Comparison of vaginal and oral administration of emergency contraception

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Objective: To compare the physiologic effects of vaginally and orally administered emergency contraception.
Design: Prospective, open-label, crossover study.
Setting: University research center.
Patient(s): Nine regularly menstruating volunteers.
Intervention(s): Five subjects received 1,000 μg of levonorgestrel with 200 μg of ethinyl E_2 (twice the standard Yuzpe regimen dose) vaginally, and the standard Yuzpe regimen dose orally 1 week later. Four subjects received 1,500 μg of levonorgestrel (twice the standard Plan B regimen dose) vaginally and received the standard Plan B dose orally 1 week later. Serum samples were obtained at baseline and at frequent intervals after each dose.
Main Outcome Measure(s): Serum gonadotropin, hepatic globulin, and androgen levels measured at baseline, at the time of peak levonorgestrel, and 24 hours later.
Result(s): Gonadotropin, hepatic globulin, and androgen levels were suppressed to a similar degree among the four regimens, with a return to baseline levels after 24 hours.
Conclusion(s): We conclude that high doses of levonorgestrel found in emergency contraception regimens lead to a transient direct suppression of gonadotropin, hepatic globulin, and androgen levels. This effect is similar after vaginal and oral administration of emergency contraception. Therefore, the vaginal route of administration of emergency contraception regimens may be as efficacious as the oral route. (Fertil Steril® 2005;84:40–5. ©2005 by American Society for Reproductive Medicine.)

Key Words: Emergency contraception, vaginal administration, Yuzpe regimen, Plan B regimen, levonorgestrel, gonadotropins, androgens, hepatic globulins

The observation that postcoitally administered steroids may prevent conception has led to the development of so-called emergency contraceptive formulations. The Yuzpe regimen, containing both ethinyl E_2 (EE) and levonorgestrel, is the most commonly used emergency contraceptive (1). Although effective in preventing up to 75% of unwanted pregnancies with proper use, about 50% of treated women report nausea, and >20% vomit after ingesting the medications (2). Recently, Plan B, an oral progestin-only regimen containing a slightly higher dose of levonorgestrel, was found to be more effective than the Yuzpe regimen, with a lower incidence of nausea and vomiting. However, nausea was still present in 23% of cases, along with vomiting, dizziness, fatigue, headache, low abdominal pain, and diarrhea, which occurred in 5%–17% of patients (3). Vaginal, as opposed to oral, hormonal administration avoids exposure to the gastrointestinal tract as well as first-pass metabolism in the liver, while allowing a direct local effect of sex hormones on the endometrium (4–6).

The mechanism of action of orally administered emergency contraception is thought to be via a delay in ovulation with a possible direct action on the endometrium (7, 8). However, data regarding the effect of vaginally administered emergency contraception on pituitary gonadotropin secretion are lacking. Furthermore, despite being accepted as generally safe, data pertaining to acute effects of hepatic perfusion by high concentrations of orally and vaginally administered contraceptive steroids are also lacking. We have previously shown that low-dose combination oral contraceptives containing EE combined with levonorgestrel or norethindrone acetate suppress production of androgens, whereas sex hormone–binding globulin (SHBG) production is increased (9). However, data regarding effects of the substantially higher amounts of steroids present in emergency contraception on androgens are also lacking.

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The purpose of this study was to evaluate pharmacodynamic effects of the Yuzpe and Plan B regimens when administered vaginally, as compared with the oral route.

MATERIALS AND METHODS

The study received institutional review board approval and informed written consent was obtained from each volunteer before participation. Nine healthy women between the ages of 20–28 years with regular menses (25–35 days) volunteered to participate in the study. Subjects were excluded from participation if they were using any contraceptive hormones or if they had any contraindications to hormonal contraception, such as abnormal liver function, clotting disorders, or personal or family history of thromboembolic events. A negative urine pregnancy test was obtained from all subjects before administration of any study medications.

