Session IV
PHASIC APPROACH TO ORAL CONTRACEPTION

ON THE HORMONAL BALANCE OF TRIPHASIC ORAL CONTRACEPTIVES CONTAINING ETHINYL ESTRADIOL (EE) AND LEVONORGESTREL (LNG): A STUDY IN HEALTHY DUTCH WOMEN

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Triphasic EE- and LNG-containing oral contraceptives are widely used due to their good tolerance and cycle control. During the recent introduction of oral contraceptives containing new progestins, the contraceptive effectiveness of the triphasic LNG-containing preparations and their androgenic 'rest activity' have been questioned in some publications, claiming the newer progestins to be superior to LNG both for their suppressive effect on ovarian function and their lack of androgenic 'rest activity'.

Study design: In response to this, a prospective study has been undertaken in 22 healthy volunteers to use a triphasic preparation containing EE and LNG (first 6 days, 30 mcg EE and 50 mcg LNG dd; days 7–11, 40 mcg EE and 75 mcg LNG dd; and days 12–21, 30 mcg EE and 125 mcg LNG dd; brand names: Trinordiol/Trigynon) for 12 months. A control cycle was evaluated previous to pill intake. The following parameters were registered or measured during the follicular and luteal phases of the control cycle and during the 3rd week of pill intake during pill-cycles 3, 6, 9 and 12: weight, blood pressure, LH, FSH, estradiol-17-beta (E), progesterone (P), total testosterone (T), SHBG and HDL-cholesterol (HDL-c). All volunteers were healthy and between 19 and 35 years of age (mean 28.5 years). They did not smoke at all or smoked fewer than 10 cigarettes a day.

Results: Body weight did not change significantly during the control cycle or during the 12-month period of pill intake. Blood pressure, both systolic and diastolic, also remained within normal limits without any changes to be attributed to pill use. Ovarian suppression: during the control cycle, FSH, LH, E and P showed the normal cycle patterns and all women had P-levels during the luteal phase in accordance with an ovulatory cycle (P > 15 nmol/L). During pill use, FSH, LH and E declined

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significantly ($p<0.001$) while P in all instances remained below 6 nmol/L. In a normal ovulatory cycle P reaches a value of approximately 5–6 nmol/L on the day of the LH peak and higher concentrations would be indicative of ovulation or luteinization. This clearly demonstrates the good suppressive effect of the triphasic preparation on ovarian function allowing no ovulations to occur. During the observation period, serum T declined significantly from a mean value of 2.40 nmol/L to 1.75 nmol/L ($p<0.001$). At the same time SHBG increased significantly ($p<0.001$) from a mean value of 46 nmol/L to 101 nmol/L. The decrease of T is in agreement with good suppressive effect on ovarian function, whereas the significant increase of SHBG is explained through the estrogenic dominance of the used preparation. As a consequence of this, free T must decrease even more than indicated by the decrease of total T and this explains the good clinical response to these preparations in women with mild or moderate acne and/or seborrhea. HDL-c remained constant throughout the observation period. Mean HDL-c during the control cycle was 1.51 mmol/L versus 1.46 mmol/L during the 12th pill-cycle ($p=0.45$). It can therefore be concluded that these preparations have no 'androgenic' dominance, since if so, a significant decrease of HDL-c was to be expected.

Conclusions: The triphasic EE- and LNG-containing oral contraceptives (Trinordiol/Trigynon)* tested in healthy Dutch women did not influence weight or blood pressure significantly, induced hormonal changes in agreement with good suppression of ovarian function, including inhibition of ovulation and suppression of total testosterone, and showed slight but distinctive estrogenic dominance without androgenic side effects as judged from T, SHGB and HDL-c.

*Trigynon is also available as Triquilar.

12 EFFECTS OF 12 MONTHS' USE OF A LOW-DOSE TRIPHASIC ORAL CONTRACEPTIVE (TRIQUILAR) ON CARBOHYDRATE AND LIPID METABOLISM

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Triquilar, a low-dose combined triphasic oral contraceptive (OC) containing ethinyl estradiol (EE) and levonorgestrel (LNG) was administered in a prospective study to a group of 24 healthy young female volunteers. During the 12 months of the study, no pregnancy was observed, control of the cycle was very satisfactory, and no significant changes in weight and blood pressure were recorded. Glucose tolerance, evaluated by

standardized repeated OGTTs, was normal after 12 months of Triquilar treatment, though a slight glucose-induced hyperinsulinemic response with an enhanced simultaneous glucagon decrease was transiently recorded at 6 months of study before returning to starting levels thereafter. Concomitantly, no change in erythrocyte insulin receptor levels and affinity was observed during the whole study period.

As relates to lipid metabolism, total triglycerides were slightly but significantly increased until the 6th month but declined to starting values at 12 months of study. Total phospholipids were slightly increased. Total cholesterol and its free and esterified forms were only marginally changed, whereas HDL-cholesterol was transiently increased at 3 months and unchanged afterwards, with an ensuing well-maintained HDL-chol:total chol ratio. LDL-chol levels were unchanged and the important LDL-chol:HDL-chol ratio declined slightly until 3 months and was stable afterward. Apolipoprotein A_1 was not significantly changed, while Apo B was moderately but significantly increased during Triquilar treatment; however the Apo A_1:Apo B ratio was not significantly decreased.

Collectively, these data point to very restricted metabolic and endocrine effects of this OC, which behaves as a slightly estrogen-dominant preparation.

PHASIC APPROACH AND ITS CLINICAL APPLICATION

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Oral contraceptives have evolved significantly since their first introduction in the 1960s. The early formulations contained high amounts of estrogens and progesterones and were associated with high rates of side effects and complications. As a result, the quantities in subsequent formulations has been significantly reduced. Recently, a new approach has been developed which results in an alteration of the amount of estrogen and progesterone within the monthly cycle. This has been called the phasic approach. The newest of these contraceptives is a 'tri-phasic'. Three basic formulations are currently available. In two of these, estrogen is constant throughout the cycle while progesterone is altered. The third formulation changes both estrogen and progesterone in a way designed to mimic the natural cycle of the female. A review of the development and results of the changes in these formulations will be presented.

14 TRIPHASIC PILLS – BENEFIT v. RISK

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The triphasic concept of oral contraception mimics the fluctuating levels of hormones of the menstrual cycle. Additionally, in the case of the gonane progestogen, levonorgestrel, the total amount of progestogen administered per cycle is reduced. Good cycle control is facilitated by the early estrogenic influence ensuring proliferation and growth of the endometrium and the late progestogenic dominance is ensured by its effective secretory and anti-estrogenic effect. The formulation of content estrogen dose and incremental progestogen at 7 day intervals in the estrogen–estrane product with norethisterone, has greater anti-estrogenic effect in the late phase of the pill cycle, and hence a greater styptic action, which may be particularly appropriate for young women who have difficulties with cycle control.

A close relation to the menstrual cycle has ensured less adverse biochemical changes and a metabolic state more closely resembling the woman's own background. The extra effort and attention of the acceptor to this type of oral contraception ensures a high level of effectiveness and seems worthwhile, since the low total dose of contraceptive steroid is associated with minimal side-effects.