## MASTER CLASS Neighbors a World Apart

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Leaders in the medical community and government have long recognized that the United States has unacceptably high infant mortality in comparison with other nations. I served, in fact, on the Department of Health and Human Services' Secretary's Committee on Infant Mortality under President George H.W. Bush, as part of a major effort to reduce by half our infant mortality. We still have not suc-

ceeded, despite concerted efforts. Because this is a complex issue that will be solved only by using multiple strategies, we may do well to learn from other countries' successes. The Scandinavian countries, which boast very low infant mortality, have homogeneous populations that are difficult to compare with our own. But right next door is Canada, a country with an increasingly diverse population that may serve as a more analogous example of how programs can work to reduce infant mortality.

For a commentary on this important issue, we turn to C. Robin Walker, M.D., Ch.B., president of the Canadian Paediatric Society and professor of pediatrics at the University of Ottawa. He has studied infant mortality as an international issue, publishing on such topics as populationbased approaches to prevention of preterm birth, an important contributor to infant mortality.

We hope his thoughts will provide fresh insight into a very important health measure that we continue to try to improve.

DR. REECE, who specializes in maternalfetal medicine, is the vice chancellor and dean of the college of medicine at the University of Arkansas in Little Rock.

# Infant Mortality in the U.S. and Canada

Infant mortality is a complex issue, influenced by social, statistical, political, and geographic factors as well as medical ones. Looking at a chart of international infant mortality, one can see that the United States, as well as my native Canada, are light-years better off than politically unstable regions such as Angola, which leads the world at more than 191 infant deaths per 1,000 live births, or Afghanistan (163 per 1,000), by estimates of the Cen-

tribute to the number of babies who sur-

vive in a given country, making infant

mortality a rather unrefined gauge of

overall health. Yet it has been accepted

worldwide as a generally fair and realistic

tral Intelligence Agency's "World Factbook 2004."

However, we're far from being the best in the world.

Forty nations surpass the United States in infant mortality, including Singapore (2.29 per 1,000), Sweden (2.77 per 1,000), and Japan (3.26 per 1,000).

Because we are neighbors and share a border, similar economies, and comparable levels of technologic sophistication, it may be of inter-

est that Canada's infant mortality is fully 30% lower than that of the United States, which was optimistically estimated by the CIA to be 6.5 per 1,000 in 2004.

In both of our nations, 2002 infant mortality worsened slightly, prompting renewed scrutiny of an ever-important issue.

The Centers for Disease Control and Prevention reported that in 2002, U.S. infant mortality edged upward to 7.0 per 1,000 live births from 6.8 per 1,000 in 2001.

That's the first rise in 44 years, and even if—as preliminary reports suggest—it was a one-time blip, it's concerning to see even a 0.02% increase in the context of more than 4 million births.

The same trend occurred in Canada, where infant mortality rose from 5.2 per 1,000 in 2001 to 5.4 per 1,000 in 2002 after progressively falling since the 1960s.

I'd like to suggest a number of factors that may help to explain this troubling trend, which at the very least indicates we are not making the progress we would like to make in addressing one of the most important measures of a nation's health.

I'll also put forth some suggested explanations for the substantially unequal infant mortality in the United States and Canada, superficially similar nations.

Infant mortality can be divided accord-

ing to two basic contributors: neonatal deaths occurring within the first month of life, and postneonatal deaths occurring later in the first year.

Postneonatal deaths have not increased; in fact, tremendous advances in the understanding and prevention of sudden infant death syndrome have substantially reduced postneonatal deaths over the past decade.

The neonatal increases noted in 2002 and indeed the disparity between the United States and Canada—

have occurred in the early weeks of life, when the most common causes of death include congenital anomalies, problems of transition, and complications of preterm birth. Among these factors, only preterm birth stands out as a significant contributor to rising infant mortality.

In the United States, preterm births increased to 12.1%, from 11.9% the previous year.

But here is a telling statistic: Although the preterm birth rate also rose slightly in Canada, it was 7.6% in 2002, nearly 40% lower than in the United States.

