Journal Title: Progress in clinical and biological research.
ISSN: 0361-7742 (Print)
Volume: 112 Pt A **Issue:**
Month/Year: 1982
Pages: 287-300

Article Author: Greenblatt RB
Article Title: Contraception for middle aged women.

**Recent Advances in Fertility Research, Part A:
Developments in Reproductive Endocrinology, pages 287-300**

CONTRACEPTION FOR MIDDLE AGED WOMEN

Robert B. Greenblatt, M.D.

Professor Emeritus of Endocrinology
Medical College of Georgia
Augusta, Georgia 30912

The term middle aged is employed to signify that part of a woman's lifetime when the period of greatest reproductivity has passed, though the chances of conception still remain. She is at risk even though such an eventuality diminishes considerably after the age of 40. Fertility supposedly comes to an end with the onset of the menopause. But does it? The so-called menopausal baby is not mythological but an occasional happening. For several years before the actual onset of the menopause a woman experiences erratiy menstrual cycles, ovulation becomes more and more sporadic, and episodes of amenorrhea occur, lasting from a few months to a year or longer. Such women, believing they are in the menopause, throw caution to the winds and fail to guard against conception. Then the unexpected can and does happen.

Though pregnancy in women after age 50 is extremely rare, a review of New York City statistics for the years 1940-50 reveals 20 childbirths to women in this age group or one among 1,500,000 deliveries (Kaufman 1969). The epidemiological data of risk of death from pregnancy, according to Tietze and Lewit (1977), increases with age: 8.1/100,000 in those under age 25 and 22.6/100,000 in those over 40. There are many other undesirable aspects to pregnancy and these are maternal morbidity and genetic disorders in the offspring. Apart from maternal mortality and morbidity, the mere threat of an unwanted pregnancy carries with it considerable emotional and psychological trauma. It is therefore far more vital for the middle aged woman to be properly protected than it is for the younger woman. However, the U.S. Food and Drug Administration and the International Planned Parenthood Federation recommend

that women over the age of 40 should utilize forms of contraception other than the pill. This decision was reached as a result of the 1975 clinical papers by Mann and his associates (Mann et al. 1975; Mann, Inman 1975) and the epidemiological reports of the Royal College of General Practitioners (1977), Mann et al. (1976) and Vessey et al. (1977). Several authoritative bodies believed it prudent to suggest that the age limit for oral contraceptive use be lowered to 35, and even to 30 years (Anon 1977; Planned Parenthood memorandum 1977). The investigations of Inman and Vessey (1968) point to a precarious rise in mortality figures for women over age 35 on oral contraceptives.

Though there is increasing evidence that the benefits of the pill should be rigorously weighed against associated risks, I question the wisdom of abandoning all forms of hormonal contraception until the evidence of alleged danger is more thoroughly evaluated. Many students of the subject have rejected the retrospective and prospective reports as statistical games (Drill 1972; Goldzieher, Dozier 1975; Geller 1978). Even hormone replacement therapy for the ageing female has been inveighed against by a number of American publications (Smith et al. 1975; Ziel and Finkle 1975; Mack et al. 1976) alleging a cancer linkage; but at the same time this treatment is also staunchly defended by others (Gordon, Greenberg 1976; Greenblatt, Stoddard 1978; Hammond et al. 1979; Gambrell 1978). More thought therefore needs to be given to the dilemma.

Oral contraceptives in the premenopausal woman have been indicated as responsible for the markedly increased incidence of myocardial infarction, thromboembolic disease and liver and gall bladder disorders. The reports of Mann et al. (1975), and Mann and Inman (1975) emphasize the interaction between myocardial infarction and oral contraceptive use and other predisposing risk factors, especially after 35 years of age. Vessey et al. (1977) reported 43 deaths among 17,032 women participating in the Oxford/Family Planning Association contraceptive study. Nine deaths from cardiovascular causes were observed among the women on oral contraceptives (49,681 women-years of observation), while no such deaths occurred among women who entered the study using a diaphragm or an IUD (39,146 women-years of observation). A perfunctory study of this report, however, raises some doubts as to the real meaning of the data. Of the 9 deaths, 3 had prior heart disease, 3 had a history of toxemia and all but 2 were smokers (Table 1). Sturtevant (1977) was concerned with this myocardial infarct/

