Therapeutic Uses of Contraceptive Steroids

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During the past 20 years, contraceptive steroids have undergone significant changes as the result of an increased understanding of their metabolic, pharmacologic, and hormonal activities. During this time, prospective and retrospective epidemiologic studies have elucidated several noncontraceptive health benefits of oral contraceptive steroids, including their therapeutic effects for endometriosis, dysmenorrhea, polycystic ovarian disease, and benign breast disease. From this review it appears that the benefits of oral contraceptive steroids in young, healthy, nonsmoking women far outweigh their more publicized, infrequent risks.

The uses of contraceptive steroids have undergone a vast evolution during the past 20 years.[1] In general, some of the major changes are (1) elimination of sequential steroid agents (secondary to increased endometrial cancer), (2) introduction and increased usage of low-dose (less than 50 μg) contraceptive steroids, (3) a significantly decreased usage of high-dose steroid agents (80 μg estrogen components or greater), (4) a refinement of dosage combinations (lower estrogen-progestin combinations: Ortho Novum 1/35, Lo-Ovral) with fewer major and minor side effects, and (5) the introduction of biphasic and triphasic oral contraceptive steroids.

During this 20-year period, the metabolic, pharmacologic, and contraceptive properties of these steroids have been extensively studied with further delineation of their risks as well as their significant benefits.[2,3] Most physicians are quite familiar with the voluminous literature concerning the major and minor side effects as well as the relative and absolute contraindications of oral contraceptive steroids.[2,3]

Steroid contraceptive agents have been successfully used therapeutically and diagnostically in the treatment of many gynecological problems. It is now generally accepted that their major mode of action is exerted at the hypothalamic-pituitary-ovarian and uterine sites, thus making them suitable for treatment of many abnormal states related to these areas. In addition, because of their varying dosage combinations (estrogen and progestin), their versatility and therapeutic applications are increased.

This paper will focus on the therapeutic (noncontraceptive) uses and benefits of combination oral contraceptive steroids with special emphasis on their clinical application.

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Endometriosis

Endometriosis has been found to vary from 5 to 28 percent for menstruating women,[2] but it is

impossible to assess accurately the true incidence. Recent reports indicate a hereditary tendency toward initiation and propagation of this disease in certain families.[3] It is likely, however, that endometriosis may be caused by more than one histogenetic mechanism, particularly in women with an inherited propensity to develop the disease during their menstrual years.

For the clinician the major problems concerning endometriosis relate to establishing the diagnosis and choosing suitable treatment for the individual patient. Clinically the symptom complex of progressively severe dysmenorrhea, dyspareunia, painful defecation, chronic, progressive pelvic pain, and menstrual irregularity should alert the physician to the possibility of endometriosis.

Following the diagnostic verification of endometriosis, several factors become important in determining the appropriate therapeutic approach: infertility, desire for retention of reproductive capability, and completion of childbearing.

When infertility exists secondary to endometriosis, Kistner,[4,5] Grant,[5] and others have recommended the use of oral contraceptive steroids for hormonal suppression (medical therapy). If mild disease (Kistner classification) is present, four to six months of chronic suppression is recommended, followed by cyclic therapy thereafter. If moderate or severe disease is found, however, preoperative therapy (four to eight weeks) using oral contraceptive steroids is advised.[4,5] Findings suggest that softening of the endometriotic implants occurs, lesions are easier to identify, implants are simpler to excise, and surgical planes are easier to define and dissect.

In the second group of patients (retention of reproductive capabilities), medical therapy using oral contraceptive steroids has been shown to be efficacious by multiple investigators.[6,7] This "pseudopregnancy" therapy is effective because of the multisystem actions of these steroids. They exert their effects peripherally, as well as centrally, to diminish menstrual flow, decrease proliferation and bleeding of ectopic endometrium, promote atrophy and necrosis of implants, prevent new implant formation, suppress ovarian steroidogenesis, decrease prostaglandin production and secretion, and suppress hypothalamic pituitary function, ie, luteinizing hormone and follicle-stimulating hormone.

Kistner observed that once contraceptive steroid therapy had been initiated, it had to be continued for a minimum of six months to realize any significant gain.[4,5,7] He found that during the first three months of therapy there was extensive edema of the endometriotic stroma, followed in the fourth month by necrosis and fibrosis, and ultimately in the sixth month by scarring and resorption.[8] Similarly, Andrews,[9] Reva et al,[10] and Chalmers[11] demonstrated progressive morphologic changes in uterine and ectopic endometrium following pseudopregnancy.

