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ORIGINAL ARTICLE

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Comparison of NuvaRing and Desogen in IVF cycles with ganirelix acetate

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OBJECTIVE(S): To compare NuvaRing with Desogen for cycle pretreatment prior to controlled ovarian lyperstimulation (COH) in vitro fertilization (IVF) cycles.

METHOD(S) : In this prospective randomized study conducted from May 2003 to August 2004, 79 patients undergoing COH for IVF cycles were included and randomized to received pretreatment with or Desogen estradiol (n=40) or NuvaRing (n=39) for 12-21 days starting from day 3 of their cycle. Cycle monitoring was done by transvaginal ultrasound or estradiol (E_2) levels. The main outcome measure was ovarian suppression. Chi square test and t test were used for statistical analysis.

RESULTS : Ovarian volumes and antral follicle counts were similar before and after hormonal manipulation. E_2 levels before and after contraceptive use were similar in both the groups. The luteinizing hormone (LH) level after contraceptive use was significantly suppressed in both the groups. The NuvaRing group required less total dose of follitropin ß. Pregnancy and implantation rates were similar in both the groups.

CONCLUSION(S) : Both NuvaRing and the oral contraceptive Desogen are good and comparable choices for cycle pretreatment prior to IVF.

Key words : NuvaRing, vaginal contraception, IVF, controlled ovarian hyperstimulation, oral contraceptive pills

Introduction

Oral contraceptive pills (OCPs) are used prior to controlled ovarian hyperstimulation (COH) by many in in vitro fertilization (IVF) programs [1-3]. There are several advantages of using OCPs pretreatment prior to COH – i) OCPs facilitate programed cycle starts by varying the number of days the patients take the pill. This is important for programs with large patient volumes, as they can control the number of cycle starts on a particular day. ii) OCPs help with patient scheduling, as patients can postpone cycle starts by a few days if so desired. iii) OCPs can be used to induce a withdrawal bleed prior to COH in patients with irregular cycles or amenorrhea. iv) OCPs can improve ovarian response in patients using gonadotropin releasing hormone agonist (GnRHa) flare protocols. Without OCP pretreatment, the initial flare effect of the GnRHa results in the release of progesterone from a residual corpus luteum with premature luteinization of the endometrium and a decrease in implantation rates.

A disadvantage of using OCPs is the requirement of daily dosing [3,4]. This results in daily fluctuations in hormone levels and may be affected by poor compliance by some users. OCPs also result in hepatic first-pass metabolism of the contraceptive steroids requiring the administration of higher doses with a concomitant increase in side effects such as nausea and vomiting [5].

NuvaRing (Organon Pharmaceuticals, Roseland, NJ, USA) is a combined contraceptive vaginal ring containing etonogestrel (ENG) and ethinyl estradiol (EE). ENG is the biologically active metabolite of desogestrel. NuvaRing is a flexible, soft, transparent ring with an outer diameter of 54

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mm and a cross-section of 4 mm that can easily be inserted and removed by the woman herself. Each ring releases an average of 120 µg ENG and 15 µg EE per day, and is designed for one cycle, comprising 3 weeks of continuous use followed by a 1 week ring-free period [6].

There are several advantages of vaginal drug administration [7]. Vaginal administration avoids gastrointestinal absorption and the hepatic first-pass effect. This enables lower dosing, lower systemic exposure, and lower side effects while achieving the same pharmacodynamic effect. Since the ring can be left in place for up to 3 weeks, it may result in increased patient compliance. The ring is also easy to use, painless, discreet, and noninterfering with coitus [5].

This study was designed to compare NuvaRing with Desogen a commonly used OCP containing 30 µg of EE and 150 µg of desogestrel (Desogen, Organon Pharmaceuticals, Roseland, NJ, USA) for cycle pretreatment prior to COH in IVF cycles. The main outcome measure was ovarian suppression.

Methods

This prospective randomized study was conducted between May 2003 and August 2004 at our private practice clinic. The study was approved by the Institutional Review Board at Sherman Hospital, Elgin, Illinois and all patients entering the trial provided written informed consent.