TABLE 1. Clinical history of 9 women users of oral contraceptives who died from cardiovascular disease

Clinical history	N	Cigarettes smoked/day	Age
Heart disease	3	12; 0; 5	47;37;32
Mitral valve disease Bundle branch block, age 27 Fallot' tetrology			
Toxemia	3	20;20;20	37;36;28
None	3	17;15; 0	37;36;35

(After Vessey et al. 1977)

oral contraceptive problem, and showed that Mann's original data project poorly to actual mortality in the United Kingdom and hardly at all in the United States. Actually, Mann and Inman (1975) did recommend that their statistics be interpreted with caution, since the margin of error was fairly wide. The FDA recommendation was to warn all women over 40 years of age against using oral contraceptives. Berger (1977) reanalyzed the studies by Mann and his associates and concluded that the existence of other predisposing risk factors was more important than age. Moreover, Berger believes that for roughly 75% of women in this age group who do not have other predisposing conditions, this warning has no validity. He believes that high risk women of any age should be cautioned against the use of oral contraceptives. Furthermore, according to a recent analysis by Jain (1976), the excess risk of non-fatal myocardial infarction among oral contraceptive users observed in England and Wales can be explained by the high proportion of smokers in the study population. Jain felt that much better results in reducing risk could be achieved by eliminating smoking than by eliminating oral contraceptives.

Nonetheless, it would be imprudent to ignore the data offered by the Royal College of Practitioners study (1977), which shows that acute myocardial infarction is more than 3 times greater in oral contraceptive users than in controls, and which also shows a similarly alarming incidence of cerebrovascular accidents (subarachnoid hemorrhage, cerebral hemorrhage, and thrombosis). However, the impact of the data is defused when one goes on to read that pill users have a 3 times greater risk of committing suicide or being murdered than non-users (Table 2).

TABLE 2. Mortality rate of oral contraceptive users per 100,000 women-years

Cause of death	Ever users	Controls
Breast cancer	3	6
Acute myocardial infarction	7	2
Cerebro-vascular diseases	10	3
Complication of pregnancy	0	2
Suicide-homicide	7	2
Other causes	29	30
Total	56 (58%)	45 (40.9%)

(Modified from Royal College of General Practitioners, 1977, Table II)

Following the first publication on myocardial infarction by Boyce (1963) in the United Kingdom, a rash of individual case reports appeared in the journals of many other countries; but it was only after the publication of Mann and Vessey's Oxford/Family Planning study that the problem began to seriously be considered outside the United Kingdom. Their findings found ready corroboration in the United States (Jick et al. 1978; Rosenberg 1976). Jain (1976), however, refuted the British studies and injected the concept that there was a strong association between cigarette smoking and mortality rates in oral contraceptive users (Table 3). Ory (1978), and Ramarcharan et al.'s Walnut Creek Study (1980) pointed out, as Jain had done, that myocardial infarction was due more to smoking than to the pill.

Newer reports by the 2 major groups in the United Kingdom are now far less alarming and it appears that they are having second thoughts. At one time, a limitation on the length of contraceptive use was suggested; the latest Royal College of General Practitioners study (1981) admits, "We no longer find an increasing risk of death due to vascular disease with increasing duration of the pill" (Layde et al. 1981). A very recent publication in the *New England Journal of Medicine* contradicts the British experience, thus further obfuscating the issue (Slone et al. 1981).

TABLE 3. Mortality associated with pregnancy and childbirth, legal abortion, oral contraceptives (by smoking status), and IUD's, by age.

