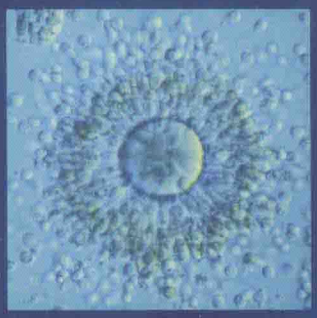
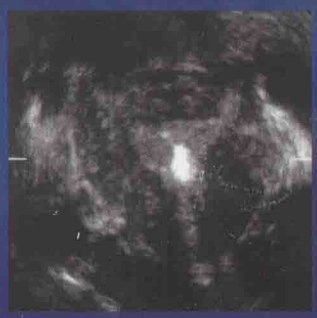
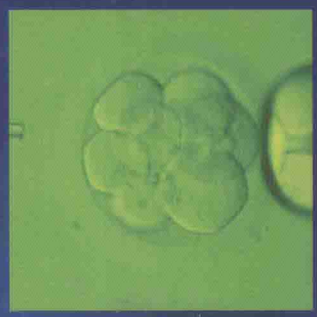
SECOND EDITION

SURGERY, ASSISTED REPRODUCTIVE TECHNOLOGY AND INFERTILITY

Diagnosis and Management of Problems in Gynecologic Reproductive Medicine







GERARD S LETTERIE

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Surgery, Assisted Reproductive Technology and Infertility

Diagnosis and Management of Problems in Gynecologic Reproductive Medicine

Second edition

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Dedication

To the memory of Elizabeth and Joe

And once again:

To Theresa, Jan, Mia and Ava, whose signatures of kindness, so distinct in time and place, have shaped and enhanced my own sense of caring

Preface

Infertility evaluations and treatments have undergone remarkable and very positive evolutions over the past decade. Improvements have been made in virtually every way we diagnose and treat our patients. Innovations in imaging techniques and endoscopic procedures and markedly improved success rates with *in vitro* fertilization (IVF) have led to both subtle and dramatic improvements in care for our patients. Detailed information of structure and function of the reproductive tract has expanded what we do, and when we do it, to maximize the chances for pregnancy in an ever-expanding group of patients. Sensitive two- and three-dimensional ultrasound and magnetic resonance imaging techniques provide structural information. Microarray technology will refine our ability to evaluate function and genomic expression in an increasing number of settings. This technique is already providing insight into the pathophysiology of endometriosis and polycystic ovary syndrome.

Surgery, for so long the stand-alone treatment for infertility, has yielded in many circumstances to assisted reproductive technologies. The evolution of *in vitro* fertilization to a highly successful process has reduced the number of settings in which surgery is appropriate. Surgery has a continued, though redefined, role in infertility therapies. Though its role has been minimized in some settings, surgical intervention has expanded in two critical areas: in preparation for IVF in patients with factors possibly impacting outcomes negatively and as a conservative, organ-sparing procedure in patients for whom reproduction prior to ART was either not an option or a highly unsuccessful proposition at best. The challenge has been to match the most efficacious and cost-effective technique to that clinical setting where success is most likely. Careful patient selection is the order of the day.

The corollary to these improvements is the critical analysis of outcomes and better definition of populations most likely to benefit from these procedures. Success is improved not only by technical innovations but our ability to define who will and will not benefit. Decision trees guiding patient selection have evolved and matured. Our basis for making decisions has increasingly become data driven. Reliance on results of well-designed clinical trials has emerged as the contemporary paradigm of evidence-based medicine. The overall result of this reliance has been a remarkable improvement in clinical care, and improvements in the quality and cost-effectiveness of care.

This text presents contemporary techniques in diagnosis and management of the infertile patient. It describes the intersection of assisted reproductive technologies and surgery, increasingly two complementary techniques to achieve our patient's goals of family building. A balance between structure and function as cardinal to our understanding of normal and abnormal

underpins the text. It is not intended as a surgical atlas, one to be used solely for guidance on the *how to* of a particular procedure. Instead, it provides guidance on not only *how to*, but also *when to* and *why* – the technical aspects of the diagnosis and explanations of appropriate treatment. The text stresses clinical and basic science data from both classic and contemporary research. Emphasis has been placed equally on etiology, diagnosis and management with surgery and assisted reproductive technologies. The rationale for choosing one technique over another is discussed. Most importantly, because the text is grounded in evidence-based medicine, it emphasizes outcomes analysis as a guideline for management.

