8.1. PROGESTINS

8.1.1. Introduction

Development and maintenance of the female reproductive system are dependent on the cyclical interaction between estrogens, primarily estradiol-17β, and progesterone. The principal target tissues for these steroid hormones include the uterus, vagina, fallopian tubes, and mammary glands, as well as the anterior pituitary and hypothalamus. Although estrogens are recognized as promoters of cellular proliferation, progestins are known to facilitate cellular differentiation. In addition, progesterone and related drugs exert significant antiestrogenic effects. It is the balance between estrogen and progesterone actions that regulates the state of the female reproductive system. Some of the therapeutically useful derivatives of progesterone share a structural similarity to androgens, and these agents in some instances also produce androgenic or antiandrogenic activity.

8.1.2. History

It was apparent as early as 1897, following the studies by Beard, that ovulation failed to occur during pregnancy. Subsequently, the studies by Haberlandt indicated that hormones derived from the ovary and placenta could be used for regulation of fertility. In 1929 the Corner and Allen bioassay for detecting progestational activity was developed and
became instrumental in the isolation of progesterone from the corpus luteum. By 1932, Butenandt had elucidated the structure of progesterone. The observation by Inhoffen in 1938 that alkylation of the 17α-position of the steroid nucleus converted estradiol-17β and testosterone into orally active compounds provided the basis for the development of progestational compounds. Yet the evolution of the orally active synthetic progestins required the availability of significant quantities of progesterone. This was made possible by Marker’s recognition in 1943 that the Mexican sweet potato contained high levels of progesterone.

Allen and Ehrenstein revealed in 1944 that 19-norprogesterone possessed oral progestational activity. In 1950 Birch outlined an efficient procedure for synthesizing 19-nortestosterone, which would subsequently become an important precursor for the development of synthetic progestational drugs. Djerassi derived 19-norethisterone in 1951, and norethynodrel was synthesized by Colton in 1952, using 19-nortestosterone as the parent molecule.

Pincus and Chang subsequently demonstrated the antifertility activity of progesterone in females in 1953. By 1957, the initial studies of the clinical use of progestational drugs as orally active contraceptives in females were described by Rice-Wray. During the same year, Enovid, containing norethynodrel, was approved by the Food and Drug Administration for menstrual regulation and was subsequently approved as a contraceptive agent in 1960. Ortho-Novum containing norethisterone was approved as a menstrual regulator in 1957 and was approved for birth control needs in 1962.

Today’s principal use of progestational drugs was born during the early 1960s. Currently, at least 28 drug formulations containing a progestin alone or a combination of a synthetic progestin and an estrogenic substance are available for fertility regulation in women. One of six progestins differing in potency and spectrum of action and one of two synthetic estrogens are utilized in these products. It is the difference in hormonal constituents and content that pharmacologically distinguishes the various oral contraceptive agents.

8.1.3. Chemistry

The progestins are classified according to their molecular structure. Progesterone is the endogenous progestational substance produced by the cells of the corpus luteum during normal menstrual cycles and in early pregnancy as well. The placenta serves as an important source of progesterone during later stages of pregnancy.

A number of synthetic progesterone derivatives are available for