EXHIBIT 1013

Clinical Gynecologic Endocrinology and Infertility

Sixth Edition

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4 The Uterus

Anatomical knowledge of the uterus was slow to accumulate.[1,2] Papyrus writings from 2500 BC indicate that the ancient Egyptians made a distinction between the vagina and uterus. Because the dead had to be embalmed, dissection was precluded, but prolapse was recognized because it was important to return the uterus into its proper place prior to mummification. Next to the Egyptian papyri in antiquity were Hindu writings in which descriptions of the uterus, tubes, and vagina indicate knowledge gained from dissections. This was probably the earliest description of the fallopian tubes.

There is little information in Greek writings about female anatomy; however, Herophilus (4th century BC), the great anatomist in Alexandria and the originator of scholarly dissection, recorded the different positions of the uterus. Soranus of Ephesus (98–138 AD) accurately described the uterus (probably the first to do so), obviously from multiple dissections of cadavers. He recognized that the uterus is not essential for life, acknowledged the presence of leiomyomata, and treated prolapse with pessaries.

Herophilus and Soranus were uncertain about the function of the fallopian tubes, but Galen, Rufus, and Aetisu guessed correctly their function. Galen promoted the practice of bleeding for the treatment of almost every disorder. In his argument that nature prevented disease by discharging excess blood, Galen maintained that women were healthier because their superfluous blood was eliminated by menstruation.[3] The writings of Galen (130–200 AD) represented the knowledge of medicine for over 1000 years until the end of the medieval dark ages. Galen's description of the uterus and tubes indicates that he had only seen the horned uteri of animals.

In the 16th century, Berengarius, Vesalius, Eustachius, and Fallopius made significant contributions to the anatomical study of the female genitalia. Berengarius (Giacomo Berengario da Carpi) was the first anatomist to work with an artist. His anatomical text, published in 1514, depicted dissected subjects as if they were still alive.

Gabriele Fallopio (or Fallopius) published his work, *Observationes Anatomicae,* in Venice in 1561, one year before his death from pleurisy at age 40. He provided the first descriptions of the clitoris and the hymen, and the first exact descriptions of the ovaries and the tubes. He named the

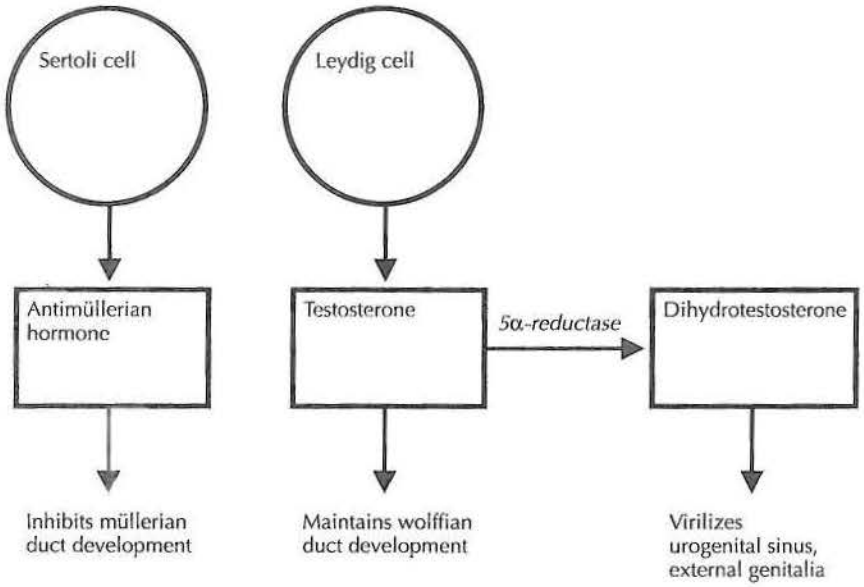
vagina and the placenta and called the tubes the uteri tuba (the trumpet of the uterus), but soon they were known universally as the fallopian tubes. It was his professor and mentor at the University of Padua, however, Andreas Vesalius, who was the first to accurately reveal the presence of the endometrial cavity.

Development of the Müllerian System

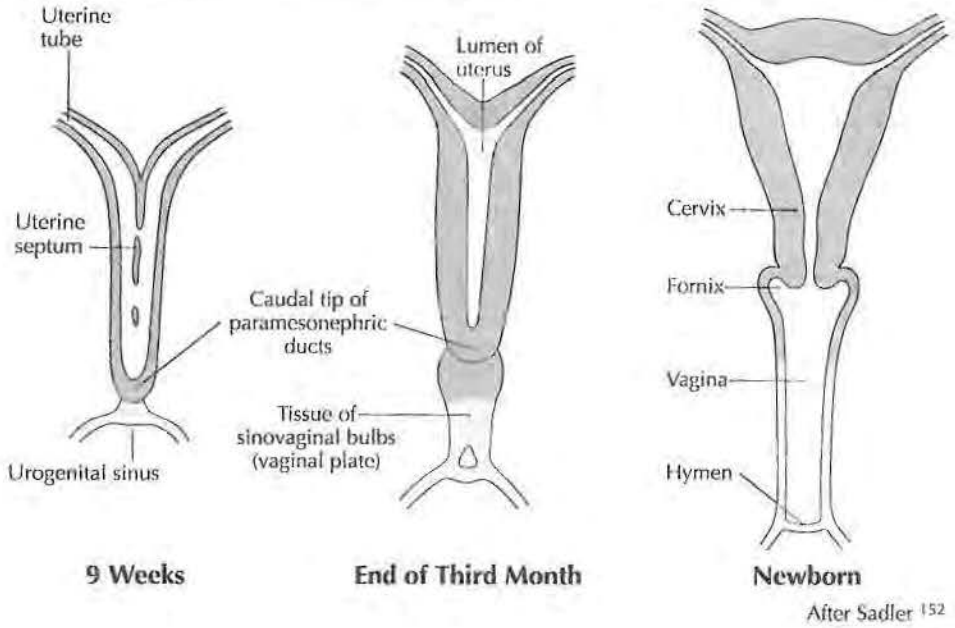
The wolffian (mesonephric) and müllerian (paramesonephric) ducts are discrete primordia that temporarily coexist in all embryos during the ambisexual period of development (up to 8 weeks). Thereafter, one type of duct system persists normally and gives rise to special ducts and glands, whereas the other disappears during the 3rd fetal month, except for nonfunctional vestiges.

Hormonal control of mammalian somatic sex differentiation was established by the classic experiments of Alfred Jost.[4] In Jost's landmark studies, the active role of male determining factors, as opposed to the constitutive nature of female differentiation, was defined as the directing feature of sex differentiation. This principle applies not only to the internal ducts but to the gonad, external genitalia, and perhaps even the brain. The critical factors in determining which of the duct structures stabilize or regress are the secretions from the testes: AMH (anti-müllerian hormone, also known as müllerian inhibiting substance or müllerian inhibiting factor) and testosterone.

AMH is a member of the transforming growth factor-β family of glycoprotein differentiation factors that include inhibin and activin. The gene for AMH has been mapped to chromosome 19. AMH is synthesized by Sertoli cells soon after testicular differentiation and is responsible for the ipsilateral regression of the müllerian ducts by 8 weeks. Despite its presence in serum up to puberty, lack of regression of the uterus and tubes is the only consistent expression of AMH gene mutations. In the absence of AMH, the fetus will develop fallopian tubes, uterus, and upper vagina from the paramesonephric ducts (the müllerian ducts). This development requires the prior appearance of the mesonephric ducts, and for this reason, abnormalities in development of the tubes, uterus, and upper vagina are associated with abnormalities in the renal system.



The internal genitalia possess the intrinsic tendency to feminize. In the absence of a Y chromosome and a functional testis, the lack of AMH allows retention of the müllerian system and development of fallopian tubes, uterus, and upper vagina. In the absence of testosterone, the wolffian system regresses. In the presence of a normal ovary or the absence of any gonad, müllerian duct development takes place.



After Sadler [152]

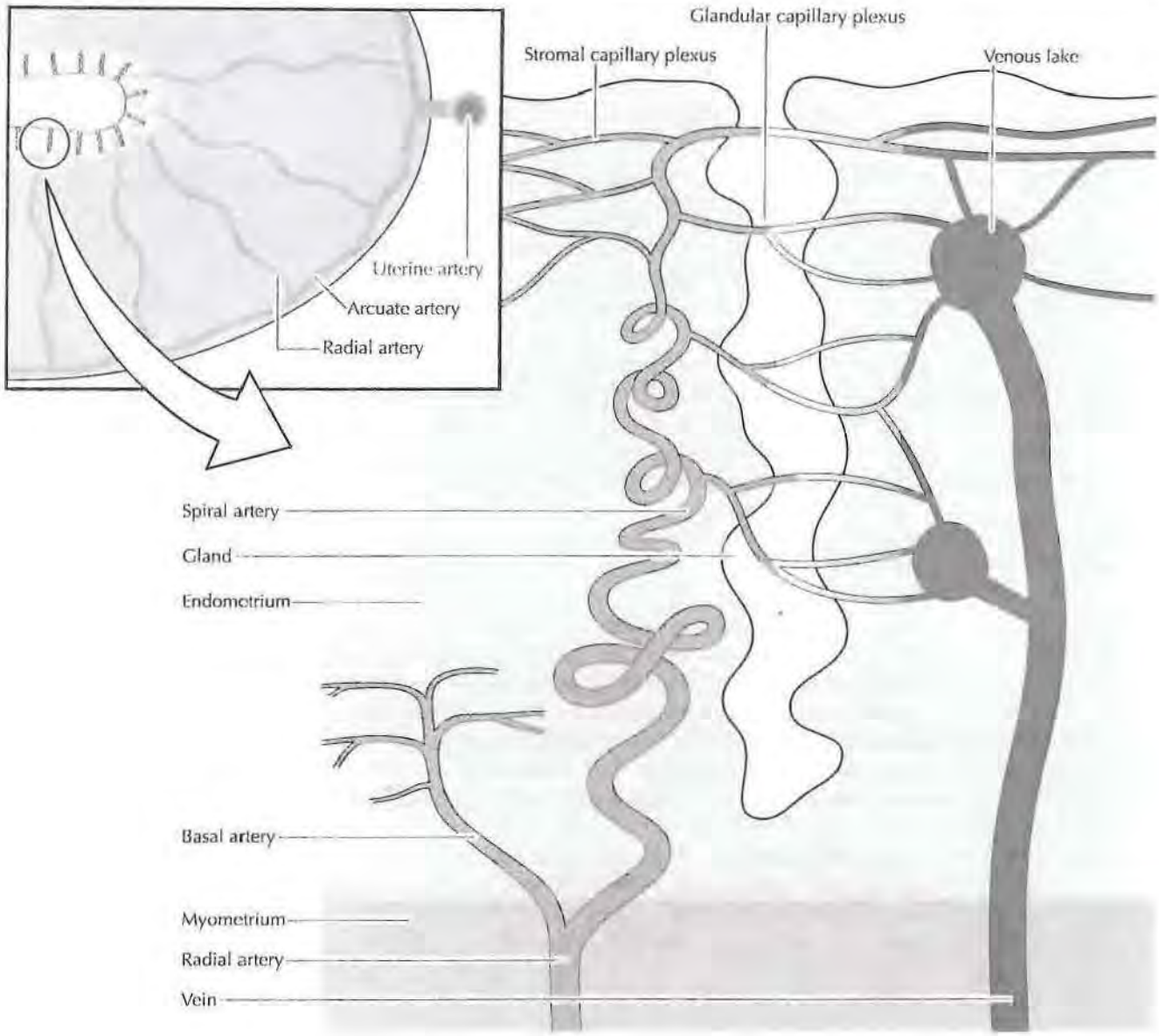
The paramesonephric ducts come into contact in the midline to form a Y-shaped structure, the primordium for the uterus, tubes, and the upper one-third of the vagina.[5] The fallopian tubes, uterus, and the upper portion of the vagina are created by the fusion of the müllerian ducts by the 10th week of gestation. Canalization to create the uterine cavity, the cervical canal, and the vagina is complete by the 22nd week of gestation. Under the epithelium lies mesenchymal tissue that will be the origin of the uterine stroma and smooth muscle cells. By the 20th week of pregnancy, the uterine mucosa is fully differentiated into the endometrium.

The endometrium, derived from the mucosal lining of the fused müllerian ducts, is essential for reproduction and may be one of the most complex tissues in the human body. It is always changing, responding to the cyclic patterns of estrogen and progesterone of the ovarian menstrual cycle, and to a complex interplay among its own autocrine and paracrine factors.[6]

The Uterine Changes in Endometrium During an Ovulatory Cycle

The sequence of endometrial changes associated with an ovulatory cycle has been carefully studied by Noyes in the human and Bartlemez and Markee in the subhuman primate.[7–11] From these data a description of menstrual physiology has developed based upon specific anatomic and functional changes within glandular, vascular, and stromal components of the endometrium.[12] These changes will be discussed in five phases: 1) the menstrual endometrium, 2) the proliferative phase, 3) the secretory phase, 4) preparation for implantation, and finally 5) the phase of endometrial breakdown. Although these distinctions are not entirely arbitrary, it must be recalled that the entire process is an integrated evolutionary cycle of endometrial growth and regression, which is repeated some 400 times during the adult life of the human female.

The endometrium can be divided morphologically into an upper two-thirds "functionalis" layer and a lower one-third "basalis" layer. The purpose of the functionalis layer is to prepare for the implantation of the blastocyst and, therefore, it is the site of proliferation, secretion, and degeneration. The purpose of the basalis layer is to provide the regenerative endometrium following menstrual loss of the functionalis.

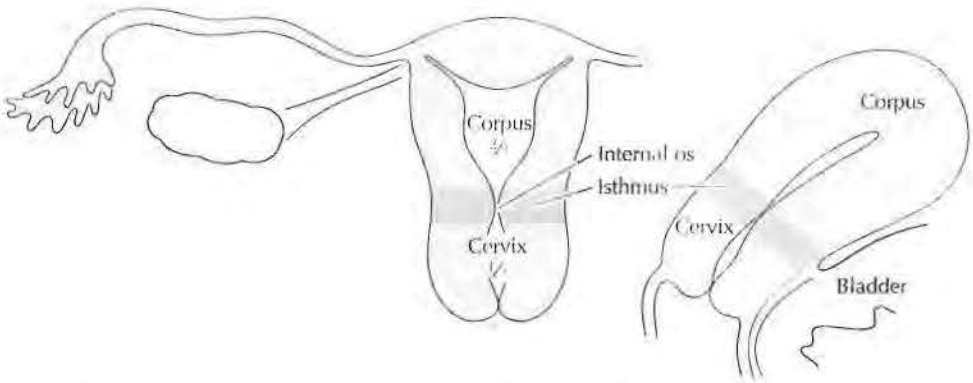


The Uterine Vasculature

The two uterine arteries that supply the uterus are branches of the internal iliac arteries. At the lower part of the uterus, the uterine artery separates into the vaginal artery and an ascending branch that divides into the arcuate arteries. The arcuate arteries run parallel to the uterine cavity and anastomose with each other, forming a vascular ring around the cavity. Small centrifugal branches (the radial arteries) leave the arcuate vessels, perpendicular to the endometrial cavity, to supply the myometrium. When these arteries enter the endometrium, small branches (the basal arteries) extend laterally to supply the basalis layer. These basal arteries do not demonstrate a response to hormonal changes. The radial arteries continue in the direction of the endometrial surface, now assuming a corkscrew appearance (and now called the spiral arteries), to supply the functionalis layer of the endometrium. It is the spiral artery (an end artery) segment that is very sensitive to hormonal changes. One reason the functionalis layer is more vulnerable to vascular permutations is that there are no anastomoses among the spiral arteries. The endometrial glands and the stromal tissue are supplied by capillaries that emerge from the spiral arteries at all levels of the endometrium. The capillaries drain into a venous plexus and eventually into the myometrial arcuate veins and into the uterine veins. This unique vascular architecture is important in allowing a repeated sequence of endometrial growth and desquamation.

The Menstrual Endometrium

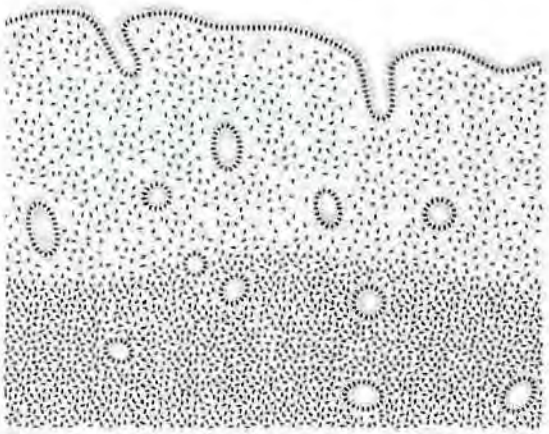
The menstrual endometrium is a relatively thin but dense tissue. It is composed of the stable, nonfunctioning basalis component and a variable, but small, amount of residual stratum spongiosum. At menstruation, this latter tissue displays a variety of functional states including disarray and breakage of glands, fragmentation of vessels and stroma with persisting evidence of necrosis, white cell infiltration, and red cell interstitial diapedesis. Even as the remnants of menstrual shedding dominate the overall appearance of this tissue, evidence of repair in all tissue components can be detected. The menstrual endometrium is a transitional state bridging the more dramatic proliferative and exfoliative phases of the cycle. Its density implies that the shortness of height is not entirely due to desquamation. Collapse of the supporting matrix also contributes significantly to the shallowness. Reticular stains in rhesus endometrium confirm this "deflated" state. Nevertheless, as much as two-thirds of the functioning endometrium is lost during menstruation. The more rapid the tissue loss, the shorter the duration of flow. Delayed or incomplete shedding is associated with heavier flow and greater blood loss.

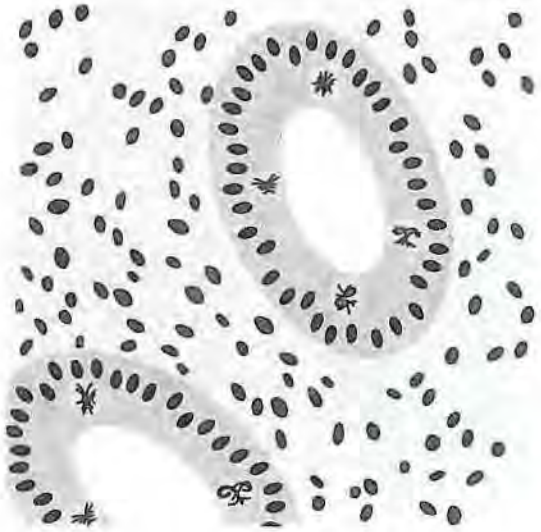


DNA synthesis is occurring in those areas of the basalis that have been completely denuded by day 2–3 of the menstrual cycle (the endometrium in the isthmic area, the narrow area between the cervix and the corpus, and the endometrium in the cornual recesses at the ostia of the tubes remain intact). The new surface epithelium emanates from the flanks of stumps of glands in the basalis layer left standing after menstrual desquamation.[13] Rapid reepithelialization follows the proliferation of the cells in the basalis layer and the surface epithelium in the isthmic and tubal ostial endometrium. This epithelial repair is supported by underlying fibroblasts. The stromal fibroblast layer forms a compact mass over which the resurfacing epithelium can "migrate." In addition, it is likely that the stromal layer contributes important autocrine and paracrine factors for growth and migration. Because hormone levels are at their nadir during this repair phase, the response may be due to injury rather than hormone mediated. However, the basalis layer is rich in its content of estrogen receptors. This "repair" is fast; by day 4 of the cycle, more than two-thirds of the cavity is covered with new epithelium.[13] By day 5–6, the entire cavity is reepithelialized, and stromal growth begins.

The Proliferative Phase

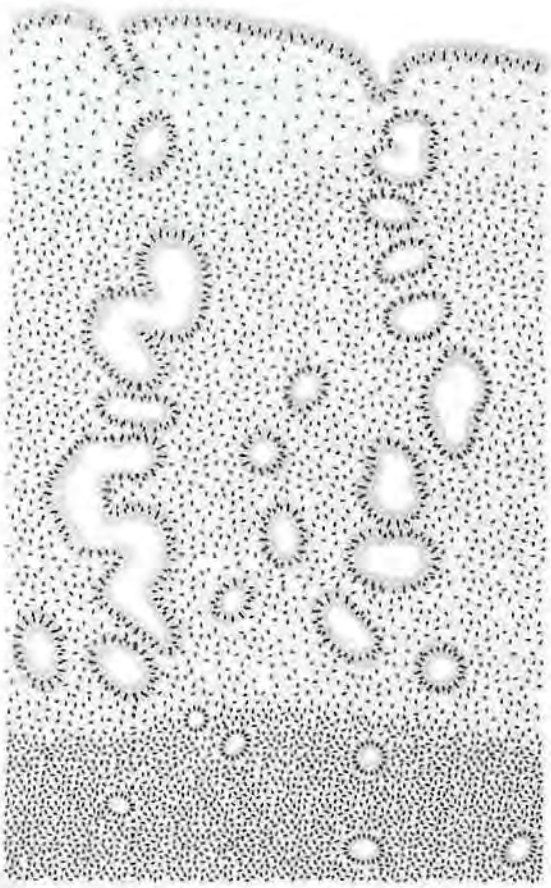
The proliferative phase is associated with ovarian follicle growth and increased estrogen secretion. Undoubtedly as a result of this steroidal action, reconstruction and growth of the endometrium are achieved. The glands are most notable in this response. At first they are narrow and tubular, lined by low columnar epithelium cells. Mitoses become prominent and pseudostratification is observed. As a result, the glandular epithelium extends peripherally and links one gland segment with its immediate neighbor. A continuous epithelial lining facing the endometrial cavity is formed. The stromal component evolves from its dense cellular menstrual condition through a brief period of edema to a final loose syncytial-like status. Coursing through the stroma, spiral vessels extend (unbranched and uncoiled in the early proliferative phase) to a point

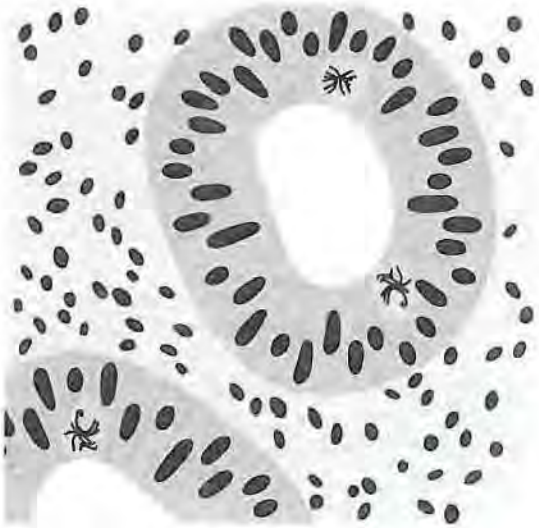




Early Proliferative

immediately below the epithelial binding membrane. Here they form a loose capillary network. All of the tissue components (glands, stromal cells, and endothelial cells) demonstrate proliferation, which peaks on days 8–10 of the cycle, corresponding to peak estradiol levels in the circulation and maximal estrogen receptor concentration in the endometrium.[14] This proliferation is marked by increased mitotic activity and increased nuclear DNA and cytoplasmic RNA synthesis, that is most intense in the functionalis layer in the upper two-thirds of the uterus, the usual site of blastocyst implantation.





Late Proliferative

During proliferation, the endometrium grows from approximately 0.5 mm to 3.5–5.0 mm in height. This proliferation is mainly in the functionalis layer. Restoration of tissue constituents has been achieved by estrogen-induced new growth as well as incorporation of ions, water, and amino acids. The stromal ground substance has reexpanded from its menstrual collapse. Although true tissue growth has occurred, a major element in achievement of endometrial height is "reinflation" of the stroma.

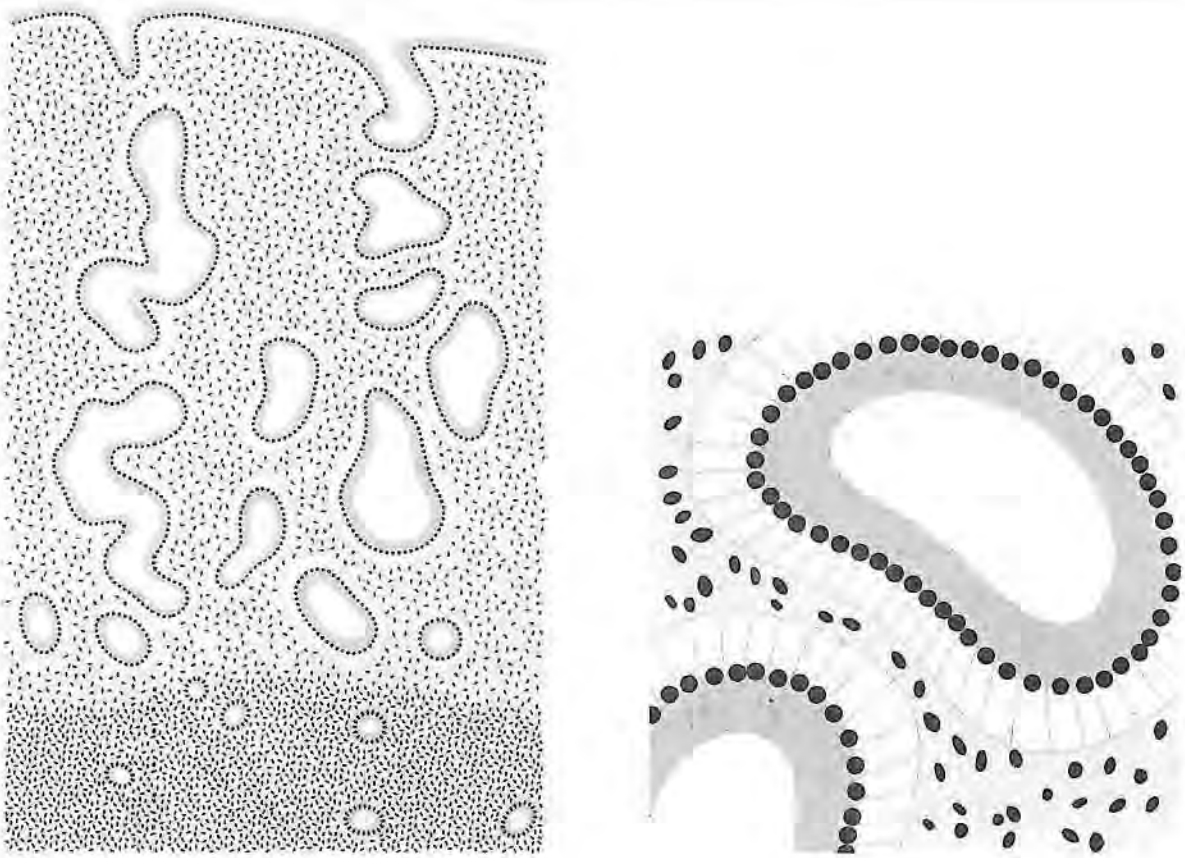
An important feature of this estrogen dominant phase of endometrial growth is the increase in ciliated and microvillous cells. Ciliogenesis begins on days 7–8 of the cycle.[13] This response to estrogen is exaggerated in hyperplastic endometrium that is the result of hyperestrogenism. The concentration of these ciliated cells around gland openings and the ciliary beat pattern influence the mobilization and distribution of endometrial secretions during the secretory phase. Cell surface microvilli, also a response to estradiol, are cytoplasmic extensions and serve to increase the active surface of cells.

Ciliated Cells

At all times, a large number of cells derived from bone marrow are present in the endometrium. These include lymphocytes and macrophages, diffusely distributed in the stroma.

The Secretory Phase

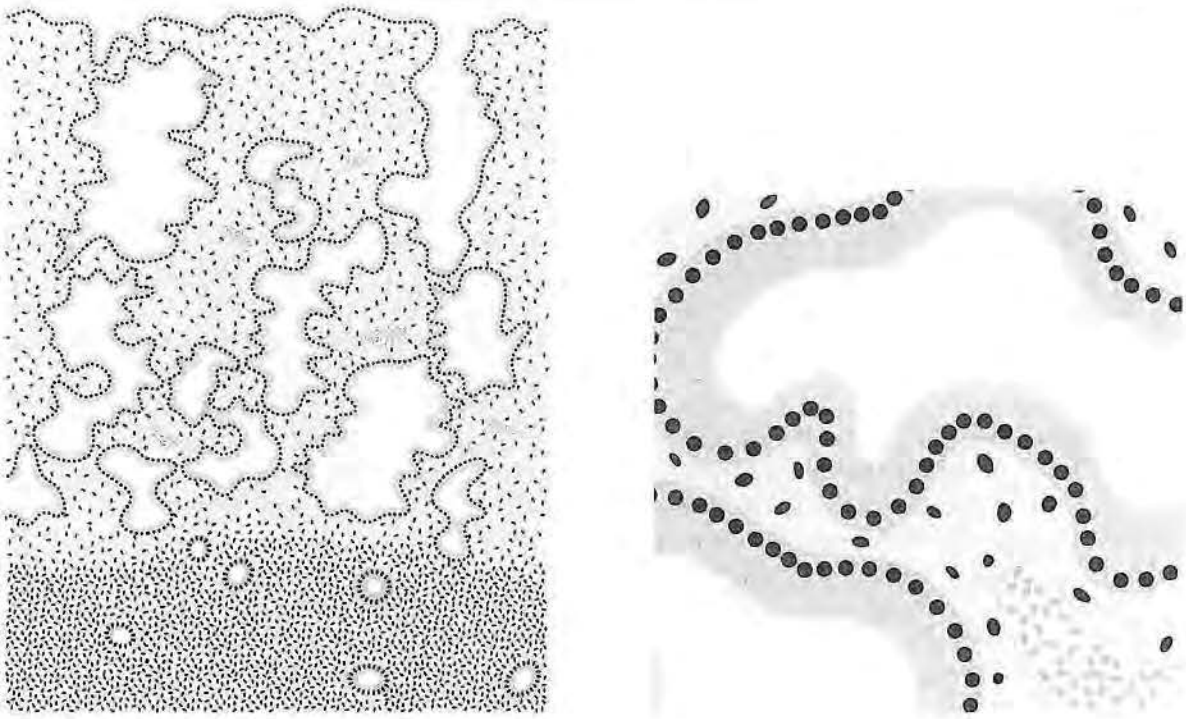
After ovulation, the endometrium now demonstrates a combined reaction to estrogen and progesterone activity. Most impressive is that total endometrial height is fixed at roughly its preovulatory extent (5–6 mm) despite continued availability of estrogen. Epithelial proliferation ceases 3 days after ovulation.[15] This restraint or inhibition is believed to be induced by progesterone. This limitation of growth is associated with a decline in mitosis and DNA synthesis, significantly due to progesterone interference with estrogen receptor expression and progesterone stimulation of 17β-hydroxysteroid dehydrogenase and sulfotransferase, which convert estradiol to estrone sulfate (which is rapidly excreted from the cell).[16, 17] In addition, estrogen stimulates many oncogenes that probably mediate estrogen-induced growth. Progesterone antagonizes this action by suppressing the estrogen-mediated transcription of oncogene mRNA.[18]



Early Secretory

Individual components of the tissue continue to display growth, but confinement in a fixed structure leads to progressive tortuosity of glands and intensified coiling of the spiral vessels. The secretory events within the glandular cells, with progression of vacuoles from intracellular to intraluminal appearance, are well known and take place over a 7-day postovulatory interval. At the conclusion of these events, the glands appear exhausted, the tortuous lumina variably distended, and individual cell surfaces fragmented in a sawtooth appearance. Stroma is increasingly edematous, and spiral vessels are prominent and densely coiled.

The first histologic sign that ovulation has occurred is the appearance of subnuclear intracytoplasmic glycogen vacuoles in the glandular epithelium on cycle days 17–18. Giant mitochondria and the "nucleolar channel system" appear in the gland cells. The nucleolar channel system has a unique appearance due to progesterone, an infolding of the nuclear membranes. Individual components of the tissue continue to display growth, but confinement in a fixed structure leads to progressive tortuosity of glands and intensified coiling of the spiral vessels. These structural alterations are soon followed by active secretion of glycoproteins and peptides into the endometrial cavity. Transudation of plasma also contributes to the endometrial secretions. Important immunoglobulins are obtained from the circulation and delivered to the endometrial cavity by binding proteins produced by the epithelial cells. The peak secretory level is reached 7 days after the midcycle gonadotropin surge, coinciding with the time of blastocyst implantation.



Late Secretory

The Implantation Phase

Significant changes occur within the endometrium from the 7th to the 13th day postovulation (days 21–27 of the cycle). At the onset of this period, the distended tortuous secretory glands have been most prominent with little intervening stroma. By 13 days postovulation, the endometrium has differentiated into three distinct zones. Something less than one-fourth of the tissue is the unchanged basalis fed by its straight vessels and surrounded by indifferent spindle-shaped stroma. The midportion of the endometrium (approximately 50% of the total) is the lace like ***stratum spongiosum***, composed of loose edematous stroma with tightly coiled but ubiquitous spiral vessels and exhausted dilated glandular ribbons. Overlying the spongiosum is the superficial layer of the endometrium (about 25% of the height) called the ***stratum compactum***. Here the prominent histologic feature is the stromal cell, which has become large and polyhedral. In its cytoplasmic expansion one cell abuts the other, forming a compact, structurally sturdy layer. The necks of the glands traversing this segment are compressed and less prominent. The subepithelial capillaries and spiral vessels are engorged.

At the time of implantation, on days 21–22 of the cycle, the predominant morphologic feature is edema of the endometrial stroma. This change may be secondary to the estrogen- and progesterone-mediated increase in prostaglandin production by the endometrium. An increase in capillary permeability is a consequence of this local increase in prostaglandins. Receptors for the sex steroids are present in the muscular walls of the endometrial blood vessels, and the enzyme system for prostaglandin synthesis is present in both the muscular walls and the endothelium of the endometrial arterioles. Mitoses are first seen in endothelial cells on cycle day 22. Vascular proliferation leads to the coiling of the spiral vessels, a response to the sex steroids, the prostaglandins, and to autocrine and paracrine factors produced in response to estrogen and progesterone.

During the secretory phase, so-called K (Körnchenzellen) cells appear, reaching a peak concentration in the first trimester of pregnancy. These are granulocytes that have an immunoprotective role in implantation and placentation. They are located perivascularly and are believed to be derived from the blood. By day 26–27, the endometrial stroma is infiltrated by extravasated polymorphonuclear leukocytes.

The stromal cells of the endometrium respond to hormonal signals, synthesize prostaglandins, and, when transformed into decidual cells, produce an impressive array of substances, some of which are prolactin, relaxin, renin, insulin-like growth factors (IGFs), and insulin-like growth factor binding proteins (IGFBPs). The endometrial stromal cells, the progenitors of decidual cells, were originally believed to be derived from the bone marrow (from cells invading the endometrium), but they are now considered to emanate from the primitive uterine mesenchymal stem cells.[6]

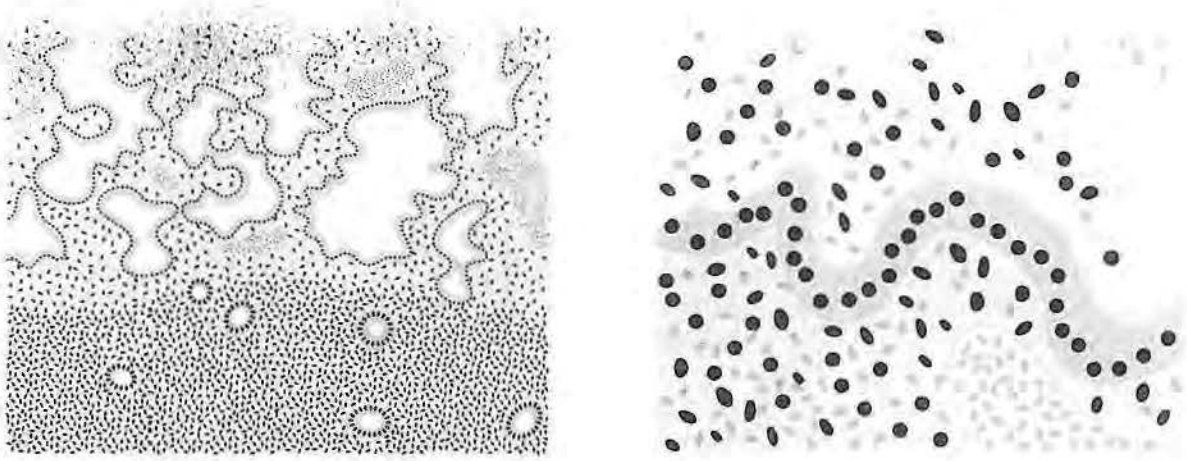
The decidualization process begins in the luteal phase under the influence of progesterone and mediated by autocrine and paracrine factors. On cycle days 22–23, predecidual cells can be identified, initially surrounding blood vessels, characterized by cytonuclear enlargement, increased mitotic activity, and the formation of a basement membrane. The decidua, derived from stromal cells, becomes an important structural and biochemical tissue of pregnancy. Decidual cells control the invasive nature of the trophoblast, and the products of the decidua play important autocrine and paracrine roles in fetal and maternal tissues.

Lockwood assigns a key role to decidual cells in both the process of endometrial bleeding (menstruation) and the process of endometrial hemostasis (implantation and placentation).[19] Implantation requires endometrial hemostasis and the maternal uterus requires resistance to invasion. Inhibition of endometrial hemorrhage can be attributed, to a significant degree, to appropriate changes in critical factors as a consequence of decidualization; e.g., lower plasminogen activator levels, reduced expression of the enzymes that degrade the stromal extracellular matrix (such as the metalloproteinases), and increased levels of plasminogen activator inhibitor-1. Withdrawal of estrogen and progesterone support, however, leads to changes in the opposite directions, consistent with endometrial breakdown.

The Phase of Endometrial Breakdown

Predecidual transformation has formed the "compacta" layer in the upper part of the functionalis layer by day 25 (3 days before menstruation). In the absence of fertilization, implantation, and the consequent lack of sustaining quantities of human chorionic gonadotropin from the trophoblast, the otherwise fixed life span of the corpus luteum is completed, and estrogen and progesterone levels wane.

