Human Reproduction Vol.16, No.11 pp. 2288–2294, 2001

A prospective study evidencing rhinomanometric and olfactometric outcomes in women taking oral contraceptives

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BACKGROUND: The aim of this prospective study was to evaluate the changes in olfactory sensitivity of oral contraceptive (pill) users. METHODS: Sixty women underwent rhinomanometric and olfactometric determinations during the follicular, periovular and luteal phases of the menstrual cycle, and at day 7, 14 and 21 of contraceptive intake. Thirty-one women used 30 μg ethinyl oestradiol plus 75 μg gestodene and 29 women used 20 μg ethinyl oestradiol plus 150 μg desogestrel. RESULTS: Rhinomanometry showed higher but not statistically significant values during the periovular phase than in the follicular and luteal phases. Olfactometry showed a higher sensitivity during the follicular and periovular phases than during the luteal phase of the menstrual cycle. The rhinomanometric surveys in pill users were statistically different from those of the luteal phase ($P < 0.02$) and the follicular and periovular phases ($P < 0.001$). The olfactometric thresholds during the period of contraceptive use were statistically different from those of the follicular phase for a few odorous substances, and from those of the periovular phase for each odorous substance, but similar to those of the luteal phase (P = NS). CONCLUSIONS: Unlike the rhinomanometric airflow and trans-nasal pressure, the olfactory threshold to odours seems to depend on the variations of the ovarian steroids during the menstrual cycle and on the iatrogenic effects of oral contraceptives.

Keywords: menstrual cycle/olfactometry/oral contraceptives/rhinomanometry

Introduction

The ability to detect chemical stimuli in the external environment is of fundamental importance to all animals (Finger and Silver, 1991). For reasons not yet completely understood, females exhibit greater sensitivity to some odours than males (Vierling and Rock, 1967; Doty *et al*., 1985). The female advantage appears to derive from hormonal factors (Russell *et al*., 1980; Evans *et al.*, 1995) or from variables associated with changes in hormonal status (Doty, 1997). The influence of the major histocompatibility complex (MHC) on individual body odour has been well documented (Wedekind *et al*., 1995). Increased levels of soluble MHC were found during the follicular phase, but not during the other phases, of the menstrual cycle. This is not the case with women taking oral contraceptives (Wedekind and Furi, 1997; Wobst *et al*., 1998). The relationship between the phases of the menstrual cycle and olfactory threshold was examined. The variations in olfactory sensitivity observed between ovulation and menstruation could depend on odorant volatility and may result from peripheral mechanisms limiting the access of odorant molecules to the olfactory receptors (Mair *et al*., 1978). In addition to vaginal odours, other body odours also tend to be more pleasant during ovulation. The odours emitted around ovulation tend to stimulate more and linger longer and at the same time produce a desire for more chemosensory stimulation (Poran, 1995). Moreover, it has been demonstrated that the components of the olfactory evoked potentials in women are influenced by the phase of the menstrual cycle. Results of research showed that women perceive olfactory stimuli with a higher sensitivity during the ovulatory phase and describe odours differentially during this period (Pause *et al*., 1996).

One of the variables associated with changes in female hormonal status is oral contraceptive (pill) intake. Worldwide there are currently ~400 million contraceptive users, with ~1/6 taking the pill. Use of the pill declines with age; 75% of users are 19–30 years.

Oral contraceptives influence the olfactory performance of women (Wedekind and Furi, 1997). Just before and during ovulation, women preferentially seek men who evidence phenotypic markers of genetic benefits. These subjects are defined as symmetrical men. Normally-ovulating women using a contraceptive pill show no significant preference for the scent of either symmetrical or asymmetrical men, with respect to normally-cycling women, who tend to prefer the scent of shirts

worn by symmetrical men during the ovulatory phase of the cycle (Gangestad and Thornhill, 1998). The contact between odorous substances and receptors could depend on flow quantity and trans-nasal pressure during respiration. In turn, the contact between substances and receptors could depend on the different degree of oedema of the nasal mucous during the three phases of the menstrual cycle. Accessibility of odourants to the olfactory epithelium may vary with cyclical changes in the mucus layer, thus resulting in changes in olfactory sensitivity (Mair *et al*., 1978). The combined effect of these variables may convey a message of increased alertness and attention during ovulation. Threshold values are subject to large individual differences and can vary considerably. This variation may be due, in part, to the different methodologies employed by various investigators.

