# AN APPROACH TO QUANTIFYING BREAKTHROUGH BLEEDING IN ORAL CONTRACEPTIVE STUDIES

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## INTRODUCTION

Breakthrough bleeding has been reported as one of the important causes of dissatisfaction with fertility control methods. Its importance was amply indicated when the WHO Task Force on Acceptability of Fertility Regulating Methods recommended at its 1973 meeting that multinational social science research be initiated on patterns and perceptions of menstrual bleeding (1). Although the methodology and approaches adopted differ from one study to another, every study of contraceptive methods, especially those concerning IUDs and steroidal contraceptives, has described the phenomenon of bleeding associated with the contraception. In some studies, the bleeding is described quantitatively by indices such as the percentage of women reporting the symptoms, or the number of days or number of episodes of bleeding, or by more than one of these indices. In other studies, women are asked to report subjectively whether "increase", "decrease" or "no change" occurs in menstrual bleeding when the period of contraceptive use is compared to the period of precontraception (2,3,4,5). These different approaches in analysis, in addition to differences in the design of the study and conceptual definitions, have made it difficult, if not impossible, to compare results of different studies. In 1976, Rodriguez attempted to standardize the definitions and the method of analysis of the menstrual patterns (6). In a later workshop, problems related to the study of menstrual patterns were discussed more thoroughly, and most of the recommendations made by Rodriguez were accepted with or without modifications (7).

The framework of standardized methodology (6, 7) is more appropriate when the contraceptive method under study tends to disrupt the menstrual cycle completely. In that situation, the use of indices showing only bleeding episodes (which includes all types of bleeding--menstrual or intermenstrual) is valid. But with oral contraceptives (OCs), there are two distinct types of bleeding which occur cyclically; combining the two and ignoring their distinctiveness can in no way be justified. Equating the effects of one episode of breakthrough bleeding with withdrawal bleeding on acceptability and continuation is not only undesirable, but also objectionable. Moreover, there is a definite need for treating each contraceptive cycle, especially the earlier ones, separately because of (a) evidence of a stabilization trend in breakthrough bleeding during the use of the first few contraceptive cycles, and (b) higher differences in the incidence of breakthrough bleeding among different OCs during the first and second cycles of use (2). Therefore, it is recommended that for the study of oral and other contraceptives which have cyclical patterns of bleeding, a reference period should consist of one contraceptive cycle rather than a period of 60 or 90 days (6,7).

This paper presents an approach, differing from that of Rodriguez, for quantifying breakthrough bleeding in oral contraceptive users. A method of computing an index of breakthrough bleeding is discussed which not only can be used to compare bleeding patterns of different OCs but is also useful to relate this symptom to a woman's medical, physiological, and biological profile. It is assumed that there are two main dimensions of this symptom, namely, persistence and severity (Snowden, reference 7, has described them by duration of bleeding and volume of blood loss), and each dimension has more than one level. Thus, a multivariate observation consisting of two levels of persistence (number of days of bleeding and number of episodes of bleeding in a contraceptive cycle) and three levels of severity (spotting, and light and heavy bleeding) describes the breakthrough bleeding pattern of a woman. Three severity levels of bleeding have been considered instead of two (considered in references 6 and 7) because of the different effects they may have on acceptability and continuation rates. These three levels can be suitably defined or modified to reflect the degree of dissatisfaction in the cultural context of the country. This six-variate information was converted to a composite index because any index based on one of the variates was not found to be comprehensive enough to include information on all aspects of bleeding. The composite index thus derived was used to study differential patterns of breakthrough bleeding for three groups of women using Ovral (ethinyl estradiol 0.05 mg and dl-norgestrel 0.5 mg), Norinyl (mestranol 0.05 mg and norethindrone 1.0 mg), and Norlestrin (ethinyl estradiol 0.05 mg and norethindrone acetate 1.0 mg).

## MATERIALS AND METHOD

The data were obtained in a double-blind comparative study on Ovral, Norinyl and Norlestrin carried out in 1974 at the Planned Parenthood Clinic of Seattle, Washington. A sample of 480 women who had no contraindications for OC use, including no irregularities in their menstrual cycles, and who had not used steroidal contraceptives in the preceding three months were randomly assigned to one of these study OCs and given three cycles of supply, each containing 21 hormonal and seven placebo tablets. Information on 27 symptoms associated with OC use was collected by a public health nurse who telephoned each subject every two weeks to ask whether she had experienced any symptom (which women associate with OC use) since her last contact. Inquiry was made about each such symptom in order to ensure the reporting of all pertinent events, and the information was recorded on a symptom grid by the day on which symptoms appeared (2).