The withdrawal of estrogen and progesterone initiates important endometrial events: vasomotor reactions, the process of apoptosis, tissue loss, and finally, menstruation. The most prominent immediate effect of this hormone withdrawal is a modest shrinking of the tissue height and remarkable spiral arteriole vasomotor responses. The following vascular sequence has been constructed from direct observations of rhesus endometrium.[7,8] With shrinkage of height, blood flow within the spiral vessels diminishes, venous drainage is decreased, and vasodilatation ensues. Thereafter, the spiral arterioles undergo rhythmic vasoconstriction and relaxation. Each successive spasm is more prolonged and profound, leading eventually to endometrial blanching.

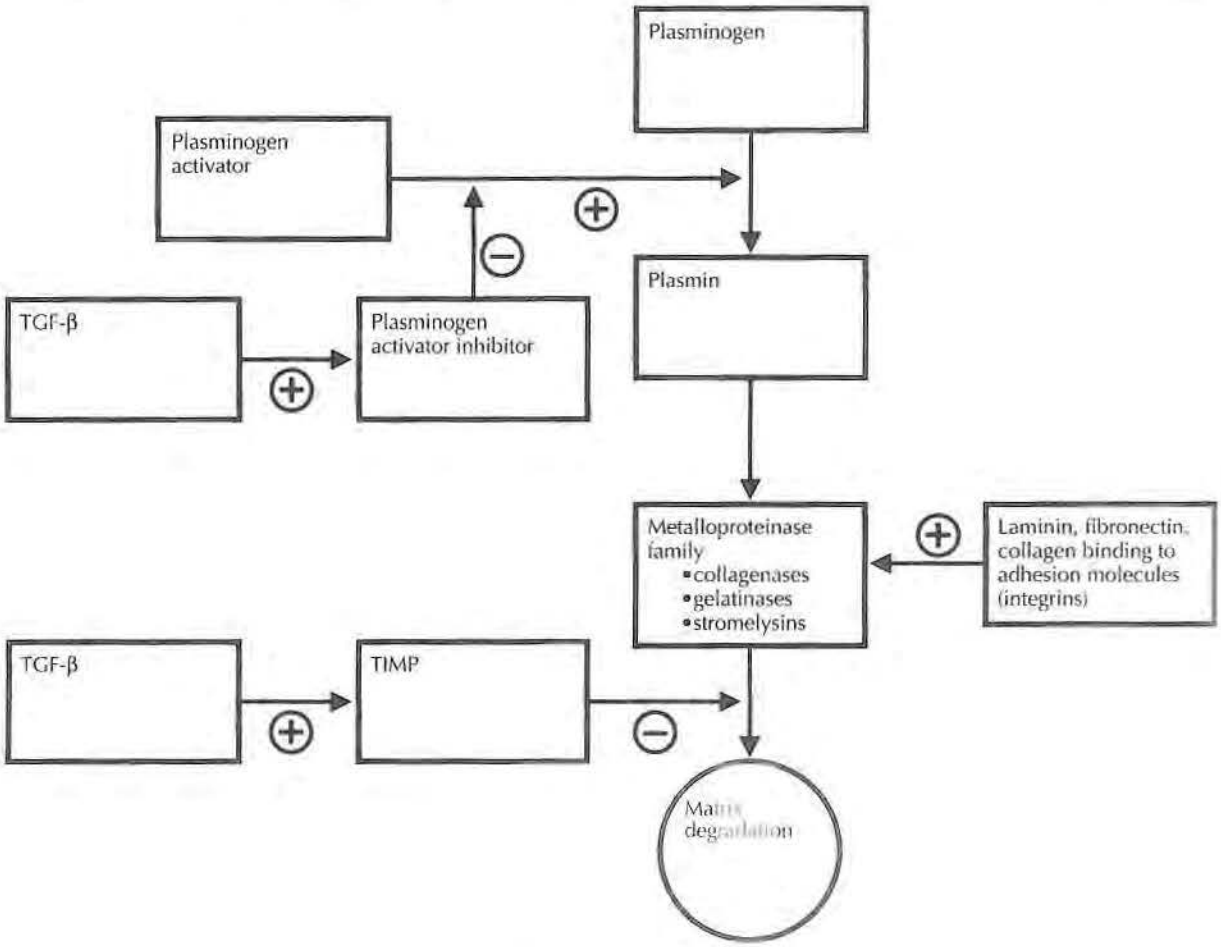


Menstruation

Within the 24 hours immediately preceding menstruation, these reactions lead to endometrial ischemia and stasis. White cells migrate through capillary walls, at first remaining adjacent to vessels, but then extending throughout the stroma. During arteriolar vasomotor changes, red blood cells escape into the interstitial space. Thrombin-platelet plugs also appear in superficial vessels. The prostaglandin content ($PGF_{2\alpha}$ and PGE_2) in the secretory endometrium reaches its highest levels at the time of menstruation. The vasoconstriction and myometrial contractions associated with the menstrual events are believed to be significantly mediated by $PGF_{2\alpha}$ from glandular cells and the potent vasoconstrictor, endothelin-1, derived from stromal decidual cells.

In the first half of the secretory phase, acid phosphatase and potent lytic enzymes are confined to lysosomes. Their release is inhibited by progesterone stabilization of the lysosomal membranes. With the waning of estrogen and progesterone levels, the lysosomal membranes are not maintained, and the enzymes are released into the cytoplasm of epithelial, stromal, and endothelial cells, and eventually into the intercellular space. These active enzymes will digest their cellular constraints, leading to the release of prostaglandins, extravasation of red blood cells, tissue necrosis, and vascular thrombosis. This process is one of ***apoptosis***, (programmed cell death, characterized by a specific morphologic pattern that involves cell shrinkage and chromatin condensation culminating in cell fragmentation) mediated by cytokines.[20] An important step in this breakdown is the dissolution of cell to cell adhesion by key proteins. Binding of endometrial epithelial cells utilizes transmembrane proteins, ***cadherins***, that link intercellularly with each other and intracellularly with catenins that are bound to actin filaments.[21]

Endometrial tissue breakdown also involves a family of enzymes, matrix metalloproteinases, that degrade components (including collagens, gelatins, fibronectin, and laminin) of the extracellular matrix and basement membrane.[22] The metalloproteinases include collagenases that degrade interstitial and basement membrane collagens, gelatinases that further degrade collagens, and stromelysins that degrade fibronectin, laminin, and glycoproteins. The expression of metalloproteinases in human endometrium follows a pattern correlated with the menstrual cycle, indicating a sex steroid response as part of the growth and remodeling of the endometrium, with a marked increase in late secretory and early menstrual endometrium.[23] Progesterone withdrawal from endometrial cells induces matrix metalloproteinase secretion, which is followed by the breakdown of cellular membranes and the dissolution of extracellular matrix.[24]



Appropriately, this enzyme expression increases in the decidualized endometrium of the late secretory phase, during the time of declining progesterone levels. With the continuing progesterone secretion of early pregnancy, the decidua is maintained and metalloproteinase expression is suppressed, in a mechanism mediated by TGF-β.[25] In a nonpregnant cycle, metalloproteinase expression is suppressed after menses, presumably by increasing estrogen levels. Metalloproteinase activity is restrained by specific tissue inhibitors designated as TIMP. Thus, progesterone withdrawal can lead to endometrial breakdown through a mechanism that is independent of vascular events (specifically ischemia), a mechanism that involves cytokines.[20] During bleeding, both normal and abnormal, there is evidence indicating that specific genes are activated in the endometrium; one such gene has the structural features of the TGF-β family.[26]

There is considerable evidence to support a major role for a cytokine, tumor necrosis factor-α (TNF-α) in menstruation.[20] TNF-α is a transmembrane protein whose receptor belongs to the nerve growth factor/TNF family for inducing apoptotic signals. The key change is an increase in secretion because TNF-α secretion by endometrial cells reaches a peak at menstruation, but there is no cycle change in receptor content. TNF-α inhibits endometrial proliferation and induces apoptosis; this cytokine causes a loss of adhesion proteins (the cadherin-catenin-actin complex) and induces cell-to-cell dissolution. In addition to endometrial cells, TNF-α also causes damage to vascular endothelium.

Eventually, considerable leakage occurs as a result of diapedesis, and finally, interstitial hemorrhage occurs due to breaks in superficial arterioles and capillaries. As ischemia and weakening progress, the continuous binding membrane is fragmented, and intercellular blood is extruded into the endometrial cavity. New thrombin-platelet plugs form intravascularly upstream at the shedding surface, limiting blood loss. Increased blood loss is a consequence of reduced platelet numbers and inadequate hemostatic plug formation. Menstrual bleeding is influenced by activation of clotting and fibrinolysis. Fibrinolysis is principally the consequence of the potent enzyme, plasmin, formed from its inactive precursor, plasminogen. Endometrial stromal cell tissue factor (TF) and plasminogen activators and inhibitors are involved in achieving a balance in this process. TF stimulates coagulation, initially binding to factor VII. TF and plasminogen activator inhibitor-1 (PAI-1) expression accompanies decidualization, and the levels of these factors may govern the amount of bleeding.[27] PAI-1, in particular, exerts an important restraining action on fibrinolysis and proteolytic activity.[28]

With further tissue disorganization, the endometrium shrinks even more and coiled arterioles are buckled. Additional ischemic breakdown ensues with necrosis of cells and defects in vessels adding to the menstrual effluvium. A natural cleavage point exists between basalis and spongiosum, and, once breached, the loose, vascular, edematous stroma of the spongiosum desquamates and collapses. The process is initiated in the fundus and inexorably extends throughout the uterus. In the end, the typical deflated, shallow, dense, menstrual endometrium results. Within 13 hours, the endometrial height shrinks from 4 mm to 1.25 mm.[12] Menstrual flow stops as a result of the combined effects of prolonged vasoconstriction, tissue collapse, vascular stasis, and estrogen-induced "healing." In contrast to postpartum bleeding, myometrial contractions are not important for control of menstrual bleeding. Thrombin generation in the basal endometrium in response to extravasation of blood is essential for hemostasis. Thrombin promotes the generation of fibrin, the activation of platelets and clotting cofactors, and angiogenesis.

The basalis endometrium remains during menses, and repair takes place from this layer. This endometrium is protected from the lytic enzymes in the menstrual fluid by a mucinous layer of carbohydrate products that are discharged from the glandular and stromal cells.[29]

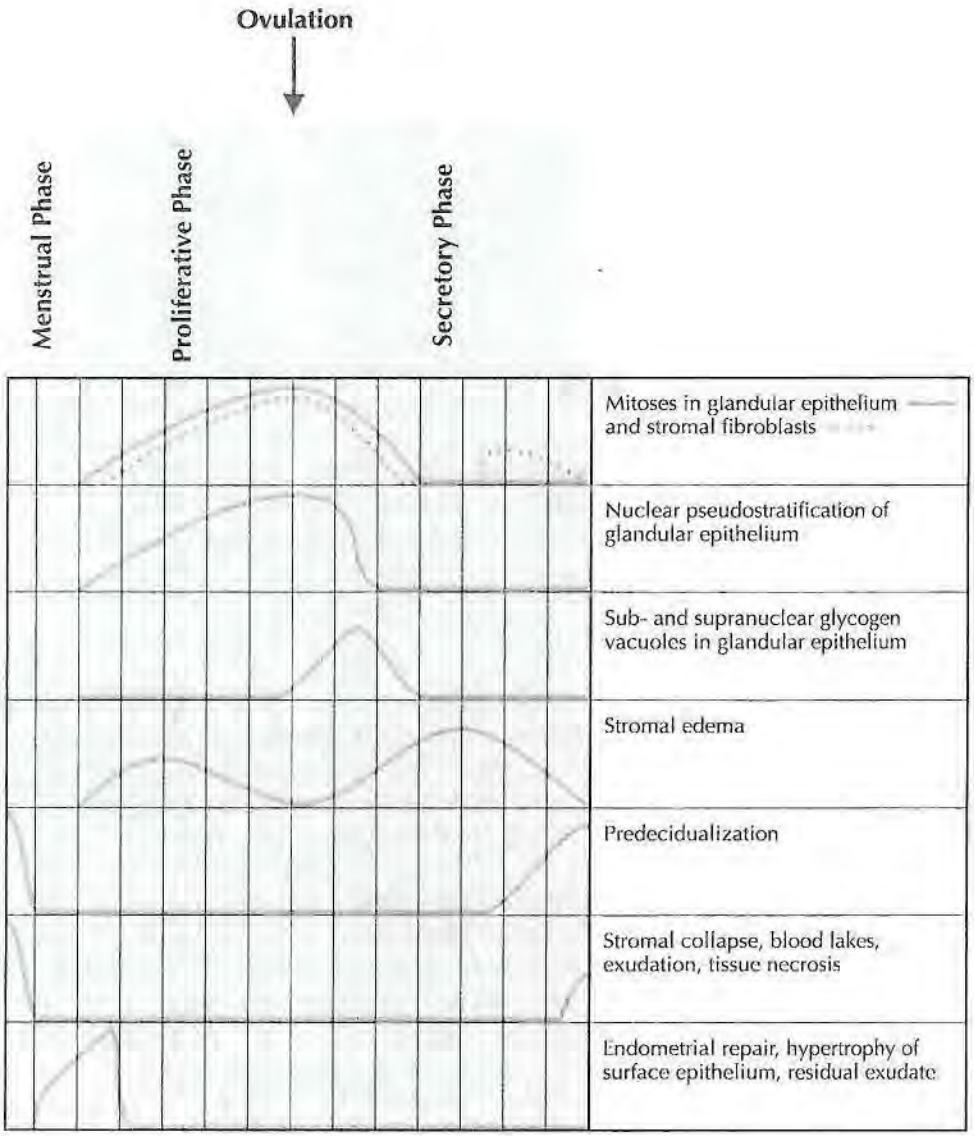
Normal Menses

Approximately 50% of the menstrual detritus is expelled in the first 24 hours of menstrual flow. The menstrual fluid is composed of the autolysed functionalis, inflammatory exudate, red blood cells, and proteolytic enzymes (at least one of which, plasmin, lyses fibrin clots as they form). The high fibrinolytic activity advances emptying of the uterus by liquefaction of tissue and fibrin. If the rate of flow is great, clotting can and does occur.

Most women (90%) have menstrual cycles with an interval of 24 to 35 days (Chapter 6).[30, 31] Menarche is followed by approximately 5–7 years of increasing regularity as cycles shorten to reach the usual reproductive age pattern. In the 40s, cycles begin to lengthen again. The usual duration of flow is 4–6 days, but many women flow as little as 2 days and as much as 8 days. The normal volume of menstrual blood loss is 30 mL; greater than 80 mL is abnormal (Chapter 15).

Dating the Endometrium

The postovulatory endometrium can be dated according to the histologic changes throughout a hypothetical 28-day menstrual cycle. These changes were described by Noyes, Hertig, and Rock in the lead article of the first volume of *Fertility and Sterility* in 1950.[9] Dating of the endometrium is most accurately accomplished with biopsy specimens obtained 2–3 days before the onset of menses. This method continues to be the most accepted way to diagnose an inadequate luteal phase (endometrium inadequate to sustain a pregnancy because of deficient progesterone secretion by the corpus luteum).



After Noyes, et al [9]

A Teleologic Theory of Endometrial-Menstrual Events

Menstruation is a very recent phenomenon in the evolutionary time line. It occurs in very few species, even among viviparous animals. An unabashedly teleologic view of menstrual events was offered by Rock et al.[32] The basic premise of this thesis is that every endometrial cycle has, as its only goal, nourishing support of an early embryo. Failure to accomplish this objective is followed by orderly elimination of unutilized tissue and prompt renewal to achieve a more successful cycle.

The ovum must be fertilized within 12–24 hours of ovulation. Over the next 2 days, it remains unattached within the tubal lumen utilizing tubal fluids and residual cumulus cells to sustain nutrition and energy for early cellular cleavage. After this stay, the solid ball of cells (morula) which is the embryo leaves the tube and enters the uterine cavity. Here the embryo undergoes another 2–3 days of unattached but active existence. Fortunately, by this time endometrial gland secretions have filled the cavity and they bathe the embryo in nutrients. This is the first of many neatly synchronized events that mark the conceptus-endometrial relationship. By 6 days after ovulation, the embryo (now a blastocyst) is ready to attach and implant. At this time, it finds an endometrial lining of sufficient depth, vascularity, and nutritional richness to sustain the important events of early placentation to follow. Just below the epithelial lining, a rich capillary plexus has been formed and is available for creation of the trophoblast-maternal blood interface. Later, the surrounding zona compactum, occupying more and more of the endometrium, will provide a sturdy splint to retain endometrial architecture despite the invasive inroads of the burgeoning trophoblast.

Failure of the appearance of human chorionic gonadotropin, despite otherwise appropriate tissue reactions, leads to the vasomotor changes associated with estrogen-progesterone withdrawal and menstrual desquamation. However, not all the tissue is lost, and, in any event, a residual basalis is always available, making resumption of growth with estrogen a relatively rapid process. Indeed, even as menses persists, early regeneration can be seen. As soon as follicle maturation occurs (in as short a time as 10 days), the endometrium is ready once again to perform its reproductive function.

The Uterus Is an Endocrine Organ

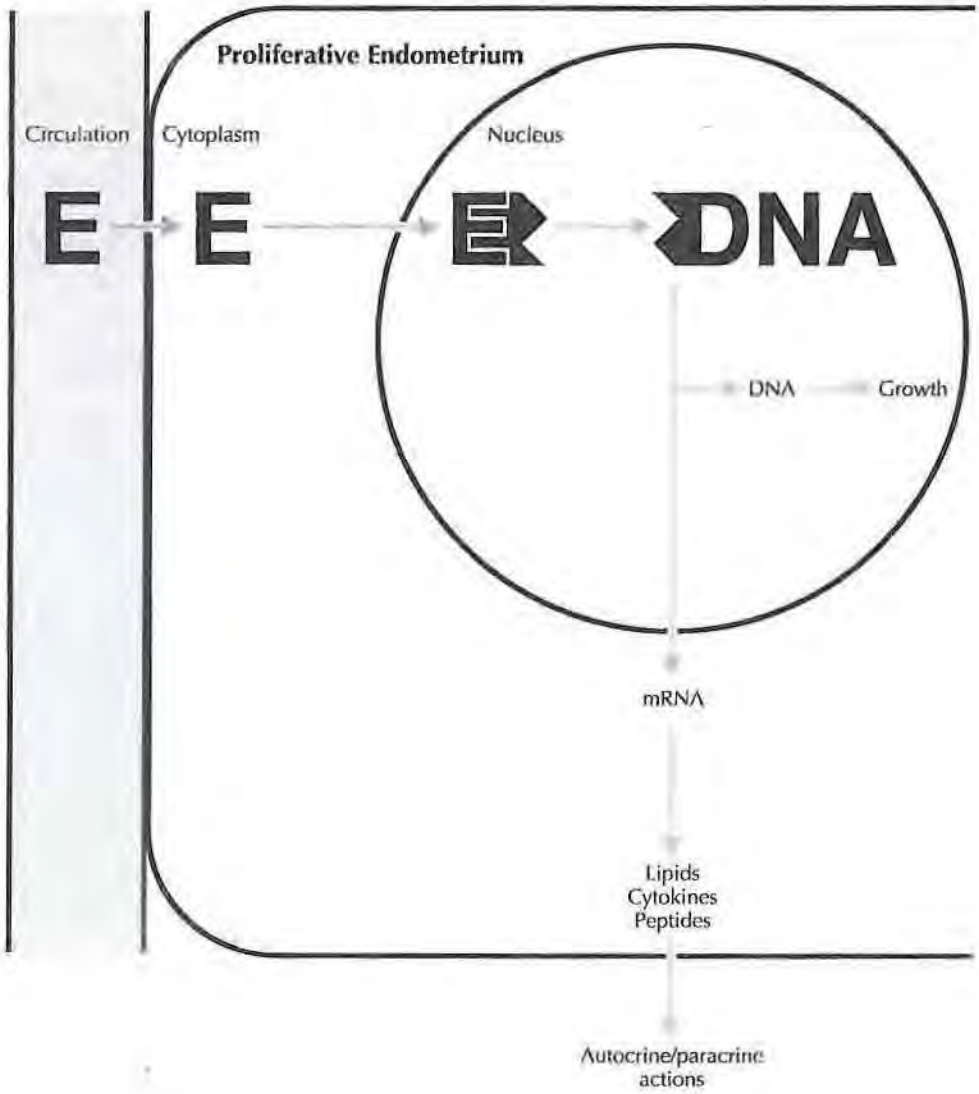
The uterus is dynamic. It not only responds and changes in a sensitive fashion to classic hormonal signals (the endocrine events of the menstrual cycle), but it is also composed of complex tissues, with important autocrine and paracrine functions that serve not only the uterus but the contiguous tissues of the fetoplacental unit during pregnancy. The most dynamic component of the uterus is the endometrium.

Endometrial Products

The endometrium secretes many substances, the functions of which (and their interrelationships) represent a major investigative challenge.[33] In addition to producing a nourishing, supportive environment for the early embryo, the endometrium plays an important role in suppressing the immune response within the pregnant uterus. The mechanisms controlling the immune response in decidual cells are not understood, but hormonal influence is undoubtedly important.

Lipids	Cytokines	Peptides
Prostaglandins	Interleukin-1α	Prolactin
Thromboxanes	Interleukin-1β	Relaxin
Leukotrienes	Interleukin-6	Prorenin and renin
	Interferon-γ	Endorphin
	Colony-stimulating factor-1	Endothelin-1
	Tumor necrosis factor-α	Corticotropin-releasing hormone
	Leukemia-inhibiting factor	Fibronectin
		Uteroglobin
		Lipocortin-1
		Parathyroid hormone-like protein
		Integrins
		Epidermal growth factor family
		EGF
		Heparin-binding EGF
		TGF-α
		Insulin-like growth factor family
		IGF-I
		IGF-II
		IGFBPs 1–6
		Platelet-derived growth factor
		Transforming growth factor-β
		Fibroblast growth factor
		Vascular endothelial growth factor

The presence of the cytokine family, involved in inflammation and immune responses, is not surprising in a tissue that undergoes cyclic degeneration. The interleukins stimulate prostaglandin production as well as other cytokines.[34] Colony-stimulating factor-1 is a cytokine that influences cellular proliferation and the presence of macrophages. Interferon-γ is produced by activated T-lymphocytes and inhibits endometrial epithelial proliferation. Leukemia-inhibiting factor (LIF) is expressed in response to a variety of other cytokines and growth factors. Like the interleukins, LIF is most abundant during the progesterone-dominated secretory phase and early decidua, and may have a role in embryo implantation.[35,36] Tumor necrosis factor-α (TNF-α) gene expression is present in endometrium, and its activity is increased during the proliferative phase, decreased early in the secretory phase, and increased again in the midsecretory phase.[37] TNF-α exerts multiple influences on cellular growth.



Growth factors are peptides that bind to specific cell membrane receptors and initiate intracellular signaling pathways. Because the growth factors are potent mitogens, it is also not surprising that the follicular phase of the cycle, associated with proliferative activity of the endometrium, is marked by dramatic alterations in growth factors. Estrogen stimulates gene expression for epidermal growth factor (EGF) (and its receptor) and insulin-like growth factor (IGF) production. In turn, EGF elicits estrogen-like actions by interacting with the estrogen receptor mechanism.[38] EGF, a potent mitogen, is present in endometrial stromal and epithelial cells during the follicular phase of the cycle and in the stromal cells during the luteal phase.[39] Transforming growth factor-α (TGF-α) and EGF work through the same receptor and are important mediators of estrogen-induced growth of the endometrium. TGF-α levels peak at midcycle, in contrast to EGF levels, which are relatively stable and noncyclic.[40–42] Platelet-derived growth factor is a potent mitogen localized to stromal cells.

The insulin-like growth factors promote cellular mitosis and differentiation. They are expressed in a pattern controlled by estrogen and progesterone. IGF-I is predominant in proliferative and early secretory endometrium, while IGF-II appears in the mid to late secretory phase and persists in early pregnancy decidua.[43] Endometrial IGF-I expression is correlated with the circulating estrogen levels during the menstrual cycle.[44] This suggests that IGF-I synthesis is regulated by estrogen and mediates estrogen-induced growth of the endometrium, and IGF-II is involved in differentiation in response to progesterone. Evidence in the monkey indicates that IGF-I is the primary regulator of myometrial growth in response to estrogen as well as to estrogen plus progesterone.[45]

As elsewhere in the body, the myometrial IGF activity is modulated by the IGF binding proteins, which respond to the sex steroids in a differential manner; IGFBP-2 parallels IGF-I response, whereas IGFBP-3 is decreased in muscle but increased in vascular endothelium by estrogen.[46] IGFBP-4 and IGFBP-5 respond to estrogen but are unaffected by the addition of progesterone. IGFBP-1, as discussed later, is a major product of decidualized endometrium.

Human myometrial smooth muscle and endometrial stromal cells express mRNA for parathyroid hormone-like protein, the function of which is unknown.[47] Transforming growth factor-β (TGF-β) stimulates the production of the parathyroid hormone-like protein. TGF-β production is greatest in the secretory phase and may inhibit cellular proliferation by increasing IGFBP-3 synthesis.

Prostaglandins are produced by both epithelial and stromal cells, and the prostaglandin content in the endometrium reaches a peak level in late secretory endometrium. The predominant prostaglandin produced by endometrium is prostaglandin $F_{2\alpha}$, a potent stimulus for myometrial contractions.[48] Endometrial prostaglandin production decreases dramatically after implantation, suggesting the presence of an active mechanism for suppression.[49] The production of prostaglandins requires estrogen support, but the increased production by secretory endometrium suggests progesterone enhancement, and acute withdrawal of progesterone promotes a further increase.[48] Endometrial stromal cells produce prostacyclin and thromboxane in response to estrogen, a response that can be blocked by progestins.[50] The myometrium principally produces prostacyclin, utilizing precursors derived from the endometrium. However, receptors for all members of the prostaglandin family are present on human myometrial cells, and contraction of the myometrium is a major consequence of prostaglandin $F_{2\alpha}$.[51]

Thromboxane is synthesized by uterine tissues. Gene expression for the thromboxane synthase and for the thromboxane receptor can be identified in endometrial glands, stromal cells, myometrial smooth muscle, and uterine blood vessels.[52] Thromboxane A_2 is a potent vasoconstrictor and stimulator of smooth muscle cells. Because of its rapid metabolism, it is limited to autocrine and paracrine activity.

Women with excessive menstrual bleeding have alterations in the normal rates of prostaglandin production. For this reason, effective reductions in menstrual blood loss can be achieved with treatment utilizing one of the nonsteroidal anti-inflammatory agents that inhibit prostaglandin synthesis. These agents are also effective treatment for prostaglandin-mediated dysmenorrhea.

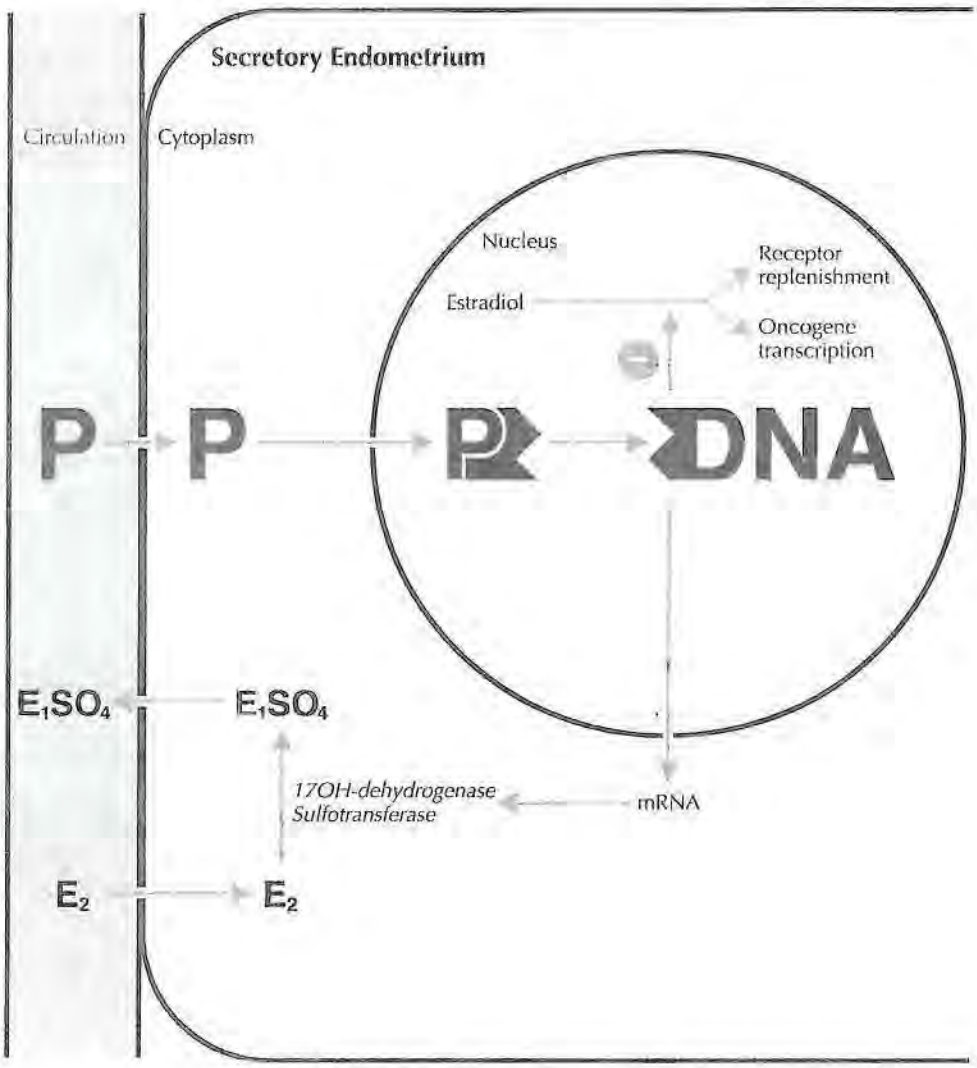
Fibronectin and laminin are extracellular matrix substances that are secreted by stromal cells of the endometrium in response to progesterone.[53] These proteins are important adhesion molecules during implantation. Integrins are a family of glycoproteins that function as receptors for proteins such as collagen, fibronectin, and laminin. The integrins are highly expressed in endometrium and are important for cell-to-cell and cell-to-matrix interactions.[54] The expression of integrins appears to be regulated by cytokines and growth factors, not estrogen and progesterone.[55]

Uteroglobin is a small protein expressed in endometrial epithelial cells.[56] The physiologic function of uteroglobin is uncertain. Uteroglobin, with high affinity, binds progestins and may play a role in immunosuppression. Uteroglobin gene expression is stimulated by estrogen, and this response is enhanced by progesterone. Human endometrium can secrete β-endorphin, yet another candidate for involvement in endometrial immunologic events, and its release is inhibited by both estrogens and glucocorticoids.[57]

Endothelins are potent vasoconstrictors produced in the vascular endothelial cells. The vasoconstrictor activity of endothelin-1, present in the endometrium, is balanced by the fact that it promotes the synthesis of the vasodilators, nitric oxide and prostacyclin. Endothelin-1 is synthesized in endometrial stromal cells and the glandular epithelium, stimulated by both TGF-β and interleukin-1α.[58] Endothelin-1 is at least one agent responsible for the vasoconstriction that shuts off menstrual bleeding. It is also a potent stimulator of myometrial contractions and can contribute to dysmenorrhea. Finally, endothelin-1 is a mitogen and can promote the healing reepithelialization of the endometrium. Human decidual cells also synthesize and secrete endothelin-1, from where it may be transported into the amniotic fluid.[59]

Angiogenesis, the formation of new blood vessels, is an essential process in tissue growth and development. Angiogenesis is necessary for tumor growth, and in normal tissues, it is usually kept in check by regulating factors. The female reproductive tissues (specifically ovarian follicles, the trophoblast, and the endometrium), however, must experience periodic and rapid growth and regression. In these tissues, angiogenesis is part of normal events. The endometrium is a major source for angiogenic factors during the menstrual cycle and during pregnancy.[60] Vascular endothelial growth factor, a specific mitogen for endothelial cells, is abundantly expressed in human endometrium, reaching a peak that correlates with the maximal angiogenesis reached during the secretory phase.[61] Angiogenesis is also influenced by many of the growth factors, and other substances such as fibronectin and prostaglandins. Fibroblast growth factor, in particular, is highly mitogenic for endothelial cells as well as endometrial stromal cells.

In all types of endometrial and myometrial cells, estrogen receptor expression reaches a maximum in the late follicular phase.[62, 63] The concentration is greatest in the glandular epithelium. During the early luteal phase, estrogen receptor expression declines, followed by an increase in the mid and late luteal phases. These changes reflect the cyclic changes in estradiol (which increases estrogen receptor expression) and progesterone (which decreases estrogen receptor expression).



Progesterone receptor expression in endometrial glandular epithelium reaches a maximum in the late follicular and early luteal phases (reflecting induction of progesterone receptor by estrogen), and then declines to nearly undetectable levels by the midpoint of the secretory phase. Stromal cells in the endometrium show only minor fluctuations in progesterone receptors during the menstrual cycle. Decidualizing stromal cells exhibit strong progesterone receptor expression, although progesterone receptors are absent from decidual epithelial cells. Smooth muscle cells of the uterus demonstrate strong progesterone receptor expression throughout the menstrual cycle. Many of the events in uterine growth and function are regulated by the interplay between estrogen and progesterone. In general, progesterone antagonizes estrogen stimulation of proliferation and metabolism. This antagonism can be explained by the effects of progestins on the estrogen receptor (a decrease in levels) and on the enzymes that lead to excretion of estrogen from cells and by progesterone suppression of estrogen-mediated transcription of oncogenes.

Androgen receptor is present in endometrium at all stages of the menstrual cycle, in postmenopausal endometrium, and in the decidua of pregnancy.[64] Surprisingly, the androgen receptor concentration is constant throughout the cycle.

The Decidua

The decidua is the specialized endometrium of pregnancy. The biochemical dialogue between the fetoplacental unit and the mother must pass back and forth through the decidua. The classic view of the decidua conformed to its designation as a thin line in anatomical diagrams, a minor, inactive structural component. We now know that the decidua is a vigorous, active tissue.

The glycoprotein α-subunit, common to follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and HCG, is secreted into the circulation by the pituitary and placenta. A specific role for the α-subunit has not been apparent; however, gonadotropin receptors are present in the endometrium and in vitro, α-subunit acts synergistically with progesterone to induce decidualization of endometrial cells.[65] In addition, the α-subunit stimulates decidual prolactin secretion.[66]

Decidual cells are derived from the stroma cells of the endometrium, under the stimulation of progesterone. Thus, they appear during the luteal phase and continue to proliferate during early pregnancy, eventually lining the entire uterus, including the implantation site. The decidual cell is characterized by the accumulation of glycogen and lipid droplets and the new expression of a host of substances, including prolactin, relaxin, renin, insulin-like growth factors (IGFs), and insulin-like growth factor binding proteins (IGFBPs). There is no evidence that these proteins are secreted into the circulation, therefore they serve as autocrine and paracrine agents.[67, 68]

Riddick was the first to detect prolactin in the decidualizing endometrium of the late luteal phase.[69] The amino acid sequence and the chemical and biological properties of decidual prolactin are identical to those of pituitary prolactin. Decidual prolactin synthesis and release are controlled by the placenta, fetal membranes, and decidual factors. Dopamine, bromocriptine, and thyroid-releasing hormone (TRH), in contrast to their action in the pituitary, have no effect on decidual synthesis and release of prolactin. A protein named decidual prolactin-releasing factor has been purified from the placenta, and an inhibiting protein, which blocks the stimulatory activity of the releasing factor, has been purified from decidua.[68] IGF-1, relaxin, and insulin all stimulate decidual prolactin synthesis and release, each through its own receptor. The same decidual cells produce both prolactin and relaxin.

Lipocortin-1 is a calcium and phospholipid binding protein, present in the placenta and decidua, that inhibits phospholipase A_2 and responds to glucocorticoids. Lipocortin-1 inhibits decidual prolactin release but in a mechanism independent of phospholipase action and independent of glucocorticoids. The prostaglandin system is not involved in decidual prolactin production, and corticoid steroids do not affect decidual prolactin release.[70]

There is good reason to believe that the amniotic fluid prolactin is derived from the decidua. In vitro experiments indicate that the passage of prolactin across the fetal membranes is in the direction of the amniotic cavity. The amniotic fluid concentration correlates with the decidual content, not maternal circulating levels. Amniotic fluid prolactin reaches peak levels in the first half of gestation (about 4000 ng/mL) when maternal plasma levels are approximately 50 ng/mL and fetal levels about 10 ng/mL. Maternal circulating prolactin reaches maximal levels near term. Finally, amniotic fluid prolactin is unaffected by bromocriptine treatment (which reduces both fetal and maternal circulating levels to baseline levels).

It is believed that decidual prolactin regulates amniotic fluid volume and electrolyte concentrations. It can be demonstrated that prolactin regulates water and ion transport in lower animals, and prolactin binds to amniotic membranes. Disorders in human pregnancy associated with abnormal amniotic fluid volumes may be explained by this mechanism, especially idiopathic polyhydramnios (which is associated with a decrease in the number of prolactin receptors in the membranes). Prolactin may be involved in the regulation of surfactant synthesis in the fetus, and prolactin may inhibit uterine muscle contractility. Prolactin suppresses the immune response and contributes to the prevention of immunologic rejection of the conceptus. Prolactin can also

function as an autocrine and paracrine growth factor in the uterus.[71]

Fibroblast growth factor, derived from decidua, stimulates blood vessel growth in early pregnancy. Another factor, endothelial-cell-stimulating angiogenesis factor (a nonprotein mitogen), is also derived from decidua and contributes to the vascularization of the decidua during the first trimester of pregnancy.[72] The expression of corticotropin-releasing hormone (CRH) has been demonstrated in human decidua, and many actions for decidual CRH are possible: activation of prostaglandins, stimulation of myometrial contractions, and a contribution to both maternal and fetal stress responses during pregnancy and labor.[73]

Prorenin (the inactive precursor of renin) is produced in decidua in response to IGF-1, insulin, endothelin, and relaxin.[74, 75] A uterine role for renin has not been determined. The insulin-like growth factor binding proteins, IGFBP-1, -2, -3, and -4, are produced by endometrial stromal cells.[76] Large amounts of IGFBP-1 are present in amniotic fluid. The IGFBPs appear to be regulated by insulin, the IGFs, and relaxin.[77] Relaxin is related structurally to insulin and the IGFs. However, in contrast to insulin and IGF, it stimulates IGFBP-1 production in endometrial stromal cells.[78]

IGFBP-1 begins to appear in midluteal phase endometrium and reaches a level of major production in decidua by late in the first trimester of pregnancy. IGFBP-1, when first identified, was known as placental protein 12 and then as pregnancy-associated α-globulin. By the second trimester of pregnancy, high levels of IGFBP-1 are present in the amniotic fluid and the circulation, which then fall significantly during the third trimester. The decidual production of IGFBP-1 is correlated with the morphologic and histologic changes induced by progesterone and regulated by progesterone, relaxin, insulin, IGF-I, and IGF-II. Binding of the insulin-like growth factors to the IGFBPs would limit further mitogenic activity in the endometrium in the secretory phase and during pregnancy. In addition, decidual IGFBP-1 may contribute to the limitation of trophoblast invasion.

