosages were as small as 2.5 mg every eight hours but usually were 2.5 or 5 mg four times daily.[10–13] Although these dosages do not impair resistance to stress, in fact they enhance this resistance, it is probably safer to give additional cortisol at delivery, especially if caesarian section is performed, because of recent evidence that autoimmune disorders may result from a defective response of the hypothalamus-pituitary-adrenal (HPA) axis to more severe stresses (see p. 99). Because the dosages are physiologic, they may be continued during lactation without harm to either the mother or her infant.

These findings were initially reported in 1958,[1] but meanwhile reports of harmful side effects of large doses of glucocorticoids were becoming so frequent that any dosage was viewed with alarm. By the time that I was able to report results on a significant series of cases,[14] patents had expired on cortisone acetate and cortisol, and there was no incentive for pharmaceutical houses to seek further clinical uses of these agents even though the results of this therapy were impressive. Over 80 percent of women with ovarian dysfunction not related to some other disorder such as pituitary insufficiency or primary ovarian deficiency experienced a restoration of normal menstrual cycles, and of those who had associated fertility problems, 62 percent conceived and carried their

pregnancies normally to term, provided they continued to take the medication throughout the pregnancy.

Meanwhile, clomiphene sulfate had been introduced as an agent to help stimulate ovulation and promote fertility in patients experiencing difficulty in conceiving. Clomiphene is not a natural hormone, but it is effective in some patients, and it had the protection of a patent to cause the pharmaceutical company marketing it to promote its sale enthusiastically. Because it does not correct the underlying hormone disorder but instead stimulates ovulation in a relatively artificial manner, a smaller percentage of patients conceive with clomiphene therapy than with small doses of cortisone acetate or cortisol, and of those who do conceive, a higher incidence of multiple births and of miscarriages occurs.[15,16]

Patients treated with physiologic dosages of cortisone acetate or cortisol, on the other hand, not only conceived, but they carried their pregnancies with an incidence of miscarriages no greater than that of the general population, provided the steroid was continued through the pregnancy.[14] In other words, small dosages of cortisone acetate or cortisol seemed to protect against miscarriage as well as improve conception rate. For these reasons, small doses of cortisone acetate or cortisol are preferable to clomiphene, and we have tried the latter only in patients who fail to respond to physiologic cortisone therapy. On occasion, a patient has conceived with clomiphene administration after low dosage glucocorticoid had failed, but numerous women have conceived on low dosage glucocorticoid therapy after having failed to conceive with clomiphene that had been prescribed prior to referral to me.

Most women who have androgenic changes such as acne and hirsutism associated with ovarian dysfunction have an increased excretion of urinary 17-KS or elevated levels of testosterone or DHEA-sulfate in the blood, and the adequacy of treatment is reflected by the return of such measurements to normal. Hence, initially it was postulated that the ovarian dysfunction was caused by an excess of androgen. Later when it was found that dysfunction could occur without any excess androgen and still be corrected by small doses of cortisone acetate or cortisol, it was concluded that an excessive production of estrogen by the adrenals, or at least under ACTH control, must be the cause of the disorder.[17,18] An excessive production of estrogen can often be demonstrated in patients with functional uterine bleeding, and the restoration of normal ovulatory cycles by small doses of glucocorticoids suggests that the

excessive estrogen either was being produced by the adrenals or was under ACTH control.

Two reports may be pertinent relative to the etiology of this type of hormonal disorder. Herrenkohl[19] has noted that prenatal stress of mother rats resulted in reduced fertility in their female offspring, with fewer conceptions, more spontaneous abortions and vaginal hemorrhages, longer pregnancies, lower birth weight, and fewer newborns likely to survive the neonatal period. Gupta et al.[20] reported that phenobarbital administration to pregnant rats also produced detrimental effects on reproductive function in their offspring, including delays in the onset of puberty, disorders in the estrous cycle, and infertility, associated with altered concentrations of sex steroids, gonadotrophic hormones, and estrogen receptors.

