Clinical Gynecologic Endocrinology and Infertility

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Preface

With very few exceptions, physicians feel uncomfortable when confronted with endocrine problems. This uneasiness reflects both deficiencies in knowledge and lack of a systematic approach to these clinical situations. Some physicians attempt to overcome this difficulty by mastering a ritualistic series of steps to follow for each presenting symptom. The rigidity of such an empiric approach leaves the physician ill-prepared to deal with the specific needs of the individual patient. One result is the overuse of laboratory tests, such as 17-ketosteroid determinations and skull x-rays, with no real benefit to the patient.

This book is directed to relieving these shortcomings by providing both factual knowledge and systematic approaches to clinical problems. The text is an expression of our collective professional activities as teachers, investigators, and most importantly, as clinicians in the field of female endocrinology. Because it is based on clinical experience, the book should be useful not only to the specialist in gynecology, but to all physicians (current and future) who practice medicine and are therefore responsible for the care of women.

Our objectives in offering this text are twofold: first, we hope to transmit our conviction that the field of reproductive endocrinology has matured beyond a mystifying catalogue of clinical and research observations on the performance of an organ system. It has become a clinical science which, despite its complexity, possesses a logical orderliness based on physiology. Second, we have tried to avoid the pitfall of being encyclopedic, a style which burdens rather than informs. The book is not intended to be a reference work, but rather a formulation of clinical diagnosis and management founded on physiologic principles. Our approach has survived the most rigorous proof of validity—clinical success.

If we have attained our goals, then the reader will emerge a more confident and competent physician when dealing with female endocrine problems.

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Chapter 1

Hormone Biosynthesis, Metabolism, and Mechanism of Action

To lead off a clinical book with a chapter on biochemistry only serves to emphasize that competent clinical judgment is founded upon a groundwork of basic knowledge. On the other hand, clinical practice does not require a technical and sophisticated proficiency in a basic science. *The purpose of this chapter is not therefore to present an intensive course in biochemistry, but rather to present a selective review of the most important principles of how hormones are formed and metabolized, and how hormones work.* This information is essential for the development of the physiologic concepts to follow, and it is intended that certain details which we all have difficulty remembering will be available in this chapter for reference.

The classical definition of a hormone is a substance which travels from a special tissue where it is released into the bloodstream to distant responsive cells where the hormone exerts its characteristic effect. What was once thought of as a simple voyage is now becoming appreciated as an odyssey which daily becomes more complex as new facets of the journey are unraveled in research laboratories throughout the world. Let us follow an estradiol molecule throughout its career, and in so doing gain an overview of how hormones are formed, how hormones work, and how hormones are metabolized. After this survey, each subject will be considered in detail.

Estradiol begins its lifespan with its synthesis in a specialized cell suited for this task. For this biosynthesis to take place, the proper enzyme capability must be present along with the proper precursors. In the human female the principal sources of estradiol are the theca cells of the developing follicle and the granulosa cells of the corpus luteum. These cells possess the unique ability to respond to a specific stimulus with estradiol production. This stimulus is the gonadotropin, luteinizing hormone (LH). Therefore, an initial step in the process which will give rise to estradiol is the transmission of the message from the stimulating agent, LH, to the steroid-producing mechanism within the cell.

The basic message to stimulate estradiol production must be transmitted through the cell membrane. LH, being a large glycopeptide structure, does not enter the cell, but communicates with the cell by joining with a specific receptor on the cell membrane and in so doing activates a line of communication. A considerable amount of investigation has been devoted to determining the methods by which this communication takes place. E. M. Sutherland received the Nobel Prize in 1971 for proposing the concept of a second messenger.

LH, the first messenger, activates an enzyme in the cell membrane called adenyl cyclase. This enzyme transmits the message by catalyzing the production of a second messenger within the cell, cyclic AMP. The message passes from LH to cyclic AMP, much like a baton in a relay race.

Cyclic AMP, the second messenger, in a still unknown way, initiates the process of steroidogenesis, leading to the synthesis and secretion of the hormone, estradiol. This process requires protein synthesis, and at least one rate-limiting step is the conversion of cholesterol to pregnenolone within the mitochondria.