The continuous stimulation of IGFBP-1 production by human endometrium can be maintained in women as long as they retain an intrauterine device that releases a progestin into the endometrial cavity.[79] In endometrial samples from these women, areas of endometrial atrophy correlate with intense staining for IGFBP-1. This makes a strong argument for the importance of insulin-like growth factors for endometrial growth and the potential for prevention of endometrial growth by providing IGFBP-1.

The chorion laeve, villous trophoblast, and decidua are all sites of TGF-β production.[80] TGF-β can signal its own production; thus, TGF-β can be a messenger from fetal tissues to decidua. TGF-β is also believed to play a role in limiting trophoblastic invasion.[81] This may be accomplished by stimulating the production of plasminogen activator inhibitor and the factor that causes tissue inhibition of metalloproteinases.[82]

Summary: The Uterus Is an Endocrine Organ

One cannot dispute the fact that the uterus is an endocrine organ, but the vast array of active substances can be bewildering and overwhelming. It is helpful to keep in mind a fundamental and relatively simple description: the endometrium is necessary for reproduction, and the synchronous, complex cycle of events is dependent on the endocrine guidance of estradiol and progesterone, modulated and mediated by the plethora of locally produced biochemical agents. Each and every signaling substance utilizes one of the pathways discussed in Chapter 2, and makes a contribution to the dynamic sequence of morphological and biochemical events repeatedly dedicated to nourishing and supporting an early embryo.

Congenital Abnormalities of the Uterus

Congenital abnormalities of the müllerian ducts are relatively common and contribute to the problems of infertility, recurrent pregnancy loss, and poor outcome in pregnancy (encountered in approximately 25% of women with uterine anomalies).[83-86] The problems encountered in pregnancy include preterm labor, breech presentations, and complications that lead to interventions and greater perinatal mortality. Cervical cerclage is often indicated for prevention of preterm labor due to these anomalies. In addition, these abnormalities can produce the symptoms of dysmenorrhea and dyspareunia, and even amenorrhea. Because the embryologic origin of the ovaries is separate and distinct from that of the müllerian structures, patients with müllerian anomalies have normal ovaries and ovarian function.

Incidence of Müllerian Defects[87]

Overall	**5%**
Fertile women	**2–3%**
Infertile women	**3%**
Women with recurrent miscarriages	**5–10%**
Women with late miscarriages and preterm deliveries	**>25%**

Anomalies can originate in the failure of the müllerian ducts to fuse in the midline, to connect with the urogenital sinus, or to create the appropriate lumen in the upper vagina and uterus by resorption of the central vaginal cells and the septum between the fused müllerian ducts. Because fusion begins in the midline and extends caudally and cephalad, abnormal results can exist at either end. Formation of the uterine cavity begins at the lower pole and extends cephalad with dissolution of midline tissue; hence, incomplete resorption of tissue commonly yields persistence of the midline uterine wall intruding into the cavity. The molecular pathophysiology of these abnormalities has been insufficiently studied; however, the association with other somatic anomalies and occasional reports of familial transmission suggest genetic linkages.

Vaginal outflow tract obstruction can be minimal with a transverse septum or complete due to agenesis. A septum is the result of a defect in the connection of the fused müllerian ducts to the urogenital sinus or a failure of canalization of the vagina. The location of the septum varies, although it is usually in the upper or middle third of the vagina. Vaginal agenesis is the result of a complete failure in canalization; these patients present with amenorrhea or pain due to accumulated menstrual effluvium. Surgical correction is frequently necessary to relieve the relative constriction (and obstruction) of the vaginal canal. An absent vagina is usually accompanied by an absent uterus and tubes, the classic müllerian agenesis of the Mayer-Rokitansky-Kuster-Hauser syndrome (discussed in Chapter 11).

Distribution of Specific Anomalies[87]

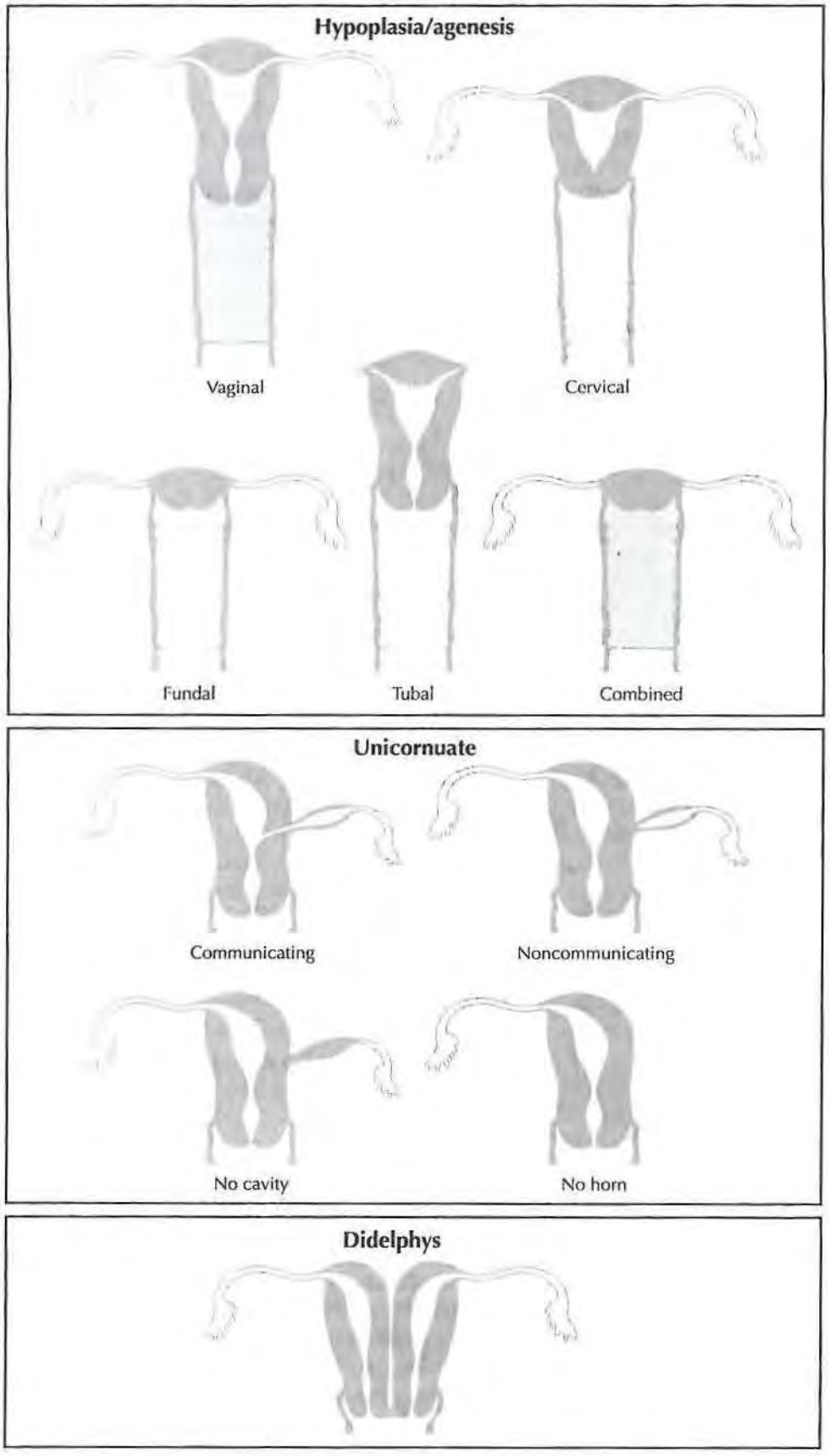
Bicornuate uterus	**37%**
Arcuate uterus	**15%**
Incomplete septum	**13%**
Uterus didelphys	**11%**
Complete septum	**9%**
Unicornuate uterus	**4.4%**

Uterine anomalies can be organized into the following categories.[88] Each of these can be associated with obstructions that present during adolescence with amenorrhea and cyclic pain.[89]

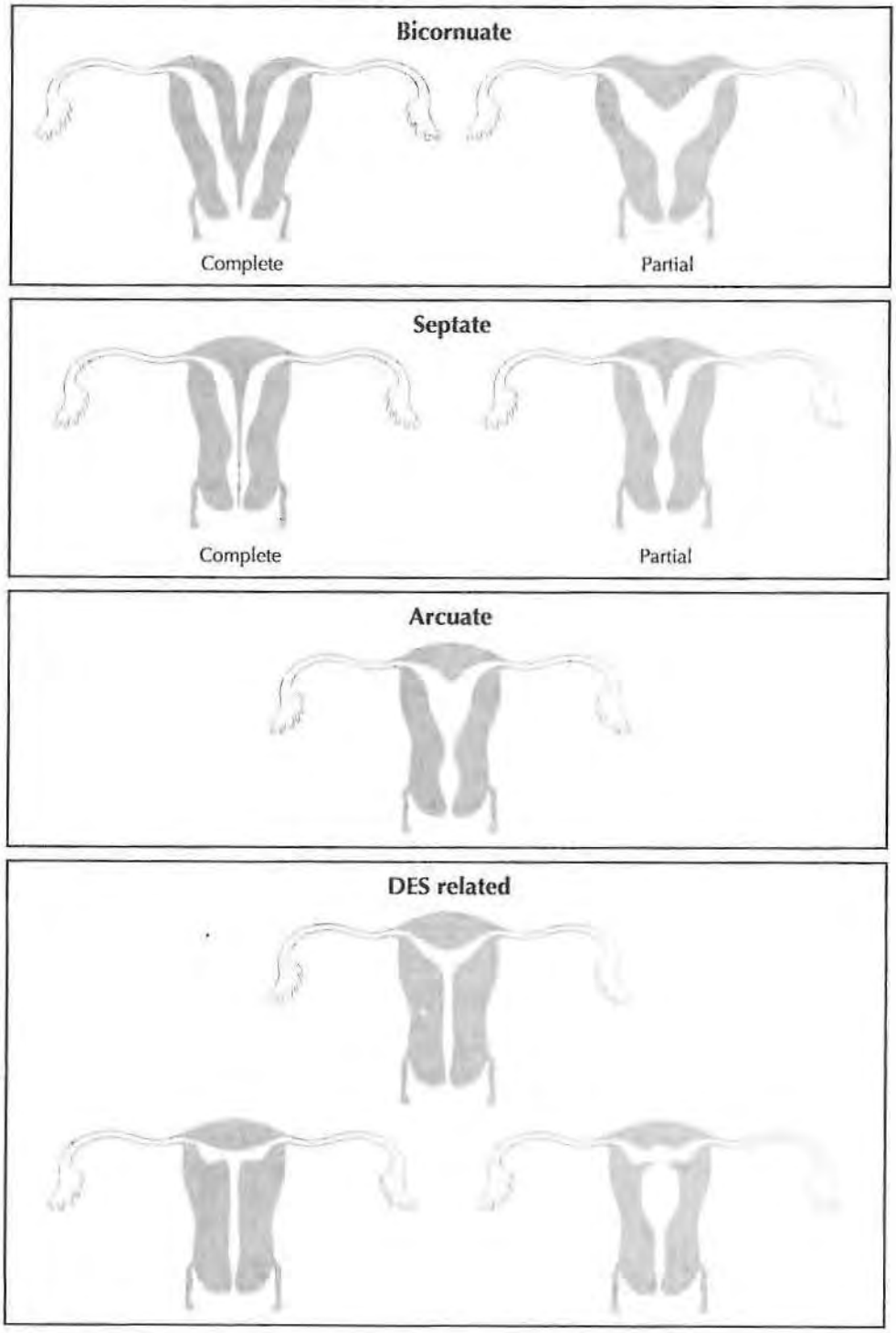
Unicornuate Uterus

An abnormality that is unilateral obviously is due to a failure of development in one müllerian duct (probably a failure of one duct to migrate to the proper location). The altered uterine configuration is associated with an increase in obstetrical complications (early spontaneous miscarriage, ectopic pregnancy, abnormal presentations, intrauterine growth retardation, and

Classification of Müllerian Anomalies[88]



Classification of Müllerian Anomalies[88]



premature labor).[90-92] There may be a rudimentary horn present, and implantation in this horn is followed by a very high rate of pregnancy wastage or tubal pregnancies. A rudimentary horn can also be a cause of chronic pain, and surgical excision may be worthwhile. However, most rudimentary horns are asymptomatic because they are non-communicating, and the endometrium is not functional. Because of the potential for problems, prophylactic removal of the rudimentary horn is recommended when it is encountered during a surgical procedure. Approximately 40% of patients with a unicornuate uterus will have a urinary tract anomaly (usually of the kidney).[93]

Uterus Didelphus (Double Uterus)

Lack of fusion of the two müllerian ducts results in duplication of corpus and cervix. These patients usually have no difficulties with menstruation and coitus. Occasionally, one side is obstructed and symptomatic. In addition, a double uterus is occasionally associated with an obstructed hemivagina (often with ipsilateral renal agenesis); early diagnosis and excision of the obstructing vaginal septum will preserve fertility. Pregnancy is associated with an increased risk of malpresentations and premature labor, although many patients will have no reproductive difficulties.[92]

The Bicornuate Uterus

Partial lack of fusion of the two müllerian ducts produces a single cervix with a varying degree of separation in the two uterine horns. This anomaly is relatively common, and pregnancy outcome has usually been reported to be near normal. Some, however, find a high rate of early miscarriage, preterm labor, and breech presentations.[86, 92].

The Septate Uterus

Partial lack of resorption of the midline septum between the two müllerian ducts results in defects that range from a slight midline septum (the arcuate, heart-shaped cavity) to a significant midline division of the endometrial cavity. A total failure in resorption can leave a longitudinal vaginal septum (a double vagina). This defect is not a cause of infertility, but once pregnant, the greater the septum the greater the risk of recurrent spontaneous miscarriage. The complete septate uterus is associated with a high risk of preterm labor and breech presentation.[86] Outcomes are excellent with treatment by hysteroscopy.[94, 95] Posttreatment miscarriage rates are approximately 10% in contrast to the 90% pretreatment rates. A longitudinal vaginal septum usually does not have to be excised (unless dyspareunia is a problem). In some reports, the arcuate uterus had no adverse impact on reproductive outcome.[92]

Very Rare Anomalies

Isolated agenesis of the cervix or the endometrium is incredibly rare. Absence of the cervix can lead to so much pain and obstruction that hysterectomy is the best solution. Attempts to preserve fertility by creating a fistulous communication between uterus and vagina have achieved little success, and repeat surgery due to reappearance of obstruction is common.[96] In asymptomatic patients, consideration should be given to preservation of structures for the possibility of pregnancy that can be achieved by means of one of the techniques of assisted reproduction. (Chapter 31)

The Diethylstilbestrol-Associated Anomaly

We are still encountering women whose mothers were treated with high doses of estrogen during their pregnancies. Exposure to these high levels of estrogen during müllerian development caused a variety of anomalies, ranging from the hypoplastic "T" shaped uterus to irregular cavities with adhesions.[97] Women with uterine abnormalities usually also have cervical defects. In these individuals, the chance of term pregnancy is decreased because of higher risks of ectopic pregnancy, spontaneous miscarriage, and premature labor. An incompetent cervix is common. Poor outcome is correlated with an abnormal uterus on hysterosalpingography. No treatment is available beyond cervical cerclage.

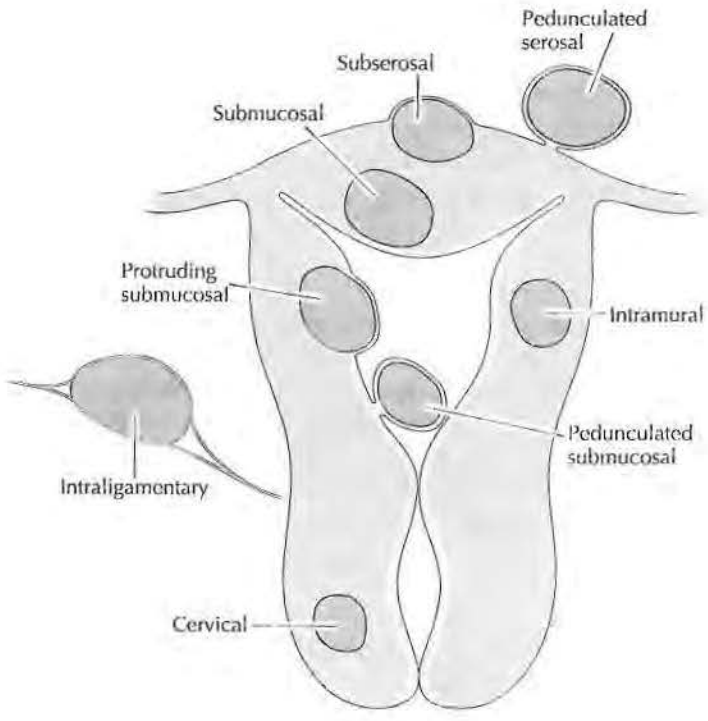
Accurate Diagnosis of Anomalies

In the past, full diagnosis has required surgical intervention, first laparotomy and then, more recently, laparoscopy. Today, vaginal ultrasonography and magnetic resonance imaging are highly accurate, and surgical intervention is usually not necessary.[98] Hysterosalpingography is relatively inaccurate, and decisions should not be based upon hysterosalpingography alone. Congenital anomalies of the müllerian ducts are frequently accompanied by abnormalities in the urinary tract. Renal agenesis is often present on the same side as a müllerian defect.

Leiomyomata (Uterine Fibroids)

Uterine leiomyomas are benign neoplasms that arise from uterine smooth muscle. It is hypothesized that leiomyomas originate from somatic mutations in myometrial cells, resulting in progressive loss of growth regulation.[99, 100] The tumor grows as genetically abnormal clones of cells derived from a single progenitor cell (in which the original mutation took place). Studies indicate that leiomyomas are monoclonal. Different rates of growth can reflect the different cytogenetic abnormalities present in individual tumors. Multiple myomas within the same uterus are not clonally related; each myoma arises independently. The presence of multiple myomas (which have a higher recurrence rate than single myomas) argues in favor of a genetic predisposition for myoma formation; however, the familial inheritance of uterine myomas has not been well studied. It is not certain whether leiomyosarcomas arise independently or from leiomyomas. However, the incidence of leiomyosarcomas in patients with leiomyomata is very low (less than 1%).[101]

If surgical specimens are serially sectioned, about 77% of women who come to hysterectomy will have myomas, many of which are occult.[102] Overall, about 17% of hysterectomies are performed for myomas in the U.S. (44% in women 45–54 years old).[103] The peak incidence for myomas requiring surgery occurs around age 45, approximately 8 cases per 1000 women each year. In the U.S., approximately 10–15% of women require hysterectomy for myomas. For unknown reasons, uterine leiomyomas are 2–3 times more prevalent in black women compared with white, Hispanic, and Asian women.[104] The major symptoms associated with myomas are menorrhagia and the physical effects produced by large myomas.



Myomas will be encountered in about 1% of pregnant women. The risk of myoma is decreased with increasing parity and with increasing age at last term birth.[105] Women with at least two full term pregnancies have half the risk for myomas. Smoking decreases the risk (presumably by decreasing estrogen levels), and obesity increases the risk (presumably by increasing estrogen levels). Although a lower risk for myomas is associated with factors that decrease estrogen levels, including leanness, smoking, and exercise, the use of oral contraceptives is not associated with an increased risk of uterine myomas, although the Nurses' Health Study reported a slightly increased risk when oral contraceptives were first used in early teenage years.[105–107]

The hormone sensitivity of leiomyomas is indicated by the following clinical observations. Leiomyomas develop during the reproductive (hormonally active) years and regress after menopause. Occasionally, leiomyomas grow during pregnancy, and the hypogonadal state induced by treatment with gonadotropin-releasing hormone (GnRH) agonists often causes shrinkage of myomas.

The environment within the leiomyoma is hyperestrogenic. The estradiol concentration is increased, and leiomyomas contain more estrogen and progesterone receptors.[108–110] Aromatase gene and enzyme expression are present in significant levels in leiomyomata.[111] Indeed, leiomyoma tissue is hypersensitive to estrogen and appears to have lost a regulatory influence that limits estrogen response.[112] Endometrial hyperplasia is frequently observed at the margins of submucous myomas.[113] In the myometrium and in leiomyomas, peak mitotic activity occurs during the luteal phase, and mitotic activity is increased by the administration of high doses of progestational agents.[114, 115] These facts indicate that progesterone stimulates mitotic activity in leiomyomas, but animal studies indicate both stimulation and inhibition of myometrial growth. Similarly, clinicians have reported both regression and growth with progestational treatment. Nevertheless, most of the evidence supports a growth-promoting role for progestins (the association with estrogen can be explained by the estrogen enhancement of progesterone receptor expression).[116, 117] Treatment with RU486, the progesterone antagonist, is associated with a reduction in leiomyomata size.[118]

The *bcl-2* protooncogene, presumably a cell survival gene, produces a protein that prevents apoptosis and promotes cell replication. Bcl-2 protein expression is increased in leiomyoma cells, and markedly increases in response to progesterone.[119] In contrast, normal myometrial cells do not respond to estradiol or progesterone with Bcl-2 protein expression, and there is no cyclic change throughout the menstrual cycle. This further supports a key role for progestins in leiomyoma growth.

As in the normal uterus, the effects of estrogen and progestins on leiomyomata are mediated by growth factors.[120] EGF is overexpressed in myomas, EGF receptors are present in leiomyomata, and GnRH agonist treatment (and hypogonadism) decreases EGF concentration in myomas (but not in normal myometrium).[121, 122] IGF-I and IGF-II and their receptors are abundant in myometrium, and actively overexpressed in leiomyomas.[123, 124] Leiomyomas express more IGF-II and less IGFBP-3 than myometrium, a situation that would enhance growth factor availability and activity in the tumor.[125] Leiomyomata cells express more parathyroid hormone-related protein (another growth factor) than normal myometrium.[126] Like the endometrium and myometrium, leiomyomas secrete prolactin, and prolactin functions in the uterus as a growth factor.[71] Even hematopoiesis is possible in a leiomyoma.[127]

One of the consequences of altered growth factor expression in myomas is an abnormal vasculature, characterized by a dilated venous plexus.[128] This morphologic feature may be the result of specific vascular regulators of angiogenesis, such as basic fibroblast growth factor and vascular endothelial growth factor. These changes probably contribute to the heavy menstrual bleeding associated with submucosal myomas.

Reproductive Function and Leiomyomata

Leiomyomas are an infrequent cause of infertility, either by mechanical obstruction or distortion (and interference with implantation).[129] When a mechanical obstruction of fallopian tubes, cervical canal, or endometrial cavity is present and no other cause of infertility or recurrent miscarriage can be identified, myomectomy is usually followed by a prompt achievement of pregnancy in a high percentage of patients (usually within the first year).[130] Submucous myomas are best treated by hysteroscopic resection. Preoperative visualization is important, and mapping of myomas by magnetic resonance imaging (MRI) is superior to ultrasonography (which is relatively inaccurate).[131] It is difficult to distinguish between submucous myomas and endometrial polyps with ultrasonography.[132] Very large myomas (greater than 4–5 cm) and myomas that do not have greater than 50% protrusion into the cavity are not good candidates for hysteroscopic removal.

The short-term recurrence rate after myomectomy (either abdominal myomectomy or hysteroscopic resection) is about 15%, with subsequent hysterectomy necessary in 1–5% of patients.[133] In a series with long-term follow-up, the recurrence rate over 10 years reached 27%.[134] Women who gave birth after myomectomy had a recurrence rate (over 10 years) of 16%, compared to a rate of 28% in those who did not give birth. In an Italian study of recurrence, the rate at 5 years reached 55% in those who did gave birth after surgery and 42% in those with no childbirth.[135] These differences may reflect the diligence and sensitivity of the ultrasonographic assessments.

An increased incidence of spontaneous miscarriage because of myomas has not been definitively documented in the literature. Myomectomy for infertility or recurrent miscarriage requires a deliberate and careful decision after all factors have been considered. Intracavitary myomas, however, usually require surgery. Because of the rapid regrowth of myomas following cessation of GnRH agonist therapy, medical therapy for infertility is not recommended.

Myomas are present (diagnosed by ultrasonography) in about 1–2% f pregnancies.[136] Most myomas do not grow during pregnancy.[137] When they do, most of the growth is in the first trimester, and most myomas regress in size after the pregnancy. The size of a myoma will not predict its course; large myomas will not necessarily grow more than small ones. Most pregnancies, in the presence of myomas, will, therefore, be uncomplicated (although a higher incidence of cesarean section has been observed).[136] So-called red degeneration of myomas is occasionally observed during late pregnancy, a condition due to central hemorrhagic infarction of the myoma. Pain is the hallmark of this condition, occasionally associated with rebound tenderness, mild fever, leukocytosis, nausea, and vomiting. Usually pain is the only symptom and resolution follows rest and analgesic treatment.[138] Surgery should be a last resort. The larger the myoma, the greater the risk of premature labor.[139]

Medical Therapyof Leiomyomata

The goals of medical therapy for leiomyomas are to ***temporarily*** reduce symptoms and to reduce myoma size, and the therapy of choice is treatment with a GnRH agonist.[140]

The short half-life of GnRH is due to rapid cleavage of the bonds between amino acids 5-6, 6-7, and 9-10. By altering amino acids at these positions, analogues of GnRH can be synthesized with different properties. Substitution of amino acids at the 6 position or replacement of the C-terminal glycine-amide (inhibiting degradation) produces agonists. An initial agonistic action (the so-called flare effect) is associated with an increase in the circulating levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). This response is greatest in the early follicular phase when GnRH and estradiol have combined to create a large reserve pool of gonadotropins. After 1–3 weeks, desensitization and down-regulation of the pituitary produce a hypogonadotropic, hypogonadal state. The initial response is due to desensitizatiion, the uncoupling of the receptor from its effector system, whereas the sustained response is due to a loss of

receptors by down-regulation and internalization. Furthermore, postreceptor mechanisms lead to secretion of biologically inactive gonadotropins, which, however, can still be detected by immunoassay.

The GnRH analogues cannot escape destruction if administered orally. Higher doses administered subcutaneously can achieve nearly equal effects as observed with intravenous treatment; however, the smaller blood peaks are slower to develop and take longer to return to baseline. Other forms of administration include nasal spray, sustained release implants, and intramuscular injections of biodegradable microspheres.

Treatment With GnRH Agonists

Summarizing the experience with GnRH agonist treatment of leiomyomata, the mean uterine size decreases 30–64% after 3–6 months of treatment.[140] Maximal response is usually achieved by 3 months. The reduction in size correlates with the estradiol level and with body weight. Menorrhagia, anemia, pelvic pressure, and urinary requency all respond favorably to GnRH agonist treatment. A decrease in operative blood loss can be achieved when the pretreatment uterus is as large or larger as a 16-week pregnancy. Why is there a variation in response? When one considers the many factors involved in myoma growth (estrogen, progesterone, growth factors, and receptors), it makes sense that not every myoma is the same. After cessation of GnRH agonist therapy, menses return in 4–10 weeks, and myoma and uterine size return to pretreatment levels in 3–4 months. The rapid regrowth is consistent with the fact that reduction in size is not due to a cytotoxic effect.

Preoperative GnRH agonist therapy offers several advantages for hysteroscopic removal of submucous tumors. In addition to a decrease in myoma size, endometrial atrophy will improve visualization, and decreased vascularity will reduce blood loss.

Leiomyomatosis Peritonealis Disseminata is a condition in which multiple small nodules of benign smooth muscle are found throughout the abdominal cavity, and occasionally in the pulmonary cavity. This condition appears to be sensitive to estrogen because it has been aggravated by postmenopausal estrogen treatment, and regression has been achieved with GnRH agonist treatment.[141]

Adenomyosis is the ectopic presence of endometrial glands within the myometrium. This diagnosis can be made by magnetic resonance imaging, and successful treatment with a GnRH agonist has been reported.[142, 143]

Side Effects With GnRH Agonists

Hot flushes are experienced by more than 75% of patients, usually in 3–4 weeks after beginning treatment. Approximately 5–15% of patients will complain of headache, vaginal dryness, joint and muscle stiffness, and depression. About 30% of patien will continue to have irregular (although light) vaginal bleeding. It is useful to measure the circulating estradiol level. If the level is greater than 30 pg/mL, suppression is inadequate. On the other hand, Friedman and colleagues have suggested that maintaining the estradiol level in the early follicular phase range (30–50 pg/mL) can protect against osteoporosis and reduce hot flushes, but not allow the growth of myomas.[144] The efficacy of this titration of response requires validation by clinical studies.

A small number (10%) of patients will experience a localized allergic reaction at the site of injection of depot forms of GnRH analogues. More serious reaction is rare, but immediate and delayed anaphylaxis can occur, requiring intense support and management.[145]

Bone loss occurs with GnRH therapy, but not in everyone, and it is reversible (although it is not certain if it is totally reversible in all patients). A significant vaginal hemorrhage 5–10 weeks after beginning treatment is encountered in about 2% of treated women, due to degeneration and necrosis of submucous myomas.[146] A disadvantage of agonist treatment is a delay in diagnosis of a leiomyosarcoma. Keep in mind that almost all leiomyosarcmas present as the largest or only

uterine mass. Close monitoring is necessary and surgery has been the usual recommendation when either enlargement or no shrinkage of myomas occurs during GnRH agonist treatment.[147] The use of Doppler ultrasonography or magnetic resonance imaging offers greater accuracy of evaluation. However, the incidence of leiomyosarcoma, even in patients with "rapidly growing leiomyomata," is very low (less than 0.5%) and almost unheard of in premenopausal women.[101] In premenopausal women, a conservative approach is warranted.

Escape of suppression an result in an unexpected pregnancy. No adverse effects of fetal exposure to GnRH agonists have been reported, even when exposure has persisted throughout the early weeks of pregnancy.[148]

GnRH Agonists and Steroid Add-Back

Treatment with a GnRH agonist with steroid add-back has been explored to permit long-term therapy without bone loss.[140] Two strategies have been employed: simultaneous agonist and steroid add-back treatment or a sequential regimen in which the agonist is used alone for 3 months, followed by the combination of the agonist and steroid add-back. This long-term treatment is attractive for women who are perimenopausal, perhaps avoiding surgery. In addition, long-term treatment would be useful for women with coagulopathies, and in women with medical problems who need to postpone surgery.

Simultaneous treatment with agonist and medroxyprogesterone acetate (20 mg daily) or norethindrone (10 mg daily) effectively reduced hot flushing, but was less effective (consistent with a major supportive role for progestins in myomas) in reducing uterine volume.[140, 149] A sequential program, adding a traditional postmenopausal hormone regimen (0.625 mg conjugated estrogens on days 1–25 and 10 mg medroxyprogesterone acetate on days 16–25) effectively reduced uterine volume and maintained the reduced volume for 2 years (and avoided any loss in bone density)/[140] A daily 2.5 mg dose of tibolone also prevents bone loss and inhibits vasomotor symptoms without reducing the therapeutic efficacy of GnRH agonist treatment.[150]

We recommend 1 month of GnRH agonist treatment followed by agonist treatment combined with a daily, continuous add-back of estrogen and progestin using one of the available postmenopausal daily regimens. In view of the sensitivity of leiomyomata tissue to progestational agents, it makes sense to keep the dose of progestin relatively low.

Summary of Clinical Advantages With GnRH Agonist Treatment

Reduction in menstrual blood loss.
Improvement in anemia prior to surgery.
Time for autologous blood donation.
Less operative blood loss.
Hysterectomy less likely.
More likely to allow laparoscopic technique.
Possible conversion from abdominal to vaginal hysterectomy.

Treatment with a GnRH Antagonist

GnRH antagonist treatment can suppress pituitary-gonadal function without the initial stimulatory (flare) response observed with GnRH agonists. Results with depot Cetrorelix preoperative treatment of uterine fibroids are similar to those with GnRH agonist treatment; however, the response is faster (a maximal reduction in size within 14 days), probably because there is no initial flare response.[151]

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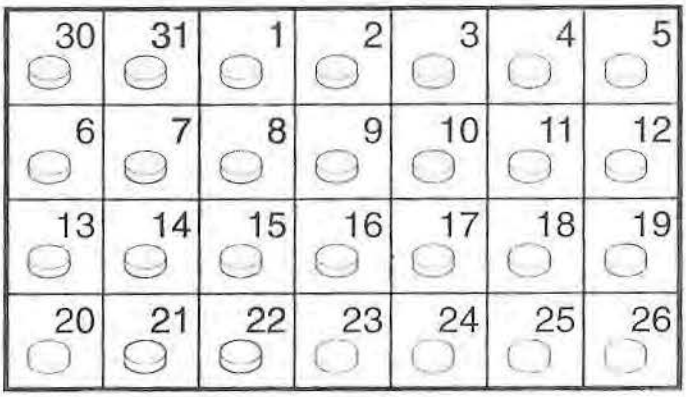
22 Oral Contraception



Contraception is commonly viewed as a modern event, a recent development in human history. On the contrary, efforts to limit reproduction predate our ability to write about it. It is only oral contraception with synthetic sex steroids that is recent.

History

It wasn't until the early 1900s, that inhibition of ovulation was observed to be linked to pregnancy and the corpus luteum. Ludwig Haberlandt, professor of physiology at the University of Innsbruck, Austria, was the first to demonstrate that ovarian extracts given orally could prevent fertility (in mice). In the 1920s, Haberlandt and a Viennese gynecologist, Otfried Otto Fellner, were administering steroid extracts to a variety of animals and reporting the inhibition of fertility. By 1931, Haberlandt was proposing the administration of hormones for birth control. An extract was produced, named Infecundin, ready to be used, but Haberlandt's early death in 1932, at age 47, brought an end to this effort. Fellner disappeared after the annexation of Austria to Hitler's Germany.

The concept was annunciated by Haberlandt, but steroid chemistry wasn't ready. The extraction and isolation of a few milligrams of the sex steroids required starting points measured in gallons of urine or thousands of pounds of organs. Edward Doisy processed 80,000 sow ovaries to produce 12 mg of estradiol.

Russell Marker

The supply problem was solved by an eccentric chemist, Russell E. Marker, who completed his thesis, but not his course work, for his Ph.D. Marker, born in 1902 near Hagerstown, Maryland, received his Bachelor's degree in organic chemistry and his Master's degree in colloidal chemistry from the University of Maryland. After leaving the University of Maryland, Marker worked with the Ethyl Gasoline Corporation, and in 1926, developed the process of octane rating, based on the discovery that knocking in gasoline was due to hydrocarbons with an uneven number of carbons.

From 1927 to 1935, Marker worked at the Rockefeller Institute, publishing a total of 32 papers on configuration and optical rotation as a method of identifying compounds. He became

interested in solving the problem of producing abundant and cheap amounts of progesterone, but he was told to continue with his work in optical technology. In 1935, he moved to Pennsylvania State University at a reduced salary, but with the freedom to pursue any field of research. At that time, it required the ovaries from 2500 pregnant pigs to produce 1 mg of progesterone. In 1939, Marker devised the method (called the Marker degradation) to convert a sapogenin molecule into a progestin. Marker became convinced that the solution to the problem of obtaining large quantities of steroid hormones was to find plants (in the family that includes the lily, the agave, and the yam) that contained sufficient amounts of diosgenin, a plant steroid (a sapogenin) that could be used as a starting point for steroid hormone production. This conviction was strengthened with his discovery that a species of *Trillium,* known locally as Beth's root, was collected in North Carolina and used in the preparation of Lydia Pinkham's Compound, popular at the time to relieve menstrual troubles. The active ingredient in Beth's root was diosgenin, but the rhizome was too small to provide sufficient amounts for commercial production. Marker's search for an appropriate plant took him to California, Arizona, and Texas.

On a visit to Texas A & M University, Marker found a picture of a large dioscorea (*Dioscorea mexicana)* in a book that he just happened to pick up and browse through while spending the night at the home of a retired botanist. After returning to Pennsylvania, he decided to go to Veracruz, Mexico (it took 3 days by train), to search for this dioscorea. He made several attempts in 1941 and early 1942, but was frustrated first by the lack of a plant-collecting permit from the Mexician government and then by his failure to find the plant. He remembered that the book with the picture reported that this dioscorea was known locally as "cabeza de negro," black tubers that grew near Orizaba and Cordoba. Marker took a bus to Cordoba, and near Orizaba, an Indian who owned a small store brought him two plants. Each tuber was 9–12 inches high and consisted of white material like a turnip, used by local Mexicans as a poison to catch fish.

Marker managed to get one bag of tubers back to Pennsylvania State University and isolated diosgenin. Unable to obtain support from the pharmaceutical industry, Marker used his life savings, and in 1942, he returned to Veracruz, collected the roots of the Mexican yam, and prepared a syrup from the roots. Back in Pennsylvania with his 5-gallon cans of syrup, Marker worked out the degradation of diosgenin to progesterone. One 5-gallon can yielded 3 kg of progesterone. United States pharmaceutical companies still refused to back Marker, and even the University refused, despite Marker's urging, to patent the process.

