

# Four Decades of Research on Hormonal Contraception

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## Introduction

The first hormonal contraceptive was approved for marketing in the United States in 1960. This contraceptive, known then and now as “the pill,” was taken orally and consisted of an estrogen and a progestin designed to be taken by women.

The combined estrogen/progestin oral contraceptive was a breakthrough in contraception for three reasons: because it was highly effective for preventing conception; because, unlike the condom and the diaphragm, the effectiveness of the oral contraceptive does not depend on its being used in conjunction with the act of intercourse; and because, unlike tubal ligation and vasectomy, the effect of the oral contraceptive is reversible. Female hormonal contraceptives administered by injection, transdermally, vaginally, and released from a subdermal implant are now available in the United States and elsewhere. All these contraceptive agents are based on the same general physiologic-biochemical principles as “the pill.” Hormonal contraceptives have been used by at least 500 million women alive today.

Kaiser Permanente (KP) became involved in oral contraceptives in the mid-1960s and has been actively involved in research on hormonal contraceptives since the late 1960s. This review describes the historical background of KP initial research

on oral contraceptive safety and the contributions of KP research on hormonal contraception in the subsequent four decades.

## Walnut Creek Contraceptive Drug Study

Even before oral contraceptives were marketed, concern about the noncontraceptive health effects of these drugs was acute. Similar concerns about safety have accompanied introduction of other forms of hormonal contraception.

All hormonal contraceptives designed for use by women involve exogenous administration of synthetic estrogen, progestin, or both at doses that have been termed “unphysiologic.” Administration of exogenous estrogen and progestin can alter secretion of hypothalamic, ovarian, and other hormones and thus can theoretically affect multiple organ systems and physiologic processes. As early as the 1930s, exogenous administration of estrogen was known to cause breast malignancy in some rodent species.

Soon after these drugs were first marketed, the US Food and Drug Administration (FDA) began to receive spontaneous reports of venous thromboembolic events and stroke in users of oral contraceptives. Published reports of thromboembolic events<sup>1,2</sup> heightened concern about the safety of oral contraceptives.

By the mid-1960s, the need for epidemiologic studies of the noncontraceptive effects of oral contraceptives on women's health had become apparent. The enormous popularity of “the pill” brought recognition that tens of millions of women in the United States and hundreds of millions worldwide would be exposed to exogenous hormones over many years. Thus, any effect of oral contraceptives on cancer or other health conditions had enormous public health implications.

In 1966, in response to concern about the safety of “the pill,” Dr James Shannon (then Director of the National Institutes of Health, NIH) transferred \$3 million to the National Institute of Child Health and Human Development (NICHD) to study this problem, and a decision was made to commission a large cohort study to evaluate the noncontraceptive health effects of oral contraceptives. Dr Philip Corfman (later to become NICHD's Director of the Center for Population Research) and Dr Daniel Siegel (an NIHCD statistician) investigated several possible sites for such an ambitious study—including the Mayo Clinic, the Health Insurance Plan of New York, and the US Department of Defense—but none appeared to have as much interest or ability as the KP Northern California Region to conduct such a study.

KP was considered a potential research site because personnel at

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# Special Feature

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the FDA had worked with Morris Collen, MD—a founder of The Permanente Medical Group (TPMG)—on a project to collect electronic data on prescriptions and on outpatient and inpatient diagnoses to facilitate identification of adverse drug effects. Personnel at NICHD were familiar with the capabilities of KP because they had worked with Jacob Yerushalmy, PhD, (a University of California at Berkeley statistician affiliated with KP) on the Collaborative Perinatal Project. This was an epidemiologic study that included data collection from more than 50,000 pregnant

women and long-term follow-up of outcomes in these women as well as their offspring. The KP Oakland Medical Center was a research site in the project.

In 1967, NICHD officials approached Dr Collen about KP's interest in conducting the epidemiologic cohort study. KP decision makers decided to conduct the study at the KP Walnut Creek Medical Center. The study began in 1968 with Fred Pellegrin, MD, and Irwin Fisch, MD, as the Co-Principal Investigators. Later, Drs Pellegrin and Fisch recruited Savitri Ramcharan, MD—who had trained in epidemiology at the Uni-

versity of California Berkeley School of Public Health under Dr Yerushalmy—to head the study, which was named the Walnut Creek Contraceptive Drug Study (WCCDS).

