MEDICAL GRAND ROUNDS

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MEDICAL COMPLICATIONS OF ORAL CONTRACEPTIVES

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The first report of the inhibition of ovulation by hormones was by Makepeace et al in 1937 who found that progesterone did so in rabbits (1). In 1940, Sturgis and Albright suggested the use of estrogen for suppression of ovulation to relieve painful menstruation (2). Three years later, Lyon reported the successful use of cyclic estrogen therapy to inhibit ovulation and control the recurrent symptoms of dysmenorrhea (3). But since the dysmenorrhea recurred despite the continued use of cyclic estrogen therapy, the mistaken belief that "pituitary escape" with ovulation occurred was generally held and the use of estrogens for contraception was overlooked.

After World War II and the rise of interest in population control, G. Pincus and co-workers demonstrated suppression of ovulation, first in rabbits by progesterone in 1953, and by synthetic progestogens in 1956 and then, in 1958, by a combination of estrogen and progestogens, in women (4). Until the last few years, almost all oral contraceptives have been a combination of an

estrogen and a progestogen. But the increasing awareness that the estrogen component was responsible for many of the side effects has prompted the investigation and use of low-dose progestogens alone, the "mini-pill". In addition, the need for a "morning-after" pill has led to approval of high dose estrogen, usually diethylstilbesterol, despite its known propensity to cause cancer in girls whose mothers had received estrogens during their pregnancy.

Problems with all of these oral contraceptives have led to the development of new techniques such as the IUD and the more widespread application of older techniques such as vasectomy. Research into multiple possible methods of contraception continues.

This presentation will only consider problems with the presently available oral contraceptives: estrogen-progestogen combinations, progestogens alone and high dose estrogens alone.

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4. Pincus G, Garcia CR, Rock J, et al: Effectiveness of an oral contraceptive. Science 130:81, 1959.

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7. Advisory Committee on Obstetrics and Gynecology: Second Report on the Oral Contraceptives. Food and Drug Administration, 1969. (Library #QV 177 U57s)

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I. THE NEED AND CURRENT USE OF CONTRACEPTIVES

American women in 1965 preferred a family size of 3 children (12). In 1965, the total fertility rate per woman in the U.S. was 2.92. Since then the fertility rate has continued to fall, reaching 2.48 in 1968. But many want to limit the growth of our population further and all wish to provide adequate contraceptive protection to all who need and want it. There are still many women who have more children than they want. Fewer of them do so for religious reasons; the birth control practices of U.S. Roman Catholics now closely approximate those of non-Catholics with 78% of those Catholic women ages 20-24 using methods other than rhythm (13). And this defection from Church teaching has been pronounced among women who receive Communion at least once a month (bottom, Table I).

But many women are denied adequate contraception because of social-economic-cultural factors. In 1965, the following percentages of wives 18 to 39 years of age had never used contraception of any type:

- 35% of whites and 42% of blacks with an elementary school education
- 15% of whites and 18% of blacks with a high school education

The situation has improved. Westoff and Ryder's National Fertility Study of 1970 showed that the number of unwanted births had declined by 35% for whites and 56% for blacks between 1965 and 1970 (14). As shown in Table I, more women are using the more effective methods. But many are still using no or inadequate contraceptives, partly from ignorance, partly from inadequate means and partly from undesirable effects of available techniques.

TABLE I: CONTRACEPTIVE USE BY MARRIED COUPLES IN U.S.
(from Westoff. Family Plan Perspect 4:9, 1972 and Science 179:41, 1973)

	All Couples		Older couples (wife 30-44)			
			White		Black	
	1965	1970	1965	1970	1965	1970
Pill	24%	34%	13%	21%	13%	22%
IUD	1	7	1	6	1	5
Condon	22	14	24	17	16	7
Diaphragm	10	6	13	8	7	7
Sterilization						
Wife	7	8	8	12	22	32
Husband	5	8	7	13	1	2

	Roman Catholics		
	1955	1965	1970
Methods other than rhythm	30%	51%	68% (78% among ages 20-24)

If more effective and acceptable contraception, such as those listed in the bottom of Table II, were available, the collective and individual problems of population growth and birth control could be solved (15). But a mathematical model study of present practices in the U.S. found that for every 100 couples, each desiring a family size of 3 children, the use of various contraceptives would result in the following (16):

- Diaphragm or condom: 80% would have more children than planned, 3 to 6% ending up with 7 children
- Pill or IUD: 30% would have more children than planned

TABLE II: AVAILABLE AND PROPOSED TECHNIQUES FOR CONTRACEPTION

	Efficacy, expressed as pregnancies/100 women-years
Available	
1. Estrogen-progestogen pills	
a. Combined	0.7
b. Sequential	1.7
2. Progestogen "mini-pills"	1 to 4
3. Estrogen, as a morning-after pill	0.5%
4. Intra-uterine devices (IUD)	2 to 3
5. Vasectomy	0.15
6. Tubal ligation	0.06
7. Diaphragms	14 to 18
8. Vaginal spermicides	20
9. Condoms	14
10. Withdrawal	17
11. Rhythm method	38
12. Douche	41
13. No contraception	70 to 100
Proposed	
1. Vaginal rings with progestogen (1 month)	
2. Once-a-month, or even less frequent, injection of progestogen	
3. IUD with progesterone (1-3 years)	
4. Luteolytic agents, removing source of progesterone	
a. Prostaglandins	
b. Aminoglutethimide	
5. Reversible sterilization	
a. Valves in vas deferens	
b. Plugs in Fallopian tubes	
6. Antagonism to LH-Releasing Hormone	
a. LH-RH analogues for competitive binding	
b. LH-RH antiserum	
7. Immunization against sperm or sperm-specific enzymes	
8. Male oral contraceptives: Danagol, analogue of ethinyl-testosterone	

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II. THE EFFECTIVENESS AND ACCEPTANCE OF CONTRACEPTIVES

Since we and our patients must choose from those methods now available, additional consideration is needed for their effectiveness and acceptance. As shown in Table III, the combination estrogen-progestogen oral contraceptive, theoretically 100% effective, still fails in a few women and will not be tolerated in many more. The mini-pill and IUD are less effective but the latter may be better accepted (17,18,19).

TABLE III: MECHANISMS AND EFFECTIVENESS OF CONTRACEPTIVE TECHNIQUES

Method	Mode of Action	Pregnancy Rate per 100 Woman Years	Continuation Rate After One Year
Cyclic estrogen and progestogen	Inhibition of LH release prevents ovulation	0.7	70%
Low-dose progestogen	Inhibit endometrial glandular proliferation (anti-estrogenic); thicken cervical mucus	1 to 4	60%
Post-coital high-dose estrogen	Interfere with ova transport or nidation	2 pregnancies in 800 cases	-
Intrauterine devices	"Hostile" endometrial environment	2 to 3	60-80%

The following generalities can be made:

- continuation rates after 2 years of use are 11-12% higher for women under 30 and for those having been pregnant fewer times
- continuation rates are related to the woman's level of education, ranging from 50% for those not completing high school to 71% for those with one or more years of college
- women selecting IUD's tend to be older and more persistent users of contraception; younger women tend to continue using the pill better than the IUD
- no technique will work well when the patients are not followed with some frequency and consideration (20)
- even among private patients, as many as 1 of 3 will discontinue their contraceptive (21)
- continuation rates seem to be improving with newer pills and IUD's, better public awareness and information; but care needs to be taken not to shake patients' confidence in what they are using without providing suitable alternatives; in England at least 20,000 unwanted pregnancies followed newspaper and TV reports of dangers from higher-dose estrogen pills in 1969 (22); following U.S. Senate hearings in January, 1970, 18% of American women stopped taking the pill

Before turning to a detailed look at complications from the pill, a needed perspective is provided by Tables IV and V comparing mortality resulting from the various forms of contraception and the pregnancies which result from their failures in England (23) and the U.S. (15). It appears that any form of contraception is safer than the unwanted pregnancies that occur without contraception. Considering the many burdens and cost of unwanted pregnancies, the pill compares favorably. Only permanent sterilization, not suitable for many, is better.

TABLE IV: MORTALITY RESULTING FROM VARIOUS FORMS OF CONTRACEPTION
(from Potts and Swyer. Brit Med Bull 26:26, 1970)

Method	Failure Rate (pregnancies/100 women-years)	Pregnancies per million users	Deaths per million users caused by: Pregnancy	Contraceptive	Total
Oral contraceptives	0.1	1,000	0	21	21
IUD	2.0	20,000	5	Unknown	Unknown
Condoms, diaphragms	15.0	150,000	33	-	33
Spermicides, rhythm, withdrawal	25.0	250,000	56	-	56
Sterilization	0.02	400	0	15	15
Legal abortion	-	800,000	-	20	20
No contraception	-	800,000	223	-	223

TABLE V: MORTALITY FROM CONTRACEPTIVE TECHNIQUES IN U.S.
(from Southam. Contraception 8:1, 1973)

Technique	Per 100,000
Oral contraceptives	
Age 20-34	1.5
Age 35-44	3.9
Intrauterine devices	2
Sterilization	
Vasectomy	0
Tubal ligation (laparotomy)	25
Maternal deaths per 100,000 live births, U.S., 1969	29

Another factor that needs to be considered, even more so in less affluent societies than ours, is the economic cost of various techniques. In the third year of operation of Family Planning clinics in semi-rural Louisiana in 1967-68, the per patient costs were (24):

Pill	- $49.81
IUD	- 36.11
Foam, condom	- 26.09

Obviously, after the initial higher cost, sterilization would be the cheapest.

A final word about the use of contraceptives among adolescents (25). Considering that the most common age of first pregnancies delivered at Parkland is 15, we obviously have a long way to go in providing useful sex education to every child and contraceptives to those that need and want them.