Why is the preterm birth rate trending upward? The evidence is fairly clear that it is driven by the use of reproductive technology leading to multiple births, by mothers having babies at later ages, by obstetricians intervening to deliver babies earlier when the fetus is in jeopardy, and by complications attributed to a lack of early, consistent prenatal care.

Not all of these factors are things we can, or would want to, control.

Early delivery to attempt to save an infant in trouble is a good thing. Some of these preemies will not live, but would have been stillborn in years past.

Social trends influence the ages at which women decide to have their children. In Ottawa, where I practice, over 60% of moms in 2003 gave birth when they were older than 30 years, and 23.2% when they were older than 35 years. Although women have a right to be informed about their chances of conceiving and delivering healthy singletons at different ages, physicians have no desire to dictate social policy or individual choice. I have a 5-year-old, and I'm not a young man. We understand that older women have a higher risk of having a preterm baby, in part because they have a higher risk of having multiples, having pregnancy complications, and having babies with congenital anomalies, three factors that contribute to infant mortality.

Older mothers also are more likely to require assisted reproductive technology (ART).

Although ART procedures are similar in the United States and Canada, and are basically patient-funded in both countries, reproductive technology is increasingly subject to oversight in Canada. A bill that recently passed both the House of Commons and the Senate would strictly regulate clinics and procedures, for example.

A great many ART centers in Canada are university-affiliated, not-for-profit programs, rather than independent clinics. As a result, a controversial issue—such as the implantation of multiple embryos—is debated within the wide academic community of endocrinologists, ob.gyns., neonatologists, pediatricians, and ethicists.

When three sets of quadruplets were born in 1 year at the University of Ottawa, the university-affiliated fertility center demonstrated its responsibility by revising its policies to limit the number of embryos transferred during each cycle. Now, we

### Sources

► The National Center for Health Statistics publishes regular reports on infant mortality. The final data for 2002 can be found in Natl. Vital Stat. Rep. 2003;52:1-113. The center's latest annual report on trends in health statistics is "Health, United States, 2004," which includes a chartbook on trends in the health of Americans as well as interactive links (www.cdc. gov/nchs/hus.htm).

The Central Intelligence Agency publishes the World Factbook each year in printed and Internet versions. Data noted in this Master Class can be found online at www.cia.gov/cia/publications/factbook/rankorder/2091rank.html.
 Canadian infant mortality statistics can be found at www.statcan.ca/start/html. The Public Health Agency of

hardly ever see quads, although triplets are still not a rarity.

All over Canada, rates of multiple birth are lower than in the United States, contributing to lower rates of preterm birth. However, in looking at overall preterm birth statistics, it is worth noting that both nations have unequal rates across populations.

The U.S. National Center for Health Statistics reports that African American infants are nearly twice as likely as non-Hispanic white infants to be born prematurely.

In Canada, the disparity is most clear when looking at income, with those in the lowest income quintile having an infant mortality rate two-thirds higher than that of the highest income quintile. As infant mortality secondary to congenital anomalies and other causes has fallen significantly, the differential is largely a result of a higher rate of preterm birth in lower-income families.

Canada's First Nation and Inuit people face serious health problems, including infant mortality in many communities that is twice the national rate, as do America's Native American populations. Although Canada is an increasingly racially diverse country, other racial disparities are less obvious in measures of health care, such as prena-*Continued on following page* 

Canada has published the 2003 Canadian Perinatal Health Report online at www.phac-aspc.gc.ca/publicat/cphr-rspc03.

► The United Nations Children's Fund (UNICEF) uses data collected in annual report cards from its Innocenti Research Centre. The first report card was published in June 2000, and along with more recent report cards can be accessed at www.unicef-icdc. org/publications. Click on the link "For a brief description of our series," and then click on "Innocenti Report Cards."

► Simon Hales, M.B., and colleagues published the results of their study of the relationship among infant mortality, gross national product, and income distribution (Lancet 1999;354:2047).





#### Continued from previous page

tal care or preterm birth. Income is perhaps a more fitting measure of comparison, and deserving of a wider perspective.

One interesting study examined the gross national products and income distribution in 20 poor and 15 rich nations, determining, as one would expect, that overall infant mortality was inversely proportionate to income.

