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Prospective randomized trial to evaluate the efficacy of a vaginal ring releasing progesterone for IVF and oocyte donation

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A polysyloxane vaginal ring containing 1 g of natural progesterone was developed as luteal supplementation for women treated with IVF–embryo transfer and for agonadal women participating in an oocyte donation programme. The ring provides continuous release of progesterone (10-20 nmol/l) for 90 days. The efficacy of this form of progesterone supplementation was evaluated in two multicentre prospective randomized trials. IVF–embryo transfer trial: After oocyte aspiration, 505 women were randomly allocated to progesterone supplementation with vaginal ring or i.m. progesterone (50 mg/day). The clinical pregnancy rate was 36.6% in both groups. Implantation rate was 15.9% in the vaginal ring and 16.0% in i.m. progesterone. Oocyte donation trial: After endometrial proliferation with micronized oestradiol, 153 women were allocated to progesterone replacement with a vaginal ring or i.m. progesterone (100 mg/day). Clinical pregnancy rate was 39.8 and 28.6% respectively. Implantation rate was significantly higher with the vaginal ring compared with i.m. progesterone (19.9 and 11.6% respectively, $P = 0.006$). The vaginal ring is a novel development which provides continuous release of progesterone for 90 days. In IVF–embryo transfer, its effectiveness is similar to daily i.m. injections. In oocyte donation the ring provides a progestative milieu which improves the implantation rate and eliminates the discomfort of daily i.m. injections.

Key words: IVF/oocyte donation/progesterone supplementation/vaginal ring

Introduction

Exogenous progesterone supplementation has been well established in the treatment of ovulatory dysfunction as well as in standard IVF–embryo transfer (Soliman *et al*., 1994). Furthermore, exogenous progesterone is mandatory as part of hormonal replacement therapy (HRT) in agonadal women subjected to IVF–embryo transfer after oocyte donation. Natural progesterone can be administered orally; however, due to its rapid clearance by the liver, its bioavailability in the circulation is low and therefore ineffective (Maxson and Hargrove, 1985). Moreover, metabolites of orally administered progesterone may induce hypnotic effects (Arafat *et al*., 1988). A recent randomized study that compared oral versus i.m. progesterone showed significant decreases in implantation rates when using 600 mg of micronized (oral) progesterone (Licciardi *et al*., 1999). Oral administration of micronized progesterone has also been compared with the vaginal route, also showing significant reduction in implantation rate (Friedler *et al*., 1999). To date, the i.m. route remains the most widely used form of progesterone replacement. Although i.m. progesterone has been proved to be effective as luteal support, its rapid clearance from circulation requires daily injections for ~30 days in IVF–embryo transfer and 100 days in oocyte donation. In the past few years, micronized progesterone formulated in capsules has been used to release the hormone through the vagina. This delivery system has been successful in the preparation of the endometrium for implantation. The dose required is ~600-800 mg per day, requiring the insertion of progesterone tablets in the vagina at least twice a day. In regular IVF, the vaginal route has been compared with parenteral administration; both exhibit similar pregnancy and implantation rates. However, a significant decrease in first trimester abortion was observed in women using the vaginal route (Smitz *et al*., 1992). A similar study (Perino *et al*. 1997) was conducted in 250 patients showing a significantly higher percentage of pregnancies in women using i.m. progesterone compared with micronized progesterone administered via vagina. In the last 3 years, a progesterone gel has also been successfully used, exhibiting similar pregnancy and delivery rates when compared with orally administered micronized progesterone (Pouly *et al*., 1996). A similar effect was reported when comparing the gel with i.m. progesterone (Gibbons *et al*., 1998).

In recent years, a polysyloxane vaginal ring with an external diameter of 60 mm and a cross-section of 9 mm was developed with the aim of delivering natural progesterone continuously (Jackanicz, 1983). This delivery system, which proved to be effective as a contraceptive for lactating women (Massai *et al*.,1999), was later re-formulated and used as luteal supplementation for women participating in (IVF–embryo transfer), and as the only source of progesterone in functionally agonadal women participating in oocyte donation. This vaginal ring contains 1 g of natural progesterone and its in-vitro release is 10 mg/day. When placed in the vagina, it provides continuous release of progesterone for as long as 90 days. In a previous study (Zegers-Hochschild *et al*., 1996), progesterone concentration in peripheral circulation and endometrial histology was