Secretion of estradiol into the bloodstream seems to be a function of its synthesis. Stimulation of biosynthesis results in estradiol secretion. Once in the bloodstream, estradiol does not necessarily exist in a free-floating state, but a majority (80%) of the hormone is bound to a protein carrier, chiefly a beta globulin. The purpose of this binding is not totally clear. The biologic activity of a hormone may be limited by binding in the blood, and potent changes may thus be avoided. In addition, binding may prevent rapid metabolism, allowing the hormone to exist for the length of time necessary to ensure a biologic effect. It is unlikely that specific transportation to a specific site is a function of this binding since distribution of the hormone in the bloodstream is probably homogeneous.

The biologic and metabolic effects of a hormone are determined by a responsive cell's ability to receive and retain a hormone. The estradiol which is not bound to a protein, but floating free in the bloodstream, readily enters cells by rapid diffusion. However, for estradiol to produce its effect, it must be grasped by a receptor within the cell. Thus, only those cells which contain estradiol-specific receptors will respond to estradiol. The job of the receptor is then to transport the hormone to the nucleus, resulting in transmission of the hormone's message to the nuclear chromatin. The result is production of messenger RNA leading to protein synthesis and a cellular response characteristic of the hormone.

Now that estradiol has accomplished its mission, it is probably released back into the bloodstream. In the bloodstream it is possible that estradiol may perform its duty several times before being cleared from the circulation by metabolism. On the other hand, many molecules will be metabolized without ever having the chance of producing an effect. Other hormones, such as testosterone, are metabolized and altered within the cell in which an effect has been produced. In the latter case, a steroid which is then released into the bloodstream is an inactive compound. Clearance of steroids from the blood varies according to the structure of the molecule.

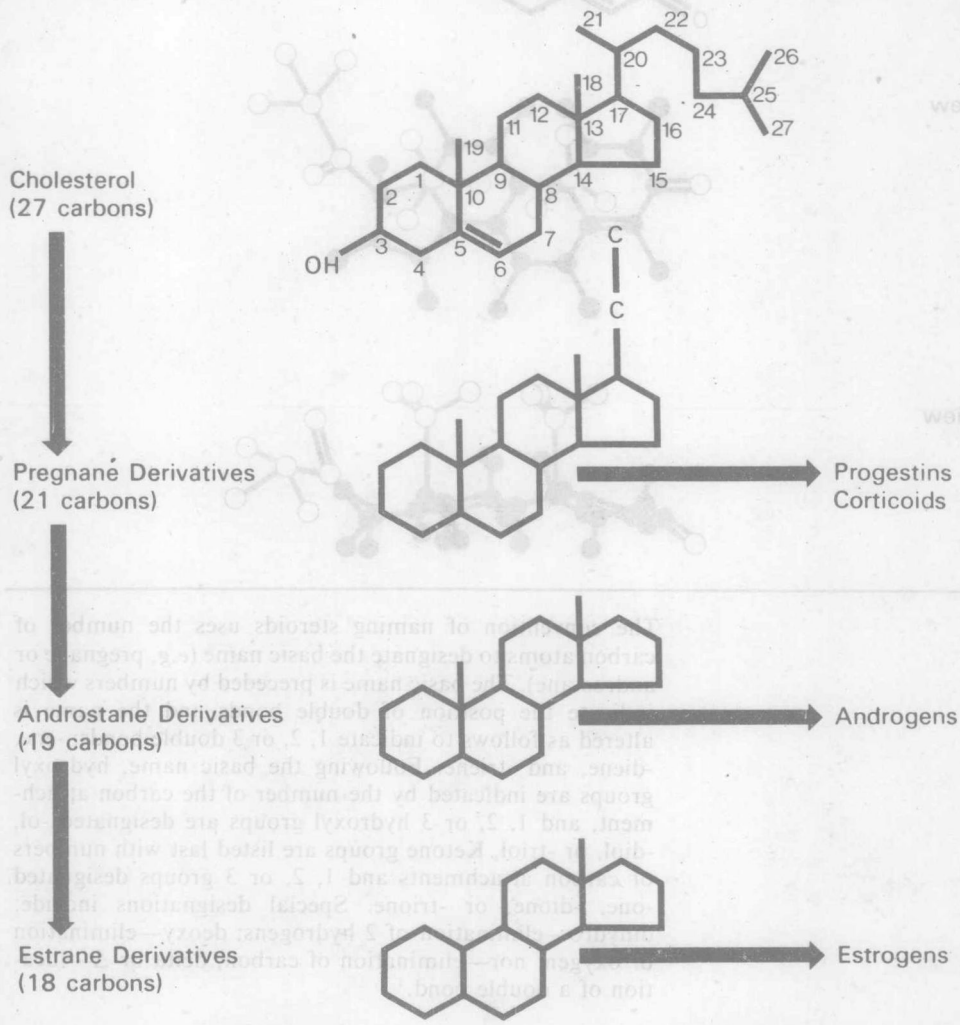
Cells which are capable of clearing estradiol from the circulation accomplish this by biochemical means (conversion to estrone and estriol, moderately effective and very weak estrogens, respectively) and conjugation to products which are water-soluble and excreted in the urine and bile (sulfo- and glucuro-conjugates).