Other recent studies have brought to light another type of abnormality that can cause clinical disorders that might improve with physiologic dosages of glucocorticoid, namely, autoimmune phenomena. Because ovarian hormones as well as adrenocortical hormones are steroids, they do not stimulate the production of antibodies, but steroid hormone receptors are protein molecules and, hence, can stimulate antibodies that could interfere with normal estrogen effect. Such cases might have normal or elevated plasma estrogen levels, normal or slightly high plasma FSH, and amenorrhea or irregular menses. Breast development might also be poor. Ovarian dysfunction associated with severe insulin resistance has been described as the "Type A Syndrome,"[21] so it seems likely that ovarian dysfunction could occur as an autoimmune disorder without insulin resistance. If such occurs, the beneficial effect of glucocorticoids in autoimmune disorders, even in subreplacement dosages (Chapters 6, 7 and 8), might account for favorable therapeutic responses.

Once the disturbed ovarian function has been corrected, the remission may be maintained in some cases after the glucocorticoid has been discontinued, but most women seem to need to continue the treatment indefinitely to maintain normal ovarian function. We have not been able to follow a sufficient number of daughters of patients with ovarian dysfunction into adolescence to determine whether they can inherit this type of disorder, but there is considerable evidence from patient histories that this clinical problem does tend to be inherited.

It should be remembered that amenorrhea may be caused by other disorders such as hypopituitarism, prolactin-producing tumors of the

pituitary, hypothyroidism, and primary ovarian deficiency, as well as by congenital defects in genital development, and that irregular menses can result from relative ovarian deficiency, but the majority of women with irregular menses, secondary amenorrhea, functional uterine bleeding, and luteal phase disorders will benefit from low dosage glucocorticoid therapy, and associated infertility, if present, will often be corrected.[14]

In the field of ovarian dysfunction, some confusion has arisen in the use of the term Stein-Leventhal syndrome. This syndrome as originally described[22] included not only ovarian dysfunction and androgenic changes but also bilateral polycystic enlargement of the ovaries. It has been found to be associated with an abnormality of steroid metabolism in the ovaries, but in our experience, such patients usually require small doses of cortisone acetate or cortisol in addition to small doses of estrogen to have a restoration of normal menstrual cycles and fertility. This syndrome, therefore, results from a more severe degree of steroid abnormality than is encountered in the majority of women with ovarian dysfunction and androgenic changes, so it does not seem wise to apply the term Stein-Leventhal syndrome to the milder, more common disorder. The tendency to apply the term loosely to all types of ovarian dysfunction is, therefore, misleading, and the diagnosis should be limited to those women who have not only ovarian dysfunction but also bilaterally enlarged polycystic ovaries.

Several case histories demonstrate the promising potential and safety of low dosage glucocorticoid therapy in ovarian dysfunction.

Case 1

The patient was a seventeen-year-old female referred for primary amenorrhea. She had experienced slight breast development for several years but no spontaneous menses. Premarin, 1.25 mg daily for three weeks, plus Provera, 10 mg daily for the last five days, cyclically, for four months, had produced withdrawal flow but no subsequent menses. Her general health and energy had been good. She had no acne or hirsutism, and temperature tolerance was normal. She had no history of serious illness and no allergies. Her younger sister, age fifteen, had the menarche at age fourteen, and her cycles were regular but with a prolonged flow of nine days. The patient's paternal aunt had had a goiter removed, and grandparents on both sides had senile type of diabetes mellitus.

Physical examination revealed a pleasant, attractive girl with a clear complexion. Height was 67½ inches, weight 119½ pounds, blood pressure 90/60, pulse 76 and regular. She shaved her thighs but otherwise had no excessive hair growth.

cycles after it was withdrawn, but patients frequently relapsed to metropathia within a few months. In this case, the normal plasma FSH with low total estrogens suggested the presence of estrogens that were not being measured in the assay. Cortisol therapy resulted in an increase in plasma estrogen level, consistent with an abnormality in steroid metabolism, but ovulation did not occur until she also received thyroid in a sufficient dosage, even though T_3 sponge uptake and T_4 had been normal prior to therapy. Patients with metropathia frequently require physiologic dosages of thyroid medication as well as cortisol or cortisone acetate, suggesting an associated mild thyroid deficiency even though T_3 sponge uptake and T_4 may be within normal limits. As stated previously, T_3 by RIA is a more sensitive indicator of thyroid function, but this test was not available at the time this patient was studied.

