CHAPTER I

INTRODUCTION

Various hypotheses have been presented to explain the mechanism of action of the intra-uterine device (IUD), namely it causes; a) local release of the antifertility substance (1, 2, 3), b) inflammation of the endometrium (4), and c) the rapid transport of the ovum through the fallopian tube (5). However, the mechanism of the antifertility effect of an IUD is not yet properly understood.

IUD and the release of antifertility substances

There are many reports on biochemical changes caused by the presence of an IUD in the uterus. In rats, the uterine anastomosis induced the bilateral effect of an IUD (6). This finding suggested that the presence of an IUD in one horn led to liberation of a substance or substances which passed to the control uterine horn through the anastomosis and prevented implantation in that horn. Batta and Chaudhury (1) and Yaovapolkul (3) further demonstrated that this antifertility substance(s) present in the intraluminal fluid in rats with an IUD could be transferred to the control pregnant rats and inhibit implantation when injected on day 4 of pregnancy. These results strongly supported that there should be some antifertility substances increasing in the IUD fluid which exerted the antifertility effect in that uterine horn or in the transferee horn.

In women fitted with Lippes loop, there was a marked increase in

total protein (about 4-fold) and non protein nitrogen levels (about 2-fold) of the uterine fluid (7). In the rats, an IUD caused a similar increase of the total protein (3) of the uterine fluid. Greenwald (4) suggested that lysis of leukocytes or breakdown products of leukocytes, which were found to increase in IUD-bearing horn and was essential to anti-implantation effect of the device may contribute to the elevation in protein content associated with an IUD. In addition, Yaovapolkul (3) reported that the storage of IUD fluid at -70°C longer than 8 weeks or heated at 100°C longer than 10 min absolutely destroyed the contraceptive activity of the IUD fluid. Separation of IUD fluid by dialysis and Sepharose 4B column chromatography, and assay for biological activity of each fraction showed that F_s 1, a macromolecular fraction of approximately 3×10^6 dalton or larger could involve in contraception (3).

In addition to the increase of macromolecules such as DNA, RNA (8), protein (3) and several enzymes (9, 10), the presence of an IUD in the rat uterus was associated with the increase in many amino acids (11), P_i and Ca^{++} (3). Among these increasing micromolecules, P_i showed a marked increase of 20-fold to that in control fluid (3). Moreover, Yaovapolkul (3) demonstrated that addition of P_i into the control fluid until the P_i concentration reached that found in IUD fluid resulted in mild antifertility effect by allowing implantation to occur but inhibited the normal growth of the fetuses on day 4 of pregnancy (3). All these results lead to a hypothesis that the antifertility effect of an IUD and IUD fluid should be mediated by a complex, and this biological active complex requires high concentration of P_i to be functioning, and requires, also, a certain extensive amount of protein.

To test this hypothesis, the antifertility effect of P_i, alone or mixing with normal control fluid or physiological saline, were studied under various conditions. The distribution of P_i after injection into the rat uterus *in vivo* was also investigated by using ^{32}P-P_i. Besides, the binding and the nature of binding between P_i and the uterine fluid component(s) was performed on Sephadex G-25 column using ^{32}P-P_i as the radioactive marker.