Thus, a steroid hormone has a varied career packed into a short lifetime, and it is now appropriate to review the important segments of this lifespan in greater detail.

Nomenclature

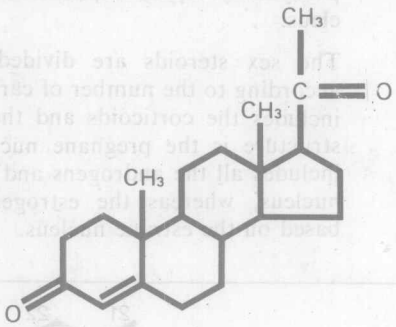
All steroid hormones are of basically similar structure with relatively minor chemical differences leading to striking alterations in biologic activity. The basic structure is the perhydrocyclopentanephenanthrene ring. One ring is benzene, two rings naphthalene, and three rings phenanthrene; add a cyclopentane (5-carbon ring) and you have the perhydrocyclopentanephenanthrene ring or the steroid nucleus.

The sex steroids are divided into three main groups according to the number of carbon atoms. The C-21 series includes the corticoids and the progestins and the basic structure is the pregnane nucleus. The 19-carbon series includes all the androgens and is based on the androstane nucleus, whereas the estrogens are 18-carbon steroids based on the estrane nucleus.

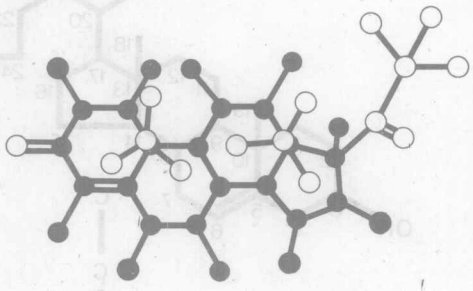


There are six centers of asymmetry on the basic ring structure, and there are 64 possible isomers. Almost all naturally occurring and active steroids are nearly flat, and substituents below and above the plane of the ring are designated alpha (dotted line) and beta (solid line), respectively. Changes in the position of only one substituent may lead to inactive isomers. For example, 17-epitestosterone is considerably weaker than testosterone, the only difference being a hydroxyl group in the alpha position at C-17 rather than in the beta position.

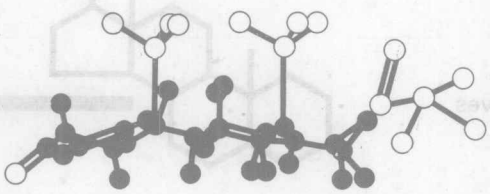
Progesterone



top view

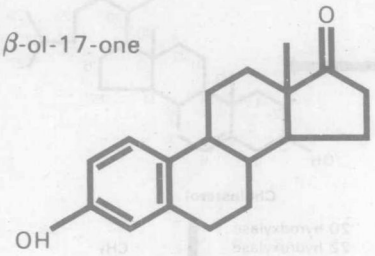


side view

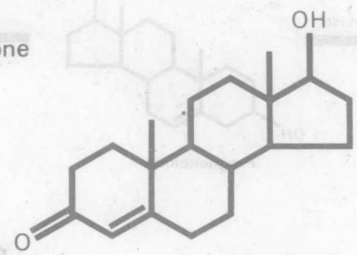


The convention of naming steroids uses the number of carbon atoms to designate the basic name (*e.g.* pregnane or androstane). The basic name is preceded by numbers which indicate the position of double bonds and the name is altered as follows to indicate 1, 2, or 3 double bonds: -ene, -diene, and -triene. Following the basic name, hydroxyl groups are indicated by the number of the carbon attachment, and 1, 2, or 3 hydroxyl groups are designated -ol, -diol, or -triol. Ketone groups are listed last with numbers of carbon attachments and 1, 2, or 3 groups designated -one, -dione, or -trione. Special designations include: dihydro—elimination of 2 hydrogens; deoxy—elimination of oxygen; nor—elimination of carbon; delta or Δ—location of a double bond.

