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The World Health Organization Special Program of Research, Development and Research Training in Human Reproduction was established in 1972. In five years, it has grown to an annual fifteen million dollar program involving scientists from 69 countries including 45 developing countries, largely supported by voluntary contributions from member states.[1] Having been closely involved with the task force for the methods for the determination of the fertile period, it is my pleasure to present for WHO an overview of its research work in human reproduction and on the fertile period in particular.

The Special Program addresses itself to all aspects of research in human reproduction including pregnancy, labor, lactation, fetal wastage and infertility. However, the major emphasis of the program is on the regulation of fertility[2] where the principal objectives are:

- to provide WHO member states with a variety of safe, effective and acceptable fertility regulating methods to meet differing needs and different situations, and to assist national authorities in devising the best ways of providing these methods on a continuing basis;
- to strengthen the resources for research in this field, particularly in developing countries, and also to build up, on a world-wide basis, the needed disciplines.

Research in the program is primarily conducted through task forces which are multidisciplinary groups of scientists from different countries and different institutions. Each of these mission-oriented groups is focusing on specific approaches to fertility regulation, bringing

together whatever skills and facilities are required to achieve a given objective in the shortest possible time.

At present there are 17 task forces supporting research on a variety of methods that include pills for women and men; injectable preparations, again for both sexes; intra-uterine devices; methods based on periodic abstinence; sterilization; termination of pregnancy; post-coital preparations; and birth control vaccines.

I have been asked to speak about the work of the Task Force on Methods for the Determination of the Fertile Period as the WHO staff member (Mr. J. Spieler) responsible for this activity was unable to attend this meeting. Reasearch in this task force aims at:

1. assessing in different countries and cultures the currently available methods based on periodic abstinence;
2. improving the service delivery of these methods;
3. evaluating physiological parameters which determine the duration of the fertile period;
4. developing assay kits and devices for predicting and detecting the time of ovulation.

Methods based on periodic abstinence appeal to persons who wish to capitalize on knowledge of the fertile and infertile phases of their menstrual cycle for their approach to family planning, and/or who do not wish to use drugs or devices either because they are concerned about their side effects or for religious or other reasons. Since there is controversy on the effectiveness of methods based on periodic abstinence, even when a considerable effort is made in motivation and teaching, family planning administrators have hesitated to include them in national programs despite their apparent advantages in terms of cost and simplicity of delivery.

The appeal of such methods would perhaps increase if techniques were developed to permit women to determine objectively and precisely the fertile and infertile phases of the menstrual cycle. The development of simple "do-it-yourself" methods for distinguishing these phases should:

1. enhance the effectiveness and perhaps simplify the use of methods based solely on periodic abstinence;
2. allow couples who use certain methods of fertility regulation such as the condom, diaphragm and coitus interruptus, to limit these to the days of the fertile period;
3. allow the use of other new methods which are being developed; e.g., post-coital agents, to be restricted to the ovulatory period; and
4. improve the time of intercourse for conception when pregnancy is desired (especially for infertile couples).

Assessment of currently available methods based on periodic abstinence

Basically there are four main methods of fertility regulation based on periodic abstinence: the calendar method (rhythm); the temperature method (BBT); cervical mucus methods (CM), e.g., the ovulation method (OM) and sympto-thermal method(s) (S-TM). The first method is considered obsolete by most workers in this field because it does not take into consideration normal biological variation and thus does not offer a satisfactory level of protection against unplanned pregnancies. Although the BBT method alone is relatively effective if intercourse is confined to the postovulatory phase of the menstrual cycle, the degree of abstinence required, especially during long or anovulatory cycles, detracts from its use and acceptability. The cervical mucus methods are based on the changes during the menstrual cycle in the quantity and quality of cervical mucus which may be subjectively assessed by women. The sympto-thermal method basically relies on a variety of indications of ovulation including cervical mucus changes, *mittelschmerz*, calendar calculations, etc., combined with BBT measurements. In certain circumstances the sympto-thermal method may be more suitable for a given woman than a cervical mucus method alone, e.g., when difficulty in assessing the changing characteristics of the mucus is experienced. On the other hand, for women using a sympto-thermal method who find that the mucus symptom and BBT end-points which signal the beginning of the postovulatory infertile phase coincide, perhaps the somewhat tedious task of temperature-taking and recording can be abandoned. Nevertheless, the effectiveness of these methods has not yet been unequivocally determined, although it appears to depend greatly upon the motivation of the couple, the quality of the teaching of the methods and the regularity of the phenomena monitored in different women.