In rich countries, however, the main contributor to higher infant mortality was not income, but income disparity (Lancet 1999;354:2047).

The United Nations, in its annual Innocenti report card for 2000, explored child poverty in rich nations by using consistent indices to identify the percentage of children living in families with incomes below 50% of each nation's median income.

Child poverty levels ranged from 2.6% in Sweden to 26.6% in Mexico. Canada was 15.5%, and the United States was 22.4%.

Some governments, including those in Scandinavia, take a very active role in making sure that people don't live in poverty. Income disparity is low.

Conversely, income inequality is very high in the United States and may contribute to exceedingly elevated preterm birth rates and infant mortality among African Americans.

A related issue, of course, is access to medical care, which varies greatly among the industrialized nations of the world.

In Canada, where we have universal medical care, prenatal care is available to all at no cost, with no disincentives to seeking care in the system. Even pregnant women who do not have a primary care physician can walk into a clinic in any city and be seen that day.

As a result, in 2000, well over 95% of Canadian women received prenatal care beginning in the first trimester, compared with 83.7% of American women.

Once again, disparity is evident in the U.S. numbers, with only about 75% of

### Infant Mortality in **Selected** Nations

	Deaths per
	1,000 live births
Angola	191.19
Afghanistan	163.07
Haiti	73.45
India	56.29
Iraq	50.25
Guatemala	35.93
China	24.18
Israel	7.03
United States	6.50
New Zealand	5.85
Greece	5.53
Ireland	5.39
United Kingdom	5.16
Canada	4.75
Australia	4.69
Austria	4.66
Germany	4.16
Japan	3.26
Sweden	2.77
Singapore	2.29

Note: Based on estimated data for 2004 Source: The World Factbook

African Americans and fewer than 70% of Native Americans receiving early prenatal care. Indeed, 3.6% of women delivered

with no prenatal care, or with care initiated only in the last trimester. Although the U.S. rate of early prenatal care has improved quite dramatically in the last 15 years,

rising 10% since 1990, it still falls short of In Canada, one faces a long wait for a hip the care rates in most Western nations. I replacement. Far too many Canadians should point out that the Swedes think (about 10%) depend on walk-in clinics be-

**ORTHO TRI-CYCLEN® Lo Tablets** 

(norgestimate/ethinyl estradiol)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases. ORHHO TH-CVC-We Lo: Each white tablet contains 0.180 mg norgestimate and 0.025 mg ethinyl estadol. Each light blue tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estadol. Each dight blue tablet contains 0.215 mg norgestimate and 0.025 mg estadol. Each dight blue tablet contains 0.215 mg norgestimate and 0.025 mg ethinyl estadol. Each green tablet contains only inert ingredients. MPORTAIT NOTE – This information is a BRIEF SUMMARY of the complete prescrib-ing information provided with the product and therefore should not be used as the basis for prescribing the orduct. This summary was preared by deleting from the com-

ing information provided with the product and unergive shown in our uses as no search for prescribing the product. This summary was prepared by deleting from the com-plete prescribing information certain text, tables and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing

INDICATIONS AND USAGE: ORTHO TRI-CYCLEN® Lo Tablets are indicated for the prevention

of pregnancy in women who elect to use oral contraceptives as a method of contraception CONTRAINDICATIONS: Oral contraceptives should not be used in women who have any o the following conditions:1. Thrombophlebitis or thromboembolic disorders 2. A past history

of deep vein thrombophlebitis or thromboembolic disorders 3. Cerebral vascular or coronary af deep vein thrombophlebitis or thromboembolic disorders 3. Cerebral vascular or coronary aftary disease (current or history) 4. Valvular heart disease with complications 5. Severe hypertension 6. Diabetes with vascular involvement7. Headaches with focal neurological

ripertension U biacetes with vascular information: ineatacities with road interview symptoms 3. Major surgery with prolonged immobilization 9 Known or suspected carcinoma of the breast or personal history of breast cancer 10. Carcinoma of the endometrium or other known or suspected estrogen-dependent neoplasia 11. Undiagnosed abnormal genital

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Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use. This risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use oral contraceptives should be strongly advised not to smoke.