The recommendations are literature-based. This approach de-emphasizes anecdotal data, intuition, or unsystematic clinical experience as sufficient grounds for clinical decision making. Instead, the text emphasizes practice and management guidelines based on reviews of the published data and on specific outcome measurements. Potential studies for analysis and review were identified by searching MEDLINE from 1971 to 2004. When possible, the recommendations in the text are based on randomized, controlled clinical studies. For several clinical problems, such data simply do not exist. In these circumstances, the recommendations are based on observational and descriptive studies with clearly defined outcome measures and an adequate follow-up interval. For certain clinically rare entities, limited trials, case series and case reports are used for guidance. In keeping with the trends and mandates of contemporary practice, reviews of costs for management are discussed. The bottom clinical line is recommendations for the most efficient and cost-effective diagnostic techniques and treatments.

A word about statistical analysis is appropriate. The literature describing outcomes in reproductive medicine is of extremely variable quality. Many of the early studies that provide insight regarding outcomes were observational, used the treatment groups as their own controls and provided very poor definitions of outcomes or successes. This profile makes calculating accurate statistics regarding success rates difficult. In only isolated circumstances could both odds ratios and confidence intervals be calculated to profile a particular therapy for a particular problem. In lieu of this more accurate and detailed analysis, the likelihood of success has expressed in the text as pregnancy rates and 95% confidence levels calculated where possible. In spite of these shortcomings these data do provide us with a gauge for the outcomes we can expect for a given procedure.

Hopefully the text will provide a keyhole view of the history of each disorder and give insight into what our predecessors did and how truly innovative they were. One tenet that underlies the text may be expressed as a rudimentary proverb (which I like to pass along to our residents and fellows);

Read text before surgery,
Avoid complications
Read text after surgery,
Understand them.

G.S.L.

Acknowledgments

The task of taking a textbook from initial concept to final publication is a complex and complicated enterprise. Several lines of effort by several individuals must converge at a common point at precisely the right moment if the project is to succeed. Such convergence prevailed in the case of this text. Several people were involved in this task and their efforts are herein acknowledged. A word of sincere gratitude is due to Bonnie Marston for her focused efforts in preparing the manuscript in a timely fashion (which she consistently does). Her ability to interpret various cut-and-paste formats and follow the road maps of early drafts carries my sincere compliments. My colleagues in the Medical Photography Department at Virginia Mason Medical Center, including Bob Riedlinger, Morris Ferensen, Terry King and Taylor Ubben, provided consistent support of a very high quality. Interpretation of the various images was aided by the staff of the Department of Radiology, who lent assistance in separating fact from fiction within the shades of gray of each study. Acknowledgments are also due to Dr. Joseph Mancini for his general counsel on the good and bad of it all and the general direction things should go to; Dr. Scott Rose for setting the bar so high – "you're where we all oughta be"; to Mr. Robert Hartfield for the humor; to Mr. Geoff Reiss for the referral to Mr. Tufte ("Edward who?" "Edward Tufte. Check out his depiction of Napoleon's army"); to Mr. John Holt for sharing insight, encouragement and definitions of friendship and partnership; to Drs Kennedy, Opsahl and Wiemer whose belief in an idea and willingness to step up, made it happen; thanks also to my friends and colleagues at Cook (Dan, Boz and Neal) for permission to use the artwork; and most importantly to my family, Jan, Mia and Ava, ever constant and present, who endured a preoccupation with the book and at times, its intrusion into our family life. These are very special people, unwavering and consistent. Their support cannot be overestimated. For the efforts of all these individuals, a sincere thanks is extended.

G.S.L.

