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Review article

Antiprogestin-releasing intrauterine devices: a novel approach to endometrial contraception☆

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Abstract

Intrauterine devices (IUDs) that release progestins are highly effective contraceptives, but they induce breakthrough bleeding that some women find unacceptable. Because progesterone (P) antagonists [antiprogestins (APs)] are known to suppress the endometrium, induce amenorrhea and inhibit fertility, AP-releasing IUDs (AP-IUDs) may provide an effective contraceptive that also controls endometrial bleeding. Here, we assessed the effects of empty (blank) vs. AP-IUDs (ZK 230 211) on bleeding patterns and endometrial growth in ovariectomized, artificially cycled macaques. The AP-IUDs (but not the blank controls) induced extended, frank menstruation when inserted during the late luteal phase, an indication of local AP action. Over time, endometrial glandular and arterial proliferation were inhibited, steroid receptors were elevated, spiral arteries showed degenerative changes, P withdrawal bleeding was prevented, and estradiol (E_2)-dependent proliferation was suppressed by the AP-IUDs. In sum, AP-IUDs suppressed the effects of P on endometrial progestational development and blocked the effects of E_2 on endometrial proliferation, as previously shown for systemic treatment with APs. Therefore, AP IUDs may provide novel contraceptive devices with minimal breakthrough bleeding.

Keywords: Antiprogestins; Progesterone withdrawal; Uterine bleeding; Macaque monkeys; Endometrial changes

1. Introduction

Intrauterine devices (IUDs) are highly effective contraceptives that act primarily to block fertilization [1]. However, patient compliance is sometimes less than optimal because of heavy menstrual bleeding, breakthrough bleeding (BTB) and cramping that can occur, especially with various nonhormonal IUDs. The recently developed levonorgestrel-releasing intrauterine system (Mirena) is an extremely effective contraceptive that reduces overall menstrual blood loss, but many women find the amount of BTB that typically occurs during the first 3 months of use to be unacceptable [2]. Consequently, there is a need for a contraceptive IUD that could completely suppress BTB.

Several studies indicate that progesterone (P) antagonists [antiprogestins (APs)] can act as contraceptive agents [3–5] and are also associated with amenorrhea [6–8]. Therefore, AP-releasing IUDs may provide a novel form of intrauterine contraception with minimal BTB. Chronic, *systemic* administration of low-dose APs, including RU486 (mifepristone) and the potent Schering P antagonists, ZK 137 316 and ZK 230 211 [9], induce endometrial atrophy in nonhuman primates [10]. Such treatment is contraceptive in macaques, and its effects on menstruation are dose-dependent [4]. In women, chronic oral administration of mifepristone suppressed endometrial mitotic activity, induced amenorrhea and was contraceptive [11]. Periodic treatment with mifepristone in women treated with Norplant reduced BTB [12].

APs suppress endometrial growth in primates by two mechanisms: blockade of P action and suppression of the proliferative effects of estrogen; the latter effect is known as the endometrial antiproliferative effect [13,14]. Although the exact mechanism of the endometrial antiproliferative effect remains unclear, reduction in uterine blood flow [14], along with an elevation in the androgen receptor [15], are important factors. Overall, the evidence indicates that

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chronic, systemic administration of low-dose AP can block endometrial proliferation and suppress endometrial bleeding, effects that are desirable in a contraceptive IUD. In a preliminary report, we noted that an AP-releasing IUD could inhibit the macaque endometrium [16]. Here, we describe the effects of AP-releasing IUDs (AP-IUDs) on endometrial growth and bleeding patterns in ovariectomized macaques during hormonally induced cycles.

2. Materials and methods

2.1. The macaque IUD

Prior to the experiments, we measured the distance from internal os to fundus, cervical length and uterine luminal diameter in a number of macaques. Based on these measurements, Leiras OY, Finland manufactured AP-IUDs (ZK 230 211) that consisted of straight Silastic tubes 1.2 cm in length that were either empty (controls) or filled with different amounts of steroid to allow release at either low-dose (LD; 3.3–4.5 μg/day) or high-dose (HD; 24.6–30.2 μg/day) rates. A thread, attached to each IUD was sewn through the myometrium to hold the IUD within the uterine lumen.