The use of oral contraceptives is associated with increased risks of several serious confilment including myocardial intarction, thromboenholism, stroke, hepatic neoplasia, and galblad der disease, although the risk of serious morbidity or mortality is very small increases significantly in without underlying risk factors. The risk of morbidity and mortality increases significantly in the presence of other underlying risk factors such as hypertension, hyperlipidemias, obesity and diabetes.

Practitioners prescribing oral contraceptives should be familiar with the following informa-tion relating to these risks.

Practitioners prescribing of a comaceptives should be animal with the tonowing intorna-tion retaring to these risks. The information contained in this package insert is principally based on studies carried out in patients who used orai contraceptives with higher formulations of estrogens and progesto-gens than those in common use today. The effect of long-term use of the oral contraceptives with lower formulations of both estrogens and progestopens remains to be determined. Throughout this labeling, epidemiological studies reported are of two types: retrospective or case control studies and prospective or contor studies. Case control studies provide a measure of the relative risk of a disease, namely, a ratio of the incidence of a disease among oral con-traceptive users to that among nonusers. The relative risk does not provide information on the actual clinical occurrence of a disease. Cohort studies provide a measure of attributable risk, which is the difference in the incidence of disease between oral contraceptive users and nonusers. The attributable risk does provide information about the actual occurrence of a disease in the population (adapted from refs. 2 and 3 with the suthor's permission). For further information, the reader is referred to a text on epidemiological methods. 1. **Thromboembolic Disorders and Other Vascular Problems** a. Myocardial Infarction

a. Myocardial Infarction An increased risk of myocardial infarction has been attributed to oral contraceptive use. This risk is primarily in smokers or women with other underlying risk factors for coronary artery disease such as hypertension, hypercholesterolemia, morbid obesity, and diabetes. The relative risk of heart attack for current oral contraceptive users has been estimated to be two to six. The risk is very low under the age of 30.

contraceptives. Oral contraceptives may compound the effects of well-known risk factors, such as hyper-tension, diabetes, hyperlipidemias, age and obesity. In particular, some progestogens are known to decrease HDL cholesterol and cause glucose intiblerance, while estrogens may create a state of hyperinsulinsm. Oral contraceptives have been shown to increase biod pressure among users (see section 9 in WARNINGS). Similar effects on risk factors have been associ-ated with an increase frisk of heart disease. Oral contraceptives must be used with caution in women with cardiovascular disease risk factors.

the activity is greater. In a contract prives a set of the progestogen maximized inductive that when the activity is greater. In The momentum and the progestogen maximized and the maximized and the compared to nonuesers to be 3 for the first episode of superficial evolution three maximized contraceptives is well established. Case control studies have shown the relative risk of users conditions for venous thrombosins of superficial evolution three maximized and contraceptives is well established. Case control studies have shown the relative risk to be somewhat lower, about 3 for new cases and about 4.5 for new cases requiring hospi-tizatation. The relative risk of thromboenbolic disease associated with nori contraceptives is not related to length of use and disappears after pill use is stopped. A how- to four-foil increase in relative risk of performabilic complications have been reported with the use of oral contraceptives. The relative risk of venous thrombosis is in women who have predictive surger of a phg associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Since the immedi-ate postpartum period is also associated with an increased risk of thromboembolism, oral contraceptives should be stated on earlier than four weeks after delivery in women who elect not for oral of to rotest feed. C. Cerebrowscular diseases

not to breast reeo. C cerebrovascular diseases Oral contraceptives have been shown to increase both the relative and attributable risks of cerebrovascular events (thromotic and hemorrhagic strokes), atthough, in general, the risk is greatest among older (-35 years), hypertensive women who also smoke. Hypertension was found to be a risk factor for holh users and nonusers, for both types of strokes, and smoking interacted to increase the risk of hemorrhagic stroke.

