

Most Hormonal Contraception Effective in Obese

BY ROBERT FINN

SAN FRANCISCO — Oral contraceptives provide effective birth control in very heavy or obese women, but “OCs are less forgiving of imperfect use among” this population, according to James Trussell, Ph.D., director of the office of population research, Princeton (N.J.) University.

Speaking at a conference on contraceptive technology sponsored by Contemporary Forums, Dr. Trussell said he based his conclusions on his analysis of the shortcomings of the data from two studies by Victoria Holt, Ph.D., professor of epidemiology at the University of Washington School of Public Health, Seattle. Dr. Holt’s studies have formed the basis of the conventional wisdom that OCs fail more often in heavy women.

Findings from the first of her studies, which was a retrospective cohort analysis of 755 HMO enrollees, showed that there was a 60% increase in the risk of OC failure in this population, who were of reproductive age and weighed at least 70.5 kg. That risk was especially high for low-dose and very low-dose formulations, with increases in risk of 2.6-fold and 4.5-fold (Obstet. Gynecol. 2002; 99[pt. 1]:820-7).

The study’s flaws were its reliance on self-reports of confirmed pregnancies, because that allowed for the possibility that abortions might have been underreported.

Each patient’s weight just before pregnancy was unknown.

The weight used in the analysis was a single self-reported measurement taken an average of 77 months after the last use of oral contraceptives. Finally, the study did not detail OC use patterns.

Dr. Holt’s second study was a case-control study with 248 cases and 538 age-matched controls (Obstet. Gynecol. 2005;105:46-52). This study did not find a significant increase in the risk of contraceptive failure among all women in the highest-weight quartile, but it did find a statistically significant 70% increase in risk among consistent OC users weighing 75 kg or greater.

The increase in risk was also significant among all women in the highest BMI quartile (1.6-fold) and in consistent OC users in the highest BMI quartile (2.2-fold).

This study’s flaws included self-reporting of weight, retrospective reporting of pill taking an average of 7 months after the reference month, and statistically significant differences between cases and controls in the number of previous pregnancies and the number of those previous pregnancies that occurred during OC use. In addition, women who missed more than five pills during the reference month were excluded from the study.

Findings from six other studies found no association between high weight, BMI, and OC failure. Dr. Trussell conceded that each of those studies had limitations as well, and he said that the question was unlikely to be settled convincingly except in large prospective studies. Even then the question might never be answered for perfect use because it’s very difficult to assess adherence.

Even if the increases in relative risk found in the Holt studies prove to be reproducible, the absolute risk of failure is still likely to be modest, Dr. Trussell said.

Oral contraceptives ‘are less forgiving of imperfect use among’ very heavy or obese women.

“Beware of relative risk,” he said. A 120% increase in the relative risk of contraceptive failure during perfect use implies an increase in the absolute risk of contraceptive failure only from 0.23% to 0.51%.

A 60% increase in relative risk during typical use implies an increase in contraceptive failure from 8% to 12% during the first year, which is still lower than the failure rate of condoms.

There is little evidence that high BMI affects the failure rate of Implanon (etonogestrel) or Depo-Provera (medroxyprogesterone). But it’s hard to draw a firm conclusion from this because there were no pregnancies at all in either product’s clinical trials, whether the women were obese or not.

Furthermore, the Implanon trials excluded women who were heavier than 130% of ideal body weight. New Food and Drug Administration rules require that drugmakers include obese women in contraceptive trials.

Obese women were included in the phase III efficacy trials of NuvaRing (etonogestrel/ethinyl estradiol), and there were no pregnancies among 74 women weighing 189-272 lb (86-123 kg).

But the situation with the contraceptive patch is different.

Women weighing 80 kg or more have almost eight times the risk of contraceptive failure as do women weighing less, perhaps because of difficulties in hormone transit through subcutaneous fat, he said.

Whether hormonal contraception, which is reasonably effective in obese women, is also safe is another question.

Several studies have made it clear that obesity by itself is a risk factor for pulmonary embolism and for deep venous thrombosis, with fivefold increases in risk.