Case 6 is an example of ovarian and thyroid dysfunction with infertility.

Case 6

This twenty-five-year-old female was referred because of a thyroid disorder, irregular menses, and infertility. The menarche had occurred at age eleven, and cycles had always been irregular with intervals of four to six weeks, menses lasting three to five days with cramps. She had experienced acne since the menarche, and hirsutism for the previous two years. She was married at age twenty, took an oral contraceptive from age twenty to age twenty-three, and had used no precautions for eighteen months prior to her visit. After stopping the oral contraceptive, she developed abdominal pain and had a laparotomy for a "pseudocyst" of the ovary. When she failed to conceive, she received a bilateral wedge resection for sclerocystic ovaries six months prior to her referral. Meanwhile, she had been given injections of a progestational agent to try to correct her ovarian function. After the wedge resection, she had two menses a month apart, then cycles became irregular again. Her energy had been poor for about five years, she was sensitive to cold and had a tendency to constipation. She had experienced frequent palpitations and tremor in the previous year. Her brother was married and had two children. Her mother had ovarian dysfunction and had had difficulty in conceiving.

Physical examination revealed a height of 67 inches, weight 137-1/2 pounds, blood pressure 124/80, pulse 96 and regular. There was mild acne of the chin and mild periareolar hair. The thyroid was two-and-one-half times normal size, rather firm, with no lymphadenopathy. Breasts were hypoplastic, but within lower limits of normal and contained no masses. Heart, lungs, and abdomen were normal except for laparotomy scars. Reflexes were equal and hyperactive. T_3 sponge uptake was 52%, T_4 was 6.2 mcg%, thyroid antibodies were negative, total estrogen was 47 pg/ml (normal 100–200), plasma cortisol at 4 PM was 14.0,

and thirty minutes after an I.M. injection of 25 units of Cortrosyn, this rose to 39.3 mcg%.

She was given Euthroid, gr 1 daily, and Cortef, 5 mg four times daily. A month later her thyroid had returned to normal size and her menstrual cycles became more regular with evidence of ovulation on the twelfth to fourteenth days of twenty-five to twenty-eight day cycles, but she failed to conceive.

Plasma estrogen was 133 pg/ml. Premarin, 0.3 mg daily except during menses, was added to her regimen and she conceived in the second cycle after this program was started. After conception, T_3 sponge uptake was 38%, and T_4 was 8.1 mcg%, but her thyroid began to enlarge, so the dosage of Euthroid was increased to gr 1 twice a day, Cortef being continued at 5 mg four times daily. She had a full term, normal delivery and nursed her baby for a month.

Because her tubes reportedly showed considerable scarring, her obstetrician advised another pregnancy as soon as possible. After delivery she resumed Cortef, 5 mg four times daily, and Euthroid, gr 1 daily. The Premarin had been discontinued as soon as her pregnancy had been diagnosed, and this was not resumed. She had two normal cycles and then conceived again. Euthroid was again increased to gr 1 twice daily, the continued at 5 mg four times daily, and she delivered a normal female infant by breech three weeks early. She did not nurse this baby, and menses resumed normally.

This patient was an example of the Stein-Leventhal syndrome with only transient improvement following wedge resection. She also had a nontoxic goiter with a normal T_3 sponge uptake and T_4. Plasma estrogen was low, but plasma FSH was in the low normal range, suggesting that she was either producing an estrogen that was not being measured or that pituitary function was mildly impaired. On a combination of Euthroid and Cortef, she resumed regular menstrual cycles, and her thyroid returned to normal size, but she failed to conceive until a small dose of estrogen was added. She had a second pregnancy on Cortef and Euthroid, but without estrogen. This case typifies the necessity of having not only ovarian but also adrenal and thyroid function normal before conception can occur.

Although the pathologic cause of the Stein-Leventhal syndrome (polycystic ovary syndrome) has not yet been completely clarified, a recent review by Ehrmann et al.[23] summarizes the present status of the problem. On the basis of our experience, it appears to be associated with abnormal function of the adrenals, the ovaries, and at least sometimes also the thyroid, and often may be corrected by administration of a proper combination of small, physiologic dosages of cortisol, estrogen and thyroid, as occurred in this case.