ENOVID

The Combined Oral Contraceptive Pill (COCP)

Introduction

The Combined Oral Contraceptive Pill (COCP), often referred to as the birth control pill, includes a combination of an *estrogen*, a group of steroid compounds, and a *progestin*, a group of synthetic steroid hormones called *progesterone*.

Lead Compound Discovery

A lead compound is a chemical compound whose chemical structure is used as a starting point for chemical modifications to improve its pharmaceutical use.

By the 1930s, scientists had isolated and determined the structure of the steroid hormones. They found that high doses of *androgens*, *estrogens* or *progesterone* inhibited ovulation, but obtaining them from animal extracts was extraordinarily expensive.

In 1939, Russell Marker, a professor of organic chemistry at Pennsylvania State University, developed a method to synthesize progesterone from plant steroid *sapogenins*, initially using sarsapogenin from sarsaparilla, which was proved expensive.

Three years later, he discovered a better starting material, the *saponin*, which can be converted to sapogenins in laboratory, from inedible Mexican yams, *Dioscorea mexicana*, found in the rain forests of Mexico.

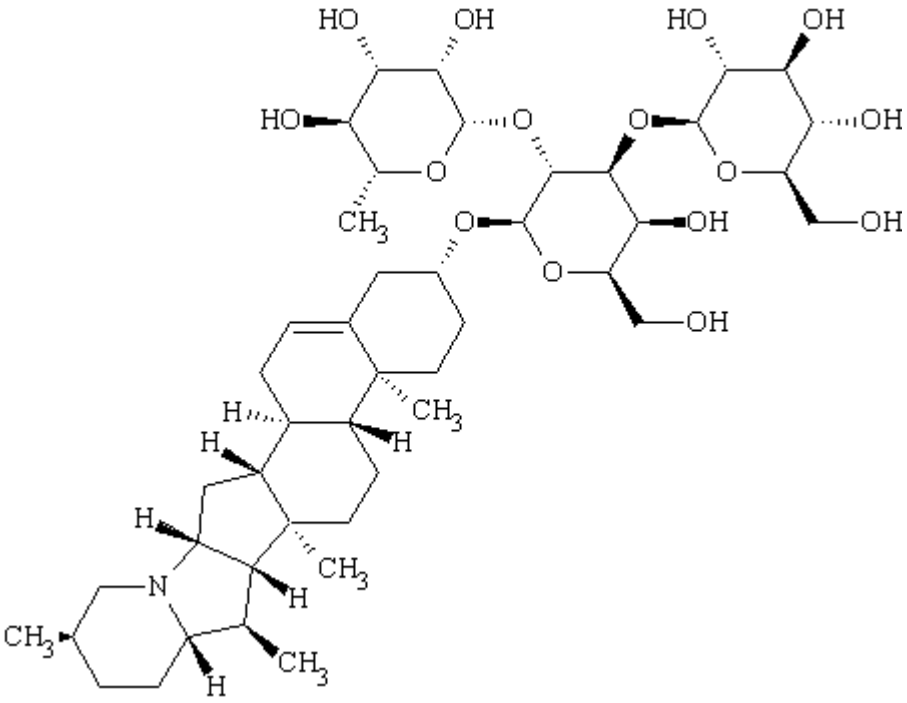

Fig 1: Solanine, a kind of saponin

Molecular Modification and Human Trials

In early 1951, reproductive physiologist *Gregory Pincus* began hormonal contraceptive research. She repeated and extended the experiments in 1937 with another reproductive physiologist, *Min Chueh Chang*, which showed injections of progesterone suppressed ovulation in rabbits.

In 1952, *John Rock*, an expert in the treatment of infertility, induced a three-month anovulatory pseudo-pregnancy state in 80 infertility patients with continuous increasing oral doses of *estrogen* and *progesterone*, which resulted in a 15% pregnancy rate only in the following 4 months. However, this method brings along the troubling absence of menstrual period.