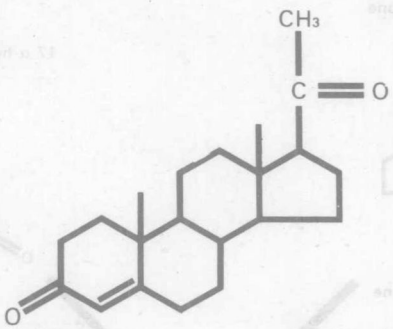
Estrone
1,3,5(10)-Estratriene-3β-ol-17-one



Testosterone
4-Androstene-17β-ol-3-one



Progesterone
4-pregnene-3,20-dione



Steroidogenesis

The overall steroid biosynthetic pathway shown in the figure is based primarily on the cumulative work of Ryan and his co-workers (1). These pathways follow the fundamental pattern displayed by all steroid-producing endocrine organs, and it should immediately be emphasized that the normal human ovary produces all three classes of sex steroids: estrogens, progestins, and androgens. The importance of the androgens has only recently been appreciated, not only as obligate precursors to estrogens, but also as clinically important secretory products. The ovary differs from the testis in its functional capacity of critical enzymes and, hence, its distribution of secretory products. The ovary is distinguished from the adrenal gland in that it appears to be deficient in 21-hydroxylase and 11 β-hydroxylase enzymes. Glucocorticoids and mineralocorticoids, therefore, are not produced in normal ovarian tissue.

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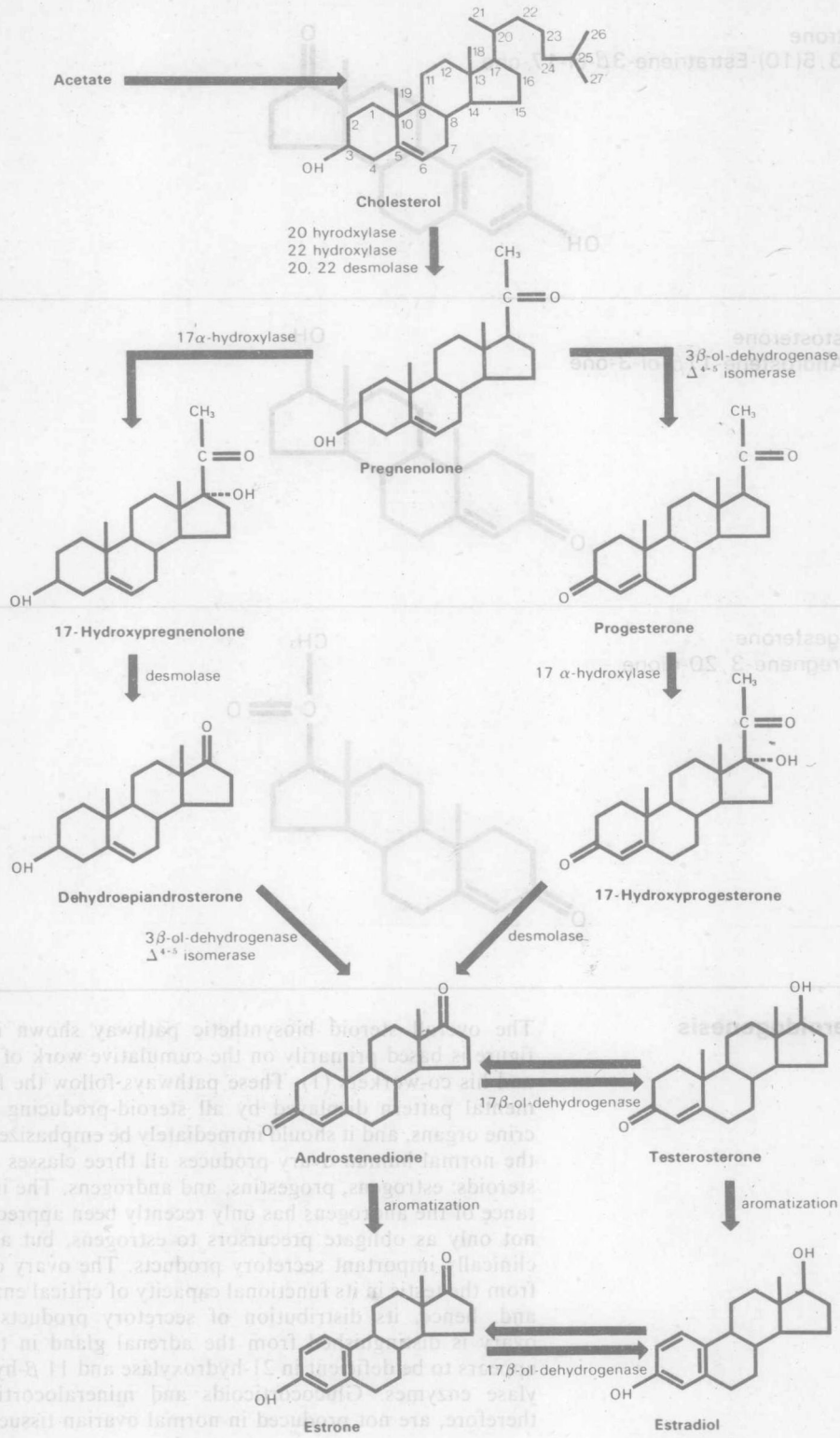

