Side of ovulation and cycle characteristics in normally fertile women

René Ecochard1,3 and Alain Gougeon2

1Unite´ de Biostatistiques du Departement d’Information Medicales, Hospices Civils de Lyon, 162 avenue Lacassagne 69003 Lyon and 2INSERM U-407, Faculte´ de Medecine Lyon-Sud, BP 12, 69921 Oullins Cedex, France
3To whom correspondence should be addressed

This study was undertaken to establish whether ovulation in humans alternates consistently from right to left ovary in successive cycles and whether the site of ovulation affects the next cycle length or the hormonal profiles. A total of 199 cycles in 80 normally fertile women were studied. The volunteers were monitored with ultrasonography to determine the day and side of ovulation and to calculate follicular and luteal phase lengths. Urinary hormone concentrations were also assayed. Right-sided ovulations occurred in 104 of the 199 cycles (52.3%; not significantly different from 50%). Alternate ovulations occurred in 61 of the 119 pairs of succeeding cycles (51.3%; not significant). The follicular phase length in contralateral ovulation (14.59 ± 0.33 days; mean ± SEM) did not differ significantly from that of ipsilateral ovulation (14.59 ± 0.37 days). There were also no significant differences in urinary concentrations of oestrone-3-glucuronide, pregnanediol-3-glucuronide, follicle stimulating hormone, and luteinizing hormone between ipsilateral and contralateral ovulation in either early follicular, peri-ovulatory or luteal phase of the cycle. It is concluded that in normally fertile women, the cycle length and the hormonal profile are independent of the most probably random, site of ovulation.

Key words: contralateral ovulation/dominant follicle/follicular phase length/hormonal profile/ultrasound

Introduction

The side sequence in which successive ovulations occur is still a matter of controversy. In primates, some authors believed that most monotocous mammals ovulate alternately (Zuckerman and Parkes, 1932), some did not observe a particular ovulation pattern (Hartman, 1932; Morse and Van Wagenen, 1936; Clark et al., 1978), while others linked the side of ovulation to certain ovarian or hormonal conditions (Wallach et al., 1973; Goodman and Hodgen, 1979; Di Zerega et al., 1981). In humans, there was a subtler debate. Some authors stated that it is unlikely to be random and that ovulation is more likely to occur in the contralateral ovary (Marinho et al., 1982; Gougeon and Lefèvre, 1984) or in the ipsilateral ovary (Werlin et al., 1986). Other studies reported cases of single-sided ovulation (Katz et al., 1986) or demonstrated that ovulation tends to occur more frequently in the right ovary and that alternation is closely related to hormonal factors (Potashnik et al., 1987). On the contrary, Check et al. (1991), using ultrasound to determine the side of ovulation, concluded for the first time in humans that ovulation in succeeding cycles is a random event (Check et al., 1991). However, this study concerned infertile women.

A renewed interest for side of ovulation arose with evidence that, in infertile women, the dominant follicles in contralateral ovulation are ‘healthier’ than those of ipsilateral one (Fukuda et al., 1996), that corpus luteum affects the diameters of follicles in the ipsilateral ovary during the luteal phase (Fukuda et al., 1997), and that contralateral ovulation shortens the follicular phase length (Fukuda et al., 1996, 1998). Unfortunately, many of the above-cited human studies implicated infertile women and lacked confirmation studies in normally fertile women.

Recently, Quidel Corporation (San Diego, CA, USA) established a bank of first morning void specimens and collected clinical, hormonal, as well as ultrasound data on a sizeable number of cycles in normally fertile women. These data were used in this study to assess whether ovulation alternates consistently from right to left ovary in successive cycles, and whether the site of ovulation affects the size of the follicles, the length of the cycles or the hormonal profiles, these latter parameters being indirect criteria for adequate follicle growth.

Materials and methods

The study protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Lyon (France), all subjects gave their written informed consent, and all study procedures were carried out in accordance with the Ethical Standards for Human Experimentation established by the Declaration of Helsinki, 1975.

The protocol was written for a multi-centre collaborative study under the auspices of Claude Bernard University, Lyon (France). The subjects were recruited from eight centres: Aix-en-Provence, Dijon, and Lyon (France); Milano and Verona (Italy); Düsseldorf (Germany); Liège (Belgium); and Madrid (Spain).

