

The Puerto Rico oral contraceptive study: An evaluation of the methodology and results of a feasibility study

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Summary

The Puerto Rico oral contraceptive study, begun in 1961, was the first attempt to evaluate the long-term safety of oral contraceptives (OCs). In addition, it was the only large-scale study employing randomisation of healthy subjects into OC and non-OC groups. Financial support ended in 1976. In 1979, the International Fertility Research Program (IFRP) undertook a feasibility study to assess the value of resuming the project's funding. The systematic sample was generally representative of the original cohort. Only 24.5 per cent of the 212 patients in the feasibility sample had been active (visited the clinic) in the last six months of 1976. More than half of the long-term users (two years or more of their assigned contraceptive) were not active in 1976. A pilot field study estimated that approximately half of those inactive in 1976 could be located. It is concluded that loss to follow-up and lack of full information on contraceptive usage are too great to restart the project as originally conceived.

Purpose, design and execution of the study

In 1961, Dr Gregory Pincus originated the idea of a long-term study of oral contraceptive use among Puerto Rican women. It was a pioneer undertaking, several years in advance of epidemiological studies conducted on the same drugs in Europe and the United States.

The primary purpose of the Puerto Rico oral contraceptive study is reflected in its original study title: 'Clinical trials of anticancer effect on the breast and genital system of women using an

oral contraceptive.'^{*} The study began in 1961, one year after oral contraceptives (OCs) were marketed in the United States. In addition to the study of breast and genital cancer, the project was also designed to investigate various clinical phenomena (varices, hirsutism, chloasma, obesity and effect on menstrual cycles, etc) among OC users.

Prospective enrollees for the trial were recruited from women attending the Puerto Rican family planning clinics in Rio Piedras, Caguas and Ponce. Volunteers who fulfilled the eligibility requirements were randomly allocated into two groups: one group using oral contraceptives,^{**} and the other (control) group using diaphragms, jellies, creams or foams, but excluding any form of intracervical or intra-uterine devices. At admission, women were given the assigned contraceptives and instructed to return at the end of the first month and every other month thereafter to receive a fresh supply of contraceptives, at which time a bimonthly visit form was completed. A physical examination was performed if indicated; all women remaining in the study were scheduled to have a physical examination at least once a year after admission. When a patient missed a bimonthly appointment, she was to be visited at her home by a nurse or social worker. The specifications for these procedures are described in greater detail elsewhere.^{1, 2}

^{*}The study title was later changed to 'Program for maternal health and family planning.'

^{**}Enovid: 5 mg norethynodrel and 0.075 mg mestranol, G. D. Searle and Co, Chicago, Illinois.

The study began shortly after oral contraceptives were introduced and before some of the major questions concerning the use of this contraceptive method had been defined. The logistics of running a large epidemiologic study of contraceptive users had not yet been explored. But the study was close to an ideal, well-controlled experimental design, and had the following unique features:

- It was the only prospective study for which the OC and non-OC users were assigned at random; hence, self-selection of the subjects at the time of the study was avoided.
- The study began in 1961 and ran until 1976. The observational period was one of the longest of any prospective study of contraceptives, and evaluation of the possible long-term effects of OCs on women as well as on their offspring was therefore possible.
- The study recruited a group of women who had never been exposed to OCs or IUCDs prior to admission to the study, so that the study population was 'pure and homogeneous' in this respect.
- The study was begun before associations of OCs with thromboembolic disorders and other rare events were suspected; hence, women categorised as high-risk were included. Therefore, possible interactions between OCs and these predisposing factors in terms of incidence of the suspected associated diseases could be examined.

In addition, Puerto Rico is an island and it offered its population general accessibility to medical care, two features that facilitated the execution and analysis of a prospective study.

A total of 9,757 women were recruited for the study from July 1961 to October 1969: 4,925 in the OC group and 4,832 in the comparison group. The successful randomisation of subjects was confirmed in a study by Dr Abelardo Fuertes-de La Haba (the principal investigator from 1968 to 1978) *et al.*¹ Relevant information at admission and at each follow-up was loaded on computer tape. Follow-up of the subjects was discontinued in 1976 because of lack of funds.

Thus far, several publications have been generated from these data. Comparisons of OC and non-OC users failed to demonstrate

significant or meaningful differences in deaths, incidence of thromboembolic disorders, thyroid status, carbohydrate metabolism, changes in cervical cytology, or intelligence quotients and congenital malformations of offspring.²⁻³

Further studies—Sample size considerations

Data on the incidence of breast and cervical cancer are available from the Puerto Rico cancer registration system for the year 1976.⁹ Women aged 30–59 years in 1976 roughly approximate the present age structure of the Puerto Rican women who were admitted to the prospective oral Pill study during the years 1961–1969 and who were between the ages of 21 and 39 years at the time of admission.

The desirable sample sizes for studying these two types of cancers were estimated under the following assumptions:

- The distribution of women in this age range and the average incidences of these two cancers in the past ten years were similar to those of 1976. One obtains estimated ten-year incidence rates among those who were not exposed to the agent under investigation (OCs):
 - rate = 0.006 for breast cancer
 - rate = 0.009 for cervical cancer
- Type 1 error (α) is set at 0.05 (two-sided) and type 2 error (β) at 0.10.
- A relative risk (R) of 2.0 or more is considered to be scientifically important to detect.

