CHAPTER I

INTRODUCTION AND AIMS

Iodine deficiency is now recognized as a major international public health problem. It is estimated that 800 million people may be at risk of the effects of iodine deficiency (Hetzel, 1983). In Thailand, it appears that some 39% of Thai population (about 20.5 million) lives in areas where environmental iodine deficiency is a significant health problem, particularly in the northern and northeastern parts of the country (Clugston *et al.*, 1987). Some 14.7% are estimated to have goiter, 0.76% are cretins and 2.29% may have some impaired neurological functions. The effects of iodine deficiency induce miscarriages, stillbirths, congenital anomalies as well as the more familiar goiter, cretinism, impaired brain function and hypothyroidism in children and adults (Hetzel, 1983;1987; Hetzel and Mano, 1989).

It is now accepted that iodine deficiency produces abnormally maternal low serum T4 and fT4 in man (Pharoah *et al.*, 1981). These are reported in later by using the animal model study in rats (Obregon *et al.*, 1984 a; 1984 b; Morreale De Escobar *et al.*,1985; Escobar Del Rey *et al.*, 1986; 1987), sheeps (McIntosh *et al.*,1984; Potter *et al.*, 1984; 1986; Mano *et al.*,1989), and marmosets (Mano

et al., 1985; 1987; Hetzel and Mano, 1989). Additionally, iodine deficiency effects are mediated by a combination of both maternal and fetal hypothyroidism relevant to the human observations. Hence, the idea of fetal requirement for T4 is implicited in a hypothesis advanced by Ekins and his colleagues (1985; 1987) in which the increase in maternal thyroxine binding globulin (TBG) is regard as fascilitating T4 deliver to the fetoplacental unit, particularly during the first trimester.

Common reproductive failure usually reports with the production of abortion, stillbirth and prematurity in human (Hodges *et al.*, 1952; Goldsmith *et al.*, 1952; Ross *et al.*, 1958; Scott *et al.*, 1964; Greenman *et al.*, 1962; Montoro *et al.*, 1981; Hembrec and Vande Wiele,1986; Longcope, 1986). However, scattered reports in women with ovulation and conception compatible with the state of mild hypothyroidism delivered the congenital mental retardation and deformity babies are mostly found in the severe iodine deficiency area (Hodges *et al.*, 1952; Montoro *et al.*, 1981; Pharoah *et al.*, 1983; Hembrec and Vande Wiele, 1986; Longcope, 1986). The mechanisms of thyroid hormones deficiency in mother affect the full term pregnanay are obscure, eventhough there are many cases of cretinism in human. In animal model, it is very difficult to obtain the offspring from maternal hypothyroidism (Hetzel and Mano, 1983). Most of the dams are induced to be hypothyroidism during mid or late gestations but a few

successful fetal hypothyroidism delivered from hypothyroid dams is obtained (Escobar Del Rey, 1986; 1987; McIntosh *et al.*,1984). It is noticed that iodine deficiency induction is less severe than maternal hypothyroidism (Morreale De Escobar *et al.*,1985; Escobar Del Rey,1986; Mano *et al.*,1985;1987; Hetzel and Mano, 1989). Furthermore, hyperprolactinemia is very common syndrome concurrently with primary hypothyroidism which believes to be one cause of infertility in women (Ross *et al.*,1986; Edwards *et al.*,1971; Boroditsky *et al.*,1973; Kleinberg,1977).

At present, natural hypothyroid patients are relatively rare and difficult to follow up the obscure mechanisms of thyroid hormones as determining the early mental development of the child. One of the representatives of old world mankey, *Macaca fascicularis*, which has similar menstrual cycle length with human female and proved to be no breeding seasonality (Varavudhi *et al.*,1982). Additionally, these monkeys also show spontaneous galactorrhea and infertility which resemble to the clinical manifestation in human subjects (Tangpraprutigul *et al.*,1987). Furthermore, the results of pituitary and thyroid functions in male cynomolgus monkeys are also similar to human (Smallridge *et al.*,1981). In this study the fertile female cynomolgus monkeys were used as the animal model. Hypothyroidism were planned to induce in various degree (severe, mild and recovery states) by using methimazole (MMI). Methimazole

is one of the popular drug currently use in treatment of hyperthyroidism (Cooper,1984a; Green,1986). This drug can inhibit effectively the coupling process of iodotyrosine in thyroid gland and shows the prolonged plasma half-life (5-6 hrs) as well as high bioavailability (F = 0.93) (Janssen *et al.*,1985). Therefore, MMI is also a suitable treatment drug for induction of hypothyroidism by adjusted the dosage from the initial dose (10 mg/day) to be maintenance dose (5-2.5 mg/day). In order to gain further insight into the influences of various degree of hypothyroidism upon ovulation and ovarian steroidogenesis, MMI is used and adjusted the dosage for establishment of different degree of hypothyroidism. The main speculated point stress on whether mild hypothyroidism is capable of inducing ovulation and normal ovarian function. Additionally, if the ovulation occur during mild hypothyroidism, further study will refer this criteria for set up the maternal hypothyroidism model in cynomolgus monkeys which are capable of producing their offspring during mild hypothyroidism state and may offer a chance for future investigate the fetal brain development in experimentally induced monkey model.

In view of the foregoing, this study is aimed to

1. determine the changes in thyroid hormones, TSH, E_2, P, PRL and TBG during pretreatment menstrual cycle.

2. determine the relationship of thyroid hormones, TSH, TBG and PRL during different various degree of MMI induced hypothyroidism and its withdrawal.
3. investigate the influence of hypothyroidism upon E_2, P during severe, mild and recovery states of hypothyroidism.
4. determine the alterations of TBG, thyroid hormone, TSH, E_2, P and PRL levels during pregnancy and compare between these hormones in previous MMI treatment pregnancy and those in normal pregnancy.