The study population was limited to infertile patients undergoing IVF. Inclusion criteria were age < 40 years, an ovarian volume > 3 mL for each ovary, a combined antral follicle count > 5, and a body mass index (BMI) < 35 kg/ m^2. All study patients had a day-3 FSH level < 10 mIU/mL and normal thyroid and prolactin levels. Exclusion criteria were age > 40 years, ovarian volume < 3 mL in each ovary, combined antral follicle count < 5, BMI > 35 kg/m^2 and a surgically removed ovary. Patients with ovarian cysts, hydrosalpinx, history of ovarian surgery, and a history of previous low response to COH were also excluded from the study. All patients had a normal Papanicolou smear and infectious disease screen. Male factor patients were included, but patients requiring testicular sperm retrieval were excluded.

Seventy-nine patients undergoing COH for IVF were randomized by sealed envelope method to pretreatment with Desogen (n-40) or NuvaRing (n-39) for 12 -21 days starting from day 3 of their cycle.

Four days after discontinuing the contraceptive, patients underwent COH with follitropin ß (Follistim, Organon Pharmaceuticals, Roseland, NJ, USA) with a daily dose of up to 300 IU subcutaneously. Ganirelix acetate (Organon Pharmaceuticals, Roseland, NJ, USA) 250 µg daily subcutaneously was initiated when the lead follicle measured 13 mm.

Baseline ovarian volumes and antral follicle counts were obtained by ultrasound using a 6.5 mHz transvaginal transducer (Philips Ultramark 400C, Philips Medical Systems, Bothell, WA, USA). The machine is equipped with software that calculates the ovarian volume based on ovarian length, width and height. Ovarian measurements were obtained prior to and on the day of discontinuing the contraceptive in both groups. The presence of any cystic structure > 20 mm in diameter was noted. Patients with polycystic appearing ovaries were omitted while antral follicle counts were compared in the two groups. The baseline scans were performed by a single physician who was blinded to the type of contraceptive.

Hormonal measurements for estradiol (E_2), follicle stimulating hormone (FSH) and luteinizing hormone (LH) were obtained before hormonal manipulation.E_2, LH, and progesterone (P) levels were obtained after the contraceptive was discontinued.. All assays were performed with an automated chemiluminescence system (Chiron Diagnostics ACS:180, Chiron Diagnostics, Medfield MA, USA). The Chiron Diagnostics' ACS:180 assays use paramagnetic particles as the solid phase and acridinium ester as the chemiluminescent label. The interassay and intraassay coefficient of variation was less than 10% for all hormones measured.

Cycle monitoring was by serial transvaginal ultrasound and E_2 levels. Human chorionic gonadotropin (hCG,) (Pregnyl, Organon Pharmaceuticals, Roseland, NJ, USA) 10,000 units was administered intramuscularly when at least two lead follicles measured 18 mm in diameter. Oocyte retrieval was scheduled 36 hours later and performed transvaginally under ultrasound guidance. Embryo culture, micromanipulation, and transfer were performed using techniques described by Alexander et al [7]. Intracytoplasmic sperm injection (ICSI) was used in all patients with male factor. In patients with mild male factor or unexplained infertility, ICSI was performed on some of the oocytes, whereas the rest had regular insemination (ICSI split). Embryo transfer (ET) was performed 3 or 5 days later under ultrasound guidance, and the number of embryos transfered was limited to no more than two [8].

The luteal phase was supported with progesterone-in-oil 50 mg intramuscularly or with Crinone® gel 8% (Serono Pharmaceuticals, Waltham, MA, USA) vaginally, daily. A pregnancy test was scheduled approximately two weeks after embryo transfer. Pregnancy monitoring was done initially

with hCG levels, and then with serial transvaginal ultrasound.

Comparison between the two groups was done by Chi-squared analysis and t tests. P value < 0.05 was considered significant.

Results

Of the 79 patients, 40 were randomized to the Desogen group and 39 to the NuvaRing group. Patient demographics and diagnoses were similar in both the groups (Table 1). Baseline hormonal evaluation was normal in all patients. Despite a short course of hormonal manipulation, the LH levels were significantly suppressed in both the groups (Table 2).

