Mechanism of action of the intrauterine contraceptive device: evidence for a specific biochemical deficiency in the endometrium

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The precise mechanism of action of the intrauterine contraceptive device (IUCD) is uncertain. In this study we compared the circulating concentrations of a specific endometrial protein, placental protein 14 (PP14), in 62 women with an IUCD and 16 controls. The concentrations of PP14 were substantially lower in IUCD users. There was no difference in the concentrations of another and less specific endometrial protein, insulin-like growth factor binding protein-1 (IGFBP-1). There was no difference in PP14 concentrations between those women with and without intermenstrual bleeding. We conclude that the reduced concentrations of PP14 in IUCD users reflect defective endometrial function in these women, probably related to the contraceptive effect. We propose that the measurement of PP14 might be a means of comparing the efficiency of different devices.

Key words: contraception/endometrium/intrauterine contraceptive device/pregnancy proteins

Introduction

The intrauterine contraceptive device (IUCD) is one of the commonest methods employed in current contraceptive practice (Connell, 1979; Sivin and Schmidt, 1987). The mechanism of action is not well understood. However, it is generally believed that all IUCD stimulate an inflammatory response in the uterus (Vessey et al., 1979; Belhadj et al., 1986; Newton and Tacchi, 1990). Numerous polymorphonuclear leukocytes appear in the endometrium followed by foreign-body giant cells, mononuclear cells and macrophages (Van Bogaert, 1983). Copper increases all aspects of these inflammatory reactions (Liskin and Fox, 1982). As a result, the normal cyclic changes of the endometrium may be delayed or deranged, making the endometrium inhospitable to the implanting blastocyst. In women using copper IUCD, sensitive assays for human chorionic gonadotrophin provide evidence of implantation in <1% of menstrual cycles (Segal et al., 1985; Wilcox et al., 1987).

In the present study we aimed to evaluate the effect of the presence of an IUCD on the endometrium by measurement of circulating concentrations of specific endometrial proteins. Two proteins are secreted in relatively large quantities by this tissue. These are known as placental protein 12 and placental protein 14 (PP12 and PP14). The nomenclature arises from the fact that both were originally isolated from placental extracts, though in reality the origin was the maternal endometrium. Subsequent work has shown that PP12 is identical with insulin-like growth factor binding protein-1 (IGFBP-1) and that PP14 is an analogue of β-lactoglobulin. It is believed that both proteins may play a significant role in the implantation process and subsequent development of the embryo/fetus (reviewed by Chard, 1994, and Chard and Olajide, 1994). We present here evidence for a substantial defect in the synthesis of one of these proteins, PP14, in women with an IUCD in situ.

Materials and methods

The study included 78 women. Sixteen of these women had a normal regular cycle (mean length 28.5 ± 2.4 days and duration 4.5 ± 1.6 days). None was using any form of contraception. These women constituted the control group. The study group consisted of 62 women who had had an IUCD (TCu-380A; Ortho, High Wycombe, UK) in place for 15-24 months. The mean length of their menstrual cycles was 27.5 ± 1.4 days and duration of bleeding was 5.6 ± 1.4 days. Forty of these women had intermenstrual bleeding but the remainder had no symptoms attributable to the presence of an IUCD. The age of the women with an IUCD ranged from 27 to 40 years (mean 33.6) and that of controls was 26–39 years (mean 31.9). The parity range was 2–6 (mean 3.9) for IUCD users and 2–6 (mean 3.7) for controls.

Blood samples (one from each woman in the study) were collected at various stages of the cycle. To avoid confusion by the higher concentrations of PP14 associated with the late luteal and menstrual phase, only samples collected between days 5 and 25 of the cycle were included in the present analysis. Serum was separated and stored at −20°C until assayed for IGFBP-1 and PP14 by radioimmunoassay as described previously (Howell et al., 1989; Wang et al., 1991).

Results

The concentrations of PP14 at days 5–25 of the cycle were substantially lower (Mann–Whitney test; P = 0.0037) in IUCD users (median <1 μg/l, range <1–5) than in the controls (median 2.5 μg/l, range <1–21) (Figure 1). There was no difference according to whether or not the IUCD users had abnormal bleeding. There was no difference in the circulating concentrations of IGFBP-1 between the IUCD users (median 25 μg/l, range 5–134) and controls (median 19 μg/l, range 5–71). IGFBP-1 and PP14 concentrations did not vary according to the day of the menstrual cycle. The within-assay variations associated with this study were <5% for both
The overall inflammatory response to an IUCD is intensified in the presence of copper (Newton and Tacchi, 1990). The copper IUCD (TCU-380.A) releases free copper and copper salts which have both a biochemical and a morphological impact on the endometrium (Vessey et al., 1979). Copper has many specific actions, including enhancement of prostaglandin production and interference with glycogen metabolism and oestrogen uptake by the uterine mucosa. It can be speculated that the low concentrations of PP14 after IUCD insertion may be related to the local endometrial pseudo-inflammatory reaction between the copper and synthesis of endometrial proteins, including PP14.

The finding of reduced concentrations of PP14 (Figure 1) is clear-cut. Superficially, it might appear surprising that a similar phenomenon was not observed with the other specific endometrial protein, IGFBP-1. However, unlike PP14, IGFBP-1 is produced by numerous tissues throughout the body, and the total contribution from the endometrium is relatively small (Suikkari et al., 1988; Singh et al., 1990; Thraikill et al., 1990). Thus, there might be an equivalent effect of the IUCD on endometrial synthesis of IGFBP-1, but this would not be detected by measurement in the general circulation.

The definition of an important biochemical change in IUCD users suggests that measurement of this compound might be a useful means of determining the relative efficacy of different types of device, for example, those with or without the addition of specific progestagens.

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References
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