Age (years)	Pregnancy and childbirth*	Legal abortion†	Oral contraceptives‡§		IUDs‡
			Non-Smokers	Smokers	
15-19	11.1	1.2	1.2	1.4	0.8
20-24	10.0	1.2	1.2	1.4	0.8
25-29	12.5	1.4	1.2	1.4	1.0
30-34	24.9	1.4	1.8	10.4	1.0
35-39	44.0	1.8	3.9	12.8	1.4
40-44	71.4	1.8	6.6	58.4	1.4

* Per 100,00 live births (excluding abortion), USA, 1972-1974
† Per 100,000 first trimester abortions, USA, 1972-1974
‡ Per 100,000 users per year
§ Estimates by Dr. AK Jain
(Reproduced from: Greenblatt RB (1980). "The Development of a New Triphasic Oral Contraceptive," Lancaster, Engl: MTP Press, p 9)

TABLE 4. Clinical history of women users of oral contraceptives who died from cardiovascular disease: additional series.

Age at death	Smoker	Pill use	History	Cause of death	Months pill use discontinued
44	Yes	114 mos.	Hypertension; By-pass one year later	Myocardial infarction after surgery	18 mos.
32	Yes	53 mos.	Preeclampsia	Inhaled vomitus 2 wks. later	50 mos.
46	Yes	23 mos.	Toxemia	Miocardial infarction	96 mos.
44	Yes	109 mos.	Hypertension	Coronary insufficiency from trimiparamine overdose	84 mos.
42	No	No	Cerebrovascular accicent after delivery	Hepatic artery aneurism	—
41	No	No	Rheumatic aortic valve disease	Cardiac arrest	—
44	No	No	Hypertension	Subarachnoid hemorrhage	—

(Data compiled from Vessey et al. (1981))

In a "Letter to the Editor," Vessey et al. (1981) of the Oxford group commented, "Our findings do not suggest that the pill is a cause of subarachnoid hemorrhage." In their continued cohort studies, 7 more deaths were recorded: 4 myocardial deaths in sometime pill users, all smokers, occurred at age 44, 32, 46 and 44, respectively, and 18, 50, 96 and 84 months after cessation of pill use. Each had a poor history: one had hypertension with by-pass surgery, another had pre-eclampsia with inhalation of vomitus; one had hypertension, and another had toxemia (Table 4). Should oral contraceptives be condemned on such evidence? Both the Oxford group and the Royal College of General Practitioners, nonetheless, maintain that the pill is involved in the etiology of myocardial infarction.

Jordan (1961) suggested a link to thromboembolism; Lorentz (1962) to cerebral thrombosis; Boyce et al. (1963) to coronary thrombosis; and Woods (1967) to hypertension. Many other anecdotal case reports kindled the interest and imagination of the epidemiologist. Some published their findings with complete scientific detachment; others, rapacious, were anxious for the kill. At first, case control and later cohort studies were undertaken to determine the risk factor. Table 5 (retrospective studies) and Table 6 (prospective studies) list the risk

TABLE 5. Retrospective studies on deep vein thrombosis in pill users.

Investigators	Year	Risk
Royal College of General Practitioners	1967	3.0
Vessey, Doll	1968-9	6.3
Inman, Vessey	1968	8.3
Sartwell	1969	4.4
Boston Collaborative Drug Surveillance	1973	11.0
Stolley	1975	7.2

(Data compiled from Guichoux JY (ed): "Bilan Medical des Traitements Oestroprogestatifs," Paris: Maloine SA Editeur, 1979)

TABLE 6. Prospective studies on deep vein thrombosis in pill users.