Table 1. Patient demographics (Mean ± SD) and Diagnosis

Parameter	Desogen group (n=40)	NuvaRing group (n=39)
Age (years, means ± SD)	32.65 ± 4.41	31.69±3.27
Primary infertility (number)	25	24
Secondary infertility (number)	15	15
Body mass index (kg/m^2; (mean ± SD)	26.22 ± 6.81	23.43±7.87
Cause of infertility		
Male factor	12	15
Ovarian dysfunction	7	2
Tubal factor	8	8
Unexplained	13	14

Table 2. Hormonal measurements (mean ± SD) prior to and after hormonal manipulation.

Parameter	Desogen group (n=40)	NuvaRing grup (n=39)
Before hormonal manipulation		
E_2 (pg/mL)	45.83 ± 15.49	47.39 ± 23.29
FSH (mIU/mL)	6.03 ± 1.78	5.98 ± 1.66
LH (mIU/mL)	6.42 ± 3.52	5.14 ± 3.08
After hormonal manipulation		
E_2 (pg/mL)	48.00 ± 23.56	26.24 ± 15.94
Progesterone (ng/mL)	0.57 ± 0.28	0.77 ± 0.93
LH (mIU/mL)	2.96 ± 2.34 [a]	2.56 ± 2.10 [a]

[a] P <0.05

Baseline ultrasound scans showed that the ovarian volume and antral follicle counts were normal in both the groups. After contraceptive treatment,17.5% (7/40) of patients in the Desogen group and 12.82% (5/39) in the NuvaRing group developed ovarian cysts (Table 3). In most cases, the cysts were nonfunctional and disappeared when the contraceptive was continued for an additional week. In five cases (two with NuvaRing and three with Desogen) the cysts were aspirated transvaginally under ultrasound guidance. Cyst aspiration was performed only when patients chose this option instead of continuing the contraceptive and awaiting spontaneous resolution. COH was started several days later, once the E_2 levels were below 100 pg/mL.

Table 3. Ultrasound measurements (mean ± SD) prior to and after hormonal manipulation.

Parameter	Desogen group (n=40)	NuvaRing group (n=30)
Before hormonal manipulation		
Ovarian volume (mm^3)	16.65 ± 10.07	14.42 ± 8.66
Antral follicle count	9.31 ± 4.02	8.36 ± 4.23
After hormonal manipulation		
Ovarian volume (mm^3)	15.50 ± 12.54	11.82 ± 6.17
Antral follicle count	9.95 ± 3.24	8.67 ± 3.85
Ovarian cyst	7/40 (17.5%)	5/39 (12.82%)

The stimulation characteristics in the two groups are summarized in Table 4. Both groups were stimulated with a similar daily dose of follitropin ß (228 ± 78 IU in the NuvaRing group and 238±75 IU in the Desogen group; P > 0.05). The NuvaRing group, however, required a lower total dose of follitropin ß (2003 ± 717 IU vs 2340 ± 729 IU in the Desogen group, P = 0.038). The total number of follicles on the day of hCG were similar in both the groups (14.77 ± 4.18 in the NuvaRing group vs 14.95 ± 4.53 in the Desogen group, P > 0.05). The number of follicles measuring > 16 mm in diameter on the day of hCG was 5.65 ± 3.1 in the Desogen group and 6.3 ± 3.23 in the NuvaRing group. There were no cycle cancellations prior to retrieval.

Table 4. Stimulation characteristics in the two groups (mean ± SD).

Parameter	Desogen group (n=40)	NuvaRing group (n=39)
Days on hormonal manipulation	15.32 ± 8.37	15.65 ± 7.28
rFSH dose (IU/day)	238 ± 75	228 ± 78
Total rFSH dose (IU)	2340 ± 729 [a]	2003 ± 717 [a]
Days on ganirelix acetate	3.92 ± 1.04	4.32 ± 0.87
Peak E_2 level (pg/mL)	1568 ± 1004	1544 ± 938
Total follicle count on day of hCG	14.95 ± 4.53	14.77 ± 4.18
Number of follicles > 16 mm on day of hCG	5.65 ± 3.1	6.3 ± 3.23

[a] P = 0.038

The total number of oocytes retrieved was similar in the two groups (17.47 ± 8.5 in the NuvaRing group vs 14.30 ± 7.19 in the Desogen group, P > 0.05). The number of mature oocytes retrieved was similar (13.10 ± 5.77 in the NuvaRing group vs 10.77 ± 5.49 in the Desogen group, P>0.05). The fertilization rate in the NuvaRing group (372/511, 72.79%) was significantly higher (P = 0.001) than that in the Desogen group (255/419, 60.85%). This could not be explained by the use of intracytoplasmic sperm injection (ICSI), which was similar in both the groups (Table 5).