Only the information on intermenstrual vaginal bleeding during the period hormonal pills were taken in the first cycle of OC use was

utilized in the analysis. Questions were asked about the day when breakthrough spotting or bleeding occurred, whether protection by tampons or pads was required, and in what quantity. Events of breakthrough bleeding were defined in this study as spotting, when no protection was needed; light bleeding, requiring one pad a day; and heavy bleeding, when two or more pads were used. Future studies may alter these definitions, when appropriate, to reflect the degree of dissatisfaction in the cultural context of the population under study.

The choice of a composite index based on both the dimensions of breakthrough bleeding was made because of its comprehensiveness in covering information on all aspects of bleeding; this is not possible if one or more levels of one dimension is used as an index (Table I). The first component of the Principal Component Analysis was used as an index. Because more than one such index can be obtained by adopting variations of the Principal Component technique on the same set of variables or by using different subsets of the variables, a choice of the "best" index was made based on the degree of information on different aspects of breakthrough bleeding contained in the index. (Eigenvectors vary by the choice of the matrix used to extract eigenvalues. Variance-Covariance matrix gives a set of eigenvectors different from the ones obtained from the correlation matrix.)

## DEVELOPING AN INDEX TO QUANTIFY BREAKTHROUGH BLEEDING

### Choice of variables

The combinations of two levels of persistence and three levels of severity resulted in the following six variables ($X_1$, $X_2 \ldots X_6$) which cover most of the information on breakthrough bleeding on an individual woman:

$X_{1(2,3)}$ = Number of days of spotting (light bleeding, heavy bleeding)

$X_{4(5,6)}$ = Number of episodes of spotting (light bleeding, heavy bleeding)

Because the first set of three variables are different in measurement units from the second, it was desirable either to convert them into comparable units or make them unitless (dimensionless) so that they might be combined into one index. For this purpose, the observed measurements (X's) were converted to percentages (P's) by relating them to the overall value for the population. (Because the purpose was to obtain dimensionless variables, any average value could have served.) That is, the new variables $P_i$'s were obtained in the following fashion:

$$P_i = [X_i / X_i(A)] \times 100$$

Where:

$X_i$ = observed value of the $i$th variable

$X_i(A)$ = average value of $X_i$ $\left(\frac{\sum_{j=1}^{n} x_{ij}}{n}\right)$,

where n is the number of women on whom the information on the $X_i$ variable was available

Thus, the redefined six-variate information for women used in the development of the index is:

$P_{1(2,3)}$ = Number of days of spotting (light or heavy bleeding) for a woman as the percentage of the average number of days of spotting (light or heavy bleeding) in the population under study

$P_{4(5,6)}$ = Number of episodes of spotting (light or heavy bleeding) for a woman as the percentage of the average number of episodes of spotting (light or heavy bleeding) in the population

### Choice of several indices

Once these variables were made dimensionless, the next step was to look for a comprehensive index which includes the most information contained in the six variables. The first consideration was whether one of the variables could serve as the index. To test it, a correlation matrix consisting of correlation coefficients between different P's was computed. It may be seen (Table I) that a single variable is not sufficient to be an index because it does not contain information on the other variables. Thus, a need for a composite index was indicated. The first component of the Principal Component Technique on the six-dimensional vector ($P_1, P_2 \ldots P_6$) is a valid index, often used by statisticians to represent a multivariate observation more parsimoniously (8, 9, 10). Geometrically, this index is a linear combination of the variables which cover the maximum variance in the sample scatter configuration. For computations, BMD computer programs prepared by the University of California, Los Angeles, were used (10). The first principal component was obtained by deriving the weights from the eigenvector corresponding to the largest eigenvalue of the variance-covariance or correlation matrix of the multivariate observations. The breakthrough bleeding score for an individual was then obtained from the product of the vector of the standardized variables and the eigenvector. That is, if $(b_1, b_2 \ldots b_k \ldots)$ is an eigenvector corresponding to the largest eigenvalue, the breakthrough bleeding score for the individual is obtained as

$$\frac{b_1(P_{i1}-\bar{P}_1)}{\sigma_{P_1}} + \frac{b_2(P_{i2}-\bar{P}_2)}{\sigma_{P_2}} + \ldots + \frac{b_k(P_{ik}-\bar{P}_k)}{\sigma_{P_k}} + \ldots$$

where $\sigma_{P_k}$ is the standard deviation for variable $P_k$, $P_{ik}$ is the observed measurement (as derived for this study), and $\bar{P}_k$ is the mean measurement of the variable $P_k$. Two modifications were done to derive scores for this analysis.