References:

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III. COMPLICATIONS OF ORAL CONTRACEPTIVES

The pill has been subjected to more intensive scrutiny than any other medication. Yet surprises keep arising such as the occurrence of serious hypertension first reported in 1962 and publicized in 1967, well over 10 years after the pill was introduced, but still a greatly under-rated and inadequately recognized complication.

A good deal is known concerning various adverse effects of oral contraceptives mainly by the retrospective analysis of groups of women having reactions who are compared to comparable women not on the pill, the case-control method. In addition, individual case reports have provided useful information. Of course, the use of commonly preferred "double-blind" technique can hardly be justified; one such study of adverse reactions (26) has been harshly criticized since the control subjects were exposed to unwanted pregnancy.

These analyses and reports have not provided the data needed to assess the risks of therapy. Doll and Vessey provide three reasons for these inadequacies (27).

1) the reporting of adverse reactions is variable and incomplete, estimated to be as few as 1 in 10

2) too little is known concerning the number and characteristics of women using oral contraceptives

3) the frequency of adverse reactions among non-users is largely unknown

The problem can be solved by appropriately designed, large-scale, prospective studies. Though many have called for them, few have responded since, according to Doll and Vessey (27) these formidable difficulties stand in the way:

1) The numbers of women to be studied are large, at least 10,000 for more common problems, even more for less common ones.

2) The period of follow-up would have to be at least 10 to 15 years to recognize possible long-range adverse effects, as those of triglyceride metabolism on atherosclerosis.

3) Close contact would have to be maintained since the pattern of use of contraceptive techniques varies considerably.

4) Morbidity figures would be harder to obtain than mortality rates.

5) The formulation of the pills continues to be changed frequently.

6) The biases of selection and the Hawthorne effect, the closer attention to those under study, may tend to color the results.

Nonetheless such large-scale prospective studies have been undertaken, two in England and one in the U.S., among subscribers to the Kaiser-Permanente Medical Care Program. Until these results are available, we must depend upon the retrospective analyses and case-reports available to base our judgments and decisions.

In considering these complications, the 3 types of oral contraceptives now available will be covered separately. At this time, most of the 8 to 10 million American women taking oral contraceptives are on a combination of estrogen and progestogen, with increasing numbers on those containing only 50 µg of estrogen. Fewer are taking sequential estrogen-progestogen preparations since they have a two-fold greater failure rate and have been said to cause more side effects. The "mini-pill", progestogen alone, has recently been approved for use in the U.S. and is gaining in popularity with increasing awareness that the estrogen is responsible for most of the side effects of combination and sequential pills. And high-doses of estrogen have recently been approved for use as a "morning-after" pill to prevent pregnancy in those exposed while unprotected.

Table VI details the content and trade names of the combination pills available in the U.S. Figures 1 and 2 are the formulas of the currently used progestogens and Figure 3 of the estrogens.

References:

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27. Doll R and Vessey MP: Evaluation of rare adverse effects of systemic contraceptives. Brit Med J 26:33, 1970.

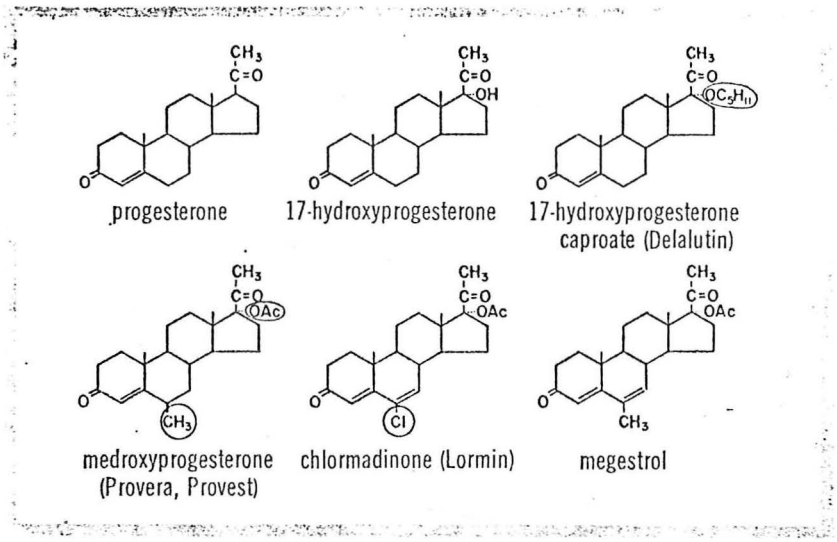

FIGURE 1. THE ACETOXY PROGESTINS.

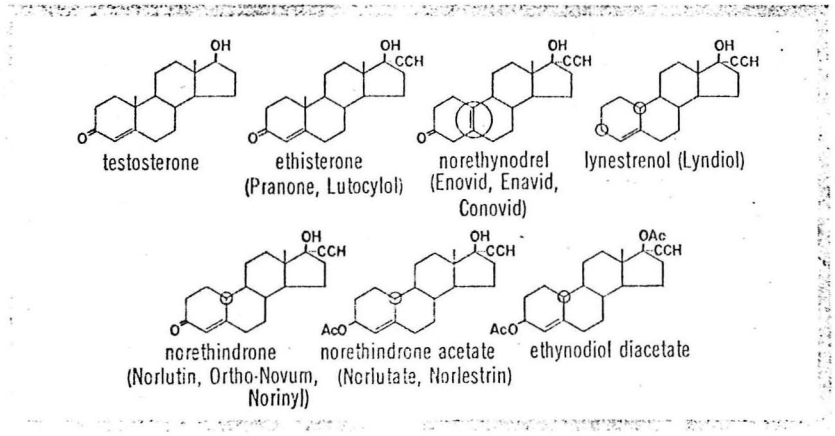

FIGURE 2. THE 19-NOR PROGESTINS.

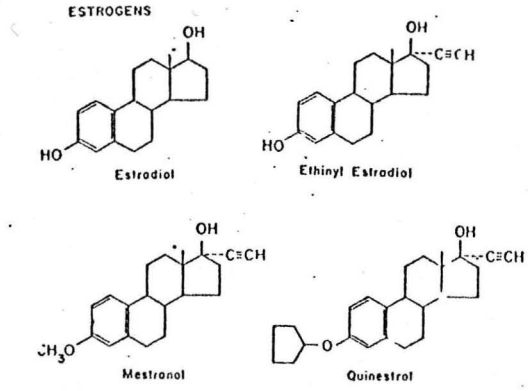

Figure 3: Estrogens

TABLE VI:

Oral Contraceptives Available in the United States

	Progestogen: Estrogen	Trade Names (Manufacturers)	Administration
Combination			
Ethynodiol diacetate	1 mg: 100μg mestranol	Ovulen (Searle)	From 5th through 24th or 25th day of cycle or 21 days of treatment followed by 7 days during which no pills are taken or inert or iron-containing (75 mg ferrous fumarate) tablets are taken (the numbers 20, 21, or 28 following the trade name indicate number of tablets in package).
Ethynodiol diacetate	1 mg: 50μg ethinyl estradiol	Demulen (Searle)	
Norethindrone	10 mg: 60μg mestranol	Norinyl 10 mg (Syntex) Ortho-Novum 10 mg (Ortho)	
	2 mg: 100μg mestranol	Norinyl 2 mg (Syntex) Ortho-Novum 2 mg (Ortho)	
	1 mg: 80μg mestranol	Norinyl 1 + 80 (Syntex) Ortho-Novum 1/80 (Ortho)	
	1 mg: 50μg mestranol	Norinyl 1 + 50 (Syntex) Ortho-Novum 1/50 (Ortho)	
Norethindrone acetate	2.5 mg: 50μg ethinyl estradiol	Norlestrin 2.5 mg (Parke, Davis)	
	1 mg: 50μg ethinyl estradiol	Norlestrin 1 mg (Parke, Davis)	
Norethynodrel	9.85 mg: 150μg mestranol	Enovid 10 mg (Searle)	
	5 mg: 75μg mestranol	Enovid 5 mg (Searle)	
	2.5 mg: 100μg mestranol	Enovid-E (Searle)	
Norgestrel	0.5 mg: 50μg ethinyl estradiol	Ovral (Wyeth)	
Sequential			
Dimethisterone	25 mg: 100μg ethinyl estradiol	Oracon (Mead Johnson)	Ethinyl estradiol for 16 days, then dimethisterone plus ethinyl estradiol for 5 days.
Norethindrone	2 mg: 80μg mestranol	Norquen (Syntex) Ortho-Novum SQ (Ortho)	Mestranol for 14 days, then norethindrone plus mestranol for 6 days.

A. *Estrogen-progestogen combinations*

1. Common but relatively minor. Most women who quit the pill do so because of side effects. They are rarely serious but are responsible for most of our problems with oral contraceptives.

a. Symptoms and signs: Some are obviously related to the estrogen including nausea, vomiting, headache and weight gain. But before blaming the estrogen or the progestogen for these complaints, examine Table VII, comparing the frequency of complaints with a sequential pill to those with an IUD (28). More revealing are the data in Table VIII, from the only double-blind study which included a placebo period (26). This study has been criticized since the women were inadequately protected with vaginal cream or foam during the placebo period and 6 of the 380 became pregnant during that interval. But it provides proof that much of what women complain about is psychogenic. Pincus made the same observation in a small group of women (Table IX) and Mexican investigators observed frequent problems (Table X), along with 72 pregnancies in 147 women given just placebo for 1 to 12 months (29).

TABLE VII:

FREQUENCY OF COMPLAINTS* WITH ORAL OR INTRAUTERINE CONTRACEPTIVES
(from Goldzieher JW. Amer J Obst Gynec 102:91, 1968)

	Frequency/100 cycles	
	IUD	Oral
Nausea	1.1	1.4
Vomiting	0.6	0.3
Abdominal pain	7.0	1.7
Headache	2.0	3.5
Depression	0.1	0.9
Edema, weight gain	0.3	1.2
A-or hypomenorrhea	1.3	10.2
Hypermenorrhea	15.2	11.0
Spotting	5.8	3.6
Dysmenorrhea	31.8	23.5
Vaginal itching, discharge	11.6	3.5

* These symptoms and signs were elicited by simply asking the patients "(1) How was your period? and (2) How were you otherwise?" No probing or other manner of eliciting symptoms was used.