Table 5. Embryology data (mean ± SD) and cycle outcome in the two groups.

Parameter	Desogen group (n=40)	NuvaRing group (n=39)
Oocytes retrieved (mean ± SD)	14.23 ± 7.33	17.38 ± 8.42
Mature oocytes retrieved (mean ± SD)	10.77 ± 5.49 [a]	13.10 ± 5.77 [a]
Number of patients with ICSI	15	15
Number of patients with ICSI split	22	20
Number of patients with insemination of oocytes	2	4
Fertilization rate	255/419 (60.85%)[a]	372/511 (72.79%)[a]
Cleavage rate	249/255 (97.65%)	358/372 (96.24%)
Cycle cancellation rate	4/39 (10.26%)	2/39 (5.13%)
Embryos transferred	2.11 ± 0.53	1.97 ± 0.37
Days in culture for embryos	2.95 ± 1.53	3.39 ± 1.6
Number of patients with cryopreserved embryos	9	14
Number of cryopreserved embryos	3.78 ± 2.17	3.79 ± 1.93
Implantation rate	28/74 (37.83%)	25/73 (34.24%)
Biochemical pregnancy rate per cycle start	22/39 (56.41%)	27/39 (69.2%)
Ongoing pregnancy rate per cycle start	19/39 (48.72%)	16/39 (41.0%)
Biochemical pregnancy rate per transfer	22/35 (62.9%)	27/37 (72.9%)
Ongoing pregnancy rate per transfer	19/35 (54.3%)	16/37 (43.2%)
Singleton pregnancy	14	11
Twin pregnancy	5	5

[a] P = 0.001

The cleavage rate, number of days of embryo culture, number of embryos transferred, number of embryos cryopreserved, and pregnancy and implantation rates (gestational sacs per embryos transferred) were similar in both the groups (P >0.05). There were 10 biochemical pregnancies in the NuvaRing group and 3 in the Desogen group. One patient with a twin pregnancy in the NuvaRing group miscarried at 8 weeks after fetal heart tones were visualized on ultrasound. Products of conception were not sent for chromosomal study by the refering physician. There were no high-order multiple pregnancies in either group.

Four patients in the Desogen group did not undergo ET. Of these, three had no viable embryos, and one had all of her embryos cryopreserved due to a family emergency. Two patients in the NuvaRing group did not undergo ET. In both of them, all embryos were cryopreserved to prevent severe ovarian hyperstimulation syndrome. The one patient in the Desogen group with cryopreserved embryos conceived twins on her first thaw cycle. Of the two patients in the NuvaRing group with cryopreserved embryos, one has an ongoing twin pregnancy from her first thaw cycle, and the other has an ongoing singleton pregnancy from her first thaw cycle.

Discussion

This study was designed to compare NuvaRing and Desogen for cycle pretreatment prior to COH in IVF cycles. In clinical practice, there are patients who do not wish to take oral contraceptives. This may be due to a history of prior adverse reactions like nausea and vomiting, concerns regarding daily pill administration, and compliance issues.

There are additional advantages in using the NuvaRing. The vagina is a highly effective site for drug delivery. There is an extensive vascular connection between vagina and uterus, and a first uterine pass effect has been hypothesized when hormones are administered vaginally [9]. Vaginally administered P induces a normal secretory transformation of the endometrium even though low serum P levels are measured [10]. In fact, several groups have demonstrated that endometrial concentrations of P were higher with vaginal administration than with intramuscular administration [10]. The same has been noted with E_2. Miles et al [11], have shown that endometrial E_2 levels were significantly higher with vaginal administration as compared with levels following the same dose administered orally. No such data are available on the endometrial concentrations of synthetic progestogens or EE after vaginal administration. It is however possible to use the lower dose of hormones in the NuvaRing. In fact the release of EE (15 µg daily) is lower than that used in even the lowest dose OCP.

