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30. Contraception

THE PLACE OF PROGESTERONE IN HUMAN CONTRACEPTION

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Summary—Progesterone, the natural hormone produced by the corpus luteum and other steroid-secreting glands, is endowed with antiestrogenic action and has a fundamental role in the initiation and maintenance of pregnancy and in the regulation of gonadotropin secretion. Although it was discovered half a century ago, it has found little clinical use as a therapeutic agent due to its low potency and extensive degradation following oral administration in comparison with a variety of highly potent synthetic analogs that became available in the last three decades.

When delivered systemically, a large proportion of the dose bypasses degradation in the gut and liver, and progesterone can achieve effective levels in target tissues for clinical use. Sustained administration via compressed pellets implanted subdermally or silicone rubber rings placed in the vagina produced circulating levels of progesterone within the lower third of those found in the luteal phase of the human menstrual cycle. Those levels were shown to delay the recovery of fertility in nursing women without adverse effects to the mother or the infant. Progesterone transferred to the babies via the breast milk did not change their rate of pregnandiol-3-alpha glucuronide excretion. It is concluded that sustained administration of the natural hormone progesterone may be an effective and safe contraceptive method for nursing women.

Work leading to the discovery of the hormone of the corpus luteum was started at the onset of this century by Fraenkel and culminated by the end of the third decade with the discoveries of Corner and Allen[1]. Its essential role in the establishment and maintenance of pregnancy led to its being named progesterone [2]. This function of the hormone suggested that progesterone administration could be used to help fertility, but no-one anticipated at that time that it could be used to prevent pregnancy. Notwithstanding, over the next 25 yr it was discovered that exogenous progesterone could inhibit ovulation and that this property was potentially applicable to control fertility [3]. Unfortunately, due to its short half-life and extensive degradation following ingestion it was only effective if given orally at very high doses (300 mg daily) or by frequent injections [4]. The obvious inconvenience of both alternatives stimulated the search for orally active synthetic progestins. As they became available, these progestins replaced progesterone from the therapeutic scene and in due time entered as components of the contraceptive pill and subsequent steroid contraceptive formulations. Although progesterone was never used in contraceptive pills, it played an indirect role in contraceptive development by inspiring the use of more potent orally active progestins or long-lasting injectable substitutes to suppress ovulation.

Several delivery systems, different from intramuscular injection, have been attempted to circumvent the gastrointestinal and hepatic routes of entry of progesterone for obtaining systemic effects. These include rectal and vaginal suppositories [7] and vaginal rings of silicone rubber impregnated with progesterone [8–11]. In these studies, blood levels of the hormone were used to monitor absorption from the rectal or vaginal site. Suppositories containing 25 mg or more were able to replicate luteal phase plasma levels, but only for 6–8 h [7]. In a menopausal woman treated for 2 weeks with a vaginal ring releasing 2.2 mg/day the plasma progesterone concentration increased to a level between 1.5 and 2.0 ng/ml during treatment [8]. Other vaginal rings expected to release nearly 10 mg/day for 90 days were able to maintain levels around 4 ng/ml during the follicular phase. These levels did not inhibit ovulation in all women [9].

Although these studies did not demonstrate the feasibility of suppressing fertility in women with these methods of progesterone administration, they suggested that "at higher doses the Silastic vaginal ring offers a mode of administration of natural steroids to be used in hormonal contraception" [8].

It was not until the early seventies that progesterone was used as such for contraception, based on its ability to antagonize the endometrial proliferation induced by estrogen in the human uterus. Progesterone released at a rate of 65 μg/day from an intrauterine device was shown to prevent pregnancy with an efficacy comparable to that of oral contraceptives [5] and without exerting systemic effects [6].

Progesterone administration was thought to be an adequate contraceptive method for lactating women [14, 15]. What represents a disadvantage for therapeutic use, that is, being practically inactive by the oral route, could also be considered a major advantage during breastfeeding, because the infant would be free of the influence of the drug excreted in milk. It was also assumed, based on experience with other pure progestin contraceptives, that proges-

terone should not interfere with breast-feeding [12, 13]. Additionally, progesterone is well tolerated and expected to be innocuous for the mother.

Research was conducted to find an adequate delivery system for long-term progesterone administration, to identify a dose that would inhibit fertility during the breastfeeding period and to assess the influence of the steroid on lactation, infant growth and maternal and infant health.

The first delivery system tested was the subdermal implantation of compressed pellets each containing 100 mg of pure progesterone. The pilot study showed that insertion of 2, 4 or 6 pellets caused an initial elevation of plasma progesterone around 6, 10 and 14 nmol/l, respectively. This elevation was followed by a gradual decline so that basal levels were attained at 70, 100 and 150 days after insertion of 2, 4 or 6 pellets respectively [14]. The dose of six compressed pellets was chosen to test the effects upon fertility in lactating women.

In 1982 we reported that subdermal implantation of six progesterone pellets inhibited the recovery of fertility in lactating women [15]. In an enlarged clinical trial [16] one pregnancy was recorded in 1614 woman-months of exposure, a failure rate similar to that observed at the same time in a group of Copper T users. This contrasted with the fertility of a comparable group of untreated nursing women where 19 pregnancies were diagnosed during 677 woman-months of observation. The progesterone implants were effective when administered either at 30, 60 or 240 days after delivery. The duration of their effective life was 5 months and fertility was quickly restored thereafter. There were no adverse effects upon maternal or infant health or upon lactation and the rate of child growth. The main problem encountered was the occurrence of pellet expulsion at a variable rate apparently related to the manufacturing process.