Currently there are three recommended regimens for treatment with oral steroid contraceptive agents: continuous suppression for 6 to 12 months, continuous suppression for six months followed by cyclic therapy, and long-term cyclic suppression for 12 to 24 months.[12] The preferred regimen for the patient not immediately desirous of pregnancy is chronic suppression (noncyclic) for six to nine months with a low-dose contraceptive agent, followed by cyclic therapy until pregnancy is desired.[5] A subsequent pregnancy rate of 40 to 50 percent can be anticipated upon termination of pseudopregnancy therapy.[5,6]

For the patient who has completed her reproductive function, additional hormonal suppression may be needed if residual endometriosis remains following a hysterectomy and bilateral salpingo-oophorectomy. In this instance, an oral contraceptive steroid for 9 to 12 months may suppress the remaining implants as well as provide estrogenic replacement for the prematurely castrated patient.[6] In general, through the use of contraceptive steroids in the treatment of endometriosis, symptomatic relief may be expected in 47 to 83 percent, fertility restoration in 40 to 72 percent, and a clinical recurrence following oral contraceptive steroid therapy in 11 to 35 percent.[6,13]

Dysmenorrhea

Dysmenorrhea causes 140 million lost work hours annually and afflicts nearly 50 percent of young female adults, particularly nulliparous women.[14] This chronic disease state has been divided into primary and secondary types, depending on the presence or absence of pelvic pathology, with primary dysmenorrhea being the most common.

Until recently the etiology of dysmenorrhea was poorly understood, and there was no effective and specific treatment for this common gynecologic disorder. However, Pickles et al[15] and other investigators[16] over the past several years have conclusively shown that prostaglandin levels ($F_2\alpha$, E_2) are elevated in young women with dysmenorrhea.

In reviewing the pathophysiology of dysmenorrhea, progesterone levels and prostaglandin synthesis and secretion appear to be primary in the mediation of uterine ischemia and pain. Newer data suggest that when progesterone levels are low or rapidly decrease at the end of the cycle, calcium is released from its binding on the myometrial cell membrane, activating the actomyocin-adenosine triphosphate interaction, ultimately causing a contraction.[17] In addition, prostaglandin synthesis and secretion is initiated by lysosomal enzymes (acid phosphatase) released at the end of the menstrual cycle. The lytic action of these enzymes results in the release of phospholipids, which provide the precursor arachidonic acid and other unsaturated fatty acids for prostaglandin synthesis.[18] Thereafter, elevated prostaglandins ultimately lead to increased myometrial contractions, spiral, and myometrial vessel constriction with consequent tissue ischemia, endometrial disintegration, bleeding, and pain. Secondary symptoms of nausea, vomiting, headaches, and diarrhea can also be attributed to the absorption of prostaglandins or their metabolites (thromboxanes) into the systemic circulation. It appears that ischemic uterine contractions (dysmenorrhea) may be caused by a combination of these two mechanisms, ie, low progesterone level, and high local levels of prostaglandins.[19]

Treatment for patients with dysmenorrhea should attempt to prevent uterine ischemia through decreasing prostaglandin production and secretion or increasing progesterone levels. The appropriate therapy should be chosen according to the patient's severity of symptoms, desire for contraception, and existence of concurrent medical disease.

In general, contraceptive steroids provide symptomatic relief in 90 percent of primary dysmenorrheic patients with the added benefits of less bleeding and fewer pregnancies.[20,21] Data from Halbert indicate that other considerations for the use of oral contraceptive steroids in primary dysmenorrhea are failure of prostaglandin agents to control pain, inability to tolerate antiprostaglandin agents, and a need for contraception in addition to pain relief.[22] Halbert concluded that the therapeutic efficacy of oral contraceptive steroids in primary dysmenorrhea can be attributed to their multisystem biochemical actions.