Acetate
Cholesterol
20 hyrodxylase
22 hydroxylase
20, 22 desmolase
17α-hydroxylase
3β-ol-dehydrogenase
Δ4-5 isomerase
Pregnenolone
17-Hydroxypregnenolone
Progesterone
desmolase
17 α-hydroxylase
Dehydroepiandrosterone
17-Hydroxyprogesterone
3β-ol-dehydrogenase
Δ4-5 isomerase
desmolase
17β-ol-dehydrogenase
Androstenedione
Testerosterone
aromatization
aromatization
17β-ol-dehydrogenase
Estrone
Estradiol

All steroid-producing organs except the placenta can synthesize cholesterol from acetate. Progestins, androgens, and estrogens, therefore, may be synthesized *in situ* from a 2-carbon molecule in the various ovarian tissue compartments via cholesterol as the common steroid precursor. An additional resource is blood cholesterol which enters the ovarian cells and can be inserted into the biosynthetic pathway or esterified and thus be available as a stored precursor. Cholesterol, therefore, is the basic building block in steroidogenesis.

Conversion of cholesterol to pregnenolone involves hydroxylation at the carbon 20 and 22 positions (20-hydroxylase and 22-hydroxylase enzymes), with subsequent cleavage of the side chain (20, 22 desmolase). The mitochondrial conversion of cholesterol to pregnenolone is a rate-limiting step in the steroid pathway, and is one of the principal effects of LH stimulation.

It is important to note that subsequent to pregnenolone, steroid synthesis in the ovary may proceed by one of two pathways: either via Δ^5-3β-hydroxyl steroids or via the Δ^4-3-ketone pathway, the first proceeding by way of pregnenolone and dehydroepiandrosterone (DHA) and the latter via progesterone and 17α-hydroxyprogesterone.

The conversion of pregnenolone to progesterone involves two enzyme steps: the 3β-hydroxysteroid dehydrogenase and Δ^{4-5} isomerase reactions which convert the 3β-hydroxyl group to a ketone and transfer the double bond from the 5-6 position to the 4-5 position. Once the Δ^4-3-ketone is formed, progesterone is hydroxylated at the 17α position to form 17α-hydroxyprogesterone, very recently shown to increase in the peripheral plasma at midcycle and during the luteal phase. 17 α-Hydroxyprogesterone is the immediate precursor of the C-19 (19 carbons) series of androgens in this pathway. By peroxide formation at C-20, followed by epoxidation of the C-17, C-20 carbons, the side chain is split off forming androstenedione. The 17-ketone may be reduced to a 17β-hydroxyl to form testosterone by 17β-hydroxysteroid dehydrogenase. Both C-19 steroids (androstenedione and testosterone) are rapidly converted to corresponding C-18 phenolic steroid estrogens (estrone and estradiol) by microsomal enzymes in a process referred to as aromatization. This process includes hydroxylation of the angular 19-methyl group, followed by oxidation, loss of the 19-carbon as formaldehyde, and ring A aromatization.