Interaction to increase the risk of netmorrhagic stroke. In a large study, the relative risk of thromototic strokes has been shown to range from 3 for normolnersive users to 14 for users with severe hypertension. The relative risk of hemorrhagic stroke is reported to be 1.2 for non-smokers who used oral contraceptives, 2.6 for smokers who did not use oral contraceptives, 7.6 for smokers who used oral contraceptives, 1.8 for normotensive users and 2.5.7 for users with severe hypertension. The attributable risk is also greater in older women. d. Dose-related risk of vascular disease from oral contraceptives A noetive association has hean observed helveen the amount of extrone and remestorem

A positive association has been observed between the amount of estrogen and progestogen in oral contraceptives and the risk of vascular disease. A decline in serum high density lipoproteins (HDL) has been reported with many progestational agents. A decline in serum high density lipoproteins has been associated with an increased incidence of ischemic heart disease. Because estrogens increase HDL cholesterol, the net effect of an oral contraceptive depends on a balance achieved between dosso of estrogen and progestogen and the achi-ity of the progestogen used in the contraceptive. The achivity and amount of both hormones should be considered in the choice of an oral contraceptive. Minimizing exposure to estrogen and progestogen is in keeping with good principles of therapeutics. For any particular estrogen/progestogen combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and the needs of the individual patient. New acceptors or oral contraceptive agents should be started on preparations containg. We acceptors gen content which is judged appropriate for an individual patient.

gen content which is judged appropriate for an individual patient. e. Persistence or risk of vascular disease There are two studies which have shown persistence of risk of vascular disease for ever-users of oral contraceptives. In a study in the United States, the risk of developing myocardial infarction after discontinuing oral contraceptives for two ern more years. Jut this increased risk vas not demonstrated in other age groups. In another study in Great Britain, the risk of developing certorvascular disease persisted for at least 9 years for women developing certorvascular disease persisted for at least 9 years after discontinuation of oral contraceptives, although excess risk was very small. However, both studies were performed with oral contraceptive formulations containing 50 micrograms or higher of estrogens. 2. Estimates of Mortality from Contraceptive los One study gathered data from a variety of sources which have estimated the mortality rate associated with different methods of contraceptive on at different ages (Table 3). These estimates include the combined risk of death associated with contraceptive methods plus the risk attributable to pregnancy in the event of method failure. Each method of contraception

the amount of estrogen and progestogen

w ost, me nost is very row under the dge of 30. Smoking in combination with oral contraceptive use has been shown to contribute tially to the incidence of myocardial infarctions in women in their mid-thirties or o smoking accounting for the majority of excess cases. Mortality rates associa circulatory diseas have been shown to increase substantially in smokers, especially 35 years of age and older and in nonsmokers over the age of 40 among women who contraceptives.

are lousy. In Sweden, virtually 100% of women receive prenatal care throughout their pregnancy.

that even Canada's prenatal care numbers

I would also be remiss if I left the impression that the Canadian health care system, the Swedish system, or any system, for that matter, is perfect.

has its specific benefits and risks. The study concluded that with the exception of oral

nas its spleanc behaviors and insist, time study childback ditat which the texplour of dia contraceptive users 33 and older who smoke, and 40 and older who be otxenke, mortality associated with all methods of birth control is low and below that associated with childbirth. The observation of an increase in risk of invision with age for oral contraceptive users is based on data gathered in the 1970s. Current dinical recommendation involves the use of lower estrogen does formulations and a careful consideration of risk factors. In 1980, the Fertility and Maternal Health Drugs Advisory Committee was asked to review the use of oral contraceptives in women 40 years of age and over. contraceptives in women 40 years of age and over. The Committee concluded that although cardiovascular disease risks may be increased with oral contraceptive use after age 40 in healthy non-smoking women (even with the newer low-does formulations), there are also greater potential health risks associated with pregnancy in older women and with the alternative surgical and medical procedures which may be necessary if such women do not have access to effective and acceptable means or contraception. The Committee recommended that the benefits of low-dose oral contraceptive use by healthy non-smoking women over 40 may outweigh the possible risks Of course, older women, as all women, who take oral contraceptives, should take an oral con-traceptive which contains the least amount of estrogen and progestogen that is compatible with a low failure rate and individual patient needs.