Hirsutism

Hirsutism usually represents excess androgen production, of either ovarian or adrenal origin, associated with a state of chronic anovulation. This hormonal imbalance usually manifests itself through the growth of hair on the midline areas of the body (ie, the lips, chin, chest, and abdomen)[23] involving principally the sexual or hormone-dependent hair follicles. There are multiple causes of hirsutism, with the major categories consisting of intrinsic factors, extrinsic factors, and endocrinologic disorders. Women with simple hirsutism constitute the largest population of hirsute women; however, 40 percent of hirsute patients have polycystic ovarian disease.[24]

A rational approach to the management of hirsutism requires an understanding of the physiology of hair growth. Androgen production, predominantly testosterone and androstenedione, contributes to this pathologic process, either directly (testosterone---->dihydrotestosterone) or indirectly (androstenedione---->estrogen) with an abnormal hypothalamic-pituitary feedback leading to a chronically elevated luteinizing hormone and its sequelae.[25] Androgen excess also disturbs folliculogenesis and the intraovarian milieu, leading to poor follicle development and a state of chronic anovulation.

Clearly the major principle of treatment is to reduce androgen excess and correct the state of chronic anovulation. Despite this goal, all current treatment modalities for hirsutism are more likely to attenuate, rather than eradicate, the problem. Nevertheless, oral contraceptive steroids are quite effective in the therapy of hirsutism and have been used extensively with good results.[26,27] Their effectiveness is due to their multisystem actions, including decreasing tonic secretion of pituitary luteinizing hormone and thereby reducing andro-

gen production and secretion, decreasing testosterone production and secretion from the ovarian stroma, enhancing production of hepatic sex-hormone–binding globulin, thereby increasing testosterone binding (decreasing unbound-free testosterone), and increasing binding and reducing testosterone clearance, thereby counteracting androgenic effects at the hair follicle.

Presumably oral contraceptive steroids decrease ovarian androgen secretion by suppressing luteinizing hormone and may also decrease adrenal secretion of dehydroepiandrosterone sulfate.[28] It is important to use a combination that will effectively lower total peripheral androgen levels. In most reported series, the combinations of 1 mg of norethindrone and 50 μg of ethinyl estradiol or 1 mg of ethynodiol diacetate and 50 μg of mestranol are effective.[27]

The available data suggest that therapy should begin with formulations (less than 50 μg) of the lower estrogen-progestin combinations, which can increase sex-hormone–binding globulin while lowering total testosterone. The total androgen levels, sex-hormone–binding globulin, and clinical response should be monitored at 6- to 12-week intervals. If the response is unsatisfactory after this period of oral contraceptive steroid administration, formulations containing higher amounts of estrogen-progestin combinations may be used. Ideally, the treatment should reduce the increased androgen levels to normal. Failure to do so implies either inadequate ovarian suppression or the presence of adrenal androgen excess.

Once oral contraceptive steroid therapy is instituted, testosterone values show a decrease within one to three months of treatment, with a latency period of ten days before a suppressive effect is actually observed. A 50 percent reduction of androstenedione and testosterone is achieved at the end of four to six weeks of therapy. Nevertheless, if therapy is discontinued after a prolonged period of treatment, a slow but definite return of the hormone pattern to the pretreatment level is found, indicating the basic endocrine disturbance persists.

Polycystic Ovarian Disease

Polycystic ovarian disease is characterized by menstrual irregularity (47 percent), dysfunctional uterine bleeding (21 percent), obesity (33 percent), infertility (75 percent), and occasionally hirsutism (33 percent).[29,30] Clinically, bilateral enlargement of the ovaries may be found; however, their presence does not characterize the disease.

At present, no known single etiologic mechanism can fully explain the variety of biochemical changes that are associated with polycystic ovarian disease. The syndrome is associated with a disturbance in the hypothalamic-pituitary-ovarian axis as well as with changes in ovarian steroidogenesis. The hormone profile of patients with polycystic ovarian disease varies from (1) tonically elevated levels of luteinizing hormone, (2) low levels of follicle-stimulating hormone, (3) increased levels of serum testosterone, androstenedione, dehydroepiandrosterone sulfate, and estrone, and (4) normal estradiol levels, to that of (5) low levels of luteinizing hormone and follicle-stimulating hormone and small ovaries.[31-33] Undoubtedly there is a spectrum of time involved in the development of this clinical syndrome, and it is useful to view the attainment of high luteinizing hormone levels and large ovaries as a stage of maximal effect of persistent anovulation. The polycystic ovary may be associated with a variety of disorders in the hypothalamic-pituitary-ovarian axis as well as extragonadal sources of androgens.