TABLE VIII: A CONTROLLED STUDY OF THE SIDE EFFECTS ATTRIBUTED TO ORAL CONTRACEPTIVES
(from Goldzieher JW, et al. Fertil Steril 22:609,1971)

	Pre-treatment	*Placebo*	Sequential 100 µg EE *Oracon*	Combination 100 µg ME *Ovulen*	Combination 50 µg ME *Norinyl-1*	Progestogen 0.5 mg *Chlormadinone*
Month		1 → 4	1 → 4	1 → 4	1 → 4	1 → 4
Nausea	8%*	9 → 2	22 → 2	15 → 6	9 → 2	4 → 6
Vomiting	3	3 → 2	15 → 0	7 → 4	5 → 2	4 → 6
Abdominal pain	7	4 → 2	9 → 6	11 → 8	5 → 4	5 → 4
Breast tenderness	13	7 → 2	10 → 4	5 → 8	8 → 2	12 → 6
Headache	25	14 → 10	15 → 2	19 → 19	15 → 8	8 → 12
Nervousness	29	11 → 7	16 → 4	21 → 18	11 → 11	7 → 12
Depression	22	5 → 2	12 → 4	11 → 12	8 → 6	4 → 6
> 5 lb gain	-	11 → 30	13 → 31	10 → 20	16 → 19	6 → 28
Rise in B.P.	-	2	5	8	4	6

* All data as % of subjects, with 50 to 80 women in each group

TABLE IX:

EFFECTS OF WARNING ABOUT SIDE EFFECTS ON FREQUENCY OF SIDE EFFECTS
(from Pincus G. The Control of Fertility, Academic Press, 1963, page 302)

	Number of subjects	Number of cycles	Reactions (%)	Spotting (%)	Amenorrhea (%)
No warning + Enovid	15	48	6	2	0
Warning + Placebo	15	41	17	5	10
Warning + Enovid	13	30	23	17	3

TABLE X: Incidence of side effects with contraceptive placebo in 147 women during 424 months of observation.

	No. of months	*%*
Asymptomatic	141	33.2
Decreased libido	125	29.5
Headache	66	15.6
Pain and bloating in lower abdomen	58	13.7
Dizziness	47	11.1
Lumbar pain	34	8.0
Nervousness	27	6.4
Increased libido	27	6.4
Dysmenorrhea	26	6.1
Abdominal pain	22	5.2
Nausea	18	4.2
Epigastric pain	7	1.6
Pain in legs	6	1.4
Leukorrhea	6	1.4
Somnolence	5	1.2
Anorexia	4	0.9
Mastalgia	4	0.9
Increased appetite	4	0.9
Paresthesias	3	0.7
Weight gain	3	0.7
Acne	3	0.7
Postcoital bleeding	3	0.7
Insomnia	3	0.7
Pyrosis	3	0.7
Increased hirsutism	2	0.5
Decreased size of breast	1	0.2
Dyspareunia	1	0.2
Pain in varicose veins	1	0.2
Blurred vision	1	0.2
Asthenia	1	0.2
Palpitations	1	0.2

They state that these women had recently aborted and "were interested in becoming pregnant," but one can only wonder about the guidelines followed for human experimentation at the Hospital de Gineco-Obstetricia in Mexico City.

References:

28. Goldzieher JW: The incidence of side effects with oral or intrauterine contraceptives. Am J Obstet Gynec 102:91, 1968.

29. Aznar-Ramos R, Giner-Velazquez J, Lara-Ricalde R, Martinez-Manautou J: Incidence of side effects with contraceptive placebo. Am J Obstet Gynec 105:1144, 1969.

1) Psychiatric side effects: A loss of libido, decreased orgasmic response and depression have been blamed on the pill. The data provided in the above studies (28,29) suggest that psychological symptoms are common in all women and not necessarily related to their use of the pill. A voluminous literature has appeared concerning psychiatric problems, particularly depression, and the use of oral contraceptives.

a) Various psychodynamic factors may be involved in the failure of the pill or any contraceptive method to prevent pregnancy or in the inability of women to continue their use. These are well described by Tourkow, Lidz and Marder in their chapter in Hafez and Evan's book, Human Reproduction (30).

In explaining the failure of some women to accept any form of contraception, they write: "Fertility as an expression of need for power is becoming

increasingly evident in people who feel powerless or unsure of themselves whether on grounds of poverty, ethnic minority problems, or personal psychological difficulty. Just as a man may feel great satisfaction in proving his virility by impregnating a woman, a woman may feel that her fertility is her power and that she cannot accept interference with it even if she does not want a child. The present, rapidly chaging world with its loosening of family ties, changing roles, and fear of loneliness may also create powerful and often unconscious urges for procreation.

"The wish for pregnancy itself as proof of personal worth is not uncommon in women. It occurs in young girls in competition with their mothers, in disillusioned or depressed women who want a positive achievement, and in women with poor self-esteem and the need to prove themselves, particularly after some disappointment or loss. Sometimes the need to produce another baby when there are already too many children arises from the mother's lack of interest and involvement with her growing children; the children grow away from her; they may get into trouble in school, and cause her anxiety. She reacts by producing another baby -- to love, to hold, and to control."

"Pregnancy may serve an individual's neurotic needs, e.g., his need to prove his potency, her need for punishment. In this case, the individual will become conflicted in motivation for contraception regardless of the method employed. This conflict will manifest itself by producing a pregnancy through contraceptive failure or by symptoms such as depression or anxiety.

Women who stop the pill tend to be less responsible, less intellectually and socially effective than their husbands and less desirous of sexual intercourse (31). Others have provided similar data concerning the misuse and rejection of contraception (32,33).

b) A decrease in the frequency of pre-menstrual depression and irritability occurs with use of the pill (34,35).

c) However, serious depression may rarely appear with use of the pill. British investigators have shown that estrogens create a functional deficiency of pyridoxine presumably by activating one or more enzymes involved in tryptophan metabolism (36). Similar changes in tryptophan metabolism were shown after dietary induction of pyridoxine deficiency (37). And more recently these investigators showed that the 11 of 22 depressed women who had biochemical evidence of pyridoxine deficiency responded clinically to pyridoxine HCl administered in a double-blind crossover trial. The other 11 women, without evidence of pyridoxine deficiency, did not respond (38).

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30. Tourkow LP, Lidz RW, Marder L: "Psychiatric considerations in fertility inhibition" in Human Reproduction, ESE Hafez and TN Evans (eds). Harper & Row, Hagerstown, 1973.

31. Ziegler FJ, Rodgers DA, Kriegsman SA, Martin PL: Ovulation suppressors, psychological functioning, and marital adjustment. JAMA 204:849, 1968.

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2) Reproductive system (The question of carcinogenesis will be considered later)

a) Hypothalamus-pituitary: The mechanism of contraception with the combination pill involves suppression by the exogenous estrogen of the release of hypothalamic releasing factors, in turn suppressing pituitary secretion of FSH. This leads to failure of ovarian follicular development and inhibition of endogenous estradiol secretion. Thereby the mid-cycle surge in pituitary LH secretion is prevented (39).

In perhaps 2 out of every 1000 women, the suppression of hypothalamic-pituitary secretion may persist after the pill is stopped and neither menses nor ovulation resume (40). This secondary amenorrhea may persist indefinitely and thereby prevent fertility (41). The syndrome may arise from ovarian or endometrial involution but the frequent association of galactorrhea (42) and the ovulatory response to pituitary gonadotrophins or clomiphene (43) in over half of those affected strongly support a hypothalamic origin.

The syndrome, sometimes called "oversuppression", may occur after as short a period of treatment as 3 months, with any type of pill, in women with previously normal menstrual habits. Women with post-pill amenorrhea have low LH and estrogen levels.

b) Ovaries

(1) Structure: In addition to evidence of suppression of follicular development, cortical stromal fibrosis may be present but is rarely severe or permanent (44,45).

(2) Function: Ovarian secretion of estradiol (46) and of the androgen, androstenedione (47), are inhibited. The latter effect presumably accounts for the beneficial effects of the pill in women with androgen excess arising from the ovary (Stein-Leventhal syndrome).

c) Oviduct: Various microscopic changes have been observed in the epithelium of the Fallopian tubes which could play a role in the contraceptive action of the pill (48).

d) Uterus: Morphological changes (49) and decreased metabolic activity (50) occur in the endometrium; these changes, including inhibition of the development of spiral arterioles and involution of glands, make the uterus poorly receptive to nidation. These changes presumably play a role in the contraceptive action of progestogens.

e) Cervix: Cervical glandular hyperplasia and stromal edema presumably reflect progestogen action; with just progestogens, an increase of pronounced squamous metaplasia is noted (51). In addition, the secretion of mucus is reduced with an increased elasticity and decreased ferning (52). These changes make the mucus hostile to sperm migration and are involved in the effectiveness of progestogen therapy.

f) Vagina: Yeast vulvovaginitis may be more common (53). Adenocarcinoma and pre-malignant adenosis of the vagina have been noted in young women whose mothers took large doses of stilbesterol early in their pregnancy (54). No evidence of such carcinogenicity of natural estrogens or of the small doses used in oral contraceptives has been presented. There may be a risk in the use of high dose estrogens as "morning-after" pills, if the pregnancy is not aborted.

g) Breast: Very little of the mother's pill is secreted into her milk (55) but it may be enough to rarely estrogenize her infant. Lactation is often inhibited (56).

