Oral contraceptives and female mortality trends

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Summary: Death rates for Ontario females aged 15 to 44 during the years 1959-61 and 1966-68 have been compared to see if there have been any changes in these rates which might be related to the widespread use of oral contraceptives since 1961. Overall mortality (all causes) has declined significantly during this time, as have the rates for deaths due to childbirth and pregnancy, and from cancer of the uterus. Death rates from ischemic heart disease and cancer of the breast have not shown any significant change, but there has been a substantial increase in the rates ascribed to venous thromboembolism and suicide.

It must be stressed that a change in the recorded death rate does not necessarily mean that there has been a corresponding change in the incidence of the disease in question, or that such a change is related to the use of oral contraceptives. However, if oral contraceptives do cause an increase in a fatal disease, the effect should show up, sooner or later, in routine mortality statistics, and periodic examination of death rates may therefore provide a useful starting point for more detailed epidemiological investigation.

To assist physicians in counselling patients, a diagram has been prepared showing the relative importance of some selected causes of death in females aged 15 to 44, and the extent to which these death rates have changed since the introduction of oral contraceptives.

There is concern among both physicians and the general public about the possibility of harmful effects from oral contraceptives. Much of this concern is based on theoretical considerations, and few well-designed epidemiological studies to explore this situation have been carried out on human populations. At the present time venous thromboembolism and cerebral thrombosis are the only diseases in which the association with the use of oral contraceptives is strong enough to suggest a causal relationship.[1-3] While there is always the chance that after a number of years there may be clear evidence of an increased incidence of some other diseases (such as ischemic heart disease, cancer of the breast or cancer of the uterus), this must remain only a theoretical possibility until such time as there is firm epidemiological evidence to support it. (It is equally possible, theoretically, that oral contraceptives will have no effect, or will lead to a reduced incidence of these other diseases.)

It is important, therefore, that information be gathered through epidemiological studies of human populations, in order that abnormal patterns of illness and death among women using oral contraceptives may be recognized as soon as possible, and appropriate corrective measures instituted. One indirect but readily available source of such information is the report on vital statistics which is published annually in most countries, and if a substantial proportion of the female population of child-bearing age is using oral contraceptives, any dramatic change in death rates in these individuals should be reflected in an alteration in rates for the group as a whole.[4, 5]

It is well recognized that the diagnostic information on death certificates (on which published mortality figures are based) may often be of doubtful validity,[6] and some might claim that no useful information can be derived from the study of such death rates. A full discussion of this contentious subject is outside the scope of this paper, but in defence of the usefulness of the figures to be presented it may be pointed out that:

(1) A fatal illness is more likely to be thoroughly investigated (ante or post mortem) in a person under the age of 45 than in the very old.

(2) Changes in diagnostic preference among physicians signing certificates are unlikely to have been very great in the short time (average seven years) under consideration. Furthermore, those changes which have occurred should be reflected in the corresponding male death rates, and the latter can therefore be used to some extent as a "control" population.

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(3) The overall death rate (all causes) is not subject to diagnostic uncertainty, and change in this rate will be misleading only if the reporting of deaths is not complete, or if census estimates of population are erroneous.

At the same time it must be admitted that for individual diseases one can never be certain that a change in the reported death rate is truly representative of a change in the incidence or severity of the disease, and mortality data can therefore rarely "prove" that such a change has occurred. If used with discretion, however, death rates can draw attention to situations which may merit further investigation, and can help to demonstrate the relative magnitude of certain disorders as causes of death. It should also be emphasized that a change in death rate which occurs at the same time as the introduction of a new type of treatment does not imply that there is a causal relationship. (On the other hand, if a causal relationship did exist it would be surprising if the new treatment did not eventually result in a change in the death rate.)

Method

The number of deaths in some of the diagnostic categories to be considered is so small in any one year that death rates have been calculated for two three-year periods, 1959-61 and 1966-68. These years were chosen because oral contraceptives were first licensed for sale in Ontario during 1961 (although large-scale use did not begin until 1963), and because 1968 was the most recent year for which mortality data were available at the time of writing.

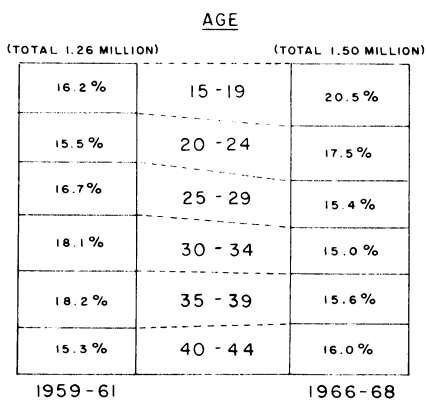

FIG. 1—Changes in age composition within the 15-44 age group, Ontario females, 1959-61 to 1966-68.