Participants were assigned to two treatment arms, with one group receiving the Yuzpe regimen (standard dose = 500 μg of levonorgestrel–100 μg of EE) and the second group receiving Plan B (standard dose = 750 μg of levonorgestrel). Five participants received twice the standard dose of the Yuzpe regimen vaginally, followed by the standard dose orally after a 1-week washout period. Four participants received twice the standard dose of Plan B vaginally, followed by the standard dose orally 1 week later. To minimize gastrointestinal side effects, a 50-mg oral tablet of dimenhydrinate (an anti-emetic) was ingested by each participant at the time of administration of study medications. Vaginally administered medications were placed in the posterior fornix of the vagina by the subjects themselves, following instruction from a physician. To minimize the possibility of tablets falling out of the vagina after administration of study medications, subjects remained in the hospital and were restricted to limited physical activity for the first 8 hours (sitting position for first 4 hours). None of the study participants reported any difficulty with vaginal retention of tablets (10). Each subject arrived in the fasting state in the midfollicular phase after completion of menses. Serum samples were obtained over a 24-hour period at baseline; then every 30 minutes for the first 4 hours; then at 5, 6, 8, 12, and finally 24 hours after oral or vaginal administration of the Yuzpe or Plan B regimens for measurement of levonorgestrel and EE and for calculation of their pharmacokinetic parameters, as described elsewhere (10). To ensure that study medications were administered in the follicular phase, serum P levels were obtained hourly for 6 hours and at 12 and 24 hours after administration of medications. All serum P values were <3.0 ng/mL.

Hormone and Globulin Assays

The following assay methods were used: LH and FSH were measured by direct chemiluminescent immunoassay (ACS180; Bayer, Tarrytown, NY); SHBG and DHEAS were measured by direct chemiluminescent immunoassay (Immulite analyzer, Diagnostic Products Corporation, Inglewood, CA); corticosteroid-binding globulin (CBG) and angiotensinogen were measured by highly specific direct RIA (intraassay coefficients of variation were 8.2%–9.6% and 7.3%–8.4%, respectively, and interassay coefficients of variation were 9.5%–10.9% and 8.1%–9.2%, respectively); androstenedione (A), T, and dihydrotestosterone were quantified by RIA with preceding organic solvent extraction and Celite column partition chromatography (11–14). Free T was calculated by a validated computer algorithm (15).

Statistical Analysis

Data were analyzed by using SPSS software (Statistical Package for the Social Sciences, version 10.0; SPSS, Inc., Chicago, IL). Because absorption of administered steroids varied among study participants, for the purpose of analysis, the measurements of LH, FSH, SHBG, CBG, angiotensinogen, A, T, free T, dihydrotestosterone, and DHEAS were individually adjusted and are reported at baseline and at the time of peak and nadir levonorgestrel levels (10). Serum hormone and globulin levels were compared among the four regimens by one-way analysis of variance. Spearman's correlation test was used for correlation analysis.

RESULTS

Overall, study medications were well tolerated. One subject reported nausea after vaginal administration of the Yuzpe regimen. A second subject reported nausea after both oral and vaginal administration of Plan B. Sleepiness was reported by all subjects for oral and vaginal administration of both regimens, consistent with the concomitant administration of dimenhydrinate. None of the subjects experienced vomiting, headache, vaginal irritation, or vaginal discharge.

Gonadotropins

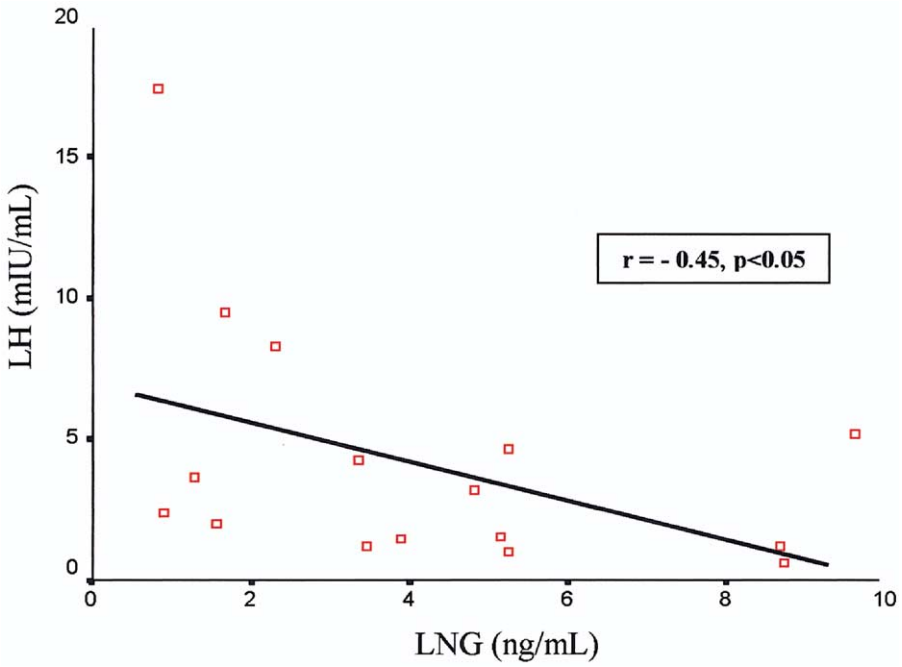
Mean LH levels were at their lowest at the time of peak levonorgestrel for both Yuzpe and Plan B, with an average decrease of 27.0% and 8.1% for the vaginal and oral routes, respectively (P= not significant [NS]). Mean FSH levels at the time of peak levonorgestrel were lower than baseline for both vaginal and oral routes, with an average percentage decrease of 5.6% and 11.2%, respectively (P=NS). There was no significant difference in mean LH or FSH values between Yuzpe and Plan B regimens administered orally or vaginally. There was a statistically significant inverse correlation between LH and levonorgestrel levels ($r = -0.45$; $P<.05$), as well as FSH and levonorgestrel levels ($r = -0.61$; $P<.05$) in the vaginally administered regimens (Figs. 1 and 2).