Investigators	Year	Risk
Fuertes de la Haba	1971	1.8
Royal College of General Practitioners	1974	5.6
Kay	1975	5.6
Vessey	1976	2-3
Diddle	1978	1

(Data compiled from Guichoux JY (ed): "Bilan Medical des Traitements Oestroprogestatifs," Paris: Maloine SA Editeur, 1979).

factors for deep vein thrombosis. The findings of the different epidemiologic studies varied considerably. For instance, in the case control studies on thromboembolism, the risk factor varied from 1 to 11; in cohort studies, from 1.5 to 8.0 (Vessey 1980). Drill (1972) and Goldzieher (1975) attacked the findings—each concluded that there was not sufficient proof to place responsibility on the pill. Barnes and his associates (1978) claim that with the use of sophisticated techniques, the clinical diagnosis of venous thromboembolism was in error in 69% of non-pill users, an error that reached 83% in pill users. In our great concern, we failed to consider the natural history of the disease. Even in men, thromboembolism is a much more frequent cause of death than hitherto suspected. Although oral contraceptives do increase the incidence of thromboembolism, the weighted incidence is much less than alleged.

Oral contraceptives probably do contribute to increased mortality and morbidity in women aged 35 and over, but if the premenopausal woman is to be denied oral contraceptives, it is necessary to know what appropriate methods of conception control are available other than the low dosage oral contraceptive regimens.

OTHER HORMONAL METHODS

The Mini-Progestagen Pill (Continuous). Progestagen pills containing very small doses, are being used for conception

control to obviate the role of oestrogens believed to be responsible for many of the untoward effects of the pill. Chlormadinone, noregestel, norethindrone acetate, lynoestrenol, megestrol acetate and ethynodiol diacetate continue to be evaluated. Martinez-Manautou felt that low-dosage progestagens were advisable in premenopausal women who do not show symptoms of hypoestrogenism. Cyclic menstruation continues until the menopause arrives; however, approximately one-third of cycles are irregular. Table 7 records the results of this study of women under and over 35 years of age, revealing a relatively high pregnancy rate (Martinez-Manautou et al. 1974). Some of the newer studies with other progestagens indicate a more favorable contraceptive potential.

TABLE 7. Contraceptive therapy with 0.5 µg chlormadinone acetate in women under and over 35 years of age.

	Age (years)	
	< 35	> 35
No. of women	2,379	100
No. of cycles	49,903	1,570
Pregnancy (Pearl Index)	4.4	3.0
Incidence of amenorrhea	2.5	3.2
Incidence of BTB	10.1	8.3
Length of menstrual cycles (days)		
21-24	21.6	14.0
25-35	65.3	61.0
36-59	19.6	21.8

Source: Martinez-Manautou et al. (1974)

Injectable Progestagens. Since 1963 medroxyprogesterone acetate has been extensively studied as an injectable contraceptive. Its contraceptive action is believed to be derived primarily from suppression of ovulation. The drug is injected intramuscularly, usually in doses of 150 mg at 3-month intervals. It has been widely used and found highly acceptable in the developing countries. In the United States, the drug has

not as yet been approved by the FDA. The method is highly effective (Ellinas, 1977). Unsatisfactory aspects are breakthrough bleeding and the required visit to the doctor every 3 months. It is said to depress some women and to have a dampening effect on libido.

Estradiol Pellet Implants at 6-Month Intervals. First, it should be understood that all estrogens are not the same. The offending agent in the oral contraceptive is thought to be the synthetic estrogen, ethinyl estradiol or mestranol, and the hazards increase with the age of the patient, duration of treatment, and strength of dose. Would this hold true if naturally occurring estrogens were employed? My group used estradiol-17β pellets for conception control in 144 women, aged 35-50 years, for 7,099 cycles with only 1 pregnancy for a Pearl Index of 0.169 (Greenblatt et al. 1979). This regimen is believed to be an excellent alternative for the hormonal control of conception and especially suitable for the premenopausal woman.

One might wish to question the rationale of using natural estrogens for conception control in this age group, in view of the condemnatory evidence already presented for oral contraceptives in general. The answer is that few of the untoward effects caused by synthetic estrogens have been observed by long-term users of natural estrogens. It may be conjectured that the body (liver and kidney) programmed to conjugate, detoxify, and excrete natural estrogens, is taxed when a foreign unphysiological preparation is administered over a prolonged period of time.