Not a drive table take and normalay based needs. 3. Carcinoma of the Reproductive Organs and Breasts Numerous epidemiological studies have been performed on the incidence of breast, endometrial, evanta, and cervical cancer in women using oral contraceptives. The risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. However, this excess risk appears to the risk of having breast cancer diagnosed may be slightly increased among current and recent users of combination oral contraceptives. recent users of combination or al contraceptives. However, this excess risk appears to decrease over time after discontinuation of a contraceptives and by 10 years after cossation the increased risk disappears. Some studies report an increased risk with duration of use while other studies do not and no consistent relationships have been found with dose or type of steroid. Some studies have found a small increase in risk for women who first use combination or cal contraceptives store age 20. Most studies show a similar pattern of risk with combination or rai contraceptive use regardless of a woman's reproductive history on her family breast cancer history.

or her family breast cancer history. Breast cancers diagnosed in current or previous oral contraceptive users tend to be less clinically advanced than in nonusers. Women who currently have on have had breast cancer should not use oral contraceptives because breast cancer is usually a hormonally-sensitive tumor. Some studies suggest that oral contraceptive use has been associated with an increase in the risk of cervical intraeptihelial neoplasia in some populations of women. However, there continues to be controversy about the event to which such findings may be due to differ-ences in sexual behavior and other factors. In spite of many studies of the relationship has not been established. **Length** theoretaria

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4. Hepatic Neoplasia Benign hepatic adenomas are associated with oral contraceptive use, atthough the incidence of benign tumors is rare in the United States. Indirect calculations have estimated the attrib-utable risk to be in the range of 3.3 cases 100,000 for users, a risk that increases after four or more years of use especially with oral contraceptives of higher does. Rupture of benign, hepatic adenomas may cause death through intra-abdominal hemorrhage. Studies from Britain have shown an increased risk of developing hepatocellular carcinoma in long-term (>8 years) oral contraceptive users. However, these cancers are extremely rare

In long-term (-8 years) oral contraceptive users. However, these cancers are extremely rare in the U.S. and the attributable risk (the excess incidence) of liver cancers in oral contracep-tive users approaches less than one per million users. 5. Octair Lesions There have been clinical case reports of retinal thrombosis associated with the use of oral contraceptives. Oral contraceptives should be discontinued if there is unexplained partial or complete loss of vision; onset ch orgotosis or otipologia, papilledema, or retinal vascular lesions. Appropriate diagnostic and therapeutic measures should be undertaken immediately. 6. Oral Contraceptive Use Before or During Early Pregnancy Extensive epidemiological studies have revealed no increased risk of birth defects in women who have used oral contraceptives prior to pregnancy. The majority of recent studies and timb reduction defects are concerned, when taken inadvertently during early pregnancy.

reduction detects are concerned, when taken inadvertemity during early pregnancy. The administration of oral contraceptives to induce withdrawal bleeding should not be used as a test for pregnancy. Oral contraceptives should not be used during pregnancy to treat threatened or habitual abortion. It is recommended that for any patient who has missed two consecutive periods, pregnancy should be ruled out. If the patient has not adhered to the prescribed schedule, the possibility of pregnancy should be considered at the time of the first missed period. Oral contraceptive use should be discontinued if pregnancy is confirmed.

use should be discontinued if pregnancy is commineu. **7. Gallbladder Disease** Earlier studies have reported an increased lifetime relative risk of gallbladder surgery in users of oral contraceptives and estrogens. More recent studies, however, have shown that the relative risk of developing allbladder disease among oral contraceptive users may minimal. The recent findings of minimal risk may be related to the use of oral contraceptive the strongend developing allblands of estrongend dress of estronges names floatenes to the strongest of r hormonal doses of estrogens and progestogens. mulations containing lo Carbohydrate and Lipid Metabolic Effects

tives have been shown to cause a decrease in glucose tolerance in a signifi-ge of users. This effect has been shown to be directly related to estrogen dose Can percentage or users insulin secretion and create insulin resistance, this effect varying with different progestational agents. However, in the non-diabetic woman, oral contraceptives appear to have no effect on fasting blood glucose. Because of these demonstrated effects, prediabetic and diabetic women in particular should be carefully monitored while taking oral

A small proportion of women will have persistent hypertriglyceridemia while on the pill. As discussed earlier (see WARNINGS 1a and 1d), changes in serum triglycerides and lipoprotein levels have been reported in oral contraceptive users.