Hepatic Globulins

At peak levels of levonorgestrel, mean levels of angiotensinogen (1,059 ± 529 pg/mL), CBG (3.5 ± 2.6 mg/dL), and SHBG (40.1 ± 17.7 nmol/L) were consistently at their lowest with any given regimen, with a mean percentage

FIGURE 1

Correlation of serum LH and levonorgestrel levels in vaginally administered Yuzpe and Plan B. LNG = leunorgestrel.



Mor. Vaginal vs. oral emergency contraception. Fertil Steril 2005.

decrease from baseline of 18.1% ($P<.05$), 27.8% ($P<.05$), and 6.7% (P=NS), respectively, in vaginal regimens, and a mean percentage decrease from baseline of 27.3% ($P<.05$), 36.6% ($P<.05$), and 6.1% (P=NS), respectively, in orally administered regimens (Fig. 3). Values returned to baseline levels after 24 hours. There was no significant difference in mean angiotensinogen, CBG, and SHBG values between Yuzpe and Plan B regimens administered orally or vaginally. There was a statistically significant inverse correlation between angiotensinogen and levonorgestrel levels ($r = -0.39$, $P<.05$), as well as CBG and levonorgestrel levels ($r = -0.45$, $P<.05$), following vaginally administered Yuzpe and Plan B regimens.

Androgens

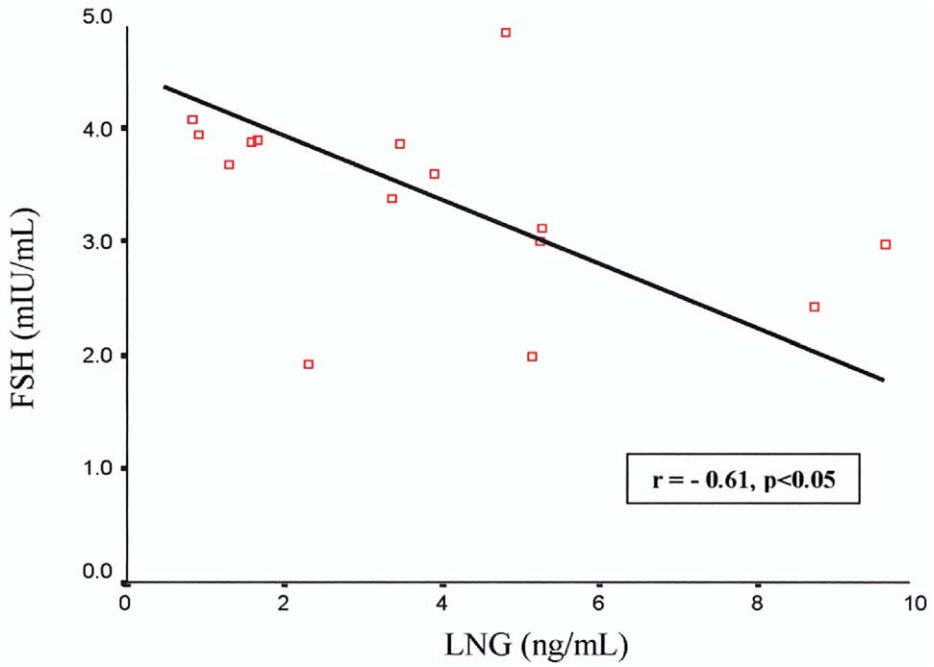
At peak levels of levonorgestrel, mean values for A (1.1 ± 0.4 ng/mL) and dihydrotestosterone (16.6 ± 6.1 ng/dL) decreased from baseline across all treatment regimens, with a mean percentage decrease of 37.0% and 23.2%, respectively, in vaginally administered regimens ($P<.05$), and a mean percentage decrease of 26.4% and 27.1%, respectively, in orally administered regimens ($P<.05$; Fig. 4). Values rebounded back to baseline after 24 hours. There was no significant difference in mean A and dihydrotestosterone values between Yuzpe and Plan B regimens administered orally or vaginally. Overall, mean T and free T levels were at their lowest at the time of peak levonorgestrel (38.3 ± 15.2 ng/dL and 6.3 ± 2.3 pg/mL, respectively), with a mean percentage decrease from baseline in vaginally administered regimens of 21.5% ($P<.05$) and 14.7% (P=NS), for T and free T, respectively, and a mean percentage decrease from baseline of 8.7% and 3.0%, respectively, in orally administered regimens (P=NS; Fig. 4). Values returned to baseline after 24 hours. At the time of peak levonorgestrel, levels of all measured androgens were consistently lower with Plan B as compared with Yuzpe regimens. This reached statistical significance for A, for which levels at peak levonorgestrel, obtained with vaginal Plan B (0.9 ± 0.2 ng/mL), were lower than those observed after the vaginal Yuzpe regimen (1.2 ± 0.4 ng/mL, $P<.05$). Mean levels of DHEAS remained similar across the four treatment groups at the time of baseline, peak levonorgestrel, and at 24 hours. There was a statistically significant inverse correlation between A and levonorgestrel levels ($r = -0.32$, $P<.05$), as well as free T and levonorgestrel levels ($r = -0.37$, $P<.05$), whereas the correlation between other androgens and levonorgestrel was weak.

