EXHIBIT 1026

Management of Common Problems in Obstetrics and Gynecology

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Noncontraceptive effects of oral contraceptives: neoplastic, reproductive, and metabolic

DANIEL R. MISHELL, JR

Introduction

Oral contraceptives (OCs) have been marketed since 1960 and millions of women have used these products during the past 33 years. Much information has accumulated regarding the various actions of these steroids in addition to their primary effect of inhibition of ovulation. These effects can be arbitrarily divided into three categories: (1) neoplastic; (2) reproductive; and (3) metabolic.

Neoplastic effects

Numerous epidemiologic studies have been performed studying the relation of use of OCs with the most common genital neoplasms, breast, cervix, endometrium, and ovary, as well as several extragenital tumors, namely, hepatic, pituitary, and malignant melanoma. Because as yet few elderly women used OCs during their early reproductive years, the studies thus far published usually restrict the analysis to women under age 60.

Breast cancer

No study has reported a significant increase or decrease in the risk of developing breast cancer among the entire population of OC users. The combined risk estimate of the 16 case-control studies and four cohort studies summarized by Peterson and Wingo in 1992 was 1.0. In Schles-

selman's review of 17 different studies in which the risk of developing breast cancer in women under 60 years of age was compared with the duration of OC use, no overall dose–response was found to exist and long-term use did not increase the risk of developing breast cancer.

The issue of latency, time since first use of OCs, and risk of breast cancer has also been studied. In groups of women using OCs for more than 10 years there was found to be no change in risk of breast cancer with increasing duration of time since first use. Thus, there is no evidence supporting a long-term latent effect. Several studies have presented data regarding the risk of developing breast cancer under age 45 by duration of OC use prior to age 25. The combined data fail to show a dose–response, indicating that early age of first OC use is not by itself a risk factor for development of breast cancer. The preponderance of data in studies estimating risk of breast cancer in women under 60 years of age by duration of OC use prior to first term pregnancy also failed to show an increased risk or a dose–response. However, analysis of the studies which estimated the relative risk of developing breast cancer in women under 45 years of age suggested that there was a trend of increasing risk with increasing duration of overall use, as well as increasing duration of use prior to first term pregnancy, with the increased risk in both groups becoming most evident after 8 years of use.

Three large studies have suggested that prolonged use of high-estrogen-dose OCs might increase the risk of developing breast cancer, but only when initially diagnosed at an early age.

Because of the concern raised by these studies, Wingo *et al.* reanalyzed the extensive data obtained by the Cancer and Steroid Hormone study organized by the Centers for Disease Control (Table 118.1). These investigators found that women who used OCs had a slightly increased risk of developing breast cancer between the ages of 20 and 34 compared to non-OC users. OC use did not alter the risk of developing breast cancer between the ages of 35 and 44, and was associated with a slightly decreased risk of developing breast cancer between the ages of 45 and 54. Because breast cancer is more common between ages 45 and 54 than under 45, OC use could be associated with an increase of about 10 cases of breast cancer per 100 000 women under age 45 but a decrease of 18 cases per 100 000 women in the 45–54-year age group.

These data are consistent with the belief that long-term use of high-dose OCs could have promoted the age at which breast cancer was diagnosed clinically among susceptible women. This promotional effect was transient, not persistent, and thus had no appreciable effect on the aggregate lifetime risk of developing breast cancer under age 60 in the population, despite the widespread use of OCs.

Because formulations with low-dose estrogen have been used by most

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