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Antiprogestins

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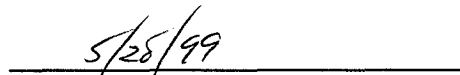
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13. ABSTRACT (Maximum 200) The goal of our research is to develop a technique for reversible menstrual suppression through use of antiprogestins. In the current year (Year 2) we have shown that the Schering antiprogestin ZK 137 316 can be administered continuously for 100 days to suppress overt menses in rhesus monkeys, and that the effects are fully reversible once treatment stops. We further conducted dose-finding trials with a new, more potent Schering antiprogestin, ZK 230 211, and defined a range of doses for future menses-suppression trials. ZK 230 211 has the virtue of being orally effective and will be the compound brought to the clinic by Schering. We also showed that vaginal administration of ZK 230 211 could be an effective mode of delivery due to the uterine first pass effect, and we began trials to fit intrauterine devices (IUDs) into rhesus monkeys for delivery of antiprogestins by IUD. Local delivery of antiprogestins by either vaginal administration or IUD would confine antiprogestin action to the uterus, minimize all systemic effects and provide useful alternative approaches to antiprogestin therapy. Finally, studies done in young rhesus females suggested that myometrial contracture plays a role in the inhibitory effects of antiprogestins on estrogen-driven endometrial proliferation.				
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FOREWORD

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INTRODUCTION

The goal of this research is to develop a safe, reversible method of menstrual suppression through antiprogestin therapy. Antiprogestins are synthetic ligands for the progesterone (P) receptor that antagonize P action. The compounds we are testing (ZK 137 316 and ZK 230 211) are manufactured by Schering AG, Berlin and are new generation compounds of enhanced potency and specificity. In year 1, we tested the ability of various doses of ZK 137 316 to inhibit menstruation in cycling rhesus monkeys during a short term trial. In that study we showed that administration of 0.1 and 0.05 mg ZK 137 316 /kg daily for 40 days would block frank menses.

In Year 2, as a natural extension of that work we tested long-term (100 day) ZK 137 316 regimens. Our goals were to determine if systemic administration of ZK 137 316 would continue to block menstruation for 100 days, and to ascertain if this treatment was reversible.

Additionally we evaluated the potency of ZK 230 211, a new Schering antiprogestin, investigated the possibility of local delivery of antiprogestins through either vaginal routes or IUDs, and began studies of the effects of antiprogestins in the uteri of young females. The latter studies aim to explore the mechanism underlying the so-called noncompetitive antiestrogenic effects (also called endometrial antiproliferative effects) of antiprogestins.

RESEARCH ACCOMPLISHED

1. Long term treatment

Animal care throughout these studies was provided by the Division of Animal Resources, at the Oregon Regional Primate Research Center (ORPRC) in accordance with the NIH "Guide for the Care and Use of Laboratory Animals." Untreated, adult cycling rhesus monkeys were monitored for 2 menstrual cycles to document normal cycle lengths for each animal. Beginning on the day after onset of the third menstruation the animals were injected i.m. daily for 100 days with ZK 137 316 dissolved in 37.5 % Hanks Balanced Salt Solution, 37% 1,2-propanediol, and 25% ethanol (HBSSPE). Control animals received vehicle only. Three groups (n=4 each) were treated: vehicle only (control), 0.05 mg/kg, and 0.1 mg/kg body weight. Daily vaginal swabs (to detect vaginal bleeding) were collected during the treatment period and daily blood samples were collected during the last 30 days of treatment and continued until the monkeys menstruated for longer than 2 days. The monkeys were further monitored for menses during the first post-treatment cycle. The experimental design is shown below:

Experimental design for long-term treatment

Pretreatment		Treatment (100 days)		Recovery	
Cycle 1	Cycle 2	Intermenstrual Interval		Cycle 1	Cycle 2
Mense	Mense	Mense		Mense	Mense

Blood samples from both experiments were analyzed for concentrations of E₂ and P by routine radioimmunoassay, performed by the ORPRC Hormone Assay Core (1). Lengths of the pre-treatment menstrual cycles, treatment-induced inter-menses interval, length of the recovery period (time to return to menses), post-treatment menstrual cycle length and serum hormone levels were compared between treatment groups. Statistical comparison of

intermenstrual interval between groups was done by analysis of variance, followed by Fisher's Protected LSD Test (2).