In 1943, Marker resigned from Pennsylvania State University and went to Mexico where he collected the roots of *Dioscorea mexicana,* 10 tons worth! Looking through the yellow pages in a Mexico City telephone directory, Marker found a company called Laboratorios Hormona, owned by a lawyer, Emeric Somlo, and a physician, Frederick Lehman. Marker arranged a meeting, and the three agreed to form a Mexican company to produce hormones. In an old pottery shed in Mexico City (the laboratories of Laboratorios Hormona), in two months, he prepared several pounds of progesterone (worth $300,000) with the help of four young women who had little education and spoke no English (Marker did not speak Spanish). The two partners and Marker formed a company in 1944 that they called Syntex (from *synthesis* and *Mexico*). In 1944, Marker produced over 30 kg of progesterone. The price of progesterone fell from $200 to $50 a gram.

During this time, Marker received expenses, but he was not given his share of the profits or the 40% share of stock due to him. Failing to reach a settlement, Marker left Syntex after only one year and started a new company in Texcoco, called Botanica-Mex. He changed to *Dioscorea barbasco,* which gave a greater yield of diosgenin, and the price of progesterone dropped to $10 a gram, and later to $5. This company was allegedly harassed (legally and physically) by Syntex, and in 1946, sold, eventually reaching ownership by Organon of Holland, which still uses it.

In 1949, Marker retired to Pennsylvania to devote the rest of his life to making replicas of antique works in silver, a successful business that allowed him, in the 1980s, to endow scientific lectureships at both Pennsylvania State University and the University of Maryland. However, he

took his know-how with him. Fortunately for Syntex, he had published a scientific description of his process, and there still was no patent on his discoveries. Syntex recruited George Rosenkranz, a Hungarian immigrant living in Cuba, to reinstitute the commercial manufacture of progesterone (and testosterone) from Mexican yams, a task that took him (with the help of the women left behind by Marker) 2 years.

In 1970, the Mexican government recognized Marker and awarded him the Order of the Aztec Eagle; he declined. In 1984, Pennsylvania State University established the annual Marker Lectures in Science, and in 1987, the Russell and Mildred Marker Professorship of Natural Product Chemistry. In 1987, Marker was granted an honorary Doctorate in Science from the University of Maryland, the degree he failed to receive in 1926. At the age of 92, Russell Earl Marker died in Wernersville, Pennsylvania, in 1995, from complications after a broken hip.

Carl Djerassi[4]

The Djerassi family lived in Bulgaria for hundreds of years after escaping Spain during the Inquisition. Carl Djerassi, the son of a Bulgarian physician, was born in Vienna (as was his physician mother). Djerassi, at the age of 16, and his mother emigrated to the United States in 1939. A Jewish refugee aid organization placed Djerassi with a family in Newark, New Jersey. With a scholarship to Tarkio College in Tarkio, Missouri, he was exposed to middle America, where he earned his way giving talks to church groups about Bulgaria and Europe. His education was further supported by another scholarship from Kenyon College in Ohio, where he pursued chemistry. After a year working for CIBA, Djerassi received his graduate degree from the University of Wisconsin. Returning to CIBA and being somewhat unhappy, he responded to an invitation to visit Syntex. Rosenkranz proposed that Djerassi head a research group to concentrate on the synthesis of cortisone.

In 1949, it was discovered that cortisone relieved arthritis, and the race was on to develop an easy and cheap method to synthesize cortisone. Carl Djerassi, at age 26, joined Syntex to work on this synthesis using the Mexican yam plant steroid diosgenin as the starting point. This was quickly achieved (in 1951), but soon after, an even better method of cortisone production using microbiologic fermentation was discovered at Upjohn. This latter method used progesterone as the starting point, and, therefore, Syntex found itself as the key supplier to other companies for this important process, at the rate of 10 tons of progesterone per year and a price of 48 cents per gram.

Djerassi and other Syntex chemists then turned their attention to the sex steroids. They discovered that the removal of the 19-carbon from yam-derived progesterone increased the progestational activity of the molecule. Ethisterone had been available for a dozen years, and the Syntex chemists reasoned that removal of the 19-carbon would increase the progestational potency of this orally active compound. In 1951, norethindrone was synthesized; the patent for this drug is the first patent for a drug listed in the National Inventor's Hall of Fame in Akron, Ohio. A closely related compound, norethynodrel, was actually the first orally active progestational agent to receive a patent, assigned to Frank Colton, a chemist at G.D. Searle & Company.

Gregory Pincus

Gregory Goodwin (Goody) Pincus was born in 1903 in New Jersey, the son of Russian Jewish immigrants who lived on a farm colony founded by a German-Jewish philanthropic organization. Pincus was the oldest of 6 children and grew up in a home of intellectual curiosity and energy, but even his family regarded him as a genius.

Pincus graduated from Cornell and went to Harvard to study genetics, joining Hudson Hoagland and B.F. Skinner as graduate students of W.J. Crozier in physiology, receiving degrees in 1927. Crozier's hero was Jacques Loeb who discovered artificial parthenogenesis working with sea urchin eggs. Most importantly, Loeb was a strong believer in applying science to improve human life. Thus, Crozier, influenced by Loeb, taught Pincus, Hoagland, and Skinner (respectively, in reproductive biology, neurophysiology, and psychology) to apply science to human problems. This was to be the cornerstone of Pincus's own philosophy.

Hoagland, after a short stay at Harvard, spent a year in Cambridge, England, and then moved to Clark University in Worcester, Massachusetts, to be the chair of biology at the age of 31. Pincus went to England and Germany, and returned to Harvard as an assistant professor of physiology.

Pincus performed pioneering studies of meiotic maturation in mammalian oocytes, in both rabbit and human oocytes. In 1934, Pincus reported the achievement of in vitro fertilization of rabbit eggs, earning him a headline in the New York Times that alluded to Haldane and Huxley. An article in Colliers depicted him as an evil scientist. By 1936, Harvard had cited Pincus's work as one of the university's outstanding scientific achievements of all time, but Harvard denied him tenure in 1937.

At Clark University, Hudson Hoagland was in constant conflict with the president of the university, Wallace W. Atwood, the senior author of a widely used textbook on geography. In 1931, the Department of Biology consisted of one faculty member and his graduate student, and their chair, Hudson Hoagland. Hoagland, upset and angry over Harvard's refusal to grant tenure to his friend (suspecting that this was because of anti-Semitism), invited Pincus to join him.

Hoagland secured funds for Pincus from philanthropists in New York City, enough for a laboratory and an assistant. This success impressed the two men, especially Hoagland, planting the idea that it would be possible to support research with private money.

Min-Chueh Chang received his Ph.D. degree from Harvard on an infamous day, December 7, 1941, and thus he was forced to remain in this country. He was drawn to Pincus because of Pincus's book, *The Eggs of Mammals*, published in 1936, a book that had a major impact on biologists at that time. The successful recruitment of M-C Chang by Hoagland and Pincus was to pay great dividends.

Soon Hoagland had put together a group of outstanding scientists, but because of his on-going antagonism with President Atwood, the group was denied faculty status. Working in a converted barn, they were totally supported by private funds. By 1943, 12 of Clark's 60 faculty were in the Department of Biology.

Frustrated by the politics of academia, Hoagland and Pincus (who both enjoyed stepping outside of convention) had a vision of a private research center devoted to their philosophy of applied science. Indeed, the establishment of the Worcester Foundation for Experimental Biology, in 1944, can be attributed directly to Hoagland and Pincus, their friendship for each other, their confidence, enthusiasm, ambition, and drive. It was their spirit that turned many members of Worcester society into financial supporters of biologic science. Hoagland and Pincus accomplished what they set out to do. They created and sustained a vibrant, productive scientific institution in which it was a pleasure to work.

Although named the Worcester Foundation for Experimental Biology, the Foundation was located in the summer of 1945 across Lake Quinsigamond in a house on an estate in Shrewsbury. The Board of Trustees was chaired by Harlow Shapley, a distinguished astronomer, vice-chaired by Rabbi Levi Olan, and included 3 Nobel laureates and a group of Worcester businessmen.

From 1945 to the death of Pincus in 1967, the staff grew from 12 to 350 (scientists and support people), 36 of whom were independently funded and 45 were postdoctoral fellows. The annual budget grew from $100,000 to $4.5 million. One hundred acres of adjoining land were acquired, and the campus grew to 11 buildings. In its first 25 years, approximately 3000 scientific papers were published.

But in those early years, Pincus was the animal keeper, Mrs. Hoagland the bookkeeper, M-C Chang was the night watchman, and Hoagland mowed the lawn. During the years of World War II, Pincus and Hoagland combined their interests in hormones and neurophysiology to focus on stress and fatigue in industry and the military.

The initial discoveries that led to an oral contraceptive can be attributed to M-C Chang (also the first to describe the capacitation process of sperm). In 1951, he confirmed the work of Makepeace (in 1937) demonstrating that progesterone could inhibit ovulation in rabbits. When norethindrone and norethynodrel became available, Chang found them to be virtually 100% effective in inhibiting ovulation when administered orally to rabbits.

Katherine Dexter McCormick was a very rich woman; in 1904, she married Stanley McCormick, the son of Cyrus McCormick, the founder of International Harvester. She was also intelligent, the second woman to graduate from the Massachusetts Institute of Technology, socially conscious, and a generous contributor to family planning efforts. McCormick's husband suffered from schizophrenia, and she established the Neuroendocrine Research Foundation at Harvard to study schizophrenia. This brought her together with Hoagland who told her of the work being done by Chang and Pincus.

Pincus attributed his interest in contraception to his growing appreciation for the world's population problem, and to a 1951 visit with Margaret Sanger, at that time president of the Planned Parenthood Federation of America. At that visit, Sanger expressed hope that a method of contraception could be derived from the laboratory work being done by Pincus and Chang.

In 1952, Margaret Sanger brought Pincus and Katherine McCormick together. During this meeting, Pincus formulated his thoughts derived from his mammalian research. He envisioned a progestational agent in pill form as a contraceptive, acting like progesterone in pregnancy. Sanger and McCormick provided a research grant for further animal research. By the time of her death, McCormick had contributed more than $2 million to the Worcester Foundation, and left another $1 million in her will. In his book, *The Control of Fertility*, published in 1965, Pincus wrote: "This book is dedicated to Mrs. Stanley McCormick because of her steadfast faith in scientific inquiry and her unswerving encouragement of human dignity."[5]

It was Pincus who made the decision to involve a physician because he knew human experiments would be necessary. John Rock, chief of gynecology and obstetrics at Harvard, met Pincus at a scientific conference and discovered their mutual interest in reproductive physiology. Rock and his colleagues pursued Pincus's work. Using oocytes from oophorectomies, they reported in vitro fertilization in 1944, probably the first demonstration of fertilization of human oocytes in vitro. Rock was interested in the work with progestational agents, not for contraception however, but because he hoped the female sex steroids could be used to overcome infertility.

Sanger and McCormick needed some convincing that Rock's Catholicism would not be a handicap, but they were eventually won over because of his stature. Rock was a physician who literally transformed his personal values in response to his recognition of the problems secondary to uncontrolled reproduction. With the help of Luigi Mastroianni, the first administration of synthetic progestins to women was to Rock's patients in 1954. Of the first 50 patients to receive 10–40 mg of synthetic progestin (a dose extrapolated from the animal data) for 20 days each month, all failed to ovulate during treatment (causing Pincus to begin referring to the medication as "the pill"), and 7 of the 50 became pregnant after discontinuing the medication (pleasing Rock who all along was motivated to treat infertility).

Pincus and Chang decided to announce their findings at the International Planned Parenthood meeting in Tokyo, in the fall of 1955. Rock refused to join in this effort, believing that Pincus and Chang were moving too fast. Despite this disagreement (which apparently was spirited and strong), it was done, and the Tokyo presentation generated worldwide publicity.

In 1956, with Celso-Ramon Garcia and Edris Rice-Wray, working in Puerto Rico, the first human trial was performed. The initial progestin products were contaminated with about 1% mestranol. In the amounts being used, this added up to 50–500 μg of mestranol, a sufficient amount of estrogen to inhibit ovulation by itself. When efforts to provide a more pure progestin lowered the estrogen content and yielded breakthrough bleeding, it was decided to retain the estrogen for

cycle control, thus establishing the principle of the combined estrogen-progestin oral contraceptive. Early clinical trials were conducted by J.W. Goldzieher in San Antonio and E.T. Tyler in Los Angeles.

Pincus, a longtime consultant to Searle, picked the Searle compound for extended use, and with great effort, convinced Searle that the commercial potential of an oral contraceptive warranted the risk of possible negative public reaction. Pincus also convinced Rock, and together they pushed the U.S. Food and Drug Administration for acceptance of oral contraception. In 1957, Enovid was approved for the treatment of miscarriages and menstrual disorders, and in 1960, for contraception. Neither Pincus nor the Worcester Foundation got rich on the pill; alas, there was no royalty agreement.

The Pill did bring Pincus fame and travel. There is no doubt that he was very much aware of the accomplishment and its implications. As he traveled and lectured in 1957, he said: "How a few precious facts obscurely come to in the laboratory may resonate into the lives of men everywhere, bring order to disorder, hope to the hopeless, life to the dying. That this is the magic and mystery of our time is sometimes grasped and often missed, but to expound it is inevitable."[5]

Pincus was the perfect person to bring oral contraception into the public world, at a time when contraception was a private, suppressed subject. Difficult projects require people like Pincus. A scientific entrepreneur, he could plow through distractions. He could be hard and aggressive with his staff. He could remain focused. He hated to lose, even in meaningless games with his children. Yet he combined a gracious, charming manner with his competitive hardness. He was filled with the kind of self-confidence that permits an individual to forge ahead, to translate vision into reality. Pincus died in 1967 (as did Katherine McCormick at the age of 92), of aplastic anemia that some have argued was caused by his long-term exposure to solvents and chemicals. Rock died in 1984, at the age of 94, and Chang, in 1991, was buried at the age of 82, in Shrewsbury, near his laboratory and close to the grave of Pincus.

Pincus wrote his book, *The Control of Fertility*, in 1964–65, only because "a break came in the apparent dam to publication on reproductive physiology and particularly its subdivisions concerned with reproductive behavior, conception, and contraception."[5]

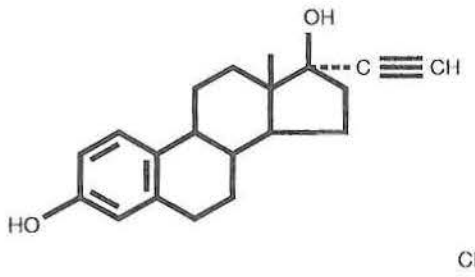
> "We have conferred and lectured in many countries of the world, seen at first hand the research needs and possibilities in almost every European, Asiatic, Central, and South American country. We have faced the hard fact of overpopulation in country after country, learned of the bleak demographic future, assessed the prospects for the practice of efficient fertility control. This has been a saddening and a heartening experience; saddening because of the sight of continuing poverty and misery, heartening because of the dedicated colleagues and workers seeking to overcome the handicap of excess fertility and to promote healthy reproductive function. Among these we have made many friends, found devoted students."[5]

Syntex, a wholesale drug supplier, was without marketing experience or organization. By the time Syntex had secured arrangements with Ortho for a sales outlet, Searle marketed Enovid in 1960 (150 μg mestranol and 9.85 mg norethynodrel). Ortho-Novum, using norethindrone from Syntex, appeared in 1962. Wyeth Laboratories introduced norgestrel in 1968, the same year in which the first reliable prospective studies were initiated. It was not until the late 1970s that a dose-response relationship between problems and the amount of steroids in the pill was appreciated. As a result, health care providers and patients, over the years, have been confronted by a bewildering array of different products and formulations. The solution to this clinical dilemma is relatively straightforward: the theme of this chapter, use the lowest doses that provide effective contraception.

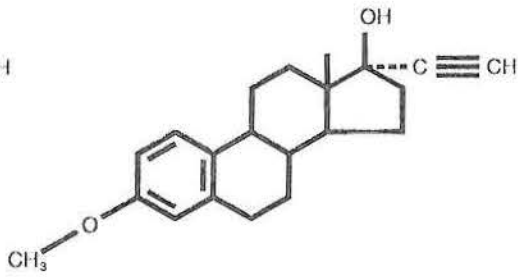
Pharmacology of Steroid Contraception

The Estrogen Component of Combination Oral Contraceptives

Estradiol is the most potent natural estrogen and is the major estrogen secreted by the ovaries. The major obstacle to the use of sex steroids for contraception was inactivity of the compounds when given orally. A major breakthrough occurred in 1938 when it was discovered that the addition of an ethinyl group at the 17 position made estradiol orally active. Ethinyl estradiol is a very potent oral estrogen and is one of the two forms of estrogen in every oral contraceptive. The other estrogen is the 3-methyl ether of ethinyl estradiol, mestranol.



Ethinyl estradiol



Mestranol

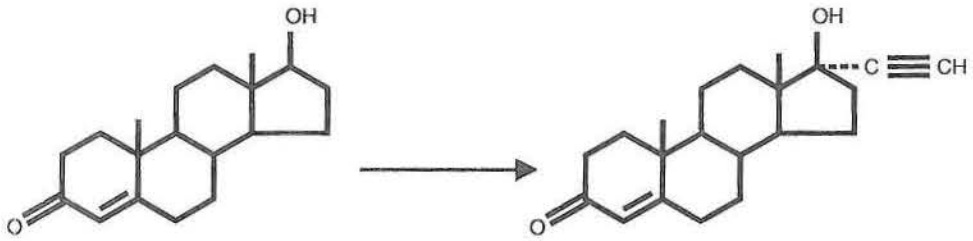
Mestranol and ethinyl estradiol are different from natural estradiol and must be regarded as pharmacologic drugs. Animal studies have suggested that mestranol is weaker than ethinyl estradiol, because mestranol must first be converted to ethinyl estradiol in the body. Indeed, mestranol will not bind to the cellular estrogen receptor. Therefore, unconjugated ethinyl estradiol is the active estrogen in the blood for both mestranol and ethinyl estradiol. In the human body, differences in potency between ethinyl estradiol and mestranol do not appear to be significant, certainly not as great as indicated by assays in rodents. This is now a minor point because all of the low-dose oral contraceptives contain ethinyl estradiol.

The metabolism of ethinyl estradiol (particularly as reflected in blood levels) varies significantly from individual to individual, and from one population to another.[6] There is even a range of variability at different sampling times within the same individual. Therefore, it is not surprising that the same dose can cause side effects in one individual and none in another.

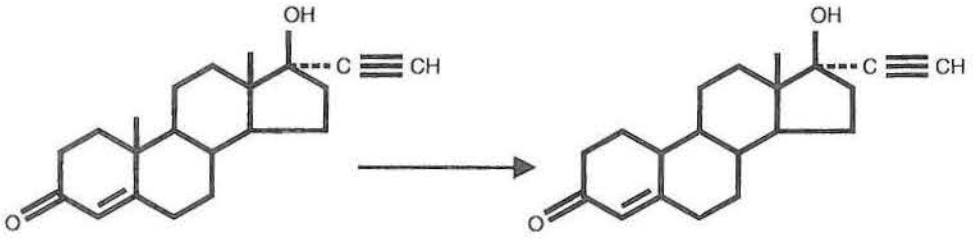
The estrogen content (dosage) of the pill is of major clinical importance. Thrombosis is one of the most serious side effects of the pill, playing a key role in the increased risk of death (in the past with high doses) from a variety of circulatory problems. This side effect is related to estrogen, and it is dose related. Therefore, the dose of estrogen is a critical issue in selecting an oral contraceptive.

The Progestin Component of Combination Oral Contraceptives

The discovery of ethinyl substitution and oral potency led (at the end of the 1930s) to the preparation of ethisterone, an orally active derivative of testosterone. In 1951, it was demonstrated that removal of the 19-carbon from ethisterone to form norethindrone did not destroy the oral activity, and most importantly, it changed the major hormonal effect from that of an androgen to that of a progestational agent. Accordingly, the progestational derivatives of testosterone were designated as 19-nortestosterones (denoting the missing 19-carbon). The androgenic properties of these compounds, however, were not totally eliminated, and minimal anabolic and androgenic potential remains within the structure.



Testosterone Ethisterone



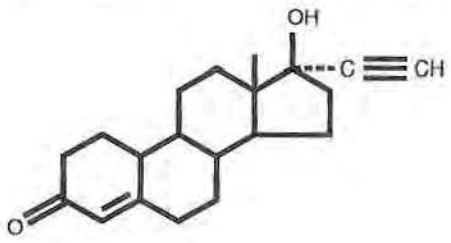
Ethisterone Norethindrone

The "impurity" of 19-nortestosterone, i.e., androgenic as well as progestational effects, was further complicated in the past by a belief that they were metabolized within the body to estrogenic compounds. This question was restudied, and it was argued that the previous evidence for metabolism to estrogenic compounds was due to an artifact in the laboratory analysis. More recent studies indicate that norethindrone can be converted to ethinyl estradiol; however, the rate of this conversion is so low that insignificant amounts of ethinyl estradiol can be found in the circulation or urine following the administration of the commonly used doses of norethindrone.[7] Any estrogenic activity, therefore, would have to be due to a direct effect. In animal and human studies, however, only norethindrone, norethynodrel, and ethynodiol diacetate have estrogen activity, and it is very slight due to weak binding to the estrogen receptor.[8] Clinically, androgenic and estrogenic activities of the progestin component are, therefore, insignificant due to the low dosage in the current oral contraceptives. As with the estrogen component, serious side effects have been related to the high doses of progestins used in old formulations, not the particular progestin, and routine use of oral contraceptives should now be limited to the low-dose products.

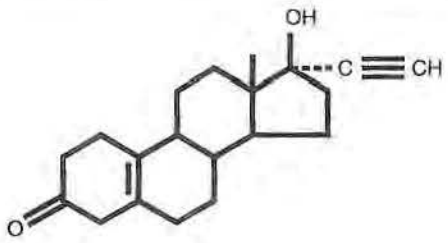
The norethindrone family contains the following 19-nortestosterone progestins: norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, lynestrenol, norgestrel, norgestimate, desogestrel, and gestodene.

Most of the progestins closely related to norethindrone are converted to the parent compound. Thus the activity of norethynodrel, norethindrone acetate, ethynodiol diacetate, and lynestrenol is due to rapid conversion to norethindrone.

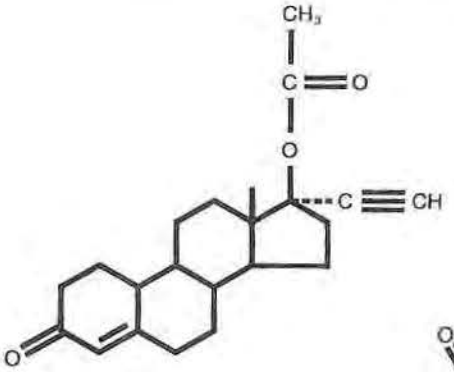
Norgestrel is a racemic equal mixture of the dextrorotatory enantiomer and the levorotatory enantiomer. These enantiomers are mirror images of each other and rotate the plane of polarized light in opposite directions. The dextrorotatory form is known as d-norgestrel, and the levorotatory form is l-norgestrel (known as levonorgestrel). Levonorgestrel is the active isomer of norgestrel.



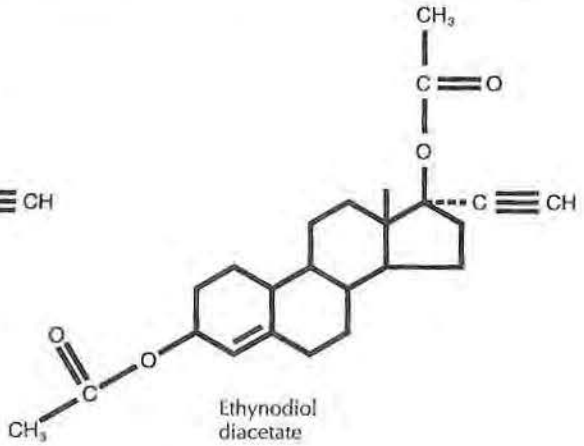
Norethindrone



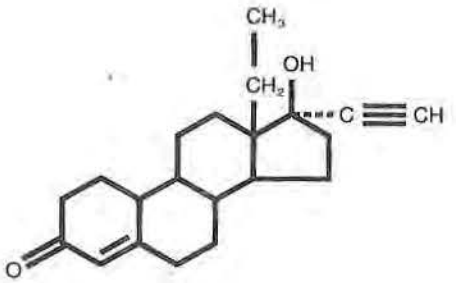
Norethynodrel



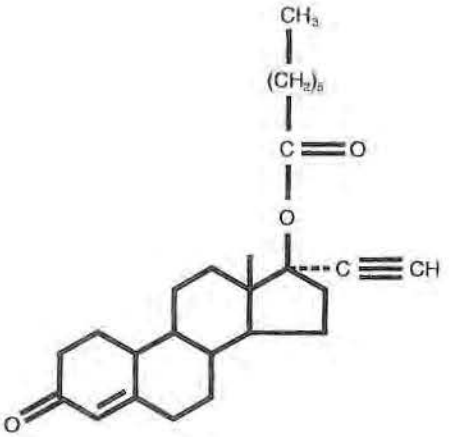
Norethindrone acetate



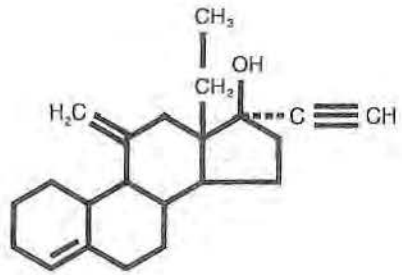
Ethynodiol diacetate



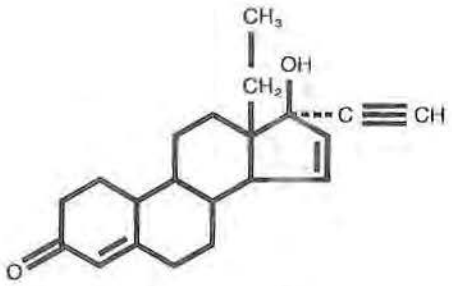
Levonorgestrel



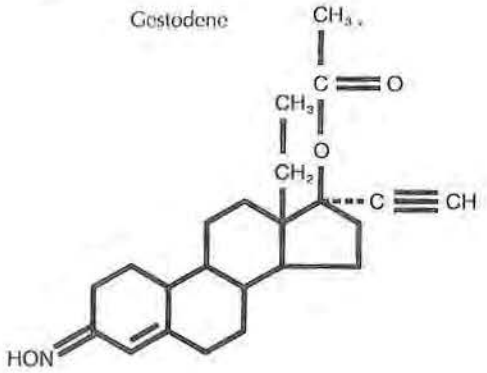
Norethindrone enanthate



Desogestrel



Gestodene



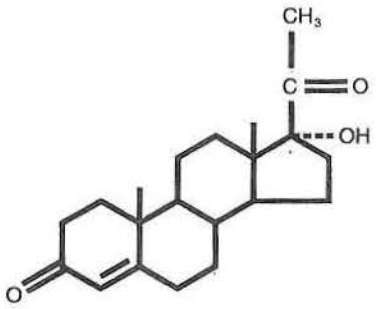
Norgestimate

Desogestrel undergoes two metabolic steps before the progestational activity is expressed in its active metabolite, 3-keto-desogestrel. This metabolite differs from levonorgestrel only by a methylene group in the 11 position. Gestodene differs from levonorgestrel by the presence of a double bond between carbons 15 and 16; thus, it is Δ-15 gestodene. It is metabolized into many derivatives with progestational activity, but not levonorgestrel. Several metabolites contribute to the activity of norgestimate, including 17-deacetylated norgestimate, 3-keto norgestimate, and levonorgestrel. Although norgestimate is a "new" progestin, epidemiologists have included it in the oral contraceptive second generation family because its activity is believed to be largely due to levonorgestrel and levonorgestrel metabolites, although this may not be totally accurate.[9, 10]

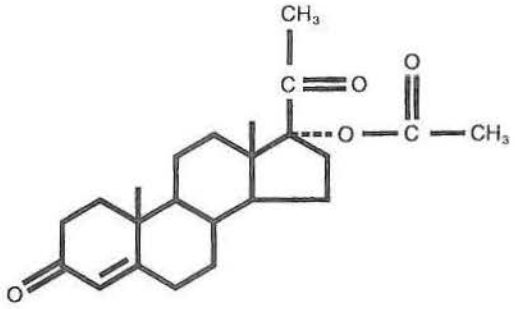
Definitions Used in Epidemiologic Studies

Low-Dose Oral Contraceptives — Products containing less than 50 μg ethinyl estradiol

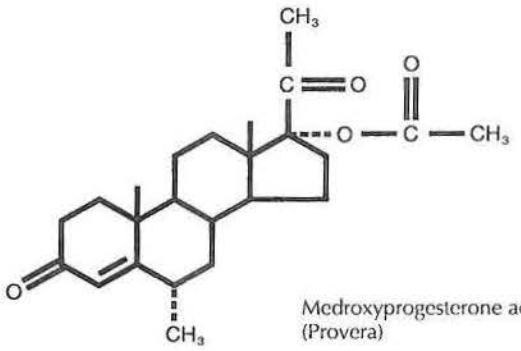
First Generation Oral Contraceptives — Products containing 50 μg or more of ethinyl estradiol



17α-Hydroxyprogesterone



17-Acetoxy progesterone



Medroxyprogesterone acetate
(Provera)

Second Generation Oral Contraceptives — Products containing levonorgestrel, norgestimate, and other members of the norethindrone family and 30 or 35 μg ethinyl estradiol

Third Generation Oral Contraceptives — Products containing desogestrel or gestodene with 20 or 30 μg ethinyl estradiol

A second group of progestins became available for use when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone produced an orally active but weak progestin. An addition at the 6 position is necessary to give sufficient progestational strength for human use, probably by inhibiting metabolism. Derivatives of progesterone with substituents at the 17 and 6 positions include the widely used medroxyprogesterone acetate.

Potency

For many years, clinicians, scientists, medical writers, and even the pharmaceutical industry have attempted to assign potency values to the various progestational components of oral contraceptives. An accurate assessment, however, has been difficult to achieve for many reasons. Progestins act on numerous target organs (e.g., the uterus, the mammary glands, and the liver), and potency varies depending upon the target organ and end point being studied. In the past, animal assays, such as the Clauberg test (endometrial change in the rabbit) and the rat ventral prostate assay, were used to determine progestin potency. Although these were considered acceptable methods at the time, a better understanding of steroid hormone action and metabolism, and a recognition that animal and human responses differ, have led to greater reliance on data collected from human studies.

Historically, this has been a confusing issue because publications and experts used potency ranking to provide clinical advice. There is absolutely no need for confusion. Oral contraceptive progestin potency is no longer a consideration when it comes to prescribing oral contraception.

because the potency of the various progestins has been accounted for by appropriate adjustments of dose. In other words, the biologic effect (in this case the clinical effect) of the various progestational components in current low-dose oral contraceptives is approximately the same. The potency of a drug does not determine its efficacy or safety, only the amount of a drug required to achieve an effect.

Clinical advice based on potency ranking is an artificial exercise that has not stood the test of time. There is no clinical evidence that a particular progestin is better or worse in terms of particular side effects or clinical responses. Thus oral contraceptives should be judged by their clinical characteristics: efficacy, side effects, risks, and benefits. Our progress in lowering the doses of the steroids contained in oral contraceptives has yielded products with little serious differences. Potency is no longer an important clinical issue.

New Progestins

Probably the greatest influence on the effort that yielded the new progestins was the belief throughout the 1980s that androgenic metabolic effects were important, especially in terms of cardiovascular disease. Cardiovascular side effects are now known to be due to a dose-related stimulation of thrombosis by estrogen. In the search to find compounds that minimize androgenic effects, however, the pharmaceutical companies succeeded.

The new progestins include desogestrel, gestodene, and norgestimate, and even newer progestins are in development.[11] In regard to cycle control (breakthrough bleeding and amenorrhea), the new formulations are comparable with previous low-dose products. All progestins derived from 19-nortestosterone have the potential to decrease glucose tolerance and increase insulin resistance. The impact on carbohydrate metabolism of the previous low-dose formulations was very minimal, and the impact of the new progestins is negligible. Most changes are not statistically significant, and when they are, they are so subtle as to be of no clinical significance. The decreased androgenicity of the progestins in the new products is reflected in increased sex hormone-binding globulin and decreased free testosterone concentrations to a greater degree than the older oral contraceptives. This difference may be of greater clinical value in the treatment of acne and hirsutism, but appropriate comparative clinical studies to document a better response have not been performed.

The new progestins, because of their reduced androgenicity, predictably do not adversely affect the cholesterol-lipoprotein profile. Indeed, the estrogen-progestin balance of combined oral contraceptives containing one of the new progestins may even promote favorable lipid changes. Thus, the new formulations have the potential to offer protection against cardiovascular disease, an important consideration as we enter an era of women using oral contraceptives for longer durations and later in life. But one must be cautious regarding the clinical significance of subtle changes, and it will be difficult to accumulate data with these rare events.

New Formulations

The multiphasic preparation alters the dosage of both the estrogen and progestin components periodically throughout the pill-taking schedule. The aim of these new formulations is to alter steroid levels in an effort to achieve lesser metabolic effects and minimize the occurrence of breakthrough bleeding and amenorrhea, while maintaining efficacy. We are probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy. Metabolic studies with the multiphasic preparations indicate no differences or slight improvements over the metabolic effects of low-dose monophasic products.

Mechanism of Action

The combination pill, consisting of estrogen and progestin components, is given daily for 3 of every 4 weeks. The combination pill prevents ovulation by inhibiting gonadotropin secretion via an effect on both pituitary and hypothalamic centers. The progestational agent in the pill primarily suppresses luteinizing hormone (LH) secretion (and thus prevents ovulation), while the estrogenic agent suppresses follicle-stimulating hormone (FSH) secretion (and thus prevents the selection and emergence of a dominant follicle). Therefore, the estrogenic component significantly contributes to the contraceptive efficacy. However, even if follicular growth and development were not sufficiently inhibited, the progestational component would prevent the surge-like release of LH necessary for ovulation.

The estrogen in the pill serves two other purposes. It provides stability to the endometrium so that irregular shedding and unwanted breakthrough bleeding can be minimized; and the presence of estrogen is required to potentiate the action of the progestational agents. The latter function of estrogen has allowed reduction of the progestational dose in the pill. The mechanism for this action is probably estrogen's effect in increasing the concentration of intracellular progestational receptors. Therefore, a minimal pharmacologic level of estrogen is necessary to maintain the efficacy of the combination pill.

Because the effect of a progestational agent will always take precedence over estrogen (unless the dose of estrogen is increased many, many-fold), the endometrium, cervical mucus, and perhaps tubal function reflect progestational stimulation. The progestin in the combination pill produces an endometrium that is not receptive to ovum implantation, a decidualized bed with exhausted and atrophied glands. The cervical mucus becomes thick and impervious to sperm transport. It is possible that progestational influences on secretion and peristalsis within the fallopian tubes provide additional contraceptive effects. Even if there is some ovarian follicular activity (especially with the lowest dose products), these actions serve to ensure good contraceptive efficacy.[12]

Efficacy

In view of the multiple actions of oral contraceptives, it is hard to understand how the omission of a pill or two can result in a pregnancy. Indeed, careful review of failures suggests that pregnancies usually occur because initiation of the next cycle is delayed allowing escape from ovarian suppression. Strict adherence to 7 pill-free days is critical in order to obtain reliable, effective contraception. For this reason, the 28-day pill package, incorporating 7 pills that do not contain steroids, is a very useful aid to ensure adherence to the necessary schedule. The most prevalent problems that can be identified associated with apparent oral contraceptive failures are vomiting and diarrhea.[13, 14] ***Even if no pills have been missed, patients should be instructed to use a backup method for at least 7 days after an episode of gastroenteritis.***

The contraceptive effectiveness of the new progestin oral contraceptives, multiphasic formulations, and lowest estrogen dose products are unequivocally comparable with older low-dose (less than 50 μg estrogen) and higher dose monophasic combination birth control pills.[12] While carefully monitored studies with motivated subjects achieve an annual failure rate of 0.1%, typical usage is associated with a 3.0% failure rate during the first year of use.[15] Efficacy decreases slightly when the estrogen component is removed, and only a small dose of the progestin is administered (the progestin-only minipills).

Failure Rates During the First Year of Use, United States[16]

Method	Percent of Women with Pregnancy	
	Lowest Expected	Typical
No method	85.0%	85.0%
Combination Pill	0.1	3.0
Progestin only	0.5	3.0
IUDs		
Progesterone IUD	1.5	2.0
Levonorgestrel IUD	0.6	0.8
Copper T 380A	0.1	0.1
Norplant	0.05	0.05
Female sterilization	0.05	0.05
Male sterilization	0.1	0.15
Depo-Provera	0.3	0.3
Spermicides	6.0	26.0
Periodic abstinence		25.0
Calendar	9.0	
Ovulation method	3.0	
Symptothermal	2.0	
Post–ovulation	1.0	
Withdrawal	4.0	19.0
Cervical cap		
Parous women	26.0	40.0
Nulliparous women	9.0	20.0
Sponge		
Parous women	9.0	28.0
Nulliparous women	6.0	18.0
Diaphragm and spermicides	6.0	20.0
Condom		
Male	3.0	14.0
Female	5.0	21.0

Metabolic Effects of Oral Contraception

Cardiovascular Disease

In October, 1995, the United Kingdom Committee on Safety of Medicines sent a letter to all U.K. physicians and pharmacists stating that women taking oral contraceptives containing desogestrel or gestodene should be urged to complete their current cycle and to continue a formulation with these progestins only if prepared to accept an increased risk of venous thromboembolism. The Committee on Safety of Medicines took this action because of observational studies that indicated a two-fold increase in the risk of venous thromboembolism when desogestrel- and gestodene-containing contraceptives were compared with products with other progestins (mostly levonorgestrel). This action and the studies on which it was based immediately became controversial. The controversy went beyond the validity of the epidemiologic data. The publicity surrounding these events reverberated throughout Europe, leading to an immediate overall decrease in oral contraceptive use, an increase in unwanted pregnancies, and an increase in induced abortions.[17, 18]

The controversy involving new progestin oral contraceptives that began in late 1995, continued through 1996, and began to reach resolution in 1997. The fundamental question is whether oral contraceptives containing desogestrel and gestodene have a different risk of thrombosis compared with oral contraceptives containing older progestins. Thrombosis can be divided into two major categories, venous thromboembolism and arterial thrombosis. Venous thromboembolism includes both deep vein thrombosis and pulmonary embolism. Arterial thrombosis includes acute myocardial infarction and stroke.