Several psychophysical tests are available to assess the sense of smell in a clinical setting. These tests can be useful in differential diagnosis and in assessing the extent of chemosensory loss. Tests of olfactory sensitivity employ squeezable polypropylene bottles containing pyridine (Amoore and Ollman, 1983) or butane (Cain *et al*., 1983). Another test, which measures suprathreshold function, is the University of Pennsylvania Smell Identification Test (Doty, 1997).

From previous studies, it seems that there is currently only fragmentary research being carried out on olfactory cyclicity in oral contraceptive users. Thus, rhinomanometry could be useful in evaluating the olfactory differences during oral contraceptive use, and the olfactory threshold could depend on rhinomanometric characteristics.

Any endogenous or iatrogenic hormonal modification can influence physiological and dysfunctional mechanisms, and the following study was set up to investigate ways in which the airflow and olfactory threshold change during the use of oral contraceptives with respect to the different phases of the menstrual cycle. Although the results may not be clear, it appears that there may be a cause and effect relationship among oral contraceptives and olfaction. This was the endpoint. A prospective trial was set up in which the airflow and olfactory threshold changes before and after taking oral contraceptives in premenopausal cyclic women were studied.

Materials and Methods

The study was performed at the Family Planning Centre of the Research Group for Sexology of the Department of Gynaecological Science, and at the Institute of Otorhinolaryngology, School of Medicine, University of Catania, Italy. The research committees of both Centres approved it and all women gave their written informed consent.

Subjects

Sixty-four healthy volunteers ranging from 18–40 years (mean age 28.2 ± 4.1), who were attending the Family Planning Centre and were planning to take oral contraceptives, participated in the study. All subjects had normal body mass index (23.1 ± 1.4 kg/m^2). None was using any oral contraceptive. Each woman had no subjective olfactory pathology during enrolment. Subjects with tobacco use and/or drug abuse were excluded from the study. Moreover, the women enrolled in the study did not have any dysendocrinism and no metabolic or neoplastic pathologies. Menstrual cycles were regular (mean cycle length 28.5 ± 3.1 days), with ovulation. To confirm the ovulatory cycle, sonography was performed on day 10, 12 and 15 of the cycle, and serum progesterone concentrations were measured at day 21 and 25 of the cycle. Hormone concentrations were measured by enzyme-linked immunoassorbent assay (ELISA) using commercially available kits (Roche, Monza, Italy). Menstrual cycle was defined as ovulatory when the serum progesterone was >18 IU/ml.

Clinical Testing

Each woman was referred to the Olfactology Service to evaluate both the objective and the instrumental aspects. All women underwent ear, nose and throat checks to look for inflammation of the upper airways. Screening tests using endoscopy, rhinomanometry and olfactometry were carried out.

Endoscopy was used because it can aid in the differential diagnosis of olfactory dysfunctions. We used a Pentax FNL 10S endoscope (Pentax, Asahi Optical, Osaka, Japan) with a television camera and an SWHS AG: 4700 VHS Panasonic recorder (Matsushita Electric Industrial Co., Osaka). This permitted an unobstructed view of the nasal cavity and the rhinopharynx, without using a local anaesthetic, and the subsequent recording of the images obtained. Rhinomanometry is defined as the simultaneous measurement of nasal airflow resistance (R) before and after nasal decongestion during spontaneous respiration. This resistance can be expressed by the formula R = P/V, where P is the trans-nasal pressure and V is the volume of airflow. We used a Rhinospir 164 (Sibelmed, Barcelona, Spain) for this test. To test the olfactory threshold we used the Fortunato-Niccolini olfactometer (Fortunato-Niccolini, Catania, Italy) with six different odour substances. To evaluate the sensitivity differences during the menstrual cycle, rhinomanometric and olfactometric surveys were carried out during the follicular phase (day 5–8), the periovular phase (day 13–16) and the luteal phase (day 18–23). Rhinomanometry was performed on each woman during both inhalation and exhalation, with trans-nasal pressure ranging between 300 and –300 mmHg, and with airflow ranging between 800 and –800 cm^3/s.