Contents

1 Development of the Reproductive Tract

Ontogeny recapitulates phylogeny
— von Baer's law

Structure and function are tandem forces in reproductive medicine. Abnormalities in either within the reproductive tract may adversely influence reproductive potential. Clinical solutions to these problems and enhancements of fertility may require surgery and/or assisted reproductive technology (ART). These abnormalities vary in degree and etiology and provide a prism through which clinical care is viewed. Changes may be subtle and detected during an evaluation for infertility or poor obstetric outcome and require no immediate therapy or may be emergent presenting at puberty and require immediate surgical intervention. These abnormalities may be congenital such as the spectrum of uterine duplication, and vaginal agenesis, or acquired such as pelvic adhesive disease after acute pelvic inflammatory disease, intrauterine adhesions after a dilation and curettage or the progressive development of endometriosis or uterine myoma. Though of differing etiologies, congenital and acquired structural abnormalities impact function and share the common clinical expression of a relative or absolute compromise to reproductive potential. This textbook discusses the structural and functional aspects of congenital and acquired abnormalities of the reproductive tract, their diagnoses and management, and outcomes from surgery and/or ART.

Congenital abnormalities of the reproductive tract are surprisingly common with an incidence ranging from 1 in 200 to 1 in 600 women.[1] Approximately 25 to 35% of women with congenital uterine anomalies have impaired reproductive potential ranging from an inability to ever achieve a pregnancy to repeated pregnancy loss, malpresentation, and premature labor. Clinical problems associated with acquired changes such as ovarian endometriomas, pelvic adhesive disease, or tubal obstruction range from chronic pelvic pain and dyspareunia to infertility. Management may be surgical in select cases but increasingly relies on ART.

An understanding of normal embryology is essential to appreciate the significance of these abnormalities and the deviations in structure and function in clinical practice. The threshold issues in development of the female reproductive tract are the determination of genotype leading to a cascade of specific sequential anatomic and endocrine events that direct end-organ development.[2] Each embryonic landmark event must be met in a specific and precise fashion. Full functional differentiation and progression to sexual identity during puberty and adulthood are events that occur as a

continuation of these early developmental events. The clinical consequences of perturbations of any one of these determinants may result in what is clinically observed as congenital, anatomic abnormalities and, in some cases, abnormal sexual development. This chapter outlines the key events at each stage of embryologic development and describes the congenital abnormalities that may result from any disturbance in this developmental sequence. The etiologies of acquired abnormalities are varied; they are discussed in the specific chapters dealing with them.

Development of the Mullerian Tract

Normal Sexual Differentiation

Wolff in 1760 and Muller in 1830 described paired structures present in early embryonic development that contributed to the formation of the male and female reproductive tracts, respectively.[3,4] The more generic terms, mesonephric and paramesonephric ducts, are used commonly in clinical parlance coincident with a trend from the tradition of using the names of investigators to designate anatomic structures. Both terms, however, are appropriate and continue in common usage. The terms "mesonephric" or "wolffian," and "paramesonephric" or "mullerian" designate laterally placed structures that develop between 5 to 16 weeks' gestation. These structures give rise to the male and female reproductive organs, respectively. The mesonephric ducts develop into the epididymis, vas deferens and seminal vesicles. The mullerian ducts are mesodermal derivatives of the paramesonephric duct and develop into the fallopian tubes, uterus, cervix, and probably the upper one-third of the vagina.

Early Development: The Genetics of Bipotential Gonad

The factors that contribute to the development of male and female anatomy and identity have intrigued investigators and clinicians for centuries. Theories progressed from the initial identification of the X and Y chromosomes to a focused search for ever smaller regions of the Y chromosome responsible for sexual determination (Table 1-1). Sexual dimorphism was one of the first characteristics to be shown to have a chromosomal basis.[5] Using *Drosophila* as a model, investigations in 1902 suggested that sex determination was based on the number of X chromosomes. This theory persisted through the 1950s, despite the discovery in 1923 of X and Y chromosomes in the human, and the suggestion that sex-role determination in the human, unlike that in *Drosophila*, may be based on the pairing of two different chromosomes. In 1959, however, the critical role of the Y chromosome in the development of males was determined. The entire Y chromosome was theorized in early studies as the determinant that triggered a cascade of events in the development of the genital ridges into testes rather than ovaries. This critical event, under the influence of testicular hormones,[6] resulted in the regression of