In August, 1976, subject recruitment began for a multicenter clinical evaluation of the ovulation method (Billings). Specifically the study is attempting to:

- determine the percentage of women capable of recognizing changes in cervical mucus during the menstrual cycle;
- correlate in a selected number of cycles the changes in cervical mucus with an objective parameter of ovulation, namely progesterone levels;
- correlate the ability or inability of women to observe cervical mucus changes with social and medical data available for the subjects;
- determine the theoretical effectiveness and use-effectiveness of the method in subjects who are capable of detecting changes in the cervical mucus.

In order to obtain a cross-cultural assessment of this method, centers were selected in El Salvador, Ireland, India, New Zealand and the Philippines. The centers were chosen from among those which had previous experience in the method being studied and available qualified teachers. Some special features of the study include:

- selection of women (150-200 subjects per center) who had not previously practiced a cervical mucus method and who were of proven fertility in their marriage/union;
- the inclusion of only "normal" ovulatory women with regular menstrual cycles of intervals between 23—35 days;
- successful completion of a three to five month training period before entry into the main part of the effectiveness study;
- inclusion of subjects from both urban and rural settings at each center.

On May 16-19, at the Task Force Steering Committee meeting in Geneva, Dr. Henry Burger, coordinator of the study, presented these preliminary findings:

a. **The teaching phase** (first three months) has a sufficient number of analyzed results to indicate significant findings, namely:
   - in the first teaching cycle, 95% of charts showed interpretable mucus patterns;
   - within the first three teaching cycles, 90% of the subjects were interpreted as producing good or excellent records.

b. **The effectiveness phase of the study:** Not yet half of the data has been returned and analyzed and it therefore appears premature to present any significant findings. Yet, as a trend, it is interesting that when the conception records of 86 pregnancies occurring in either the teaching or early effectiveness phase were looked at, only 5 could be definitely classified as method failures.

Final results of the teaching phase should be ready around November or December, 1978.

The steering committee, impressed by this low method failure rate confirming the results of other studies, recommended that an *inter-study comparison and analysis of all pregnancies and dropouts* be undertaken to better delineate this phenomenon.

The task force is also supporting a study in Colombia which aims at comparing in 500 randomized subjects the effectiveness of the ovulation method with that of one form of the sympto-thermal method in two cities (Bogota and Cali) and through different health service channels. The investigators in Colombia have experienced more difficulty than they anticipated in recruiting couples for this study. Although preliminary data were presented and discussed in Geneva, these appear too incomplete for any significant presentation at this time. The drop-

out rates were very high during the study and no significant differences are evident between the O.M. and S.T. method effectiveness in the Colombia part of the study. These findings should be more complete one year from now.

Both of the task force trials should be completed in 1979.

Improvement of the service delivery of methods based on periodic abstinence

The educational component of methods based on periodic abstinence plays an even more important role than in other methods of family planning. The extremely wide range of unplanned pregnancies reported for these methods (approximately 0.8—26 pregnancies per 100 women-years as calculated by the Pearl Index) may be due in part to the quality of the instruction provided.

The major emphasis of the work of the task force in this area is to develop, field test and evaluate educational materials (an NFP "Learning Package") which would form the core of a standardized curriculum for instructing NFP non-physician teachers (from nurses to lay members of the community and user-couples) in the use of the two currently most widely practiced methods based on periodic abstinence — the ovulation method and the sympto-thermal method.