As an alternative, pregnenolone may be directly converted to the corresponding Δ^5-3β-hydroxy C-19 steroid, DHA, by 17α-hydroxylation followed by desmolase cleavage of the side chain. It is thought that conversion of each of the Δ^5 compounds to their corresponding Δ^4 compounds can occur at any step; however, the principal pathways are via progesterone and DHA. Regardless of the precursor source, C-19 Δ^4-3-ketone substrates proceed to estrogens as noted above.

The selection of pathways is not a chance event, but rather is governed by the cell type involved. Whereas the Δ^4-3-ketone pathway seems to be predominant in luteal tissue, the Δ^5-3β-hydroxy pathway is characteristic of nonluteinized tissue (2). Thus, the corpus luteum secretes mainly progesterone and estrogens via the Δ^4-3-ketone pathway, whereas in the follicle, 17-hydroxylation of pregnenolone is the primary reaction leading to the C-19 steroids, DHA and androstenedione, which act mainly as precursors for estrogens. In stromal tissue, DHA and androstenedione are principal secretory products. Finally, a major steroid secreted by human luteal tissue is a reduction product of progesterone, 20α-hydroxypregn-4-en-3-one, or 20α-hydroxyprogesterone. The 20β-hydroxy derivative is present in ovarian tissue, but is not a significant secretory product in humans.

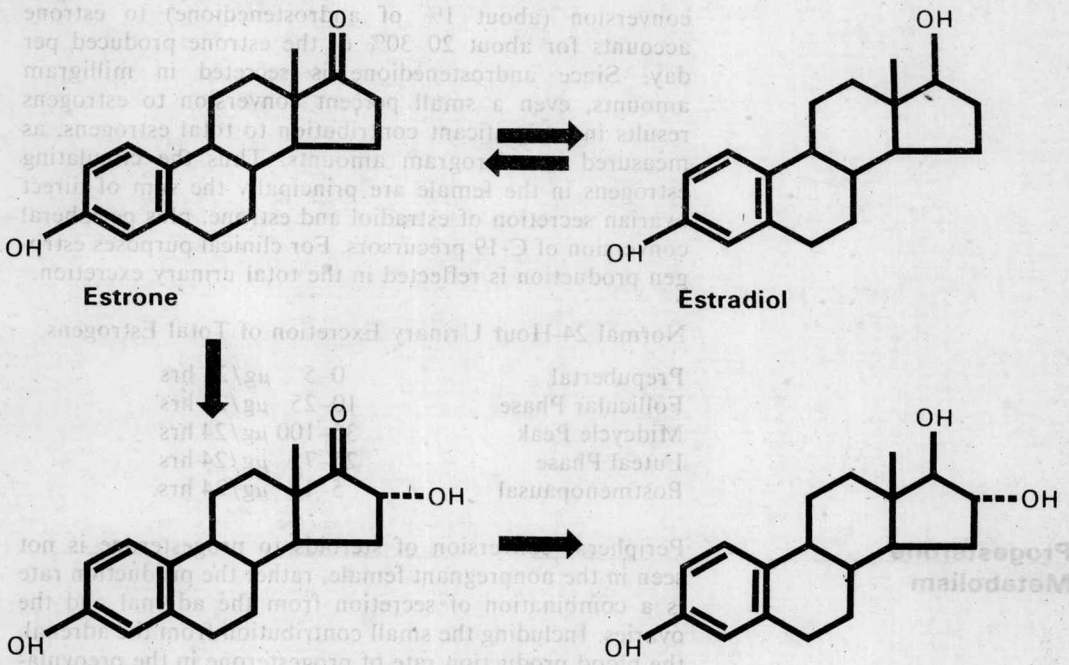
Ryan *et al.* (3) have isolated the follicular granulosa cells and shown that the principal product of the granulosa layer is progesterone. The predominant steroid in ovarian vein blood prior to ovulation, however, is estradiol; and *in vitro* studies of isolated follicular cells indicate that the thecal cells are the principal source of estrogens. Ryan has further shown that combining granulosa and thecal cells yields greater amounts of estrogens than separate incubations. The implication, therefore, is that the progesterone synthesized by granulosa cells during the preovulatory period serves as a precursor for estrogen synthesis in the theca. Limitation of a vascular supply to the theca until luteinization ensures that progesterone must diffuse toward the theca, and the principal secretory product of the preovulatory period is estradiol via the Δ^5 pathway.