Subjects

The following criteria had to be fulfilled before a subject was admitted into the study: ostensibly healthy menstruating women with two intact ovaries, aged 18–45 years inclusive, with previous menstrual cycle lengths of 24–34 days inclusive, and experience in natural family planning methods (basal body temperature and signs of cervical mucus). Subjects were excluded if they met at least one of the following criteria: women with frequent anovulatory cycles; women on programmes to stimulate hormonal responses for fertility reasons;
women on oral, transdermal or other hormonal contraceptives, or on
an abortive drug programme (<3 months); women on hormonal
replacement therapy; women with abnormal cycles—polycystic
ovarian disease, ovarian cyst, or luteal defect; women with special
medical circumstances—hysterectomy, tubal ligation(s), pelvic
inflammatory disease, history of fertility problems; women with
special habits or circumstances such as runners, breastfeeding, post-
partum (<3 months).

The age span of the women was large. This choice was made to
cover the largest part of the reproductive life, at the price of an
increased heterogeneity of the group.

Keeping with these criteria, 205 cycles were analysed and 81
women, aged 19–42 years (mean 32.3) were observed during at least
two consecutive ovulatory cycles. Therefore, being free from any
illness that might cause subfertility, these women were considered as
normally fertile. Besides, 54 out of 81 (66%) were of proven fertility
having had at least one child before the study.

Ultrason o n and investigation
To monitor ovulation, transvaginal (58%) or transabdominal ultra-
son were performed after the onset of fertile type cervical mucus
observed at the opening of the vagina (Hilgers et al., 1978) and/or
luteinizing hormone (LH) surge detected by a rapid assay (Bluetest
Ovulation test, Quidel). It may be difficult to find dominant follicles
by transabdominal ultrasound. This difficulty was partially circum-
vented by the repetition of ultrasound examinations by the same
investigator for each woman.

Scanning was first performed on alternate days as long as the
follicle size was less than 16 mm. Once 16-mm follicles were observed, scanning was performed on a daily basis until the presumed
day of ovulation. The dominant follicle was defined as the cystic
structure having the greatest diameter. The side of ovulation was that
of the ovary bearing the dominant follicle. The day of ovulation
was defined as the day of maximum follicular enlargement followed
the next day by evidence of rupture. All ovulations were documented by
a sonogram of the dominant follicle collapse. The length of the
follicular phase was the delay from the onset of menses to the
ultrasound-estimated day of ovulation, inclusive. The length of the
luteal phase was the delay from the first day with evidence of
follicle rupture to the day preceding the onset of the following
menses, inclusive.

Hormonal assays
Daily collected early morning urine samples were assayed for
quantitative detection of oestrone-3-glucuronide (E1-3-G) and preg-
nandiol-3-glucuronide (Pd-3-G) by competitive enzyme-linked
immunosorbent assays (ELISA) as well as that of FSH and LH by
the time-resolved fluorometric immunoasorbent assays (Delfia).
Average hormonal concentrations were estimated at three periods of the cycle;
at days 3 ± 1 for the early follicular phase, at the ultrasound estimated
day of ovulation ±1 for the peri-ovulatory phase, and at ultrasound
estimated day of ovulation +5, +7 and +9 for the luteal phase.

Statistical analysis
Statistical comparisons were performed using unpaired Student’s
t-test for continuous variables (length of cycle, follicle diameter,
hormonal concentrations) and χ² test for categorical variables, i.e. to
study the relation between the follicular phase length and the ovulation
side. The statistical analysis relative to the side of ovulation was
based on the binomial distribution, assuming that in normal circum-
stances there is a 50% chance of ovulation occurring in either ovary.

All analyses were performed using S-plus statistical package
(MathSoft, Inc., Seattle, WA, USA). Significance was defined as P <
0.05 in all analyses.

Results
Side of ovulation
In six cycles out of 205 (3%), two follicles collapsed, one in
each ovary. These six cycles were excluded from further
analysis, leaving 199 cycles and 80 women to be analysed in
a total of 119 pairs of succeeding cycles (Table I). Right-sided
ovulation was seen in 104 of 199 cycles (52.3%), which was
not significantly different from 50% and means that ovulation
frequency was equal between the two ovaries.