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55. Wijmenga HG and van der Molen HJ: Studies with 4-^{14}C-Mestranol in lactating women. Acta Endocr 61:665, 1969.

56. Koetsawang S, Bhiraleus P, Chiemprajert T: Effects of oral contraceptives on lactation. Fertil Steril 23:24, 1972.

3) Skin and hair: Darkening of the face (melasma or "mask of pseudo-pregnancy) was seen in 29% of women on various combination pills (57). Diffuse alopecia was reported in 5 patients (58) but is probably not related to the use of presently available pills (59).

References:

57. Resnik S: Melasma induced by oral contraceptive drugs. JAMA 199:601, 1967.

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b. Laboratory values

1) Hepatic: Estrogens and, to a lesser degree, progestogens markedly affect liver function and structure. In general, estrogens mainly affect protein synthesis in the rough endoplasmic reticulum, progestogens mainly affect the smooth endoplasmic reticulum and the drug-metabolizing enzymes.

Though all women have changes in liver function, the changes are usually subtle, rarely the cause of juandice (estimated as 1 per 10,000 women) and hardly ever implicated as responsible for permanent damage. The major clinical problem is that caused by estrogen effects on various carrier-globulins, resulting in changes in blood levels of hormones and other substances. Failure to account for these estorgen-induced changes can lead to mistakes in the interpretation of various laboratory data.

a) Changes in hepatic function

(1) BSP retention occurs in all recipients but is demonstrable by usual testing in only 10 to 40% of women and may disappear during continued intake of oral contraceptives. The BSP retention reflects a 40 to 60% decrease in the maximal transport (Tm) of the dye from the liver cell into the bile (60) similar to that seen in late pregnancy (61). This effect is seen with steroids having a phenolic A-ring structure and an alkyl group at the C-17 position; with progestogens it has been reported only for those with the 19-norsteroid structure (62).

(2) Cholestatic jaundice will appear in the absence of hemolysis or liver disease if the transport maximum is reduced by more than 90%. Thus women with pre-existing congenital or other defects in bile transport (benign familial recurrent cholestasis, recurrent jaundice of pregnancy, Dubin-Johnson or Rotor syndromes) may develop or note worsening of jaundice with intake of oral contraceptives (63). Since estrogens are normally metabolized (conjugated) and excreted in the bile, their retention and regurgitation into the blood would occur in such patients, perhaps thereby further affecting liver function.

(3) Surgically confirmed gallstones and cholecystitis were found twice as often among users of oral contraceptives as among non-users (64). Gallbladder disease usually occurred within 6 to 12 months of pill use but the risk persists even after prolonged intake. This increase was attributed to decreases in bile-salt concentration without change in biliary cholesterol, rendering cholesterol less soluble.

(4) Hepatic porphyria and porphyria cutanea tarda may be provoked in genetically-susceptible women by contraceptive steroids (65) presumably by their induction of delta-aminolevulinic acid (ALA) synthetase, the rate-limiting enzyme in heme biosynthesis, resulting in the enhanced production of porphyrins. Paradoxically, the pill may prevent menstruation-related attacks of acute intermittent porphyria.

(5) Increases in liver enzymes (progestogen-induced)

(a) serum transaminases (usually transient) in 6 to 7% of women (66).

(b) ornithine carbamoyl transferase

(c) β-glucuronidase

(d) isocitrate dehydrogenase

(e) ceruloplasminoxidase

(6) Decreases in liver enzymes

(a) lactic dehydrogenase

(b) alkaline phosphatase (67)

(c) serum cholinesterase (68)

(7) Interference with hepatic microsomal drug-metabolizing enzyme systems may occur, probably by the steroids competing with the drugs as substrate for the action of the enzymes.

I found no evidence that drug metabolism is effected enough to produce clinical problems; a recent compilation of adverse interactions of drugs listed oral contraceptives as a cause of diminished anticoagulant effect but gave "increase in activity of some clotting factors" as the probable mechanism (69).

References:

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61. Combes B, Sjibato H, Adams R, Mitchell B and Trammell V: Alterations in sulfobromophthalein sodium removal mechanisms from blood during normal pregnancy. J Clin Invest 42:1431, 1963.

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66. Larsson-Cohn U: Oral contraceptives and liver function tests. Brit Med J 1:1414, 1965.

67. Pulkkinen MO and Willman K: The effect of oral contraceptives on serum enzymes. Acta Obstet Gynec Scand 46:526, 1967.

68. Robertson GS: Serum protein and cholinesterase changes in association with contraceptive pills. Lancet 1:232, 1967.

69. The Medical Letter 15:77, Sept. 14, 1973.

b) Changes in plasma protein concentrations

In general, the concentrations of those proteins synthesized in the liver are increased by the action of estrogens though a few are decreased. Plasma proteins synthesized elsewhere,such as the immunoglobulins produced in plasma cells, are usually unaffected. A depressed lymphocyte response to phytohemagglutinin has been reported (96a).
The following table is taken from a study of 16 serum proteins in 94 women aged 18 to 42 (Control Group I), 102 women on various oral contraceptives for longer than 3 months (Group III) and 25 women during the third trimester of pregnancy (Group IV) (70).

The elevated ceruloplasmin levels may cause the plasma of pill-users to turn green (71).

69a. Fitzgerald PH, Pickering AF, Ferguson DN: Depressed lymphocyte response to P.H.A. in long-term users of oral contraceptives. Lancet 1:615, 1973 (Letter).

Table 4. *Concentrations of 16 serum proteins in controls (I), in women taking various oral contraceptives (group III), and in pregnant women (group IV). Changes are expressed as percentages of the standard value*

Protein	Standard value (control group) in mg/100 ml	Significant changes during oral contraception and pregnancy as % of the standard value	
	(N = 94 group I	(N = 102) group III	(N = 25) group IV
prealbumin	26	+ 8.5	— 9.5
albumin	4706	— 9.5	— 31.9
alpha-1-glycopr.	71	—21.0	— 26.6
alpha-1-lipoprot.	96%	+19.0	+ 46.0
alpha-1-antitryp.	290	+32.8	+ 82.5
ceruloplasmin	29	+96.5	+124.0
alpha-2-SH-glyco.	50	+40.0	+ 72.0
haptoglobin	192	—12.5	— 34.0
alpha-2-macroglob.	286	—	+ 15.9
beta-1-lipoprot.	77%	+19.2	+101.0
beta-1-A,C-glob.	75	+13.2	+ 15.0
transferrin	277	+24.4	+ 45.5
beta-2-glycopr.	23	—	— 31.5
Ig A	215	—11.5[a]	— 19.5
Ig M	215	—10.5[a]	—
Ig G	1309	—	— 24.5

[a] 19 women after three months' treatment.

70. Gleichmann W. Bachmann GW, Dengler HJ, et al: Effects of hormonal contraceptives and pregnancy on serum protein pattern. Europ J Clin Pharmacol 5:218, 1973.

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Perhaps of greater interest is the effect of estrogens upon various hormone carrier-proteins:

(a) Transcortin

Plasma 17-hydroxycorticoid levels were found to increase after estrogen administration (72). This increase was found to represent an increase in the protein-bound fraction, later shown to reflect an increase in the specific cortisol binding protein, transcortin, with a prolongation of the half-life of exogenous cortisol also resulting from protection of destruction by the liver by the greater protein binding (73). Secretion rates of cortisol were decreased (74), again presumably reflecting the prolonged half-life of the steroid. Subsequently the levels of nonprotein-bound cortisol have also been shown to be elevated, but only in the early morning hours (75).

The following data are taken from studies by Sandberg et al (76):

	Normal	Pregnancy	Estrogen R_X
Plasma cortisol	12-14 µg %	35	40
Unbound	1.1-1.2 µg %	2.2	3.2
Albumin-bound	1.4-1.6 µg %	2.9	4.2
Transcortin-bound	9 µg %	30	33
Transcortin	17-25 µg	45-55	40-60
$T_{½}$	70-90 min	120-150	> 240
Secretion rate	16-28 mg	11-14.5	8-16

Despite these increased levels of non-protein bound cortisol, no features of hypercorticism have been documented to appear even after prolonged use of estrogens. One possible case of pill-induced adrenal insufficiency has been reported (77).

Inhibition of adrenocortical responsiveness to metyrapone has been noted in the presence of normal responsiveness to exogenous ACTH (78) and pyrogen (79). Though this decreased response to metyrapone has been interpreted as pituitary inhibition of ACTH release (78) or interference with 11-hydroxylation by the estrogen (79), a more likely explanation may be a decreased effect of the metyrapone by its more rapid hepatic inactivation, similar to that demonstrated with Dilantin therapy. I could find no data on this point.

Progesterone will produce no effects on cortisol levels (74) but the progestogen, norethindrone 0.35 mg daily ("mini-pill"), did lower cortisol secretion slightly and urinary free cortisol levels significantly (80).

References:

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77. Das G and Becker M: Adrenocortical insufficiency related to oral contraceptives. JAMA 207:2438, 1969.

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80. Beck RP, Morcos F, Fawcett D, et al: Adrenocortical function studies during the normal menstrual cycle and in women receiving norethindrone with and without mestranol. Am J Obstet Gynec 112:364, 1972.

(b) Thyroxine-binding globulin (TBG)

Estrogen rapidly increases TBG levels 2 to 3 fold (81) raising the PBI and total thyroxine (T_4 isotope) levels and lowering the T_3-resin uptake. These alterations in thyroid tests appear within 7 days and take up to 6 weeks to disappear after the pill is stopped.

Presumably the thyroid quickly responds to the increase in binding protein with a brief period of increased secretion to saturate the increased number of binding sites and then re-establishment of function at the pre-pill level. This is reflected by maintenance of normal 24 hour RAI uptake values (82).

