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Is There Seasonality in Human Ovulation?

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Abstract To study seasonality in human ovulation in a direct way, we measured the occurrence of ovulation in infertile patients with spontaneous menstrual cycles (<6 weeks) who visited the fertility clinic at the University Hospital Nijmegen in the Netherlands for the first time in 1991 or 1992 ($n = 407$). Ovulation was detected using serial transvaginal ultrasound and midluteal progesterone measurement and was performed during one screening cycle. The frequency of ovulatory cycles per month varied from 73% to 93% (not statistically significant). No seasonal pattern in ovulation was found in subfecund Dutch women with spontaneous menstrual cycles. This finding was not confounded by the effects of age of the women, body mass index, or disorders that could influence ovulation.

Seasonality of births is found throughout the world (Lam and Miron 1987; Roenneberg and Aschoff 1990a,b). Such a birth pattern can be influenced by social and cultural factors, but biological factors also may be involved (Roenneberg and Aschoff 1990a,b). For instance, decreased ovarian function was measured in women younger than 25 years and in women older than 35 years and in women with decreased energy intake or increased energy expenditure (Ellison 1993). In several populations the changes in energy balance show seasonal variation (Bailey et al. 1992; Panter-Brick et al. 1993; Jasienka and Ellison 1993). Seasonal reproduction is common in mammals. For example, in rhesus monkeys seasonal variation in ovulation has been found (Walker et al. 1984).

A mechanism that may cause seasonality in ovulation, other than influencing energy balance, is photoperiodicity. The information from the retina about light and darkness is transported by way of the suprachiasmatic nucleus in the hypothalamus to the pineal gland. The pineal gland produces melatonin

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from serotonin during darkness (Tamarkin et al. 1985). In humans, however, the role of the pineal gland and melatonin is still unclear (Speroff et al. 1994).

It is unknown whether birth seasonality in humans is caused by seasonal variation in ovulation. Indications of seasonal patterns of ovulation were found by Timonen et al. (1964) and Rameshkumar et al. (1992). In Finland Timonen et al. (1964) found less cystic glandular hyperplasia during the light season than during the dark season (30.1% vs. 34.6%) in 9750 endometrial biopsies. This finding indicated more ovulatory cycles during the light season (i.e., the months surrounding June). In contrast, an increase in anovulatory cycles was observed from May to July in the endometrial biopsies of 1036 women living in India (Rameshkumar et al. 1992). In that study a negative correlation was found between the percentage of ovulatory cycles and the environmental temperature, whereas in Finland Timonen et al. (1964) found no relation between these two factors. Possibly, ovulation was suppressed because of low energy intake in India during spring and summer. Because these results are contradictory and based on indirect measurement of ovulation, we studied seasonality in human ovulation directly in a population with rather constant energy balance and moderate environmental temperature throughout the year. The convenient method of serial measurements of salivary progesterone cannot reliably discriminate between ovulatory and anovulatory cycles (Ellison 1993); therefore we used the laborious method of serial transvaginal ultrasound and midluteal serum progesterone measurement.

Materials and Methods

In 1991 and 1992, 1021 couples visited the fertility clinic of the University Hospital Nijmegen, the Netherlands, for the first time. At the time of their first visit a detailed reproductive history was taken. The standard infertility workup consisted of a semen analysis, ultrasonographic ovulation detection during one cycle, assessment of cervical mucus quality, and a timed postcoital test. The luteal phase was assessed by midluteal progesterone level seven days after follicular rupture and length of the luteal phase. The tubal status was determined by hysterosalpingography and/or laparoscopy. Hormonal screening was performed based on the menstrual history or if the history or clinical exam suggested an endocrine disturbance. Ultrasonographic ovulation detection was performed only in women with menstrual cycles shorter than 6 weeks ($n = 422$). Women with amenorrhea or oligomenorrhea (i.e., a menstrual cycle of 6 weeks or longer) were not screened because they were expected to have anovulatory cycles. In addition, women were not screened if they had been referred to the fertility clinic for specific treatments, such as in vitro fertilization or microsurgery. In this study retrospective data were used for the 422 women with spontaneous menstrual cycles less than 6 weeks.