Oral contraceptives further increase the effect of obesity on deep venous thrombosis.

Although those increases in serious side effects are real, Dr. Trussell said that they are not as clinically significant as some fear.

According to the World Health Organization Medical Eligibility Criteria, combined hormonal contraceptives are given a rating of 1 (no restrictions on use) for women with BMIs less than 30 kg/m² and a rating of 2 (benefits generally outweigh risks) for women with higher BMIs.

The version of these Medical Eligibility Criteria adopted in the United Kingdom, on the other hand, give a rating of 3 (risks generally outweigh benefits) for women with BMIs between 35 and 39, and a rating of 4 (unacceptable risk) for women with BMIs of 40 and above, said Dr. Trussell, who also is the John Foster Dulles Professor in International Affairs and Professor of Economics and Public Affairs at Princeton.

A study of OC safety in women with a BMI over 40 has never been done. There’s only one study in the literature of women in the BMI category of greater than or equal to 35. The WHO ratings have a firmer evidence base than the U.K. ratings, according to Dr. Trussell.

Dr. Trussell stated that he had no conflicts of interest related to his presentation.

Contemporary Forums and this news organization are both owned by Elsevier. ■

PCOS Development May Begin With Insulin Resistance

BY BETSY BATES

INDIAN WELLS, CALIF. — Insulin resistance precedes and may set the stage for hyperandrogenism in peripubertal girls at risk for polycystic ovary syndrome, researchers concluded in what is believed to be the first prospective, longitudinal study of PCOS development.

Dr. Marc J. Kalan and his associates at the University of Southern California, Los Angeles, enrolled 57 prepubescent Hispanic girls aged 8-13 years who were at high risk for polycystic ovary syndrome (PCOS) because they were obese (defined by the investigators as a body mass index greater than or equal to the 85th percentile for age and sex), and had a first-degree family member with diabetes.

At yearly intervals for a mean of 4 years, the girls underwent interviews, physical examinations, dual-energy x-ray absorptiometry, and MRI studies to assess body composition and visceral fat accumulation, fasting serum hormone measurements, and oral and intravenous glucose tolerance testing. Dr. Kalan reported the results at the annual meeting of the Pacific Coast Reproductive Society.

Of the 57 girls, 15 (26%) developed what investigators termed a “PCOS-like” condition, in that their menses became irregular at least 2 years after menarche and they had clinical evidence of androgen excess.

No differences were seen between these girls and study subjects who did not develop PCOS-like findings in terms of adiposity, prepubertal insulin and sex hormone levels, or the

In the 57 prepubertal, obese Hispanic girls studied, 15 (26%) developed irregular menses at least 2 years after menarche and they had clinical evidence of androgen excess.

age at menarche (average, 12 years).

However, within a year of menarche, they were significantly more insulin resistant than their peers (mean insulin sensitivity index [ISI]), 1.2 M/mU per liter, compared with 1.6 M/mU per liter), reported Dr. Kalan of the division of

reproductive endocrinology and infertility at USC.

The girls’ testosterone levels were similar to those of girls who did not develop PCOS-like findings at 1 year post menarche.

However, at 2 years post menarche, they had significantly higher mean testosterone levels (47.5 ng/dL, compared with 22.5 ng/dL).

The insulin resistance disparity widened during the second year post menarche (mean ISI, 1.2 M/mU per liter vs. 1.8 M/mU per liter).

All differences in study parameters persisted after statistical adjustment for adiposity, the researcher reported.

The study results offer important evidence suggesting

that testosterone is not the driver of events leading to PCOS. “Insulin resistance came first,” Dr. Kalan commented in an interview.

Assessing insulin values, specifically, insulin resistance, “may be clinically useful to predict PCOS in an overweight, high-risk [Hispanic] population,” the study investigators concluded.

Dr. Kalan said the group is still following the girls and evaluating other factors such as leptin.

Future research may be aimed at early prevention.

“Obviously, the next thing to do is to intervene earlier. Maybe you could head this off,” he said.

Dr. Kalan’s research was supported by the National Institutes of Health. ■