Alternate ovulation occurred in 61 of the 119 succeeding
ovulations (51.3%, not significant) which means that there was
no consistent tendency to alternation.

Follicular phase length and lengths of other phases of
the cycle
When the follicular phase was <13 days (n = 26), 46% (n = 12) of the cycles showed contralateral ovulation while in
cycles with a follicular phase ≥13 days (n = 93), contralateral
ovulation occurred in 53% of the cycles (n = 49), which was
not significant. Therefore, short follicular phases could not be
associated with change of ovulation side.

The follicular phase length in contralateral ovulation
(14.59 ± 0.33 days, mean ± SEM) did not differ significantly
from that of ipsilateral ovulation (14.59 ± 0.37 days). Similarly,
as shown in Table II, it was not possible to demonstrate
statistically significant differences for other lengths of the
cycle phases.

In the studied population, no significant correlation was
observed between the age of the women and the cycle length,
but as previously observed (Lenton et al., 1984), age and the
follicular phase length were inversely associated.

Dominant follicle
The mean diameter of the dominant follicle in the contralateral
ovulation cycles was 21.78 ± 0.68 mm, which did not differ
In conclusion, the data suggest that in normally fertile women the side of ovulation is rather a random event independent of the side of the previous cycle, which corroborates previous results (Check et al., 1991) in unstimulated cycles of infertile women. The discrepancy observed between the results of the present study and those obtained in a previous work based on a histological evaluation of regressing corpora lutea (Gougeon and Lefèvre, 1984) can be explained by (i) a lower number of data, 25 women and 113 cycles versus 80 women and 199 cycles in this study, and (ii) an inaccurate estimation of the age of oldest corpora lutea.

In one study on intermenstrual pain (Marinho et al., 1982), this symptom seemed to occur on the same side as follicular rupture in 86% of the subjects. However, an earlier more extended work on the same symptom in 10 women over 2052 cycles (Vollman, 1977) has shown that in successive cycles the percentage distribution of localization of this pain fluctuates irregularly and without any systematic pattern, which is consistent with the present results.

In infertile women, the duration of the follicular phase of the menstrual cycle was shown to be shorter when ovulations alternated between the two ovaries compared to when ovulation occurred in the same ovary (Potashnik et al., 1987; Fukuda et al., 1996, 1998). Moreover, analysing follicular fluids before assisted reproduction treatments, both in natural cycles and during ovarian stimulation with clomiphene citrate, it was suggested (Fukuda et al., 1996) that contralateral dominant follicles are healthier than ipsilateral ones (more successful fertilizations, cleavage, transfers, and pregnancy rates). They suggested that this could be a consequence of a negative effect of the corpus luteum on neighbouring follicular growth during the luteal phase of the previous cycle (Fukuda et al., 1997).

In the normal population of this study, no differences were observed in follicular phase length, dominant follicle size, or urinary hormonal profiles in relation to the side of ovulation in the previous cycle. This suggests that in normally fertile women the growth of selectable follicles is similar in both ovaries independently of the presence or absence of a corpus luteum in the ipsilateral ovary during the previous cycle.

Recently it was shown (Lass et al., 1997) that ovulation induction with gonadotrophin-releasing hormone/human menopausal gonadotrophin for in-vitro fertilization in patients with a solitary ovary was not associated with better results with the left than with the right ovary. They questioned a previous observation (Potashnik et al., 1987) of predominance of the right ovary in spontaneous cycles in women treated for infertility. These authors answered writing that spontaneous ovulation being a purely physiological event, the delicate balance is interrupted by drug-induced down-regulation and ovarian stimulation (Potashnik et al., 1998) and thus, the two observations may not be opposed. More generally, care must be taken when comparing the results of the current study obtained in normally fertile women with those concerning infertile women with or without hormonal treatment.

In conclusion, the data suggest that in normally fertile women the side of ovulation, the length, and the hormonal profile of a given cycle are independent of the side of ovulation in the previous cycle. However, only lengths and urinary hormonal profiles were studied, and it may be that more subtle differences between ipsilateral and contralateral ovulation might have some implication on conception probability.