The methodology for the development of the NFP Learning Package, called the "Family Fertility Education Learning Package," was designed in December, 1975 in consultation with three NFP consultants. It consisted essentially of four major stages:

1. **Broad consultation** with 30 NFP programs (groups or organizations actively engaged in teaching NFP) with both a program survey and curriculum questionnaire with the curriculum questionnaire being also sent to a further 10 control groups (individual experts conversant in all methods of fertility regulation).
2. **Two face-to-face consultations on the NFP teaching objectives** and the development of the learning package were held in November, 1976 with 14 investigators from 11 countries permitting the British Life Assurance Trust (BLAT), the Center for Health and Medical Education of the British Medical Association and a WHO collaborating center for educational technology, to proceed and develop a prototype NFP Learning Package which includes a guide to teaching and 4 NFP modules or method manuals dealing with:
   - — Fertility Awareness
   - — Sexuality and Responsibility
   - — Ovulation Method
   - — Sympto-thermal Method
3. **The pre-test and evaluation** of the NFP Learning Package in six

countries are currently being done in Canada, Colombia, Kenya, Philippines, South Korea, United Kingdom.

4. The preparation of a second generation improved NFP Learning Package.

Evaluation of physiological events relating to the fertile period

During the past several years researchers in human reproduction have assumed primarily from circumstantial evidence that ovulation occurs approximately 18—24 hours after the LH peak. Aside from a few isolated projects on small groups of women, there has not been any major study performed to obtain a truly accurate estimation of the occurrence of ovulation in relation to changes in several hormonal parameters. Such information would, of course, be extremely useful to all areas of laboratory and clinical research in human reproduction concerned with ovulation. More importantly, in terms of the objectives of the task force, this information is vital as it should lead to the identification of hormonal parameters which could be used as reference points to judge the reliability of methods developed for the prediction of ovulation which are suitable for home use.

During 1977, a 10 center study was completed. It had begun in 1975 on the correlation between ovulation, as determined by observation of the ovaries at laparotomy, and plasma levels of steroids and gonadotrophins in women. Data from approximately 185 cases is presently being analyzed and should provide accurate information on the time interval between ovulation and the LH, FSH and estradiol peaks and the first significant rises of these hormones as well as for progesterone.

At the May 16—19, 1978 task force meeting, preliminary results from 99 cases were presented by Dr. B. William Collins of London, coordinator of the study. The relationship of the LH peak to ovulation revealed no greater precision than earlier studies; 90% of ovulations appeared to occur from 20 hours before to 68 hours after the LH peak.

A method that predicts the time of ovulation and does not also take into account the fertilizing life span of spermatozoa will lead to failures since viable sperm may still be present from coitus which occurred before the immediate periovulatory period. Relatively little is known about the fertile life span of the gametes in humans and there is no practical way of ascertaining it precisely for the individual couple. Last year the task force supported a study aimed at evaluating the fertilizing life span of spermatozoa and the fertilizable life span of ova by retrospective analysis of charts obtained from women who became pregnant while practicing methods of family planning which require temperature recording.

This exploratory study of Dr. M. Bourdais, from France, was reported on at the May, 1978 meeting and its findings and analysis of some 2,300 pregnancy cycles in three different populations (France, Mauritius, Colombia) were reviewed by the steering committee.

Quality of data problems were encountered in such a retrospective approach, both in the charting of the BBT shift (the majority of which had no correlating mucus symptoms) or with the exact recording of intercourses and the data was classified accordingly. A reference point for the analysis of the BBT shift was arbitrarily chosen as the first day of the confirmed hyperthermal level and designated as day +1.

Although occasional rare conceiving intercourses were observed in the -10 to -15 day range before the BBT shift (1% from -12 to -15 inclusive) and (4% from -9 -10 -11 days) the majority of the observations revealed that *95% of all pregnancies resulted from intercourses occurring between the -8 to +1 days and 85% of all pregnancies from -5 to +1 days* giving a very indirect idea of the nature of the fertile period.

