Basic Science in Gynecology

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1. Genetics

Basic science and the mechanism of disease are concepts that a good physician should retain when advising and treating patients. For many of us, these topics have not been reviewed since medical school, when our clinical knowledge was limited. As physicians, we are faced with many challenging clinical situations, whether it be in the primary care office setting or in the surgical arena. This chapter revisits the basic science and underlying mechanisms of disease and physiology to give readers an understanding that will enable them to handle these situations confidently and appropriately.

Bleeding Disorders

In counseling patients who are attempting pregnancy, obstetricians should be well versed in the various modes of inheritance of commonly acquired blood dyscrasias, especially when a family history is elicited.

Endothelial cells and megakaryocytes synthesize von Willebrand factor (vWF). The gene encoding vWF is on band 21 of chromosome 12.[1] vWF is necessary for platelet adhesion and to stabilize factor VIII. This function of vWF is crucial in achieving hemostasis. Von Willebrand disease (vWD) is an autosomally inherited disorder in which 1 in 100 people carry a defective gene for vWF, but only 1 in 1,000 clinically manifest the disease.[2,3] Complete absence of vWF (type III disease) is extremely uncommon, with a prevalence of one per million. The most common type of vWD is inherited in an autosomal dominant fashion but type III disease requires the presence of two abnormal genes and is thus a recessive disorder.[2] Autosomal inheritance implies the equal likelihood that either male or female will have the disease. With the assistance of cDNA probes and Southern blot analysis, both complete and partial deletions of vWF have been identified. Since inheritance is autosomal dominant in nature, heterozygous offspring should be phenotypically affected. However, most individuals with complete deletion on one allele and a normal allelic complement are hemostatically normal. This implies incomplete penetrance. Type III disease is present in patients who have a complete deletion on one allele with another nonfunctioning allele, thus complete absence of vWF.[2] Although investigated, prenatal diagnosis is not possible via fetal blood sampling.[3]

Hemophilia A (factor VIII deficiency) and Hemophilia B (factor IX deficiency) are both X-linked recessive disorders. Hemophilia A occurs with a frequency of 1 in every 10,000 males and Hemophilia B affects 1 in every 100,000 males. Together, hemophilia A and B have an incidence of 20 cases per 100,000 males.[2] Both hemophilia A and B are clinically indistinguishable. Symptoms include: bleeding into soft tissues, muscles and joints. Symptomatic hemophilia B carriers are more common than those with hemophilia A.[2] Patients may manifest at the time of delivery with postpar-

tum hemorrhage or may report a history of menorrhagia since menarche. Carriers of factor VIII deficiency have a substantial increase in factor VIII during pregnancy, and are less likely to have problems at delivery versus those carriers of hemophilia B. Prenatal diagnosis of hemophilia A may be accomplished as early as 14-16 weeks via amniocentesis or chorionic villus sampling using DNA restriction fragment length polymorphism (RFLP), immunological and activity assays.[3,4] If DNA diagnosis is not possible, fetal blood may be checked for coagulant activity. Hemophilia B is more difficult to detect. Fetal blood sampling for factor IX may be misleading, secondary to contaminant by the amniotic fluid. Since hemophilia A and B display X linked inheritance, affected males should be counseled that all sons will be healthy and all daughters will be carriers (unless an affected male marries a carrier female or the offspring has XO karyotype).[5] Sons of female carriers have a 50% chance of having the disease and daughters of female carriers have a 50% chance of being carriers themselves. Thirty to 40% of patients with hemophilia have no family history of the disease.[6]

2. Recurrent Pregnancy Loss

Fifteen to 20 percent of recognized pregnancies end in spontaneous loss.[7] About half of these recognizable abortions are due to a fetal chromosomal abnormality.[8] The exact frequency of spontaneous abortion in the general population is difficult to establish secondary to the number of unrecognized pregnancies. Recurrent pregnancy loss (RPL) is defined as 3 or more fetal losses before the 20th week of gestation.[7] One-half to 1% of women meet the criteria for recurrent pregnancy loss.[9] RPL may be of genetic, anatomic, immunologic, hematologic, endocrinologic or environmental etiology, but this section will focus on the genetic basis for reproductive loss. They may arise spontaneously from random errors in meiosis and mitosis, may result from exposure to toxic agents, or may be secondary to preexisting defects in parental genes.