Table 1-1.
Historical Aspects of Theories of Sexual Differentiation

Investigator	Comment
McClung, 1902	Sexual dimorphism on chromosomal basis
Painter, 1923	Existence of X and Y chromosomes
Jost, 1953	Hormonal influence of internal and external genitalia
Jacobs, 1959	Critical role of Y chromosome
Wachtel, 1975	H-Y antigen
Page, 1987	Testicular differentiating factor (TDF)
Palmer, 1989	Sex-determining region of the Y chromosome (SRY)

female internal anatomy and the development of male anatomy. Molecular technology, however, provided further insights into the exact factors determining sexual determination.[7]

Molecular Basis of Testicular Development

The possibility that sexual differentiation and the development of male and female reproductive organs depended on a specific part of the Y chromosome or a specific, male-related antigen associated with the Y chromosome and not the entire Y chromosome was initially suggested in the early 1970s. The H-Y histocompatibility antigen was described and the H-Y hypothesis was proposed in 1975.[8] This theory held sway for nearly a decade. Studies of intersex and abnormal sexual development yielded inconsistent results, suggesting that other factors may be responsible, and the H-Y theory was eventually abandoned.[9]

During the past 10 years, the search for the gene that switches development from the female to male pathway has focused on ever-smaller regions of the Y chromosome.[10] Evidence using deletion mapping suggests that genetic determinants of male and female differentiation and the subsequent development of the male and female reproductive organs may be related to limited, Y-related DNA located on the short arm of the Y chromosome. An early candidate was the so-called zinc finger protein of the Y chromosome (ZFY) that encodes for an immune-system protein found only in males (labeled testicular differentiating factor [TDF in humans, Tdy in mice]). Data for this theory came from two sources: XX men who had inherited a small fragment of the Y chromosome from their fathers, and XY females who had lost a crucial part of their Y chromosome. Additional study narrowed the focus further and suggested that ZFY had another small piece of the Y chromosome lying close to that previously described.[11] After intensive and provocative study by two

groups of investigators, it was subsequently established that this area located at the distal region of the short arm of the Y chromosome contained a single gene for the sex-determining region of the Y chromosome (SRY).[12]

The presence of SRY represents an essential, critical, and initial event in sexual development. Complete development of testicular or ovarian tissue is a complex series of events that involve migration of bipotential germ cells and stromal precursors to the genital ridge under the influence of genes and protein in addition to SRY. SRY is best thought of as a critical switch; its role is to direct development along one of two potential paths. With SRY as a moderator, a cascade of steps necessary to form a testis from an undifferentiated gonad are set in motion. SRY is a transcription factor that encodes a 204 amino acid protein that binds to double stranded DNA through its conserved domain, the high mobility group (HMG) box.[13] Other autosomal and X-linked genes, present in both male and female and capable of activation, are also required for testicular differentiation. Under these influences undifferentiated gonads develop into testes and the internal reproductive tract subsequently develops into the wolffian structures. In the absence of SRY, the gonads develop into ovaries and the reproductive tract subsequently develops along female lines or into the mullerian reproductive tract. With the establishment of the genetic sex and, specifically, the presence or absence of SRY, the bipotential or indifferent gonadal development develops into either testis or ovary (Figure 1-1).

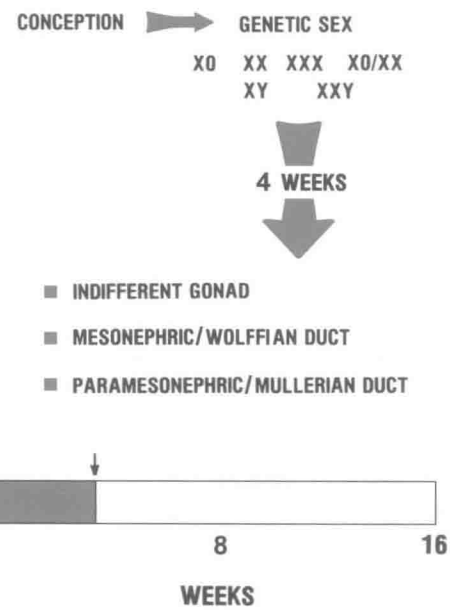

Figure 1-1 Establishment of the genetic sex at conception, and subsequent formation of an indifferent or bipotential gonad.