It was felt that in order to obtain a truer reflection of the fertile period, based on the fertility rate of intercourses occurring in different days before the BBT shift or around the peak mucus symptom, both a better association or relationship of these reference days to the physiological events should be established and a large prospective study would be necessary. However, serious methodological problems may preclude the conduct of such a study at this time.

Assay Kit Development

The main objective of the work supported in this area is to develop kits suitable for home use, primarily in developing countries, which will permit women to predict and detect the occurrence of ovulation. The task force is trying to devise, for example, a "test-tape" or "dip and read" stick system which measures the concentration of a specific compound in urine and signals in an unambiguous manner "yes" or "no" as to whether a woman is entering a fertile period.

Program efforts have been directed towards the identification of potentially useful markers in readily accessible body fluids, i.e., urine, saliva and cervical mucus.

Urine

a. estrogen and pregnanediol glucuronides

Follicular development leading to ovulation is associated with increased secretion of estradiol and rapidly increasing levels of circulating estrogens initiate the LH surge which precedes ovulation. Since a relatively large percentage of the circulating estrogens are excreted in the urine over a period of 24 hours the measurement of conjugated estrogen metabolites should provide a means of predicting ovulation. Because the relative proportions of the individual estrogen

metabolites were not known, in 1975 the task force began preparing specific reagents (antisera, standards, etc.) which were required for the development of radioimmunoassays to measure the following compounds in samples of unextracted diluted urine: estrone-3-glucuronide, estradiol-3-glucuronide, estriol-3-glucuronide, estradiol-17B-glucuronide and estriol-16α-glucuronide.

During 1976-1977, the methods developed were applied to serial samples of urine collected throughout the menstrual cycle from ovulatory women. The preliminary results indicate that for the prediction of ovulation, the excretion patterns of estriol-16α-glucuronide and estrone-3-glucuronide were more consistent and had better defined peaks than those of estradiol-3-glucuronide, estradiol-17β-glucuronide and estriol-3-glucuronide. The concentrations of estriol-16α-glucuronide and estrone-3-glucuronide significantly increase above baseline values approximately 3 to 4 days before the LH peak, respectively, i.e., approximately 4 to 5 days before ovulation.

An increase in the concentration in urine of pregnanediol-3α-glucuronide is a good indication that ovulation has occurred. Reagents were prepared by the task force for the measurement of this metabolite of progesterone by radioimmunoassay in unextracted diluted urine. The method was applied by four groups of workers to serial samples of urine obtained during 33 ovulatory menstrual cycles. The preliminary results indicate that a significant rise above mean baseline values occurs around two days after the LH peak, that there is a reasonable correlation between the values obtained for the 24 hour collection and the early morning specimens and that there is a good possibility of defining "universal" threshold values indicative of ovulation. The mean values of pregnanediol-3αglucuronide during the follicular and luteal phase of the menstrual cycle were found to be approximately 3 nmol/24 and 17 nmol/24h., respectively. Thus, there appears to be at least five-fold increase in the compound after ovulation. These findings indicate that the measurement of pregnanediol-3α-glucuronide may provide a practical means for detecting the end of the fertile period and the beginning of the postovulatory infertile phase of the menstrual cycle.

The results from the work on estrogen and pregnanediol glucuronides imply that, pending the ability to develop immunological assay systems not requiring the use of radioactive markers, estrone-3-glucuronide, estriol-16α-glucuronide and pregnanediol-3α-glucuronide could potentially form the basis of a "do-it-yourself" kit to predict and detect the occurrence of ovulation early enough to account for the fertilizing lifespan of spermatozoa. Presently, additional studies are being conducted by nine groups in different geographical settings to determine if the findings obtained to date are representative of women throughout the world. Specifically, these additional studies seek to obtain data on the inter-women and the intra-woman variation

in the excretion pattern of these metabolites, the correlation between the concentrations obtained in early morning and 24 hour samples and the temporal relationship between the first significant rise and peak of the metabolites and ovulation.