Chromosomal abnormalities are more commonly found in early first trimester loss and are a less common etiology for loss as gestational age increases.[10] Sporadic chromosomal events are not repetitive and account for 30% of all spontaneous losses.[7] Examples of these events are monosomy 45X (20-25%), polyploidy (20-25%), and trisomies (50%).[7] Monosomy and trisomy usually result from nondisjunction during meiosis or mitosis. Trisomy is commonly seen as 13, 16, 18, 21, and 22 with 16 the most common etiology for spontaneous loss.[7] Trisomy has a positive correlation to maternal age. Similarly, the probability that a spontaneous loss is chromosomally abnormal increases with maternal age. However, it has also been shown that the frequency of spontaneous losses with normal karyotypes also increases with advanced maternal age, alluding to age as an independent factor.

Several studies have confirmed that repeated aborters tend to have chromosomally normal fetuses.[10] Specimens from recurrent aborters have a smaller proportion of chromosomal abnormalities than sporadic spontaneous losses .[9] Structural chromosomal abnormalities comprise a small percentage of RPLs. To have genetically induced RPL, couples must have genetic complements that display normal phenotypes, but when combined, result in genetically abnormal fetuses.[9] Structural defects in parental genes include translocations, inversions, deletions and duplications. In a balanced chromosomal abnormality, no chromosomal material is lost

and the outcome is phenotypically normal.[10] The risk of having a spontaneous loss when one of the parents carry a balanced abnormality is increased and the risk varies depending on the type of abnormality and extent of genetic imbalance.[8] Translocations are the most common chromosomal abnormality associated with recurrent pregnancy loss. Translocations are defined as reciprocal, insertional, simple, shift and Robertsonian. Reciprocal translocations are the most common type of translocation found in couples with recurrent losses. Inversions are occasionally associated with recurrent losses and their size will determine the clinical significance.[8] Deletions and duplications are never genetically balanced. They are not significant in recurrent losses because they are rare and usually are associated with an obviously abnormal phenotype (ie, mental retardation).[8]

Data regarding the prognosis for the future pregnancy outcome in a woman who has had recurrent losses is conflicting. A study by Jacobs suggests that there is a significant correlation between chromosomal abnormalities found between the first and second abortus, especially for those with trisomy.[8,11] Boue and Boue, in their evaluation of 1,500 first trimester fetuses, found that if there was a chromosomal aberration in one conceptus, there was a higher likelihood of an abnormality in the second.[12] However, they found no correlation between karyotypes of the first and second abortuses.[12] Currently, routine chromosome analysis of all first trimester spontaneous losses is not recommended because structural rearrangements account for only 0.2% of losses.[10] Karyotypic analysis of couples with repetitive losses or previous infant with congenital anomaly of unknown etiology is suggested, although they rarely reveal abnormalities.[10] The number of miscarriages that a couple has before parental chromosomal analysis is suggested varies from two to three in the literature.[8] Counseling a couple when a balanced abnormality is discovered involves assessing the type of structural abnormality, the genetic makeup and viability of the gamete that may result, and family history of the couple.[8] Most couples however, with a history of 3 or more abortions, maintain a 60% chance of achieving a live-born infant, and couples with unexplained recurrent losses have a 70% chance of achieving a good outcome.[13]

3. Physiology

In order to maintain hemodynamic stability, the body has developed several compensatory mechanisms in response to anesthesia and surgical trauma. A decrease in blood volume leads to a decrease in preload, stroke volume and cardiac output. As blood pressure drops, the sympathetic activity is stimulated, triggering the release of catecholamines causing a subsequent increase in heart rate, contractility, cardiac output and peripheral vascular resistance. Blood flow to the kidneys is spared at the expense of less oxygen-dependent organs, but if hypotension persists, the kidneys ultimately become affected by decreased perfusion.[14] With decreased renal perfusion, the renin angiotensin system is activated, causing an increased reabsorption of sodium via the kidneys. The release of antidiuretic hormone (ADH) is also triggered, causing the kidney to retain free water. Clinically, a state of decreased urine output is observed.