All successful therapeutic modalities for polycystic ovarian disease should eliminate the persistent acyclic estrogen overproduction, counteract its mutagenic effect on the endometrium, decrease the steroid substrate (precursors) for peripheral conversion, enhance hepatic protein production for increased hormone binding, and ultimately reduce the tonically elevated luteinizing hormone level.

Therapy has to be directed at the individual patient's needs and long-term goals. If pregnancy is desired, clomiphene citrate (Clomid) is the preferred therapy of choice. When pregnancy is not a consideration, oral contraceptive steroids meet the therapeutic goals through several mechanisms that disrupt the vicious circle of endocrine dysfunction. In general, oral contraceptive steroids act centrally as well as peripherally to suppress gonadotropin secretion, decrease stromal androgens and precursors for peripheral conversion, and prevent endometrial hyperplasia or neoplasia through a progestin-dominated estrogen progestin substitution.

Givens et al[33] have shown that luteinizing hormone and testosterone levels can be reduced considerably in less than one week after the initiation of oral contraceptive steroid therapy. This treatment has been found to be effective in 85 to 90 percent of patients with the label of polycystic ovarian disease, unless there is a significant adrenal component, thereby precluding oral contraceptive steroids as the only therapy necessary.

The low-dose steroid formulations (less than 50 μg) have been shown to be efficacious in the therapy of polycystic ovarian disease, even though there is less total gonadotropin suppression. The vast majority of these combination steroids are progestin dominant, and care must be taken in selecting a contraceptive steroid if other clinical problems exist (eg, hirsutism, obesity). Nevertheless, therapy can be instituted with a low-dose contraceptive steroid, and the estrogen-progestin components can be manipulated as clinically indicated.

Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding may occur in anovulatory cycles but is more common in association with absent ovulation and progesterone production. Etiologically, the pathophysiology of dysfunctional uterine bleeding is usually defined by high, sustained levels of unopposed estrogen, postpubertal hypothalamic-pituitary-ovarian axis dysfunction, perimenopausal anovulation secondary to ovarian unresponsiveness, and obesity. Fraser and associates[34] substantiated these data by reporting that the blood concentrations of circulating estrone and estradiol were in the normal range; however, the normal positive feedback effect on the induction of the luteinizing hormone surge was absent, and consequently, ovulation failed to occur.

The mechanism or mechanisms by which the bleeding from the endometrium occurs are not entirely clear. In most instances inappropriate estrogen levels or estrogen-progesterone ratios appear to contribute to the three dysfunctional patterns of bleeding presently identified: estrogen withdrawal bleeding, estrogen breakthrough bleeding, and progesterone breakthrough bleeding. In these circumstances the usual endometrial control mechanisms are missing; therefore, the abnormal bleeding that subsequently arises involves random portions of the endometrium at variable times and in asynchronous sequences.

Medical therapy should be the primary approach in the vast majority of dysfunctional uterine bleeding patients. Although a variety of medications have been employed in treating women with dysfunctional uterine bleeding, oral contraceptive steroids readily restore synchronous endometrial shedding, structural stability, and vasomotor rhythmicity. These estrogen-progestin combinations induce the structural rigidity intrinsic in the pseudodecidual reaction, inhibit further bleeding, prevent unopposed estrogen stimulation in subsequent cycles, and ultimately allow orderly regression of excessive endometrial height to normal controllable levels.[35,36]

It is advisable that during the initial phase of therapy, a 50 μg (estrogen) formulation be used for approximately three cycles. Thereafter, once control of the abnormal bleeding state has been achieved, a low-dose (less than 50 μg) oral contraceptive steroid is quite efficacious in long-term therapy of these women, thereby reducing the sequelae of hyperplasia, neoplasia, and anemia.

Dysfunctional uterine bleeding is not a specific diagnosis, but encompasses a spectrum of endocrinologic dysfunction. Therapy must be individualized; however, an estrogen-progestin combination is the usual recommended treatment.