It is anticipated that collaboration with industry on the development of kits suitable for home use will begin during 1979-80.

To confirm the feasibility of developing such an approach to urinary assay kits for the fertile period, a two-phase study comparing urinary assays with existing NFP method signals (OM and ST parameters) will be launched by the end of 1978 or early 1979, attempting, if possible, to recruit a few selected participants willing to observe their planned pregnancies and post partum return of fertility.

b. LH

The objective of this approach is to investigate the usefulness of urinary LH measurements as a means of detecting ovulation. Although LH reaches its maximum level prior to ovulation, the measurement of this hormone would not operationally permit the prediction of ovulation as the peak does not occur early enough to allow for the fertilizing lifespan of spermatozoa. Previously a task force investigator demonstrated that the radioreceptorassay for human chorionic gonadotrophin shows an equal affinity for LH and was capable of successfully detecting the mid-cycle LH peak in urine. The assay, which has a sensitivity for LH of 50 pg/ml of untreated urine, shows levels of 3-4 ng/ml during the early follicular phase and mean mid-cycle levels of about 40 ng/ml.

In order to avoid the use of radioactive ligands and render the assay suitable for home use, attempts are presently being made to develop an enzyme receptorassay which would give a color change as the endpoint.

Device Development

In an attempt to develop devices which could be used to precisely and reliably predict ovulation, some of the techniques used by bioengineers (e.g., photoplethysmography) have been applied to an investigation of the menstrual cycle. Although the preliminary results obtained appear to indicate that ovulation could be detected by measuring, for example, changes in vaginal thermal conductivity, light reflectance and impedance, it was decided that the techniques used could probably not be transformed into devices which would be acceptable and suitable for home use, especially in developing countries. Nevertheless, the task force will continue some research in this area as the approaches being investigated may lead to the identification of physical parameters which could be used by clinicians as a reference point for determining the time of ovulation.

The clinical evaluation of a biopotential meter (not developed by

WHO) reputed to be capable of detecting ovulation was undertaken in 1976. The meter was designed to measure changes in polarity and magnitude of electrical potential of the body, ovulation being indicated by a reversal of polarity. In only 1 of 35 ovulatory cycles was a change in polarity recorded around the time of ovulation. A change in the magnitude of the potential or polarity unrelated to the time of ovulation was recorded in 5 of the 35 cycles studied. In short, the meter used (which was apparently representative of a number of such meters presently receiving publicity in the press) showed no significant or consistent pattern of change in polarity or potential which could be correlated with cervical mucus symptoms or the BBT shift associated with ovulation.

At present the Task Force is exploring the possibility of developing electronic techniques and instrumentation in an attempt to replace the clinical or basal body temperature thermometer, and the necessity to graph results, by a more acceptable, simple and convenient means to detect the post-ovulatory shift in temperature. Advances in "pocket calculator" technology are such that it now appears feasible to make very simple inexpensive instruments which could, for example, instantaneously take a temperature reading, automatically record it and, at the push of a button, display a sequence of eight previous recordings, plot a graph, or indicate, with a red or green light, if the temperature shift has occurred.

Conclusion

In conclusion, the WHO Task Force on Methods for the Determination of the Fertile Period is supporting research that aims at assessing in different cultures the currently available methods of family planning based on periodic abstinence and at improving their provision. Concurrently, studies are also being pursued to accurately determine the duration of the fertile period and to develop "do-it-yourself" methods to predict and detect ovulation which would be suitable for home use in developing countries. The work of the Task Force requires the participation of scientists from a variety of disciplines including reproduction physiology, obstetrics and gynecology, chemistry, bioengineering, natural family planning and education and should provide valuable information to all areas of human reproduction.

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