It is important to understand fluid and electrolyte changes in body fluid compartments with surgery. Water comprises 60% of total body weight in the average human.[14] Two-thirds of this fluid is intracellular and one third is extracellular. The extracellular fluid (ECF) resides in either the vascular space as plasma or between cells as interstitial fluid (IF). Fluid leaves the capillary space when hydrostatic pressure exceeds oncotic pressure. During the perioperative period, the ECF volume expands due to sodium and water retention and increase in capillary permeability.[14] Fluid shifts from the intravascular space to the IF, causing interstitial edema. This leads to decreased effective blood volume and reduced cardiac output.[14] As the kidney feels these effects, the volume is regulated by a change in the renal reabsorption of sodium, and as described above.[12] Fluid replacement of intravascular volume with colloid and crystalloid is essential. In severely anemic or bleeding patients, blood transfusions may be used to expand intravascular volume if necessary. A Swan-Ganz catheter can be used to measure pulmonary artery pressure in order to assess fluid status. A pulmonary capillary wedge pressure of 16 to 18 should be maintained.[14] Urine output should be maintained at a rate of 0.5 cc/kg per hour. When patients become oliguric, the PCWP becomes more important in assessing fluid status to distinguish between renal failure, volume depletion, or prerenal

dysfunction. A urinary fractional excretion of sodium may be useful as well (<1% suggests intravascular etiology).[14]

Hyponatremia occurs in 4 to 5% of postoperative patients.[14] Patients are usually asymptomatic, but when sodium levels fall below 124 mEq/L symptoms may occur. Symptoms include headache, nausea, lethargy, hallucinations, seizures and, rarely, coma. The most significant etiology for perioperative hyponatremia is persistent secretion of ADH. Although hypoosmolality theoretically inhibits ADH secretion, other factors such as intravascular volume depletion, nausea, anxiety, pain and narcotics can override this mechanism.[14] Other factors that may contribute to postoperative hyponatremia are decreased renal function or diuretic usage. The most common cause of hypernatremia in a postoperative patient is dehydration. Hypokalemia (K<3.5 mEq/L) may result from potassium loss via the gastrointestinal tract as a result of preoperative bowel preparation or via renal excretion in a patient who is taking diuretics.

Thermoregulation is the maintenance of balance between heat gain and heat loss.[15] Central thermoregulation is under the control of the hypothalamus, but temperature receptors are found throughout the body. The autonomic nervous system triggers shivering or sweating, and alters blood circulation and body metabolism in response to a deviation in temperature from the set point. The average temperature of the human body is 37° C (98.6° F). Anesthesia affects thermoregulation by inhibiting behavioral responses and suppressing autonomic responses to thermal stress.[15] The only thermoregulatory responses achieved by patients under general anesthesia (GET) are nonshivering thermogenesis (metabolic) and minimal superficial vasoconstriction.[15] Intraoperative hypothermia may result from exposure to a cold operating room (<22° C; 70° F), prolonged procedures, infusion of unwarmed fluids and decreased metabolic rate. Core body temperature usually decreases during the first one to three hours of surgery.[15] Once hypothermia develops, it continues to the postoperative period and may be exaggerated as the anesthesia wears off. 60% of patients in the recovery room are found to have temperatures below 36° C and 18-20% of patients begin shivering within 30 minutes of arrival.[15] Postoperative shivering is undesirable as it diverts oxygen supply from vital organs. The lowest temperatures are found in patients who have undergone intra-abdominal or cardiac surgery. Regional anesthesia may cause a greater temperature drop than GET.[15] These patients have an intact hypothalamic axis. The etiology of hypothermia in these patients is through vasodilatation and prevention of shivering and vasoconstriction below the level of the block.[15] Therefore, the anesthesiologist and surgeon should perioperatively:

1. maintain the operating room temperature above 24° C (74° F);

2. warm (humidify) inhalation agents;

3. use a convection heating blanket;

4. warm intravenous and irrigation solutions;

5. preanesthetize with narcotic, which reduces postoperative shivering by 30%.[16]

4. Embryology and Developmental Biology

Normal Müllerian Duct Development

In normal development, the gonads begin to develop at approximately 32 days gestation, migration of the primordial germ cells to the gonadal ridges being at this time. In the absence of their migration, streak gonads will form. At about seven weeks, the gonads are capable of developing into either ovaries or testes and both the Wolffian and Müllerian ducts coexist.[17] Sexual differentiation requires direction by a single gene called SRY (sex determining region Y) on the Y chromosome, which is expressed as testes determining factor (TDF). The presence of TDF initiates testicular differentiation.[18] Female sexual differentiation is the default pathway, which occurs if SRY is not present. In a female without the SRY gene, the gonad will develop into an ovary. The factor that determines which duct will regress is anti-Müllerian hormone (AMH), which is secreted by the testes (Sertoli cells).[19] If AMH is secreted, the Müllerian ducts will regress by 8 weeks. Testosterone is secreted by the testes by 9 weeks when the Leydig cells are formed.[17] Testosterone stimulates development of the Wolffian duct into epididymis, vas deferens and seminal vesicles. The external genitalia are neutral structures and will differentiate into male genitalia if stimulated by dihydrotestosterone (DHT; which is converted from testosterone by 5 alpha-reductase in the target tissue).[17] The external genitalia will form the lower part of the vagina, labia minora and majora, clitoris and urethra in the absence of stimulation by DHT. In the absence of AMH, the fetus will develop fallopian tubes, uterus and upper vagina from the Müllerian ducts (paramesonephric ducts). The Müllerian ducts elongate and descend medially, and fuse with the duct of the contralateral side. The duct continues to descend and meets the uterovaginal primordium at the sinovaginal bulb. The fused tissue above the sinovaginal bulb subsequently resorbs, resulting in a uterus with a single cavity. The sinovaginal bulb elongates to form the vaginal plate and canalizes to become the vaginal canal. Thus, the Müllerian ducts ultimately form the fallopian tubes, the uterus, and the upper four fifths of the vagina.[20]

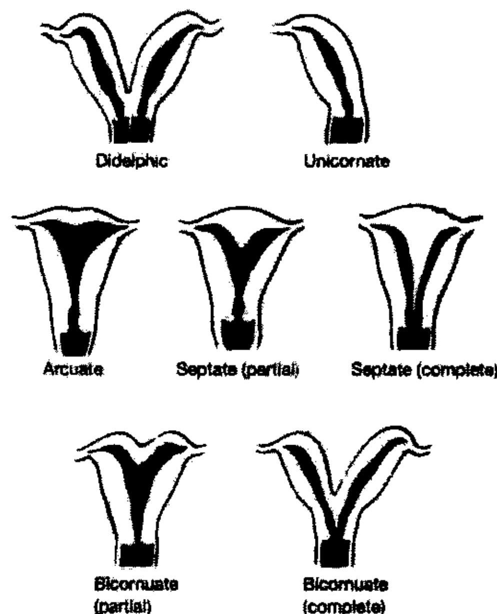
Müllerian Agenesis/Dysgenesis

The incidence of uterine anomalies range from 1 to 5 per 1000 women, although this may be underestimated as many women show no clinical symptoms and go undiagnosed.[21] Failure of the fused Müllerian wall to resorb results in a uterine septum (see Figure 1). A bicornuate uterus occurs when the Müllerian ducts fuse too far caudally and didelphys results when no fusion occurs. Fusion failure can also result in longitudinal vaginal septa. A transverse vaginal septa develops if canalization of the vagina does not occur. When the sinovaginal bulbs do not develop at all, vaginal atresia may result.[20] A unicornuate uterus results from normal differentiation of only one Müllerian duct. A portion of the other Müllerian duct descends only partially or not at all (rudimentary horn). Thus, reproductive tract abnormalities result from either failure of descent, lateral fusion, resorption, or vertical fusion.[21]