The Coagulation System

The goal of the clotting mechanism is to produce thrombin, which converts fibrinogen to a fibrin clot. Thrombin is generated from prothrombin by factor Xa in the presence of factor V, calcium, and phospholipids. The vitamin K-dependent factors include factors VII, IX, and X, as well as prothrombin. Antithrombin III is one of the body's natural anticoagulants, an irreversible inhibitor of thrombin and factors IXa, Xa, and XIa. Protein C and protein S are two other major inhibitors of coagulation and are also vitamin K-dependent. Protein C, and its helper, Protein S, inhibit clotting at the level of factors V and VIII. Tissue plasminogen activator (t-PA) is produced by endothelial cells and released when a clot forms. Both t-PA and plasminogen bind to the fibrin clot. The t-PA converts the plasminogen to plasmin which lyses the clot by degrading the fibrin. Deficiencies of antithrombin III, protein C, and protein S are inherited in an autosomal dominant pattern, accounting for 10–15% of familial thrombosis. A mutation in the prothrombin gene and the factor V Leiden mutation are the most common inherited causes of venous thromboembolism.[19]

An inherited resistance to activated protein C has been identified as the basis for about 50% of cases of familial venous thrombosis, due in almost all cases to a gene alteration recognized as the factor V Leiden mutation.[20, 21] The factor V Leiden mutation is found in approximately 30% of individuals who develop venous thromboembolism.[22] Activated protein C inhibits coagulation by degrading factors V and VIII. One of the 3 cleavages sites in factor V is the precise site of a mutation (known as the factor V Leiden mutation) that substitutes glutamine instead of arginine at this site (adenine for guanine at nucleotide 1691 in the gene).[22] This mutation makes factor V resistant to degradation (and activation in fibrinolysis). The entire clotting cascade is then resistant to the actions of the protein C system.

Coagulation and Fibrinolysis Factors

Coagulation Factors:
- **Factors that favor clotting when increased**
  - **Fibrinogen**
  - **Factors VII, VIII, X**
- **Factors that favor clotting when decreased**
  - **Antithrombin III**
  - **Protein C**
  - **Protein S**

Fibrinolysis Factors:
- **Factors that favor clotting when increased**
  - **Plasminogen**
  - **Plasminogen activator inhibitor-1 (PAI-1)**
- **Factors that favor clotting when decreased**
  - **Antiplasmin**

Heterozygotes for the factor V Leiden mutation have an 8-fold increased risk of venous thrombosis, and homozygotes, an 80-fold increased risk, and this risk appears to be further enhanced by oral contraceptive use. The highest prevalence (3–4% of the general population) of factor V Leiden is found in Europeans, and its occurrence in populations not of European descent is very rare, perhaps explaining the low frequency of thromboembolic disease in Africa, Asia, and in native Americans.[23] The mutation is believed to have arisen in a single ancestor approximately 21,000 to 34,000 years ago.[24] It has been suggested that this was a useful adaptation in heterozygotes in response to life-threatening bleeding, such as with childbirth.

The next most common inherited disorder (after the factor V Leiden mutation) is a mutation, a guanine to adenine change, in the gene encoding prothrombin.[19, 25] The prevalence of this abnormality in the white population is estimated to range from 0.7% to 4%.[26]

The administration of pharmacologic amounts of estrogen as in high-dose oral contraceptives causes an increase in the production of clotting factors such as factor V, factor VIII, factor X, and fibrinogen.[27] Some studies of the blood coagulation system have concluded that both monophasic and multiphasic low-dose oral contraceptives have no significant clinical impact on the coagulation system. Slight increases in thrombin formation are offset by increased fibrinolytic activity.[28, 29] Other studies of formulations containing 30 and 35 μg of ethinyl estradiol indicate an increase in clotting factors associated with an increase in platelet activity.[30] However, these changes are essentially all within normal ranges and their clinical significance is unknown. Smoking produces a shift to hypercoagulability.[31] A 20 μg estrogen formulation has been reported to have no effect on clotting parameters, even in smokers.[31, 32] One study comparing a 20 μg product with a 30 μg product found similar mild pro-coagulant and fibrinolytic activity, although there was a trend toward increased fibrinolytic activity with the lower dose.[33]

There is no evidence of an increase in risk of cardiovascular disease among past users of oral contraception.[34–36] In the Nurses' Health Study and the Royal College of General Practitioners' Study, long-term past use of oral contraceptives was not associated with an increase in overall mortality.[37, 393] Part of the concern for a possible lingering effect of oral contraceptive use was based on a presumed adverse impact on the atherosclerotic process, which would then be added to the effect of aging and, thus, would be manifested later in life. Instead, the findings have been consistent with the contention that cardiovascular disease due to oral contraception is secondary to acute effects, specifically estrogen-induced thrombosis, a dose-related event.

Venous Thromboembolism — The Conventional Wisdom

Older epidemiologic evaluations of oral contraceptives and vascular disease indicated that venous thrombosis was an effect of estrogen, limited to current users, with a disappearance of the risk by 3 months after discontinuation.[38, 39] Thromboembolic disease was believed to be a consequence of the pharmacologic administration of estrogen, and the level of risk was believed to be related to the estrogen dose.[40–42] Smoking was documented to produce an additive increase in the risk of arterial thrombosis, [43–45] but had no effect on the risk of venous thromboembolism.[46, 47]

Is there still a risk of venous thromboembolism with the current low-dose (less than 50 μg ethinyl estradiol) formulations of oral contraceptives? In the first years of oral contraception, the available products, containing 80 and 100 μg ethinyl estradiol (an extremely high dose), were associated with a 6-fold increased risk of venous thrombosis.[48] Because of the increased risks for venous thrombosis, myocardial infarction, and stroke, lower dose formulations (less than 50 μg estrogen) came to dominate the market, and clinicians became more careful in their screening of patients and prescribing of oral contraception. Two forces, therefore, were at work simultaneously to bring greater safety to women utilizing oral contraception: (1). the use of lower dose formulations, and (2). the avoidance of oral contraception by high-risk patients. Because of these two forces, the Puget Sound study in the United States documented a reduction in venous thrombosis risk to 2-fold.[49] The new studies also reflect the importance of these two forces, but they still indicate an increased risk.

The Hierarchy of Epidemiologic Studies

I. Clinical Reports

A case report: An anecdotal report that serves to bring attention to a possible problem or condition.

A case series: A collection of similar cases that suggests more than a chance or coincidental occurrence.

II. Observational Studies (Non-experimental Studies: Observation Without Intervention)

Cross-sectional studies: A description of a group of individuals at one point in time.

Advantages: A reliable method to estimate prevalence, quick and inexpensive.

Disadvantages: Cannot assess changes over time and very susceptible to sampling error (the group is not representative of the actual population of interest).

Example: The Health and Nutritional Examination Survey

Case-control studies: A retrospective comparison of a group of individuals with a condition or problem compared with a carefully selected control group. Subjects are selected according to specific inclusion and exclusion criteria. The exposure history of those with disease and those with no disease is collected and compared.

Advantages: Relatively quick and inexpensive because of small sample sizes.

Disadvantages: Subject to biases and errors.

Example: WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception

Cohort studies: A prospective follow-up over a long period of time of a large group of individuals. Also referred to as longitudinal or follow-up studies. Exposure information is collected from all subjects who are disease-free, and subjects are followed over time to determine who develops disease.

Advantages: A relatively accurate estimation because of large numbers, can evaluate changes over time, avoids recall bias.

Disadvantages: Expensive, lengthy in time, and subject to biases (particularly surveillance bias).

Example: The Nurses' Health Study

III. Randomized Controlled Trials

A true clinical experiment in which an intervention is compared with a standard treatment, no treatment, or a placebo, with allocation to treatment by chance. More than one comparison can be made within a study.

Advantages: Provides scientific, epidemiologic proof.

Disadvantages: Very expensive and time-consuming. Only a limited number of hypotheses can be evaluated in any one study.

Example: The Women's Health Initiative

Possible Confounders and Biases of Importance

Confounders: Factors associated with the disease and the exposure, such as age, body weight, smoking, family history, duration of oral contraceptive use, preferential prescribing, healthy user effect.

Biases: Errors due to study design.

Detection or Surveillance Bias: Systematic errors in methods of ascertainment, diagnosis, or verification of cases. Not everyone in the study population has equal access to or utilization of medical interventions and diagnostic tests.

Publication Bias: Negative (null) studies and studies that confirm old results tend not to be published. An important source of bias in meta-analysis.

Reporting or Recall Bias: Inaccurate memory and dishonesty introduce errors.

Selection Bias: Differences in characteristics between those selected for study and those who are not, such as preferential prescribing, family history, preferential referral of patients, healthy user effect. For case-control studies, the source of the controls is important. Hospital-based controls are less likely to be representative of the general population than population-based controls. It is best to choose controls by random selection, but this is not always possible. Selection bias in a cohort study can result in differences between exposed and unexposed groups.

Information or observer bias: A flaw in measuring exposure or outcome that produces different results between comparison groups. Nonresponse or patients lost to follow-up can produce differences in cohort studies.

A Guide to Epidemiologic Terms Commonly Used

Relative Risk:
The ratio of the risk among those exposed to the risk among the unexposed or the ratio of the cumulative incidence rate in the exposed and the unexposed. Also called risk ratio.

Odds Ratio:
The odds ratio is the measure of association calculated in case-control studies when the prevalence of disease events is low; the estimate and interpretation are similar to relative risk.

Confidence Interval (CI):
The range of relative risk that would include 95% of the subjects being studied; the range of relative risks within which the true magnitude of effect lies, given the study data, with a certain degree of assurance. To be statistically significant, a reduced relative risk (a beneficial effect) requires the larger number (the right hand number) to be less than 1.0. An increased relative risk (an adverse effect), to be statistically significant, requires the smaller number (the left hand number) to be greater than 1.0. The tighter (more narrow) the range, the more precise the conclusion. The wider the CI, the more imprecise the conclusion, usually because of small numbers of study subjects.

Attributable risk:
The difference in actual incidence between exposed and unexposed groups, providing a realistic estimate of the change in incidence in a given population. A modest increase in relative risk will produce only a small number of cases when clinical events are rare, such as venous thromboembolism and arterial thrombosis in young women.

Venous Thromboembolism — The Controversial Studies

The World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was a hospital-based, case-control study with subjects collected from 21 centers in 17 countries in Africa, Asia, Europe, and Latin America.[50] As part of this study, the risk of *idiopathic* venous thromboembolism associated with a formulation containing 30 µg ethinyl estradiol and levonorgestrel (doses ranging from 125 µg to 250 µg) was compared with the risk with preparations containing 20 or 30 µg ethinyl estradiol and either desogestrel or gestodene (data from 10 centers in 9 countries).[51] There were only 9 cases and 3 controls using combined oral contraceptives with other progestins, precluding precise analysis. The users of the levonorgestrel formulation had an increased odds ratio (an estimation of relative risk used in case-control studies) of 3.5 compared with nonusers. Current users of a desogestrel product had an increased risk of 9.1 compared with nonusers, and with gestodene, the odds ratio was also 9.1. Thus, the increased risk for desogestrel and gestodene was 2.6 times that of levonorgestrel, when adjusted for body weight and height. Also of note, the increased risk for the desogestrel formulation containing 20 µg ethinyl estradiol was 38.2, a number that is obviously not reliable because it was based upon only 8 cases and 1 control; the confidence interval (CI) of 4.5–325 reflected this imprecision. Overall, these increased risks were lower than those estimated by earlier case-control studies of higher dose oral contraceptives.

The second case-control study (from an international team of epidemiologists and called ***the Transnational Study on Oral Contraceptives and the Health of Young Women***) analyzed 471 cases of deep vein thrombosis and/or venous thromboembolism from the United Kingdom and Germany.[52] Second generation oral contraceptives were defined as products containing 35 μg or less of ethinyl estradiol and a progestin other than desogestrel or gestodene. Comparing users of second generation products to nonusers, the odds ratio was 3.2 (CI = 2.3–4.3). Comparing users of desogestrel and gestodene products to users of second generation oral contraceptives, the risk of venous thromboembolism was 1.5-fold greater.

The third study was from Boston University, but the data were derived from ***the General Practice Research Database***, a computerized system involving the general practitioners in the U.K.[53] Using this cohort, the authors calculated the death rate from pulmonary embolism, stroke, and acute myocardial infarction in the users of levonorgestrel, desogestrel, and gestodene low-dose oral contraceptives. Over a 3-year period, they collected a total of 15 unexpected idiopathic cardiovascular deaths in users of these products, a *nonsignificant change*, and no difference in the risk comparing desogestrel and gestodene with levonorgestrel. The risk estimates for venous thromboembolism (adjusted for smoking and body size) were about 2 times greater for desogestrel and for gestodene, compared with levonorgestrel users. There were only 4 cases and 9 controls using the 20 μg ethinyl estradiol and desogestrel product, and although the risk was similar to that associated with the 30 μg ethinyl estradiol and desogestrel product, this is too small a number for analysis.

Similar results were reported when women with deep vein thrombosis in the ***Leiden Thrombophilia Study*** in the Netherlands were re-analyzed for their use of oral contraceptives.[54] As expected, the risk of deep vein thrombosis was markedly higher in women who were carriers of the factor V Leiden mutation and in women with a family history of thrombosis.

Smoking, well recognized as a risk factor for arterial thrombosis, did not affect the risk estimates in these studies. This is not a new observation; older studies of venous thromboembolism also failed to identify smoking as a risk factor.[46, 47]

Venous Thromboembolism — Subsequent Studies

The publication of the 4 reports in late 1995 and early 1996 was followed by a flood of letters to editors, as well as reviews and editorials, highlighting confounding and bias problems in these studies.[55-57] Some prominent figures were convinced the reports of increased risks with desogestrel and gestodene were real;[58, 59] others were skeptical, pointing out possible confounding biases. Subsequently, re-analysis and new studies revealed confounders and biases in the initial studies. Thus, a consistent picture gradually emerged with consideration of proper analysis of the generated data, and the adjustment for confounding biases not initially apparent.

In Denmark, Lidegaard and colleagues performed a hospital-based, case-control study of women with confirmed diagnoses of venous thromboembolism in 1994 and 1995 (in Denmark, all women with this diagnosis are hospitalized, and therefore, very few, if any, cases were missed).[60] A 2-fold increased risk of venous thromboembolism was found in current users of oral contraceptives, regardless of estrogen doses ranging from 20 to 50 μg. The increased risk was concentrated in the first year of use. *Because there were more short-term users of the new progestins and more long-term users of the older progestins, adjustment for duration of use resulted in no significant differences between the different types of progestins.* Those factors associated with an increased risk of thromboembolism included coagulation disorders, treated hypertension during pregnancy, family history of venous thromboembolism, and an increasing body mass index. Notably, conditions not associated with an increased risk of venous thromboembolism included smoking, migraine, diabetes, hyperlipidemia, parity, or age at first birth. There was still insufficient strength in this study to establish the absence or presence of a dose-response relationship comparing the 20 μg estrogen dose to higher doses.

A case-control study using 83 cases of venous thromboembolism derived from the computer records of general practices in the U.K. concluded that the increased risk associated with oral contraceptives was the same for all types, and that the pattern of risk with specific oral contraceptives suggested confounding because of "preferential prescribing" (defined below).[61] *In this study, matching cases and controls by exact year of birth eliminated differences between different types of oral contraceptives.* A similar analysis based on 42 cases from a German database again found no difference between new progestin and older progestin oral contraceptives.[62] Thus, in these two studies, more precise adjustments for age eliminated a confounding bias.

A re-analysis of the Transnational Case-Control Study considered the duration and patterns of oral contraceptive use.[63] This re-analysis focused on first-time users of second and third generation oral contraceptives. *Statistical analysis with adjustment for duration of use in 105 cases who were first-time users could find no differences between second and third generation products.*

Evaluation of the Studies

An immediate problem with the initial studies was how to reconcile the results with the conventional wisdom that thrombosis is an estrogen dose-related complication. Furthermore, progestational agents, and desogestrel and gestodene in particular, have no significant impact on clotting parameters.[11] Therefore, there was inherent biologic implausibility surrounding the new studies.

The initial reports resurrected the claim by Kuhl in 1988 and 1989 that gestodene could cause more thrombosis because it affected ethinyl estradiol metabolism, resulting in higher estrogen levels.[64, 65] Other laboratories, however, could not replicate Kuhl's findings.[66, 67]

Former users discontinue oral contraceptives for a variety of reasons, and often are switched to what clinicians perceive to be "safer" products (*"preferential prescribing"*).[68–70] Individuals who do well with a product tend to remain with that product. Thus, at any one point in time, individuals on an older product will be relatively healthy and free of side effects (*"healthy user effect"*). This is also called *attrition of susceptibles* because higher risk individuals with problems are gradually eliminated from the group.[56] *Comparing users of older and newer products, therefore, can involve disparate cohorts of individuals.*

Because desogestrel- and gestodene-containing products were marketed as less androgenic and therefore "better" (a marketing claim not substantiated by epidemiologic studies), clinicians chose to provide these products to higher risk patients and older women.[68, 69] In addition, clinicians switched patients perceived to be at greater risk for thrombosis from older oral contraceptives to the newer formulations with desogestrel and gestodene. Furthermore, these products were prescribed more often to young women who were starting oral contraception for the first time (these young women will not have experienced the test of pregnancy or previous oral contraceptive use to help identify those who have a congenital predisposition to venous thrombosis). These changing practice patterns exert different effects over the lifetime of a product, and analytical adjustments are extremely difficult. The Transnational Group believed it accomplished an appropriate adjustment by focusing on first-time users and duration of use.[63] It is also unlikely that the "healthy user effect" will be dominant in first-time users. And, of course, this analysis found no differences between second and third generation oral contraceptives.

The challenge for a clinician is to make a decision: is an observational study with statistically significant results clinically (biologically) real? This controversy illustrates how difficult this can be. When faced with results from observational studies, clinicians want to see uniformity, consistency, agreement—all arguing in favor of a real clinical effect. Examples are the protective effect of oral contraceptives on the risk of ovarian cancer, and the benefits of postmenopausal

estrogen therapy on cardiovascular disease. The initial studies were impressive in their agreement. All indicated increased relative risks associated with desogestrel and gestodene compared with levonorgestrel. Nevertheless, all of the early studies, somewhat similar in design, were influenced by the same unrecognized biases. *Persistent errors will produce consistent conclusions.*

The apparent differences associated with the new progestins, it is now apparent, were due to the marketing and preferential prescribing of new products, which influenced the characteristics of the patients for whom the new products were prescribed. Most impressive and important is the fact that there is no evidence of an increase in mortality due to venous thromboembolism since the introduction of new progestin oral contraceptives.[53, 71]

Venous Thromboembolism and the Factor V Leiden Mutation

The new studies indicate that a risk of idiopathic venous thrombosis persists with low-dose oral contraceptives, at a level of approximately 3–4-fold greater than the normal, general incidence.[51–54, 72] However, an inherited resistance to activated protein C, the factor V Leiden mutation, may account for a significant portion of the patients who experience venous thrombosis while taking oral contraceptives.

Relative Risk and Actual Incidence of Venous Thromboembolism[73,74]

Population	Relative Risk	Incidence per 100,000 per year
Young women — general population	1	4–5
Pregnant women	12	48–60
High-dose oral contraceptives	6–10	24–50
Low-dose oral contraceptives	3–4	12–20
Leiden mutation carrier	6–8	24–40
Leiden carrier and oral contraceptives	30	120–150
Leiden mutation — homozygous	80	320–400

An inherited resistance to activated protein C, the factor V Leiden mutation, is the most common inherited coagulation problem, transmitted in an autosomal dominant fashion.[20, 75] Heterozygotes have a 6- to 8-fold increased risk of venous thromboembolism, and homozygotes an 80-fold increased risk. Oral contraceptive users who have this mutation have been reported to have a 30-fold increased risk of venous thrombosis.[76, 77] There is no known association between the factor V Leiden mutation and arterial thrombosis.[78]

Should screening for the factor V Leiden mutation (or for other inherited clotting disorders) be routine prior to prescribing contraceptives? The carrier frequencies of the Leiden mutation in the American population (the percentages are similar in men and women) are as follows:[74]

Caucasian Americans	5.27%
Hispanic Americans	2.21%
Native Americans	1.25%
Black Americans	1.23%
Asian Americans	0.45%

These estimates are consistent with the European assessments, indicating that this is a trait carried in people of European origin. In the United States, of the approximately 10 million women currently using oral contraceptives, about 450,000 are likely to carry the factor V Leiden mutation. However, because the incidence rate of venous thromboembolism is so low (4–5 per 100,000 young women per year),[73, 74] the number of women required to be screened to prevent one death is prohibitively large. The prevalence of all deficiencies is only about 0.5% in the asymptomatic population, and only one-third of patients at risk are detected by the present tests.[79]

Furthermore, because only a small number of women even with the Leiden mutation (less than 1 in 1000) have a clinical event, the finding of a positive screening test, especially considering the high rate of false positive tests, would be a barrier to the use of oral contraceptives, and a subsequent increase in unwanted pregnancies (which has an even greater risk of venous thromboembolism) would likely follow. ***Most experts believe that screening for inherited disorders should be pursued only in women with a previous episode of venous thromboembolism or a close positive family history (parent or sibling) of venous thrombosis.***

This aspect of the oral contraceptive venous thromboembolism controversy received a transfusion of energy with the publication of a report from the Netherlands, utilizing a laboratory test for resistance to activated protein C to compare differences in oral contraceptive non-users, users of second generation oral contraceptives, and users of third generation oral contraceptives.[80] Women who used any oral contraceptive had a decreased sensitivity to activated protein C compared with nonusers, and women who used third generation oral contraceptives were even less sensitive, and less than users of second generation products. This was presented as an explanation for the epidemiologic data indicating greater risks of venous thromboembolism associated with desogestrel and gestodene, and an editorial in the April 19, 1997, issue of Lancet concluded that this report was the "nail in the coffin" confirming the epidemiologic evidence.[59]

Subsequent epidemiologic reports not only removed the nails from the coffin, but returned the coffin to its maker. A closer look at the report from the Netherlands finds considerable overlap in the results among all the groups tested, and many of the oral contraceptive users had results comparable with the nonusers. It is always prudent to avoid making clinically meaningful conclusions from acquired changes in a single laboratory test (especially when the clinical meaning of a laboratory test is uncertain). Furthermore, the results could not be corroborated by another laboratory.[81]

Arterial Thrombosis

Because the incidence of cerebral thrombotic attacks (thrombotic strokes and transient ischemic attacks) among young women is higher than venous thromboembolism and myocardial infarction, and death and disability are more likely, stroke is the most important possible side effect. A very low incidence of stroke in young women carries with it little increase in absolute risk. However, because the incidence of cerebral thrombotic attacks is higher in women over age 40, we should do our best, as the following paragraphs will indicate, to make sure oral contraceptive users over age 40 are in good health and without significant risk factors for cardiovascular disease (especially hypertension, migraine with aura, diabetes mellitus, and smoking).

It has been difficult to establish arterial thrombosis dose-response relationships with estrogen because these events are so rare. Nevertheless, the estrogen dose is important for the risk of myocardial infarction and thrombotic strokes.[82, 83] Thus, a rationale for advocating low-dose estrogen oralontraceptives continues to be valid. It is acknowledged that the apparent higher risk of venous thromboembolism associated with 20 μg products in the WHO and Transnational studies reflects small numbers as well as preferential prescribing and healthy user effects.

Arterial Thrombosis — Myocardial Infarction

A population-based, case-control study analyzed 187 cases of myocardial infarction in users of low-dose oral contraceptives in the Kaiser Permanente Medical Care Program.[84] *There was no statistically significant increase in the odds ratio for myocardial infarction in current oral contraceptive users compared with past or never users.*

In the Transnational case-control study of myocardial infarctions collected from 16 centers in Austria, France, Germany, Switzerland, and the United Kingdom, the results were as follows:[85, 86]

	Cases	Controls	Odds Ratio	Confidence Interval
Any OC use	57	156	2.35	1.42–3.89
50 μg estrogen OCs	14	22	4.32	1.59–11.74
Old progestin OCs	28	71	2.96	1.54–5.66
New progestin OCs	7	49	0.82	0.29–2.31

These data were interpreted as indicating no *increased* risk of myocardial infarction associated with oral contraceptives containing desogestrel or gestodene. However, the *reduced* risk with the new progestin oral contraceptives was also emphasized (the comparison of third generation products to second generation products yielded a reduced risk that was statistically significant), suggesting a possible saving of deaths from myocardial infarction with desogestrel and gestodene. The problem is that the small actual incidence makes it difficult to acquire sufficient numbers. The conclusion was based on only 7 cases and 49 controls using third generation oral contraceptives and 28 cases and 71 controls using second generation products, and, in our view, the power is too limited to make any conclusion regarding the new progestin oral contraceptives. This is a good example of a conclusion that may be statistically significant, but clinically not real.

The Transnational study found that cigarette smoking carried a higher risk for myocardial infarction than oral contraceptives, and *that nonsmoking users of oral contraceptives had no evidence of an increased risk.*[85] In addition, there was an indication that patient screening is important in minimizing the impact of hypertension on the risk of myocardial infarction.

In the WHO multicenter study, there were 368 cases of acute myocardial infarction.[87] Factors associated with an increased risk of myocardial infarction included smoking, a history of hypertension (including hypertension in pregnancy), diabetes, rheumatic heart disease, abnormal blood lipids, and a family history of stroke or myocardial infarction. Duration of use and past use of oral contraceptives did not affect risk. Although there was about a 5-fold overall increased odds ratio of myocardial infarction in current users of oral contraceptives, essentially all cases occurred in women with cardiovascular risk factors. There was no apparent effect of increasing age on risk; however, there were only 12 cases among oral contraceptives users ls than 35 years old. There was no apparent relationship with estrogen dose, and there was no apparent influence of type or dose of progestin. However, the rare occurrence of this condition produced such small

numbers that there was insufficient statistical power to accurately assess the effects of progestin type, and estrogen and progestin doses. *The conclusion of this study was that the risk of myocardial infarction in women who use oral contraceptives is increased only in smokers.*

In a Danish case-control study of acute myocardial infarction in young women, a statistically significant increase in risk was noted only in current users of 50 μg ethinyl estradiol.[83] There was a progressive increase in risk with the number of cigarettes smoked, (accounting for 80% of the acute myocardial infarctions in young women), increasing body mass index, treated hypertension, treated hypertension in pregnancy, diabetes mellitus, hyperlipidemia, frequent migraine, and family history of myocardial infarction. However, only family history of myocardial infarction and smoking affected the risk associated with oral contraceptives; no influence on oral contraceptive risk was apparent with diabetes, hypertension, and heart disease. No differences could be demonstrated according to type of progestin.

Incidence of Myocardial Infarction in Reproductive Age Women[87]

Overall incidence[88]	5 per 100,000 per year
Women less than age 35	
Nonsmokers	4 per 100,000 per year
Nonsmokers and OCs	4 per 100,000 per year
Smokers	8 per 100,000 per year
Smokers and OCs	43 per 100,000 per year
Women 35-years-old and older	
Nonsmokers	10 per 100,000 per year
Nonsmokers and OCs	40 per 100,000 per year
Smokers	88 per 100,000 per year
Smokers and OCs	485 per 100,000 per year

Note: The above incidences are estimates based on oral contraceptive use paired with cardiovascular risk factors prevalent in the general population. Effective screening would produce smaller numbers. The increased risks in the smokers and OC groups reflect the impact of undetected cardiovascular risk factors, especially hypertension.

Arterial Thrombosis — Stroke

Older case-control and cohort studies indicated an increased risk of cerebral thrombosis among current users of high-dose oral contraceptives.[89–91] However, thrombotic stroke did not appear to be increased in healthy, nonsmoking women with the use of oral contraceptives containing less than 50 μg ethinyl estradiol.[90, 91] A case-control study of all 794 women in Denmark who suffered a cerebral thromboembolic attack during 1985–1989 concluded that there was an almost two-fold increased relative risk associated with oral contraceptives containing 30–40 μg estrogen, and the risk was significantly influenced by both smoking and the dose of estrogen in additive (not synergistic) fashion.[45] A case-control analysis of data collected by the Royal College of General Practitioners' Oral Contraception Study concluded that current users were at increased risk of stroke (with a persisting effect in former users); however, this outcome was limited mainly to smokers and to formulations with 50 μg or more of estrogen.[91]

A population-based, case-control study of 408 strokes from the California Kaiser Permanente Medical Care Program found no increase in risk for either ischemic stroke or hemorrhagic

stroke.[92] The identifiable risk factors for ischemic stroke were smoking, hypertension, diabetes, elevated body weight, and low socioeconomic status. The risk factors for hemorrhagic stroke were the same plus greater body mass and heavy use of alcohol. *Current users of low-dose oral contraceptives did not have an increased risk of ischemic or hemorrhagic stroke compared with former users and with never users.* There was no evidence for an adverse effect of increasing age or for smoking (for hemorrhagic stroke, there was a suggestion of a positive interaction between current oral contraceptive use and smoking, but the numbers were small, and the result was not statistically significant).

The Transnational study also analyzed their data for ischemic stroke in a case-control study of 220 ischemic strokes in the United Kingdom, Germany, France, Switzerland, and Austria.[93] Overall, there was a 3-fold increase in the risk of ischemic stroke associated with the use of oral contraceptives, with higher risks observed in smokers (more than 10 cigarettes per day), in women with hypertension, and in users of higher dose estrogen products. No differences were observed comparing second and third generation progestins. A case-control study from the state of Washington concluded that there is no increased risk of stroke in current users of low-dose oral contraceptives.[94]

The World Health Organization data on stroke come from the same collaborative study that yielded the publications on venous thromboembolism. The results with stroke were published as two separate reports, one on ischemic stroke and the other on hemorrhagic stroke.[95, 96]

This hospital-based, case-control study from 21 centers in 17 countries accumulated 697 cases of ischemic stroke, 141 from Europe and 556 from developing countries.[95] The overall odds ratio for ischemic stroke indicated about a 3-fold increased risk. In Europe, however, the risk was statistically significant only for higher-dose products, and ***NOT*** statistically significant for products with less than 50 μg ethinyl estradiol. In developing countries, there was no difference in risk with low-dose and higher dose oral contraceptives. This is believed to be due to the strong influence of hypertension. In Europe, it was uncommon for women with a history of hypertension to be using oral contraceptives; however, this was not the case in developing countries. Duration of use and type of progestin had no impact, and past users did not have an increased risk, but smoking 10 or more cigarettes daily exerted a synergistic effect with oral contraceptives, increasing the risk of ischemic stroke, approximating the effect of hypertension and oral contraceptives. The risk was greater in women 35 years and older; however, this, too, was believed to be due to an effect of hypertension. *Thus, the conclusion of this study was that the risk of ischemic stroke is extremely low, concentrated in those who use higher dose products, smoke, or have hypertension.*

In the WHO study on hemorrhagic stroke, there were 1068 cases.[96] Current use of oral contraceptives was associated with a slightly increased risk of hemorrhagic stroke only in developing countries, not in Europe. This again probably reflects the presence of hypertension, because the greatest increased risk (about 10- to 15-fold) was identified in current users of oral contraceptives who had a history of hypertension. Current cigarette smoking also increased the risk in oral contraceptive users, but not as dramatically as hypertension. For hemorrhagic stroke, the dose of estrogen had no effect on risk, and neither did duration of use or type of progestin. *This study concluded that the risk of hemorrhagic stroke due to oral contraceptives is increased only slightly in older women, probably occurring only in women with risk factors such as hypertension.*

A second Danish case-control study included thrombotic strokes and transitory cerebral ischemic attacks analyzed together as cerebral thromboembolic attacks.[82] In this study, the 219 cases during 1994 and 1995 included 146 cases of cerebral infarction and 73 cases of transient ischemic attacks. Only users of 2nd generation oral contraceptives (levonorgestrel, norgestrel, and norgestimate) had a statistically significant increased risk (about 2.5-fold). There was a dose-response relationship with estrogen in the dose ranges of 20, 30–40, and 50 μg ethinyl estradiol, although the number of 20 μg users (5 cases, 22 controls) was not sufficient to establish a lower risk at this lower dose. This analysis claimed a reduced risk associated with desogestrel and

gestodene; however, the odds ratio did not achieve statistical significance. Risk was increased with smoking, treated hypertension, diabetes, heart diseases, frequent migraine, a family history of myocardial infarction, but not duration of use, or family history of venous thromboembolism.

Incidence of Stroke in Reproductive Age Women [88, 92, 95, 96]

Incidence of ischemic stroke	5 per 100,000 per year 1–3 per 100,000 per year in women under age 35 10 per 100,000 per year in women over age 35
Incidence of hemorrhagic stroke	6 per 100,000 per year
Excess cases per year due to OCs, including smokers and hypertensives	2 per 100,000 per year in low-dose OC users 1 per 100,000 per year in low-dose OC users under age 35 8 per 100,000 per year in high-dose OC users

Arterial Thrombosis — Current Assessment

There has been no evidence with respectable statistical power that the new progestins have an appreciable difference in risk for arterial disease, an event that is already ***NOT*** increased with low-dose older type progestin oral contraceptives. It is possible that as these studies continue and acquire greater statistical power, a difference will emerge, but even if this is the case, the difference will be minor and likely unmeasureable. Conclusions based on a limited number of cases are premature, and a critical attitude toward arterial thrombosis is appropriate just as such an approach finally revealed explanations for the initial findings with venous thrombosis.

Most importantly, the new studies fail to find any substantial risk of ischemic or hemorrhagic stroke with low-dose oral contraceptives in healthy, young women. The WHO study did find evidence for an adverse impact of smoking in women under age 35; the Kaiser study did not. This difference is explained by the confounding effect of hypertension, the major risk factor identified. In the WHO study, a history of hypertension was based on whether a patient reported ever having had high blood pressure (other than in pregnancy) and not validated by medical records. In the Kaiser study, women were classified as having hypertension if they reported using antihypertensive medication (less than 5% of oral contraceptive users had treated hypertension, and there were no users of higher dose products). In the WHO study, the effect of using oral contraceptives in the presence of a high-risk factor is apparent in the different odds ratios when European women who received good screening from clinicians were compared with women in developing countries who received little screening; therefore, more women with cardiovascular risk factors in developing countries were using oral contraceptives.

Over the years, there has been recurring discussion over whether to provide oral contraceptives over the counter on a non-prescription basis. The data in the WHO report make an impressive argument against such a move. The increased risk of myocardial infarction was most evident in developing countries where 70% of the cases received their oral contraceptives from a non-clinical source. Deprived of screening, women with risk factors in developing countries were exposed to greater risk.

Oral contraceptives containing less than 50 μg ethinyl estradiol do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age. The effect of smoking in women under age 35 is, as we have long recognized, not detectable in the absence of hypertension. After age 35, the subtle presence of hypertension makes analysis difficult, but the Kaiser study indicates that increasing age and smoking by themselves have little impact on the risk of stroke in low-dose oral contraceptive users. The screening of patients in the Kaiser program was excellent, resulting in few women with hypertension using oral contraceptives. ***The new studies indicate that hypertension should be a major concern, especially in regards to the risk of stroke.*** Certainly, women with uncontrolled hypertension should not use oral contraceptives. Generally, family planning experts have believed that well-treated hypertension should not be a contraindication for oral contraceptive use. The new data do not help us with this problem because it is impossible to accurately categorize hypertensive patients in the studies into groups representing successful and unsuccessful treatment. Nevertheless, the outstanding safety of low estrogen dose oral contraceptives in these studies supports the continued use of low-dose oral contraceptives in treated and well-controlled hypertensive women.

Smoking

Smoking continues to be a difficult problem, not only for patient management, but for analysis of data as well. In large U.S. surveys in 1982 and 1988, the decline in the prevalence of smoking was similar in users and nonusers of oral contraception; however, 24.3% of 35- to 45-year-old women who used oral contraceptives were smokers![97] In this group of smoking, oral contraceptive-using women, 85.3% smoked 15 or more cigarettes per day (heavy smoking). Despite the widespread teaching and publicity that smoking is a contraindication to oral contraceptive use over the age of 35, more older women who use oral contraceptives smoke and smoke heavily, compared with young women. This strongly implies that older smokers are less than honest with clinicians when requesting oral contraception, and this further raises serious concern over how well this confounding variable can be controlled in case-control and cohort studies. ***A former smoker must have stopped smoking for at least 12 consecutive months to be regarded as a nonsmoker. Women who have nicotine in their bloodstream obtained from patches or gum should be regarded as smokers.***

Lipoproteins and Oral Contraception

The balance of estrogen and progestin potency in a given oral contraceptive formulation can potentially influence cardiovascular risk by its overall effect on lipoprotein levels. Oral contraceptives with relatively high doses of progestins (doses not used in today's low-dose formulations) do produce unfavorable lipoprotein changes.[98] The levonorgestrel triphasic exerts no significant changes on HDL-cholesterol, LDL-cholesterol, apoprotein B, and no change or an increase in apoprotein A, while the levonorgestrel monophasic combination (with a higher dose of levonorgestrel) has a tendency to increase LDL-cholesterol and apoprotein B, and to decrease HDL-cholesterol and apoprotein A. The monophasic desogestrel and desogestrel pills have a favorable effect on the lipoprotein profile, while the triphasic norgestimate and gestodene pills produce beneficial alterations in the LDL:HDL and apoprotein B:apoprotein A ratios.[99–102] Like the triphasic levonorgestrel pills, norethindrone multiphasic pills have no significant impact on the lipoprotein profile over 6–12 months.[103] *In summary, studies of low-dose formulations indicate that the adverse effects of progestins are limited to the fixed-dose combination with a dose of levonorgestrel that exceeds that in the multiphasic formulation.*

An important study in monkeys indicated a protective action of estrogen against atherosclerosis, but by a mechanism independent of the cholesterol-lipoprotein profile. Oral administration of a combination of estrogen and progestin to monkeys fed a high-cholesterol, atherogenic diet decreased the extent of coronary atherosclerosis despite a reduction in HDL-cholesterol levels.[104–106] In somewhat similar experiments, estrogen treatment markedly prevented arterial lesion development in rabbits.[107–109] In considering the impact of progestational agents, lowering of HDL is not necessarily atherogenic if accompanied by a significant estrogen impact. These animal studies help explain why older, higher dose combinations, which had an adverse impact on the lipoprotein profile did not increase subsequent cardiovascular disease.[34, 37] The estrogen

component provided protection through a direct effect on vessel walls, especially favorably influencing vasomotor and platelet factors such as nitric oxide and prostacyclin.