The substances used to test olfactory sharpness with the Fortunato-Niccolini olfactometer were among the best known monomolecular substances and the most suitable for a complete investigation: anise and musk-ketone with an exclusive olfactory component; clove and pyridine which, apart from the olfactory effect, add to the stimulation of taste and trigeminal terminations; citral with an exclusive olfactory and trigeminal effect; ammonia with a prevalent trigeminal component (Fortunato *et al.*, 1972; Murphy and Cain, 1980; Lawless and Zwillenberg, 1983; Keverne *et al*., 1986). Each substance was used in the liquid state. Anise, musk-ketone, citral and clove were pure essences; pyridine was a pure liquid substance; ammonia was a liquid substance diluted to 22% in distilled water (Pharmacia, Milan, Italy). We considered the olfactory coefficient of each substance, which is the quantity of odorous air sufficient to reach the level of identification >5 s: 2 ml for anise, musk-ketone, citral and clove; 0.5 ml for ammonia; 1 ml for pyridine. Usually, subjects who do not perceive any substance in the range of its specific olfactory coefficient >5 s are defined as being affected by hyposmia/anosmia. The Fortunato-Niccolini olfactometer is shown in Figure 1. Each odour was delivered to the nasal mucous during normal inspiration. Bearing in mind the different degree of edema of nasal mucous during the three phases of the menstrual cycle, the test was repeated for each of the odorous substances until the patient no longer perceived the odour, by stopping the pressure syringe system. The threshold perception was given by the smallest volume of air able to make the subject perceive the odour.