DISCUSSION

In the current study, mean LH and FSH levels decreased from baseline with the administration of all four regimens, supporting the hypothesis that one of the modes of action of emergency contraception is inhibition of follicular development and ovulation. There was no significant difference in LH and FSH suppression between the Yuzpe and Plan B regimens, suggesting that when high doses of levonorgestrel

FIGURE 2

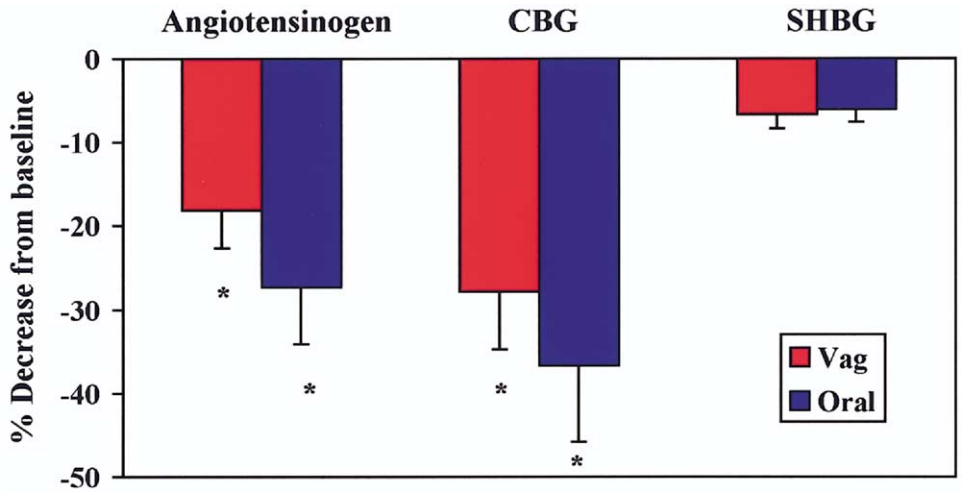
Correlation of serum follicle-stimulating hormone (FSH) and levonorgestrel levels in vaginally administered Yuzpe and Plan B. LNG = levonorgestrel.



Mor. Vaginal vs. oral emergency contraception. Fertil Steril 2005.

FIGURE 3

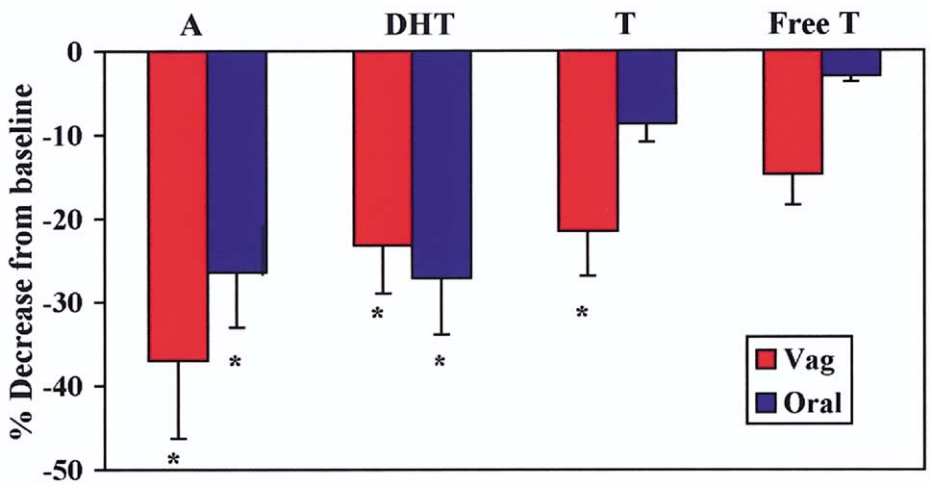
Mean percentage decrease from baseline to time of peak levonorgestrel of angiotensinogen, corticosteroid –binding globulin (CBG), and sex-hormone-binding globulin (SHBG) levels after vaginally (*red bars*) and orally (*blue bars*) administered Yuzpe and Plan B regimens. No significant difference was detected between vaginal and oral regimens. A significant reduction from baseline was encountered in some hepatic globulins (*$P<.05$).