This conclusion is reinforced by angiographic and autopsy studies. Young women with myocardial infarctions who have used oral contraceptives have less diffuse atherosclerosis than nonusers.[110, 111] Indeed, a case-control study indicated that the risk of myocardial infarction in patients taking older, high-dose levonorgestrel-containing formulations is the same as that experienced with pills containing other progestins.[34]

In the past decade, we have been subjected to considerable marketing hype about the importance of the impact of oral contraceptives on the cholesterol-lipoprotein profile. If indeed certain oral contraceptives had a negative impact on the lipoprotein profile, one would expect to find evidence of atherosclerosis as a cause of an increase in subsequent cardiovascular disease. There is no such evidence. Thus, the mechanism of the cardiovascular complications is undoubtedly a short-term acute mechanism—thrombosis (an estrogen-related effect).

Hypertension

Oral contraceptive-induced hypertension was observed in approximately 5% of users of higher dose pills. More recent evidence indicates that small increases in blood pressure can be observed even with 30 mg estrogen, monophasic pills, including those containing the new progestins. However, an increased incidence of clinically significant hypertension has not been reported.[112–115] The lack of clinical hypertension in most studies may be due to the rarity of its occurrence. The Nurses' Health Study observed an increased risk of clinical hypertension in current users of low-dose oral contraceptives, providing an incidence of 41.5 cases per 10,000 women per year.[116] Therefore, an annual assessment of blood pressure is still an important element of clinical surveillance, even when low-dose oral contraceptives are used. Postmenopausal women in the Rancho Bernardo Study who had previously used oral contraceptives (probably high-dose products) had slightly higher (2–4 mm Hg) diastolic blood pressures.[117] Because past users do not demonstrate differences in incidence or risk factors for cardiovascular disease, it is unlikely this blood pressure difference has an important clinical effect.

Variables such as previous toxemia of pregnancy or previous renal disease do not predict whether a woman will develop hypertension on oral contraception.[118] Likewise, women who have developed hypertension on oral contraception are not more predisposed to develop toxemia of pregnancy.

The mechanism for an effect on blood pressure is thought to involve the renin angiotensin system. The most consistent finding is a marked increase in plasma angiotensinogen, the renin substrate, up to 8 times normal values (on higher dose pills). In nearly all women, excessive vasoconstriction is prevented by a compensatory decrease in plasma renin concentration. If hypertension does develop, the renin-angiotensinogen changes take 3–6 months to disappear after stopping combined oral contraception.

One must also consider the effects of oral contraceptives in patients with preexisting hypertension or cardiac disease. In our view, with medical control of the blood pressure and close follow-up (at least every 3 months), the patient and her clinician may choose low-dose oral contraception. Close follow-up is also indicated in women with a history of preexisting renal disease or a strong family history of hypertension or cardiovascular disease. It seems prudent to suggest that patients with marginal cardiac reserve should utilize other means of contraception. Significant increases in cardiac output and plasma volume have been recorded with oral contraceptive use (higher dose pills), probably a result of fluid retention.

Cardiovascular Disease — Summary

The outpouring of epidemiologic data in the last few years allows the construction of a clinical formulation that is evidence-based. The following conclusions are consistent with the recent reports.

SUMMARY: Oral Contraceptives and Thrombosis

- **Pharmacologic estrogen increases the production of clotting factors.**
- **Progestins have no significant impact on clotting factors.**
- **Past users of oral contraceptives do not have an increased incidence of cardiovascular disease.**
- **All low-dose oral contraceptives, regardless of progestin type, have an increased risk of venous thromboembolism. The actual risk of venous thrombosis with low-dose oral contraceptives is lower in the new studies compared with previous reports. Some have argued that this is due to preferential prescribing and the healthy user effect. However, it is also logical that the lower risk reflects better screening of patients and lower estrogen doses.**
- **Smoking has no effect on the risk of venous thrombosis.**
- **Smoking and estrogen have an additive effect on the risk of arterial thrombosis. Why is there a difference between venous and arterial clotting? The venous system has low flow with a state of high fibrinogen and low platelets, in contrast to the high-flow state of the arterial system with low fibrinogen and high platelets. Thus, it is understandable why these two different systems can respond in different ways.**
- **Hypertension is a very important additive risk factor for stroke in oral contraceptive users.**
- **Low-dose oral contraceptives (less than 50 μg ethinyl estradiol) do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age.**
- **Almost all myocardial infarctions and strokes in oral contraceptive users occur in users of high-dose products, or users with cardiovascular risk factors over the age of 35.**
- **Arterial thrombosis (myocardial infarction and stroke) has a dose-response relationship with the dose of estrogen, but there are insufficient data to determine whether there is a difference in risk with products that contain 20, 30 or 35 μg ethinyl estradiol.**

The recent studies reinforce the belief that the risks of arterial and venous thrombosis are a consequence of the estrogen component of combination oral contraceptives. Current evidence does not support an advantage or disadvantage for any particular formulation, except for the greater safety associated with any product containing less than 50 μg ethinyl estradiol. Although it is logical to expect the greatest safety with the lowest dose of estrogen, the rare occurrence of arterial and venous thrombosis in healthy women makes it unlikely that there will be any measurable differences in the attributable incidence of clinical events with all low-dose products.

The new studies emphasize the importance of good patient screening. The occurrence of arterial thrombosis is essentially limited to older women who smoke or have cardiovascular risk factors, especially hypertension. The impact of good screening is evident in the repeated failure to detect an increase in mortality due to myocardial infarction or stroke in several studies.[53, 88] Although the risk of venous thromboembolism is slightly increased, the actual incidence is still relatively rare, and the mortality rate is about 1% (probably less with oral contraceptives, because most deaths from thromboembolism are associated with trauma, surgery, or a major illness). The minimal risk of venous thrombosis associated with oral contraceptive use does not justify the cost of routine screening for coagulation deficiencies. Nevertheless, the importance of this issue is illustrated by the increased risk of a very rare event, cerebral sinus thrombosis, in women who have an inherited predisposition for clotting and use oral contraceptives.[19, 119]

If a patient has a close family history (parent or sibliing) or a previous episode of idiopathic thromboembolism, an evaluation to search for an underlying abnormality in the coagulation system is warranted.[77] The following measurements are recommended, and abnormal results require consultation with a hematologist regarding prognosis and prophylactic treatment. The list of laboratory tests is long, and because this is a dynamic and changing field, the best advice is to consult with a hematologist. If a diagnosis of a congenital deficiency is made, screening should be offered to other family members.

Hypercoaguable Conditions	Thrombophilia Screening
Antithrombin III deficiency	Antithrombin III
Protein C deficiency	Protein C
Protein S deficiency	Protein S
Factor V Leiden mutation	Activated protein C resistance ratio
Prothrombin gene mutation	Activated partial thromboplastin time
Antiphospholipid syndrome	Hexagonal activated partial thromboplastin time
	Anticardiolipin antibodies
	Lupus anticoagulant
	Fibrinogen
	Prothrombin G mutation (DNA test)
	Thrombin Time
	Homocysteine level
	Complete blood count

Combination oral contraception is contraindicated in women who have a history of idiopathic venous thromboembolism, and also in women who have a close family history (parent or sibling) of idiopathic venous thromboembolism. These women will have a higher incidence of congenital deficiencies in important clotting measurements, especially antithrombin III, protein C, protein S, and resistance to activated protein C.[120] Such a patient who screens negatively for an inherited clotting deficiency might still consider the use of oral contraceptives, but this would be a difficult decision with unknown risks for both patient and clinician, and it seems more prudent to consider other contraceptive options. Other risk factors for thromboembolism that should be considered by clinicians include an acquired predisposition such as the presence of lupus anticoagulant or malignancy, and immobility or trauma. Varicose veins are not a risk factor unless they are very extensive.[48]

The conclusion once again is that low-dose oral contraceptives are very safe for healthy, young women. By effectively screening for the presence of smoking and cardiovascular risk factors, especially hypertension, in older women, we can limit, if not eliminate, any increased risk for arterial disease associated with low-dose oral contraceptives. And it is very important to emphasize that there is no increased risk of cardiovascular events associated with duration (long-term) use.

Carbohydrate Metabolism

With the older high-dose oral contraceptives, an impaired glucose tolerance test was present in many women. In these women, plasma levels of insulin as well as the blood sugar were elevated. Generally, the effect of oral contraception is to produce an increase in peripheral resistance to insulin action. Most women can meet this challenge by increasing insulin secretion, and there is no change in the glucose tolerance test, although 1-hour values may be slightly elevated.

Insulin sensitivity is affected mainly by the progestin component of the pill.[121] The derangement of carbohydrate metabolism may also be affected by estrogen influences on lipid metabolism, hepatic enzymes, and elevation of unbound cortisol. The glucose intolerance is dose-related, and once again effects are less with the low-dose formulations. ***Insulin and glucose changes with low-dose monophasic and multiphasic oral contraceptives are so minimal, that it is now believed they are of no clinical significance.***[115, 122–124] This includes long-term evaluation with hemoglobin A1c.

The observed changes in studies of oral contraception and carbohydrate metabolism are in the nondiabetic range. In order to measure differences, investigators have resorted to analysis by measuring the area under the curve for glucose and insulin responses during glucose tolerance tests. A highly regarded cross-sectional study utilizing this technique reported that even lower dose formulations have detectable effects on insulin resistance.[121] The reason this is important is that it is now recognized that hyperinsulinemia due to insulin resistance is a contributor to cardiovascular disease. However, there are several critical questions that remain unanswered. Can the results from a cross-sectional study be duplicated in a study of sufficient size with patients serving as their own controls? Is a statistically significant hyperinsulinemia, detected in a study, clinically meaningful?

Because long-term, follow-up studies of large populations have failed to detect any increase in the incidence of diabetes mellitus or impaired glucose tolerance (even in past and current users of high-dose pills),[117, 125, 126] the concern now appropriately focuses on the slight impairment as a potential risk for cardiovascular disease. If slight hyperinsulinemia were meaningful, wouldn't you expect to see evidence of an increase in cardiovascular disease in past users who took oral contraceptives when doses were higher? As we have emphasized before, there is no such evidence. The data strongly indicate that the changes in lipids and carbohydrate metabolism that have been measured are not clinically meaningful.

It can be stated definitively that oral contraceptive use does not produce an increase in diabetes mellitus.[125–128] The hyperglycemia associated with oral contraception is not deleterious and is completely reversible. Even women who have risk factors for diabetes in their history are not affected. In women with recent gestational diabetes, no significant impact on glucose tolerance could be demonstrated over 6–13 months comparing the use of low-dose monophasic and multiphasic oral contraceptives with a control group, and no increase in the risk of overt diabetes mellitus could be detected with long-term follow-up.[129, 130] A high percentage of women with previous gestational diabetes develop overt diabetes and associated vascular complications. Until overt diabetes develops, it is appropriate for these patients to use low-dose oral contraception.

In clinical practice, it may, at times, be necessary to prescribe oral contraception for the overt diabetic. No effect on insulin requirement is expected with low-dose pills.[131] According to the older epidemiologic data, the use of oral contraceptives increases the risk of thrombosis in women with insulin-dependent diabetes mellitus; therefore, women with diabetes have been encouraged to use other forms of contraception. However, this effect in women under age 35 who are otherwise healthy is probably very minimal with low-dose oral contraception, and reliable protection against pregnancy is a benefit for these patients that outweighs the small risk. A case-control study could find no evidence that oral contraceptive use by young women with insulin-dependent diabetes mellitus increased the development of retinopathy or nephropathy.[132] In a 1-year study of women with insulin-dependent diabetes mellitus who were using a low-dose

oral contraceptive, no deterioration could be documented in lipoprotein or hemostatic biochemical markers for cardiovascular risk.[133]

The Liver

The liver is affected in more ways and with more regularity and intensity by the sex steroids than any other extragenital organ. Estrogen influences the synthesis of hepatic DNA and RNA, hepatic cell enzymes, serum enzymes formed in the liver, and plasma proteins. Estrogenic hormones also affect hepatic lipid and lipoprotein formation, the intermediary metabolism of carbohydrates, and intracellular enzyme activity. Nevertheless, an extensive analysis of the prospective cohorts of women in the Royal College of General Practitioners' Oral Contraception Study and the Oxford-Family Planning Association Contraceptive Study could detect no evidence of an increased incidence or risk of serious liver disease among oral contraceptive users.[134]

The active transport of biliary components is impaired by estrogens as well as some progestins. The mechanism is unclear, but cholestatic jaundice and pruritus were occasional complications of higher dose oral contraception, and are similar to the recurrent jaundice of pregnancy, i.e., benign and reversible. The incidence with lower dose oral contraception is unknown, but it must be a very rare occurrence.

The only absolute hepatic contraindication to oral contraceptive use is acute or chronic cholestatic liver disease. Cirrhosis and previous hepatitis are not aggravated. Once recovered from the acute phase of liver disease, a woman can use oral contraception.

Data from the Royal College of General Practitioners' prospective study indicated that an increase in the incidence of gallstones occurred in the first years of oral contraceptive use, apparently due to an acceleration of gallbladder disease in women already susceptible.[135] In other words, the overall risk of gallbladder disease was not increased, but in the first years of use, disease was activated or accelerated in women who were vulnerable because of asymptomatic disease or a tendency toward gallbladder disease. The mechanism appears to be induced alterations in the composition of gallbladder bile, specifically a rise in cholesterol saturation that is presumably an estrogen effect.[136] The Nurses' Health Study reported no significant increase in the risk of symptomatic gallstones among ever-users, but slightly elevated risks among current and long-term users.[137] Although oral contraceptive use has been linked to an increased risk of gallbladder disease, the epidemiologic evidence has been inconsistent. Indeed an Italian case-control study and a report from the Oxford Family Planning Association cohort found no increase in the risk of gallbladder disease in association with oral contraceptive use and no interaction with increasing age or body weight.[138, 139] Keep in mind that even though some studies found a statistically significant modest increase in the relative risk of gallbladder disease, even if the effect were real, it is of little clinical importance because the actual incidence of this problem is very low.

Gastrointestinal Effects

Nausea, breast discomfort, and weight gain continue to be disturbing effects, but their incidence is significantly less with low-dose oral contraception. Fortunately, these effects are most intense in the first few months of use and, in most cases, gradually disappear. Weight gain usually responds to dietary restriction, but for some patients, the weight gain is an anabolic response to the sex steroids, and discontinuation of oral contraception is the only way that weight loss can be achieved. This must be rare with low-dose oral contraception because data in published studies fail to indicate a difference in body weight between users and nonusers.[140, 141]

There is no association between oral contraception and peptic ulcer disease or inflammatory bowel disease.[142, 143] Oral contraception is not recommended for patients with problems of

gastrointestinal malabsorption because of the possibility of contraceptive failure.

Chloasma, a patchy increase in facial pigment, was, at one time, found to occur in approximately 5% of oral contraceptive users. It is now a rare problem due to the decrease in estrogen dose. Unfortunately, once chloasma appears, it fades only gradually following discontinuation of the pill and may never disappear completely. Skin-blanching medications may be useful.

Hematologic effects include an increased sedimentation rate, increased total iron-binding capacity due to the increase in globulins, and a decrease in prothrombin time. The continuous use of oral contraceptives may prevent the appearance of symptoms in porphyria precipitated by menses. Changes in vitamin metabolism have been noted: a small nonharmful increase in vitamin A and decreases in blood levels of pyridoxine (B_6) and the other B vitamins, folic acid, and ascorbic acid. Despite these changes, routine vitamin supplements are not necessary for women eating adequate, normal diets.

Mental depression is very rarely associated with oral contraceptives. In studies with higher dose oral contraceptives, the effect was due to estrogen interference with the synthesis of tryptophan that could be reversed with pyridoxine treatment. It seems wiser, however, to discontinue oral contraception if depression is encountered. Though infrequent, a reduction in libido is occasionally a problem and may be a cause for seeking an alternative method of contraception.

Adverse androgenic voice changes were occasionally encountered with the use of the first very high-dose oral contraceptives. Vocal virilization can be a serious and devastating problem for some women, especially when vocal performance is important. Careful study of women on low-dose oral contraceptives indicates that this is no longer a side effect of concern.[144]

The Risk of Cancer

Endometrial Cancer

The use of oral contraception protects against endometrial cancer. Use for at least 12 months reduces the risk of developing endometrial cancer by ***50%***, with the greatest protective effect gained by use for more than 3 years.[145–147] This protection persists for 20 or more years after discontinuation (the actual length of duration of protection is unknown) and is greatest in women at highest risk: nulliparous and low parity women.[148] This protection is equally protective for all 3 major histologic subtypes of endometrial cancer: adenocarcinoma, adenoacanthoma, and adenosquamous cancers. Finally, protection is seen with all monophasic formulations of oral contraceptives, including pills with less than 50 µg estrogen.[145] There are no data as yet with multiphasic preparations or the new progestin formulations, but because these products are still dominated by their progestational component, there is every reason to believe that they will be protective.

Ovarian Cancer

Protection against ovarian cancer, the most lethal of female reproductive tract cancers, is one of the most important benefits of oral contraception. Because this cancer is detected late and prognosis is poor, the impact of this protection is very significant. Indeed, a decline in mortality from ovarian cancer has been observed in several countries since the early 1970s, perhaps an effect of oral contraceptive use.[149] The risk of developing epithelial ovarian cancer of all histologic subtypes in users of oral contraception is reduced by ***40%*** compared with that of nonusers.[147, 150–152] This protective effect increases with duration of use and continues for at least 10–15 years after stopping the medication. This protection is seen in women who use oral contraception for as little as 3 to 6 months (although at least 3 years of use are required for a

notable impact), reaches an 80% reduction in risk with more than 10 years of use, and is a benefit associated with all monophasic formulations, including the low-dose products.[153] The protective effect of oral contraceptives is especially observed in women at high risk of ovarian cancer (nulliparous women and women with a positive family history).[154] Continuous use of oral contraception for 10 years by women with a positive family history for ovarian cancer can reduce the risk of epithelial ovarian cancer to a level equal to or less than that experienced by women with a negative family history.[154] Again, the multiphasic and new progestin products have not been in use long enough to yield any data on this issue, but because ovulation is effectively inhibited by these formulations, protection against ovarian cancer should be exerted. The same magnitude of protection has been observed in a case-control study of women with *BRCA1 or BRCA2* mutations.[155]

Cancer of the Cervix

Studies have indicated that the risk for dysplasia and carcinoma in situ of the uterine cervix increases with the use of oral contraception for more than one year.[156-160] Invasive cervical cancer may be increased after 5 years of use, reaching a two-fold increase after 10 years. It is well recognized, however, that the number of partners a woman has had and age at first coitus are the most important risk factors for cervical neoplasia. Other confounding factors include exposure to human papillomavirus, the use of barrier contraception (protective), and smoking. These are difficult factors to control, and, therefore, the conclusions regarding cervical cancer are not definitive. An excellent study from the Centers for Disease Control and Prevention (CDC) concluded there is no increased risk of invasive cervical cancer in users of oral contraception, and an apparent increased risk of carcinoma in situ is due to enhanced detection of disease (because oral contraceptive users have more frequent Pap smears).[159] In the World Health Organization Study of Neoplasia and Steroid Contraceptives, a Pap smear screening bias was identified, nevertheless the evidence still suggested an increased risk of cervical carcinoma in situ with long-term oral contraceptive use.[160]

A case-control study of patients in Panama, Costa Rica, Colombia, and Mexico concluded that there was a significantly increased risk for invasive adenocarcinoma.[161] Similar results were obtained in a case-control study in Los Angeles and in the World Health Organization Collaborative Study.[162, 163] In Los Angeles, the relative risk of adenocarcinoma of the cervix increased from 2.1 with ever use to 4.4 with 12 or more years of oral contraceptive use.[162] Because the incidence of adenocarcinoma of the cervix (10% of all cervical cancers) has increased in young women over the last 20 years, there is concern that this increase reflects the use of oral contraception.[164] Oral contraceptives increase cervical ectopia, but whether this increases the risk of cervical adenocarcinoma is unclear.

This concern obviously is an important reason for annual Pap smear surveillance. Fortunately, steroid contraception does not mask abnormal cervical changes, and the necessity for prescription renewals offers the opportunity for improved screening for cervical disease. It is reasonable to perform Pap smears every 6 months in women using oral contraception for 5 or more years who are also at higher risk because of their sexual behavior (multiple partners, history of sexually transmitted diseases). Oral contraceptive use is appropriate for women with a history of cervical intraepithelial neoplasia (CIN), including those who have been surgically treated.

Liver Adenomas

Hepatocellular adenomas can be produced by steroids of both the estrogen and androgen families. Actually, there are several different lesions, peliosis, focal nodular hyperplasia, and adenomas. Peliosis is characterized by dilated vascular spaces without endothelial lining, and may occur in the absence of adenomatous changes. The adenomas are not malignant; their significance lies in the potential for hemorrhage. The most common presentation is acute right upper quadrant or

epigastric pain. The tumors may be asymptomatic, or they may present suddenly with hemoperitoneum. There is some evidence that the tumors and focal nodular hyperplasia regress when oral contraception is stopped.[165, 166] Epidemiologic data have not supported the contention that mestranol increased the risk more than ethinyl estradiol.

The risk appears to be related to duration of oral contraceptive use and to the steroid dose in the pills. This is reinforced by the rarity of the condition ever since low-dose oral contraception became available. The ongoing prospective studies have accumulated many woman-years of use and have not identified an increased incidence of such tumors.[134] In our view it is not even worth mentioning during the informed consent (choice) process.

No reliable screening test or procedure is currently available. Routine liver function tests are normal. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) is the best means of diagnosis; angiography and ultrasonography are not reliable. Palpation of the liver should be part of the periodic evaluation in oral contraceptive users. If an enlarged liver is found, oral contraception should be stopped, and regression should be evaluated and followed by imaging.

Liver Cancer

Oral contraception has been linked to the development of hepatocellular carcinoma.[167, 168] However, the very small number of cases, and, thus, the limited statistical power, requires great caution in interpretation. The largest study on this question, the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, found no association between oral contraception and liver cancer.[169] Even case-control analysis of oral contraceptives containing cyproterone acetate (known to be toxic to the liver in high doses) could detect no evidence of an increased risk of liver cancer.[170] In the United States, Japan, Sweden, England, and Wales, the death rates from liver cancer have not changed over the last 3 decades despite introduction and use of oral contraception.[171, 172]

Breast Cancer

Because of its prevalence and its long latent phase, concern over the relationship between oral contraception and breast cancer continues to be an issue in the minds of both patients and clinicians. Unfortunately, the issue is not totally resolved and probably will not be until another decade passes, allowing data to emerge from the modern era of lower dose oral contraception.

Worth emphasizing is the protective effect of higher dose oral contraception on benign breast disease, an effect that became apparent after 2 years of use.[173] After 2 years there was a progressive reduction (about 40%) in the incidence of fibrocystic disease of the breast. Women who used oral contraception were one-fourth as likely to develop benign breast disease as nonusers, but this protection was limited to current and recent users. It is still uncertain whether this same protection is provided by the lower dose products. A French case-control study indicated a reduction of nonproliferative benign breast disease associated with low-dose oral contraceptives used before a first full-term pregnancy, but no effect on proliferative disease or with use after a pregnancy.[174]

The Royal College of General Practitioners,[175] Oxford Family Planning Association,[176, 177] and Walnut Creek[178] cohort studies (and more recently, the Nurses' Health Study)[179] indicated no significant differences in breast cancer rates between users and nonusers. However, patients were enrolled in these studies at a time when oral contraception was used primarily by married couples spacing out their children. Beginning in the 1980s, oral contraception was primarily being used by women early in life, for longer durations, and to delay an initial pregnancy (remember, a full-term pregnancy early in life protects against breast cancer).

Over the last decade, case-control studies have focused on the use of oral contraception early in life, for long duration, and to delay a first, full-term pregnancy. Because the cohort of women who have used oral contraception in this fashion is just now beginning to reach the ages of postmenopausal breast cancer, the studies have had to focus on the risk of breast cancer diagnosed before age 45 (only 13% of all breast cancer). The results of these studies have not been clear-cut. Some studies have indicated an overall increased relative risk of early, premenopausal breast cancer,[180–187] while others indicated no increase in overall risk.[188–190] The most impressive finding indicates a link in most studies,[191–196] but not all,[197–201] of early breast cancer before age 40 with women who used oral contraception for long durations of time.

A collaborative group composed of an enormous number of epidemiologists and cancer investigators from around the world re-analyzed data from 54 studies in 26 countries, a total of 53,297 women with breast cancer and 100,239 without breast cancer, in order to assess the relationship between the risk of breast cancer and the use of oral contraceptives.[202] Oral contraceptives were grouped into 3 categories: low, medium, and high dose (which correlated with <50μg, 50 μg, and >50 μg of estrogen). At the time of diagnosis, 9% of the women with breast cancer were under age 35, 25% were 35–44, 33% were 45–54, and 33% were age 55 and older. A similar percentage of women with breast cancer (41%) and women without breast cancer (40%) had used combined oral contraceptives at some time in their lives. Overall, the relative risk (RR) of breast cancer in ever users of oral contraceptives was very slightly elevated and statistically significant: RR = 1.07; CI = 1.03–1.10.

The relative risk analyzed by duration of use was barely elevated and not statistically significant (even when long-term use, virtually continuous, was analyzed). Women who had begun use as teenagers had about a 20% statistically significant increased relative risk. In other words, recent users who began use before age 20 had a higher relative risk compared with recent users who began at later ages. The evidence was strong for a relationship with time since last use, an elevated risk being significant for current users and in women who had stopped use 1–4 years before (recent use). No influence on this risk was observed with the following: a family history of breast cancer, age of menarche, country of origin, ethnic groups, body weight, alcohol use, years of education, and the design of the study. There was no variation according to specific type of estrogen or progestin in the various products. Importantly, there was no statistically significant effect of low, medium, or high dose preparations. Ten or more years after stopping use, there was no increased risk of breast cancer. Indeed, the risk of metastatic disease compared with localized tumors was reduced: Relative Risk = 0.88; CI = 0.81–0.95.

Oral Contraceptives and the Risk of Breast Cancer Re-analysis of the World's Data[202]

Current users	RR = 1.24, 95% CI 1.15–1.33
1–4 years after stopping	RR = 1.16, 95% CI 1.08–1.23
5–9 years after stopping	RR = 1.07, 95% CI 1.02–1.13

Data were limited for progestin-only methods. The re-analysis indicated that the results were similar to those with combined oral contraceptives, but a close look at the numbers reveals that not one relative risk reached statistical significance.

Overall, this massive statistical exercise yielded good news. No major adverse impact of oral contraceptives emerged. ***Even though the data indicated that young women who begin use before age 20 have higher relative risks of breast cancer during current use and in the 5 years after stopping, this is a time period when breast cancer is very rare; and, thus, there would be little impact on the actual number of breast cancers.*** The difference between localized disease

and metastatic disease was statistically greater and should be observable. Thus many years after stopping oral contraceptive use, the main effect may be protection against metastatic disease. Breast cancer is more common in older years, and 10 or more years after stopping, the risk was not increased.

What other explanation could account for an increased risk associated only with current or recent use, no increase with duration of use, and a return to normal 10 years after exposure? The slightly increased risk could be influenced by detection/surveillance bias (more interaction with the health care system by oral contraceptive users). It is also possible that this situation is analogous to that of pregnancy. Recent studies indicate that pregnancy transiently increases the risk of breast cancer (for a period of several years) after a woman's first childbirth, and this is followed by a lifetime reduction in risk.[203] And some have found that a concurrent or recent pregnancy adversely affects survival.[204, 205] It is argued that breast cells that have already begun malignant transformation are adversely affected by the hormones of pregnancy, while normal stem cells become more resistant because of a pregnancy. It is possible that early and recent use of oral contraceptives also accelerates the growth of a pre-existing malignancy, explaining the limitation of the finding to current and recent use and the increase in localized disease. With the accumulation of greater numbers of older women previously exposed to oral contraceptives, a protective effect may become evident. In a case-control study of women in Toronto, Canada, age 40–69 years, those women who had used oral contraceptives for 5 or more years, 15 or more years previously, had a 50% reduced risk of breast cancer.[206]

Conclusion

Adding up the benefits of oral contraception, the possible slight increase in risk of breast cancer is far outweighed by positive effects on our public health. But the impact on public health is of little concern during the private clinician–patient interchange in the office. Here personal risk receives highest priority; fear of cancer is a motivating force, and compliance with effective contraception requires accurate information. For these reasons, we provide the following summary of our assessment of the impact of oral contraceptives on the risk of breast cancer.

SUMMARY: Oral Contraceptives and the Risk of Breast Cancer

- **Current and recent use of oral contraceptives may be associated with about a 20% increased risk of early premenopausal breast cancer, essentially limited to localized disease and a very small increase in the actual number of cases (so small, there would be no major impact on incidence figures). This finding may be due to detection/surveillance bias and accelerated growth of already present malignancies, a situation similar to the effects of pregnancy and postmenopausal hormone therapy on the risk of breast cancer (as reviewed in Chapter 18). Further comfort can be derived from the fact that the increase in breast cancer in American women was greater in older women from 1973 to 1994, those who did not have the opportunity to use oral contraception.[207] In women under 50 years of age, there was only a slight increase during this same time period.**

- **Previous oral contraceptive use may be associated with a reduced risk of metastatic breast cancer later in life, and possibly with a reduced risk of postmenopausal breast cancer.**

- **Oral contraceptive use does not further increase the risk of breast cancer in women with positive family histories of breast cancer or in women with proven benign breast disease.**

- **The clinician should not fail to take every opportunity to direct attention to all factors that affect breast cancer. Breastfeeding and control of alcohol intake are good examples, and are also components of preventive health care. Especially important is this added motivation to encourage breastfeeding. The protective effect of breastfeeding is exerted (although it is probably a small one; see Chapter 16) on premenopausal breast cancer, the cancer of concern to younger women using oral contraception.**

Other Cancers

The Walnut Creek study suggested that melanoma was linked to oral contraception; however, the major risk factor for melanoma is exposure to sunlight. More recent and accurate evaluation utilizing both the Royal College General Practitioners and Oxford Family Planning Association prospective cohorts and accounting for exposure to sunlight did not indicate a significant difference in the risk of melanoma comparing users to nonusers.[208, 209] There is no evidence linking oral contraceptive use to kidney cancer, gallbladder cancer, or pituitary tumors.[210] Long-term oral contraceptive use may slightly increase the risk of molar pregnancy, but there is no convincing evidence of a cause-and-effect association.[211] Although previous studies have not been in agreement, the Nurses' Health Study reports about a 40% reduced risk of colorectal cancer associated with 8 years of previous use of oral contraceptives (most likely higher dose products).[212]

Endocrine Effects

Adrenal Gland

Estrogen increases the cortisol-binding globulin (CBG). It had been thought that the increase in plasma cortisol while on oral contraception was due to increased binding by this globulin and not an increase in free active cortisol. Now it is apparent that free and active cortisol levels are also elevated. Estrogen decreases the ability of the liver to metabolize cortisol, and in addition, progesterone and related compounds can displace cortisol from transcortin, and thus contribute to the elevation of unbound cortisol. The effects of these elevated levels over prolonged periods of time are unknown, but no obvious impact has become apparent. To put this into perspective, the increase is not as great as that which occurs in pregnancy, and, in fact, it is within the normal range for nonpregnant women.

The adrenal gland responds to adrenocorticotropic hormone (ACTH) normally in women on oral contraceptives; therefore, there is no suppression of the adrenal gland itself. Initial studies indicated that the response to metyrapone (an 11β-hydroxylase blocker) was abnormal, suggesting that the pituitary was suppressed. However, estrogen accelerates the conjugation of metyrapone by the liver; and, therefore, the drug has less effect, thus explaining the subnormal responses initially reported. The pituitary-adrenal reaction to stress is normal in women on oral contraceptive pills.

Thyroid

Estrogen increases the synthesis and circulating levels of thyroxine-binding globulin. Prior to the introduction of new methods for measuring free thyroxine levels, evaluation of thyroid function was a problem. Measurement of TSH (thyroid-stimulating hormone) and the free thyroxine level in a woman on oral contraception provide an accurate assessment of a patient's thyroid state. Oral contraception affects the total thyroxine level in the blood as well as the amount of binding globulin, but the free thyroxine level is unchanged.

Oral Contraception and Reproduction

The impact of oral contraceptives on the reproductive system is less than initially thought. Early studies that indicated adverse effects have not stood the test of time and the scrutiny of multiple, careful studies. There are two major areas that deserve review: (1). Inadvertent use of oral contraceptives during the cycle of conception and during early pregnancy, and (2). Reproduction after discontinuing oral contraception.

Inadvertent Use During the Cycle of Conception and During Early Pregnancy

One of the reasons, if not the major reason, why a lack of withdrawal bleeding while using oral contraceptives is such a problem is the anxiety produced in both patient and clinician. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the concerns stemming from the retrospective studies that indicated an increased risk of congenital malformations among the offspring of women who were pregnant and using oral contraception.

Organogenesis does not occur in the first 2 embryonic weeks (first 4 weeks since last menstrual period); however, teratogenic effects are possible between the third and eighth embryonic weeks (5 to 10 weeks since LMP).

Initial positive reports linking the use of contraceptive steroids to congenital malformations have not been substantiated. Many suspect a strong component of recall bias in the few positive studies due to a tendency of patients with malformed infants to recall details better than those with normal children. Other confounding problems have included a failure to consider the reasons for the administration of hormones (e.g., bleeding in an already abnormal pregnancy), and a failure to delineate the exact timing of the treatment (e.g., treatment was sometimes confined to a period of time during which the heart could not have been affected).

An association with cardiac anomalies was first claimed in the 1970s.[213, 214] This link received considerable support with a report from the U.S. Collaborative Perinatal Project; however, subsequent analysis of these data uncovered several methodologic shortcomings.[215] Simpson, in a very thorough and critical review in 1990, concluded that there was no reliable evidence implicating sex steroids as cardiac teratogens.[216] In fact, in his review, Simpson found no relationship between oral contraception and the following problems: hypospadias, limb reduction anomalies, neural tube defects, and mutagenic effects which would be responsible for chromosomally abnormal fetuses. Even virilization is not a practical consideration because the doses required (e.g., 20–40 mg norethindrone per day) are in excess of anything currently used. These conclusions reflect use of combined oral contraceptives as well as progestins alone.

In the past there was a concern regarding the VACTERL complex. VACTERL refers to a complex of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies. While case-control studies indicated a relationship with oral contraception, prospective studies have failed to observe any connection between sex steroids and the VACTERL complex.[217] A meta-analysis of 26 prospective studies of the risk of birth defects with oral contraceptive ingestion during pregnancy concluded that there was no increase in risk for major malformations, congenital heart defects, or limb reduction defects.[218]

Women who become pregnant while taking oral contraceptives or women who inadvertently take birth control pills early n pregnancy should be advised that the risk of a significant congenital anomaly is no greater than the general rate of 2–3%. This recommendation can be extended to those pregnant woman who have been exposed to a progestational agent such as medroxyprogesterone acetate or 17-hydroxyprogesterone caproate.[219, 220]

Reproduction After Discontinuing Oral Contraception

Fertility

The early reports from the British prospective studies indicated that former users of oral contraception had a delay in achieving pregnancy. In the Oxford Family Planning Association study, former use had an effect on fertility for up to 42 months in nulligravida women and for up to 30 months in multigravida women.[221] Presumably, the delay is due to lingering suppression of the hypothalamic-pituitary reproductive system.

A later analysis of the Oxford data indicated that the delay was concentrated in women age 30–34 who have never given birth.[222] At 48 months, 82% of these women had given birth compared with 89% of users of other contraceptive methods, not a big difference. No effect was observed in women younger than 30 or in women who had previously given birth. Childless women age 25–29 experienced some delay in return to fertility, but by 48 months, 91% had given birth compared with 92% in users of other methods. It should be noted that after 72 months the proportions of women who remained undelivered were the same in both groups of women.

This delay has been observed in the United States as well. In the Boston area, the interval from cessation of contraception to conception was 13 months or greater for 24.8% of prior oral contraceptive users compared with 10.6% for former users of all other methods (12.4% for intrauterine device {IUD} users, 8.5% for diaphragm uses, and 11.9% for other methods).[223] Oral contraceptive users had a lower monthly percentage of conceptions for the first 3 months, and somewhat lower percentage from 4 to 10 months. It took 24 months for 90% of previous oral contraceptive users to become pregnant, 14 months for IUD users, and 10 months for diaphragm users. Similar findings in Connecticut indicate that this delay lasts at least a year, and the effect is greater with higher dose preparations.[224] Despite this delay, there is no evidence that infertility is increased by the use of oral contraception. In fact, in young women, previous oral contraceptive use is associated with a lower risk of primary infertility.[225]

Spontaneous Miscarriage

There is no increase in the incidence of spontaneous miscarriage in pregnancies after the cessation of oral contraception. Indeed, the rate of spontaneous miscarriages and stillbirths is slightly less in former pill users, about 1% less for spontaneous miscarriages and 0.3% less for stillbirths.[226] A protective effect of previous oral contraceptive use against spontaneous miscarriage has been observed to be more apparent in women who become pregnant after age 30.[227]

Pregnancy Outcome

There is no evidence that oral contraceptives cause changes in individual germ cells that would yield an abnormal child at a later time.[216] There is no increase in the number of abnormal children born to former oral contraceptive users, and there is no change in the sex ratio (a sign of sex-linked recessive mutations).[226, 228] These observations are not altered when analyzed for duration of use. Initial observations that women who had previously used oral contraception had an increase in chromosomally abnormal fetuses have not been confirmed. Furthermore, as noted above, there is no increase in the miscarriage rate after discontinuation, something one would expect if oral contraceptives induce chromosomal abnormalities because these are the principal cause of spontaneous miscarriage.

In a 3-year follow-up of children whose mothers used oral contraceptives prior to conception, no differences could be detected in weight, anemia, intelligence, or development.[229] Former pill users have no increased risks for the following: perinatal morbidity or mortality, prematurity, and low birth weight.[230, 231] Dizygous twinning has been observed to be nearly two-fold (1.6% versus 1.0%) increased in women who conceive soon after cessation of oral contraception.[226] This effect was greater with longer duration of use.