Results. No untoward effects of ZK 137 316 treatment were detected in the monkeys during the study. Effect of long-term ZK 137 316 treatment on menstrual cycle length are presented in Table 1. All of the monkeys exhibited normal pretreatment menstrual cycles. Injection with ZK 137 316 blocked menstruation and significantly extended the intermenstrual interval in all of the monkeys during the treatment period. Mean ($\pm$ SE) treatment intermenstrual interval in the control, 0.05 and 0.1mg/kg groups were 28.1 ± 0.83 , 131.1 ± 10.1 and 134 ± 8.7 days, respectively ($P < 0.001$). During the last 30 days of treatment the monkeys in the control group expressed normal menstrual cycle patterns of E_2 and P (Figure 1). In addition, all of the monkeys in the 0.05 mg/kg ZK 137 316 group, (n=4) had normal follicular phase levels of E_2 (including an E_2 surge) and normal luteal phase levels of P. In this group, ZK suppressed menstruation despite normal decline in luteal phase P at the end of the cycle. However all of the monkeys in the 0.1 mg/kg group failed to develop either a normal E_2 surge or normal luteal phase levels of P. Despite blockade of ovulation in this group, all of the monkeys showed normal nonsurge levels of E_2 (~30-100 pg/ml). Posttreatment cycle lengths were normal in all of the groups (29.8 ± 3.0 days).

Table1. Effect of ZK 137 316 treatment for 100 days on intermenstrual interval in cycling rhesus monkeys¹.

	Control	0.05 mg ZK 137 316	0.1 mg ZK 137 316
Pretreatment cycle lengths	28.0 ± 1.0^a	31.6 ± 1.46^a	28.7 ± 0.76^a
Treatment- induced intermenstrual interval	28.1 ± 0.83^a	131 ± 10.1^b	134.3 ± 8.72^b
Post-treatment cycle lengths	28.3 ± 0.47^a	29.6 ± 3.6^a	30.8 ± 1.55^a

¹ Values represent mean ($\pm$ SE) intermenstrual interval in days. Means with different superscripts are statistically different ($P < 0.001$).

2. DOSE FINDING STUDIES WITH ZK 230 211

ZK 230 211 is a new generation antiprogesterin that has several features that make it an ideal drug for studies of menstruation control. First, ZK 230 211 is a pure antiprogesterin that is more potent than ZK 137 316 or RU 486, suggesting that lower doses may effectively inhibit menses. Second, ZK 230 211 can be administered orally, as well as systemically, which is essential for future clinical trials. Lastly, preliminary studies conducted by Schering AG in rodents and cynomolgus monkeys suggest that ZK 230 211 may have a greater effect on the endometrium than the ovary, thus reducing the chances that antiprogesterin therapy would block ovulation and alter the steroid hormone milieu. We anticipate that all new studies in years 3 and 4 of this contract will be conducted with ZK 230 211.

The induction of menstruation in $E_2 + P$ stimulated monkeys is a convenient, non-invasive method for evaluating the potency of an antiprogestin. Efficacy is assessed by administering the test compound to ovariectomized animals whose endometrium is maintained by continuous treatment with $E_2 + P$. Successful blockade of P action is indicated by induction of menstrual bleeding. We performed menses-induction studies with ZK 230 211 as follows.

Artificial cycles were initiated in ovariectomized monkeys by inserting a 3 cm Silastic capsule (0.34 cm i.d.; 0.64 cm o.d.; Dow Corning, Midland MI) packed with crystalline E_2 (Steraloids, Inc., Wilton, NH) for 14 days to produce an artificial follicular phase. After 14 days of E_2 priming, a 6 cm Silastic capsule containing crystalline P (Steraloids Inc.) was inserted s.c. for 14 days to stimulate an artificial luteal phase. ZK 230 211 was dissolved in HBSSPE. Beginning on day 14 of the artificial luteal phase, the monkeys were injected daily with ZK 230 211 (i.m.) in vehicle for 7 days. Five doses of ZK 230 211 (mg/kg) were tested: 0.005 mg ZK 230 211 (n=2), 0.01 mg ZK 230 211 (n=4), 0.03 mg ZK 230 211 (n=4), 0.05 (n=2), and 0.1 mg ZK 230 211 (n=2). Vaginal swabs were performed daily for 9 days and the ability of the various doses to induce frank, overt menses (blood detectable in the cage and on the external genitalia) or minor bleeding detectable only by vaginal swab was recorded.