Benign Breast Disease

It has been estimated that 20 to 25 percent of women experience significant problems with benign breast disease. These benign conditions are known by a variety of names: fibrocystic disease, cystic breast, breast dysplasia, and cyclic breast pain, to mention several. The etiology of these conditions is probably related, at least in part, to an alteration of the body's response to normal cyclic hormonal changes during the menstrual cycle. These changes frequently produce an increase in the production of fibrous tissue in the breast, thus leading to symptoms of pain, particularly in the premenstrual period. Fibrocystic disease is the most common of the benign breast disease group; nevertheless, the vast majority of patients with cyclic breast pain or nodularity will not have de-

finable breast disease at the time of ovulation.[37,38]

Clinically, benign breast disease has been treated with a host of agents including progestins, androgens, diuretics, bromocriptine, danazol, and oral contraceptive steroids.[39,40] In those cases where the nodularity and pain cannot be controlled by supportive measures, oral contraceptive steroids have proven efficacious in providing excellent relief.[41] The therapeutic improvement of this clinical condition by oral contraceptive agents involves prevention of cyclic stimulation of breast tissue, constancy of circulating sex steroids, reduction of sex steroids for tissue binding (ie, fewer receptors), elevation of sex-hormone–binding globulin with less free estrogen, decrease in cyst formation and nodularity, and a decrease in ductal ectasia.

Studies by Vessey and associates[42] found that women aged 40 years and under sustained a protective effect through the use of oral contraceptive steroids if they continued their usage for two years or more. Their data reflect that the chance that such women would be admitted to the hospital for a breast biopsy was 25 percent less than that of nonusers of contraceptive steroids.[43] Overall, the protective effect seemed to apply to both fibroadenomas and chronic cystic disease of the breast. These findings have been demonstrated in three prospective and eight retrospective studies.[43]

In general, oral contraceptive steroids have been efficacious in the treatment of many benign breast conditions including cyclic breast pain and nodularity, and through their continued use, a cause-and-effect association with breast cancer has not been found.

Ovarian Cyst Suppression

Benign ovarian cysts are commonly classified as either nonneoplastic or epithelial in origin. Nonneoplastic cysts may be functional in character responding to circulating estrogens and gonadotropins, and perhaps the cyst formation may be the result of a hypothalamic-pituitary dysfunction with an abnormal process of cyclical follicular maturation and corpus luteum formation.[44]

The most common type of functional cyst (follicle cyst) is usually small and asymptomatic. Functional cysts usually undergo spontaneous resorption and for the most part remain undiagnosed. Occasionally, such cysts become large enough, based on a number of pathologic causes, to produce pain and discomfort. Such functional cysts are capable of producing elevated levels of estrogen or progesterone, thereby leading to menstrual abnormalities, including menorrhagia and dysfunctional uterine bleeding.

Polycystic ovarian disease is a related disease process contributing to the formation of multiple ovarian cysts. The mechanism here has been well delineated as hypothalamic-pituitary-ovarian in origin with luteinizing hormone being the primary mediator in cyst formation.

Oral contraceptive steroids have been used as the first line of medical therapy in women aged less than 35 years with functional ovarian cysts. The proposed mechanism of action for cyst regression is by means of gonadotropin suppression at the level of the hypothalamic-pituitary axis, leading to decreased receptor formation and binding as well as decreased ovarian estrogen and progesterone production.[45] These findings have been confirmed in three large prospective studies and one large population-based case series.[46] As reported by multiple investigators, the combination steroid agents prevent ovulation by inhibition of gonadotropin secretion, exerting their principal effect on hypothalamic-pituitary centers. The progestational agent suppresses luteinizing hormone secretion by a negative feedback action on the hypothalamus with the estrogenic component suppressing follicle-stimulating hormone secretion in a similar fashion; this in turn leads to ovulation and ovarian steroid suppression. Because oral contraceptive steroids suppress cyclical ovarian activity, their use prevents an estimated 3,000 surgical procedures for ovarian cyst each year among users.[46] Ovaries surgically removed while under the suppressive effects of contraceptive steroids grossly appear to be inactive. Ovarian sections revealed an early arrest of follicular development. These ovaries were devoid of corpora lutea and larger follicles and overall gave a compact histologic appearance. Therefore, young women with recurrent or persistent ovarian follicular cysts are good candidates for medical intervention using contraceptive steroids rather than a primary surgical approach. Through the mechanism of decreased gonadotropin production and ovulation inhibition, the ovary is allowed to as-

sume a state of quiescence, thereby allowing cyst regression and ultimately atresia. The efficacy of this conservative approach has been corroborated by multiple authors using various combination contraceptive steroids.[45,46]

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