Savard and his co-workers have clearly shown that the stromal tissue (cells from the theca and surrounding stroma) forms mainly androstenedione, DHA, and testosterone, with androstenedione being the major steroid isolated from *in vitro* incubation studies. This tissue responds to gonadotropins (LH and human chorionic gonadotropin (HCG)) with increased overall steroidogenesis, but especially with secretion of androstenedione and DHA.

A high level of androstenedione in the ovarian vein just before ovulation has been measured in both sheep and humans (4, 5); therefore it is clear that androstenedione is the major androgen secreted by the ovary, and there is a menstrual cycle fluctuation. Postmenopausally, when only stromal tissue remains, androstenedione is the chief secretory product in the ovarian vein.

Estrogen Metabolism

Androstenedione is the common precursor of estrogens. 17β-Hydroxydehydrogenase activity leads to testosterone which is not a major secretory product of the normal ovary, but is rapidly demethylated at the C-19 position and aromatized to estradiol, the major estrogen secreted by the human ovary. Estradiol also arises to a major degree from androstenedione via estrone, and estrone itself is secreted in significant daily amounts. Estriol is the peripheral metabolite of estrone and estradiol, and not a secretory product of the ovary. As such, the formation of estriol is typical of general metabolic "detoxification," conversion of biologically active material to less active forms.



The conversion of steroids in peripheral tissues, however, is not always a form of inactivation. Free androgens are peripherally converted to free estrogens. This process does not seem to be affected by adrenalectomy or castration, thus the conversion does not seem to be aromatization of blood androgens by the adrenal or the ovary (6). The work of MacDonald and Siiteri has elegantly shown that enough estrogen may be derived from circulating androgens to produce bleeding in the postmenopausal woman. The adrenal gland remains the major source of circulating androgens, in particular androstenedione.

It can be seen therefore that the pattern of circulating steroids in the female is influenced by the activity of various processes outside the ovary. Because of the peripheral contribution to steroid levels, "secretion rate" is reserved for direct organ secretion, whereas "production rate" includes organ secretion plus peripheral contribution via conversion of precursors.

The secretion rate of a hormone is the amount of the hormone released by an endocrine gland into the circulation per unit of time. The production rate is the total rate at which the hormone enters the circulation, including peripheral sources as well as secretion. The metabolic clearance rate is related to the blood production rate in that it equals the volume of blood which is cleared of the hormone per unit of time. The blood production rate then equals the metabolic clearance rate multiplied by the concentration of the hormone in the blood (7).

In the normal nonpregnant female, estradiol is produced at the rate of 100–300 μg/day (7, 8). The production of androstenedione is about 3 mg/day, and the peripheral conversion (about 1% of androstenedione) to estrone accounts for about 20–30% of the estrone produced per day. Since androstenedione is secreted in milligram amounts, even a small percent conversion to estrogens results in a significant contribution to total estrogens, as measured in microgram amounts. Thus the circulating estrogens in the female are principally the sum of direct ovarian secretion of estradiol and estrone, plus peripheral conversion of C-19 precursors. For clinical purposes estrogen production is reflected in the total urinary excretion.