Based on this pathophysiology the American Society of Reproductive Medicine has created a classification system.[22] Class I disorders involve dysgenesis of the Müllerian ducts, which include Mayer-Rokitansky-Kuster-Hauser syndrome (MRKH). MRKH

Figure 1

Müllerian dysgenesis



syndrome is characterized by vaginal agenesis with a rudimentary uterine primordia (anlagen). Fallopian tubes and ovaries are present and appear normal. External genitalia are normal but the vagina ends in a blind pouch. Class II anomalies describe disorders of vertical fusion including transverse vaginal septum (IIA) and cervical agenesis or dysgenesis (IIB). Class III describes disorders of lateral fusion and is divided into asymmetric—obstructed (IIIA) and symmetric—unobstructed (IIIB) anomalies. The former are almost always associated with ipsilateral renal agenesis, and are further subdivided into:

1. unicornuate uterus with a noncommunicating, menstruating, rudimentary anlagen;

2. unilateral obstruction of one cavity of a double uterus;

3. unilateral vaginal obstruction.

Class IIIB anomalies include didelphyic uterus, septate uterus, bicornuate uterus, T-shaped uterus (DES related), and unicornuate uterus (+/- rudimentary horn). Class IV encompasses all other unusual configurations of vertical-lateral fusion defects.

Urinary tract anomalies occur frequently in association with all types of uterine anomalies, so a renal evaluation is indicated in patients with known Müllerian defects.

Abnormalities in Sexual Differentiation

Female hermaphrodites have an XX karyotype but the external genitalia are masculinized.[23,24] Of infants with ambiguous genitalia, 54-85% are diagnosed with congenital adrenal hyperplasia (CAH).[25,26] Rarer causes of elevated androgens causing masculinization are drug ingestion, tumor secretion or aromatase deficiency.[17] Masculinization may manifest as fusion of labioscrotal folds, clitoromegaly or anatomic changes of the urethra and vagina. In CAH, the fallopian tubes, uterus and upper vagina develop normally because there is no secretion of AMH in females with CAH. The clinical picture of CAH results from a specific enzyme deficiency, whether 21-hydroxylase, 11β-hydroxylase, or 3β-hydroxysteroid dehydrogenase, which divert the production of cortisol to the production of excess androgens. 21-Hydroxylase deficiency is the most common form of CAH causing sexual ambiguity.[27] Early androgen excess (10-12 weeks) may fully masculinize, while late (12-14 weeks) may lead to labial fusion.[17] Clitoromegaly without labial fusion will result if androgen exposure occurs after 14 weeks.[28] Aromatase deficiency is uncommon and occurs at the level of aromatization in the placenta. This results in accumulation of androgen precursors used by the placenta to synthesize estrogen. Clinically, this results in virilization by the mother in the third trimester. At the time of birth, the female infant is masculinized and cord blood exhibits low levels of estrogen and high androgen levels.[29] Pubertal development is delayed because the ovary cannot aromatize androgens to produce estrogens.[24]

Male hermaphrodites possess an XY karyotype and testes, but have external and occasionally internal genitalia that are characteristically female. The possible etiologies of this include androgen insensitivity syndrome (AI), 5-alpha-reductase deficiency, abnormal androgen synthesis, gonadotropin resistant testes, AMH deficiency and gonadal defects (Swyer syndrome, anorchia). Complete AI (also known as testicular feminization) is transmitted via an X linked recessive gene which codes for the androgen receptor.[30] This defect leads to insensitivity to androgens. Therefore, the androgen induction of the Wolffian duct does not occur but since AMH is present, the Müllerian ducts regress. Testes develop but are abnormally placed. Since there is normal secretion of AMH, the uterus and cervix are absent or incomplete. Complete AI is not usually diagnosed until puberty so affected individuals are raised as females.[17] Complete AI indicates no androgen response. Testosterone production is normal or slightly elevated. Incomplete AI is much less common but is caused by a defect in the same gene. There are different clinical pictures with varying degrees of masculinization due to the range of mutations in this gene. The defect may be at the level of the receptor or in post receptor function.[24] 5-Alpha-reductase deficiency is an autosomal recessive trait that causes a deficiency in this enzyme. 5-Alpha-reductase is responsible for the conversion of testosterone to dihydrotestosterone (DHT). The karyotype is XY and there may be an abnormally low concentration of the enzyme, reduced enzyme

