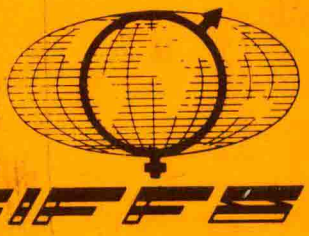

Research on Fertility and Sterility

The Proceedings of the Xth World Congress on Fertility and Sterility

Edited by J.Cortés-Prieto, A.Campos da Paz and M.Neves-e-Castro

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Edited by
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Contents

Section 1
Ovulation

CHAIRMAN: J. Rosner

1

Temporal relationships between ovulation and defined changes in the concentration of plasma 17β-oestradiol, luteinizing hormone, follicle-stimulating hormone and progesterone

WORLD HEALTH ORGANIZATION, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Methods for the Determination of the Fertile Period.*

INTRODUCTION

The principal aim of this study was to relate defined changes in the concentrations of 17β-oestradiol (E_2), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and progesterone (P) in peripheral plasma to the process of ovulation.

MATERIAL AND METHODS

Protocol

At least 20 women in whom laparotomy was to be performed during the periovulatory period were studied in each centre. The subjects were selected according to the following criteria: age between 21 and 40; indication for

*Paper presented by P. R. Figueroa Casas

laparotomy other than the purpose of the study; no evidence or history of endocrine disease, nor of pelvic pathology which could prevent adequate visualization of the ovaries; clinical and auxiliary parameters showing ovulatory cycles (25–32 days long) in the last three cycles; no hormonal contraception during the same time, or during the last six cycles for long-acting contraceptives; and normal haematological parameters. Each woman received detailed explanations about the aim and procedures of the study, and written consent was obtained.

Experimental design

For hospital admission and surgery schedules the expected day of ovulation (EDO) was estimated as the L-13 day of a cycle in which L was the mean length of the last three menstrual cycles. The operation (taken to be on day 0) was provisionally scheduled for the EDO. The time of operation was adjusted according to clinical parameters, and/or results of rapid hormone assays for monitoring follicular maturation, and the availability of local facilities.

A blood sample was taken, at the same time every morning, from days −8 to −4 and on days +3 and +10. The frequency of sampling was increased to three samples daily, usually at 0800, 1600 and 2400 hours, from 3 days before the operation to 2 days afterwards.

Hormone determinations

The plasma concentrations of E_2 (pg/ml), LH and FSH (mIU/ml), and P (pg/ml) were measured, in duplicate, by radioimmunoassay in all samples. All centres were participants in a WHO international quality control scheme for measuring these hormones, and their performance was closely monitored during this study.

Surgical procedure

During laparotomy, ovarian morphology was carefully studied; photographs of the anterior and posterior surface of both gonads against a centimetre scale were taken. An excision biopsy of the mature follicle or corpus luteum was also performed. All these data, including a statement by the surgeon as to whether ovulation had occurred, were noted on a form provided by the WHO.

Ovarian tissues were fixed in Bouin's solution and embedded in paraffin wax. The specimens were sectioned, stained with haematoxylin and eosin, and examined by Dr M. Maqueo with light microscopy, who prepared a report without any clinical information.

Analysis of results

Results from all centres were reviewed by a committee which comprised a clinician, a biochemist, a histologist, a statistician and a member of the

WHO secretariat. A categorical statement (YES or NO) on the occurrence of ovulation before operation was made only if there was agreement between the surgeon's assessment and the histologist's report. Criteria for excluding entire cases were: presence of ovarian abnormalities; violations of protocol; incorrectly labelled specimens or doubtful assay results; and irreconcilable discrepancies between hormonal, clinical and histological results.

Definitions of hormonal events

The first circulating hormone concentration that was one-and-a-half times the mean of the preceding baseline values was regarded as the first significant rise in concentration.

The highest value of LH that was at least three times greater than the preceding mean baseline value was considered as the peak value; similarly, the highest values of FSH and E_2 that were more than double the preceding mean baseline value were regarded as peak values.

Statistical analysis

The statistical analysis included the following steps. Women were grouped by intervals of 8 h from each hormonal event to operation and divided into those who had ovulated and those who had not ovulated at the time of surgery. The range of observed times for each hormonal event within which ovulation occurred were calculated.

The median interval between hormonal events and ovulation were estimated using probit analysis. This technique uses only the information on whether a woman had ovulated before operation and is not dependent on histological dating of the corpus luteum.

The number of subjects who had ovulated among those who underwent the operation less than 8 h after each hormonal event was calculated, giving a normal distribution curve; a cumulative distribution curve was then obtained.

The cumulated distribution data were then transformed, giving a linear distribution, to permit the use of probit analysis.

The time from each hormonal event at which 50% of the women had ovulated and the corresponding confidence limits were estimated. Similarly, the times from each hormonal event at which 5% and 95% of women had ovulated were calculated, thus giving an estimate of the time from each hormonal event within which 90% of women had ovulated. The standard errors of these estimates were also calculated.

RESULTS

A total of 177 women were studied. Of these, 70 were excluded (31 for ovarian abnormalities, 13 for protocol violations, 11 for incorrect labelling

or doubtful assay results and 15 for irreconcilable discrepancies between results); 107 provided results for analysis, although significant rises and peaks could not always be identified for all four hormones due to a lack of baseline values.

Ovulation had occurred at the time of operation in 78 of the acceptable cases.

The distribution of time intervals (in groups of 8 h) from the first significant rises of E_2 concentration to the time of operation (time 0) ranged between −8 and −168 h, and from the peak value of E_2 to operation between 0 and −168 h; from the first significant rise of LH concentration to operation, the range was between +32 and −168 h and from the peak value of LH to operation between +32 and −152 h; from the first significant rise of FSH concentration to operation the range was between +16 and −168 h and from the peak value to operation between +32 and −152 h; the first significant rise of P concentration to operation ranged between +8 and −128 h.

The times from each of the hormonal events within which ovulation occurred were E_2 – rise 48 to 168 h, peak 0 to 48 h; LH – rise 24 to 56 h, peak 8 to 40 h; FSH – rise 8 to 24 h, peak 8 to 40 h; P – rise 0 to 32 h. The median time intervals (in hours) from the first significant rise in the concentration of circulating hormones to ovulation and the 95% confidence limits of the estimates were: E_2, 82.5 (54.0–100.5); LH, 32.0 (23.6–38.2); FSH, 21.1 (14.1–30.9); P, 7.8 (−12.5–15.9).

The first significant rise in E_2 usually occurred when only one blood sample was being taken daily, and the distribution of time interval from this hormonal event to ovulation was so wide that the proportions of women who had ovulated at operation were calculated over 24 h periods. The median time intervals (in hours) from the peak concentrations of circulating hormones to ovulation and the 95% confidence limits of the estimates were: E_2, 24.0 (16.9–32.1); LH, 16.5 (9.5–23.0); FSH, 15.3 (8.1–21.7).

The estimated range of values (in hours) within which 90% of the individual observations could be expected to lie, together with the standard errors of the estimates, were: E_2 – rise 5–160 (SE±22), peak 3–45 (±6); LH – rise 16–48 (±6), peak −3–36 (±5); FSH – rise 9–33 (±12), peak 0–31 (±5); P – rise −12 to 27 (±10).

DISCUSSION

These results have enabled the times between ovulation and defined changes in the concentrations of plasma gonadotrophins and ovarian steroids to be calculated with reasonable confidence. The median time interval from the first significant rise of E_2 to ovulation was 82.5 h, but the confidence limits associated with this estimate were relatively wide (54.0–100.5). This finding raises doubts as to whether this parameter could be safely used