The first transvaginal ultrasound scan was performed on cycle day 10 or, if the cycles were much shorter or longer than 28 days, 18 days before the expected onset of the next menstrual period. Scans were repeated on alternate days or daily, according to the follicular size. An ovulatory cycle was defined according to the ultrasonographic criteria of follicular rupture, that is, the observation of considerable loss of volume in a preexisting follicle, as described by Wetzels and Hoogland (1982), in combination with a mid-luteal progesterone level above 20 nmol/L. Luteinized unruptured follicle syndrome was diagnosed if the dominant follicle did not rupture but instead showed rapid growth after reaching a diameter of 22 mm and remained a cystic structure throughout the luteal phase (Hamilton et al. 1985).

Three groups of women at a higher risk for anovulatory cycles were distinguished on the basis of the following criteria: (1) age 35 years or older, (2) body mass index (BMI) less than 20 kg/m² or more than 27 kg/m², and (3) a disorder that could influence ovulation. BMI is defined as weight (kg)/height² (m²). The cutoff point of 27 kg/m² was used because this is the criterion for obesity (Must et al. 1991). We use the general term "disorders" to mean disorders that could influence ovulation, specifically, endocrine disorders (e.g., polycystic ovary syndrome, hyperprolactinemia), endometriosis, or cervical mucus disturbance. For the analyses concerning such disorders couples with unexplained infertility were excluded. Furthermore, a group of women at higher overall risk was formed from the women who met one or more of the three criteria.

To study seasonality, we used the month of the first day of the last menstrual period preceding the screening. Percentages of women with ovulatory cycles were computed for each month. Using logistic regression analysis, we studied whether these percentages differed between months and whether the seasonal variation followed a pattern that could be described by a sine function with a unimodal or bimodal pattern. Therefore the months were entered into a logistic model as a sine function with a period of 0.5 year or 1 year and with variable amplitude and horizontal shift. Likelihood ratio test results gave information about the effects of including the season in the model on the explanation of the variation in ovulatory cycles. Furthermore, we studied whether the seasonal effect was more obvious in any of the groups of women at higher risk because of an interactive effect.

Next, we performed logistic regression analysis for studying whether confounding by other risk factors influenced the relation between season and ovulation. Finally, logistic regression analysis was used to test whether the low percentage of women with ovulatory cycles found in a cluster of months differed from that in the rest of the year and if this difference remained after adjusting for confounding by other risk factors. We computed odds ratios with 95% confidence intervals for comparing the proportions of ovulatory cycles in the high- and low-risk groups.

Table 1. Characteristics of the 407 Women with Ovulatory or Anovulatory Cycles

	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>SD</i>	<i>Median</i>	<i>n</i>	<i>Unknown</i>	<i>%^a</i>
Age (years)	19	45	30.5	4.3	31			
BMI (kg/m ²)	16	45	22.8	3.9	22			
Weight (kg)	42	126	64.1	11.7	62			
Height (m)	1.48	1.89	1.68	0.07	1.68			
Primary infertility						272	0	67
Age <35 years						345	0	84
Age ≥35 years						62	0	15
BMI <20 kg/m ²						60	55	17
BMI >27 kg/m ²						35	55	10
Disorder ^b						132	98	43
Overall risk ^c						227	93	72

a. Percentage of the women with known values.

b. Women with an endocrine disorder, endometriosis, or a cervical mucus disturbance (98 women with unexplained infertility were excluded).

c. Defined as high if a woman met one or more of the following criteria: (1) 35 years of age or older, (2) BMI less than 20 or greater than 27 kg/m², (3) disorder.

To determine whether we could find a seasonal pattern with the available data, we calculated the power of the study. Because no standard formula for power calculation for seasonal variation is available, we used simulations for both a unimodal seasonal pattern (with the peak in June because of a possible influence of the photoperiod) and a bimodal seasonal pattern (with the peaks in June and December because of possible negative feedback mechanisms during the dark period).

Results

Four hundred twenty-two women were screened for ovulation. Most of the cycles were ovulatory ($n = 354$, 84%), but 53 (13%) were anovulatory (including 7 cycles with luteinized unruptured follicles). In 15 women the outcome of the screening was unknown because the screening cycle was incomplete or the ultrasonographic picture was ambiguous. These women were excluded from further analyses.