activity, or defective affinity for testosterone. The Wolffian duct forms, but the urogenital sinus and external genitalia, which are DHT dependent, are female in appearance. Most patients have perineal hypospadias with separate urethral and vaginal orifices with a urogenital sinus.[31] Some are phenotypically female. Masculinization begins at puberty, secondary to testosterone dependent events. Less commonly, a defect in testosterone synthesis may occur due to a defect in 3β-hydroxysteroid dehydrogenase, 17β-hydroxysteroid dehydrogenase or 17-alpha-hydroxlase. These enzymes convert cholesterol to testosterone. The degree of genital ambiguity depends on the severity of the enzyme deficiency.[17] Gonadal dysgenesis describes all patients with female genitalia, normal Müllerian structures and streak gonads. Pure gonadal dysgenesis refers to anyone with bilateral streak gonads regardless of the karyotype. In a patient with a 46,XX karyotype, the only way to distinguish between pure gonadal dysgenesis and premature ovarian failure is to visualize the ovaries.[17] Patients with 46,XY karyotype also have gonadal dysgenesis with female external genitalia, a uterus, tubes and streak gonads. The etiology of this form of gonadal dysgenesis is thought to result from a deletion involving the SRY gene.[24] These patients are at risk for bilateral gonadoblastomas, dysgerminomas and embryonal carcinoma. Bilateral streak gonads with a normal uterus and tubes are more commonly secondary to an abnormality or absence of one X chromosome, resulting in Turner syndrome. Sixty percent of Turner patients have an XO karyotype and 99% abort spontaneously before 28 weeks gestation.[17] Ovulatory function occurs in 10% of this population, manifested by spontaneous dysfunctional uterine bleeding, ovarian cysts, hirsutism and masculinization.[32] This may be explained by a mosaic XX complement cell line, but malignancy of the streak gonads should be ruled out.[17]

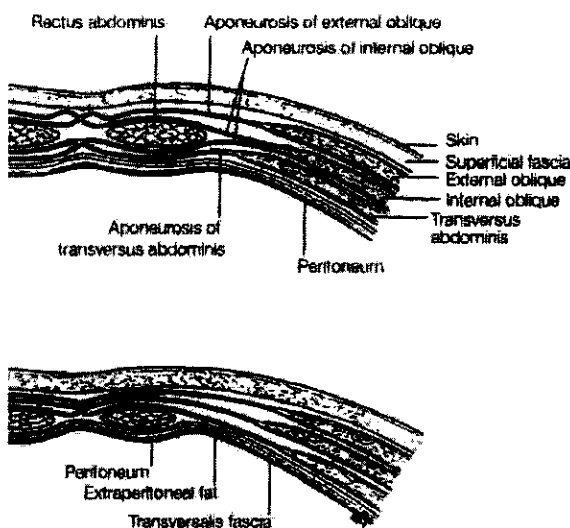
5. Anatomy

Anterior and Posterior Abdominal Wall

The anterior abdominal wall is comprised of superficial fascia known as Campers and Scarpas fascia. Inferior to this fascia are the following layers (Figure 2).

Figure 2

Anterior and posterior abdominal wall



1. External oblique muscle – most superficial; as fibers pass medially they become aponeurotic. The aponeurosis forms the linea alba in the midline.

