Over the last five to ten years, a few rare case reports and a short list of published research have brought to light the possibility that St. John’s wort may interfere with oral contraceptive (OC) pills. The main issue is that St. John’s wort induces cytochrome P450 (CYP) enzymes, and therefore may alter the pharmacokinetics of the estrogen and/or progestin and result in a reduction of their contraceptive efficacy.

Two reports have shown breakthrough bleeding and spotting with co-administration of St. John’s wort and OCs. Three studies have indicated an adverse interaction between St. John’s wort and OCs. St. John’s wort was tested for its effect on Ortho-Novum 1/35, an OC pill containing ethinyl estradiol and norethindrone. Twelve healthy reproductive-aged women had been using Ortho-Novum for three consecutive menstrual cycles. During the second and third cycles, they received 300 mg of St. John’s wort three times daily. Serum concentrations of ethinyl estradiol, norethindrone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, and IV and oral midazolam were determined in blood samples. Breakthrough bleeding was also evaluated.

Use of St. John’s wort with the OC was associated with a significant increase in the clearance of norethindrone and a significant reduction in the half-life of ethinyl estradiol. Oral clearance of midazolam was significantly increased during the herb usage, but the systemic clearance of midazolam was stable with no change. FSH, LH, and progesterone were not significantly affected by the St. John’s wort. Two of the women experienced breakthrough bleeding in the control phase, and seven women did during the St. John’s wort phase.

In another earlier study, 18 healthy premenopausal women were treated with a low-dose OC pill of 0.02 mg ethinyl estradiol and 0.150 desogestrel either alone during the control cycle or combined with St. John’s wort 300 mg b.i.d. (cycle A) or t.i.d. (cycle B). FSH, serum estradiol, progesterone levels, and pelvic ultrasounds were tested as a measure of ovarian activity. Breakthrough bleeding was assessed, and the pharmacokinetics of the OC were tested under proper conditions. During the coexisting use of OC and St. John’s wort, there was no significant change in estradiol levels compared with OC alone. However, 13 of 17 women had intermenstrual bleeding during cycle A and 15 of 17 during cycle B, and only 6 of 17 during OC alone. There was no evidence of ovulation any time during use of St. John’s wort with the OC, despite the increase of intracyclic bleeding episodes. In this study, there were no changes in blood levels of FSH, estradiol, or progesterone. A weakness of this study was that there was no washout period and no amount of hyperforin was reported. With the blood tests and the advantage of the pelvic ultrasounds, there was no evidence that St. John’s wort increased ovulation in either cycle A or cycle B. Although there was no change in estradiol levels during the St. John’s wort, there was a significant decrease in the amount of the desogestrel present after St. John’s wort use. This does in fact demonstrate that St. John’s wort induces CYP3A4, as does the first study.

In a third study, the effect of St. John’s Wort on OC therapy, with respect to the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity, and breakthrough bleeding, was evaluated. Sixteen healthy women were treated with a low-dose OC (Loestrin 1/20) and a placebo for two consecutive 28-day cycles in a single-blind sequential trial. Co-treatment with St John’s Wort 300 mg three times daily was
then added for two additional 28-day menstrual cycles. Outcomes compared the pharmacokinetics of norethindrone and ethinyl estradiol, daily bleeding diaries, follicle growth, changes in cervical mucus, and progesterone levels drawn at 7- to 10-day intervals. Co-treatment with St. John’s Wort was associated with a 13% to 15% reduction in the dose exposure from the contraceptive, based on increased metabolism of norethindrone and ethinyl estradiol. Breakthrough bleeding increased in the two co-treatment cycles, as well as evidence of follicle growth and probable ovulation. The authors concluded that women using OCs should be cautioned that St. John’s wort might interfere with contraceptive effectiveness.

In the most recent study, the participants were 16 healthy women who had taken a low-dose OC with 20 mcg ethinyl estradiol + 0.15 mg desogestrel for at least 3 months. A 50% ethanol extract of St. John’s wort 250 mg twice daily standardized to 0.2% hypericin (1 mg/day) and ≤ 0.2% (< 1mg/day) hyperforin was initiated day 7 through day 21 of the OC administration. Blood samples were taken on days 7 and 14. The activities of CYP3A4 for the estrogen metabolism, and CYP2C19 and CYP2D6 for the progestin metabolism, were used to measure metabolism of the OC and interaction of the OC with St. John’s wort. Results demonstrated that co-medication of the St. John’s wort extract with the OC did not elicit any differences in the pharmacokinetic measures of ethinyl estradiol in this study. The pharmacokinetics of the desogestrel were also not affected by co-administration of the St. John’s wort extract. There was a small decrease in ethinyl estradiol and 3-ketodesogestrel, but it was not considered significant. In addition, there was no breakthrough bleeding induced by the addition of the St. John’s wort extract.

It is apparent that St. John’s wort causes a change of ethinyl estradiol-progestin metabolism that is consistent with increased CYP3A, CYP2C19, and CYP2D6 activity. In addition, there is an increase in breakthrough bleeding with concomitant use of OCs and St. John’s wort in three of the four published co-treatment studies.

The three earlier studies used a different St. John’s wort preparation (80% methanolic extract) and a much higher dose (900 mg) containing a much higher amount of hyperforin (20–35 mg) than the most recent 2009 study. The lower daily total dose and hyperforin intake would appear to be the likely reason for the lack of interaction of the St. John’s wort extract with the OC pharmacokinetics in this most recent study. According to the current study, using a lower-dose St. John’s wort extract with reduced hyperforin content does not interact with OC nor cause breakthrough bleeding (an indication of possible ovulation). There are subgroups of patients who may react more strongly to CYP3A inducers, and they may be at a greater risk for an adverse interaction between St. John’s wort and OCs. This can be tested using single nucleotide polymorphism testing. Breakthrough bleeding is a common cause of noncompliance with OCs. In light of this, women should be counseled to expect breakthrough bleeding if they are taking an OC and St. John’s wort. In addition, it would be prudent to consider adding a barrier method of contraception if using St. John’s wort with OCs, or look at the alternatives: switching contraceptives or using botanical/nutritional alternatives other than St. John’s wort.

Notes