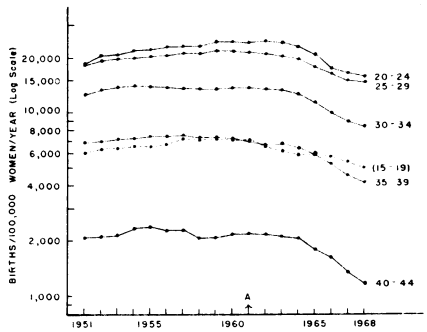

FIG. 2—Trends in age-specific birth rates in Ontario females from 1951 to 1968. The rates for the 15-19 age group are joined by a broken line, to avoid confusion with the 35-39 line.
A—Oral contraceptives introduced (1961).

The average number of deaths (per year) per 100,000 population has been calculated for the age group 15-44, and the 1966-68 rates have been "age-standardized" to the age distribution that existed in 1959-61. This was done in order to avoid possible distortion in the rates as a result of the changes in age distribution that have occurred within the age group 15-44 during this period (Fig. 1).

An exact figure is not available for the proportion of women in Ontario using oral contraceptives in 1966-68, but it is estimated that in 1969 the figure for women in Canada as a whole was approximately 20%.[7] The relatively stable birth rates in Ontario between 1951 and 1961 (Fig. 2) and the marked decline since 1959-61 suggest that the Ontario figure may be closer to 30% (Table I). No information is available on the age distribution of oral contraceptive users within this age range, but the general similarity of the decline in births in each five-year age group (especially those over age 20) suggests that the use of oral contraceptives has not been confined to any one age group (Fig. 2).

Between 1959 and 1968 the classification of causes of death in Ontario was made according to the International Classification of Diseases,[8] and ICD rubric numbers have been given where appropriate. Published reports of vital statistics have been used as a source of mortality data for all years except 1968.[9-12] For this year figures were kindly supplied in advance of publication by the office of the Registrar General of Ontario, who also provided the detailed figures for ICD categories 332, and 463 to 466.

To provide some indication of whether an observed change in rate represented a real difference rather than a chance fluctuation due to small numbers, approximate levels of statistical significance were calculated, using the formula: Standard deviation of rate = rate/$\sqrt{N}$ (where N is the number of deaths).

Results

As might be anticipated, the decline in the birth rate since the introduction of oral contraceptives has been accompanied by a significant decrease in the number of deaths associated with childbirth and pregnancy (ICD 640-689) (Table I and Fig. 3). Proportionately, the decrease in deaths has been greater (− 58%) than the decline in births (− 31%). This may be due, among other things, to a relatively greater increase in the

TABLE I

Number of births and deaths in 1959-61 and 1966-68, rates per 100,000 population, and change in rates, Ontario females aged 15-44

		Female					
	ICD categories	*1959-61 Total*	*Rate*	*1966-68 Total*	*Rate*	*Change*	*Change (male)*
BIRTHS		473,025	12,499	384,807	8,593	− 31%†	
DEATHS							
Childbirth and pregnancy	640-689	191	5.0	87	2.1	− 58%†	
Venous thromboembolism	463-466	12	0.32	42	0.97	+200%†	+25%
Cerebral thrombosis	332	9	0.24	16	0.38	+ 58%	+17%
All vascular lesions of central nervous system	330-334	165	4.4	180	4.2	− 5%	+ 6%
Arteriosclerotic and degenerative heart disease	420-422	166	4.4	194	4.5	+ 2%	− 8%*
Diseases of circulation	400-468	435	11.5	429	10.0	− 13%*	−12%†
Cancer of breast	170	284	7.5	327	7.6	+ 1%	
Cancer of uterus	173-4	184	4.9	154	3.6	− 27%†	
Suicide	E970-979	138	3.6	309	7.2	+100%†	+11%
Motor vehicle accidents	E810-835	364	9.6	571	11.9	+ 24%*	+17%*
All causes		3685	97.3	3915	89.2	− 8%†	− 1%

Changes in comparable male death rates are shown in the final column. All 1966-68 rates have been age-standardized to the 1959-61 population.

Approximate levels of statistical significance: *P < .05 †P < .01

use of oral contraception among poor-risk patients, since in terms of maternal deaths per 100,000 births mortality has declined 44%, from 40.4 in 1959-61 to 22.6 in 1966-68.