Ieves have been reported in oral contraceptive users.
9. Elevated Blood Pressure
Women with significant hypertension should not be started on hormonal contraception. A increase in blood pressure has been reported in women taking oral contraceptives and the increase is more likely in older cal contraceptive users and with exclended duration of us Data from the Royal College of General Practitioners and subsequent randomized trials has shown that the incidence of hypertension increases with increasing progestational activit and concentrations of progestogens.

nen with a history of hypertension or hypertension-related diseases, or renal disease should Women wina answir on nybratismoli on nybratismoli on nybratismoli etadu useades, to teria useade si obudi be encouraged to use another method of contraception. If women elect to use oral contra-ceptives, they should be monitored closely and if significant elevation of blood pressure occurs, oral contraceptives should be discontinued. For most women, elevated blood pressure will return to normal after stopping oral contraceptives, and there is no difference in the occurrence of hypertension between former and never users.

10. Headache The onset or exacerbation of migraine or development of headache with a new pattern which is recurrent, persistent or severe requires discontinuation of oral contraceptives and evalua-tion of the cause.

111 Bleeding Irregularities Breakthrough bleeding and spotting are sometimes encountered in patients on oral contra Breakthrough bleeding and spotting are sometimes encountered in patients on oral contra-ceptives, especially during the first three months of use. Non-hormonal causes should be considered and adequate diagnostic measures taken to rule out malignancy or pregnancy in the event of breakthrough bleeding, as in the case of any abnormal vaginal bleeding. If pathology has been excluded, time or a change to another formulation may solve the problem. In the event of amenorthea, pregnancy should be ruled out. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was previstent. **12. Ectopie Pregnancy** Ectopic as wells a intrauterine pregnancy may occur in contraceptive failures.

PRECAUTIONS 1. General

 General Patients should be counseled that this product does not protect against HIV infection (ADS) and other sexually transmitted diseases.
 Physical Examination and Follow-Up It is good medical practice for all women to have annual history and physical examinations, It is good medical practice for all women to have annual instory and physical examinators, including women using oral contraceptives. The physical examination, however, may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinican. The physical examination should include special reference bollood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. In case of undigenced, persistent or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy. Women with a strong family heary of treast cancer or who here breast nodules should be motioned with particular care.

Lipid Disorders
 Women who are being treated for hyperlipidemias should be followed closely if they elect to use oral contracptives. Some progestogens may elevate LDL levels and may render the control of hyperlipidemias more difficult.

Control on type: Index and the control of the co

5. Fuid Retention Oral contraceptives may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention.

cause they can't find a primary care physician of their own. Canadians who make more money tend to live longer, and certain groups, such as First Nation and Inuit people, have unequal health outcomes despite access to free care.

In Canada, we learn a lot from the United States, from the abundance of medical research and education to the excellent health care available to many. But in the spirit of learning from each other, U.S. physicians may be interested in studying a neighbor that spends less on health care yet produces not only lower preterm birth rates and infant mortality, but also lower mortality overall. 

6. Emotional Disorders Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. is ers who develop visual changes or changes in lens tolerance should be

sed by an ophthalmologist 8. Drug Interactions Changes in contraceptive effectiveness associated with co-administ products:

products: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadmin-istered with antibiotics, anticonvulsants, and other drugs that increase the metabolism of contraceptive steroids. This could result in unintended pregnarcy or break/through bledding. Examples include riffampin, barbitrartes, phenylbutazone, phenytofin, cardbarazeptine, felibarnate, oxcarbazeptine, topiramate, and griseofubrin. Several cases of contraceptive failure and breakthrough bledding have been reported in the literature with concomitant administration of antibiotics such as ampleillin and tetracyclines. However, clinical pharma-

administration of antibiotics such as ampiculin and tetracyclines. However, clinical pharma-cology studies investigating drug interaction between combined oral contraceptives and these antibiotics have reported inconsistent results. Several of the anti-HIV protases inhibitors have been studied with co-administration of oral combination hormoral contraceptives; significant charges (increase and decrease) in the plasma levels of the estrogen and progestin have been noted in some cases. The safety and efficacy of oral contraceptive products may be affected with coadministration of anti-HIV protease inhibitors. Health care providers should refer to the label of the individual anti-HIV protease inhibitors for further drug-drug interaction information.