Normal 24-Hour Urinary Excretion of Total Estrogens

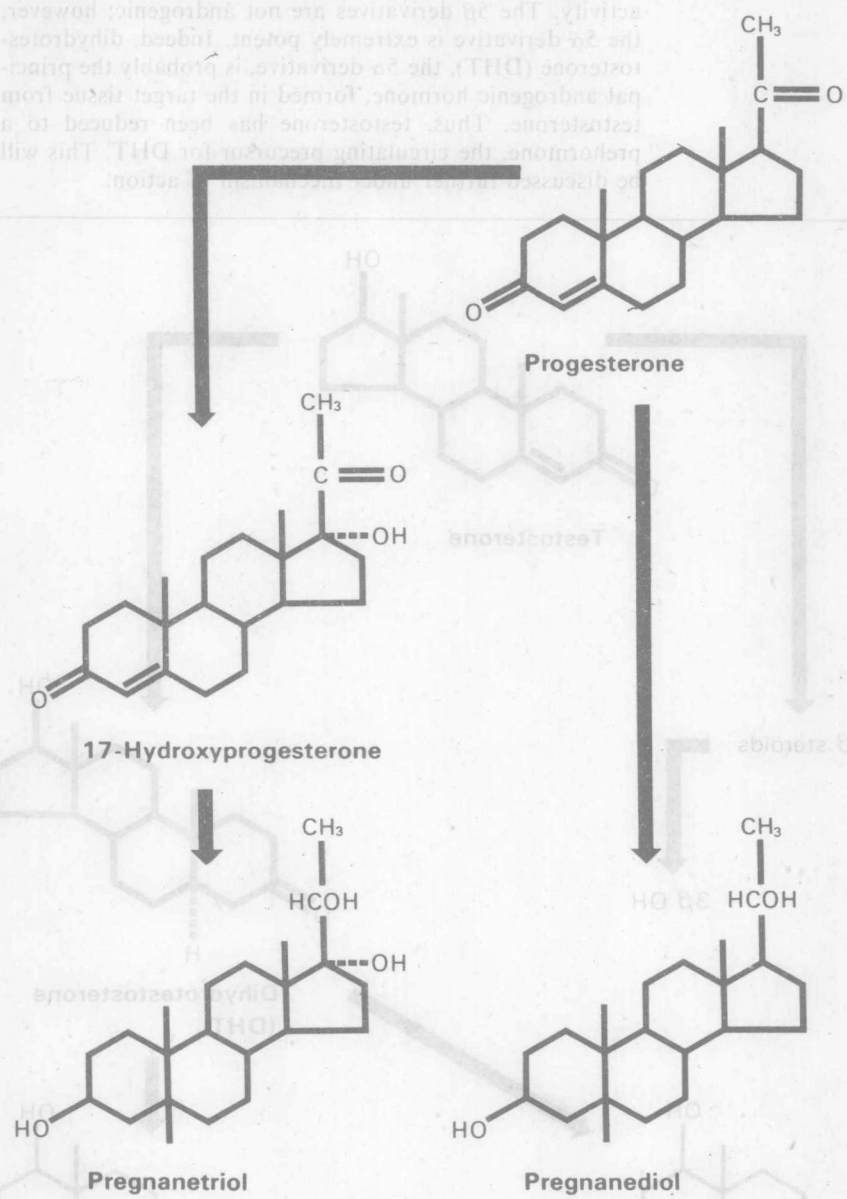
Prepubertal	0–5 μg/24 hrs
Follicular Phase	10–25 μg/24 hrs
Midcycle Peak	35–100 μg/24 hrs
Luteal Phase	25–75 μg/24 hrs
Postmenopausal	5–15 μg/24 hrs.

Progesterone Metabolism

Peripheral conversion of steroids to progesterone is not seen in the nonpregnant female, rather the production rate is a combination of secretion from the adrenal and the ovaries. Including the small contribution from the adrenal, the blood production rate of progesterone in the preovulatory phase is about 2–3 mg/day. During the luteal phase, production increases to 20–30 mg/day. The metabolic fate of progesterone, as expressed by its many excretion products, is more complex than estrogen. About 10–20% of progesterone is excreted as pregnanediol.

Pregnanediol glucuronide is present in the urine at concentrations less than 1 mg/day until ovulation. Postovulation pregnanediol excretion reaches a peak of 3–6 mg/day, which is maintained until 2 days prior to menses. The assay of pregnanediol in the urine now has limited use. The new methods utilizing binding proteins or antibodies to measure plasma levels of progesterone are more rapid, more sensitive, and more precise. From a clinical point of view, however, the basal body temperature, endometrial biopsy, and cervical mucus changes continue to be the most practical measures of ovulation and the luteal phase. Plasma progesterone levels might be of some value in the occasional patient with habitual abortion due to inadequate luteal function.

Pregnanetriol is the chief urinary metabolite of 17α-hydroxyprogesterone, and has clinical significance in the adrenogenital syndrome, where an enzyme defect results in accumulation of 17α-hydroxyprogsterone and increased excretion of pregnanetriol.



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