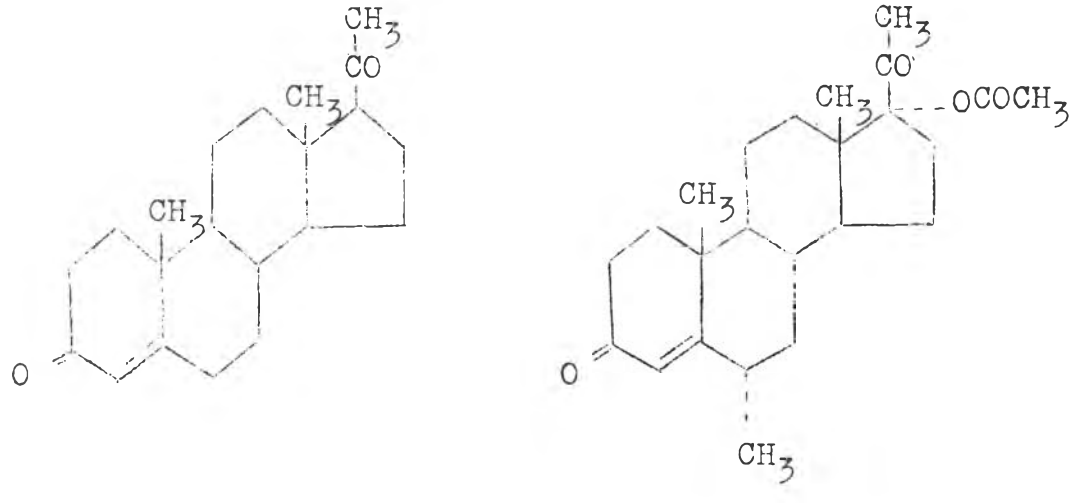
Chapter 1

Introduction

Explosive population growth is becoming recognized as a major obstacle to economic and social progress especially in the underdeveloped countries. Experiments have been preceeding for some time to develop contraceptive agents. The first report of the possibility of estrogenic steroid as the antifertility agent was noticed in 1933 by Hartman. In1937 Makepeace, Weinstein and Friedman further noted that another type of female gonadal steroid, progesterone, can also effective in inhibition of ovulation. Further development of steroid contraceptives claimed that estrogen as well as progesterone could relieved painful dysmenorrhea (Sturgis and Albright, 1940). A decade later, synthetic progestins has been developed and used in tests carried out in Puerto Rico (Rock, Pincus and Garcia, 1956). Attempts to find structural and functional features of steroid compounds essential to enhance ovulation inhibiting potency, low side effects, effective in fertility control and return of ovulation after discontinuation had extensively studied by Pincus (1957). The mechanism of steroid approach to fertility control in women is based upon gonadotrophin inhibition and prevent ovulation. They vary, however, in their ability to block gonadotrophin release (Pincus, 1965;

Jackson, 1966; Mishell, 1969; Jeppssen, 1972).

Depo medroxyprogesterone acetate (DMPA), a 6α-methyl, 17α- hydroxyprogesterone acetate, synthetic derivative of progesterone or depo provera (Figure 1) has extensively used for women since 1958 for such condition as treatened abortion, habitual abortion, endometriosis and carcinoma of uterus (Anderson, 1965; Kistner, Griffiths, Craig, 1965; Mc Daniel, 1971, 1973).



Progesterone Depo medroxyprogesterone acetate

Figure 1 Chemical structure of Depo medroxyprogesterone acetate as compared to progesterone

It was observed that parturient women who had received a single massive dose of DMPA during clinical trials of its use in the management of premature labour became sterile for 12 - 21 months post-partum (Caspo, 1966; Mc Daniel, 1973) and this sterility was reversible,

the patient eventually returns to normal cycles and normal pregnancy. Since then many investigators had studied the contraceptive effects of DMPA either used alone or in various combination with oral or injectable estrogen and given at intervals of one month to one year, the commonest being 3 months in dose of 150 mg.

In Thailand, DMPA was first used as a contraceptive in Chiang Mai in April, 1965 (Mc Daniel, 1973). Soon followed by clinical trials in Chulalongkorn and Siriraj hospitals in Bangkok. In Chiang Mai it was first used in women for whom IUDC had proven unsatisfactory and the demand of this method steadily increased in popularity. Women who discontinued contraception by 3 month injections of DMPA for planned pregnancy experienced, a return of fertility of approximately 87% within the first year (Mc Daniel, 1973) and showed sign of regular ovulation within 12 - 18 months of their final injection (Gardner and Mishell, 1970; Tyler, Levin, Elliot and Dolman, 1970).

DMPA apparently exerts its contraceptive action for prolonged period and the duration of action is dose related (Chinnatamby, 1971; Mc Daniel, 1973). It prevented conception by :

a) Inhibiting the secretion of gonodotrophic hormone from the anterior pituitary and thus inhibiting ovulation (Bloch, 1971; Chinnatamby, 1971). During the

use of DMPA pre-ovulatory LH-peak was inhibited, while the basal LH and FSH production appeared not to be affected (Mishell, Talas, Parlow, El-Habashy and Moyer, 1968; Mishell, 1967; Mishell, 1969; Jeppssen, 1972). Even after long treatment with DMPA, the microscopic examination of the ovaries shows growth of primodial follicles up to the stage of Graffian follicles and the theca interna shows evidence of luteinization (Zanartu, Purkin, Rosenberg, Davensens, Guerrero, 1970). Both findings suggested evidences of FSH and LH activity, though not sufficient to induce ovulation.

b) Altering the nature of cervical mucus, increasing the viscosity of it, thus forming a natural barrier to the passage of the spermatozoa (Mishell, Talas, Parlow and Moyer, 1968; Zanartu, Purkin, Rosenberg, Dovansen, Guerrer, 1970; Mc Daniel, 1973).

c) Thinning the endometrium, to provide a poor site for nidation of the fertilized ovum (Mc Daniel, 1973).