The first participants in the WCCDS were recruited in late 1968. From 1968 through early 1972, a total of 16,638 women aged 18 to 54 years were recruited into the follow-up study of oral contraception. An additional 1800 women who were pregnant or recently postpartum were recruited to a special cross-sectional study. Active follow-up of women in the WCCDS continued through 1978. From its start

**Table 1. Kaiser Permanente studies of hormonal contraception**

Study	Regions	Description	Kaiser Permanente investigators	Publications	
				About hormonal contraception	Ancillary questions
Walnut Creek Contraceptive Drug Study	Northern California	Prospective cohort study involving 16,638 women aged 18-54 years at entry	S Ramcharan, MD F Pellegrin, MD I Fisch, MD D Petitti, MD	3-13	14-18
Kaiser Permanente Birth Defects Study	Northern California	Study of pregnancy outcome in 34,350 women whose contraceptive history was recorded at time of first antenatal visit	S Ramcharan, MD F Pellegrin, MD P Shiono, PhD	19-24	25,26
Kaiser Permanente Cardiovascular Disease Study	Northern and Southern California	Case-control study examining risks of myocardial infarction (MI) and stroke in oral contraceptive users on the basis of interviews with 187 MI cases, 347 stroke cases, and 1552 controls	D Petitti, MD S Sidney, MD C Quesenberry, PhD A Bernstein, MD A Klatsky, MD S Wolf, MD	27-31	32,33
Emergency Contraception Demonstration Project	Southern California	Demonstration project to assess feasibility and acceptability of repackaging combination estrogen/progestin oral contraceptives as emergency contraception	D Petitti, MD D Preskill, MD D Postlethwaite, RNP	34-38	--
Venous Thromboembolism Study	Northern and Southern California	Case-control study examining risk of venous thromboembolism (VTE) in oral contraceptive users on the basis of interviews with 299 VTE cases and 819 controls	S Sidney, MD D Petitti, MD C Quesenberry, PhD	39	--
Walnut Creek Lipid and Lipoprotein Study	Northern California	Cross-sectional analysis of lipid levels in relation to oral contraceptive and other hormone use in 4978 women aged 21-62 years	D Bradley, MD J Wingerd, MS S Ramcharan, MD	40	41,42
Cervical Cancer Study	Northern California	Case-control study examining risk of invasive cervical cancer in oral contraceptive users on the basis of interviews with 69 cases and 216 controls	S Swan, PhD W Brown, MD	43	--

-- = no references address ancillary questions

until its last publication, the study included analyses conducted by a number of visiting researchers, including Susan Harlap, MD (an Israeli scientist then on sabbatical), Valerie Beral, PhD (a United Kingdom scientist then on sabbatical), and Diana Petitti, MD, MPH (then an Epidemic Intelligence Service (EIS) officer with the US Centers for Disease Control and Prevention [CDC]). Dr Petitti continued to work with data from the study well into the 1980s. Supplemented by data from record linkage, from chart review, and from reexamining subjects, data from the study were used in studies published as late as 1993.

Table 1<sup>3-43</sup> separately lists WCCDS publications that address issues of contraception<sup>3-13</sup> and that address other topics related to women's health.<sup>14-18</sup> The total number of these publications is large. Equally important are other contributions of the WCCDS to research in the KP Northern California Region specifically and in KP more generally. The WCCDS helped to establish the reputation of KP in epidemiologic research, demonstrated KP's ability to recruit subjects for large studies, and helped develop the infrastructure for conducting federally funded research at KP.

### The Kaiser Permanente Birth Defects Study

In the early 1970s, studies from other countries raised concern about the possibility that use of hormonal contraceptives might affect a fetus in either of two circumstances: 1) when the fetus was conceived during use of oral contraceptives (which failed to prevent pregnancy) or 2) as a carry over from past exposure to hormones. Success of the WCCDS led the WCCDS team to receive an award from NICHD to conduct a study evaluating the effects of hormone exposure during

early gestation on birth defects. At the first antenatal visit, the study collected information from more than 35,000 women receiving prenatal care at the KP Oakland, Hayward, Richmond, and Walnut Creek Medical Centers in Northern California. Pregnancy outcomes were ascertained by chart review.

Publications from this study—the KP Birth Defects Study—are listed in Table 1.<sup>19-26</sup> As with the WCCDS, data from the Birth Defects Study were used to answer not only questions about the effect of contraceptives on birth defects but also many other questions about pregnancy outcome. In addition to its substantive contribution to knowledge about birth defects, the study further demonstrated the research capabilities of KP, enhanced the reputation of KP in the community, and contributed to the development of an infrastructure for conducting research in KP Northern California.