However the situation, as with cortisol, may not be so simple. But unlike the situation with cortisol, a decrease in serum free thyroxine levels has been found in a recent study in only 10 women before and after 9 months therapy with mestranol, 100 µg and norethindrone, 2 mg (83):

	PBI µg%	T_3 resin %	Free T_4-I_2 mµg%
Before	5.96	30.8	2.65
During Rx	8.58	21.9	1.83

This same study showed no effect of norethindrone alone, 0.35 mg daily ("mini-pill"), on the PBI or T_3 resin uptake but there was a significant fall in serum free T_4 levels with the progestogen as well.

The alterations in the PBI and T_3 resin uptake persist for up to 10 years (84). Lower RAI uptake values were found in 40% of these 53 women but this may reflect a lowering of the normal RAI uptake, ascribed to increased dietary iodine ingestion. No evidence of thyroid disease was noted in these women after prolonged pill intake.

References:

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83. Beck RP, Fawcett DM, Morcos F: Thyroid function studies in different phases of the menstrual cycle and in women receiving norethindrone with and without estrogen. Am J Obstet Gynec 112:369, 1972.

84. Rodriguez GV-D, La Haba AF-D, Pelegrina I: Thyroid status in long-term, high-dose oral contraceptive users. Obstet Gynec 39:779, 1972.

(c) Renin substrate

The level of this protein, synthesized in the liver, uniformly increases with estrogen intake and may lead to slight degrees of secondary aldosteronism and significant hypertension. This will be considered below.

2) Other laboratory values

Most of the changes in laboratory values listed in preceding pages are thought to be secondary to changes in hepatic protein synthesis. Some of the following changes may also be caused by the same mechanism. Those related to the clotting system, renin-angiotensin-aldosterone, lipid-carbohydrate metabolism and folate will be considered in the next section (Rare but serious complications) of the protocol.

a) Hematological

(1) These changes in serum iron and TIBC were found in 2 studies (85,86) comparing pill-users to non-users:

	Non-Users			Users		
Reference	No.	Serum-Fe	TIBC	No.	Serum-Fe	TIBC
85	30	89	361	30	157	504
86	21	94	368	76	116	445

Serum iron increases probably because pill-users have less menstrual blood loss; TIBC rises because of increased levels of the carrier-protein, transferrin (86).

(2) A slight but statistically significant decreased hemoglobin, hematocrit and RBC count with an increased MCV was seen among 1,083 pill users compared to 1,574 non-users (87). The findings were thought consistent with folate or B_{12} deficiency but the danger of a clinically significant macrocytic anemia arising from the pill was considered to be "minimal".

References:

85. Burton JL: Effect of oral contraceptives on haemoglobin, packed-cell volume, serum-iron, and total iron-binding capacity in healthy women. Lancet 1:978, 1967.

86. Mardell M, Symmons C, Zilva JF: A comparison of the effect of oral contraceptives, pregnancy and sex on iron metabolism. J Clin Endocr 29: 1489, 1969.

87. Fisch IR and Freedman SH: Oral contraceptives and the red blood cell. Clin Pharm & Ther 14:245, 1973.

b) Vitamins

(1) Vitamin A levels are increased by 50 to 75% (88).

(2) Thiamine: No data found

(3) Riboflavin: There may be a need for more riboflavin along with pyridoxine (89)

(4) Niacin: No data found

(5) Pyridoxine (B_6): As noted on page 15, a functional pyridoxine deficiency may result from increased tryptophane metabolism, which in turn has been claimed to be responsible for some of the depression noted with pill use (References 36-38).

(6) B_{12}: Decreased serum B_{12} levels (221 μμg/ml) were found among 20 pill-users compared to the levels (372 μμg/ml) among 23 non-users (90). However these workers found no changes in tissue B_{12} levels nor in serum B_{12} binding proteins; the binding-protein capacity was found to be elevated (from 1606 pg/ml in 32 controls to 1877 in 52 pill-users) by Bianchine et al (91).

(7) Serum folate levels are probably normal but folate clearance is increased perhaps due to a binder protein in the serum (See under Rare but serious complications).

(8) Vitamin C: Leucocyte ascorbic acid levels were lower in 63 pill-users (19 mg%) than in 63 matched non-users (26 mg%). This may be attributable to the inhibition by the pill of the normal ovulation-related rise in plasma ascorbic acid. No evidence for vitamin C deficiency has been reported.

(9) Vitamin D: No data found

(10) Vitamin K: No important effects

c) Minerals

(1) Calcium: Serum Ca^{++} was lower (9.38 ± 0.77) in 84 pill users than in 127 controls (9.86 ± 0.62) (93) but not as low as in 19 women in their last month of pregnancy (8.49 ± 0.38). But this lower Ca^{++} level was observed regardless of duration of pill use, being equally as low in those using them less than 3 months than in those using

them longer than 12 months. A logical explanation could be the 10% decrease in serum albumin noted during pill use and the 32% decrease during pregnancy (Reference 70). I could find no data on ionized calcium or other indices of calcium metabolism.

Estrogens in the amounts present in the pill do seem to prevent osteoporosis after oophrectomy when given within the 3 years post-operative (94). It is unlikely that replacement of endogenous estrogen with exogenous would cause any changes. Some of the pills (Demulen, Ovulen, Oracon) contain 10 to 30 mg calcium per pill (95).

(2) Serum phosphorus: Serum P was similarly reduced (3.94 ± 0.53) in pill-users compared to non-users (4.38 ± 0.51) but not in pregnant women (4.56 ± 0.59) (93).

(3) Serum magnesium is unaffected (93).

(4) Plasma zinc is lower in pill-users and pregnant women (96).

(5) Plasma copper is higher, presumably secondary to the increased ceruloplasmin levels (96).

(6) Sodium retention is common, probably from the secondary aldosteronism to be described below. Changes in neither plasma sodium or plasma potassium have been described.

In order to protect against all of these real and imagined changes in vitamin and mineral levels with the pill, Mead Johnson has marketed a pill with 11 vitamin supplements plus iron and zinc (Feminins). A recent Medical Letter (97) concludes that this or similar vitamin-mineral supplements is unneeded in women on the pill.

d) Plasma amino acid: total plasma levels and those of proline, glycine, alanine, valine, leucine and tyrosine are significantly decreased (98). In the inter-cycle interval off active ingredients, total plasma levels and those of each individual amino acid but glycine revert to normal.

References:

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89. Theuer RC: Effect of oral contraceptive agents on vitamin and mineral needs: A review. J Reprod Med 8:13, 1972.

90. Wertalik LF, Metz EN, LoBuglio AF, et al: Decreased serum B_{12} levels with oral contraceptive use. JAMA 221, 1371, 1972.

91. Bianchine JR, Bonnlander B, Macaraeg PVJ Jr, et al: Serum Vitamin B_{12} binding capacity and oral contraceptive hormones. J Clin Endocr 29: 1425, 1969.

92. McLeroy VJ and Schendel HE: Influence of oral contraceptives on ascorbic acid concentrations in healthy, sexually mature women. Am J Clin Nutrition 26:191, 1973.

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94. Aitken JM, Hart DM, Lindsay R: Oestrogen replacement therapy for prevention of osteoporosis after oophorectomy. Brit Med J 3:515, 1973.

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96. Halsted JA, Hackley BM, Smith JC Jr: Plasma zinc and copper in pregnancy and after oral contraceptives. Lancet 2:278, 1968.

97. Medical Letter. 15:81, Sept. 28, 1973.

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2. Rare but serious complications

a. Thromboembolism:

Whether oral contraceptives cause thromboembolic disease is still being debated. Two reviews of the available evidence end in opposite conclusions: Doll and Vessey (27) believe they do; Hougie (99) believes they do not. My conclusion is that they do but that the risk is small and must be considered in relation to the decrease in mortality and morbidity obtained by the effectiveness of the pill in preventing unwanted pregnancies. (Table XI)

TABLE XI: RISKS OF DEATH IN USERS AND NON-USERS OF ORAL CONTRACEPTIVES
(from Inman WHW and Vessey MP. Brit Med J 2:193, 1968)

Age	Estimated Annual Death Rate per 100,000 from Thromboembolism		Death Rate per 100,000 Pregnancies		Death Rate per 100,000 Women		
	Users	Non-users	Abortions	Complications of Pregnancy, Delivery and Puerperium	From Cancer	From Motor Accidents	From All Causes
20-34	1.5	0.2	5.6	17.2	13.7	4.9	60.1
35-44	3.9	0.5	10.4	47.2	70.1	3.9	170.5

1) Evidence for a causal relationship

a) Retrospective case-control studies in England (27,100) and the U.S. (64,101,102) show an increased frequency of pill use over that expected among women dying or admitted to hospitals with pulmonary emboli, deep-vein thromboses, cerebral and coronary thromboses. (Table XII) In most studies only "idiopathic" cases of thromboembolism have been accepted for analysis. If a randomly selected population with various predisposing conditions were studied, the thrombogenic potential of oral contraceptives added to these other factors might give rise to an even higher risk figure.

