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The effect of follicle maturing drugs on side of ovulation in successive cycles

J.H.Check[1], C.Dietterich and H.Adelson

The University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School at Camden, Cooper Hospital/University Medical Center, Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology and Infertility, Camden, NJ, USA

[1]To whom correspondence should be addressed at: 8002 E. Greentree Commons, Marlton, NJ 08053, USA

Our previous study has demonstrated that ovulation in unstimulated cycles is random with an equal likelihood of ipsilateral or contralateral ovulation occurring in the following cycle. This study evaluated women taking ovulation-inducing drugs to see if the side of ovulation in the preceding cycle has an influence on the side of ovulation in the succeeding cycle. Ovulatory patterns in consecutive pairs of cycles in anovulatory women treated with ovulation-inducing drugs were evaluated through sonographic studies of follicular maturation. The results demonstrated that when unilateral ovulation occurred, there was an equal likelihood of ipsilateral or contralateral ovulation in the succeeding cycle. However, ovulation-inducing drugs increase the incidence of bilateral or multiple ovulation.

Key words: Bilateral ovulation/contralateral ovulation/ipsilateral ovulation/ovulation drugs/sonography

Introduction

There is still considerable debate as to whether ovulation in successive cycles is more likely to be ipsilateral (Werlin *et al.*, 1986), contralateral (Dukelow, 1977; Hodgen, 1982; Marinho *et al.*, 1982; Speroff *et al.*, 1983; Gougeon and Lefevre, 1984; Knobil and Neill, 1988), right sided (Potashnik *et al.*, 1987) or random (Clark *et al.*, 1978; Check *et al.*, 1991). Our previous study demonstrated that ovulation in unstimulated cycles is a random phenomenon, with an equal likelihood of ipsilateral ovulation or contralateral ovulation occurring in the succeeding cycle.

The present study addresses the question of whether clomiphene citrate or human menopausal gonadotrophins affect the side of ovulation in the succeeding cycle. Also evaluated was the relative frequency of unilateral and bilateral ovulation in patients undergoing therapy with the ovulation-inducing drugs, human menopausal gonadotrophin (HMG) or clomiphene citrate.

Materials and methods

A total of 200 consecutive anovulatory patients were enrolled in the study. The protocol consisted of using the smallest amount of medication to try to develop just one mature follicle. One technique for patients with unexplained infertility is to stimulate ovulation in the patient and then perform intrauterine insemination (Dodson *et al.*, 1987). Purposeful ovarian stimulation was sometimes given because of pelvic adhesions. Any patient who had ovarian stimulation to try to create multiple follicles was excluded from this investigation; 11 patients were eliminated for these reasons.

Sequential sonographic studies of follicular maturation were evaluated in 189 anovulatory women treated with ovulation-inducing drugs. Of these women, 116 were treated with human menopausal gonadotrophin (HMG); of these, 24 were oestrogen-deficient with low gonadotrophins (hypogonadotrophic hypogonadism) and 92 had normal oestrogen levels. Seventy-three eu-oestrogenic women were treated with clomiphene citrate. Polycystic ovarian syndrome was diagnosed in 18 of the HMG-treated patients and 29 clomiphene-treated patients on the basis of clinical hirsutism and a ratio of luteinizing hormone (LH): follicle stimulating hormone (FSH) $\geq$2:1.

The lowest dose of clomiphene used was 25 mg for 5 days and the highest was 150 mg for 5 days. The lowest HMG dosage was 1 ampoule (75 IU) for 3 days and the highest dosage was 300 IU daily. The maximum number of ampoules used by any patient was 38. The mean total dosage of clomiphene citrate was 330 mg and the mean HMG dosage was 14.6 ampoules. Patients were also excluded if they had hyperprolactinaemia (serum prolactin $\geq$25 pg/ml) or previous surgery involving the ovaries. The mean age of the HMG-treated patients was 32.3 years, and 33.7 years for those treated with clomiphene citrate.

Any follicle which attained 18–24 mm in diameter, as demonstrated by real-time ultrasonography (Advanced Technology Laboratory, Inc., Bothnell, WA, USA) using a 5 HMz transvaginal tranducer, was considered dominant as long as the serum oestradiol level was $\geq$200 pg/ml per dominant follicle. The follicle(s) which collapsed by at least 5 mm on repeat sonography 2–3 days later was considered the source of the oocyte. If a woman had follicles which luteinized without rupture, then the follicle(s) which enlarged were considered the ones that ovulated; however, when multiple follicles were present, if one or two but not all follicles collapsed, only those releasing were considered the ovulated ones.