### Vascular Disease Case-Control Studies

Epidemiologic studies conducted in the 1970s and 1980s established the increased risk of venous thromboembolism, ischemic stroke, and myocardial infarction from use of combined estrogen/progestin oral contraceptives. Shortly after reports first appeared describing vascular disease in oral contraceptive users, doses of estrogen in combined estrogen/progestin oral contraceptives were lowered in an attempt to reduce the vascular risks of oral contraceptive use. Attempts were also made to limit oral contraceptive use to women who were not at high risk for vascular disease (because of smoking or hypertension, for example). By the middle of the 1980s, confidence was high that changes in estrogen dose and in selection by clinicians of women for oral contra-

ceptive use had successfully reduced the vascular risks of oral contraceptive use; however, empirical data to prove this point were limited.

In 1988, NICHD issued a request for proposals for case-control studies of the risk of stroke and myocardial infarction in users of low-estrogen-dose oral contraceptives. KP was successful in its bid for a contract to conduct this study. The study was a milestone for KP insofar as data collection for the research spanned both the KP Northern and Southern California Regions.

The study of stroke and myocardial infarction was followed by an identically designed study that assessed the risk of venous thromboembolic disease in users of low-estrogen-dose oral contraceptives. For the study, data were collected in both the KP Northern and Southern California Regions. These data were the subject of publications addressing the primary question at the outset of the research<sup>27-31,39</sup> as well as ancillary questions<sup>32,33</sup> about vascular disease epidemiology in women of reproductive age (Table 1). The studies were important for establishing the success of interregional collaborative research.

### Emergency Contraception Demonstration Project

As early as 1975, researchers and clinicians recognized that a high dose of combination estrogen/progestin oral contraceptives could prevent pregnancy if taken shortly after an unprotected act of intercourse. (A hormonal contraceptive drug taken this way was initially called "the morning-after pill" and was later renamed "emergency contraception.") This practice constituted off-label use of combined estrogen/progestin oral contraceptives and was not widespread.

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**Table 2. Other publications on hormonal contraception involving Kaiser Permanente members, data, and researchers**

Description	Kaiser Permanente contribution	Publications
Multicenter collaborative study	KP members were subjects. KP researchers coauthored study publications.	44-46
Case reports of adverse events in oral contraceptive users	Data derived from medical records of KP members. Publications authored by KP researchers.	47,48
Discussion of methodologic problems in the study of oral contraceptives	Publications authored by KP researchers.	49,50
Review of the effects of hormonal contraception	Publications authored by KP researchers.	51-57

Beginning in the mid-1990s, several women's advocacy groups began to promote emergency contraception and to educate the public and physicians about it. Emergency contraception was difficult to promote, in part because it required physicians to provide individualized instruction on how to break up a package of combined oral contraceptives. Moreover, combined estrogen/progestin oral contraceptives exist in many different formulations containing different amounts of estrogen and progestin. Thus, the number of pills to be taken differs for different formulations of combined estrogen/progestin oral contraceptives.

In 1996, KP was approached by the Pacific Women's Health Institute (a not-for-profit women's health research institute based in Los Angeles) about a possible joint project designed to demonstrate the feasibility and acceptability of promoting hormonal emergency contraception in a community setting. External funds were secured to conduct such a project in San Diego County, but partner organizations in San Diego withdrew from the project because of concern about legal liability of promoting off-label use of a drug. The project went forward through KP in San Diego.

The project was highly successful

and was the KP Southern California Region's nominee for the Vohs Award for Quality<sup>37</sup> as well as the basis for several publications (Table 1).<sup>34-36,38</sup> The success of the project at KP was influential in the decision of other organizations (for example, Planned Parenthood and various community clinics) to get involved in promoting emergency hormonal contraception.

### Other Studies and Contributions

Table 1 lists other research studies on hormonal contraception conducted solely at KP.<sup>40-42</sup> KP researchers and KP data made additional contributions to knowledge about hormonal contraception (Table 2).<sup>44-57</sup> These contributions take many forms, including case reports, new methodology for contraceptive research, and reviews and summaries of the relevant medical literature.

### Summary and Conclusion

The availability of hormonal contraceptives spawned changes in the social relations between men and women and enabled revolutionary changes in the roles of women in society. The contribution of hormonal contraception to improving the status of women worldwide is difficult to overestimate. Studies that

have established the magnitude of risks and benefits of hormonal contraception have been instrumental for developing policies regarding hormonal contraception and for providing information that helps individuals and couples to make informed choices about childbearing.

For almost four decades, KP researchers have made sustained contributions to the advancement of knowledge on hormonal contraception. Data collected in studies of hormonal contraception have been used to address a variety of other important questions about women's health. Participation in research on hormonal contraception has made important contributions to the research infrastructure of the KP Northern and Southern California Regions and at KP nationally. Research on hormonal contraception has enhanced the research reputation of KP locally, nationally, and internationally. ❖

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## The Impossible

The difficult is that which can be done immediately; the impossible takes a little longer.

— George Santayana, 1863-1952, Spanish-American philosopher, poet and critic