2.2. Animal species and insertion of IUDs

All animal care was provided by the Division of Animal Resources at the Oregon National Primate Research Center under protocols approved by the Institutional Animal Care and Use Committee. We initiated the study in stump-tailed macaques (*Macaca arctoides*) because of reports that their cervix is straight compared to the S-shaped cervix of other common laboratory macaques [17]. However, we found that the canal of the internal os in this species is not straight but sigmoidal, which made it impossible to reliably insert IUDs by the vaginal route. Consequently, we placed IUDs in the uterine lumen of all animals by hysterotomy and anchored the IUD in place by sewing the attached thread through the inner myometrial wall. Pig-tailed macques (*M. nemestrina*) were used when stump-tailed macaques became unavailable. Fig. 1 illustrates the position of an AP-IUD in the uterine lumen.

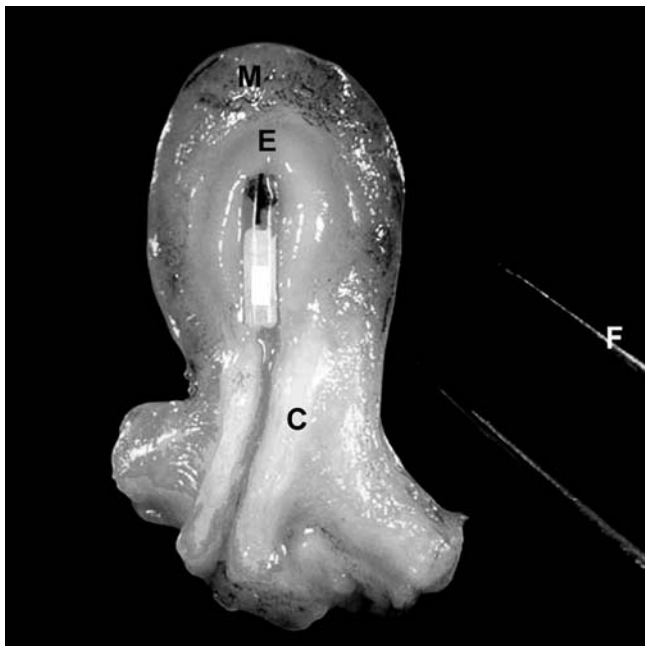

Fig. 1. An AP-IUD in utero. The photograph shows an IUD in place within the uterine lumen of a pig-tailed macaque after hysterectomy. E, endometrium; M, myometrium; C, cervix; F, the tines of a Dumont #5 forceps for scale.

2.3. Experimental procedures

Nine animals including six stump-tailed and three pig-tailed macaques were ovariectomized and allowed to rest several weeks. All animals were treated sequentially first with an estradiol (E_2) silastic implant (6 cm) for 14 days and then a P silastic implant (9 cm) for 14 days to simulate a full cycle and induce an endometrium that would menstruate if P action was blocked. The E_2 implant remained in place continuously throughout all treatments in all animals. Serum samples were obtained from each animal biweekly to assess their E_2 and P levels.

On the 28th day of the cycle, the animals were randomly assigned to three groups, each containing three animals (two stump-tailed and one pig-tailed macaque). Each group of three received either blank IUDs (controls), LD or HD IUDs. All animals were checked daily for evidence of vaginal bleeding. If no blood was evident on the cage floor or in the perineum region, the vagina was swabbed with cotton-tipped swabs to detect spotting.

In all animals, the systemic P implant remained in place for the next 7 days, during which time, we recorded menstrual bleeding patterns to determine whether the AP-IUDs (compared to control IUDs) could induce menstrual bleeding in the P-primed endometrium. After 7 days, the P implants were removed, bleeding patterns were assessed and all animals were again hormonally cycled with sequential E_2 and P to induce a second 28-day cycle. Endometrial biopsies were taken from all animals on Day 28 to determine the histological effects of continuous treatment with the IUDs on endometrial growth and development. Subsequently, the P implant was removed, and all animals were hormonally cycled to induce a third cycle. At the end of the third cycle, P was removed and menstrual bleeding patterns were again assessed. After this point, all nine animals were treated solely with E_2 for 28 days to determine whether the proliferative effects of E_2 on the endometrium could be blocked by the AP-IUDs. On Day 28 of continuous E_2 treatment, all animals were necropsied. The entire reproductive tract was removed, the uterus was quartered along the longitudinal axis and cross-sections (2 mm thick) were cut from each quarter and prepared for immunocytochemistry (ICC) and