Results. Table 3 shows a summary of the effects of various doses of ZK 137 316 on menses induction in spayed, artificially cycled monkeys. Serum levels of E_2 and P in these monkeys were 103 ± 39 pg/ml and 4.09 ± 0.6 , respectively. ZK 230 211 treatment at 0.005 mg/kg did not induce either menses or vaginal bleeding, 0.01 mg induced vaginal bleeding in one monkey and mense in one monkey, while 0.03, 0.05 and 0.1 mg/kg consistently induced menses in all animals.

Table 2. Effects of various doses of ZK 230 211 on menstruation in artificially cycled monkeys after 14 days of E_2 plus P treatment.¹

	Days Observed								
	1	2	3	4	5	6	7	8	9
0.005 mg ZK 230 211 /kg (n=2)	U	U	U	U	U	U	U	U	U
0.01 mg ZK 230 211 /kg (n=4)	U	U	U	U	M n=1	S n=1	U	U	U
0.03 mg ZK 230 211 /kg (n=4)	U	U	U	S n=4	M n=4	M n=4	S n=4	U	U
0.05 mg ZK 230 211 /kg (n=2)	U	U	S n=2	M n=2	M n=2	M n=2	M n=2	U	U
0.1 mg ZK 230 211 (n=2)	U	U	S n=2	S n=2	M n=2	M n=2	M n=2	M n=2	S n=2

¹ U indicates menses undetectable. S indicates minute bleeding detectable by vaginal swab only. M frank menses detectable externally. N in parentheses indicate the number of monkeys within each group. N in each box indicate those showing bleeding or menstruation.

These results provide a full range of effects, from no effect at 0.005 mg/kg to full blockade of P action (greater than 0.01 mg) in all animals. Based on these findings we plan to test doses ranging from 0.01-0.05 mg ZK 230 211/ kg as menses-suppressing doses in cycling monkeys during year 3.

3. LOCAL DELIVERY OF ANTIPROGESTINS VIA VAGINAL GEL PREPARATIONS AND INTRAUTERINE DEVICES.

Overall the evidence indicates that chronic, systemic antiprogesterin therapy can block the key endometrial effects of both estrogens and progestins, suppress endometrial growth and development, inhibit endometrial bleeding and act as a contraceptive. While low doses (e.g. 0.01-0.03 mg ZK 137 316/kg) have these effects without affecting ovarian cyclicity, somewhat higher doses (e.g. 0.05-0.1 mg ZK 137 316/kg) may be antiovarulatory. Our goal is to achieve effective local concentrations of antiprogesterins (to block the endometrium and menstruation) without producing significant systemic effects. Consequently we have begun studies with both vaginal administration and dosing by intrauterine device in rhesus macaques as follows.

a. Vaginal administration of antiprogesterins

Ovariectomized monkeys were treated systemically with implants of E_2 and P (as described above) to produce secretory endometrium in order to test the effects of various doses of vaginally delivered P and antiprogesterin on the endometrium.

In our first experiments we evaluated Replens™, an over-the-counter vaginal lubricant, as a solvent for P to determine whether Replens™, would serve as well as Crinone™ (Wyeth), a proprietary vehicle (3) known to facilitate the absorption of P by the vaginal mucosa. Three groups (n=3 each) of E_2 + P-treated monkeys were treated with Replens™, containing 6 mg, 10 mg and 20 mg P daily for 7 days. On day 2 of vaginal P treatment, the P implant was withdrawn from each monkey, and the ability of these preparations to block menstruation was monitored by daily vaginal swabbing. An effective dose would be one that blocked P-withdrawal menses by elevating P concentrations within the endometrium.

In a second experiment, 2 groups (n=3 each) of E_2 + P treated monkeys were treated for 5 days with 6 and 10 mg of ZK 230 211 in Replens™ daily. The ability of these doses to induce menses was monitored daily by vaginal swab. Finally, we tested the endometrial suppressive ability of 10 mg ZK 230 211 administered vaginally every day for 19 days in either E_2 or E_2 + P-treated animals.

Results. Daily administration of vaginal gels containing 20 mg P per monkey prevented the menses that normally follows P implant withdrawal without producing serum P levels in these monkeys greater than 0.5 ng/ml. We concluded that Replens™ was a suitable vehicle for vaginal administration of effective levels of P.