Despite 10 years of research, its biologic targets as well as its mechanism of action are complex and interdependent. Other important genes in addition to SRY may be involved in sex determination. Several other key regulators of male development have also been identified over the past decade.[14–16] Genetic factors such as SRY-related factor Sox9 appear to be key players in early testicular differentiation.[17,18] Sox9 belongs to a family of transcription factors, the Sox genes, that contain an HMG box similar to that of SRY. It has been shown that Sox9 binds to the same DNA targets in vitro as SRY.[19] Sox9 is highly conserved among mammals as well as other vertebrates.[20] High expression of Sox9 is always correlated with testicular differentiation and may act as a transcription factor in the Sertoli cells.[21,22] Though strongly implicated in testicular development, the precise and ultimate physiologic targets of Sox9 remain unclear. Numerous other factors have also been identified directing crucial steps in early gonadal development in both sexes, including Dmrt1, WT1, Sf1, Lm1, Lhx9, Emx2 and M33 (Table 1-2).[23–25]

Table 1-2.
Transcription Factors in Gonadal Differentiation

Gene	Localization	Phenotypic Expression of Mutations
Testicular Differentiating Pathway		
SRY	Xp11	XY gonadal dysgenesis
DAx1	Xp21.3	XY gonadal dysgenesis
Sox9	17q24	XY male-to-female reversal
SF1	9q33	Gonadal dysgenesis
WT-1	11p13	Deny-Dash and Frasier syndromes
Ovarian Differentiating Pathway		
FoxL2	3q23	Premature ovarian failure and eyelid defects

Molecular Basis of Ovarian Development

In contrast to the understanding of testicular development, ovarian development has remained relatively obscure. Female development is a default pathway in the absence of genetic male-promoting signals. Ovarian development proceeds in the absence of the genetic influences for testicular development. Genetic control of early ovarian development is largely unknown. Molecular regulation of fetal ovarian development depends on poorly understood signal pathways of cell differentiation. Though a few molecules have been implicated, their precise mechanisms and sites of action are undetermined. No genes have yet been demonstrated to play the equivalent role of

SRY or Sox9 genes. Development is dependent in part on the action of certain steroidal hormones and yet to be defined genes and target sites.

In female embryos, the germ cell lineage shows random X chromosome inactivation. On entry into the genital ridges, the silent X becomes reactivated so that both X chromosomes are expressed throughout oogenesis. Beyond these events, the molecular mechanisms involved in early ovarian differentiation and follicular development are poorly understood in spite of insights gained from several mouse models and the genetic study of patients with ovarian failure. The X-linked zinc finger gene (ZFX) is a candidate gene for ovarian maintenance that maps to the X chromosome.[26] X chromosomal abnormalities can result in gonadal dysgenesis and premature ovarian failure. Terminal deletions at Xp11 result in amenorrhea and premature ovarian failure in approximately 50% of affected patients. Deletions at Xq13 may result in primary amenorrhea.

Ultimately, in the ovarian anlage, in the absence of SRY, granulosa cells will develop. The granulosa cells become admixed with clusters of germ cells so that each surviving oocyte is surrounded by layers of flattened cuboidal cells forming the primordial follicle at approximately 16 weeks' gestation. The pool of primordial follicles is gradually depleted from this point forward. Seven million primordial follicles are initially present at completion of ovarian development. Two million are present in the newborn and 300,000 at puberty.