Estradiol Pellet Implants. In an earlier study the experience with 42 premenopausal women was reported (Greenblatt et al. 1977). The series was then extended to 144 women; 65 women aged 35-39, 52 aged 40-44, and 27 aged 45-50 years (Greenblatt et al. 1979). Because women of these ages are less fertile than younger women, many were started with only three pellets, while others had only two (Table 8). The maintenance dose of one pellet may be continued indefinitely with satisfactory results. Only one patient conceived while on that dosage. Fortunately, she aborted spontaneously early in the first trimester. It is mandatory that a 7-10 day course of an oral progestagen such as medroxyprogesterone acetate (10 mg) or norethindrone acetate (5 mg) be administered at monthly intervals to induce orderly withdrawal uterine bleeding. The most common untoward effects were hypermenorrhea, and masto-

TABLE 8. Step-down courses of estradiol pellets in 144 premenopausal women.

Pellets	Courses	Cycles	Pregnancy
4	50	300	0
3	65	780	0
2	285	3,427	0
1	216	2,592	1
TOTAL	616	7,099	1

(Reproduced from Greenblatt et al. (1979). J biosoc Sci Suppl 6:119)

dynia. Many of the presenting complaints before the start of estrogen therapy were ameliorated by the estradiol pellet implantations. In those with sexual dysfunction (loss of libido) that did not respond to estradiol alone, a pellet of testosterone was added to the regimen with excellent results (Table 9).

TABLE 9. Amelioration of incidental systems in premenopausal women while receiving estradiol pellets for contraception.

Symptoms	No. of patients	Relief of Symptoms	
		No. of Patients	%
Headaches	20	18	90
Loss of Libido	44	38	86.4*
Irregular menses	17	17	100
Nervousness	26	23	88.5
Depression	13	12	92.3

** A pellet of testosterone was often added*

(Reproduced from Greenblatt et al. 1979)

Incidents such as myocardial infarction, cerebrovascular accidents, or thromboembolic disease were not encountered in this limited series; many women were under observation for 5-10 years or longer. If, as has been frequently implied, endogenous estrogens in the normally menstruating women play a role in lessening the tendency to heart attacks, then there is no reason to believe that the use of natural estrogens for conception control would not offer the same protective cover.

The method is particularly suited for the premenopausal woman who may wish to continue the low-dosage estrogen (one pellet every 6 months or longer) in her advancing years—effectively preventing the onset of hot flushes and sweats, minimizing the tendency to osteoporosis, and in most instances, eliminating or decreasing the frequency and severity of menopausal migrainoid headaches and the annoying mood changes so prevalent at this time in a woman's life.

REFERENCES

Anon (1977). Editorial. Lancet 2:747.

Barnes RW, Krapf T, Hoak JC (1978). Erroneous clinical diagnosis of leg and vein thrombosis in women on oral contraceptives. Obstet Gynecol 51:556.

Berger GS (1977). Oral contraceptives and myocardial infarction. N C Med J 38:323.

Boyce J, Fawcett JW, Noall EWO (1963). Coronary thrombosis and Conovid. Lancet 1:111.

Drill VA (1972). Oral contraceptives and thromboembolic disease. JAMA 219:583.

Ellinas SP (1977). Experience with medroxyprogesterone acetate as an injectable contraceptive. Int J Gynaec Obstet 14:145.

Gambrell RD Jr (1978). The prevention of endometrial cancer in postmenopausal women with progestogens. Maturitas 1:107

Geller S (1978). "La Pillule, 20 Ans Apres," Marseille: Medi print.

Goldzieher JW, Dozier TS (1975). Oral contraceptives and thromboembolism: a reassessment. Am J Obstet Gynec 123:878

Gordon GS, Greenberg BG (1976). Exogenous estrogen and endometrial cancer. Postgrad Med 59:66.

Greenblatt RB, Asch RH, Mahesh VB, et al. (1977). Implantation of pure crystalline pellets of estradiol for conception control. Am J Obstet Gynecol 127:520.