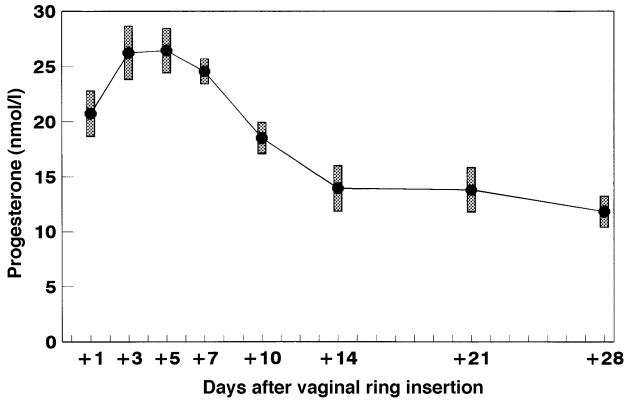

Figure 1. Plasma progesterone concentrations after vaginal ring insertion in eight women with premature ovarian failure, during a cycle prior to oocyte donation. Data from Zegers-Hochschild *et al.* (1996). Values correspond to mean ± SD.

studied in eight women with premature ovarian failure, during a cycle prior to oocyte donation. The vaginal ring was inserted after the endometrium had proliferated with a daily dose of oral oestradiol-17β (4 mg per day). While endogenous progesterone was <1 nmol/l before vaginal ring insertion, the mean ± SE of plasma progesterone measured 24 h after was 20.7 ± 2.1 and fell to 15.7 ± 0.3 nmol/l 18 days later (Figure 1).

Circulatory progesterone remains fairly stable thereafter (90 days), with minimum concentration of 10 nmol/l. Despite these low circulatory concentrations, in every case, endometrial histology (obtained 3 and 7 days after vaginal ring insertion) exhibited progestational transformation in glands and stroma similar to the luteal phase of a normal menstrual cycle, except for an advancement in stromal oedema and perivascular decidual reaction (Zegers-Hochschild *et al.*, 1996).

The objective of this study was to evaluate the efficacy in the establishment and maintenance of pregnancy of this vaginal ring when compared with daily i.m. injections of progesterone in women treated with IVF–embryo transfer and oocyte donation.

Materials and methods

This is a prospective randomized study conducted in the Red Latinoamericana de Reproducción Asistida. It included three affiliated centres located in Santiago, Chile; Bogotá, Colombia and Sao Paulo, Brazil. In all centres, patients were recruited among those participating in either IVF–embryo transfer or intracytoplasmic sperm injection (ICSI). Inclusion criteria included all diagnostic categories irrespective of the age of female partners. Patients with premature ovarian failure or lack of response to ovarian stimulation, were recruited for the oocyte donation programme, after being adequately informed and with appropriate consent provided to the principal investigator or a designated professional. Each centre used simple randomization tables.

IVF–embryo transfer trial

A total of 505 patients participated in this study. All patients were subjected to ovarian stimulation, which included daily s.c. injections of leuprolide acetate starting in the luteal phase of the previous cycle, or after discontinuing oral contraceptives. The time of exposure to the agonist prior to ovarian stimulation varied between patients, depending on clinical judgement and the need to coordinate dates of follicular aspiration. Follicular recruitment and maturation was induced with variable doses of human menopausal gonadotrophin (HMG), starting on the second or third day of menstruation and maintained until at least three follicles were 16 mm in diameter. Daily doses were established according to clinical judgement, based on the number of follicles, their size and plasma oestradiol. Follicular aspiration was performed 36 h after exposure to 10 000 IU of human chorionic gonadotrophin (HCG). Embryos were transferred to the uterine cavity 48-72 h after follicular aspiration. On the day of oocyte retrieval, patients were randomly allocated to either i.m. progesterone (50 mg/day) or a vaginal ring containing 1 g of progesterone. Plasma HCG was measured 12 days after embryo transfer. If pregnancy was documented the vaginal ring (Laboratorio Silesia S.A., Santiago, Chile) was left *in situ* for 5 more weeks. Patients allocated to i.m. progesterone continued daily injections for the same length of time. Transvaginal ultrasounds were performed 3 and 5 weeks after embryo transfer. A clinical pregnancy was diagnosed after sonographic visualization of an intrauterine gestational sac. Multiple gestation was diagnosed when two or more gestational sacs were visualized 5 weeks after embryo transfer.