We excluded smokers from our study and requested each woman

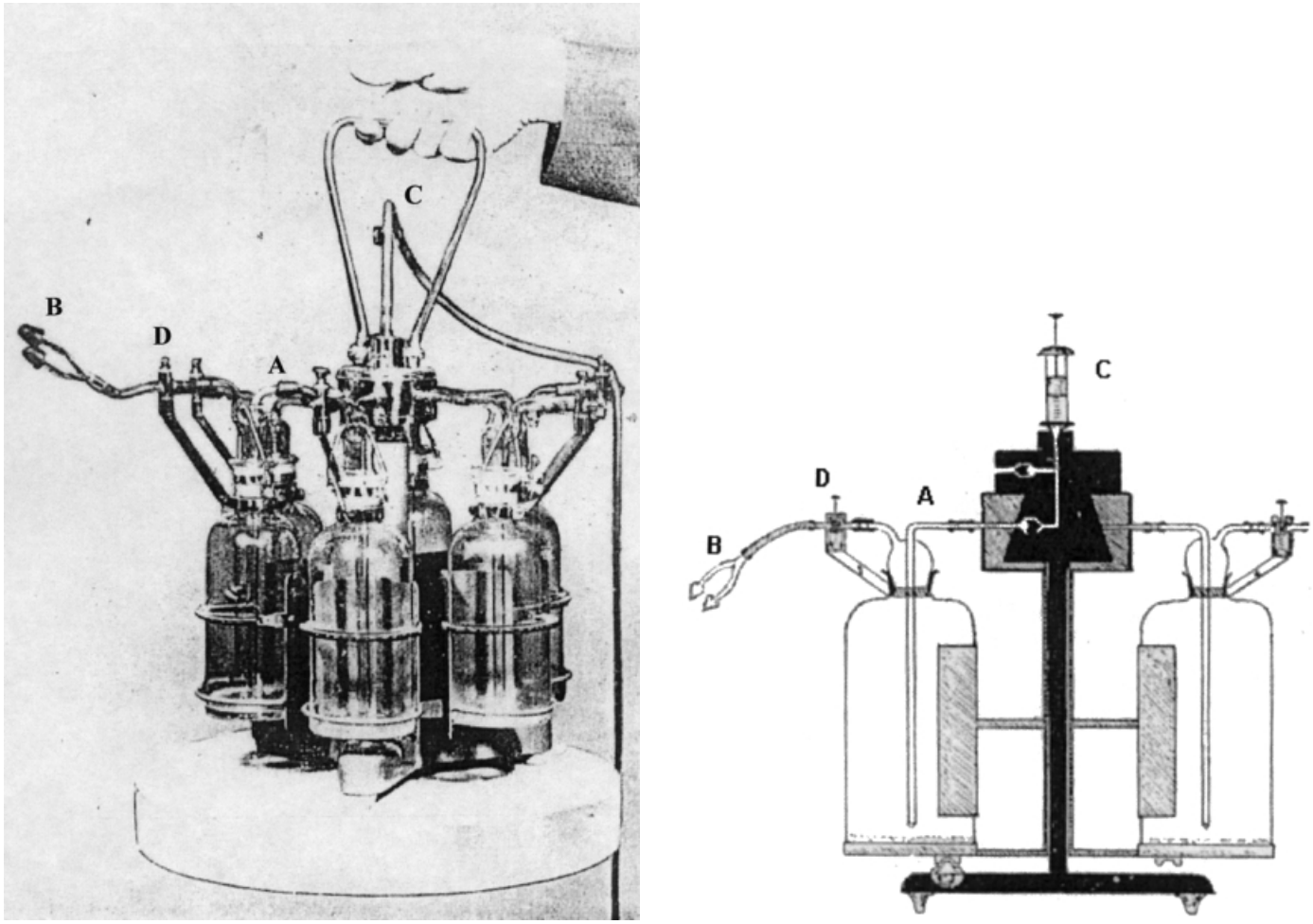

Figure 1. (**Left**) Drawing of the Fortunato-Niccolini olactometer showing six glass bottles of 500 cm^3. Each of the six bottles contained 30 ml of a single substance. Each bottle was hermetically sealed by a rubber cap through which two tubes were passed, one connected to a specially graduated syringe (A), the other to a connector leading to the nostrils (B). The graduated syringe was actuated by a controlled pressure system (C). The pressure was created so as to blow an increasing quantity of the specific substance into each bottle, with a increase of 0.2 ml per test, up to its olfactory coefficient. The olfactometric test was made on all patients sitting in front of the terminal fork, which conducted the odours contemporarily to both the right and the left nasal vestibules. In turn, the valve of the tube connected to the nostrils (D) was opened allowing the passage of air saturated with that odour. (**Right**) Cross section of the apparatus.

not to start smoking, smoke an occasional cigarette, or to stay in environments with smokers for a least one day before the experiments started. Moreover, each woman was requested to avoid strong olfactory stimuli and not to use perfume for a similar time. Duration of one measuring session was ~1 h.

Oral Contraceptives

After clinical testing, oral contraceptives were prescribed to each woman. Table I shows the types and formulations of the monophasic oral contraceptives containing either gestodene or desogestrel used for the subjects. During month 3 of oral contraception, rhinomanometric and olfactometric surveys were performed at day 7, 14, and 21.

Statistics

Assuming that a standard deviation of 1 and a mean difference of 0.5 between before and after pill use, olfactory values at $P = 0.05$, the sample size calculation indicated that 62 subjects would be the minimum number required for the study to have 80% power.

Rhinomanometric values between phases of the menstrual cycle were explored using Spearman's rank correlation. The rhinomanometric values of each phase of the menstrual cycle were compared with those obtained from the oral contraceptive intake using Wilcoxon's rank sum test. Olfactometric values obtained from each phase of the menstrual cycle were compared to the other phases by analysis of variance. Paired data *t*-test was used to compare each phase of the menstrual cycle to the oral contraceptive values. Finally, two-sided *t*-test for independent samples was used to compare the effects of the two monophasic oral contraceptives on both

Table I. Types and formulations of the monophasic oral contraceptives used by women during rhinomanometric and olfactometric tests

Number of users	Ethinyl oestradiol (μg)	Gestodene (μg)	Desogestrel (μg)	
18	30	75		Gynoden[a]
13	30	75		Minulet[b]
15	20		150	Securgin[c]
14	20		150	Mercilon[d]

[a]Schering, Milan, Italy.
[b]Wyeth-Lederle, Aprilia -Latina, Italy.
[c]Menarini, Florence, Italy.
[d]Organon Italia, Roma, Italy.