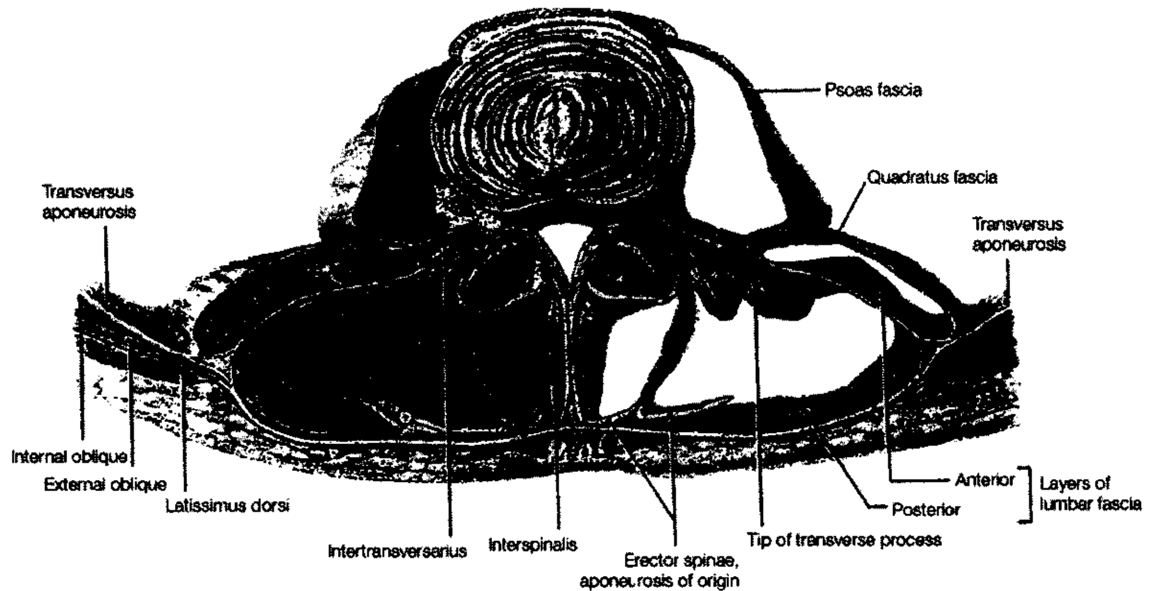
2. Internal oblique – fibers run perpendicular to the external oblique; its aponeurosis splits to form the rectus sheath (anterior and posterior to rectus abdominus).

3. Rectus abdominus – the vertical muscle of the anterior abdominal wall.

4. Transversus abdominus – inferior to the internal oblique.

Figure 3

Posterior abdominal wall



The posterior abdominal wall is also composed of muscles and fascia (Figure 3):

1. Psoas major – lateral to the lumbar vertebrae.

2. Psoas minor – present in 50 to 60% of people and may be unilateral;[33] lies anterior to psoas major.

3. Iliacus – lateral to inferior portion of psoas major.

4. Quadratus lumborum – thick muscular layer adjacent to the lumbar vertebrae.

Pelvic Visceral Relationships

The relationship of the pelvic organs is fairly straightforward. The bladder is the most anterior and lies immediately posterior to the pubic symphysis. The posterior peritoneum of the bladder joins to the peritoneum on the anterior surface of the uterus to form the vesico-uterine fold. Posterior to the uterus is the rectum and sigmoid colon. The ureter is a structure that is commonly injured during gynecologic surgery. The ureter runs along the psoas muscle into the pelvis, passes behind the ovary parallel to the infundibulopelvic ligament, and then under the uterine and superior/middle vesicle arteries. The ureter continues down and passes less than one centimeter lateral to the vaginal fornix and cervix, from where it proceeds to enter the bladder. It is at the point just lateral to the cervix that the ureter is most commonly ligated (Figure 4).

External Genitalia (Figure 5)

Arterial Supply

1. External pudendal arteries

2. Internal pudendal artery

- labial artery

- dorsal and deep artery of the clitoris

Venous Drainage

- internal pudendal vein via labial vein

Lymph Drainage

- superficial inguinal lymph nodes (majority of drainage)

- deep inguinal lymph nodes

Figure 4

Relationship of pelvic organs to surrounding viscera

Note the relationship of the ureter to the uterine artery, infundibulopelvic ligament and broad ligament