Greenblatt RB, Nezhat C, McNamara VP (1979). Appropriate contraception for middle-aged women. J biosoc Sci Suppl 6:119.
Greenblatt RB, Stoddard LD (1978). Estrogen-cancer controversy. J Am Geriat Soc 6:1.
Hammond CB, Jelovsek FR, Lee KL, et al. (1979). Effects of long-term estrogen replacement therapy. I. Metabolic. Am J Obstet Gynecol 113:537.
Inman WHW, Vessey MP (1968). Investigation of deaths from pulmonary, coronary and cerebral thrombosis and embolism in women of childbearing age. Br Med J 2:193.
Jain AK (1976). Cigarette smoking, use of oral contraceptives and myocardial infarction. Am J Obstet Gynecol 126:301.
Jick H, Dinan B, Rothman KJ (1978). Oral contraceptives and non-fatal myocardial infarction. JAMA 239:1403.
Jordan WM (1961). Pulmonary embolism. Lancet 2:1146.
Kaufman SA (1969). Fertility and conception after age forty. Obstet Gynec NY 3:288.
Layde PM, Beral V, Kay CR (1981). Further analysis of mortality in oral contraceptive users. Lancet 1:541.
Lorentz IT (1962). Parietal lesion and Enovid. Br Med J 2: 1191.
Mack TN, Pike MC, Henderson BE, et al. (1976). Estrogens and endometrial cancer in a retirement community. N Engl J Med 294:1262.
Mann JI, Inman WHW (1975). Oral contraceptives and death from myocardial infarction. Br Med J 2:245.
Mann JI, Inman WHW, Thorogood M (1976). Oral contraceptive use in older women and fatal myocardial infarction. Br Med J 2:445.
Mann JI, Vessey MP, Thorogood M, et al. (1975). Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 2:241.
Martinez-Manautou J, Ramos RA, Giner J (1974). The premenopausal woman: her fear of pregnancy and choce of contraception. In Greenblatt RB, Mahesh VB, McDonough PG (eds): "The Menopausal Syndrome," New York: Medcom Press, p 162.
Ory HW (1977). Association betwen oral contraceptives and myocardial infarction: a review. JAMA 237:2619.
Ramarcharan E, Pellegrin FA, Ray R, et al. (1980). The Walnut Creek Contraceptive Drug Study: a prospective study of the side effects of oral contraceptives: a comparison of disease occurrence leading to hospitalization or death in users and nonusers of oral contraceptives. J Reprod Med 25 (Suppl):345.
Royal College of General Practitioners (1977). Oral contraceptive study: mortality among oral contraceptive users. Lancet 2:727.

Slone D, Shapiro S, Kaufman DW, et al. (1981). Risk of myocardial infarction in relation to current and discontinued use of oral contraceptives. N Engl J Med 305:420.

Smith DC, Prentice R, Thompson DJ, et al. (1975). Association of exogenous estrogen and endometrial carcinoma. N Engl J Med 293:1164.

Sturtevant FM (1977). Comments on epidemiological studies relating myocarcial infarction and oral contraceptives. In Garattina S, Berendes HW (eds): "Pharmacology of Steroid Contraceptive Drugs," New York: Raven Press, p 297.

Tietze C, Lewit S (1977). Mortality and fertility control. Int J Gynaec Obstet 15:100.

Vessey MP, McPherson K, Johnson B (1977). Mortality among women participating in the Oxford/Family Planning Association contraceptive study. Lancet 2:731.

Vessey MP (1980). Female hormones and vascular disease—an epidemiological overview. Br J Fam Plann 6(Suppl):1.

Vessey MP, McPherson, Yeates D (1981). Mortality in oral contraceptive users. Lancet 1:549.

Woods JW (1967). Oral contraceptives and hypertension. Lancet 2:653.

Ziel HK, Finkle WD (1975). Increased risk of endometrial carcinoma among users of conjugated estrogens. N Engl J Med 293:1167.