In summary, the sex-determining genes that direct the fate of the bipotential gonad into either testis or ovary can be placed into three categories: (1) transcription factors involved in early gonadal morphogenesis and throughout differentiation of sex-specific cell types; (2) initiators of testicular development; (3) antagonists of testicular development and potential promoters of ovarian development.[27–29] Study of human intersexes and sex-reversed patients may prove to be one promising model to gain insight into genes involved in the sex determination cascade.[30]

Gonadal Development

Under specific genetic guidance, gonadal development is a unique process with two possible organogenic outcomes: testis or ovary.[31,32] The gonads begin to develop when the embryo has a crown–rump length of 5 to 7 mm. The primitive gonad remains in an indifferent state until 4 weeks' gestation. Both paired mullerian and wolffian ducts are present at that time.[33] Complete differentiation of normal gonads depends on the migration of viable primordial germ cells from the yolk sac to the genital ridges on the dorsal mesentery. If the germ cells fail to arrive, the gonads do not develop; only fibrous streaks persist as remnants. After migration, the germ cells are then enveloped by coelomic epithelial cells. When the embryo has a crown–rump length of 7 to 9 mm, primitive sex cords from the coelomic epithelium and

primitive germ cells from the yolk sac organize into a bipotential primitive gonad, with both cortical and medullary areas. These two anatomic regions of the primitive gonads, that is, the cortical and medullary areas, give rise to an ovary or testis, respectively.

The critical event for gonadal function is eventual enclosure of germ cells and somatic cells in specific germ-cell compartments. The primitive gonad at this point is composed of germ cells, somatic or epithelial cells destined to become either granulosa or Sertoli cells, and mesenchyme, destined to become either thecal or Leydig cells. At this point in development, essential, albeit rudimentary, architecture is present. As outlined above, male mammalian development is triggered by active signals from portions of the Y chromosome. Ultimate differentiation into an ovary or testicle depends on the presence or absence of the influence of the Y chromosome or Y-related segment of the Y chromosome (Figure 1-2). Chronologically, the formation of the testicle precedes any subsequent sexual development. Differentiation of the steroid-producing cells into Leydig cells influences subsequent development of the internal and external genital structures. Interstitial Leydig cells are formed from the mesenchyme or mesonephric-derived cells around the cords. These cells contain receptors for human chorionic gonadotropin (hCG) and produce testosterone at an early age, a critical next step in differentiation.[34]

Endocrine Events

At 4 to 5 weeks under any Y-related chromosomal influence, the indifferent gonads develop into testes and through a complex series of steps induce the development of the mesonephric or wolffian tracts. Simultaneously the

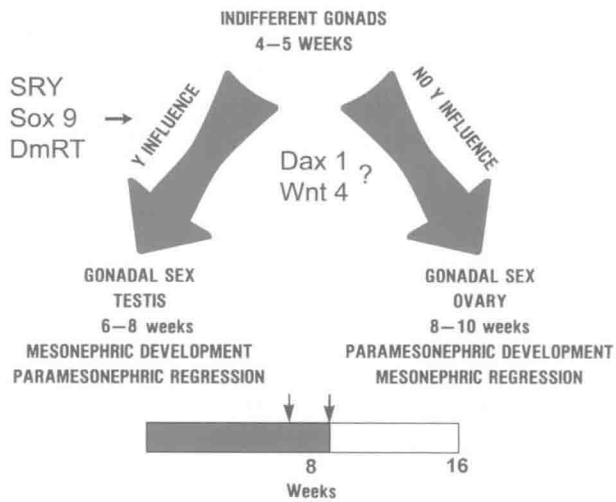

Figure 1-2 Under Y-related influence or the absence of such influence, leading to mesonephric or paramesonephric development, respectively, gonadal sex is determined to be either testicular or ovarian.

paramesonephric or mullerian ducts regress. The embryologic events of wolffian development and mullerian regression require two specific hormones produced by the testes at this critical point. The hormones are testosterone and mullerian inhibitory factor (MIF; also referred to as anti-mullerian hormone or mullerian inhibitory substance).

The discovery of endocrine influences on the development of the reproductive tract is a classic example of the intersection of basic science and clinical medicine. The mediation of the expression or regression of the mullerian or wolffian tracts by male-related hormones was described in 1930 by Alfred Jost.[35] In a series of classic and elaborate studies, Jost suggested that both local hormonal influence and the timing of this influence were essential and critical in the development of the internal reproductive tract. Jost initially demonstrated that testosterone was required for all steps of male genital differentiation, both internal and external. However, what induced mullerian regression remained a question. In studies in which a testosterone crystal was placed into a female embryo, masculinization of wolffian ducts occurred but no mullerian regression was noted, suggesting that not only was testosterone necessary for normal male development, but a second, then unknown, hormone was required to suppress mullerian development in the male. Further studies were needed to demonstrate that both hormones, testosterone and MIF, were essential for normal development of the male reproductive tract.