According to Schlesselman's tables,¹⁰ the sample size required for each group (exposed and nonexposed) in a cohort study is:

Breast cancer, $N = 5,199$

Cervical cancer, $N = 3,450$

Thus, the original sample sizes in the Puerto Rico study appeared adequate if the women had adhered to the assigned regimen, could be followed up, and were correctly diagnosed.

Feasibility study

A feasibility study by record review was carried out from March 10–18, 1979, in order to evaluate the present status of the Puerto Rico oral contraceptive study. Data on key variables such as follow-up rate, length of use of assigned contraceptive, switch-over rate and number of

live births after admission into the study were abstracted from the original files. In addition, sociodemographic and clinical information was recorded on the data collection forms.

The original plan called for the systematic selection of one out of every 30 records from Rio Piedras and one out of every 20 records from Caguas and Ponce. Given the total sample size of the Puerto Rico study, this would produce a feasibility sample of 394 records. A search of the files, however, revealed the large loss to follow-up in the latter two clinics, so it was decided to concentrate on the records from Rio Piedras and to examine only a small number from Caguas and Ponce. (These two clinics were forced to close in 1976 because of lack of funds.)

A total of 212 records were abstracted and loaded on computer tape—188 from Rio Piedras (systematic 1-in-30 sampling), 11 from Caguas (unsystematic), and 13 from Ponce (unsystematic). This sample includes 111 women from the OC group and 101 women from the comparison group (Table 1). Because of the small number of records from the Caguas and Ponce centres, a centre-specific analysis would not be illuminating, and data are hereafter presented for the pooled OC and non-OC strata.

The representativeness of this feasibility sample can be tested by using the summary data presented in Fuertes-de La Haba *et al.*¹ For year of admission to the study, the sample is distinct from the cohort; women in both the OC and non-OC sample groups were significantly more likely to be admitted to the study in the earlier part of the 1960s than were women comprising the full cohort. However, the feasibility sample is representative of the original cohort for age at admission, educational achievement and parity

at admission. Furthermore, the sample of OC and non-OC groups are not significantly different in regard to these sociodemographic variables.

Before a discussion of the follow-up data of interest, two caveats must be noted. As previously mentioned, the sample does differ significantly from the cohort in terms of centre and year of admission. It is not possible to determine whether the sample is skewed or biased for other variables that could affect the conduct of the trial (*eg*, by occupation or distance between residence and clinic), since the IFRP data collection form abstracted limited information. The other point is a methodological one. The dearth of charts from the Caguas and Ponce clinics obviates a clinic-specific analysis of the data. Pooling of data from different centres may mask differences in the subgroups and thus produce a nonsignificant summary test result. For these reasons, we recommend caution in the evaluation of the feasibility sample results.

Follow-up rates in both contraceptive groups were disturbingly low. Only 23.4 per cent (26/111) OC users and 25.7 per cent (26/101) non-OC women were active (*ie*, visited the clinic) in the last six months of 1976. Reasons for loss to follow-up are tabulated in Table 2.

Data on the duration of use of the assigned contraceptive are also discouraging. In the OC group, 37.8 per cent of the women used orals for two years or more. The corresponding figure in the vaginal contraceptive group is 52.5 per cent. For this variable, however, there are rather large percentages in both contraceptive groups with missing information (Table 3).

Among the women for whom we have data available for both of the preceding variables,

Table 1 Assignment of contraceptive by clinic in the original cohort and the feasibility sample

	Orals		Vaginals	
	Cohort	Sample	Cohort	Sample
Rio Piedras	2,807	101	2,787	87
Caguas	509	5	486	6
Ponce	1,609	5	1,559	8
Total	4,925	111	4,832	101
X ² for homogeneity:	Orals: cohort vs sample		p < .01	
	Vaginals: cohort vs sample		p < .01	
	Sample: orals vs vaginals		p = .51	

Table 2 Status at follow-up by contraceptive, feasibility sample (percentages in parentheses)

	Orals	Vaginals
Active in 1976	26 (23.4)	26 (25.7)
Dead, migrated, untraceable, refused to cooperate	49 (44.1)	38 (37.6)
Other (menopause, sterilised, pregnancy, side effects)	21 (18.9)	18 (17.8)
Missing data	15 (13.5)	19 (18.8)
Total	111	101

X² = 1.62 p = .65

Table 3 Duration of use of assigned contraceptive, feasibility sample (percentages in parentheses)

	Orals	Vaginals
Duration in months		
1-5	11 (9.9)	8 (7.9)
6-11	16 (14.4)	13 (12.9)
12-23	20 (18.0)	12 (11.9)
24-35	10 (9.0)	7 (6.9)
36-47	7 (6.3)	4 (4.0)
48-59	4 (3.6)	10 (9.9)
60-150	17 (15.3)	31 (30.7)
151-998	4 (3.6)	1 (1.0)
Missing	22 (19.8)	15 (14.9)
Total	111	101

$X^2=13.47$ $p=.10$

55.3 per cent (21/38) of those using OCs for two years or more were lost to follow-up; 67.3 per cent (33/49) of those using vaginal contraceptives for two years or more were lost. Over 70 per cent of the women using their assigned contraceptives for less than two years were lost to follow-up. About one tenth (21/212) of the women switched contraceptive mode (including eight from an OC to a non-OC and 13 from a non-OC to an OC).