TABLE XII: CASE-CONTROL STUDIES OF ORAL CONTRACEPTIVES AND THROMBOEMBOLIC DISEASES

Reference	Disease	Users Observed-Expected	Non-users Observed-Expected	Relative risk Users:Non-users
Inman and Vessey Brit Med J 2:193,1968 (deaths)	Pulmonary embolism	16 - *4.2*	10 - *21.8*	8.3 : 1
	Coronary thrombosis	18 - *11.4*	66 - *72.6*	1.7 : 1
	Cerebral thrombosis	5 - *1.5*	5 - *8.5*	
	Total	39 - *17.1*	81 - *102.9*	
Vessey and Doll B Med J 2:651,1969 (hospital admissions)	Venous thromboembolism	42 - *11.5*	42 - *72.5*	6.3 : 1
	Coronary thrombosis	2 - *2.1*	15 - *14.9*	0.9 : 1
	Cerebral thrombosis	11 - *3.5*	8 - *15.5*	6.9 : 1
	Total	55 - *17.1*	65 - *102.9*	
Sartwell et al. Amer J Epidemiol 90: 365,1969 (hospital admissions)	Thrombophlebitis	38 - *12*	81 - *107*	
	Pulmonary embolism	21 - *9*	16 - *28*	
	Retinal vascular or intracranial lesion	8 - *2*	11 - *17*	
	Total	67 - *23*	108 - *152*	
Vessey et al. Brit Med J 3:123,1970 (postoperative)	Venous thrombosis or pulmonary embolism	12 - *4.5*	18 - *25.5*	

b) A correlation between the dosage of estrogen and the risk of various thromboembolic diseases has been shown by similar retrospective studies (103). (Table XIII)

c) Death rates from thromboembolism in young women have increased in a manner compatible with the increase in the use of the pill and the estimates of their risks (104). Furthermore, fewer deaths have been reported after the dose of estrogen was reduced in 1969 (105).

d) Women on oral contraceptives have an increased incidence of venous thromboembolism following surgery or trauma. Vessey et al (106) found a 6-fold increase.

TABLE XIII: THROMBOEMBOLIC DISEASES IN RELATION TO TYPE AND DOSE OF ESTROGEN
(from Inman WHW, et al. Brit Med J 2:203, 1970)

	Mestranol				Ethinyl estradiol	
	150µg	100µg	75µg	50µg	100µg	50µg
Venous thrombo-embolism						
Observed/Expected	58/31	333/282	80/86	22/19	21/11	266/350
Ratio (O/E)	1.83	1.18	0.93	1.13	1.91	0.76
Cerebral thrombosis						
Observed/Expected	10/3	33/28	6/9.1	0/2	0/2	29/35
Ratio (O/E)	3.21	1.17	0.66	0.51	-	0.82
Coronary thrombosis						
Observed/Expected	6/2.3	26/22	2/7.1	2/1.8	2/1.1	23/27
Ratio (O/E)	2.59	1.20	0.28	1.12	1.80	0.85

e) Estrogens may be a factor in puerperal thromboembolism when used to suppress lactation (108).

f) Men with carcinoma of the prostate treated with estrogens have increased mortality rates from heart disease and cerebrovascular accidents (109).

g) Various alterations in blood clotting studies have been found, (Table XIV) including:

TABLE XIV: THE EFFECT OF ORAL CONTRACEPTIVES ON BLOOD COAGULATION

	Oral Contraceptives	Estrogens	Progestogens	Pregnancy
Platelets	Increased number and possible enhanced function	Enhanced function	No effect	Little effect
Coagulation	Definitely accelerated	Accelerated by synthetic steroids	No effect	Slightly accelerated
Level of activity of factors	Increased	Increased	No effect	Increased
Fibrinolysis	Increased	Increased	Increased	Decreased

(1) Platelets

(a) Slight increase in number with chronic use

(b) Adhesiveness may be increased (110)

(2) Acceleration of coagulation, i.e., hypercoagulability

(a) Shorter clotting times and firmer clots as measured by thromboelastogram (111)

(b) Increased generation of thrombin and decreased serum antithrombin-III activity (112,113)

(c) Chromatographically demonstrable fibrinogen complexes present in plasma (114)

(d) Three times more women using oral contraceptives were found to have cryofibrinogenemia, also recognized in various states associated with intravascular coagulation (115)

(e) More rapid activated partial thromboplastin times (116)

(3) Increase in level of activity of various clotting factors including prothrombin, Factors VII, IX, X and XII and fibrinogen (117,118)

(4) On the other hand, an increase in fibrinolytic activity has been reported (119). The levels of plasminogin, the precursor, and of plasmin, the fibrinolytic enzyme, are increased (120,121). But the levels of plasma antiplasmin are also elevated (118), so that fibrinolysis could be inhibited.

h) Peripheral veins are more distensable reducing the linear velocity of venous blood flow in recumbency and increasing the likelihood of venous thrombosis (122).

i) Vascular lesions can be produced experimentally (123) and distinctive endothelial and internal proliferations have been seen in 22 women who were taking oral contraceptives when they died from thromboembolic disease (124,125).

j) Cases of various rare thrombotic vascular diseases have been reported in young women taking oral contraceptives.

(1) Cerebral (125a)

(a) In a large collaborative sutdy, the risk of thrombotic strokes was found to be increased 9-fold, the risk of a hemorrhagic stroke only 2-fold (102).

(b) Eighteen of 70 strokes occurred in the area supplied by the vertebro-basilar-posterior cerebral artery distribution; no cases of such strokes in young non-users of oral contraceptives could be found in the literature (126).

(c) At least 10 cases of fatal intracranial venous thrombosis have been reported (127).

(2) Coronary: In most of the cases of myocardial infarction reported, other risk factors have also been present (128-130); pill use probably enhances the chance of developing a myocardial infarction in women whose risk is already increased (130). A particularly rare lesion, a dissecting aneurysm of the coronary artery has been identified (132).

(3) Pulmonary: Three patients with congenital septal defects of the heart rapidly deteriorated from increased pulmonary vascular resistance (133).

(4) Abdominal

(a) Superior mesenteric vein thrombosis in at least 9 women (134).

(b) Arterial thromboses, often with ischemic colitis (135).

(c) Hepatic vein occlusion with the Budd-Chiari syndrome in 2 women (136).

(5) Microangiopathic hemolytic anemia in 5 previously healthy women (137).

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2) Evidence against a causal relationship

a) Prospective studies do not show an increased incidence of thromboembolic disease. V. A. Drill collated data from 68 published studies of over 80,000 women treated for over 1,000,000 cycles and found an incidence of superficial and deep-vein thromboembolic disease of 0.97 cases per 1,000 women per year, lower than his estimate of 2.2 cases in non-pregnant women of childbearing age not taking oral contraceptives (138).

Drill's analysis has been sharply criticized as being "heterogenous data from uncontrolled prospective studies.... not designed to determine the frequency of adverse effects" (139). Further criticisms of Drill's paper relate to his misinterpretation of the British and American retrospective studies as well as his faulty statistical analyses (140).

In a single 8 year prospective study, almost 10,000 women were randomly divided into oral contraceptive (Enovid) and vaginal contraceptive groups (141). The incidence of thrombophlebitis was 1.8 per 1,000 in the oral group and 1.6 in the control group, a statistically insignificant difference. Though this study has also been criticized as not being "blind" it can be accepted as evidence against a causal relationship.

b) No significant relation between the doses of estrogen and the occurrence of thromboembolic disease was found in the prospective studies reviewed by Drill and Calhoun (142).

c) Death rates from thromboembolism were higher in women aged 20-44 than in men aged 20-44 and little change in this difference has occurred from 1953 through 1971. Moreover the mortality rates have progressively and similarly increased for men and women aged 45-54 and 55-64 (105). More limited data also fail to show an increase in deaths from pulmonary embolism (143).

d) The various changes in blood clotting are almost all found to an even more pronounced degree in late pregnancy, but the incidence of thromboembolism during pregnancy is decreased. And similar changes under other circumstances do not lead to an increased tendency to thrombosis. Thus the idea of pill-induced hypercoagulability may be an inappropriate projection of lab data into a clinical situation.

e) The vascular changes seen with the pill have been seen in men and women not on the pill.

f) No increase in the incidence of strokes has been noted by some (144,145).

g) Both the retrospective case-control studies and the isolated case reports do not establish a cause-and-effect relationship (146). They

may reflect a high index of suspicion of thromboembolic episodes in pill users who would be more carefully studied, more commonly subjected to pathological study and more frequently reported in the literature.

h) Additional risk factors may have been more common among those on oral contraceptives, but not taken into account:

(1) Among 32,000 women, pill-users were more likely to be smokers and to smoke heavily: among users, 48% smoked, 12% more than 20 cigarettes a day; among controls, 42% smoked, 8% more than 20 (147).

(2) Fewer women with blood group O have thromboembolism, whether on the pill, pregnant or at other times (148). (Table XV)

TABLE XV: THROMBOEMBOLISM AND ABO BLOOD TYPE
(from Jick, et al. Lancet 1:539, 1969)

	A	B	AB	O	A+B+AB / O
Controls	37%	12%	4%	47%	1.1
TE - women	47	16	5	32	2.2
TE - pregnancy	56	7	7	30	2.4
TE - pill	58	15	11	16	5.1

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b. Other vascular diseases

1) Migrane: Typical migrane headaches may develop or reoccur (149,150). Whitty et al (149) found them to occur usually during the period off the active medication; Shafey and Scheinberg (150) during their intake. Those women who develop headaches develop more arterioles in their endometrium particularly during the proliferative and early secretory phases (151).

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2) Hypertension: Hypertension is almost twice as prevalent (13.9 per 1,000) among pill users as among matched non-users (7.8 per 1,000) and appeared over a 1½ year interval with a frequency of 6.8 per 1,000 in users compared to 1.2 per 1,000 in non-users (152). Among 325 women started on the pill, the mean rise in pressures was 6.6/2.6 mm Hg after 1 year; of those followed for 4 years, the mean rise was 14.2/8.5 mm Hg (153). Figure 4 shows the frequencies of elevations of systolic B.P. over 140, diastolic over 90 and of both over 140/90 in 415 previously normotensive women in 6 months (154).

Though the true incidence of pill-related hypertension remains unknown, it can be a serious problem with malignant hypertension and death due to rapid renal failure (155).

Among 100 women who developed hypertension, the metabolic alterations seen with the pill: impaired glucose tolerance, elevated blood pyruvate and raised serum lipid concentrations -- were more exaggerated, particularly in those with diastolic levels above 110 mm Hg (156). Those developing such severe hypertension were older, more obese, of higher parity and had a higher incidence of previous toxemia of pregnancy. However hypertension may develop in previously normotensive women with none of these features.