Characteristics of the remaining 407 women are given in Table 1. The youngest woman was 19 years old and the oldest was 45 years old; 15% of the women ($n = 62$) were 35 years or older. The BMI ranged from 16 kg/m² to 45 kg/m². Seventeen percent of the women ($n = 60$) had a BMI below 20 kg/m² and 10% ($n = 35$) had a BMI above 27 kg/m². No data about height or weight were available for 55 women. Forty-three percent of the women ($n = 132$) had a disorder that could influence ovulation. In 98 couples the cause of infertility was unknown.

In Table 2 the percentages of women with ovulatory cycles per month are given for the total population and for the groups of women at higher and

Table 2. Women with Ovulatory Cycles per Month in the Total Population, the Groups at Higher and Lower Risk for Anovulatory Cycle, and Odds Ratios

Month of Screening	Total (n = 407)		Age (Years) ≥35 (n = 62)		<35 (n = 345)		Body Mass Index (kg/m ²) <20, >27 (n = 95)				Disorder ^a Yes (n = 132)				No (n = 177)				Overall Risk ^b			
															One or More Risk Factors (n = 227)		No Risk Factors (n = 87)					
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%		
January	19	73	2	100	17	71	4	57	9	82	3	60	12	86	7	64	5	100				
February	17	81	1	100	16	80	–	–	13	87	5	63	7	88	6	67	5	83				
March	37	93	10	100	27	90	7	78	27	96	10	83	15	94	21	91	8	89				
April	28	82	2	50	26	87	7	78	19	83	11	85	13	87	16	76	8	100				
May	26	90	2	67	24	92	8	80	15	94	10	83	10	91	16	84	2	100				
June	31	86	6	86	25	86	11	85	17	89	10	83	16	89	20	87	8	89				
July	40	91	8	100	32	89	12	92	23	92	11	85	20	95	23	88	9	90				
August	34	87	5	100	29	85	3	75	27	90	13	87	11	92	17	85	9	100				
September	25	83	7	100	18	78	8	89	14	78	7	78	11	79	15	83	2	50				
October	33	89	5	100	28	88	4	57	22	96	9	69	16	100	16	80	8	100				
November	40	93	5	100	35	92	7	88	30	97	9	90	17	94	18	90	10	100				
December	24	86	5	100	19	83	5	83	15	83	8	80	13	93	15	88	6	86				
Total	354	87	58	94	296	86	76	80	231	90	106	80	161	91	190	84	80	92				
Odds ratio (95% CI) ^c			2.40 (0.83–6.89)				0.45 (0.24–0.86)				0.41 (0.21–0.79)				0.45 (0.19–1.05)							

- a. Women with an endocrine disorder, endometriosis, or a cervical mucus disturbance (98 women with unexplained infertility were excluded).
- b. Defined as high if a woman met one or more of the following criteria: (1) 35 years of age or older, (2) BMI less than 20 or greater than 27 kg/m², (3) disorder.
- c. Odds ratio with 95% confidence interval for the proportion of ovulatory cycles in the group at higher risk versus the group at lower risk.

Table 3. Women with Ovulatory Cycles Differentiated by Age and BMI

	<i>n</i>	%
Age (years)		
19–24	26	90
25–29	106	82
30–34	164	88
35–39	49	94
40–45	9	90
Body mass index (kg/m ²)		
16–19	47	78
20–27	231	90
28–45	29	83

lower risk; odds ratios are included. Although not statistically significant, the women aged 35 years or older had more ovulatory cycles than the women younger than 35 years. When 5-year age groups were distinguished, the group of 25–29-year-olds showed the fewest ovulatory cycles (82%) (Table 3). An ovulatory cycle was found in 78% of women with a BMI below 20 kg/m², in 90% of women with a BMI of 20–27 kg/m², and in 83% of women with a BMI above 27 kg/m² (Table 3). The women with a low or high BMI had fewer ovulatory cycles than those with an optimal BMI. Women with a disorder that could influence ovulation showed fewer ovulatory cycles than those without a disorder (Table 2). The group of women with one or more risk factors showed fewer ovulatory cycles than those with no risk factor (Table 2).