Daily treatment for 5 days with Replens™ gels containing 10 mg ZK 230 211/ monkey induced menses in animals whose secretory endometrium was being maintained by sustained systemic E_2 + P treatment. This clearly indicated that Replens™ was also a suitable vehicle for vaginal administration of antiprogesterins, as this treatment induced menses in animals with high systemic levels of P. Additionally we showed that chronic treatment for 19 days with daily vaginal administration of 10 mg ZK 230 211/monkey in the presence of either E_2 alone or E_2 + P suppressed ability of E_2 to stimulate full proliferation of the endometrium as well as the ability

of $E_2 + P$ treatment to stimulate full secretory differentiation of the endometrium. These results (see Figure 2) are similar to what has previously been found with systemic administration of antiprogestins. Taken together these data show that the vaginal route of administration can produce physiologically effective levels of both steroids and antisteroids in the endometrium of the rhesus macaque. Further analysis of vaginal administration of antiprogestins will be pursued in Years 3 and 4.

b. STUDIES WITH IUDS.

For IUD experiments we have used stumptailed macaques because they have an elongate straight cervix and a very large uterus. To date, we have found that an IUD 1.5 cm long and 0.3 cm diameter fully filled the endometrial lumen (Fig 3). Production of antiprogesterin-releasing devices of this size is currently underway at Leiras, a Finnish subsidiary of Schering, and the first prototypes are expected in Oregon by November-December, 1998. These prototypes will be designed to release 1 ug/day ZK 230 211 and should provide highly effective concentrations of antiprogesterin within the uterine lumen. Because the internal opening of the cervix in this and other macaque species is very small, IUD placements in macaques have been done by hysterotomy. We are currently determining the most effective technique for IUD placement in stumptailed and other macaque species.

4. FAILURE OF ANTIPROGESTINS TO BLOCK ESTROGEN EFFECTS ON ENDOMETRIAL PROLIFERATION IN UTERI OF YOUNG RHESUS MACAQUES

Young rhesus macaques have a uterus that is highly responsive to ovarian steroids. For example, menstrual cycles with normal endometrial growth and secretory development can be induced in one-year-old females by sequential $E_2 + P$ treatment. However, the myometrium of young animals is strikingly thin, perhaps one-tenth the thickness of the adult myometrium. Based on our previous work (4), we hypothesized that antiprogestins may act in part by stimulating a chronic myometrial contracture, and that the consequences of such contracture, specifically tissue compression and/or reduction in blood flow may underlie the antiproliferative effects of antiprogestins. If this were correct, the thin myometrium of young females may not contract sufficiently to produce the effects seen in adults. To test this hypothesis, we treated spayed estrogen-primed one year old rhesus macaques with E_2 plus either 1 mg/kg RU486 or vehicle for 14 days.

As predicted by our hypothesis, this dose of RU 486, which dramatically inhibits the effects of estrogen in the uterus of adult rhesus macaques, failed to suppress endometrial mass or proliferation in young macaques: there was no difference between RU 486 and vehicle controls in endometrial mass or proliferation. These results indicate that the uterus of the young female is highly resistant to the "noncompetitive antiestrogenic" effects of antiprogestins. Whether this resistance is due to the thin myometrium or to some other property of the young uterus remains to be determined. We intend to pursue research with antiprogestins in young female rhesus macaques in future years.

CONCLUSIONS

We have now conducted both short-term and long-term menses suppression trials with a wide range of doses of ZK 137 316 in rhesus monkeys and have identified a range of doses that will fully block frank menses in intact cycling animals. We have further shown that this treatment is fully reversible and that the monkeys regain normal menstrual cyclicity beginning with their first menstruation following treatment.

Long-term treatment with ZK 137 316 at both 0.05 and 0.1 mg/kg permitted E₂ surges, and E₂ concentrations within the normal range for rhesus monkeys. This indicates that antiprogesterin treated animals had ample E₂ to maintain the integrity of estrogen target systems (e.g. bone, reproductive tract, heart and circulatory system, vaginal mucosa, etc.) However, the higher doses of antiprogesterins given for longer periods blocked ovulation in many animals. This suggests that effective menses-suppressing doses of ZK 137 316 are very close to the doses that block ovulation. Although the level of E₂ in such animals was within normal physiological ranges, it would be desirable to develop a therapy that had no effects on ovarian physiology.

ZK 230 211 is a new antiprogesterin that is orally active and may have fewer ovarian effects than ZK 137 316. We have started evaluating this new drug as a therapy for menses suppression. Clearly lower doses of ZK 230 211 (0.01 mg ZK 230 211 versus 0.03 mg ZK 137 316 /kg) block P action in the endometrium of artificially cycled animals. Therefore In year 3 we will test the ability of these low doses of ZK 230 211 to suppress menses in naturally cycling monkeys.