Studies by Jost also assessed the timing of the hormonal influences. He demonstrated that the removal of the testes prior to the twelfth day resulted in the development of female internal anatomy but removal of the testes after the twentieth day resulted in varying degrees of ambiguity. These results suggested that not only is the presence of two hormones required but that they must be secreted within a certain temporal window for normal development. These classical embryologic experiments suggested that phenotypic sex is correlated with the presence or absence of a testis in the embryo. These studies also implied that male mammalian development is triggered by active signals associated with specific chromosomes.

Although the testes are essential to the stimulation of male sexual development, female sexual development in the fetus does not depend on the presence of the ovaries. For example, the development of the mesonephric ducts in males may be disrupted if the testes are removed before differentiation of the genital ducts. In this circumstance, paramesonephric ducts develop. Removal of the ovaries of female embryos, however, has no effect on sexual development. These data further suggest that the testes impose the development of the wolffian ducts and repress the development of the mullerian ducts.

Normal male sexual differentiation is initiated by SRY, which directs testicular development in the gonadal ridge. SRY expression is characterized by the testicular secretion of MIF and testosterone. These two hormones are secreted (testosterone from the Leydig cells and MIF from the Sertoli cells) prior to the

twelfth week of gestation. Both MIF, and testosterone, as well as the capacity to bind and metabolize them, are essential to normal development. MIF causes regression of the mullerian ducts during male embryogenesis. It is a member of the large transforming growth factor-β, (TGF-β,) multigene family of glycoproteins involved in the regulation of growth and differentiation of tissue. It is precisely regulated at the transcriptional level by SRY and interacts post-translationally with testosterone.[36,37] The receptor for MIF has been also described.[38] The secretion of MIF by the Sertoli cells stimulates the unilateral regression of the mullerian ducts by the eighth week. Defects in secretion of MIF result in persistence of the mullerian system and differentiation into uterus, tubes, and upper vagina. The secretion of testosterone by the Leydig cells stimulates the differentiation of the wolffian ducts into epididymis, vas deferens, and seminal vesicles and is a complex series of events involving five enzymes. Defects in each reaction have been described and may result in abnormalities of varying degrees in sexual differentiation. These defects may be either abnormal testosterone biosynthesis or abnormal androgen action secondary to 5α-reductase, either a cytoplasmic receptor deficiency or a deficiency in nuclear chromatin receptors.

In the absence of any Y-related chromosomal influence, an ovary develops with the persistence of the paramesonephric or mullerian development and mesonephric regression. The development of the ovary in this setting occurs slightly later than the testicular development, at 8 to 10 weeks' gestation (Figure 1-2).

Development of Internal Genitalia and Genitourinary Systems

As noted above, two sets of potential duct systems develop simultaneously in both male and female embryos: the mesonephric and paramesonephric ducts. The dominance of one and regression of the other await specific hormonal cues. The mesonephric urinary ducts are formed and connect at the caudal end of the urogenital sinus and the cloaca. Paramesonephric or mullerian ducts develop lateral and parallel to the mesonephric ducts. During their development, the paramesonephric ducts migrate until they lie side by side in the midline. The paramesonephric ducts develop initially at the cranial ends and communicate with the future peritoneal cavity. As the ducts develop caudally, they cross the ventral aspect of the mesonephric ducts to partially fuse in the midline, resulting in a Y-shaped structure.[39,40] The caudal portions of the paramesonephric ducts coalesce and form a discrete structure known as the *mullerian tubercle* (Figure 1-3). With downward growth, this tubercle protrudes into the upgrowing urogenital sinus. The caudal ends of the mesonephric ducts enter the urogenital sinus at either side of the mullerian tubercle. Under the influence of the ovarian hormones (and the lack of any androgen influence) the paramesonephric ducts continue their development to form the genital tract while the mesonephric system regresses. Vestiges of the mesonephric ducts may persist in the adult, as Gartner's duct cysts, in the lateral vaginal wall.