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estradiol) may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitan administration of oral contraceptives. Decreased plasma concentrations of acetaminopher and increased clearance of temazepam, salicylic acid, morphine and clofibric acid, due to induction of conjugation, have been noted when drugs were administered with oral

Interactions with Laboratory Tests ertain endocrine and liver function tests and blood components may be affected by oral

contraceptives: a. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability. b. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by protein-bound iodine (PBI), T4 by column or by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG, free T4 concentration is unaftered Other binding proteins may be elevated in serum.

d. Sex hormone binding globulins are increased and result in elevated levels of total circulating sex steroids; however, free or biologically active levels either decrease or remain unchanged. e. Triglycerides may be increased and levels of various other lipids and lipoproteins may be

. Glucose tolerance may be decreased. g. Serum folate levels may be depressed by oral contraceptive therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing oral

10. Carcinogenesis See WARNINGS section

11. Pregnancy Pregnancy Category X. See CONTRAINDICATIONS and WARNINGS sections.

12. Nursing Mothers Small amounts of oral contraceptive steroids have been identified in the milk of nursing mothers and a few adverse effects on the child have been reported, including jaundice and where any a tew adverse effects on the child have been reported, including jaundice and east enlargement. In addition, oral contraceptives given in the postpartum period may terfere with lactation by decreasing the quantity and quality of breast mik. It possible, the ursing mother should be advised not to use combination oral contraceptives but to use other ms of contraception until she has completely weaned her child. V Pediatric Use

13. Pediatric Use Safety and efficacy of ORTHO TRI-CYCLEN® to Tablets have been established in women of reproductive age. Safety and efficacy are expected to be the same for postpubertal addrescents under the age of 16 and for users 16 years and older. Use of this product before menarche is not indicated.

14. Geriatric Use This product has not been studied in women over 65 years of age and is not indicated in this population.

INFORMATION FOR THE PATIENT See Patient Packane Incort

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ADVERSE REACTIONS		
ncreased risk of the following serious adverse reactions has been associated with the of oral contraceptives (see WARNINGS section).		
rombophlebitis and venous thrombosis th or without embolism terial thromboembolism ulmonary embolism yocardial infarction e is evidence of an association betweer raceptives:	Cerebral hemorrhage     Cerebral thrombosis     Hypertension     Gallbladder disease     Hepatic adenomas or benign liver tumors     the following conditions and the use of oral	
esenteric thrombosis	<ul> <li>Retinal thrombosis</li> </ul>	
following adverse reactions have been reported in patients receiving oral contraceptives are believed to be drug-related:		
usea miting astrointestinal symptoms (such as odominal cramps and bloating) eakthrough bleeding outing mange in menstrual flow moorary infertility after scontinuation of treatment fema eastna which may persist east changes: tenderness, largement, secretion	Change in weight (increase or decrease)     Change in cervical erosion and secretion     Diminution in lactation when given     immediately postpartum     Cholestatic jaundice     Wigraine     Netrai depression     Mentai depression     Reduced tolerance to carbohydrates     Vaginal candidiasis     Change in corneal curvature (steepening)     Intolerance to contact lenses	
following adverse reactions have been reported in users of oral contraceptives and the ciation has been neither confirmed nor refuted:		
e-menstrual syndrome ataracts anarges in appetite stituis-like syndrome aadache arvousness zizness zizness sutism so di scalp hair ythema multiforme	Erythema nodosum     Hemorrhagic eruption     Vaginitis     Porphyria     Impaired renal function     Hemolytic uremic syndrome     Acne     Changes in libido     Colitis     Eudd-Chiari Syndrome	
OVERDOSAGE		
as in checks have not been reported rolowing dute ingestion of large dodes of that		

Ser contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding may occur in females.

ORTHO-MCNEIL  $\smile$ 

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'I should point out that the Swedes think that even Canada's prenatal care numbers are lousy. In Sweden, virtually 100% of women receive prenatal care throughout their pregnancy.'