In several earlier studies we have shown that treatment with antiprogesterins act to both block P action and to inhibit estrogen stimulation of the endometrium. These effects are marked by increased stromal compaction, apoptosis and inhibition of endometrial development. We have now found that these inhibitory effects can be achieved by vaginal administration of ZK 230 211, and are preparing to conduct further tests of intrauterine delivery of antiprogesterins.

The uteri of young rhesus female macaques show resistance to the noncompetitive antiestrogenic actions of antiprogesterins. The underlying reasons for this striking difference between the uteri of young versus adult macaques will be investigated.

In summary, our future studies will center on the action of the new antiprogesterin ZK 230 211, on novel modes of local delivery, and on the mechanism of action of antiprogesterins in the macaque uterus. Our results already indicate that a safe, reversible antiprogesterin therapy to suppress menstruation in women for either short or moderately long periods is feasible.

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Figure 1

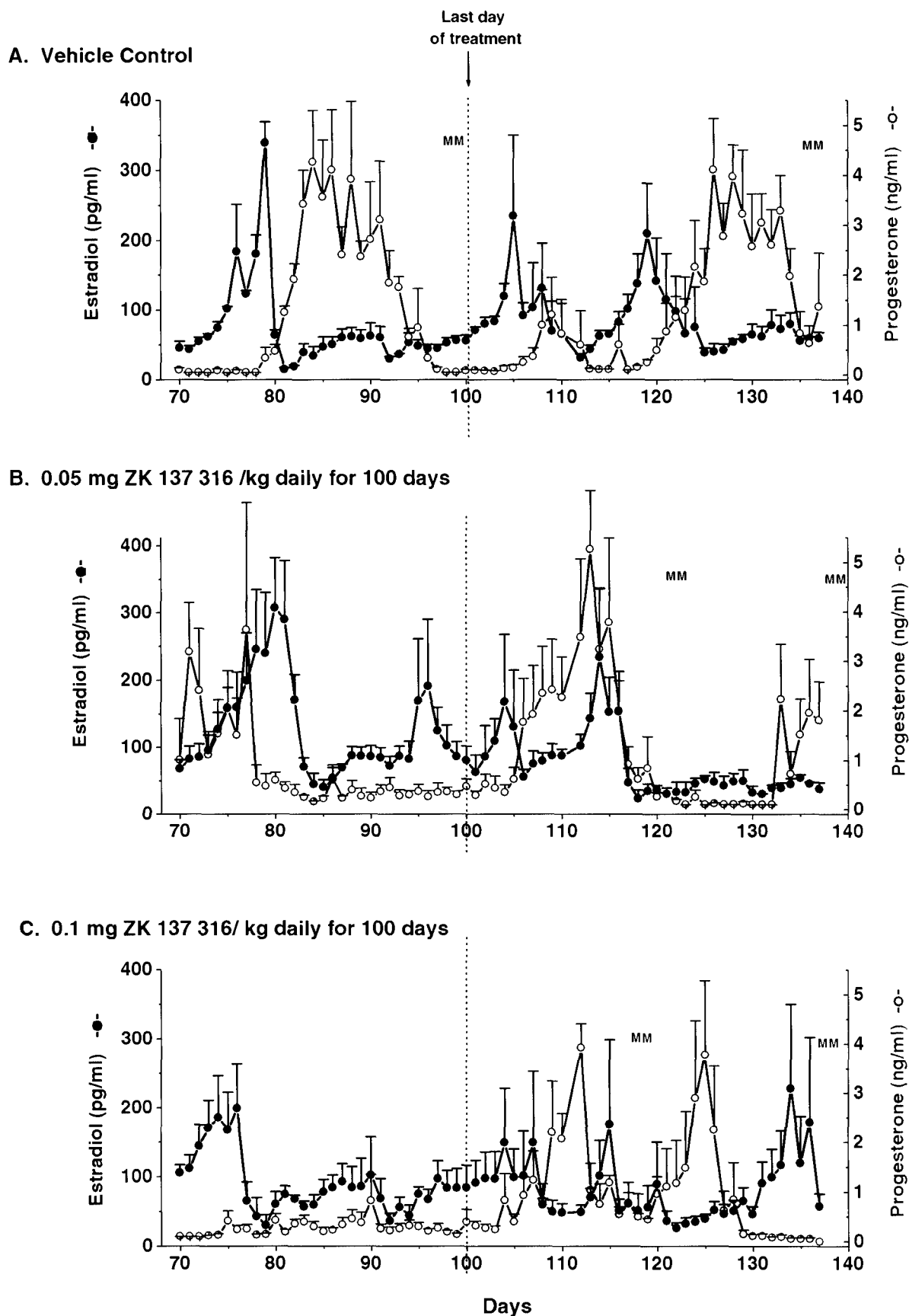


Figure 1

Serum profiles of estradiol (BLACK) and progesterone (RED) during and after the last month of a 100 day treatment with ZK 137 316.