Several large studies have evaluated the user acceptability of the NuvaRing [12-15]. In a large international study Novák et al [13] assessed 1950 women regarding clarity of instructions, ease of use, sexual comfort, cycle-related characteristics, and satisfaction after 3, 6 and 13 cycles of use. At baseline, 66% of participants preferred oral contraceptives, but after three cycles of ring use 81% preferred the ring. On completion of the study, 97% agreed that the instructions for use were clear, 85% of women and 71% of partners never/rarely felt the ring during intercourse, and 94% of partners never/rarely minded that the woman was using the ring. Overall acceptance was high; 96% were satisfied with the ring and 97% would recommend it. Reasons for liking the ring included not having to remember anything (45%) and ease of use (27%). Similar results were obtained by Szarewski [12]. Most recently, Guida et al [16] found that the NuvaRing seems to exert a positive effect on the psychological aspect of sexual function in both women and their partners, as evidenced by a higher level of sexual satisfaction as compared with that in those couples using Desogen for hormonal manipulation.

Cycle control between NuvaRing and a OCP delivering 30 µg of EE and 150 µg of levonorgestrel has been previously compared [17,18]. One of these open-label, randomized, multicenter, international studies evaluated 1030 women. The incidence of breakthrough bleeding and spotting over cycles 2 – 13 was lower with the vaginal ring (range 2.0 – 6.4%) than with the OCP (range 3.5 – 12.6%). The incidence of intended bleeding was significantly higher over all cycles with NuvaRing (58.8 – 72.8%) than with OCP (43.4 – 57.9%). It was further noted that since cycle control is known to influence contraceptive acceptability, compliance, and convenience, the NuvaRing achieves all this with a lower dose of EE.

The present study design limited the use of both NuvaRing and Desogen pretreatment for only 12- 21 days. In practice, if the duration of NuvaRing use exceeds 21 days, then a new NuvaRing should be utilized. Regardless, it is critical that the patient removes the NuvaRing prior to commencing COH. It is possible that a shorter duration of NuvaRing use may be sufficient for ovarian suppression, but this was not evaluated in a study by Mulders et al [6].

We also excluded patients with prior ovarian surgery, a single ovary or prior low response to stimulation. Our study population was limited to patients under 40 years age, with normal ovarian volume and antral follicle count. They had a normal day 3 FSH level and a BMI < 35 kg/m^2. This group of patients usually has an optimal response to a standard stimulation protocol, making it possible to compare the impact of these two contraceptives on stimulation characteristic s [19]. As expected, both groups responded well to stimulation and no cycle was cancelled prior to retrieval. Of interest is the fact that the NuvaRing group used less ? follitropin (2003 ± 717 vs 2340 ± 729, P = 0.038) but produced a similar number of mature oocytes (13.10 ± 5.77 vs 10.77 ± 5.49, P > 0.05). The incidence of polycystic appearing ovaries was similar in both the groups (7/40 in the Desogen and 5/39 in the NuvaRing group, P < 0.05) and therefore could not be an explanation for NuvaRing group needing less ? folliropin. One could postulate that the NuvaRing group had less ovarian suppression and therefore required less medication for stimulation.

The only parameter that did reach statistical significance was the fertilization rate, which was higher in the NuvaRing group (72.79% vs 60.85%, P = 0.001). The study did not control for intracytoplasmic sperm injection, and we believe this finding resulted from a Type I error. The study was designed to evaluate stimulation characteristics of the two groups. ICSI was used liberally even in patients with mild male factor and an ICSI split was used in patients with unexplained infertility. We hesitate to attribute this increased fertilization rate to NuvaRing use. Subsequent studies with strict criteria for ICSI need to be done to further evaluate this unexpected finding. We are now using OCPs and NuvaRing interchangeably in our practice. In addition, we are planning a randomized trial to evaluate the NuvaRing in low responders.

Conclusion

Similar cycle stimulation characteristics and pregnancy rates are achieved using either NuvaRing or Desogen prior to COH in normal responders. NuvaRing cycles may

require a lower dose of FSH for stimulation. NuvaRing provides clinicians another option for pretreatment in their patient's IVF cycles.

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