The only reason (and it is a good one) to recommend that women defer attempts to conceive for a month or two after stopping the pill is to improve the accuracy of gestational dating by allowing accurate identification of the last menstrual period.

Breastfeeding

Oral contraception has been demonstrated to diminish the quantity and quality of lactation in postpartum women. Also of concern is the potential hazard of transfer of contraceptive steroids to the infant (a significant amount of the progestational component is transferred into breast milk);[232] however, no adverse effects have thus far been identified. Women who use oral contraception have a lower incidence of breastfeeding after the 6th postpartum month, regardless of whether oral contraception is started at the first, second, or third postpartum month.[233–235]

In adequately nourished breastfeeding women, no impairment of infant growth can be detected; presumably, compensation is achieved either through supplementary feedings or increased suckling.[236] In an 8-year follow-up study of children breastfed by mothers using oral contraceptives, no effect could be detected on diseases, intelligence, or psychological behavior.[237] This study also found that mothers on birth control pills lactated a significantly shorter period of time than controls, a mean of 3.7 months versus 4.6 months in controls.

Because the above considerations indicate that oral contraception shortens the duration of breastfeeding, it is worthwhile to consider the contraceptive effectiveness of lactation. The contraceptive effectiveness of lactation, i.e., the length of the interval between births, depends on the level of nutrition of the mother (if low, the longer the contraceptive interval), the intensity of suckling, and the extent to which supplemental food is added to the infant diet. If suckling intensity and/or frequency is diminished, contraceptive effect is reduced. Only amenorrheic women who exclusively breastfeed (full breastfeeding) at regular intervals, including nighttime, during the first 6 months have the contraceptive protection equivalent to that provided by oral contraception (98% efficacy); with menstruation or after 6 months, the chance of ovulation increases.[238, 239] With full or nearly full breastfeeding, approximately 70% of women remain amenorrheic through 6 months and only 37% through one year; nevertheless with exclusive breastfeeding, the contraceptive efficacy at one year is high, at 92%.[239] Fully breastfeeding women commonly have some vaginal bleeding or spotting in the first 8 postpartum weeks, but this bleeding is not due to ovulation.[240]

Supplemental feeding increases the chance of ovulation (and pregnancy) even in amenorrheic women.[241] Total protection is achieved by the exclusively breastfeeding woman for a duration of only 10 weeks.[240] Half of women studied who are not fully breastfeeding ovulate before the 6th week, the time of the traditional postpartum visit; a visit during the 3rd postpartum week is strongly recommended for contraceptive counseling.

It is apparent that although lactation provides a contraceptive effect, it is variable and not reliable for every woman. Furthermore, because frequent suckling is required to maintain full milk production, women who use oral contraception and also breastfeed less frequently (e.g., because they work outside their home) have two reasons for decreased milk volume. This combination can make it especially difficult to continue nursing.

Initiation of Oral Contraception in the Postpartum Period

The individual woman is in need of contraception early in the postpartum period. In a careful study of 22 postpartum, nonbreastfeeding women, the mean time from delivery to the first menses was 45 ± 10.1 days, and no woman ovulated before 25 days after delivery.[242] A high proportion of the first cycles (81.8%) and the subsequent cycles (37%) were not normal; however, this is certainly not predictable in individual women. Others have documented a mean delay of 7 weeks

before resumption of ovulation, but half of the women studied ovulated before the 6th week, the time of the traditional postpartum visit. *The obstetrical tradition of scheduling the postpartum visit at 6 weeks should be changed. A 3-week visit would be more productive in avoiding postpartum surprises.*

The Rule of 3's:

In the presence of FULL breastfeeding, a contraceptive method should be used beginning in the *3rd postpartum month.*

With PARTIAL breastfeeding or NO breastfeeding, a contraceptive method should begin during the *3rd postpartum week.*

After the termination of a pregnancy of less than 12 weeks, oral contraception can be started immediately. After a pregnancy of 12 or more weeks, oral contraception has traditionally been started 2 weeks after delivery to avoid an increased risk of thrombosis during the initial postpartum period. We believe that oral contraception can be started immediately after a second-trimester abortion or premature delivery.

Because of the concerns regarding the impact of oral contraceptives on breastfeeding, a useful alternative is to combine the contraceptive effect of lactation with the progestin-only minipill. This low dose of progestin has no negative impact on breast milk, and some studies document an increase in milk quantity and nutritional quality.[243] Highly effective (near total) protection can be achieved with the combination of lactation and the minipill. Because of the slight positive impact on lactation, the minipill can be started soon after delivery, but at least a 3-day postpartum delay is recommended to allow the decline in pregnancy levels of estrogen and progesterone and the establishment of lactation.[244] In addition, use of the progestin-only minipill has been reported to be associated with a 3-fold increased risk of diabetes mellitus in lactating women with recent gestational diabetes.[130] This special group of women should consider other methods of contraception.

Other Considerations

Prolactin-Secreting Adenomas

Because estrogen is known to stimulate prolactin secretion and to cause hypertrophy of the pituitary lactotrophs, it is appropriate to be concerned over a possible relationship between oral contraception and prolactin-secreting adenomas. Case-control studies have uniformly concluded that no such relationship exists.[245, 246] Data from both the Royal College of General Practitioners and the Oxford Family Planning Association studies indicated no increase in the incidence of pituitary adenomas.[210, 247] Previous use of oral contraceptives is not related to the size of prolactinomas at presentation and diagnosis.[247, 248] Oral contraception can be prescribed to patients with pituitary microadenomas without fear of subsequent tumor growth.[249, 250] ***We have routinely prescribed oral contraception to patients with pituitary microadenomas and have never observed evidence of tumor growth.***

Postpill Amenorrhea

The approximate incidence of "postpill amenorrhea" is 0.7–0.8%, which is equal to the incidence of spontaneous secondary amenorrhea,[231, 251, 252] and there is no evidence to support the idea that oral contraception causes secondary amenorrhea. If a cause-and-effect relationship exists between oral contraception and subsequent amenorrhea, one would expect the incidence of infertility to be increased after a given population discontinues use of oral contraception. In those

women who discontinue oral contraception in order to get pregnant, 50% conceive by 3 months, and after 2 years, a maximum of 15% of nulliparous women and 7% of parous women fail to conceive.[231] rates comparable with those quoted for the prevalence of spontaneous infertility. Attempts to document a cause-and-effect relationship between oral contraceptive use and secondary amenorrhea have failed.[253] Although patients with this problem come more quickly to our attention because of previous oral contraceptive use and follow-up, there is no cause-and-effect relationship. Women who have not resumed menstrual function within 12 months should be evaluated as any other patient with secondary amenorrhea.

Use During Puberty

Should oral contraception be advised for a young woman with irregular menses and oligo-ovulation or anovulation? The fear of subsequent infertility should not be a deterrent to providing appropriate contraception. Women who have irregular menstrual periods are more likely to develop secondary amenorrhea whether they use oral contraception or not. The possibility of subsequent secondary amenorrhea is less of a risk and a less urgent problem for a young woman than leaving her unprotected. The need for contraception takes precedence

There is no evidence that the use of oral contraceptives in the pubertal, sexually active girl impairs growth and development of the reproductive system.[225] Again, the most important concern is and should be the prevention of an unwanted pregnancy. For most teenagers, oral contraception, dispensed in the 28-day package for better compliance, is the contraceptive method of choice.

Infections and Oral Contraception

Viral STDs

The viral STDs include human immunodeficiency virus (HIV), human papillomavirus (HPV), herpes simplex virus (HSV), and hepatitis B (HBV). At the present time, no known associations exist between oral contraception and the viral STDs. Of course, significant prevention includes barrier methods of contraception. Thus far, most studies have found no association between oral contraceptive use and HIV seropositivity, and some have indicated a protective effect.[254–256] ***For women not in a stable, monogamous relationship, a dual approach is recommended, combining the contraceptive efficacy and protection against PID offered by oral contraception with the use of a barrier method (and spermicide) for prevention of viral STDs.***

Bacterial STDs

Sexually transmitted diseases (STDs) are one of the most common public health problems in the United States. It was estimated in 1995, that 7.6% of reproductive age U.S. women reported having been treated for pelvic inflammatory disease (PID).[257] This upper genital tract infection is usually a consequence of STDs. The best estimate of subsequent tubal infertility is derived from an excellent Swedish report; approximately 12% after one episode of PID, 23% after 2 episodes, and 54% after 3 episodes.[258] Because pelvic infection is the single greatest threat to the reproductive future of a young woman, the now recognized protection offered by oral contracep-

tion against pelvic inflammatory disease is highly important.[259–261] ***The risk of hospitalization for PID is reduced by approximately 50–60%, but at least 12 months of use are necessary, and the protection is limited to current users.***[259, 262] Furthermore, if a patient does get a pelvic infection, the severity of the salpingitis found at laparoscopy is decreased.[263, 264] The mechanism of this protection remains unknown. Speculation includes thickening of the cervical mucus to prevent movement of pathogens and bacteria-laden sperm into the uterus and tubes, and decreased menstrual bleeding, reducing movement of pathogens into the tubes as well as a reduction in "culture medium."

The argument has been made that this protection is limited to gonococcal disease, and chlamydial infections may even be enhanced. Fifteen of 17 published studies by 1985 reported a positive association of oral contraceptives with lower genital tract chlamydial cervicitis.[265] Because lower genital tract infections caused by chlamydia are on the rise (now the most prevalent bacterial STD in the U.S.) and the rate of hospitalization for PID is also increased, it is worthwhile for both patients and clinicians to be alert for symptoms of cervicitis or salpingitis in women on oral contraception who are at high risk of sexually transmitted disease (multiple sexual partners, a history of STD, or cervical discharge). The mechanism for the association between chlamydial cervicitis and oral contraceptives may be the well recognized extension of the columnar epithelium from the endocervix out over the cervix (ectopia) that occurs with oral contraceptive use.[266]

Despite this potential relationship between oral contraception and chlamydial infections, it should be emphasized that there is no evidence for an impact of oral contraceptives increasing the incidence of tubal infertility.[267] In fact, a case-control study indicated that oral contraceptive users with chlamydia infection are protected against symptomatic PID.[268] A case-control study has suggested that oral contraceptive users are more likely to harbor unrecognized endometritis, and that this would explain the discrepancy between the observed rates between lower and upper tract infection.[269] However, this would not explain the lack of an association between oral contraceptive use and tubal infertility. Thus, the influence of oral contraception on the upper reproductive tract may be different than on the lower tract. These observations on fertility are derived mostly, if not totally, from women using oral contraceptives containing 50 µg of estrogen. The continued progestin dominance of the lower dose formulations, however, should produce the same protective impact, and evidence indicates that this is so.[262]

Other Infections

In the British prospective studies of high-dose oral contraceptives, urinary tract infections were increased in users of oral contraception by 20%, and a correlation was noted with estrogen dose. An increased incidence of cervicitis was also reported, an effect related to the progestin dose. The incidence of cervicitis increased with the length of time the pill was used, from no higher after 6 months to 3 times higher by the 6th year of use. A significant increase in a variety of viral diseases, e.g., chickenpox, was observed, suggesting steroid effects on the immune system. The prevalence of these effects with low-dose oral contraception is unknown.

Oral contraception appears to protect against bacterial vaginosis and infections with *Trichomonas*.[270, 271] Evidence is lacking to convincingly implicate oral contraception with vaginal infections with *Candida* species;[270] however, clinical experience is sometimes impressive when recurrence and cure repeatedly follow use and discontinuation of oral contraception.

Patient Management

Absolute Contraindications to the Use of Oral Contraception

1. Thrombophlebitis, thromboembolic disorders (including a close family history, parent or sibling, suggestive of an inherited susceptibility for venous thrombosis), cerebral vascular disease, coronary occlusion, or a past history of these conditions, or conditions predisposing to these problems.

2. Markedly impaired liver function. Steroid hormones are contraindicated in patients with hepatitis until liver function tests return to normal.

3. Known or suspected breast cancer.

4. Undiagnosed abnormal vaginal bleeding.

5. Known or suspected pregnancy.

6. Smokers over the age of 35.

Relative Contraindications Requiring Clinical Judgment and Informed Consent

1. ***Migraine headaches.*** In retrospective studies of low-dose pills, it is not clear whether migraine headaches are associated with an increased risk of stroke. Some women report an improvement in their headaches, and in our view, a trial of the lowest dose oral contraceptives is warranted. Oral contraceptives should be avoided in women who have migraine with complex or prolonged aura, or if additional stroke factors are present (older age, smoking, hypertension).[272]

2. ***Hypertension***. A woman under 35 who is otherwise healthy and whose blood pressure is well controlled by medication can elect to use oral contraception. We recommend the use of the lowest estrogen dose products.

3. ***Uterine leiomyoma.*** This is not a contraindication with low-dose oral contraceptives. There is evidence that the risk of leiomyomas was decreased by 31% in women who used higher dose oral contraception for 10 years.[273] However, case-control studies with lower dose oral contraceptives have found neither a decrease nor an increase in risk, although the Nurses' Health Study reported a slightly increased risk when oral contraceptives were first used in early teenage years.[274–276] The administration of low-dose oral contraceptives to women with leiomyomata does not stimulate fibroid growth, and is associated with a reduction in menstrual bleeding.[277]

4. ***Gestational diabetes.*** Low-dose formulations do not produce a diabetic glucose tolerance response in women with previous gestational diabetes, and there is no evidence that combined oral contraceptives increase the incidence of overt diabetes mellitus.[129, 130] We believe that women with previous gestational diabetes can use oral contraception with annual assessment of the fasting glucose level.

5. ***Elective surgery.*** The recommendation that oral contraception should be discontinued 4 weeks before elective major surgery to avoid an increased risk of postoperative thrombosis is based on data derived from high-dose pills. If possible, it is safer to follow this recommendation when a period of immobilization is to be expected. It is prudent to maintain contraception right up to the performance of a sterilization procedure, and this short, outpatient operation carries very minimal risk.

6. ***Epilepsy.*** Oral contraceptives do not exacerbate epilepsy, and in some women, improvement in seizure control has occurred.[278] Antiepileptic drugs, however, may decrease the effectiveness of oral contraception.

7. ***Obstructive jaundice in pregnancy.*** Not all patients with this history will develop jaundice on oral contraception, especially with the low-dose formulations.

8. ***Sickle cell disease or sickle C disease.*** Patients with sickle cell trait can use oral contraception. The risk of thrombosis in women with sickle cell disease or sickle C diseases is theoretical (and medicolegal). We believe effective protection against pregnancy in these patients warrants the use of low-dose oral contraception.

9. ***Diabetes mellitus.*** Effective prevention of pregnancy outweighs the small risk of complicating vascular disease in diabetic women who are under age 35 and otherwise healthy.

10. ***Gallbladder disease.*** Oral contraceptives do not cause gallstones, but may accelerate the emergence of symptoms when gallstones are already present.

Clinical Decisions

Surveillance

In view of the increased safety of low-dose preparations for healthy young women with no risk factors, such patients need be seen only every 12 months for exclusion of problems by history, measurement of the blood pressure, urinalysis, breast examination, palpation of the liver, and pelvic examination with Pap smear. Women with risk factors should be seen every 6 months by appropriately trained personnel for screening of problems by history and blood pressure measurement. Breast and pelvic examinations are necessary only yearly. It is worth emphasizing that better continuation is achieved by reassessing new users within 1--2 months. It is at this time that subtle fears and unvoiced concerns need to be confronted and resolved.

Oral contraception is safer than most people think it is, and the low-dose preparations are extremely safe. Health care providers should make a significant effort to get this message to our patients (and our colleagues). We must make sure our patients receive adequate counseling, either from ourselves or our professional staff. The major reason why patients discontinue oral contraception is fear of side effects.[279] Let's take time to put the risks into proper perspective, and to emphasize the benefits as well as the risks.

Laboratory surveillance should be used only when indicated. Routine biochemical measurements fail to yield sufficient information to warrant the expense. Assessing the cholesterol-lipoprotein profile and carbohydrate metabolism should follow the same guidelines applied to all patients, users and nonusers of contraception. The following is a useful guide as to who should be monitored with blood screening tests for glucose, lipids, and lipoproteins:

Young women, at least once.
Women 35 years or older.
Women with a strong family history of heart disease, diabetes mellitus, or hypertension.
Women with gestational diabetes melllitus.
Women with xanthomatosis.
Obese women.
Diabetic women.

Choice of Pill

The therapeutic principle remains: utilize the formulations that give effective contraception and the greatest margin of safety. You and your patients are urged to choose a low-dose preparation containing less than 50 µg of estrogen, combined with low doses of new or old progestins. Current data support the view that there is greater safety with preparations containing less than 50 µg of estrogen. The arguments in this chapter indicate that all patients should begin oral contraception with low-dose products, and that patients on higher dose oral contraception should be changed to the low-dose preparations. Stepping down to a lower dose can be accomplished immediately with no adverse reactions such as increased bleeding or failure of contraception.

The multiphasic preparations do have a reduced progestin dosage compared with some of the existing monophasic products; however, based on currently available information there is little difference between the low-dose monophasics and the multiphasics.

The pharmacologic effects in animals of various formulations have been used as a basis for therapeutic recommendations in selecting the optimal oral contraceptive pill. *These recommendations (tailor-making the pill to the patient) have not been supported by appropriately controlled clinical trials. All too often this leads to the prescribing of a pill of excessive dosage with its attendant increased risk of serious side effects.* It is worth repeating our earlier comments on potency. Oral contraceptive potency (specifically progestin potency) is no longer a consideration when it comes to prescribing birth control pills. The potency of the various progestins has been accounted for by appropriate adjustments of dose. Clinical advice based on potency is an artificial exercise that has not stood the test of time. The biologic effect of the various progestational components in current low-dose oral contraceptives is approximately the same. Our progress in lowering the doses of the steroids contained in oral contraceptives has yielded products with little serious differences.

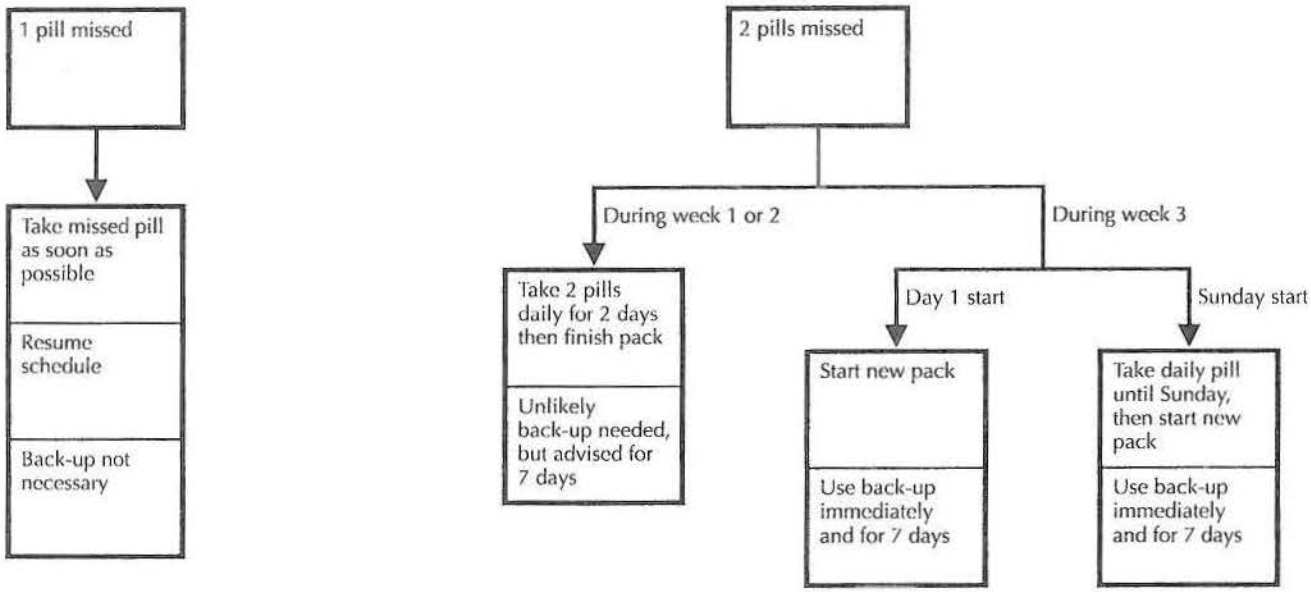
Pill Taking

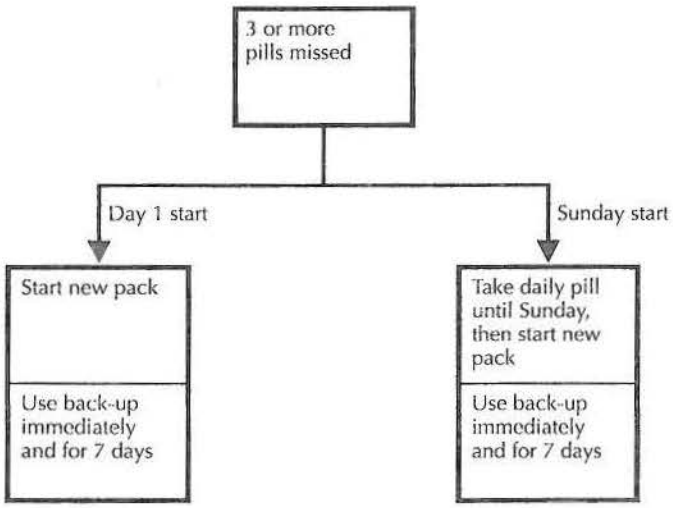
Effective contraception is present during the first cycle of pill use, provided the pills are started no later than the 5th day of the cycle, and no pills are missed. Thus, starting oral contraception on the first day of menses ensures immediate protection. In the United States, most clinicians and patients prefer the Sunday start packages, beginning on the first Sunday following menstruation. This can be easier to remember, and it usually avoids menstrual bleeding on weekends. It is probable, but not totally certain, that even if a dominant follicle should emerge in occasional patients after a Sunday start, an LH surge and ovulation would still be prevented.[280] Some clinicians prefer to advise patients to use added protection in the first week of use.

Occasionally patients would like to postpone a menstrual period; e.g., for a wedding, holiday, or vacation. This can be easily achieved by omitting the 7-day hormone-free interval. Simply start a new package of pills the next day after finishing the series of 21 pills in the previous package. Remember, when using a 28-pill package, the patient would start a new package after using the 21 *active* pills.

There is no rationale for recommending a pill-free interval "to rest." The serious side effects are not eliminated by pill-free intervals. This practice all too often results in unwanted pregnancies.

How important is it to take the oral contraceptive at the same time every day? Although not well studied, there is reason to believe precise pill taking minimizes breakthrough bleeding. In addition, compliance is improved by a fixed schedule that is habit-forming.





What To Do When Pills Are Missed

Irregular pill taking is a common occurrence. Using an electronic monitoring device to measure compliance, it was apparent that consistency of pill taking is even worse than what patients report; only 33% of women were documented to have missed no pills in cycle 1, and by cycle 3, about one-third of the women missed 3 or more pills with many episodes of consecutive days of missed pills.[281] These data indicate that women become less careful over time, emphasizing the importance of repeatedly reviewing with patients what to do when pills are missed.

If a woman misses 1 pill, she should take that pill as soon as she remembers and take the next pill as usual. No backup is needed.

If she misses 2 pills in the first two weeks, she should take two pills on each of the next two days; it is unlikely that a back-up method is needed, but the official consensus is to recommend backup for the next 7 days.

If 2 pills are missed in the third week, or if more than 2 active pills are missed at any time, another form of contraception should be used as backup immediately and for 7 days; if a Sunday starter, keep taking a pill every day until Sunday, and on Sunday start a new package; if a non-Sunday starter, start a new package the same day.

Studies have questioned whether missing pills has an impact on contraception. One study demonstrated that skipping 4 consecutive pills at varying times in the cycle did not result in ovulation.[280] Studies in which women deliberately lengthen their pill-fee interval up to 11 days have failed to show signs of ovulation.[282, 283] So far there is no evidence that moving to lower doses has had an impact on the margin of error. The studies have involved small numbers of women and given the large individual variation, it still is possible that some women might be at risk with a small increase in the pill-free interval. However, the progestational effects on endometrium and cervical mucus serve to ensure good contraceptive efficacy.[12] We may well prove that current recommendations are too conservative, and that a woman's chance of getting pregnant with missing pills is nearly zero. Nevertheless, this conservative advice is the safest message to convey.

The most prevalent problems that can be identified associated with apparent oral contraceptive failures are vomiting and diarrhea.[13, 14] ***Even if no pills have been missed, patients should be instructed to use a backup method for at least 7 days after an episode of gastroenteritis.***

Clinical Problems

Breakthrough Bleeding

A major continuation problem is breakthrough bleeding. Breakthrough bleeding gives rise to fears and concerns; it is aggravating, and even embarrassing. Therefore, on starting oral contraception, patients need to be fully informed about breakthrough bleeding.

There are two characteristic breakthrough bleeding problems: irregular bleeding in the first few months after starting oral contraception, and unexpected bleeding after many months of use. Effort should be made to manage the bleeding problem in a way that allows the patient to remain on low-dose oral contraception. ***There is no evidence that the onset of bleeding is associated with decreased efficacy, no matter what oral contraceptive formulation is used, even the lowest dose products.*** Indeed, in a careful study, breakthrough bleeding did not correlate with changes in the blood levels of the contraceptive steroids.[284]

The most frequently encountered breakthrough bleeding occurs in the first few months of use. The incidence is greatest in the first 3 months, ranging from 10–30% in the first month to less than 10% in the third. Breakthrough bleeding rates are higher with the lowest dose oral contraceptives, but not dramatically.[285] However, breakthrough bleeding is further increased in women who smoke and use formulations with 20 μg ethinyl estradiol.[286] Breakthrough bleeding is best managed by encouragement and reassurance. This bleeding usually disappears by the third cycle in the majority of women. If necessary, even this early pattern of breakthrough bleeding can be treated as outlined below. It is helpful to explain to the patient that this bleeding represents tissue breakdown as the endometrium adjusts from its usual thick state to the relatively thin state allowed by the hormones in oral contraceptives.

Breakthrough bleeding that occurs after many months of oral contraceptive use is a consequence of the progestin-induced decidualization. This endometrium and blood vessels within the endometrium tend to be fragile and prone to breakdown and asynchronous bleeding.

There are two recognized factors (both preventable) that are associated with a greater incidence of breakthrough bleeding. Consistency of use and smoking increase spotting and bleeding, but

inconsistency of pill taking is more important and has a greater effect in later cycles, whereas smoking exerts a general effect from beginning to later cycles.[287] Reinforcement of consistent pill taking can help minimize breakthrough bleeding. Cervical infection can be another cause of breakthrough bleeding; the prevalence of cervical chlamydial infections is higher among oral contraceptive users who report breakthrough bleeding.[288]

If bleeding occurs just before the end of the pill cycle, it can be managed by having the patient stop the pills, wait 7 days and start a new cycle. If breakthrough bleeding is prolonged or if it is aggravating for the patient, regardless of the point in the pill cycle, control of the bleeding can be achieved with a short course of exogenous estrogen. Conjugated estrogen, 1.25 mg, or estradiol, 2 mg, is administered daily for 7 days when the bleeding is present, no matter where the patient is in her pill cycle. The patient continues to adhere to the schedule of pill taking. Usually, one course of estrogen solves the problem, and recurrence of bleeding is unusual (but if it does recur, another 7-day course of estrogen is effective).

Responding to irregular bleeding by having the patient take 2 or 3 pills is not effective. The progestin component of the pill will always dominate; hence, doubling the number of pills will also double the progestational impact and its decidualizing, atrophic effect on the endometrium and its destabilizing effect on endometrial blood vessels. The addition of extra estrogen while keeping the progestin dose unchanged is logical and effective. This allows the patient to remain on the low-dose formulation with its advantage of greater safety. Breakthrough bleeding, in our view, is not sufficient reason to expose patients to the increased risks associated with higher dose oral contraceptives. Any bleeding that is not handled by this routine requires investigation for the presence of pathology.

There is no evidence that any oral contraceptive formulations that are approximately equivalent in estrogen and progestin dosage are significantly different in the rates of breakthrough bleeding. Clinicians often become impressed that switching to another product effectively stops the breakthrough bleeding. It is more likely that the passage of time is the responsible factor, and bleeding would have stopped regardless of switching and regardless of product.

Amenorrhea

With low-dose pills, the estrogen content is not sufficient in some women to stimulate endometrial growth. The progestational effect dominates to such a degree that a shallow atrophic endometrium is produced, lacking sufficient tissue to yield withdrawal bleeding. It should be emphasized that permanent atrophy of the endometrium does not occur, and resumption of normal ovarian function will restore endometrial growth and development. Indeed, there is no harmful, permanent consequence of amenorrhea while on oral contraception.

The major problem with amenorrhea while on oral contraception is the anxiety produced in both patient and clinician because the lack of bleeding may be a sign of pregnancy. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the medicolegal concerns stemming from the old studies which indicated an increased risk of congenital abnormalities among the offspring of women who inadvertently used oral contraception in early pregnancy. We reviewed this problem earlier, and emphatically stated that there is no association between oral contraception and an increased risk of congenital malformation, and there is no increased risk of having abnormal children.

The incidence of amenorrhea in the first year of use with low-dose oral contraception is less than 2%. This incidence increases with duration, reaching perhaps 5% after several years of use. It is important to alert patients upon starting oral contraception that diminished bleeding and possibly no bleeding may ensue.

Amenorrhea is a difficult management problem. A pregnancy test will allow reliable assessment for the presence of pregnancy even at this early stage. However, routine, repeated use of such testing is expensive and annoying, and may lead to discontinuation of oral contraception. ***A simple test for pregnancy is to assess the basal body temperature during the END of the pill-free week; a basal body temperature less than 98 degrees (36.6°C) is not consistent with pregnancy, and oral contraception can be continued.***

Many women are reassured with an understanding of why there is no bleeding and are able to continue on the pill despite the amenorrhea. Some women cannot reconcile themselves to a lack of bleeding, and this is an indication for trying other formulations (a practice unsupported by any clinical trials, and, therefore, the expectations are uncertain). But again, this problem does not warrant exposing patients to the greater risks of major side effects associated with higher dose products.

Some clinicians have observed that the addition of extra estrogen for 1 month (1.25 mg conjugated estrogens or 2 mg estradiol daily throughout the 21 days while taking the oral contraceptive) will rejuvenate the endometrium, and withdrawal bleeding will resume, persisting for many months.

Weight Gain

The complaint of weight gain is frequently cited as a major problem with compliance. Yet, studies of the low-dose preparations fail to demonstrate a significant weight gain with oral contraception, and no major differences among the various products.[140, 141, 289] This is obviously a problem of perception. The clinician has to carefully reinforce the lack of association between low-dose oral contraceptives and weight gain and focus the patient on the real culprit: diet and level of exercise. Most women gain a moderate amount of weight as they age, whether they take oral contraceptives or not.

Acne

Low-dose oral contraceptives improve acne regardless of which product is used.[122, 290-292] The low progestin doses (including levonorgestrel formulations) currently used are insufficient to stimulate an androgenic response.

Ovarian Cysts

Anecdotal reports suggested that functional ovarian cysts are encountered more frequently and suppress less easily with multiphasic formulations. This observation failed to withstand careful scrutiny.[293] Functional ovarian cysts occurred less frequently in women on higher dose oral contraception.[294] This protection is reduced with the current lower dose products to the point where little effect can be measured.[295-298] Thus, the risk of such cysts is not eliminated; and, therefore, clinicians can encounter such cysts in patients taking any of the oral contraceptive formulations.

Drugs That Affect Efficacy

There are many anecdotal reports of patients who conceived on oral contraceptives while taking antibiotics. There is little evidence, however, that antibiotics such as ampicillin, metronidazole, quinolone, and tetracycline, which reduce the bacterial flora of the gastrointestinal tract, affect oral contraceptive efficacy. Studies indicate that while antibiotics can alter the excretion of contraceptive steroids, plasma levels are unchanged, and there is no evidence of ovulation.[299, 300]

A review of a large number of patients derived from dermatology practices failed to find an increased rate of pregnancy in women on oral contraceptives and being treated with antibiotics (tetracyclines, penicillins, cephalosporins).[301]

There is good reason to believe that drugs, which stimulate the liver's metabolic capacity, can affect oral contraceptive efficacy. On the other hand, a search of a large database failed to discover any evidence that lower dose oral contraceptives are more likely to fail or to have more drug interaction problems when other drugs are used.[302]

To be cautious, patients on medications that affect liver metabolism should choose an alternative contraceptive. These drugs are as follows:

Rifampin
Phenobarbital
Phenytoin (Dilantin)
Primidone (Mysoline)
Carbamazepine (Tegretol)
Possibly ethosuximide, griseofulvin, and troglitazone.

Other Drug Interactions

Although not extensively documented, there is reason to believe that oral contraceptives potentiate the action of diazepam (Valium), chlordiazepoxide (Librium), tricyclic antidepressants, and theophylline.[303] Thus, lower doses of these agents may be effective in oral contraceptive users. Because of an influence on clearance rates, oral contraceptive users may require larger doses of acetaminophen and aspirin.[304]

Migraine Headaches

True migraine headaches are more common in women, while tension headaches occur equally in men and women. There have been no well done studies to determine the impact of oral contraception on migraine headaches. Patients may report that their headaches are worse or better.

Studies with high-dose pills indicated that migraine headaches were linked to a risk of stroke. More recent studies reflecting the use of low-dose formulations yield mixed results. One failed to find a further increase in stroke in patients with migraine who use oral contraception, another concluded that the use of oral contraception by migraineurs was associated with a 4-fold increase of the already increased risk of ischemic stroke.[305, 306] Because 20–30% of women experience migraine headaches, one would expect the study populations in the most recent studies of thrombosis to have included substantial numbers of migraineurs. An adverse effect of low-dose oral contraceptives on stroke risk in migraineurs should have manifested itself in the data. The lack of an increased risk of stroke in these studies is reassuring.

Because of the seriousness of this potential complication, the onset of visual symptoms or severe headaches requires a response. If the patient is at a higher dose, a move to a low-dose formulation may relieve the headaches. Switching to a different brand is worthwhile, if only to evoke a placebo response. True vascular headaches (classic migraine with aura) are an indication to avoid or discontinue oral contraception. Oral contraceptives should be avoided in women who have migraine with complex or prolonged aura, or if additional stroke factors are present (older age, smoking, hypertension).[272]

Clues To Severe Vascular Headaches:

- Headaches that last a long time.
- Dizziness, nausea, or vomiting with headaches.
- Scotomata or blurred vision.
- Episodes of blindness.
- Unilateral, unremitting headaches.
- Headaches that continue despite medication.

In some women, a relationship exists between their fluctuating hormone levels during a menstrual cycle and migraine headaches, with the onset of headaches characteristically coinciding with menses. We have had personal success (anecdotal to be sure) alleviating headaches by eliminating the menstrual cycle, either with the use of *daily* oral contraceptives or the daily administration of a progestational agent (such as 10 mg medroxyprogesterone acetate) or the use of depot-medroxyprogesterone acetate. Some women with migraine headaches have extremely gratifying responses. Women who experience an exacerbation of their headaches with oral contraception should consider one of the progestin-only methods.

Summary: Oral Contraceptive Use and Medical Problems

Gestational Diabetes. There is no contraindication to combined oral contraceptive use following gestational diabetes.[129, 130] There is a concern with breastfeeding women using the progestin-only minipill (discussed later in this chapter).

Diabetes Mellitus. Oral contraception can be used by diabetic women less than 35 years old who do not smoke and are otherwise healthy (especially an absence of diabetic vascular complications). A case-control study could find no evidence that oral contraceptive use by young women with insulin-dependent diabetes mellitus increased the development of retinopathy or nephropathy.[132] In a one-year study of women with insulin-dependent diabetes mellitus who were using a low-dose oral contraceptive, no deterioration could be documented in lipoprotein or hemostatic biochemical markers for cardiovascular risk.[133]

Hypertension. Low-dose oral contraception can be used in women less than age 35 years old with hypertension well controlled by medication, and who are otherwise healthy and do not smoke. We recommend the lowest estrogen dose formulations.

Pregnancy-Induced Hypertension. Women with pregnancy-induced hypertension can use oral contraception as soon as the blood pressure is normal in the postpartum period.

Hemorrhagic Disorders. Women with hemorrhagic disorders and women taking anticoagulants can use oral contraception. Inhibition of ovulation can avoid the real problem of a hemorrhagic corpus luteum in these patients. A reduction in menstrual blood loss is another benefit of importance.

Gallbladder Disease. Oral contraception use may precipitate a symptomatic attack in women known to have stones or a positive history for gallbladder disease and, therefore, should either be used very cautiously or not at all.

Obesity. An obese woman who is otherwise healthy can use low-dose oral contraception.

Hepatic Disease. Oral contraception can be utilized when liver function tests return to normal. Follow-up liver function tests should be obtained after 2–3 months of use.

Seizure Disorders. There is no impact of oral contraceptives on pattern or frequency of seizures. The concern is that anticonvulsant-induced hepatic enzyme activity can increase the risk of contraceptive failure. Some clinicians advocate the use of higher dose (50 mg estrogen) products;

however, no studies have been performed to demonstrate that this higher dose is necessary.

Mitral Valve Prolapse. Oral contraception use is limited to nonsmoking patients who are asymptomatic (no clinical evidence of regurgitation). There is a small subset of patients with mitral valve prolapse who are at increased risk of thromboembolism. Patients with atrial fibrillation, migraine headaches, or clotting factor abnormalities should consider progestin-only methods or the IUD (prophylactic antibiotics should cover IUD insertion if mitral regurgitation is present).

Systemic Lupus Erythematosus. Oral contraceptive use can exacerbate systemic lupus erythematous, and the vascular disease associated with lupus, when present, represents a contraindication to estrogen-containing oral contraceptives.[307] The progestin-only methods are a good choice. However, in patients with stable or inactive disease, without renal involvement and high antiphospholipid antibodies, low-dose oral contraception can be considered.[308] SELENA (Safety of Estrogen in Lupus Erythematosus National Assessment) is an on-going randomized, controlled clinical trial of oral contraceptive therapy in premenopausal women with systemic lupus erythematosus (as well as postmenopausal hormone therapy).

Migraine Headaches. Low-dose oral contraception (the lowest estrogen dose formulation) can be tried with careful surveillance in women with common migraine headaches. Daily administration can prevent menstrual migraine headaches. Oral contraception is best avoided in women with classic migraine headaches associated with neurologic symptoms.