Each patient was monitored for three consecutive cycles during which she remained on the same regimen of therapy. The side of ovulation as determined by ultrasonography was recorded as right sided (R) if ovulation occurred from the right ovary, left sided (L) if ovulation occurred from the left ovary, or bilateral (B) if multiple ovulation occurred involving both ovaries. Within each drug therapy group, the relationship of the side of ovulation in succeeding cycles was evaluated by comparing the side of ovulation in the first cycle to the side of ovulation in the second cycle and subsequently, the side of ovulation in the second cycle to the side of ovulation in the third cycle. Chi-square analysis, with a P level of 0.05, was used to test for the significance of this relationship.

During the course of the three consecutive cycles, the following ovulation patterns were possible. (i) Ipsilateral: ovulation was always unilateral and from the same ovary (e.g. RRR, LLL); (ii) contralateral: ovulation was always unilateral, but the side of ovulation varied each cycle (e.g. RLR, LRL); (iii) ipsilateral/contralateral: ovulation was always unilateral, but one pair of cycles was ipsilateral, the other was contralateral (e.g. RRL or LRR); (iv) bilateral: ovulation was always bilateral (e.g. BBB); (v) Bi 1/Uni 2: both bilateral and unilateral ovulation occurred, with one cycle of bilateral ovulation and two cycles of unilateral ovulation (e.g. BLR, LLB); and (vi) Bi 2/Uni 1: both bilateral and unilateral ovulation occurred, with two cycles of bilateral and one cycle of unilateral (e.g. BBR, LLB). The relative frequencies of these patterns of ovulation in patients treated with HMG and clomiphene citrate were recorded.

Results

A comparison of the side of ovulation in the first pair of consecutive cycles (cycles 1 and 2) observed in 73 women treated with clomiphene citrate is presented in Table I. There was no relationship between side of ovulation on the first cycle and side of ovulation on the second cycle ($\chi^2 = 5.9$, d.f. = 4, $P > 0.05$). Of the 49 pairs of cycles in which only unilateral ovulation was observed, 29 (59.2%) were ipsilateral and 20 (40.8%) were contralateral. For women who initially ovulated bilaterally, 66.7% (10 of 15) subsequently ovulated unilaterally (5 right, 5 left) and 33.3% (5 of 15) continued to ovulate bilaterally.

Similarly, when comparing the side of ovulation in the second pair of consecutive cycles (cycles 2 and 3) in women treated with clomiphene citrate, there was no relationship between the side of ovulation in the second cycle and the side of ovulation in the third cycle (see Table II, $\chi^2 = 6.6$, d.f. = 4, $P > 0.05$). Of the 50 pairs of cycles where unilateral ovulation only was observed, 26 (52%) were ipsilateral and 24 (48%) were contralateral. Of those who ovulated bilaterally in cycle 2, 64.3% (9 of 14) ovulated unilaterally in cycle 3; 35.7% continued to ovulate bilaterally.

For the 116 patients treated with HMG, comparisons of the side of ovulation in the first pair of consecutive cycles (cycles 1 and 2) and in the second pair of cycles (cycles 2 and 3) are presented in Tables III and IV respectively. For the first pair of cycles observed, χ^2 analysis showed that there was a significant relationship between the side of ovulation in the first cycle and the side of ovulation in the second cycle ($\chi^2 = 10.2$, d.f. = 4, $P < 0.05$). Further analysis of this relationship was performed by partitioning the degrees of freedom for the χ^2 into four independent comparisons (Maxwell, 1961).

The first comparison was between right or left side of ovulation in succeeding cycles for pairs involving unilateral ovulation only, i.e. ipsilateral versus contralateral ovulation (the first two cells in the first row of Table III versus the first two cells in the second row in Table III). The second comparison was for pairs in which the initial ovulation was unilateral or bilateral and the second cycle was unilateral (in the first two columns of Table III, cells for right and left were combined into the category unilateral and

Table I. Comparison of side of ovulation in consecutive cycles for 73 women treated with clomiphene citrate (cycles 1 and 2)[a]

Side of ovulation	Side of ovulation cycle 2			
cycle 1	Right	Left	Bilateral	Row total
Right	20(60.6)	10(30.3)	3(9.1)	33
Left	10(40.0)	9(36.0)	6(24.0)	25
Bilateral	5(33.3)	5(33.3)	5(33.3)	15
Column totals	35	24	14	73

[a]Data represent frequency counts; row percentages are in parentheses.

Table II. Comparison of side of ovulation in consecutive cycles for 73 women treated with clomiphene citrate (cycles 2 and 3)[a]

Side of ovulation	Side of ovulation cycle 3			
cycle 2	Right	Left	Bilateral	Row total
Right	15(42.9)	16(45.7)	4(11.4)	35
Left	8(33.3)	11(45.8)	5(20.8)	24
Bilateral	7(50.0)	2(14.3)	5(35.7)	14
Column totals	30	29	14	73

[a]Data represent frequency counts; row percentages are in parentheses.