The percentages of ovulatory cycles throughout the year are shown in Figure 1. There were troughs in December–February, April, and September. The difference in the percentages of ovulatory cycles between months was not statistically significant. The season did not contribute to the explanation of the variation in ovulation: The pattern did not fit a model with the months included as 11 dummy variables or as a sine function with a period of 0.5 year or 1 year (*p* value of the likelihood ratio tests was always greater than or equal to 0.59). No interactive effects of the risk factors and season were found (Table 2). Moreover, the pattern was not masked by the effects of age, BMI, and disorders or by the effect of overall risk (*p* value of the likelihood ratio tests for the effect of season was always greater than or equal to 0.51). In addition, we tested whether the low percentage of women with ovulatory cycles during the period December–February (80%) was different from the percentage found in the rest of the year (89%). The crude analysis showed an odds ratio of 0.52 (95% confidence interval, 0.27–1.00), but after adjusting for the effects of age, BMI, and disorders, this difference in ovulatory cycles disappeared considerably (odds ratio of 0.73; 95% confidence interval, 0.29–1.86).

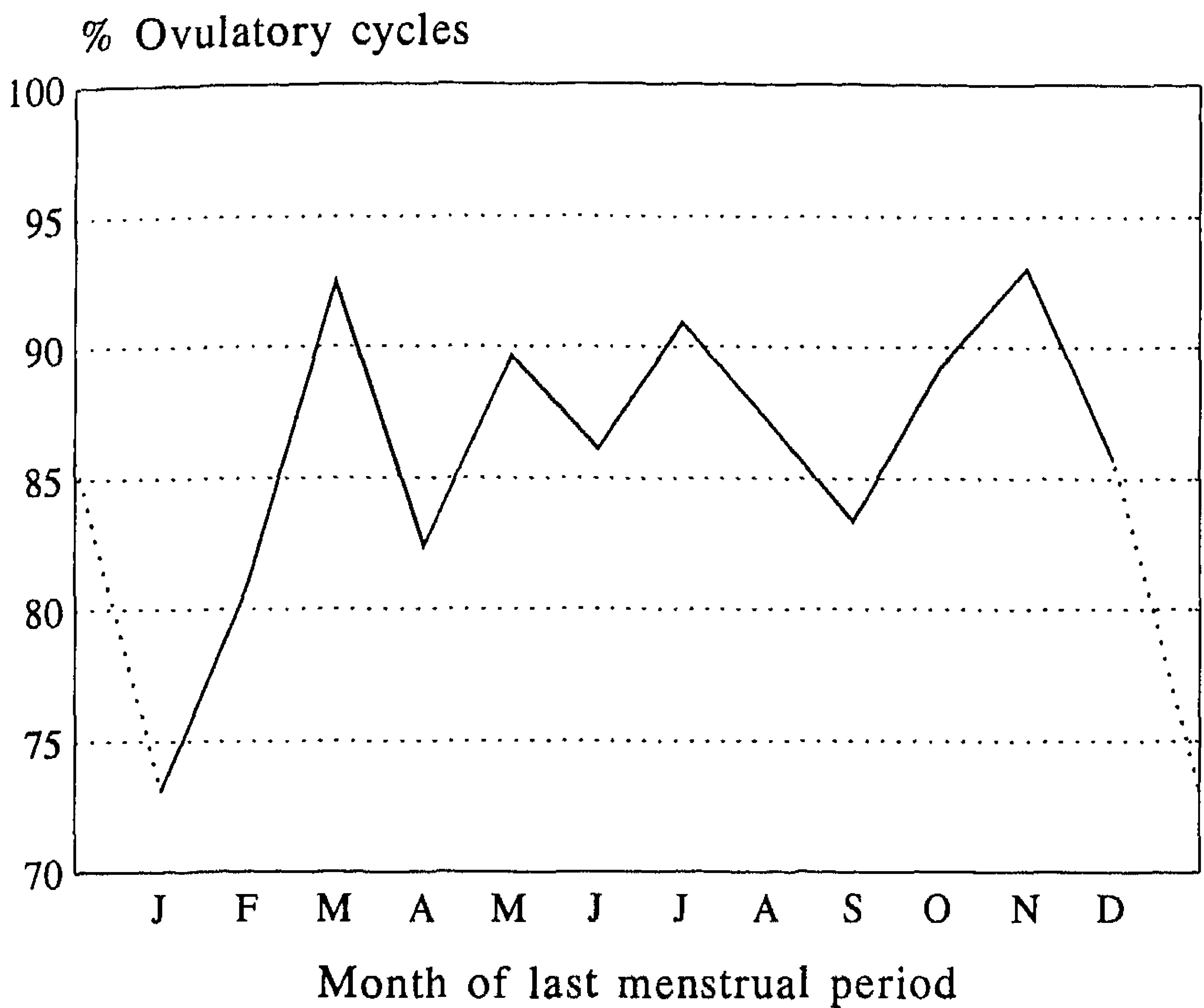


Figure 1. Percentage of women with ovulatory cycles per month ($n = 407$).

If seasonal variation exists, with the given number of screenings per month we would have been able to detect a difference of about 10% in ovulatory cycles per month between the extremes of the sine function with $\alpha = 0.10$ and a power of 70%.

Discussion

This study did not reveal a seasonal pattern in ovulatory cycles of sub-fecund Dutch women in 1991–1992. The number of women in the study was rather small, resulting in a rather low power; therefore minor seasonal variation in ovulation might have been missed. The absence of a statistically significant seasonal variation in ovulation was not explained by confounding effects of age, BMI, and disorders.

The study population was highly selected. All the women had a history of infertility. The women with primary or secondary amenorrhea or with oligomenorrhea were not screened for ovulation and therefore were excluded from the study. The ovulation frequency in this study population does not

represent the frequency in the general Dutch female population. However, seasonality itself is not likely to have influenced the selection process. Therefore, if seasonality in ovulatory frequency as a biological phenomenon does occur in the general population, such a pattern almost certainly would also appear in this selected study population, at least to a certain extent.

