Introduction

The prevalence of neural tube defects (NTDs) remains an important cause of mortality and morbidity globally. Folic acid deficiency is an identified risk factor for NTDs, which usually occurs during the first month following conception, often when a woman is not aware of her pregnancy.1 It is therefore important for women to supplement with folic acid from at least three months before falling pregnant.2 Folic acid supplementation is recommended by the World Health Organization (WHO) for all women who are trying to conceive until 12 weeks of pregnancy.1 However, in reality, most women of child-bearing age are not adequately receiving folic acid through diet, and only 28% of women take folic acid supplementation before falling pregnant.1,2 This, together with the recognition that 45% of women conceive within three months of discontinuing their oral contraception led to the novel approach to supplement with folic acid for women of reproductive age by fortifying the combined oral contraceptive with folic acid.1,3

Two novel folate-containing oral contraceptive (OC) preparations are available in South Africa1,4–6:

- Yasmin Plus® contains:
  - 21 hormone tablets each containing 3 mg drospirenone, 0.03 mg ethinylestradiol and 0.451 mg levomefolate calcium (equimolar to 0.4 mg folic acid) [pink tablets]
  - 7 hormone-free tablets each containing 0.451 mg levomefolate calcium (equivalent to 0.4 mg folic acid) [light orange tablets]

- Yaz Plus®:
  - 24 hormone tablets each containing 3 mg drospirenone, 0.02 mg ethinylestradiol and 0.451 mg levomefolate calcium (equimolar to 0.4 mg folic acid) [pink tablets]
  - 4 hormone-free tablets each containing 0.451 mg levomefolate calcium (equivalent to 0.4 mg folic acid) [light orange tablets]

Indications

Folate-containing combined OCs are indicated to improve the folate status in women who choose to use oral contraceptives.1,4,5 In addition, Yaz Plus® is indicated for the5:

- Treatment of moderate acne vulgaris.
- Treatment of symptoms of premenstrual dysphoric disorder (PMDD). However, this indication has not been assessed beyond three cycles of treatment. Yaz Plus® has not been evaluated for treatment of premenstrual syndrome (PMS).

Pharmacokinetic properties

Drospirenone

The absorption of drospirenone is rapid, reaching peak serum levels within one to two hours after ingestion, achieving bioavailability, which is not affected by the concomitant intake of food, of between 76% and 85%. Levels of drospirenone decrease in two phases after oral administration, having half-lives of 1.6±0.7 hours and 27.0±7.5 hours, respectively. Drospirenone is protein bound and metabolised extensively after ingestion by cytochrome P450 3A4. The metabolic clearance rate of drospirenone is 1.5±0.2 ml/min/kg in serum with only trace amounts excreted in unchanged form. Metabolites are excreted with faeces and urine, having a half-life of approximately 40 hours. Between day seven and fourteen of treatment, the maximum steady-state concentration of drospirenone is reached.4,5

Ethinylestradiol

The absorption of ethinylestradiol is rapid, with peak serum levels reached within one to two hours after ingestion. Bioavailability is approximately 60% and is reduced by the concomitant intake of food. Ethinylestradiol is characterised by a terminal half-life of approximately 24 hours and is highly protein bound. Aromatic hydroxylation is the main metabolic pathway for ethinylestradiol, which has a clearance rate of about 5 ml/min/kg and no significant

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excretion in an unchanged form. Steady state plasma levels are reached in the second half of the treatment cycle.4,5

**Levomefolate calcium (L-5-methyl-THF)**

The absorption of levomefolate calcium is rapid, with peak serum levels reached within 0.5 to 1.5 hours after ingestion of a dose of 0.451 mg. The terminal half-life is about four to five hours. Depending on baseline levels, steady-state plasma levels are reached after eight to sixteen weeks of treatment, while these levels are delayed in red blood cells owing to the long life-span of red blood cells (±120 days).4,5

**Dosing**

One tablet must be taken orally daily at about the same time every day, swallowed whole with some liquid. 4,5

Starting a first course of folate-containing combined OC4,5:

- Start on the first day of the menstrual period (day 1 of cycle) from the silver section of the pack.
- Take the appropriate tablet for the particular day of the week.
- One tablet must be taken daily for 28 days, following the direction of the arrow on the pack.
- Each follow-up pack must be started the day after the last intake of the previous pack.