The death rate from venous thromboembolic disease (ICD 463-466) has increased from 0.32 to 0.97 per 100,000 per year (+ 200%), with comparable figures in males of the same age of 0.36 and 0.45 (+ 25%). The rate for female deaths attributed to cerebral thrombosis (ICD 332) has also increased, from 0.24 to 0.38 (+ 58%), with comparable male rates of 0.29 and 0.34 (+ 17%) (Table I).

This group of thrombotic disorders is of particular interest, since it comprises the only conditions that have so far been demonstrated (in epidemiological studies in Great Britain[1-3]) to have a clearly increased incidence among women using oral contraceptives. It is also of interest that the magnitude of the increase in Ontario death rates is close to that which might have been anticipated from one of these studies, in which it was found that the combined incidence of fatal cases of thromboembolism and cerebral thrombosis was at least six to seven times that which might normally be expected.[3] (If 20% of the female population aged 15 to 44 are using oral contraceptives, and are thereby exposed to seven times the risk of death from these causes, then for every 100 deaths that occurred previously, there should now be 80 + (20 × 7), or 220 deaths, giving an increase in the overall rate of 120%. Similarly if the proportion using oral contraceptives is 30%, the overall increase should be 180% (70 + (30 × 7) = 280). In fact, the observed change in the combined categories in Ontario, from 0.56 to 1.35 per 100,000, was + 140%, approximately midway between these two estimates.)

A detailed breakdown of the actual number of deaths ascribed to individual categories in 1966-68 shows that the increase has occurred in all types of venous thromboembolism (Table II).

TABLE II
Deaths in females aged 15-44 in Ontario due to venous thromboembolism, 1966-68

Phlebitis and thrombophlebitis of lower extremities	(ICD 463)	9 (0)
Phlebitis and thrombophlebitis of other sites	(ICD 464)	8 (1)
Pulmonary embolism	(ICD 465)	11 (5)
Other venous embolism	(ICD 466)	14 (6)

Numbers in parentheses refer to deaths in 1959-61.

TABLE III
Suicide rates per 100,000 in females and males aged 15-44 and the change in rates between 1959-61 and 1966-67. All 1966-67 rates have been age-standardized to the corresponding 1959-61 population

	Female			*Male*		
	1959-61	*1966-67*	*Change*	*1959-61*	*1966-67*	*Change*
Ontario	3.6	6.9	+92%*	14.3	15.2	+ 6%
Canada (excluding Ontario)	3.1	5.0	+61%*	11.7	15.6	+33%*
United States						
(white)	5.3	7.5	+41%*	14.6	16.3	+12%*
(non-white)	2.9	4.8	+66%*	10.3	13.7	+33%*
England and Wales	5.6	6.0	+ 7%	10.0	10.4	+ 4%

Approximate level of statistical significance: *P < .01.

An increased tendency to intravascular thrombosis might also be expected to increase the tendency to coronary thrombosis, and the change in the reported death rate from "arteriosclerotic and other degenerative heart disease" (ICD 420-422) is consistent with this view. However, the increase in rate is very small (from 4.4 to 4.5 per 100,000) and is well within the limits of chance variation for the numbers involved, so that this increase is statistically not significant. In males there was a decrease of 8%, from 30.3 to 27.7 per 100,000, which was just significant at the 5% level of probability.

For the combination of "all diseases of the circulatory system" (ICD 400-468) and "vascular lesions of the central nervous system" (ICD 330-334), there was a decline in the death rate from 15.9 to 14.2 per 100,000 (− 11%). The comparable rate in males was higher, but showed a decline of similar magnitude (− 10%), from 41.3 to 37.2 per 100,000.

Some concern has been expressed that cancer, particularly of the reproductive organs, may be increased by the prolonged use of hormone preparations such as oral contraceptives. If such an effect exists, it has not yet shown up in the mortality statistics for this age group. The death rate from cancer of the breast has shown no significant change (7.5 to 7.6 per 100,000), while the death rate from cancer of the uterus has declined significantly, from 4.9 to 3.6 per 100,000.

Depression has been reported to be one of the most common side effects of oral contraceptives,[13, 14] and it would therefore not be surprising if there were to be an increase in the suicide rate among women using them. In fact, there has been a large increase in this rate among Ontario women, from 3.6 to 7.2 per 100,000, an increase of 100% (Table I). This is unlikely to be simply the result of increasing public acceptance of suicide as a death certificate diagnosis, since the rate for males has increased by only 11% over the same period (14.3 to 15.9 per 100,000).