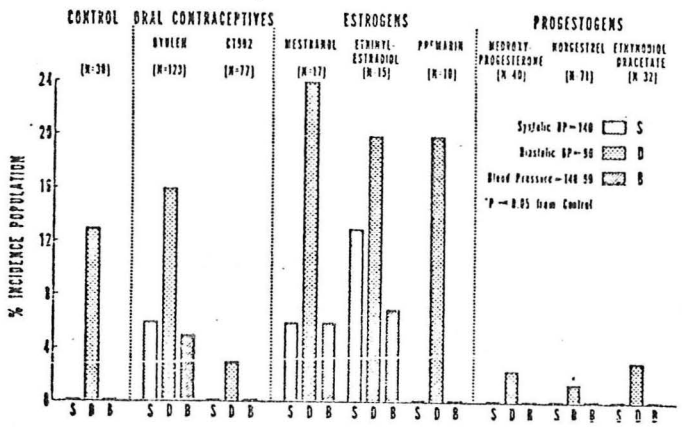

Fig. 4: The frequency of occurrence of abnormal blood pressures in normotensive women treated for 6 months' time with intrauterine devices (control), oral contraceptives, estrogens, or progestogens.

(from Spellacy WN & Birk SA. Amer J Obstet Gynec 112:912, 1972)

The mechanism is unknown but may involve alterations in the renin-angiotensin system (157). All women on estrogens have an increased plasma renin substrate which increases total plasma renin activity and plasma angiotensin II levels. We found a relative failure of feed-back suppression in renin concentration in those who developed hypertension (158) but others find no such difference between those who remain normotensive and those who become hypertensive (153).

These changes in renin-angiotensin cause a rise in plasma aldosterone from 8.3 ng% to 18.3 ng% during the first week of therapy and to 22.9 ng% during the third month (159). This secondary aldosteronism presumably is responsible for the weight gain, expansion of plasma volume and increased cardiac output seen in 6 normal women after 2 to 3 months of pill intake (160). Whether the hypertension is caused by either the vasoconstrictive effects of increased angiotensin or the hypervolemia of the secondary aldosteronism or both remains unsettled.

Regardless, all women receiving estrogens (the progestogens probably play little or no role) should have their pressures checked every 6 months. Those found to develop hypertension should have the pill stopped. No studies of renin-aldosterone should be made until at least 6 weeks thereafter. The hypertension usually disappears but it may take 2 to 3 months.

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c) Lipid and carbohydrate abnormalities

A number of alterations have been described and their mechanisms fairly well elucidated. A few women develop clinical disease attributable to these alterations. But the possible long-range deleterious effects have not been established. An excellent review of this subject has recently been published (161).

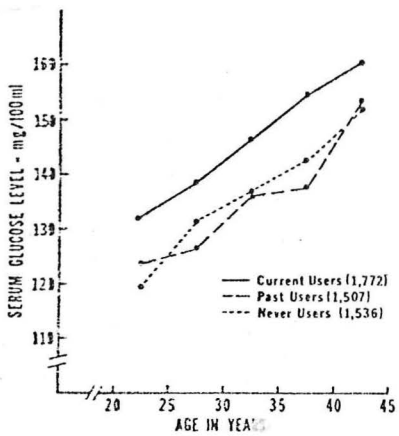

Fig. 5: Mean serum glucose concentration after oral glucose in current, past and nonusers of contraceptive steroids adjusted for age. (Phillips and Duffy)

1) Glucose tolerance is mildly diminished as shown in Figure 5 for over 4,800 women tested with 75 gm of glucose orally (162). Their responses did not vary with the type or duration of oral contraceptive. The effect of the pill was additive to the effects of age, obesity and a family history of diabetes. The tolerance in women who were prior users was the same as those who had never used the pill.

Overt diabetes, defined as fasting hyperglycemia, rarely occurs and probably only in those with previously impaired pancreatic insulin reserve. No significant changes in daily insulin requirements have been needed in diabetic women given the pill.

Plasma insulin levels are higher initially and rise to a greater degree with glucose loads after 3 months of pill use (163). In those women, serum growth hormone levels were also higher initially and did not suppress as much after glucose. The authors suggest that the increase in insulin secretion compensates for the peripheral anti-insulin effect of the estrogen-induced high levels of growth hormone. For most women, these counter-balance and glucose tolerance is minimally altered.

The type of contraceptive seems to make a difference; neither estrogens nor progesterone derivatives alone altered glucose tolerance, even though growth hormone levels were elevated (164). However, the nortestosterone-derivative progestogens alone may diminish glucose tolerance; when given with an estrogen, the incidence of abnormal glucose tolerance was much higher. The additive effect of estrogen may reflect an inhibition by the estrogen of hepatic metabolism and biliary excretion of the nortestosterone progestogens.

2) Serum triglyceride levels are increased by estrogens, the degree of elevation related to the dose of estrogen (Figure 6) (165).

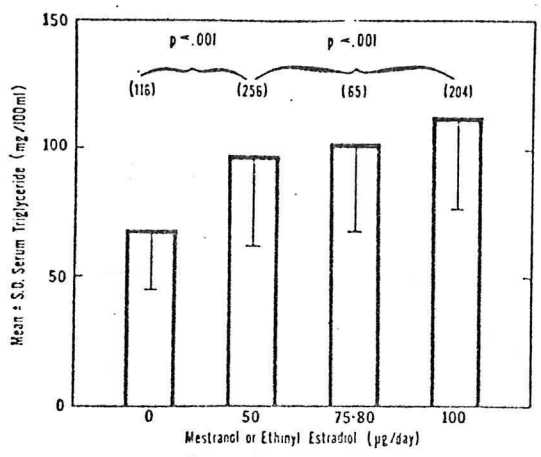

Fig. 6: Relation of estrogen dose to fasting serum triglyceride concentrations in women using birth control pills containing mestranol or ethinyl estradiol plus a derivative of nortestosterone or progesterone. (Modified after Stokes and Wynn)

This effect of estrogens appears to involve an increase in triglyceride synthesis and input into plasma (perhaps secondary to increased insulin secretion) (166). There is a depression of post-heparin lipolytic activity (PHLA) which was thought to mediate an impairment of triglyceride removal as well. Later studies showed that this decline in PHLA was due to a form of resistance to heparin and was not associated with an impairment in triglyceride removal (167).

A few cases of marked hyperlipemia have been reported, some with recurrent episodes of abdominal pain and overt pancreatitis (168). These marked changes have been observed primarily in women with obesity, glucose intolerance, pre-existing hyperlipoproteinemia or a positive family history of hypertriglyceridemia.

3) Serum cholesterol levels are minimally increased by the progestogens; estrogens alone usually lower serum cholesterol (165).

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d. Folate deficiency

A small number of pill users have been found to have anemia with folate deficiency not attributable to other known causes (169). Lower serum folate levels were reported in pill users. However, a study from our Department of Ob-Gyn found equal serum folate in 57 pill users as in 55 control women, with 4 women in each group having distinctly low levels (170). Only one of 6 patients with puerperal megaloblastic anemia failed to respond to the folate contained in a regular diet while taking oral contraceptives.

Though clinically important folate deficiency may be rare in pill users, the association seems likely. Two mechanisms have been proposed and the two may be linked:

1) Normally, most of the folate in food is present in conjugated forms or polyglutamates. This is acted upon in the gut to form monoglutamate, the form of the vitamin used therapeutically and presumably the only form which can be absorbed across the intestinal mucosa. Initial studies found that serum folates were lower in pill users after polyglutamate administration but not after monoglutamate, suggesting that the pill interfered with the break down of the poly-form in the gut (169). Subsequent studies find lower serum folates in pill users with either the mono-or the poly-forms (171).

2) In the above study (171), when the women were pre-saturated with folic acid, serum folates rose normally in pill users with either the mono-or poly-form. The authors therefore propose that the pill increases folate clearance from the blood. A recent abstract (172) suggests an explanation for this enhanced folate clearance: a folate binder in blood of women pregnant or on the pill. This binder could presumably sequester folate and prevent its activity both in the biological assay and in the physiology of hematopoesis.

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3. Unproven complications from oral contraceptives

a. Carcinogenesis

1) Breast: Some animals develop breast cancer when given massive doses of estrogens for long times. The growth of these cancers is dependent upon the presence of estrogen. Some breast cancers in women are also dependent upon estrogen and may regress when estrogens are removed. Therefore a possible carcinogenic effect of estrogens upon the breast has been searched for. As of now, no such effect has been found and, in fact, the use of the pill may protect against the development of benign breast diseases (fibroadenomas and cystic disease) which may be associated with an increased risk of breast cancer (173,174).

2) Uterus: No increase of endometrial cancer has been noted with the pill (175). However 2 cases have been seen among 24 women with gonadal dysgenesis treated for 5 or more years with stilbesterol (176).

3) Cervix: Histological changes in the endocervix are seen with pill use which, though sometimes mistaken histologically for adenocarcinoma, are benign (177). Though no increases in cervical cytological abnormalities have been reported (178) a slightly higher prevalence rate of carcinoma-in-situ was noted among New York women on the pill compared to those using the diaphragm (179). But in that study and in a later one from Los Angeles (180) women choosing the pill over other forms of contraception had a higher prevalence of cervical dysplasia before beginning pill use. This higher prevalence among pill-choosers in Los Angeles disappeared after the 1970 Senate hearings (181) and was not seen among women in Philadelphia (182) but the studies suggest the need for careful consideration of various epidemiological factors in establishing a possible causal relationsnip.

4) Vaginal: As noted before (p 17), clear-cell adenocarcinoma and premalignant adenosis of the vagina have been noted in young women whose mothers took large doses of stilbesterol early in their pregnancy (54). No such cases have been reported among pill users.

Obviously it may take many years for lesions such as that seen with large-dose stilbesterol therapy to become manifest. Therefore, despite good retrospective evidence against a relationship between pill use and carcinogenesis, the issue cannot be considered as settled.