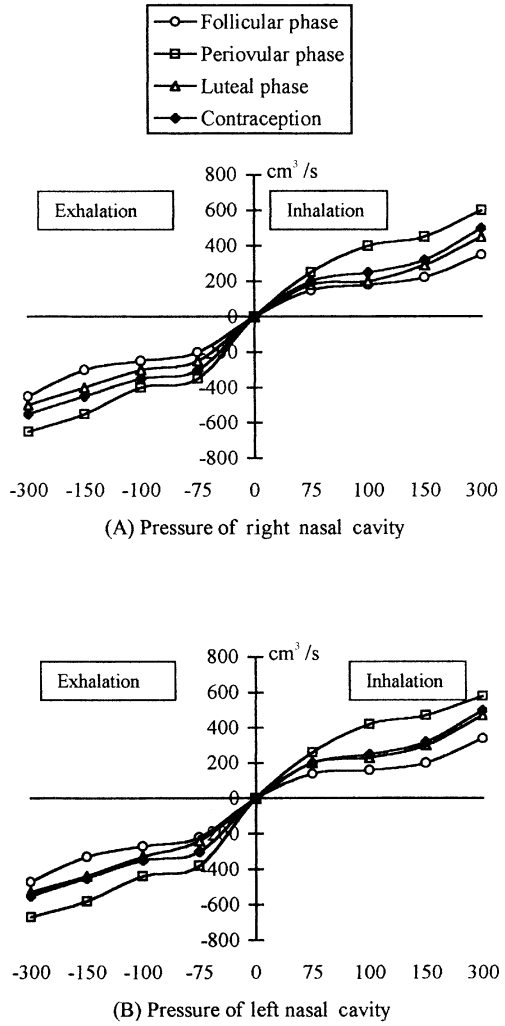

Figure 2. Inhalation and exhalation rhinomanometric values obtained during the menstrual cycle and during contraceptive use.

rhinomanometric and olfactometric aspects. All reported values are given as means ± SD. The differences were considered statistically significant for $P \leqslant 0.05$. Each statistical analysis was carried out using a software package for ™Windows 95 (Glantz, Primer of Biostatistics, McGraw-Hill, Inc. New York, 1997).

Results

After rhinoscopy, three subjects affected by polyps and one affected by deviated septum were excluded from the study. Therefore, the sample consisted of 60 women 18–40 years of age.

Figure 2 shows both the inhalation and exhalation rhinomanometric values obtained during the menstrual cycle and during contraceptive use. For each menstrual phase and during contraceptive use, mean trans-nasal pressure with respect to the airflow value during inhalation and the exhalation time of the right nasal cavity was similar to that of the left nasal cavity (P = NS). Each woman had a higher, but not statistically significant, airflow during the periovular phase than during the follicular and luteal phases. Table II shows the rank correlation analysis with Spearman's rank correlation coefficient of the values between the phases of the menstrual cycle. Table III shows the Wilcoxon's rank sum statistical comparisons of inhalation and exhalation rhinomanometric values obtained during the oral contraceptive intake with those of each menstrual phase. The values of rhinomanometric surveys in pill users were statistically different from those of the luteal phase ($P < 0.02$), the follicular phase ($P < 0.001$) and the periovular phase ($P < 0.001$) of the menstrual cycle.

Table II. Rank correlation analysis of the values between the phases of the menstrual cycle during inhalation and exhalation rhinomanometric test

Phase versus phase	Inhalation		Exhalation	
	r	*P*	*r*	*P*
Follicular versus periovulatory	−0.221	NS	0.179	NS
Follicular versus luteal	−0.115	NS	0.035	NS
Periovulatory versus luteal	−0.302	NS	0.118	NS

r = Spearman's rank correlation coefficient.

Table IV shows the olfactometric thresholds during each phase of the menstrual cycle and during contraceptive use. Each value is expressed as mean ± SD ml of air able to make the subjects perceive the odour. Table V shows the statistical comparison analysis obtained from each phase of the menstrual cycle compared with the other phases. Olfactometric threshold data indicates a higher sensitivity during the follicular phase than the luteal phase for clove and ammonia ($P < 0.001$) and anise and pyridine ($P < 0.05$), and a higher sensitivity during the periovular phase than the follicular phase for clove, anise and pyridine ($P < 0.001$) and citral (< 0.05), and than the luteal phase for each substance ($P < 0.05$ for musk-ketone, $P < 0.001$ for citral, clove, anise, ammonia and pyridine). Finally, Table VI shows the statistical comparison analysis between the contraceptive intake values and those obtained from each menstrual phase during the olfactometric test. The olfactometric thresholds of contraceptive users were (i) statistically different from those of the follicular phase for clove and ammonia ($P < 0.001$) and for pyridine ($P < 0.05$); (ii) statistically different from those of the periovular phase for each odorous substances; (iii) similar to those of the luteal phase for each odorous substances (P = NS).

Finally, no statistically significant difference was observed among women using pill formulations containing either 30 µg ethinyl oestradiol and 75 µg gestodene or 20 µg ethinyl oestradiol and 150 µg desorgestrel on both rhinomanometric (P = NS) and olfactometric (P = NS) surveys.