Table I

CORRELATION COEFFICIENTS BETWEEN DIFFERENT VARIABLES AND INDICES

| Variables & Indices | Variables $P_1$ | $P_2$ | $P_3$ | $P_4$ | $P_5$ | $P_6$ |
|---|---|---|---|---|---|---|
| $P_1$ | 1.000 | | | | | |
| $P_2$ | 0.073 | 1.000 | | | | |
| $P_3$ | -0.055 | 0.141 | 1.000 | | | |
| $P_4$ | 0.744 | 0.125 | -0.045 | 1.000 | | |
| $P_5$ | 0.104 | 0.707 | 0.123 | 0.197 | 1.000 | |
| $P_6$ | 0.0002 | 0.184 | 0.820 | -0.009 | 0.227 | 1.000 |
| $I_1$ | 0.6850 | 0.656 | 0.198 | 0.718 | 0.681 | 0.305 |
| $I_2$ | 0.317 | 0.693 | 0.595 | 0.369 | 0.733 | 0.688 |
| $I_3$ | 0.125 | 0.695 | 0.778 | 0.062 | 0.513 | 0.635 |
| $I_4$ | 0.303 | 0.576 | 0.430 | 0.445 | 0.811 | 0.659 |

(1) The scores were approximated as

$$\frac{b_1}{\sigma_{P_1}}(P_{i1}) + \frac{b_2}{\sigma_{P_2}}(P_{i2}) +\ldots+ \frac{b_k}{\sigma_{P_k}}(P_{ik})+\ldots$$

and

(2) $(\frac{b_1}{\sigma_{P_1}}, \frac{b_2}{\sigma_{P_2}}, \ldots)$ were so chosen that

$$\Sigma_k(\frac{b_k}{\sigma_{P_k}}) = 1$$

These two modifications were advantageous in that a woman whose breakthrough bleeding measurements for all six variables were equal to the average in the sample, would score 100.

Using this method, several indices could be developed from the six-variate information on breakthrough bleeding. This was done in two stages. In the first stage, two indices were developed by introducing slight variation in the Principal Component Technique--one of them used a variance-covariance matrix of the six variates to extract eigenvalues and eigenvector and the other used the correlation matrix. As we will see in the next section, the index corresponding to the correlation matrix was found to be better. Thus, in the next stage, correlation matrix was used to extract the eigenvectors. In this stage an attempt was made to determine whether all six variables were needed or whether a subset of them, either $P_1$ to $P_3$ or $P_4$ to $P_6$, could by itself lead to an index as good as the one based on $P_1$ to $P_6$. Thus, two more indices were computed, one based on ($P_1$, $P_2$, and $P_3$) and the other on ($P_4$, $P_5$, and $P_6$).

Choice of the "best" index of breakthrough bleeding

The "best" index is the one which contains most of the information on breakthrough bleeding available in each of the six variates ($P_1$, $P_2 \ldots P_6$). The operational meaning of this definition is that the index which has the maximum correlation with the individual variable $P_1, P_2 \ldots P_6$ will be the "best". Four indexes considered for the selection of the "best" were the following:

$I_1$: Index based on ($P_1$, $P_2 \ldots P_6$), eigenvector obtained from the variance-covariance matrix of the six variables

$I_2$: Index based on ($P_1, P_2 \ldots P_6$), eigenvector obtained from the correlation matrix of the six variables

$I_3$: Index based on ($P_1$, $P_2$, $P_3$), eigenvector obtained from the correlation matrix of the three variables

$I_4$: Index based on ($P_4$, $P_5$, $P_6$), eigenvector obtained from the correlation matrix of the three variables