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b. Fetal abnormalities

1) Cytogenetic studies *in vitro* show no effect of the pill on chromosomes. Though a few women on the pill have been found to have abnormalities, the only published study looking at chromosomes before and after pill use in the same women noted no significant change in chromosome breaks or mitotic index (183).

2) Aborted fetuses from women who became pregnant within 6 months of stopping the pill were found to have a much higher frequency of polyploidy but not of trisomy or XO anomalies (184). Polyploidy is incompatible with life. No increase in congenital defects among live, term infants of prior pill users has been documented (185). However, scattered reports have pointed to a possible increase in congenital defects if the mother continued to take oral contraceptives mistakenly after she became pregnant (186).

3) Masculinization of female infants born to mothers given large doses of nortestosterone-derivative progestogens has long been recognized. But these were used in much larger doses than present in most presently available oral contraceptives.

4) The sex-ratio does not appear to be affected by prior pill use (187).

5) Infants with birth-weight less than 2.5 kg whose mothers had received the pill before pregnancy had less frequent and less severe respiratory distress (188).

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B. Complications with progestogens alone, the "mini-pill"

Most of the complications described in the preceding pages are caused by the estrogen. The idea of using just progestogen for contraception was introduced in 1965 and subsequent experience with a variety of progestogens has shown that they are reasonably effective and quite safe but often unacceptable because of the irregular menses occurring with their use. In early 1973, the FDA approved norethindrone, 0.35 mg daily, for use and the drug is now available as Micronon® (Ortho) or Nor-Q.D.® (Syntex).

These must be given continuously since they act as contraceptives not by inhibiting ovulation, but by one or more of these mechanisms (189):

(1) Altering the properties of cervical mucus so that sperm migration is inhibited

(2) Changing the endometrial morphology so that implantation is prevented

(3) Suppressing the mid-cycle surge of LH

(4) Interfering with ovarian steroid synthesis

(5) Preventing capacitation of sperm

When used daily in women who had not used oral contraceptives before, a pregnancy rate of 3.72 per 100 woman years was noted; with women who switched over from other oral contraceptives, the pregnancy rate was 1.95 per 100 women years. These rates are 2 to 5 times higher than experienced with estrogen-progestogen combination pills and about what has been achieved with the IUD (see Table II, p 4).

In addition to being less effective as contraceptives, these mini-pills may also prove to be less acceptable to many women because of the marked irregularity in menses that often occurs with their continuous use. With 0.35 mg norethindrone, average cycle length was 30 days but 21% of cycles were less than 21 days and only 45% were from 26 to 35 days. Over half of the 40% who quit using a mini-pill did so because of the irregular menstrual pattern (190).

Beyond the inconvenience of never knowing when to expect the next menses, there is a potential hazard of continuing progestogen intake during the early days of an unwanted pregnancy. Therefore the directions accompanying the mini-pills instruct the patient to stop therapy after 60 days of amenorrhea or, if she has missed 1 or 2 pills, after 45 days.

Other than for irregularity of menses, reported complications have been minor, including weight gain, nausea and breast tenderness. Caution is advised since more problems may be noted with longer use but assurance is provided since most of the various changes in blood and other lab tests seen with combination therapy do not occur with progestogen alone: (Note that some of these studies are with other progestogens than norethindrone; most are also 19-norsteroids).

1. Clotting tests and platelet function were unchanged with 0.35 mg norethisterone daily for 6 months (191).

2. No significant changes in blood glucose, calcium, iron, alkaline phosphatase, albumin or PBI occurred with 75 µg norgestrel daily (190). Decreases were seen in serum globulin (2.71 to 2.52) and cholesterol (219 to 198) concentrations.

3. Both blood sugars and plasma insulin levels were normal during I.V. glucose tolerance tests on 37 women taking 0.5 mg norethindrone for up to 1 year (192). However, slightly higher plasma glucoses and insulins during oral glucose tolerance tests were seen in 53 women on 0.35 mg norethindrone for 6 months (193).

4. Serum triglycerides fell from 78 to 65 in the latter group of patients (193).

5. Blood pressure is not affected.

References:

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C. "Morning-after" estrogen (194)

The need to prevent unwanted pregnancy in unprotected women has prompted the introduction and approval of high-dose estrogen therapy as a "morning-after" contraceptive. This works probably by interfering with implantation though it may also accelerate ovum transport in the oviduct and inhibit the function of the corpus luteum.

The FDA has approved the use of diethylstilbesterol for this purpose but in view of its carcinogenic potential in the exposed fetus, I see little reason to use it when other estrogens do as well. Of course, there will be no such concern if, as most suggest, therapeutic abortion is performed on those in whom the estrogen fails to prevent pregnancy.

The daily doses must be large: 50 mg of diethylstilbesterol, 5 mg of ethinyl estradiol or 30 mg of conjugated estrogens. The timing must be correct: as soon as possible after coitus, preferably within 24 hours but no later than 72 hours, and continued for 5 consecutive days.

Following these guidelines in the treatment of unprotected women with midcycle exposure, only 1 pregnancy occurred in 5,593 cases (195). Among these women, 7 pregnancies occurred from improper timing and 18 from inadequate doses; resulting in a failure rate of 0.5%.

The major complication is rather severe nausea and vomiting, which may preclude the oral intake of the estrogen. Headache, breast tenderness and menstrual irregularity have also been noted.

References:

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IV: Guidelines for the present and prospects for the future

All of the preceding might suggest that the many complications and problems with currently available oral contraceptives should limit their use severly. But the relative risk of oral contraceptive use has been put in proper perspective by Potts and Swyer (23). They make these comparisons:

- a prescription for barbiturates involves 100 times the chance of causing a death as one for oral contraceptives
- there is 10 times the likelihood of death in a family if an outboard motor boat is purchased than if oral contraceptives are used
- on average, every car driver will be admitted to a hospital once in 20 years as a result of a road accident; a woman would have to use oral contraceptives for 2,000 years for a similar chance of being admitted with a thrombotic episode
- one contraceptive pill is as dangerous as smoking 1/3 of a cigarette once a day for 3 weeks out of 4

The authors conclude "With the possible exception of sustained use of oral contraceptives or the IUD, no reversible method of contraception provides an adequate method of fertility control for a Western woman who marries early and desires a small family. The evaluation of risks is complex but the mortality associated with the use of oral contraceptives or the IUD is of the same order of magnitude as the mortality due to unplanned pregnancies when less effective methods are used. (Table XVI) In countries where the maternal mortality remains high there is a marked differential in favor of using the most effective methods of family planning.

TABLE XVI: MORTALITY FROM TWO PLANNED PREGNANCIES AND THE USE OF VARIOUS METHODS OF BIRTH CONTROL*
(from Potts and Swyer. Brit Med Bull 26:26, 1970)

	Vasectomy	Tubal ligation	Oral contraceptives	IUD	Condoms & diaphragms	Spermicides, rhythm, withdrawal	No contraception
No unplanned pregnancies	3,400	3,400	17,000	340,000	2,300,000	3,500,000	11,000,000
Mortality due to:							
planned pregnancies	446	446	446	446	446	446	446
unplanned pregnancies	0.8	0.8	4	67	513	781	2,453
contraceptive method	0	15	442	Unknown	-	-	-
Total mortality	447	462	892	Unknown	959	1,227	2,899

These figures are based on 1,000,000 women who are fertile from ages 20 through 40 and who use contraceptives up to age 45.

"On grounds of mortality alone, the use of a method without side-effects, such as the condom (or even coitus interruptus), combined with legal abortion when unintended pregnancies occur, provides a method presenting the mother with approximately one-seventh the hazard of other options, except sterilization.

"Three rational possibilities are open to a couple planning two or three children: the prolonged use of oral contraceptives (or an IUD), the use of less effective reversible methods combined with induced abortion, or sterilization. Each possibility has its merits and in a large community it is likely that all three will be used separately and often in sequence" (23).

Obviously, we should continue to improve the safety of these agents. The "mini-pill" progestogen may do so but may not be well accepted. Another approach, recently introduced in the U.S., is to use even lower doses of estrogen in a combination pill. As shown in Table XVII, lower doses are almost as effective and have reasonably few side-effects causing women to stop their use (196,197). The formulation now available is 1.0 mg norethindrone and 20 µg ethinyl estradiol (Loestrin 1/20, Parke-Davis). Beyond these, many new approaches as listed in Table II, p 4, are being examined. One or more of them may prove to be even better than what we now have available.

196. Preston SN; A report of a collaborative dose-response clinical study using decreasing doses of combination oral contraceptives. Contraception 6:17, 1972.

197. Bye PGT and Elstein M: Clinical assessment of a low-oestrogen combined oral contraceptive. Brit Med J 2:389, 1973.

TABLE XVII: THE EFFECTIVENESS AND SIDE EFFECTS OF LOW-DOSE COMBINATION ORAL CONTRACEPTIVES
(from Preston SN, Contraception 6:17, 1972 and Bye PGT and Elstein M. Brit Med J 2:389, 1973)

	Dose of Norethindrone(mg)/Ethinyl estradiol(µg)				Norgestrel/Ethinyl estradio
	2.0/40	1.5/30	0.6/30	1.0/20	0.5/30
Effectiveness (pregnancies/100 woman years)	0	0.53	0.91	0.87	0.16
Drop-outs from adverse reactions (%)	9.8	11.8	11.3	15.3	13.8
Irregular bleeding	2.1	4.4	8.0	8.4	3.4*
Headaches	2.9	2.5	1.5	1.2	3.4
Nausea, vomiting	0.5	1.6	1.0	0.7	1.3
Number of subjects	378	1102	1296	1218	1085
Number of woman years	167	748	662	690	563

* 35% experienced spotting but 80% of these for only the first 1 or 2 cycles; 21% had breakthrough bleeding, but 82% of these for only 1 or 2 cycles.