Another objective of the feasibility study was to measure the size of the cohort of offspring of the volunteers. Among the 111 oral users, 40 children had been born since entrance into the study (28 boys and 12 girls). Fifty-one children were listed among the vaginal users (30 boys and 21 girls).

Regular Papanicolaou smears were included in the medical examinations of the volunteers, and the results of these tests were abstracted. Eleven women in the OC group (9.9 per cent) had ever had at least one abnormal Papanicolaou smear, and the same number had ever had at least one abnormal result in the non-OC group (10.9 per cent). There were two cases of invasive cancer of the cervix detected in this sample, both in women who had used vaginal contraceptives. Light, moderate or severe dysplasia was noted in nine OC users and in seven vaginal contraceptive users.

A pilot study was conducted in order to gauge what percentage of those women designated as lost to follow-up by our record review could be located. The first 30 cases that were lost to follow-up from the Rio Piedras clinic were chosen. Two social workers identified 14 of

these women; most had moved within Puerto Rico, one resided in Massachusetts, two dropped out of the study following hysterectomies, and one woman had been committed to a psychiatric hospital.

Conclusions

The original cohort study, launched in 1961, was a responsible and reasonable attempt to examine the risks and benefits of OC use. The initial randomisation procedure was flawless and produced very 'congruent' cohorts of oral and vaginal contraceptive users. Unfortunately, this well designed study appears to have suffered from the serious logistical and financial problems of any long-term follow-up study. Records cannot be maintained properly in the face of changes in funding, changes in personnel, and eventual lack of these key resources. The family planning and public health community should recognise the value of long-term epidemiologic studies on physiologically active contraceptives and make every effort to continue them.

The sample taken in 1979 suggests that the only types of studies that should be pursued with the Puerto Rico data are small-scale investigations not dependent on randomisation for their validity. Problems with adherence to regimen, switching of regimen, the large amount of loss to follow-up and the lack of complete information in the patient charts preclude the study of rare events and the monitoring of gynaecological cancers. However, the children born to these women after they joined the study could form the population for an examination of any trans-generational effects of long-term OC use. The possibility of anatomical or physiological abnormalities of the reproductive system in the female offspring of the OC users is an important matter. A substantial number of these girls are entering puberty and attaining adulthood, and an analysis of their morbidity experience and menstrual patterns would be one way in which the usefulness and significance of the Puerto Rico OC study could be extended.

Acknowledgements

Partial support for this work was provided by the International Fertility Research Program with funds from the US Agency for International Development. The authors are grateful for the cooperation of the Maternal Health Program, Department of Obstetrics and Gynecology of the University of Puerto Rico.

References

1. Fuertes-de La Haba A., Bangdiwala I. S., Pelegrina I. Success of randomisation in a controlled contraceptive experiment. *J Reprod Med* 1973; 11: 142-8.
2. Fuertes-de La Haba A., Curet-Cuevas J. O., Pelegrina I. *et al.* Deaths among users of oral and non-oral contraceptives. *Obstet Gynecol* 1970; 36: 597-602.
3. Fuertes-de La Haba A., Vega-de Rodriguez G., Pelegrina I. Carbohydrate metabolism in long-term oral contraceptive users. *Obstet Gynecol* 1971; 37: 220-4.
4. Fuertes-de La Haba A., Curet-Cuevas J. O., Pelegrina I. *et al.* Thrombophlebitis among oral and non-oral contraceptive users. *Obstet Gynecol* 1971; 38: 259-63.
5. Vega-de Rodriguez G., Fuertes-de La Haba A., Pelegrina I. Thyroid status in long-term, high-dose oral contraceptive users. *Obstet Gynecol* 1972; 39: 779-83.
6. Fuertes-de La Haba A., Pelegrina I., Bangdiwala I. S. *et al.* Changing patterns in cervical cytology among oral and non-oral contraceptive users. *J Reprod Med* 1973; 10: 3-10.
7. Fuertes-de La Haba A., Santiago G., Bangdiwala I. S. Measured intelligence in offspring of oral and non-oral contraceptive users. *Am J Obstet Gynecol* 1976; 125: 980-83.
8. Ortiz-Pérez H. E., Fuertes-de La Haba A., Bangdiwala I. S. *et al.* Abnormalities among offspring of oral and non-oral contraceptive users. *Am J Obstet Gynecol* 1979; 134: 512-17.
9. Cancer en Puerto Rico, Registro Central del Cancer, Programa Control del Cancer, Departamento de Salud, 1976.
10. Schlesselman J. Tables of the sample size requirement for cohort and case-control studies of diseases. National Institute of Child Health and Human Development, Bethesda, Maryland, 1974.

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