### Table II. Comparison of cycle characteristics during consequent ipsilateral and contralateral ovulation

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral</th>
<th>Contralateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lengths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle (days)</td>
<td>28.22 (0.39)</td>
<td>28.20 (0.41)</td>
</tr>
<tr>
<td>Menstruation (days)</td>
<td>5.02 (0.18)</td>
<td>5.44 (0.15)</td>
</tr>
<tr>
<td>Follicular phase (days)</td>
<td>14.59 (0.37)</td>
<td>14.59 (0.33)</td>
</tr>
<tr>
<td>Luteal phase (days)</td>
<td>13.64 (0.25)</td>
<td>13.53 (0.26)</td>
</tr>
<tr>
<td>Follicle diameter (mm)</td>
<td>21.73 (0.50)</td>
<td>21.78 (0.68)</td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early follicular phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1-3-G (ng/ml)</td>
<td>11.17 (0.96)</td>
<td>10.69 (0.83)</td>
</tr>
<tr>
<td>Pd-3α-G (μg/ml)</td>
<td>2.49 (0.34)</td>
<td>2.36 (0.15)</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>3.74 (0.3)</td>
<td>3.56 (0.25)</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>3.69 (0.52)</td>
<td>3.86 (0.37)</td>
</tr>
<tr>
<td>Peri-ovulatory phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1-3-G (ng/ml)</td>
<td>52.79 (3.31)</td>
<td>51.77 (3.06)</td>
</tr>
<tr>
<td>Pd-3α-G (μg/ml)</td>
<td>3.06 (0.27)</td>
<td>2.89 (0.21)</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>16.16 (1.36)</td>
<td>15.67 (1.5)</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>5.49 (0.62)</td>
<td>5.93 (0.64)</td>
</tr>
<tr>
<td>Luteal phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1-3-G (ng/ml)</td>
<td>32.00 (2.61)</td>
<td>28.78 (2.08)</td>
</tr>
<tr>
<td>Pd-3α-G (μg/ml)</td>
<td>12.87 (0.88)</td>
<td>12.01 (0.65)</td>
</tr>
<tr>
<td>LH (mIU/ml)</td>
<td>5.69 (0.58)</td>
<td>5.84 (0.49)</td>
</tr>
<tr>
<td>FSH (mIU/ml)</td>
<td>1.82 (0.21)</td>
<td>1.78 (0.22)</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

E1-3-G = oestrone-3-glucuronide; Pd-3α-G = pregnanediol-3α-glucuronide; LH = luteinizing hormone; FSH = follicle stimulating hormone.

There were no statistical differences between the two groups.

Significantly from ipsilateral cycles (21.73 ± 0.50, P = 0.95). It can therefore be concluded that a former ipsilateral ovulation did not inhibit the current dominant follicle growth.

**Hormonal profiles**

The urinary concentrations of E1-3-G, Pd-3α-G, FSH, and LH in early follicular, peri-ovulatory and luteal phase are shown in Table II. No significant differences were found for any of these hormones at any of the three phases. Therefore, it could be assumed that (i) during the early follicular phase high residual progesterone concentrations secreted by the regressing former corpus luteum were not associated with contralateral ovulation; (ii) during the peri-ovulatory phase, since hormonal concentrations reflect follicular growth, the fact that no differences were found in these concentrations between former ipsilateral and contralateral ovulation suggests no difference in the current process of follicular growth; (iii) during the luteal phase, since hormonal concentrations reflect the evolution of a follicle into a corpus luteum, the lack of difference in hormone concentrations suggested no difference in follicle transformation.

**Discussion**

While several studies, most in infertile women, insist on alternation or side-preference in the occurrence of ovulation (Marinho et al., 1982; Gougeon and Lefèvre, 1984; Katz et al.; 1986; Werlin et al., 1986) the current study shows that in normally fertile women the side of ovulation is rather a random event independent of the side of the previous cycle, which...
Acknowledgements

The authors wish to thank Drs Sophie Dubus, Anne Leduy, Isabelle Ecochard, Marie Grisard Capelle, Enriqueta Barranco, Michele Barbato, Sandro Girotto and Marion Gimmler from the natural family planning clinics as well as all the women who took part in this study. We also thank Jean Iwaz, Ph.D., scientific advisor, for suggestions and criticisms of the manuscript. The work was partially supported by Quidel Corporation, San Diego, CA, USA.

References