The correlation coefficients between these indices and the individual variables ($P_1$, $P_2$, $\ldots P_6$) are shown in Table I. $I_3$ has very low correlation with $P_1$ and $P_4$ and thus can be omitted when compared to others. Between $I_2$ and $I_4$, $I_2$ is preferred for higher correlation with most of the variables $P_1$ to $P_6$, though $I_4$ has higher correlation coefficients with $P_4$ and $P_5$. $I_2$ is to be preferred over $I_1$ because of (1) overall higher correlation with all variables $P_1$ to $P_6$ and (2) higher correlation with the heavy breakthrough bleeding (variables $P_3$ and $P_6$), a more serious side effect. Thus $I_2$, the "best" index of breakthrough bleeding, is given by

$$I = 0.0676P_1 + 0.163P_2 + 0.200P_3 + 0.104P_4 + 0.205P_5 + 0.255P_6$$

The order of the magnitude of weights may be noted--variables corresponding to heavy bleeding get more weight than those corresponding to

Table II

DISTRIBUTION OF WOMEN USING OVRAL, NORINYL AND NORLESTRIN BY THE BREAKTHROUGH BLEEDING SCORE

| Breakthrough Bleeding Score | Types of Oral Contraceptives | | |
|---|---|---|---|
| | Ovral (%) | Norinyl (%) | Norlestrin (%) |
| 0 | 128 (90.1) | 72 (51.4) | 66 (47.8) |
| 0-10.0 | 2 (1.4) | 3 (2.1) | 3 (2.2) |
| 10.0-20.0 | 5 (3.5) | 8 (5.7) | 7 (5.1) |
| 20.0-30.0 | 4 (2.8) | 20 (14.3) | 20 (14.5) |
| 30.0-40.0 | 1 (0.7) | 9 (6.4) | 9 (6.5) |
| 40.0-50.0 | 0 (0.0) | 6 (4.3) | 7 (5.1) |
| 50.0-60.0 | 0 (0.0) | 8 (5.7) | 8 (5.8) |
| 60.0-70.0 | 0 (0.0) | 4 (2.9) | 8 (5.8) |
| 70.0-80.0 | 1 (0.7) | 1 (0.7) | 3 (2.2) |
| 80.0-100.0 | 1 (0.7) | 3 (2.1) | 4 (2.9) |
| Over 100.0 | 0 (0.0) | 6 (4.3) | 3 (2.2) |
| Mean Score (all users) | 2.7 | 20.9 | 22.6 |
| Mean Score (breakthrough bleeders) | 27.5 | 43.0 | 43.4 |

light bleeding which, in turn, get more weight than those for spotting. Also, those corresponding to number of episodes are relatively more important than those related to total number of days.

## APPLICATION

This index was used to obtain breakthrough bleeding scores for 480 women using Ovral, Norinyl, and Norlestrin in the Seattle study. The distribution of women by their scores and mean scores is given in Table II. The distribution of breakthrough bleeding scores for Ovral users was significantly different ($P<0.01$) from the similar distributions exhibited by Norinyl and Norlestrin users.

## SUMMARY AND DISCUSSION

The usual indices of breakthrough bleeding, such as the percent of women reporting breakthrough bleeding and the duration or the number of episodes of bleeding, are not adequate to quantify breakthrough bleeding associated with OC use because they do not contain information on all aspects of bleeding. A composite index was therefore developed by using information on two levels of persistence and three levels of severity of breakthrough bleeding. It was found that more severe bleeding and more frequent episodes of bleeding (rather than days of bleeding) had higher weights in the index. This index was used to quantify breakthrough bleeding scores for women using Ovral, Norinyl, and Norlestrin; Ovral users had significantly different patterns, compared to Norinyl and Norlestrin users whose patterns were similar to each other.

Because breakthrough bleeding is an important factor contributing to dissatisfaction among OC users, it is recommended that more detailed data be collected to develop the composite index. The Principal Component Technique may be used to determine the coefficients of a linear combination of the variables because the coefficients may differ from one population to the other. Such an index can assign scores to individual women; the next step is to identify some medical, physiological, and biological variables which are positively associated with these scores. Such investigation will be helpful in better education and management of the OC acceptors.

Although the index developed here has been discussed in the context of oral contraceptive use, the technique is quite general and can be used for measuring breakthrough bleeding in any setting. It is generally applicable in any situation where multivariate data are to be presented in fewer dimensions to make them more comprehensible.

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