The transfer of exogenous progesterone from the mother to the infant through the milk was assessed in women treated with six progesterone pellets at day 60 postpartum. Users of a Copper T device served as controls. The concentration of pregnanediol-3-alpha-glucuronide in the infant urine was assessed as an indirect indicator of the steroid transfer.

The average progesterone values found in maternal blood and milk and the average pregnanediol-3-alpha-glucuronide found in children's urine are shown in Fig. 1. Progesterone was found in the milk of women with progesterone pellets at an average level of 20 and 18 nmol/l during the 2 months following the first and second insertion respectively. These values are very close to the average levels observed in the contemporary plasma samples. Only minimal amounts of progesterone were detected in the milk of control women. The average level of progesterone was slightly higher in the plasma than in the milk of control women after the 6th postpartum month. This is due to the presence of ovulatory values in four plasma samples. Milk was collected in only one of these subjects, and progesterone concentration was almost the same in both fluids. The average urinary excretion of pregnanediol-3-alpha-glucuronide was around 20 nmol/l in infants from both treated and control groups up to the 6th month of age and rose to an average level around 50 nmol/l in both groups thereafter. Neither differences between groups nor any relationships between the average plasma or milk concentration of progesterone in the mother and pregnanediol-3-alpha-glucuronide excretion by the child were found.

The calculated daily amount of progesterone transferred to the nursing infant (5 μg) appeared too low to be reflected by an increase in pregnanediol-3-alpha-glucuronide concentration in the urine and was judged to entail no risk for the child [17].

In a subsequent trial, Silastic vaginal rings delivering 5 or 10 mg of progesterone per day were tested in nursing women [18]. Rings were inserted at

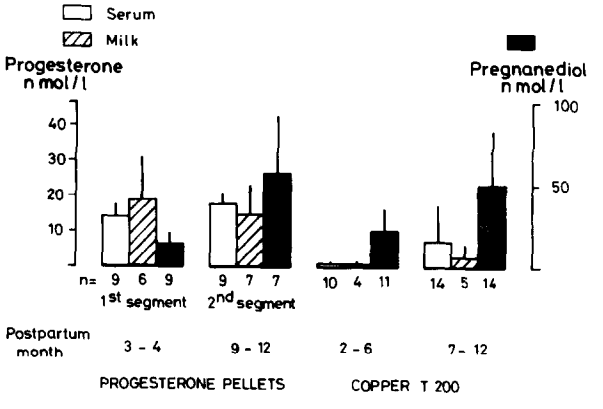

Fig. 1. Plasma and mild progesterone levels ($X \pm SE$) in nursing women treated with six progesterone pellets or a Copper T device and urinary excretion of pregnanediol-3-alpha-glucuronide by their breast-fed infants.

day 60 postpartum and replaced every 3 months with a new one. Progesterone plasma levels observed ranged from 15 nmol/l at 10 days after insertion to 10 nmol/l at 90 days for the ring releasing 10 mg/day, and were relatively constant around 10 nmol/l for the 5 mg ring, as shown in Fig. 2. Levels observed in subsequent segments of use approximated those of the first segment. One pregnancy was diagnosed in 1167 woman-months of progesterone ring use, which contrasts with the high incidence of pregnancy in a similar population of untreated nursing women [19]. This pregnancy occurred during the 5th postpartum month in a full nursing cycling woman who removed the ring for intercourse in day 12 of the cycle and did not reinsert it for more than 36 h [18].

The plasma progesterone levels required to inhibit fertility during breastfeeding are within the lower half of the normal luteal phase values. The high efficacy of such low levels poses interesting questions about the mode of action of steroids in the physiologic conditions associated to lactation. The low levels required represent also an advantage because no harmful side-effects for the mother can be expected from luteal phase progesterone value and because only minimal amounts are transferred to the infant through the milk.

In view of these findings we submit that progesterone is gaining a new place in human contraception. At the present time, systemic delivery systems of progesterone for nursing women are in various stages of development and include vaginal rings, injectable microspheres and coated biodegradable pellets. Furthermore, this application of progesterone in contraception inspires the idea that synthetic progestins, active systematically but not orally, combined with appropriate delivery systems, may become useful contraceptive agents for lactating women. The higher the ratio systemic:oral potency the more appropriate for this condition in which the infant is at risk of receiving via the breast milk the drugs taken by the mother. It is likely that progestins with these features were produced and discarded by the pharmaceutical industry during the years of intensive synthesis of orally active steroids. Considering that an average of 130 million births take place each year of the present decade [20], the potential consumer demand of contraceptives for the post-partum period justifies developing a variety of safe and effective methods adequate for the nursing women.

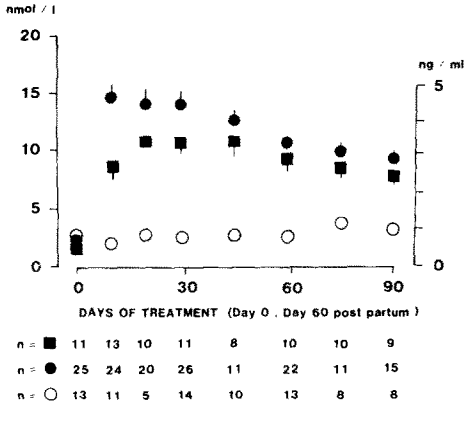

Fig. 2. Progesterone plasma levels ($X \pm SE$) in nursing women treated with progesterone-releasing vaginal rings. First segment of use. ●—CHP rings delivering 10 mg/day, ■—6P rings delivering 5 mg/day, ○—untreated. day 0—day of ring insertion (day 60 postpartum). Reproduction from Ref. [18]

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