Ultrasonography in combination with serum progesterone measurement one week after follicle rupture is a reliable method for ovulation detection (Wetzels and Hoogland 1982). In 15 women we could not determine retrospectively whether or not ovulation had occurred, partly because of incomplete data in the patient dossiers. In January a relatively large number of screening results were inconclusive (4 out of 30 screenings), so the percentage of ovulatory cycles in that month would be at most 77%, that is, still one of the lowest percentages during the year. The inconclusive screening cycles change the results only slightly.

To study seasonality in ovulation, it is not necessary to follow women for several menstrual periods. In clinical practice (using the reliable method of serial transvaginal ultrasound in combination with midluteal serum progesterone measurements) following women for more than one period is even undesirable because the screening method is too cumbersome for the patients. Measurements during one menstrual cycle per woman give the same answer to the question so long as the women are equally distributed throughout the year for the known risk factors for anovulatory cycles and so long as unknown risk factors are randomly distributed throughout the year. We presume that these assumptions are met because the fertility clinic did not change its procedure during the year. Moreover, we adjusted for possible confounding effects of age, BMI, and disorders. Thus this method was appropriate to study seasonality in ovulation.

The results of this study do not confirm the results of Timonen et al. (1964) in Finland or those of Rameshkumar et al. (1992) in India. The ovulation patterns found in those two studies were compatible with the results of Roenneberg and Aschoff (1990b), who found a negative correlation between temperature and conceptions in equatorial regions with hot summers and a positive correlation in regions with cold winters and moderate summers. However, photoperiodicity and variation in environmental temperature are not the only features of seasonal influence; variation in energy intake and expenditure also matter. Therefore another explanation might be the decreased energy intake during spring and summer in India; Ellison (1994) noticed decreased luteal function in that situation. No large seasonal variation in energy balance is expected in the Netherlands. Therefore in this study any influence of the season might be due to photoperiodicity and changes in environmental temperature. Because in the Netherlands (which is situated between 50° and 54° latitude) heterogeneity in photoperiodicity and temperature during the year is less than that in Finland, seasonal variation in ovulation may not be detectable.

In short, we conclude that no overt seasonality in human ovulation was present in these subfecund Dutch women with menstrual cycles shorter than 6 weeks.

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