Sickle Cell Disease. Patients with sickle cell trait can use oral contraception. The risk of thrombosis in women with sickle cell disease or sickle C diseases is theoretical (and medicolegal). We believe effective protection against pregnancy in these patients warrants the use of low-dose oral contraception. In the only long-term (10 years) follow-up report of women with sickle cell disease and using oral contraceptives, no apparent adverse effects were observed (at a time when higher dose products were prevalent).[309] Keep in mind that depot-medroxyprogesterone acetate used for contraception is associated with inhibition of sickling and improvement in anemia in patients with sickle cell disease.[310]

Benign Breast Disease. Benign breast disease is not a contraindication for oral contraception; with 2 years of use, the condition may improve.

Congenital Heart Disease or Valvular Heart Disease. Oral contraception is contraindicated only if there is marginal cardiac reserve or a condition that predisposes to thrombosis.

Hyperlipidemia. Because low-dose oral contraceptives have negligible impact on the lipoprotein profile, hyperlipidemia is not an absolute contraindication, with the exception of very high levels of triglycerides (which can be made worse by estrogen). If vascular disease is already present, oral contraception should be avoided. If other risk factors are present, especially smoking, oral contraception is not recommended. Dyslipidemic patients who begin oral contraception should have their lipoprotein profiles monitored monthly for a few visits to ensure no adverse impact. If the lipid abnormality cannot be held in control, an alternative method of contraception should be used.[311] Oral contraceptives containing desogestrel, noregestimate, or gestodene can increase HDL levels, but it is not known if this change is clinically significant.

Depression. Low-dose oral contraceptives have minimal, if any, impact on mood.

Smoking. Oral contraception is absolutely contraindicated in smokers over the age of 35. In patients 35 years old and younger, heavy smoking (15 or more cigarettes per day) is a relative contraindication. The relative risk of cardiovascular events is increased for women of all ages who smoke and use oral contraceptives; however, because the actual incidence of cardiovascular events is so low at a young age, the real risk is very low for young women, although it increases with age. An ex-smoker (for at least one year) should be regarded as a nonsmoker. Risk is only

linked to active smoking. Is there room for judgment? Given the right circumstances, low-dose oral contraceptives might be appropriate for a light smoker or the user of a nicotine patch. A 20 μg estrogen formulation may be a better choice for smoking women, regardless of age (because this dose of estrogen has no impact on clotting factors and platelet activation).[31, 32]

Pituitary Prolactin-Secreting Adenomas. Low-dose oral contraception can be used in the presence of microadenomas.

Infectious Mononucleosis. Oral contraception can be used as long as liver function tests are normal.

Ulcerative Colitis. There is no association between oral contraception and ulcerative colitis. Women with this problem can use oral contraceptives.[143] Oral contraceptives are absorbed mainly in the small bowel.

Occasionally, a situation may be encountered when an alternative to oral administration of contraceptive pills is required. For example, patients receiving chemotherapy can either have significant nausea and vomiting, or mucositis, both of which would prevent oral drug administration. The low-dose oral contraceptives can be administered vaginally. Initially, it was claimed that two pills must be placed high in the vagina daily in order to produce contraceptive steroid blood levels comparable with the oral administration of one pill.[312] However, a large clinical trial has demonstrated typical contraceptive efficacy with one pill administered vaginally per day.[313]

Because athletes are often amenorrheic and hypoestrogenic, oral contraceptives provide not only confidence against the risk of an unwanted pregnancy, but also estrogen support against bone loss. This is a situation where bone density measurements are worthwhile. A low bone density can help motivate an athlete to take hormone therapy, and a subsequent bone density measurement that reveals a failure of response to estrogen can indicate the presence of a hidden eating disorder.

Competing athletes are often concerned that oral contraceptives could reduce exercise performance. A rationale for the concern can be traced to the physiologic increase in ventilation during pregnancy, mediated by progesterone. Thus, progestin enhancement of ventilatory response could consume energy otherwise available for athletic performance. Indeed, reports have generated conflicting data as measured by laboratory testing. However, experimental studies that simulate athletic events can find no adverse effects on oxygen uptake or respiratory rate.[314] One study documented decreased soreness, both perceived and with palpation, after exercise in women using oral contraceptives.[315] Oral contraceptive use has no effect on prevalence or severity of low back pain, a common problem among female athletes.[316]

Oral contraceptives have a lot to offer with no serious drawbacks for athletes. In athletes who wish to avoid menstrual bleeding, oral contraceptives can be administered on a daily basis, with no breaks, preventing withdrawal bleeding.

The noncontraceptive benefits of low-dose oral contraception can be grouped into two main categories: benefits that incidentally accrue when oral contraception is specifically utilized for contraceptive purposes and benefits that result from the use of oral contraceptives to treat problems and disorders.

The noncontraceptive incidental benefits can be listed as follows:

Effective Contraception.
-less need for induced abortion.
-less need for surgical sterilization.
Less Endometrial Cancer.
Less Ovarian Cancer.
Fewer Ectopic Pregnancies.
More Regular Menses.
-less flow.
-less dysmenorrhea.
-less anemia.
Less Salpingitis.
Probably Less Endometriosis.
Possibly Less Benign Breast Disease.
Possibly Less Rheumatoid Arthritis.
Possibly Protection against Atherosclerosis.
Possibly Increased Bone Density.
Possibly Fewer Fibroids.
Possibly Fewer Ovarian Cysts.

Many of these benefits have been previously discussed. Protection against pelvic inflammatory disease is especially noteworthy and a major contribution to not only preservation of fertility but to lower health care costs. Also important is the prevention of ectopic pregnancies. Ectopic pregnancies have increased in incidence (partly due to an increase in STDs) and represent a major cost for our society and a threat to both fertility and life for individual patients.

Of course, prevention of benign and malignant neoplasia is an outstanding feature of oral contraception. High-dose oral contraceptive use decreased the incidence of benign breast disease diagnosed clinically as well as fibrocystic disease and fibroadenomas diagnosed by biopsy; hopefully, the same impact will become evident with current lower dose formulations. A 40% reduction in ovarian cancer and a 50% reduction in endometrial cancer represent substantial protection. Studies with higher dose formulations documented in long-term users a 31% reduction in uterine leiomyomata and, in current users, a 78% reduction in corpus luteum cysts and a 49% reduction in functional ovarian cysts.[294] The impact of low-dose preparations on these problems remains to be accurately measured and may be less. Case-control studies with low-dose oral contraceptives have found no impact on the risk of uterine fibroids, neither increased nor decreased.[274, 275] Epidemiologic studies have indicated that a progressive decline in the incidence of ovarian cysts is proportional to the steroid doses in oral contraceptives.[295, 296] Current low-dose monophasic and multiphasic formulations provide no protection against functional ovarian cysts.[295–298] This apparent weaker protection afforded by the current low-dose formulations makes it very likely that clinicians will encounter such cysts in their patients on oral contraceptives.

The low-dose contraceptives are as effective as higher dose preparations in reducing menstrual flow and the prevalence and severity of dysmenorrhea.[317, 318] The use of oral contraception is associated with a lower incidence of endometriosis, although the protective effect is probably limited to current or recent use.[319–321] These benefits involving two common gynecologic problems have an important, positive impact on compliance.

An Austrian study concluded that osteoporosis occurs later and is less frequent in women who have used long-term oral contraception.[322] Cross-sectional studies of postmenopausal women indicate that prior use of oral contraception is associated with higher levels of bone density and that the degree of protection is related to duration of exposure.[323, 324] However, other studies reflecting modern use of low-dose products indicate little impact of oral contraceptive use on bone.[325–327] These measurements of bone density are not as important as the clinical outcome: fractures. The available evidence suggests that any favorable effects on bone density are not

clinically important. In the Royal College of General Practitioners Study, the overall risk of fractures in ever users of oral contraceptives was actually slightly increased.[328] Similar results have been observed in the Oxford Family Planning Association Study.[329] It is likely that the increased risk reflects lifestyle effects among oral contraceptive users, but thus far, there is no evidence of a protective effect against fractures. However, previous oral contraceptive users are just now becoming elderly and reaching the age of greatest fracture prevalence. Future studies of postmenopausal women may eventually reveal a beneficial effect on osteoporotic fractures.

The literature on rheumatoid arthritis has been controversial, with studies in Europe finding evidence of protection and studies in North America failing to demonstrate such an effect. An excellent Danish case-control study was designed to answer criticisms of shortcomings in the previous literature.[330] Ever use of oral contraception reduced the relative risk of rheumatoid arthritis by 60%, and the strongest protection was present in women with a positive family history. One meta-analysis concluded that the evidence consistently indicated a protective effect, but that rather than preventing the development of rheumatoid arthritis, oral contraception may modify the course of disease, inhibiting the progression from mild to severe disease; whereas a later meta-analysis concluded there was no evidence of a protective effect.[331, 332]

Oral contraceptives are frequently utilized to manage the following problems and disorders:

Definitely Beneficial:
- **-dysfunctional uterine bleeding.**
- **-dysmenorrhea.**
- **-mittelschmerz.**
- **-endometriosis prophylaxis.**
- **-acne and hirsutism.**
- **-hormone therapy for hypothalamic amenorrhea.**
- **-prevention of menstrual porphyria.**
- **-control of bleeding (dyscrasias, anovulation).**

Possibly Beneficial:
- **-functional ovarian cysts.**
- **-premenstrual syndrome.**

Oral contraceptives have been a cornerstone for the treatment of anovulatory, dysfunctional uterine bleeding. For patients who need effective contraception, oral contraceptives are a good choice to provide hormone therapy for amenorrheic patients, as well as to treat dysmenorrhea. Oral contraceptives are also a good choice to provide prophylaxis against the recurrence of endometriosis in a woman who has already undergone more vigorous treatment with surgery or the GnRH analogues. To protect against endometriosis, oral contraceptives should be taken daily, with no break and no withdrawal bleeding.

The low-dose oral contraceptives are effective in treating acne and hirsutism. Suppression of free testosterone levels is comparable with that achieved with higher dosage.[290, 333] The beneficial clinical effect is the same with low-dose preparations containing levonorgestrel, previously recognized to cause acne at high dosage.[290, 334] Formulations with desogestrel, gestodene, and norgestimate are associated with greater increases in sex hormone-binding globulin and significant decreases in free testosterone levels. Comparison studies with oral contraceptives containing these progestins can detect no differences in effects on various androgen measurements among the various products.[335] Theoretically, these products would be more effective in the treatment of acne and hirsutism; however, this is yet to be documented by clinical studies. It is likely that all low-dose formulations, through the combined effects of an increase in sex hormone-binding globulin and a decrease in testosterone production, produce an overall similar clinical response, especially over time (a year or more).

Oral contraceptives have long been used to speed the resolution of ovarian cysts, but the efficacy of this treatment has not been established. Randomized trials have been performed with women who develop ovarian cysts after induction of ovulation.[336, 337] No advantage for the contraceptive treatment could be demonstrated. The cysts resolved completely and equally fast in both treated and non-treated groups. Of course, these were functional cysts secondary to ovulation induction, and this experience may not apply to spontaneously appearing cysts. Two short-term (5 and 6 weeks) randomized studies could document no greater effect of oral contraceptive treatment on resolution of spontaneous ovarian cysts when compared with expectant management.[338, 339] Clinical experience (untested by studies) leads us to believe that oral contraception does provide protection in women against the recurrent formation of ovarian cysts.

Continuation: Failure or Success?

Despite the fact that oral contraception is highly effective, hundreds of thousands of unintended pregnancies (close to 1 million) occur each year in the United States because of the failure of oral contraception. Worldwide, literally millions of unintended pregnancies result from poor compliance. In general, unmarried, poor, and minority women are more likely to have failures, reaching rates of 10–20%.[340, 341] Overall, the failure rate with actual use ranges from 3 to 6%. This difference between the theoretical efficacy and actual use reflects compliance and noncompliance. Noncompliance includes a wide variety of behavior: failure to fill the initial prescription, failure to continue on the medication, and incorrectly taking oral contraception. Compliance (continuation) is an area in which personal behavior, biology, and pharmacology come together. Oral contraceptive continuation reflects the interaction of these influences. Unfortunately, women who discontinue oral contraception often utilize a less effective method or, worse, fail to substitute another method.

There are 3 major factors that affect continuation:

1. The experience of side effects, such as breakthrough bleeding and amenorrhea, and perceived experience of "minor" problems, such as headaches, nausea, breast tenderness, and weight gain. Multiple side effects dramatically and progressively increase the likelihood of discontinuation.[342, 343] Because these complaints respond well even to placebo treatment,[344] it is reasonable to expect a favorable response to sensitive and attentive counseling.

2. Fears and concerns regarding cancer, cardiovascular disease, and the impact of oral contraception on future fertility.

3. Nonmedical issues, such as inadequate instructions on pill taking, complicated pill packaging, and difficulties arising from the patient package insert.

The information in this chapter is the foundation for good continuation, but the clinician must go beyond the presentation of information and develop an effective means of communicating that information. We recommend the following approach to the clinician–patient encounter as one way to improve continuation with oral contraception.

1. Explain how oral contraception works.

2. Review briefly the risks and benefits of oral contraception, but be careful to put the risks in proper perspective, and to emphasize the safety and noncontraceptive benefits of low-dose oral contraceptives.

3. Show and demonstrate to the patient the package of pills she will use.

4. Explain how to take the pills:
   -When to start.
   -The importance of developing a daily routine to avoid missing pills.
   -What to do if pills are missed (Identify a backup method).

5. Review the side effects that can affect continuation: amenorrhea, breakthrough bleeding, headaches, weight gain, nausea, etc., and what to do if one or more occurs.

6. Explain the warning signs of potential problems: abdominal or chest pain, trouble breathing, severe headaches, visual problems, leg pain or swelling.

7. Ask the patient to be sure to call if another clinician prescribes other medications.

8. Ask the patient to repeat critical information to make sure she understands what has been said. Ask if the patient has any questions.

9. Schedule a return appointment in 1–2 months to review understanding and address fears and concerns; a visit at 3 months is too late because most questions and side effects occur early.[343] Inconsistent use of oral contraceptives is more common in women who are new starters.[341]

10. Make sure a line of communication is open to clinician or office personnel. Ask the patient to call for any problem or concern before she stops taking the oral contraceptives.

The Progestin-Only Minipill

The minipill contains a small dose of a progestational agent and must be taken daily, in a continuous fashion.[345, 346] There is no evidence for any difference in clinical behavior among the available minipill products.

Minipills available worldwide:

1. Micronor, Nor-QD, Noriday, Norod -------- 0.350 mg norethindrone.
2. Microval, Noregeston, Microlut ---------- 0.030 mg norgestrel.
3. Ovrette, Neogest ---------- 0.075 mg levonorgestrel.
4. Exluton ---------- 0.500 mg lynestrenol.
5. Femulen ---------- 0.500 mg ethynodial diacetate.
6. CerazetteR ---------- 0.075 mg desogestrel.

Mechanism of Action

After taking a progestin-only minipill, the small amount of progestin in the circulation (about 25% of that in combined oral contraceptives) will have a significant impact only on those tissues very sensitive to the female sex steroids, estrogen and progesterone. The contraceptive effect is more dependent upon endometrial and cervical mucus effects, because gonadotropins are not consistently suppressed. The endometrium involutes and becomes hostile to implantation, and the cervical mucus becomes thick and impermeable. Approximately 40% of patients will ovulate normally. Tubal physiology may also be affected, but this is speculative.

Because of the low dose, the minipill must be taken every day at the same time of day. The change in the cervical mucus requires 2–4 hours to take effect, and, most importantly, the impermeability diminishes 22 hours after administration, and by 24 hours sperm penetration is essentially unimpaired.

Ectopic pregnancy is not prevented as effectively as intrauterine pregnancy. Although the overall incidence of ectopic pregnancy is not increased (it is still much lower than the incidence in women not using a contraceptive method), when pregnancy occurs, the clinician must suspect that it is more likely to be ectopic. A previous ectopic pregnancy should not be regarded as a contraindication to the minipill.

There are no significant metabolic effects (lipid levels, carbohydrate metabolism, and coagulation factors remain unchanged),[347] and there is an immediate return to fertility on discontinuation (unlike the delay seen with the combination oral contraceptive). Only one disturbing observation has been reported; progestin-only oral contraception was associated with about a 3-fold increased risk of diabetes mellitus in lactating women with recent gestational diabetes (an observation that is difficult to explain).[130] Because this increased risk is not observed with the use of combined oral contraceptives, it is speculated that the low levels of estrogen associated with breastfeeding allow an unimpeded progestin effect on insulin resistance.

Efficacy

Failure rates have been documented to range from 1.1 to 9.6 per 100 women in the first year of use.[348] The failure rate is higher in younger women (3.1 per 100 woman-years) compared with women over age 40 (0.3 per 100 woman-years).[349] In motivated women, the failure rate is comparable to the rate (less than 1 per 100 woman-years) with combination oral contraception.[350–352]

Pill Taking

The minipill should be started on the first day of menses, and a backup method must be used for the first 7 days because some women (very few) ovulate as early as 7–9 days after the onset of menses. The pill should be keyed to a daily event to ensure regular administration at the same time of the day. If pills are forgotten or gastrointestinal illness impairs absorption, the minipill should be resumed as soon as possible, and a back-up method should be used immediately and until the pills have been resumed for at least 2 days. If 2 or more pills are missed in a row and there is no menstrual bleeding in 4–6 weeks, a pregnancy test should be obtained. ***If more than 3 hours late in taking a pill, a backup method should be used for 48 hours.***

Problems

In view of the unpredictable effect on ovulation, it is not surprising that irregular menstrual bleeding is the major clinical problem. The daily progestational impact on the endometrium also contributes to this problem. Patients can expect to have normal, ovulatory cycles (40%), short, irregular cycles (40%), or a total lack of cycles ranging from irregular bleeding to spotting and amenorrhea (20%). This is the major reason why women discontinue the minipill method of contraception.[352]

Women on progestin-only contraception develop more functional, ovarian follicular cysts.[353] Nearly all, if not all, regress. This is not a clinical problem of any significance. Women who have experienced frequent ovarian cysts would be happier with methods that effectively suppress ovulation (combined oral contraceptives and depot-medroxyprogesterone acetate).

The levonorgestrel minipill may be associated with acne. The mechanism is similar to that seen with Norplant. The androgenic activity of levonorgestrel decreases the circulating levels of sex hormone-binding globulin (SHBG). Therefore free steroid levels (levonorgestrel and testosterone) will be increased despite the low dose. This is in contrast to the action of combined oral contraception where the effect of the progestin is countered by the estrogen-induced increase in SHBG.

The incidence of the other minor side effects is very low, probably at the same rate that would be encountered with a placebo.

Clinical Decisions

There are two situations where excellent efficacy, probably near total effectiveness, is achieved: lactating women and women over age 40. In lactating women, the contribution of the minipill is combined with prolactin-induced suppression of ovulation, adding up to very effective protection.[354] In breastfeeding, overweight, Latina women with prior gestational diabetes, the progestin-only minipill was associated with a 3-fold increased risk of non-insulin dependent diabetes mellitus.[130] It is not known whether this might be a risk in all women who have experienced gestational diabetes; a prudent course would be to advise other methods for this special group of women. In women over age 40, reduced fecundity adds to the minipill's effects.

There is another reason why the minipill is a good choice for the breastfeeding woman. There is no evidence for any adverse effect on breastfeeding as measured by milk volume and infant growth and development.[236, 355, 356] In fact, there is a modest positive impact; women using the minipill breastfeed longer and add supplementary feeding at a later time.[243] Because of the slight positive impact on lactation, the minipill can be started soon after delivery, but at least a 3-day postpartum delay is recommended to allow the decline in pregnancy levels of estrogen and progesterone and the establishment of lactation.[244]

The minipill is a good choice in situations where estrogen is contraindicated, such as patients with serious medical conditions (diabetes with vascular disease, severe systemic lupus erythematosus, cardiovascular disease). It should be noted that the freedom from estrogen effects, although likely, is presumptive. Substantial data, for example on associations with vascular disease, blood pressure, and cancer, are not available because relatively small numbers have chosen to use this method of contraception. On the other hand, it is logical to conclude that any of the progestin effects associated with the combination oral contraceptives can be related to the minipill according to a dose-response curve; all effects should be reduced. The World Health Organization case-control study could find no indication for increased risks of stroke, myocardial infarction, or venous thromboembolism with oral progestin-only contraceptives.[357] No impact can be measured on the coagulation system.[358, 359] The minipill can probably be used in women with previous episodes of thrombosis, and the package insert in the United States has been revised, eliminating vascular disease as a contraindication.

The minipill is a good alternative for the occasional woman who reports diminished libido on combination oral contraceptives, presumably due to decreased androgen levels. The minipill should also be considered for the few patients who report minor side effects (gastrointestinal upset, breast tenderness, headaches) of such a degree that the combination oral contraceptive is not acceptable.

Because of the relatively low doses of progestin administered, patients using medications that increase liver metabolism should avoid this method of contraception. These drugs include the following:

Rifampin.
Phenobarbital.
Phenytoin (Dilantin).
Primidone (Mysoline).
Carbamazepine (Tegretol).
Possibly ethosuximide, griseofulvin, and troglitazone.

Do the noncontraceptive benefits associated with combination oral contraception apply to the minipill? Studies are unable to help us with this issue, again because of the relatively small numbers of users. However, the progestin impact on cervical mucus, endometrium, and ovulation leads one to think the benefits will be present (reduced risks of pelvic infection, endometrial cancer, and ovarian cancer), but probably at reduced levels.

Good efficacy with the minipill requires regularity, taking the pill at the same time each day. There is less room for forgetting, and, therefore, the minipill is probably not a good choice for a disorganized adult or for the average adolescent.

Emergency Postcoital Contraception

The use of large doses of estrogen to prevent implantation was pioneered by Morris and van Wagenen at Yale in the 1960s. The initial work in monkeys led to the use of high doses of diethylstilbestrol (25–50 mg/day) and ethinyl estradiol in women.[360] It was quickly appreciated that these extremely large doses of estrogen were associated with a high rate of gastrointestinal side effects. Yuzpe developed a method utilizing a combination oral contraceptive, resulting in an important reduction in dosage.[361] The following treatment regimens have been documented to be effective:

Ovral: 2 tablets followed by 2 tablets 12 hours later.

Alesse: 5 tablets followed by 5 tablets 12 hours later.

Lo Ovral, Nordette, Levlen, Triphasil, Trilevlen: 4 tablets followed by 4 tablets 12 hours later.

Levonorgestrel in a dose of 0.75 mg given twice, 12 hours apart, is more successful and better tolerated than the combination oral contraceptive method, but this dose is equivalent to 10 pills of the levonorgestrel progestin-only minipill.[362, 363] In some countries, special packages of 0.75 mg levonorgestrel are available for emergency contraception. Greater efficacy and fewer side effects make low-dose levonorgestrel the treatment of choice.

In the United States, a kit is available containing 4 tablets, each containing 50 µg ethinyl estradiol and 0.250 mg levonorgestrel, to be used in the usual fashion, 2 tablets followed by 2 tablets 12 hours later.

This method has been more commonly called postcoital contraception, or the "morning after" treatment. Emergency contraception is a more accurate and appropriate name, indicating the intention to be one-time protection. It is an important option for patients, and should be considered when condoms break, sexual assault occurs, if diaphragms or cervical caps dislodge, or with the lapsed use of any method. In studies at abortion units, 50–60% of the patients would have been suitable for emergency contraception and would have used it if readily available.[364, 365] In the U.S., it is estimated that emergency contraception could annually prevent 1.7 million unintended pregnancies and the number of induced abortions would decrease by about 40% to 800,000 per year.[366]

Many women do not know of this method, and it has been difficult to obtain.[365, 367] In Europe and New Zealand, special packages with printed instructions are marketed specifically for emergency contraception, and this is now available in the U.S. Even if women are aware of this method, accurate and detailed knowledge is lacking.[368] A favorable attitude toward this method requires knowledge and availability. Information can be obtained from the following web site maintained by the Office of Population Research at Princeton University: http://opr.princeton.edu/ec/.

Clinicians should consider providing emergency contraceptive kits to patients (a kit can be a simple envelope containing instructions and the appropriate number of oral contraceptives) to be taken when needed. It would be a major contribution to our efforts to avoid unwanted pregnancies, for all patients without contraindications to oral contraceptives to have emergency contraception available for use when needed. In our view, this would be much more effective in reducing the need for abortion than waiting for patients to call. In a study of such an approach, self-administration by appropriately screened and educated women was found to be effective and free of unwanted effects.[369]

Mechanism and Efficacy

The mechanism of action is not known with certainty, but it is believed with justification that this treatment combines delay of ovulation with a local effect in the endometrium.[370, 371] The efficacy has been confirmed in large clinical trials and summarized in complete reviews of the literature.[372–374] Treatment with high doses of estrogen or with levonorgestrel yields a failure rate of approximately 1%, with the combination oral contraceptive, about 2–3%. The failure rate is lowest with high doses of ethinyl estradiol given within 72 hours (0.1%), but the side effects make the combination oral contraceptive a better choice. In general clinical use, the method can reduce the risk of pregnancy by about 75%; this degree of reduction in probability of conception (given the relatively low chance, about 8%, for pregnancy associated with one act of coitus[375]) yields the 2% failure rate measured in clinical studies (in other words, 98% effective).[376, 377] Results with levonorgestrel will be even better, 99% effective.

Treatment Method

Treatment should be initiated as soon after exposure as possible, and the standard recommendation is that it be no later than 72 hours. Careful assessment of the reported experience with emergency contraception indicated that the method is equally effective when started on the first, second, or third day after intercourse (which would allow user-friendly scheduling), and that efficacy might extend beyond 72 hours.[378] Data from randomized, clinical trials, however, support the importance of timing, finding a reduction in efficacy after 72 hours.[363] Because of possible, but unlikely, harmful effects of these high doses to a fetus, an already existing pregnancy should be ruled out prior to use of postcoital hormones. Furthermore, the patient should be offered induced abortion if the method fails. This patient encounter also provides an important opportunity to screen for STDs.

The combination oral contraceptive method delivers significantly less steroid hormone, and this reduction in the total dose and the number of doses reduces the side effects and limits them to a shorter time period. It is worth adding an antiemetic, oral or suppository, to the treatment; the long-acting nonprescription agent, meclizine, is recommended, to be taken one hour before the emergency contraception treatment. Side effects reflect the high doses used: nausea (50%), vomiting (20%), breast tenderness, headache, and dizziness. If a patient vomits within an hour after taking pills, additional pills must be administered as soon as possible. Although short-term treatment with combined oral contraceptives has been documented to have no effect on clotting factors, the usual contraindications for oral contraception apply to this use.[379] ***In view of the high dose of estrogen, emergency contraception with combined oral contraceptives should not be provided to women with either a personal or close family history (parent or sibling) of***

idiopathic thrombotic disease. For women with a contraindication to exogenous estrogen, the progestin-only minipill can be used for emergency contraception; e.g., administering 10 levonorgestrel tablets (75 μg), for each of the two doses, or in some countries using the special commercial package.

A 3-week follow-up visit should be scheduled to assess the result, and to counsel for routine contraception.

Could other combination oral contraceptive products be used? Because other doses and other formulations have never been tested, the efficacy is unknown. It would not be appropriate to expose patients to an unknown failure rate.

The use of danazol for emergency contraception is not effective.[380] Mifepristone (RU486), the progesterone antagonist, has been without failures and with lower side effects in clinical trials.

The 3 major problems with the available methods of emergency contraception are the high rate of side effects, the need to start treatment within 72 hours after intercourse, and the small, but important, failure rate. Mifepristone in a single oral dose of 600 mg is associated with markedly less nausea and vomiting and an efficacy rate of nearly 100%.[380, 381] Mifepristone is used for emergency contraception in China in a dose as low as 50 mg. Clinical studies have indicated that doses as low as 5 mg or 10 mg daily are effective. Because the next menstrual cycle is delayed after mifepristone, contraception should be initiated immediately after treatment. Ironically, mifepristone, around which swirls the abortion controversy, can make an effective contribution to preventing unwanted pregnancies and induced abortions.

Another method of emergency contraception is the insertion of a copper IUD, up to 5 days after unprotected intercourse. The failure rate (in a small number of studies) is very low, 0.1%.[372, 373] This method definitely prevents implantation, but it is not suitable for women who are not candidates for intrauterine contraception, e.g., multiple sexual partners, rape victim.

Oral Contraception for Older Women

Women of the post-World War II generation have faced a unique evolutionary change. They were the first to be able to exercise control over their fertility, and then as they aged and deferred pregnancy, they had to deal with the problem of unintended infertility. After World War II, the U.S. total fertility rate reached a modern high of 3.8 births per woman. The last women born in this period will not reach their 45th birthday until around 2010. For approximately a 20-year period, therefore, there will be an unprecedented number of women in the later child-bearing years. The aging of the World War II population boom is giving current times a greater number of women who are delaying marriage and childbirth. This demographic change has 3 specific impacts on couples.

1. A need for effective contraception.
2. The problem of achieving pregnancy later in life.
3. The problem of being pregnant later in life.

This combination of increasing numbers, deferment of marriage, and postponement of pregnancy in marriage is responsible for the fact that we will be seeing more and more older women who will need reversible contraception. This is underscored by the fact that from ages 20–44, American women have the highest proportion of pregnancies aborted compared to other countries, indicating an unappreciated, but real, problem of unintended pregnancy existing beyond the teenage years, especially after age 35. More than half of all pregnancies in the U.S. are estimated

to be unplanned, and more than half of these are aborted.[382] The best way to minimize the number of induced abortions is effective contraception.

From 1970 to 1986, the number of births in women over 30 quadrupled; however, since 1990, the fertility rate among women over 30 has remained relatively stable.[383] As more and more couples defer pregnancy until later in life, the use of sterilization under age 35 will decline, and the need for reversible contraception will increase. Between 1988 and 1995, oral contraceptive use decreased in women younger than 25 and increased in women aged 30–44.[384] These numbers changed because clinicians and patients have come to understand and accept that low-dose oral contraception is safe for healthy, nonsmoking older women.

Oral Contraception for the Transition Years

The years from age 35 to menopause can be referred to as the transition years. Preventive health care for women is especially important during the transition years. The issues of preventive health care are familiar ones. They include contraception, cessation of smoking, prevention of heart disease and osteoporosis, maintenance of mental well-being (including sexuality), and cancer screening. Management of the transition years should be significantly oriented to preventive health care, and the use of low-dose oral contraception can now legitimately be viewed as a component of preventive health care. A discussion of the noncontraceptive health benefits of low-dose oral contraception is especially important with patients in their transition years. This group of women appreciates and understands decisions made with the risk:benefit ratio in mind.

During this period of time, there are several medical needs that must be addressed: the need for contraception, the management of persistent anovulation, and finally, menopausal and postmenopausal hormone therapy.

At approximately 40 years of age, the frequency of ovulation decreases. This initiates a period of waning ovarian function called the climacteric that will last several years, carrying a woman through decreased fertility and menopause to the postmenopausal years. Prior to menopause, the remaining follicles perform less well. As cycles become irregular, vaginal bleeding occurs at the end of an inadequate luteal phase or after a peak of estradiol without subsequent ovulation and corpus luteum formation. Eventually, many women will live through a period of anovulation. Occasionally, corpus luteum formation and function occur, and therefore the older woman is not totally safe from the threat of an unplanned and unexpected pregnancy.

Fortunately clinicians and patients have recognized that low-dose oral contraception is very safe for healthy, nonsmoking older women. However, their use is still not sufficient to meet the need. Besides fulfilling a need, we would argue that this population of women has a series of benefits to be derived from oral contraception that tilts the risk:benefit ratio to the positive side. The benefits of oral contraceptives reviewed in this chapter are especially pertinent for older women. A case-control study could find no evidence for an increased risk of breast cancer in women who used oral contraceptives *after age 40*.[385]

Despite the widespread teaching and publicity that smoking is a contraindication to oral contraceptive use over the age of 35, more older women who use oral contraceptives smoke and smoke heavily, compared with young women.[97] This strongly implies that older smokers are less than honest with clinicians when requesting oral contraception. ***A former smoker must have stopped smoking for at least 12 consecutive months to be regarded as a nonsmoker. Women who have nicotine in their bloodstream obtained from patches or gum should be regarded as smokers.*** Smokers over age 35 should continue to be advised that combined oral contraceptives are not a good choice, regardless of the number of cigarettes smoked. In view of the unreported high rate of smoking in older women who use oral contraceptives, clinicians should consider using 20 μg estrogen products for women over age 35.

A product containing 20 μg ethinyl estradiol and 150 μg desogestrel has been demonstrated in multicenter studies of women over age 30 to have the same efficacy and side effects as pills containing 30 and 35 μg of estrogen.[386–388] In a randomized study of women over age 30, this formulation was associated with the virtual elimination of any effects on coagulation factors.[389] Indeed, the 20 μg formulation has no significant impact on the measurements of clotting factors, even in smokers.[31, 32, 389, 390]

Although it is true that the implied safety of the lowest estrogen dose remains to be documented by epidemiologic studies, it seems clinically prudent to maximize the safety margin in this older age group of women. Although there may be some increase in breakthrough bleeding, we believe that older women who understand the increased safety implicit in the lowest estrogen dose are more willing to endure breakthrough bleeding and maintain continuation. With avoidance of risk factors and use of lowest dose pills, health risks are probably negligible for healthy nonsmoking women. For healthy nonsmoking women, no specific laboratory screening is necessary, beyond that which is usually incorporated in a program of preventive health care.

We should also mention the progestin-only minipill. Because of reduced fecundity, the minipill achieves near total efficacy in women over age 40. Therefore, the progestin-only minipill is a good choice for older woman, and especially for those women in whom estrogen is contraindicated. Older women are more accepting of irregular menstrual bleeding when they understand its mechanism, and, thus, are more accepting of the progestin-only minipill.

Anovulation and Bleeding. Throughout the transitional period of life there is a significant incidence of dysfunctional uterine bleeding due to anovulation. While the clinician is usually alerted to this problem because of irregular bleeding, clinician and patient often fail to diagnose anovulation when bleeding is not abnormal in schedule, flow, or duration. As a woman approaches menopause, a more aggressive attempt to document ovulation is warranted. A serum progesterone level measured approximately one week before menses is simple enough to obtain and worth the cost. The prompt diagnosis of anovulation (serum progesterone less than 300 ng/dL) will lead to appropriate therapeutic management that will have a significant impact on the risk of endometrial cancer.

In an anovulatory woman with proliferative or hyperplastic endometrium (unaccompanied by atypia), periodic oral progestin therapy is mandatory, such as 10 mg medroxyprogesterone acetate given daily the first 10 days of each month. If hyperplasia is already present, follow-up aspiration office curettage after 3–4 months is required. If progestin treatment is ineffective and histological regression is not observed, more aggressive treatment is warranted. Monthly progestin treatment should be continued until withdrawal bleeding ceases or menopausal symptoms are experienced. These are reliable signs (in effect, a bioassay) indicating the onset of estrogen deprivation and the need for the addition of estrogen in a postmenopausal hormone program.

If contraception is desired, the clinician and patient should seriously consider the use of oral contraception. The anovulatory woman cannot be guaranteed that spontaneous ovulation and pregnancy will not occur. The use of a low-dose oral contraceptive will at the same time provide contraception and prophylaxis against irregular, heavy anovulatory bleeding and the risk of endometrial hyperplasia and neoplasia. In some patients, oral contraceptive treatment achieves better regulation of menses than monthly progestin administration.

Clinicians have been made so wary of providing oral contraceptives to older women that a traditional postmenopausal hormone regimen is often utilized to treat a woman with the kind of irregular cycles usually experienced in the transitional years. This addition of exogenous estrogen when a woman is not amenorrheic or experiencing menopausal symptoms is inappropriate, and even risky (exposing the endometrium to excessively high levels of estrogen). ***And something that is often unappreciated, the standard doses of estrogen and progestin in a postmenopausal regimen will not suppress gonadotropins and prevent ovulation.*** [391] The appropriate response

is to regulate anovulatory cycles with monthly progestational treatment or to utilize low-dose oral contraception.

When to Change From Oral Contraception to Postmenopausal Hormone Therapy

A common clinical dilemma is when to change from oral contraception to postmenopausal hormone therapy. It is important to change because even with the lowest estrogen dose oral contraceptive available, the estrogen dose is four-fold greater than the standard postmenopausal dose, and with increasing age, the dose-related risks with estrogen become significant. One approach to establish the onset of the postmenopausal years is to measure the FSH level, beginning at age 50, on an annual basis, being careful to obtain the blood sample on day 6 or 7 of the pill-free week (when steroid levels have declined sufficiently to allow FSH to rise). Friday afternoon works well for patients who start new packages on Sunday. When FSH is greater than 20 IU/L, it is time to change to a postmenopausal hormone program. Because of the variability in FSH levels experienced by women around the menopause, this method is not always accurate.[392] But there is no harm in retesting after another year or two on low-dose oral contraceptives. Some clinicians are comfortable allowing patients to enter their midfifties on low-dose oral contraception, and then empirically switching to a postmenopausal hormone regimen.

Concluding Thoughts

In the 1970s, as epidemiologic data first became available, we emphasized in our teaching and in our communication with patients the risks and dangers associated with oral contraceptives. In the 1990s, with better patient screening and epidemiologic data documenting the effects of low-dose products, we appropriately emphasized the benefits and safety of modern oral contraceptives. In the new millennium, we can with confidence promote the idea that the use of oral contraceptives yields an overall improvement in individual health, and from a public health point of view, the collection of effects associated with oral contraceptives leads to a decrease in the cost of health care.

Contraceptive advice is a component of good preventive health care, and the clinician's approach is a key factor. This is an era of informed choice by the patient. Patients deserve to know the facts and need help in dealing with the state of the art and those issues clouded by uncertainty. But there is no doubt that patients are influenced in their choices by their clinician's advice and attitude. Although the role of a clinician is to provide the education necessary for the patient to make proper choices, one should not lose sight of the powerful influence exerted by the clinician in the choices ultimately made. Emphasizing the safety and benefits of oral contraceptives, and the contribution of oral contraceptives to individual and public health, allows a clinician to present oral contraception with a very positive attitude, an approach that makes an important contribution to a patient's ability to make appropriate health choices.

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