**Efficacy**

It is understood that folic acid supplementation before conception and through the first three months of pregnancy has been associated with a reduction of NTDs by 71%. The oral contraceptive has been identified as a route to provide folate supplementation to raise folate levels in plasma and red blood cells (RBCs).1

The concomitant administration of drospirenone and ethinylestradiol does not affect the pharmacokinetics of the folate component, and vice-versa. Results from efficacy studies demonstrated that folate-fortified combined OCs significantly increases folate concentrations over 24 weeks, compared to a combined OC without folate.2

Compared to the nonfolate-fortified version, the folate-fortified contraceptive (drospirenone, ethinylestradiol plus folate), significantly increases folate levels in plasma and RBCs. Serum folate levels increased (15.8 nmol/l) and were consistently maintained while in the nonfolate-fortified arm, plasma folate levels decreased by 2.2±14.6 nmol/l. In addition, there was an increase in RBC folate levels by 34.3 nmol/l in the nonfolate-fortified, while in the folate-fortified OC group, this increase was significantly higher, 419.9±347 nmol/l.1

A double-blind 24-week trial demonstrated higher levels of folate in serum and RBC in the folate-fortified combined OC users compared to women who took folic acid supplementation in addition to combined OCs.1

The overall conclusion from a systematic review found the folate-fortified combined OC preparation was comparable to supplementation with 0.4 mg of daily folic acid. However, the folate-fortified OC combination also offers other advantages:

- Since less than 30% of women of child-bearing age take folic acid, the folate-fortified combined OC preparation offers an ideal delivery for daily folate supplementation.2,3
- The folate-fortified combined OC targets the population who needs folic acid the most – in the event of an unplanned pregnancy it provides folate levels which are reassuringly protective against NTDs. Likewise, without pregnancy, it provides folate levels for overall wellbeing of women’s health.2
- Unlike folic acid, levomefolate calcium does not need to undergo metabolism as it is in an active form in the plasma, being beneficial in women who may be unable to metabolise folic acid optimally.2

**Safety (special precautions, drug interaction, adverse effects)**

**Special precautions**

**Circulatory conditions**

The use of combined OCs including folate-containing combined OCs is associated with an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism. Data suggest that the risk of venous thromboembolism (VTE) is the highest during the first year of use.4,5

The following factors increase the risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident4,5:

- increasing age
- smoking (with heavier smoking and increasing age, the risk increases further, especially in women over 35 years of age)
- a positive family history. If a genetic predisposition is suspected, the woman should be referred to a specialist for advice before considering any combined oral contraceptive use.
- obesity (body mass index over 30 kg/m²)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma

**Cancer**

The use of OCs, including ones fortified with folate, have been found to be a risk factor for certain tumours such as cervical cancer and breast cancer as well as for benign and malignant liver tumours.4,5

**Other conditions**

Women with or a history of hypertriglyceridaemia may be at risk of pancreatitis when taking combined OCs, including folate-
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containing OCs. Additionally, combined OCs may increase blood pressure which may exacerbate existing hypertension. Women with any pre-existing condition should be evaluated before initiating any combined or folate-containing OC.4,5

**Reduced efficacy**

Missed hormone-containing tablets as well as gastrointestinal disturbances may reduce the efficacy of the folate-containing OC.

**Drug interactions (Figure 1)**

Potential drug interactions with other medicines may affect the efficacy of the folate-containing OC, leading to withdrawal bleeding and/or contraceptive failure4,5:

**Adverse effects**

The most common adverse effects include headache/migraine, nausea/vomiting, breast pain/tenderness and menstrual irregularities such as spotting, menorrhagia or metrorrhagia.1,4,5

**Important prescribing points (Yasmin Plus® / Yaz Plus®)**

- **How to start taking Yasmin Plus® or Yaz Plus®4,5:**

  **No prior hormonal contraceptive use (in the past month)**

  Start on day 1 of menstrual cycle. May start on days 2 to 5; however, a barrier method of contraception is then additionally recommended during the first cycle.

  **Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring, or transdermal patch**

  Start on the day after the last hormone-containing pill from a previous combined OC.

  Start on the day of removal of the vaginal ring or transdermal patch.

  **Changing from a progestogen-only method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)**

  Start:

  - On the next day after stopping the minipill
  - On the day of removal of an implant or IUS
  - When the next injection would be due

  Additional barrier methods should be used for the first seven days of tablet-taking

- **Management of missed pills**

  The failure rate of 1% per year may increase when pills are missed or taken incorrectly.4,5

  Missing the hormone-containing pink tablets4,5:

  - Less than 12 hours late in taking the hormone-containing pill
    Take the pill as soon as possible and further pills should be taken at the usual time

  - More than 12 hours late in taking the hormone-containing pill
    Contraceptive protection may be compromised – take pill as soon as possible but a barrier method of contraception used additionally for at least seven days.

- **Gastrointestinal disturbances**

  Absorption may be incomplete and additional contraceptive methods should be used. In the event of vomiting within three to four hours after taking the pink hormone-containing pill, this should be treated like a “missed pill” situation.4,5

A complete medical evaluation is advised prior to initiating any combined OC to take into consideration the risk factors and personal medical history of the patient.4,5

**References**


