FEMALE REPRODUCTIVE PHYSIOLOGY AND INFERTILITY

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1. Introduction

The female component of the reproductive process is more complex than that of the male. While the male is responsible for production of the male gametes (sperm) and their transportation to the female reproductive system, the female, in addition to gamete production, must transport oocytes to sperm and also provide a site for fertilization, embryo implantation, and maintenance of the developing fetus to occur. To increase the efficiency of these reproductive responsibilities, the female produces fertilizable oocytes in an intricate monthly pattern, the ***menstrual cycle***.

This chapter will begin with a review of female anatomy and histology. The next section will describe the physiological principles involved in oocyte formation (***oogenesis***) and growth of the oocyte and follicle during their morphological development (***folliculogenesis***) after activation. Section three examines the events required for final maturation of the oocyte, followed by a description of the endocrinological role of the menstrual cycle in these processes. Physiological principles involved in clinical manipulations of the menstrual cycle for assisted reproduction are discussed in a separate chapter. The female also undergoes hormone-driven changes of the mammary glands during pregnancy in preparation for the early nurturing of the baby. Although the roles of lactation and the late stages of pregnancy are of paramount importance in the success of reproduction, these topics are not covered in this chapter. Evaluation and treatment of the infertile female will be presented in the final section of this chapter. Female infertility will occur if the pattern of hormone production becomes disrupted and gamete production fails to proceed normally. Infertility may also result if the reproductive tract is blocked, or damaged due to disease or abnormal formation, making it impassable or inhospitable to the male and female gametes, or the embryo.

2. Anatomy and Histology

Fetal ***sex is determined genetically***. The ***Sry gene*** located on the Y chromosome encodes a DNA-binding protein that regulates the transcription of genes on autosomes and on the X chromosome that instruct testis formation. For many years, the development of a female fetus was observed as the "default" sex, in the absence of a Y chromosome. However, there is good evidence showing that expression of the ***Wnt4 gene*** is required to provide a key signal that channels the developmental fate of the indifferent mammalian gonad toward the ovary (Vainio et al., 1999). Development of the fetal ovary can be described as having four stages; 1) an indifferent gonad stage, 2) the stage of differentiation, 3) a period of oogonial proliferation and oocyte formation, and 4) the stage of follicle formation. Paired gonads can be identified at about 5 weeks of gestation composed of primitive germ cells intermingled with coelomic surface epithelial cells surrounding an inner core of medullary mesenchymal tissue. These gonadal ridges overlie the mesonephros and it is likely that the ***somatic cells of the gonad are derived from both coelomic epithelium and mesonephric cells***. The ***primordial germ cells*** originate within the primitive ectoderm (specific cells of origin have not been distinguished) and can only survive in the genital ridge. The germ cells migrate from the yolk sac, around the hindgut to the gonadal ridges after 4-6 weeks of gestation and begin mitotic proliferation during this migration. This ***indifferent gonad stage*** lasts about 7-10 days by which time the germ cell number has increased to approximately 10,000. ***Gonadal differentiation*** is directed by a genetic program involving hundreds of genes initiated in the indifferent gonad. ***Oogonial proliferation and oocyte formation*** requires expression of the ***WNT4*** and ***RSPO1*** genes that activate the beta-catenin signaling pathway leading to loss of cell-cell adhesion between the female germ cells, thus allowing them to enter ***meiosis*** (discussed below). In the male, the *Sry gene* inhibits *Wnt4* gene expression in the indifferent gonad and promotes the male sexual development program. In the female fetus, the ***wolffian duct*** regresses and the ***müllerian duct*** differentiates in a ***cranial to caudal*** (head to tail) direction into ***oviduct, uterus, cervix, and upper one-third of the vagina***. The developmental processes that occur to bring about this ***organogenesis*** are under the control of ***steroid hormones*** that regulate key developmental genes. Since the anatomy of the female reproductive system (Figures 1 and 2) is a reflection of its physiology, this chapter will commence with a review of female anatomy.

The major organs of the female reproductive system include:

- Genital Tract
- Ovaries
- Pituitary

A. The Genital tract

The genital tract is composed of the ***vagina***, ***cervix***, ***uterus*** and ***oviduct***. These organs share the ***same basic structural anatomy.***

a) A protective outer ***serosal layer***
b) A middle wall of ***smooth muscle***
c) An inner ***mucosal layer***

The characteristics of the ***muscular and mucosal layers vary greatly*** between the three organs and undergo dramatic changes in response to the cyclic secretions of the ovarian hormones.

I. The Vagina

The vagina forms the entrance into the female reproductive tract. It consists of a ***muscular canal*** approximately 10 cm in length that connects the uterus to the exterior (Figures 1 & 2). The superior portion is called the ***fornix*** and meets the protruding uterine cervix.

- The vaginal wall is lined by an outer, fibrous ***adventitia*** and is amazingly elastic, allowing it to function as:
  - the birth canal during parturition
  - an excretory duct for the passage of menstrual components
  - the site of sperm deposition after coitus
- **Smooth muscle** layers lie under the inner mucosal layer and are arranged in poorly defined circular and longitudinal layers with the majority of the fibers orientated longitudinally. The smooth muscle assists in the parturition process and in the subsequent involution of the vagina after