Discussion

Oral contraceptive use may either influence multiple emotional factors or be influenced by them. For instance, the impairment of sexual interest during hormonal contraceptive use is an infrequent but relevant side effect (Schanzer, 1991). This could perhaps be attributed to the kinds of progestational compounds (Dennerstein and Burrows, 1976) and could depend on the MHC or linked genes that influence human beings in their choice of mate (Wedekind *et al.*, 1995). However, no adequate double-blind trial has confirmed this observation,

Table III. Statistical comparisons of the values of each menstrual phase with those obtained from the contraceptive intake during inhalation and exhalation rhinomanometric test

Contraception versus menstrual phase	Inhalation				Exhalation			
	W	τ	Z_w	*P*	*W*	τ_i	Z_w	*P*
Follicular phase	1686	1	6.37	< 0.001	−1080	11	5.38	< 0.001
Periovulatory phase	1830	0	6.75	< 0.001	−1576	1	5.96	< 0.001
Luteal phase	210	40	3.92	< 0.02	−168	41	3.38	< 0.02

W = rank sum; τ_i = overriding rank number; Z_w = statistical Wilcoxon test.

Table IV. Olfactometric thresholds during the three phases of the menstrual cycle and during contraceptive intake

Odorous substances	Menstrual cycle phases			Contraception (*n* = 60)
	Follicular *n* = 60	Periovular *n* = 60	Luteal *n* = 60	
Mush-ketone	1.00 ± 0.5*	0.90 ± 0.3	1.10 ± 0.5	1.11 ± 0.6
Citral	1.00 ± 0.6	0.80 ± 0.2	1.20 ± 0.9	1.18 ± 0.8
Clove	0.50 ± 0.1	0.40 ± 0.1	0.60 ± 0.2	0.64 ± 0.3
Anise	0.50 ± 0.2	0.30 ± 0.1	0.60 ± 0.2	0.61 ± 0.5
Ammonia	0.20 ± 0.1	0.20 ± 0.1	0.30 ± 0.1	0.29 ± 0.1
Pyridine	0.50 ± 0.2	0.40 ± 0.1	0.60 ± 0.2	0.56 ± 0.1

*Values are mean ± SD ml of air.

Table V. Statistical comparisons analysis of the olfactometric values of the phases of the menstrual cycle during olfactometric test

Odorous substances	Follicular versus periovular phase				Follicular versus luteal phase				Periovular versus luteal phase			
	F	*t*	95% CI	*P*	F	*t*	95% CI	*P*	F	*t*	95% CI	*P*
Mush-ketone	1.76	−1.32	−0.249 to −0.049	NS	1.20	1.09	−0.080 to 0.280	NS	7.06	−2.65	−0.349 to −0.050	<0.05
Citral	6.00	−244	−0.361 to −0.383	<0.05	2.05	1.43	−0.076 to −0.476	NS	11.29	−0.36	−0.635 to −0.164	<0.001
Clove	30.00	5.47	0.063 to 0.136	<0.001	12.00	−3.46	−0.157 to −0.042	<0.001	48.00	6.92	0.142 to 0.257	<0.001
Anise	48.00	6.92	0.142 to 0.257	<0.001	7.50	−2.73	−0.172 to −0.027	<0.05	108.0	10.39	0.242 to 0.357	<0.001
Ammonia	0.00	0.00	−0.036 to 0.036	NS	30.00	−5.47	−0.136 to −0.063	<0.001	30.00	−5.47	−0.026 to −0.063	<0.001
Pyridine	12.00	3.46	0.042 to 0.157	<0.001	7.50	−2.73	−0.143 to −0.027	<0.05	48.00	−6.92	−0.257 to −0.147	<0.001

Degrees of freedom between groups = 1, within groups = 118. CI = confidence interval.
F = F-ratio between groups/within groups; *t* = *t*-test of analysis of variance

and the effects of steroids on sexual desire and motivation are still being debated. Nevertheless, some studies featured a high incidence of libido loss during oral contraceptive use (DeCherney, 2000). Although the mechanism for the adverse effects of oral contraceptives on levels of sexual interest is unknown, it is clear that this effect is not simply a consequence of pill-induced negative mood change (Graham and Sherwin, 1993).

The olfactory threshold to odours seems to depend on variations of the ovarian steroids more than on the airflow and trans-nasal pressure. These events can depend on the action of the different qualitative and qualitative ovarian hormones during the menstrual ovulatory cycle.