Table I. Age distribution and number of embryos transferred in women using vaginal ring or i.m. progesterone

Age of female partner (years)	Vaginal ring		Progesterone i.m.	
	% of patients	No. embryos transferred	% of patients	No. embryos transferred
<35	53.6	3.5 ± 1.1	57.1	3.7 ± 1.1
35-39	36.8	3.9 ± 1.4	31.5	3.7 ± 1.4
≥40	9.6	3.9 ± 2.0	11.4	4.1 ± 2.1

Numbers are means ± SD.

Oocyte donation trial

A total of 153 patients with either premature ovarian failure or repeated failure to respond to ovarian stimulation were subjected to HRT for oocyte donation. Endometrial proliferation was induced with a fixed oral dose of micronized oestradiol-17β, (4 to 6 mg/day). On the day of follicular aspiration in the oocyte donors, recipients were allocated either to i.m. progesterone, 100 mg/day (n = 70) or to a vaginal ring containing 1 g of natural progesterone (n = 83). Oral concentration of oestradiol was maintained at a fixed dose throughout the treatment period. If pregnancy was documented (12 days after embryo transfer), the vaginal ring was replaced by a new ring containing 2 g of progesterone which was left in the vagina for 7 weeks.

After proper consent, fresh oocytes were donated by women under 35 years of age who were simultaneously participating in an IVF–embryo transfer programme. Consent forms were also signed by oocyte recipients.

For both trials, comparisons were performed on the clinical pregnancy and live birth delivery rates after embryo transfer and implantation rates (number of gestational sacs/ number of embryos transferred) according to the age of the female partner. Statistical analysis used χ^2 and Fisher tests.

Results

IVF-embryo transfer trial

In all, 243 patients were included in the vaginal ring group and 262 in the injectable group. Age distribution and the mean number of embryos transferred in each group showed no

Table II. Overall results of the IVF–embryo transfer trial

	Vaginal ring	Progesterone i.m.
No. of patients	243	262
No. of pregnancies	89	96
Embryos transferred (mean)	3.73	3.72
Clinical pregnancy rate/transfer (%)	36.6	36.6
Implantation rate (%)	15.9	16.0
Implantation rate (within pregnant patients) (%)	41.4	41.2
Multiple pregnancy rate (%)	42.0	41.1
Live birth delivery rate/transfer (%)	31.7	30.9

significant difference. The median age of the female partner in both groups was 34 years (Table I).

Overall, the clinical pregnancy and implantation rates were similar in women using either vaginal ring or i.m. progesterone (36.6, 15.9%; and 36.6, 16.0% respectively). Furthermore, implantation rates within pregnant patients were also similar in both groups (41.4% and 41.2% respectively). Multiple pregnancy rate in the vaginal ring was 42.0% (22.7% twins, 19.3% triplets or more), and 41.1% (24.2% twins, 16.9% triplets or more) in women using i.m. progesterone (Table II).

When grouping the clinical pregnancy rate and implantation rates according to the age of the female partner, differences in these markers were not significant. Only patients with complete information have been included in this analysis (221 patients using vaginal ring and 238 using i.m. progesterone) (Table III).

The outcome of clinical pregnancies is reported in Table IV. No differences were found in the rate of ectopic pregnancies, clinical abortions and deliveries with one or more live births.

Oocyte donation trial

The age (mean ± SD) of recipients using vaginal ring and i.m. progesterone was 39.2 ± 5.2 and 38 ± 4.5, respectively. A mean of 3.4 and 3.5 fresh embryos were transferred in the vaginal ring and injectable groups, respectively.

Overall results are provided in Table V. The clinical pregnancy rate was not significantly higher in women using vaginal ring over i.m. progesterone, (39.8 and 28.6% respectively). However, the implantation rate was significantly higher in patients using vaginal ring, 19.9% compared to 11.6% for i.m. progesterone ($P = 0.006$). When donors achieved a pregnancy, implantation rate in their simultaneous recipients was 29.9% (23/77) in vaginal ring compared to 19.7% (12/61) in i.m. progesterone. This difference did not reach statistical significance, probably due to the small number of embryos transferred in each group (23 pairs of patients). Similarly to the IVF–embryo transfer trial, multiple pregnancy rates were as high in vaginal ring users as in i.m. progesterone (42.4 and 41.1% respectively).