Figure 2

Histological sections showing effects of vaginally administered ZK 200 211 on both estradiol and progesterone action in the rhesus macaque endometrium.

- a: E2 treatment for 21 days. Normal glandular/stromal development.
- b. E2 + ZK 200 211 for 19 days. Growth is inhibited, stroma compacted and glands dilated.
- c. E2 for 14 days, E2+P for 21 days. Normal progestational development
- d. E2 for 14 days, E2+P+ZK 200 211 for 19 days. Progestational development was inhibited, stroma compacted and glands nonsacculated.

Figure 2

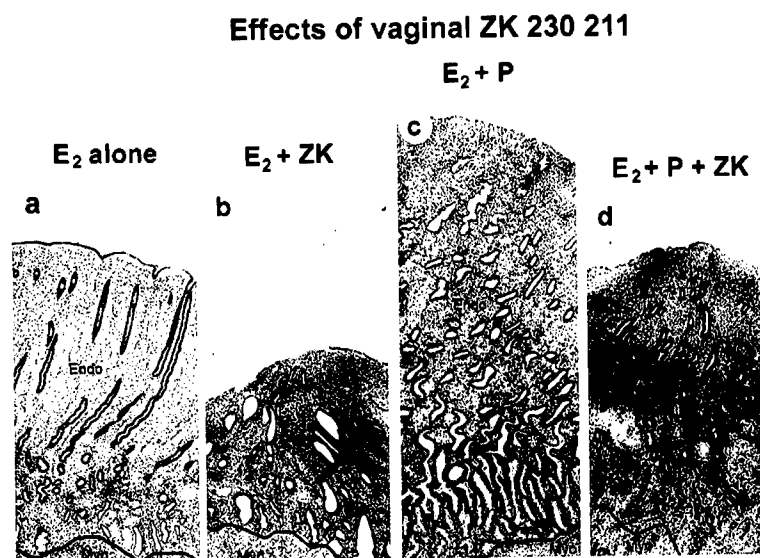
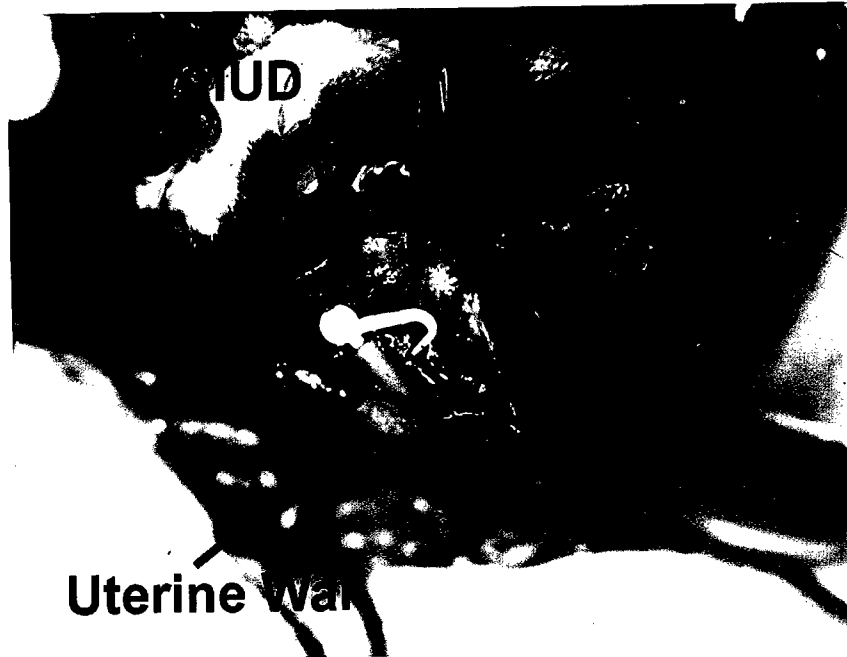


Figure 3



Placement of a "macaque size" IUD by hysterotomy in the uterus of a stumptailed macaque (*Macaca arctoides*). Photo taken during surgery.



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