We observed that the highest degree of olfactory sensitivity coincides with ovulation. Other authors did not find any changes in the olfactory sensitivity during the menstrual cycle, probably due to the fact that the exact time of ovulation was not determined (Amoore and Ollman, 1983; Cain *et al*., 1983). We confirmed, by sonography and by measuring the serum levels of progesterone, that the menstrual cycle of each woman—at the time during which the rhinomanometric and the olfactometric tests were performed—was an ovulatory one.

Our data seem to show that iatrogenic steroids, such as those contained in oral contraceptives, may affect changes in smell sensitivity. In fact, olfactory surveys emphasized that (i) smell parameters did not have any significant fluctuation with

Table VI. Statistical comparison analysis of the contraceptive intake values versus the values of each menstrual phase during the olfactometric test

Odorous substances	Pill versus follicular phase				Pill versus periovular phase				Pill versus luteal phase			
	F	*t*	95% CI	*P*	F	*t*	95% CI	*P*	F	*t*	95% CI	*P*
Mushketone	1.19	1.09	−0.089 to 0.309	NS	5.88	2.42	0.038 to 0.381	<0.05	0.01	0.09	−0.189 to 0.209	NS
Citral	1.94	1.39	−0.075 to 0.435	NS	12.74	3.56	0.162 to 0.309	<0.001	0.02	−0.12	−0.327 to 0.287	NS
Clove	11.76	3.42	−0.059 to 0.220	<0.001	34.56	5.87	0.159 to 0.320	<0.001	0.74	0.85	−0.052 to 0.132	NS
Anise	2.50	1.58	−0.027 to 0.247	NS	22.18	4.70	0.179 to 0.440	<0.001	0.02	0.14	−0.127 to 0.147	NS
Ammonia	24.3	−4.93	−0.126 to −0.053	<0.001	24.3	−4.93	−0.126 to −0.0053	<0.001	0.3	−0.54	−0.026 to 0.046	NS
Pyridine	7.68	2.77	0.022 to 0.137	<0.05	97.2	9.85	0.143 to 0.216	<0.001	0.48	−0.69	−0.077 to 0.037	NS

Degrees of freedom between groups = 1, within groups = 118.
F = ratio between groups/within groups; *t* = paired data *t* = test

respect to those noted before pill use, during which it was possible to observe different values during the three phases of the menstrual cycle; (ii) although they were statistically different, both rhinomanometric and olfactometric values during pill use showed linear outlines similar to those of the luteal phase of the menstrual cycle. The latter aspect could emphasize the particular feature of the monophasic pills whose hormonal activities are mainly progestative, similar to the natural events of luteal phase of the menstrual cycle.

Moreover, there are changes of sexual functioning during the menstrual cycle. Women report less desire to engage in sexual activity and less frequent sexual activity during the late luteal phase than during the other phases of their menstrual cycle (Clayton *et al*., 1999). This could depend on female midcycle total testosterone or free testosterone peak (Morris *et al*., 1987).

Among pill-users substantially lower levels of free testosterone have been observed (Brancroft *et al.*, 1991). Both endocrine and psycho-relational elements may interact (Dei *et al*., 1997). Libido depends on the free testosterone concentrations. Sex hormone-binding globulin concentrations are increased and, therefore, free testosterone concentrations seem to be affected by the use of birth control pills (DeCherney, 2000). The Kallman syndrome, a disorder characterized by hypogonadotrophic hypogonadism and anosmia, could help in understanding the loss of libido during oral contraceptive use. The syndrome indicates the importance of smell in sexual development through the progenitor cells in the olfactory placode because LH-releasing cells of the hypothalamus arise from these cells (Goldzieher and Zamah, 1995). The results of some studies did indeed find that the highest rate of coitus during the female cycle occurs around ovulation (Udry and Morris, 1977). Biologically, odours probably influence reproductive processes in humans and perhaps the notion of concealed ovulation in humans needs rethinking. Pheromones could guide one's sex life (Claus and Karlson, 1983). Thus, ovarian cycle parameters can be drastically changed by chemical cues originating from both male and female co-specifics. Nevertheless, data about the chemical signals that influence ovarian cycle are quite rare (Maiworm and Langthaler, 1990; Wobst *et al*., 1998).

Although our data have confirmed the existence of changes of olfactory sensitivity during oral contraceptive use with respect to non-using time, further studies are needed to investigate ways in which smell variations could vary the sexual life of the subject.

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Received on March 8, 2001; accepted on July 2, 2001