There have been no previously published reports of an increase in suicide rate in populations using oral contraceptives, and to ascertain whether the Ontario increase is a purely local phenomenon or whether a similar increase has occurred in other populations in which there has been widespread use of oral contraceptives, death rates from suicide have been calculated for the rest of Canada, the United States, and England and Wales (Table III).*

Using 1966-67 data the Ontario increase over 1959-61 was 92% in females and 6% in males. In the rest of Canada the female rate increased by 61% (males 33%),

*Mortality data were not readily available for these populations for the year 1968, and figures for 1966-67 have therefore been used to calculate the most recent annual suicide rates. In each case, rates have been age-standardized to the corresponding 1959-61 age distribution.

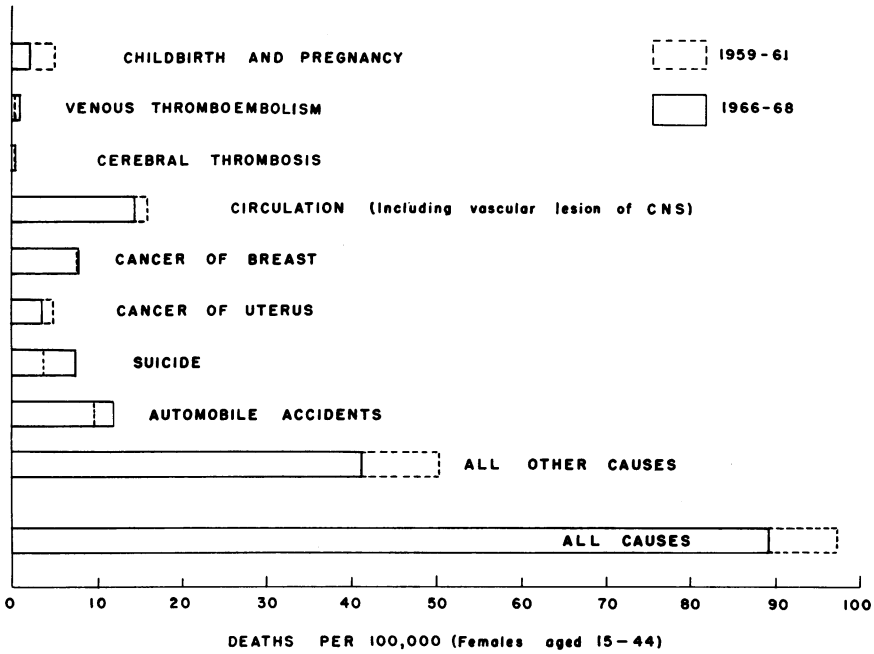

FIG. 3—Death rates per 100,000 from selected causes in Ontario females aged 15-44, 1959-61 and 1966-68.

while in the United States the rate for white females increased by 41% (males 12%), and for non-white females by 66% (males 33%). On the other hand in England and Wales there was little change in either the female (+ 7%) or male (+ 4%) rates.

On the basis of these figures it would appear that the large increase in the female suicide rate in Ontario, while reflected to a lesser extent in other parts of North America, is not necessarily related to the use of oral contraceptives, and may be due to a combination of factors. Further studies are needed to elucidate this question.

In the final analysis the overall death rate (all causes) is the most reliable mortality index, since there is here no question of the reliability of diagnosis, and it is reassuring that the female rate has declined substantially (– 8%) in the period under review, from 97.3 to 89.2 per 100,000. (Males have been less fortunate, with a decline of barely 1% from 180 to 178 per 100,000.)

Discussion

Whenever the physician attempts to control a disease process with some form of drug therapy, he must balance the anticipated benefits of such therapy against the possibility of unpleasant or even dangerous side effects. Usually it is the physician—not the patient—who must carefully consider the total situation and decide whether a certain drug should be prescribed, since it is he who best appreciates the full consequences of leaving the condition untreated, and who is most aware of the nature and likelihood of adverse reactions from the drug to be prescribed.

With oral contraceptives the situation is usually quite different. Unless there is a clear-cut medical reason for avoiding pregnancy, the treatment is aimed not at controlling a disease process, but at controlling an important aspect of the patient's personal and family life. It is inevitable that in these circumstances the reasons *for* treatment are best appreciated by the patient herself, and the physician is concerned mainly with the possibility of side effects, and with helping the patient to come to a rational decision as to whether the nature and likelihood of side effects are great enough to outweigh the benefits.

To assist the physician in this task a diagram has been prepared (Fig. 3) in which death rates from certain conditions can be related to the overall mortality risk in this age group. To the patient who is anxious to have the convenience and dependability of oral contraceptives, but who has become alarmed by the extensive publicity given to the dangers of "the Pill", it might reasonably be pointed out that:

(1) The only conditions in which there is firm evidence of an increased incidence among women using oral contraceptives are venous thromboembolism and cerebral thrombosis. These form a very small fraction of the total mortality in women of this age group, and the recent increase, although large in itself, is much less than the decrease that has occurred in deaths associated with childbirth and pregnancy.