The outcome of clinical pregnancies is reported in Table VI.

None of the patients receiving HRT for oocyte donation had uterine bleeding during their medication, irrespective of the presence or absence of pregnancy. In contrast, ~30% of IVF women had vaginal bleeding or at least 1 or 2 days of intermittent brownish discharge that started 8-12 days after embryo transfer. In 33% of these women, endometrial bleeding coincided with positive values of HCG. This condition did not seem to interfere with the outcome of pregnancy. In fact, none of the spontaneous clinical abortions in the vaginal ring group was preceeded by early uterine bleeding. Due to the fact that it had not been envisaged that endometrial spotting could be a problem, patients were not asked to record their bleeding patterns. Nevertheless, none of the pregnant patients continued bleeding 4 weeks after embryo transfer, irrespective of whether supplementary progesterone was added.

Discussion

The polysyloxane vaginal ring is a novel development that provides continuous release of natural progesterone for 90 days. Because of its flexibility, a professional or the patient may easily place it in the vagina. In oocyte donation, where the source of oocytes is more homogenous (donated by women <35 years and good responders), the quality of the endometrium can be better isolated as an independent variable. In these cases, the implantation rate was significantly higher in vaginal ring users (Table V; $P = 0.006$). Although not statistically significant, the implantation rate in a subgroup of only pregnant patients was also higher in vaginal ring users (46.3%) compared with 39.4% in women using i.m. progesterone. Similarly, when analysing implantation rates in a group of oocyte recipients whose donors had conceived during a simultaneous IVF cycle, the implantation rate was also higher in women using vaginal ring 29.9% (23/77) compared with 19.7% (12/61) in women using i.m. progesterone. These clinical studies strongly support the finding that when progesterone is released continuously via a vaginal ring, doses as low as 10 mg/day allow for embryo implantation and the continuation of pregnancy.

It has been well established that when progesterone is released from the vagina, the concentration reached in endometrial tissue is far greater than when the hormone is administered i.m. (Miles *et al*., 1994). In women treated with oocyte donation, exogenous progesterone is the only source of the hormone. When using the ring, its concentration in peripheral circulation (10-20 nmol/l) is much lower than the concentration reached after 100 mg of i.m. progesterone (>80 nmol/l) or progesterone concentration of 30-40 nmol/l found in the mid luteal phase of spontaneous conception cycles (Zegers-Hochschild, 1988). When the vaginal route is used to deliver progesterone, measurement of circulatory concentrations is therefore quite meaningless. This study supports the concept of a 'first uterine pass effect' (Fanchin *et al*., 1997). Furthermore, this study demonstrates that when progesterone is delivered in the vagina, circulatory concentrations do not have to mimic the hormonal concentration found in normal ovulatory cycles. In fact, much less is required to achieve endometrial maturation. The mechanisms by which progesterone released in the vagina reaches the uterine cavity in higher concentrations than peripheral circulation has been thoroughly reviewed (Cicinelli and de Ziegler, 1999). Progesterone concentration measured in the uterine vein in three women undergoing hysterectomy was three to seven times

Table III. Clinical pregnancy rate and implantation rate according to the type of treatment and age of female partner.

Age of female partner (years)	Vaginal ring				Progesterone i.m.			
	n	Clinical pregnancy rate (%)	Implantation rate		*n*	Clinical pregnancy rate (%)	Implantation rate	
			n	%			*n*	%
<35	118	36.4	74/419	17.7	136	46.3	107/508	21.1
35-39	81	39.0	51/320	15.9	75	26.7	36/274	13.1
>40	21	9.5	5/82	6.1	27	18.5	5/111	4.5

Table IV. IVF–embryo transfer trial: outcome

	Vaginal ring	Progesterone i.m.
No. of pregnancies	89	96
Ectopic pregnancies (%)	1 (1.1)	1 (1.0)
Spontaneous abortion (%)	11 (12.4)	14 (14.6)
Deliveries with live birth (%)	77 (86.5)	81 (84.4)

Table V. Overall results of the oocyte donation trial

	Vaginal ring	Progesterone i.m.
No. of patients	83	70
No. of pregnancies	33	20
Embryos transferred (mean)	3.4	3.5
Clinical pregnancy rate (%)	39.8	28.6
Implantation rate (%)	19.9[a]	11.6
Implantation rate (within pregnant patients) (%)	46.3	39.4
Multiple pregnancy rate (%)	42.4	41.1
Live birth delivery rate/transfer (%)	32.5	21.4

[a]Significantly different from the implantation rate in patients using i.m. progesterone ($P = 0.006$).