One year later, *Rock* induced a three-month anovulatory pseudo-pregnancy state in 27 infertility patients with *progesterone*-only regimen for a 20-day cycle, followed by a pill free period, so as to produce withdrawal bleeding. This obtains the same result as the previous trial without any absence of menstrual period. But 20% of the women experienced breakthrough bleeding.

Later, *Pincus* asked *Chang* to send him chemical compounds with progesterone activity. It was discovered that the three most promising compounds in animals were Syntex's *norethindrone*, which had been synthesized by chemists *Carl Djerassi*, *Luis Miramontes* and *George Rosenkranz* in 1951, and Searle's *norethynodrel* and *norethandrolone*, which had been synthesized by chemist Frank B. Colton in 1952 and 1953 respectively.

In 1954, *Rock* began the studies of the ovulation-suppressing potential the three oral progestins. He repeated the previous trial in 50 infertility patients with the three oral progestins of 5-50 mg for a 21-day cycle, followed by a pill free period, and then produce withdrawal bleeding. All doses of *norethandrolone* suppressed ovulation but caused breakthrough bleeding, but 10 mg or higher doses of *norethindrone* or *norethynodrel* suppressed ovulation without breakthrough bleeding and led to only 14% pregnancy rate in the following 5 months.

Formulation Development

Norethindrone or *norethynodrel* are then discovered to be contaminated by an estrogen *mestranol*, an intermediate in their synthesis. When purifying *norethynodrel* to contain less than 1% *mestranol*, breakthrough bleeding occurred. It was then decided to incorporate 2.2% of *mestranol*, which did not lead to breakthrough bleeding in the first contraceptive trial in 1956. This combination was given a name **Enovid**.

A second contraceptive trial of **Enovid** began in Jun 1956. In 1957, Searle held a reviewing gynecologic and contraceptive research on **Enovid** and concluded that estrogen content could be reduced by 33% to lower the incidence of estrogenic gastrointestinal side-effects without significantly increasing that of breakthrough bleeding.

Approval for Marketing in USA

In 1957, the Food and Drug Administration (FDA) approved **Enovid** 10 mg (9.85 mg *norethynodrel* and 150 µg *mestranol*) for menstrual disorder. Additional contraceptive trials showed it at lower doses were also effective. In 1960, the FDA announced it would approve **Enovid** 10 mg for contraceptive use.

However, Searle never marketed **Enovid** 10 mg as a contraceptive. It did not market **Enovid** 5 mg (5 mg *norethynodrel* and 75 µg *mestranol*) until the FDA approval of it.

Despite its approval, it is not available to married women in all states until 1965 and unmarried women until 1972.

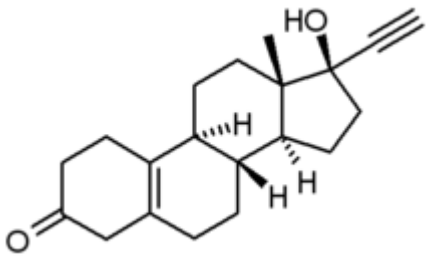

Fig 2: Norethynodrel, IUPAC: (17β)-17-ethynyl-17-hydroxyestr-5(10)-en-3-one

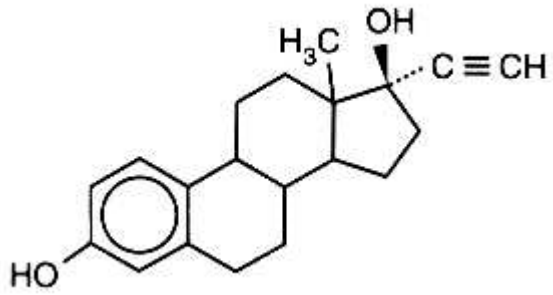

Fig 3: Mestranol, IUPAC: (17β)-17-ethynyl-3-methoxyestra-1,3,5(10)-trien-17-ol