(2) There is not, as yet, any firm evidence of an increase in the death rates from ischemic heart disease, cancer of the breast or cancer of the uterus, and the overall death rate (all causes) has declined substantially.

(3) The dilemma posed by having to make a choice between a greater degree of freedom and convenience on the one hand and an increased risk of death on the other is not restricted to the question of oral contraceptives. Motor vehicle accidents are an important cause of death in this age group, yet few patients (or physicians) would be prepared to give up the convenience of travelling by automobile in order to reduce their risk of premature death.

At the same time it would be reasonable to remind the patient that alternative methods of contraception are available, and if convenience and dependability are not of major importance (i.e. if some risk of pregnancy can be accepted) it might be prudent to refrain from using oral contraceptives. In this way the patient would not only avoid the known hazards, but would also be spared any other immediate or late effects which, although not presently recognized, are theoretically possible with the use of any potent medication.

The increase in suicide rate—whatever the reason—is disquieting, and the possibility that it may be related to the use of oral contraceptives emphasizes the importance of regular supervision of patients who are taking these drugs.

Résumé

Les contraceptifs oraux et les tendances de la mortalité féminine

L'auteur a voulu comparer la mortalité chez les femmes ontarien-

nes de 15 à 44 ans, durant les périodes 1959-61 et 1966-68, en vue de découvrir un éventuel changement de la mortalité qui pourrait être attribuable à l'usage généralisé des contraceptifs oraux depuis 1961. La mortalité globale (toutes les causes réunies) a fléchi sensiblement pendant cet intervalle, ainsi que la mortalité reliée à l'accouchement, à la grossesse et au cancer utérin. On n'a pas constaté de changement notable dans le nombre de décès causés par les cardiopathies d'origine ischémique et par le cancer mammaire, mais on a noté une augmentation substantielle des taux de décès attribuables à la thrombo-embolie veineuse et au suicide.

Il faut insister sur le fait qu'un changement du taux de mortalité enregistré ne signifie pas obligatoirement qu'il y a eu un changement correspondant dans la fréquence de la maladie en question ou que ce changement est lié à l'emploi des contraceptifs per os. Cependant, si les contraceptifs oraux doivent causer une augmentation d'une maladie fatale, l'effet se répercutera tôt ou tard sur les statistiques des tables de mortalité. Une analyse périodique des tables de mortalité peut donc constituer une base de départ pour une enquête épidémiologique plus poussée.

Pour aider les médecins dans leurs avis aux malades, nous avons préparé un diagramme illustrant l'importance relative de certaines causes de décès chez des femmes de 15 à 44 ans et montrant dans quelle mesure ces taux de décès ont changé depuis l'avènement de la pilule.

The author wishes to thank D. J. Sinclair, O. Eaton and S. McCausland for their assistance.

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YESTERDAY'S MEDICINE

The Union of Septic Compound Fractures

The treatment, therefore, of septic non-union is fairly clearly indicated. It consists of getting rid of those factors which are preventing the proper repair, that is, it consists in bringing the healthy ends of the fragments into close contact and in removing the sequestra which are obstructing the union. If this is thoroughly done, the fusion of the masses of callus on each of the fragments should be rapid and the union of the fracture assured. This plan was accordingly adopted in all suitable cases. Unfortunately, it is not applicable to all, as in some cases, such as in fractures of one of the bones of the forearm or leg, the amount of shortening necessary to obtain contact of the fragments is so great that marked deformity would result. But in the great majority, as in fractures of the humerus and femur, and of both bones of the forearm and leg, this method has proved itself applicable and has been very satisfactory. The operation consists of the free excision of the scar and sinuses, with a free opening down to the bone, as in an ordinary open operation on a simple fracture. All scar tissue, unhealthy granulations and sequestra are then removed, care being taken that no stripping of the periosteum occurs. The ends of the fragments, still covered and surrounded by spongy new bone, are brought together and, if necessary, fastened in position with an absorbable suture passed through drill holes. Sometimes it is wise to fit the fragments together by cutting slots in the end of one to receive the irregular points of the other. The wound is then closed at the extremities and the central portion packed with iodoform gauze. The parts are immobilized in a plaster of paris splint which is fenestrated for the dressings.

In the majority of cases the sutured portion of the wound heals by primary union and there is very little discharge from the drained area.—W. E. Gallie, *Canad. Med. Ass. J.*, 10: 407, 1920.