Table VI. Oocyte donation trial: outcome

	Vaginal ring	Progesterone i.m.
No. of pregnancies	33	20
Ectopic pregnancies	0	0
Spontaneous abortion (%)	6 (18.2)	5 (25.0)
Deliveries with live birth (%)	27 (81.8)	15 (75.0)

higher than peripheral circulation after 24-36 h of exposure to the vaginal ring containing 1 g. The ratio of progesterone in uterine vein/antecubital vein was 67.1/22.6, 90.5/12.4 and 65.0/9.5 nmol/l. In two other cases where surgery was indicated because of large fibroids in the isthmus region and occupying part of the vagina, progesterone concentrations in the uterine and antecubital veins were not different (32.2/27.5 and 10.9/10.6 nmol/l).

In oocyte recipients, once pregnancy was documented; the ring containing 1 g was replaced with a new ring containing 2 g of progesterone. This decision was made after some initial cases (not included in this report) experienced uterine bleeding coinciding with pregnancy. Based exclusively on empirical grounds it was decided to increase progesterone concentration in the ring once conception was documented in oocyte recipients. None of these pregnant patients exposed to the ring containing 2 g had uterine bleeding during their gestation.

Although the overall efficacy of the vaginal ring in IVF–embryo transfer is not superior to the i.m. route, women prefer the ring as it avoids the discomfort of daily punctures and skin lesions derived from repeated injections. Moreover, in comparison with the use of micronized progesterone in tablets and progesterone gel, which have to be inserted in the vagina at least twice daily, the ring is placed in the vagina only once during the whole treatment period. Preliminary data of an acceptability trial conducted in 27 women that had used vaginal ring and i.m. progesterone in two different cycles demonstrated that, provided both treatments were understood by the patient as having the same efficacy, the majority of women would prefer vaginal ring to daily injections if exposed to a new treatment cycle.

Concerning endometrial bleeding in IVF patients, when the first value and doubling time of HCG was normal, the presence of vaginal spotting did not seem to interfere with the outcome of pregnancy. Some doctors, when exposed to vaginal spotting in the presence of positive HCG, increased progesterone either by adding i.m. progesterone, or changing to a ring containing 2 g of progesterone. Others just waited until spotting stopped. In many cases where progesterone was added, vaginal bleeding ceased, but this also happened without extra medication. Furthermore, since HCG was only measured from day 12 after embryo transfer, the number of biochemical pregnancies and their outcome is unknown. It will not be possible from this study to elucidate how to treat these cases or whether other forms or doses of hormonal supplementation are required to avoid bleeding.

The mechanism of uterine bleeding in IVF patients using the ring is not well understood. Bleeding does not take place when oestradiol or the oestradiol/progesterone ratio is maintained constant, as in oocyte donation cycles, except in very few cases when the ring containing 1 g was maintained after day 12 of embryo transfer. In these cases, increasing vaginal progesterone immediately stopped bleeding. Perhaps occasional bleedings associated with IVF are related to oscillations in endogenous oestradiol or in the local ratio between oestradiol and progesterone rather than progesterone concentration alone. On the other hand it has been well documented that

in women without functional ovaries, after the endometrium has proliferated and progesterone is added, histological dating in the luteal phase is not affected by the presence or absence of oestradiol (De Ziegler *et al*., 1992). Furthermore, evidence is also available which suggests that luteal oestradiol is not required for the establishment and maintenance of pregnancy in women treated with oocyte donation (Zegers-Hochschild and Altieri, 1995). Perhaps, in the presence of an active ovary as in IVF, the luteal rise in endogenous oestradiol needs to be compensated with extra progesterone.

New studies will be required to understand the mechanism by which uterine bleeding takes place in some women undergoing ovarian stimulation supplemented with progesterone via vaginal ring.

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