Table III. Comparison of side of ovulation in consecutive cycles for 116 women treated with HMG (cycles 1 and 2)[a]

Side of ovulation	Side of ovulation cycle 2			
cycle 1	Right	Left	Bilateral	Row total
Right	18(38.3)	19(40.4)	10(21.3)	47
Left	12(32.4)	19(51.3)	6(16.2)	37
Bilateral	8(25.0)	9(28.1)	15(46.9)	32
Column totals	38	47	31	116

[a]Data represent frequency counts; row percentages are in parentheses. HMG = human menopausal gonadotrophins.

Table IV. Comparison of side of ovulation in consecutive cycles for 116 women treated with HMG (cycles 2 and 3)[a]

Side of ovulation	Side of ovulation cycle 3			
cycle 2	Right	Left	Bilateral	Row total
Right	17(44.7)	12(31.6)	9(23.7)	38
Left	21(44.7)	16(34.0)	10(21.3)	47
Bilateral	7(45.2)	10(32.3)	14(45.2)	31
Column totals	45	38	33	116

[a]Data represent frequency counts; row percentages are in parentheses. HMG = human menopausal gonadotrophin.

compared to bilateral in row 3). The third comparison was for cycle pairs in which the first cycle was unilateral and the second cycle was unilateral or bilateral (using rows 1 and 2 in Table III, again right and left were combined into the category of unilateral). Finally, in the fourth comparison, right and left-sided ovulation was combined into the category unilateral ovulation in both cycles of the pair so that we could compare unilateral versus bilateral ovulation in succeeding cycles.

The only comparison found to be statistically significant was the fourth one. If unilateral ovulation was observed in the first cycle (n = 84), 68 of 84 (81%) experienced unilateral ovulation in the second cycle; 16 of 84 (19%) experienced bilateral ovulation in the second cycle. However, if bilateral ovulation was observed in the first cycle, 46.9% (15 of 32) experienced bilateral ovulation in second cycle while 53.1% (17 of 32) experienced unilateral ovulation.

When comparing the side of ovulation in the second cycle to the side of ovulation in the third cycle in HMG patients, the overall χ^2 was not significant ($\chi^2 = 7.1$, d.f. = 4, $P > 0.05$). However, analysis of the components of the partitioned χ^2 showed that the fourth comparison was statistically significant for this pair of cycles also ($\chi^2 = 5.538$, d.f. = 1, $P < 0.05$). Thus, patients on HMG who ovulated bilaterally in the second cycle were more likely to continue to ovulate bilaterally than patients who ovulated unilaterally in their second cycle (45.2 versus 22.3%).

The relative frequencies of the ovulation patterns which can occur in three consecutive cycles within each drug therapy group are presented in Table V. In the clomiphene citrate group, 59% of women ovulated unilaterally only, whereas 41.1% experienced some bilateral ovulation. In the HMG group, 48.3% of the women ovulated unilaterally and 51.7% experienced some bilateral ovulation.

Discussion

Similar to our study of women with natural cycles, these data demonstrate that even with the use of ovulation-inducing drugs, when a single ovulation occurs, the selection of the side of ovulation in a subsequent cycle is equally likely to be ipsilateral or contralateral.

The use of ovulation-inducing drugs did, however, increase the likelihood of bilateral ovulation. Although conservative use of HMG and careful follicular monitoring by sonography were employed in an attempt to mature one follicle only, almost half of the cycle pairs observed had one cycle with multiple ovulation following HMG therapy. Multiple ovulation occurred to a lesser degree following clomiphene therapy, but no definite conclusions can be drawn concerning which drug is more likely to create multiple follicles, since there was no randomization of treatment groups and thus some patient selection bias might influence these data.

At one time there was a popular theory that ovulation would be more likely in the contralateral ovary, which has the lowest levels of progesterone in the ovarian effluents (di Zerega *et al.*, 1981; de Zerega and Hodgen, 1982; Speroff *et al.*, 1983). The hypothesis suggests that progesterone antagonizes oestrogen action through depletion of oestrogen receptors, thus inhibiting oestrogen-dependent follicular mechanisms. The data presented here using ovulation-inducing drugs confirm our previous data concerning unstimulated ovulations, which showed that the selection of the side of ovulation in the subsequent cycle is unrelated to events occurring in the previous cycle (Check *et al.*, 1991).

Table V. Relative frequencies of ovulation pattern types in women treated with ovulation inducing drugs

Ovulation pattern	HMG (n = 116)	Clomiphene citrate (n = 73)
Type 1, Ipsilateral	14(12.1)	14(19.2)
Type 2, Contralateral	15(12.9)	8(11.0)
Type 3, Ipsi./Contra.	27(23.3)	21(28.8)
Type 4, Bilateral	8(6.9)	3(4.1)
Type 5, Bi×1/Uni×2	32(27.6)	20(27.4)
Type 6, Bi×2/Uni×1	20(17.2)	7(9.6)

[a]Data represent frequency counts; row percentages are in parentheses. HMG = human menopausal gonadotrophin.

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