In the attempt to simplify the use of hormonal agents for contraception and to eliminate the need for daily oral dosage, DMPA was initially tried on domestic animals. In dogs, the injection of DMPA caused a long term delay in oestrus which however, reversible. The period of delay was related to dosage employed (Vecchio, 1967; Ahmad and Rsaul, 1970). In cattles, which normally

ovulate every 21 days, ovulation could be delayed for 4 months by injection of 500 mg. subcutaneously (Vecchio, 1967; Ahmad and Rsual, 1970). The ability of DMPA to function as a replacement for progesterone has been demonstrated in pregnancy maintainance of castrated rabbit (Wu, 1961) and rats (Stuki, 1958). DMPA can delay implantation in intact female rats, presumably by its own progestational property and its central action as inhibitor of hypothalamic-anterior pituitary release of gonadotrophins required for stimulation of estrogen release from the ovary (Barnes and Mayer, 1964). With regard to potency, DMPA is 20 to 30 times as potent as progesterone on inhibition of ovulation in the rabbit (Barn, Schmidt and Dulin, 1959). When checked in the Clauberg assay for endometrial stimulation in immature rabbits, DMPA was 10.5 times as active as progesterone (Sala, Camerino and Cavallero, 1958).

In female rats treated with DMPA from the second post-natal day to maturity showed the suppression of estrous cycle and marked ovarian inhibition (Logothetopoulos, Sharma and Kraicer, 1961). However, DMPA didnot affect the secretion of growth hormone or thyroid hormone (Logothetopoulos, Sharma and Kraicer, 1961). This drug also shown significant anti-inflammatory, glycogenic and pituitary inhibiting activity in the rats (Glenn, Richardson and Bowman, 1959).

When tested for ability to stimulate seminal vesicles and prostates in castrated or immature rats, DMPA did not have androgenic activity approaching that of standard androgens, methyl-testosterone or testosterone propionate (Lyster, Lund and Dulin, 1959). However, Progesterone and DMPA interfere with accessory gland function in the rabbit as shown by a significant decrease in semen volume (Ericson, Dutt and Archdeacon, 1964; Ericson and Dutt, 1965).

Although, it has been assumed that women have a period of natural sterility during lactation (Dickinson, 1938; Cornin, 1968), a considerable number of pregnancies have been reported during this time (Kamel, Hefnawi, Ghoneim, Talaat, Younis, Tagui, Abdalla, 1969). Ovulation might occur prior to the sixth post-partum week without a preceeding menstrual period (Sharman, 1967). It is therefore important to initiate contraceptive therapy, when required as soon as possible after delivery, because in the immediate post-partum period maternal motivation is high. However, it must be considered the effects of contraceptive therapy used on lactation, especially in developing countries where breast feeding is a vital to the adequate nutrition of the infant. The appropiate contraceptive used in the post-partum period should not adversly effect on lactation (Koetsawang, Chiemprasert & Kochanda, 1972). Problems, however, arise when choosing

a contraceptive method in the early puerperium. IUCDs have a high expulsion rate and a risk of perforation when applied shortly after delivery (Karim, Ammer, Fikri, Abdou, 1971). Pills (containing estrogens and progestins) are claimed to have suppressive effect on lactation (Kamel, Hefnawi, Talaat, Younis, Tagui & Abdalla, 1969; Kora, 1969; Borglin and Sandholm, 1971; Koetsawang, Chiemprasert and Kochanda, 1972). When DMPA became available as an experimental injectable contraceptive, attention was quickly directed to its effect on lactation. Injectable DMPA have no adverse effect on lactation (Gomez-Roger, Ibarr, Polo, Faundes and Guiloff, 1967; Hefnawi, Fawzi, Bradrawi and Bahgat, 1970; Bloch, 1971; Karim, Ammar, El Mahgouli, Fikri and Abdou, 1971). There were no significant differences in the growth curves of the infants from the control (Hefnawi, Fawzi, Badrawi and Bahgat, 1970). Milk yield was significantly increased in the DMPA-treated group, as well as the protein content, where as a decrease was noted in lipid content. Lactose content was essentially unchanged (Hefnawi, Fawzi, Badrawi and Bahgat, 1970).

DMPA, because it does not inhibit milk secretion in human when administered to the lactating mother (Hefnawi, Fawzi, Badrawi and Bahgat, 1970; Karim, Ammar, El Mahgouli, Fikri and Abdou, 1971; Koetsawang, Chiemprasert and Kochanda, 1972) is being increasingly

used as a post-partum contraceptive. The objective of this study was undertaken in order to find out whether DMPA, of a dose 5 ug/gm. body weight (double human dose) administer to the lactating mothers caused an increase in milk secretion in rats. At present, it is still not clearly known of the mechanism of this drug in increasing milk secretion. Moreover, it is still not certainly known whether the suckling babies who may, by chance, ingest some of the DMPA injected to their mothers though the ingested milk. While no data appears to be published with DMPA, this investigation was the first time to emphasize the effect of DMPA which it might affect milk secretion in lactating rats and affected growth and reproductive function in the later life of the suckling litters and confirmed experiment in mammary gland histology and pituitary cytology, because experiment in man was very limited. It is known that after administration of combined estrogen pregestrogen steroids, estrogen activity in the milk has been detected both in human and goats (Laumas, Malkani and Laumas, 1970). Therefore, the investigation was also carried out to determine the effect of DMPA administered to the lactating rats on growth and reproductive function of the suckling litters in order to be very useful in considering for future use of this drug as the contraceptive agent during the post-partum period in lactating mothers.