Mor. Vaginal vs. oral emergency contraception. Fertil Steril 2005.

FIGURE 4

Mean percentage decrease from baseline to time of peak levonorgestrel of A, dihydrotestosterone, T, and free T levels after vaginally (*red bars*) and orally (*blue bars*) administered Yuzpe and Plan B regimens. No significant difference was detected between vaginal and oral regimens. A significant reduction from baseline was encountered in most androgens (*$P<.05$).



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are used, as in Plan B, the addition of EE, as in the Yuzpe regimen, contributes little to further gonadotropin suppression. This, along with the recent finding that Plan B is more efficacious in preventing unwanted pregnancies than the Yuzpe regimen (3), suggests that the role played by EE in emergency contraception may be a redundant one.

It has been previously shown that vaginal administration of a combined oral contraceptive pill can inhibit ovulation (16). In our study, despite the fact that the peak serum levonorgestrel levels reached after vaginal administration of both regimens were significantly lower than when either regimen was administered orally (10), LH and FSH suppression was similar after vaginally and orally administered regimens. This suggests that vaginal administration of such regimens may be as efficacious in delaying ovulation as oral administration. Furthermore, it should be noted that despite adequate EE absorption after vaginal Yuzpe administration (10), no difference in LH and FSH was noted between Yuzpe and Plan B, again suggesting that EE, whether administered vaginally or orally, may play a secondary role in gonadotropin suppression.

The selective uptake of vaginally administered steroids into the endometrium (4, 6, 17, 18) makes it tempting to speculate that vaginally administered emergency contraception would result in substantially increased endometrial tissue levels of these steroids. As such, a local effect on the endometrium may serve as an added contraceptive benefit beyond ovulation inhibition.

The production of several hepatic globulins has been shown to be highly estrogen sensitive. Administrations of estrogens results in a dose-dependent increase in angiotensinogen, CBG, and SHBG (19, 20), whereas progestins suppress hepatic production of these globulins, most likely through an androgenic or anti-estrogenic effect (21, 22). Consistent with this, in the present study, angiotensinogen, CBG, and SHBG levels were at their lowest at the time of peak levonorgestrel, and a negative correlation was found between angiotensinogen and levonorgestrel levels, as well as CBG and levonorgestrel levels, suggesting a direct suppression of hepatic globulin production by high doses of levonorgestrel. Furthermore, orally administered regimens appeared to cause a more pronounced decrease in angiotensinogen and CBG as compared with the vaginal route, possibly because of direct hepatic perfusion by high doses of orally administered progestins and avoidance of hepatic first-pass metabolism by the vaginal route of administration. Because all decreases were transient, with return to baseline levels within 24 hours, administration of either of the emergency contraception regimens studied appears to be safe with regard to acute metabolic effects on angiotensinogen, CBG, and SHBG.

Administration of SC levonorgestrel–containing contraceptives has previously been reported to result in a decrease of T and A levels (23), whereas addition of levonorgestrel to genital skin in vitro leads to an inhibition of 5α-reductase activity resulting in decreased production of dihydrotestosterone (24). Our study allowed assessment and comparison of the acute effects of emergency contraceptions containing high-dose levonorgestrel on serum androgens with both the oral and vaginal routes. As expected, levels of most androgens decreased from baseline at the time of peak levonorgestrel with a return to baseline after 24 hours. This

suggests that androgen levels are responding to suppression of pituitary LH secretion. Consistent with this, levels of all measured androgens were lower at the time of peak levonorgestrel with Plan B as compared with Yuzpe regimens, likely because of higher doses of levonorgestrel found in Plan B. However, despite reaching significantly lower serum levels of levonorgestrel, vaginal routes of administration of both Yuzpe and Plan B, resulted in a similar decrease in androgen levels to those observed with the orally administered regimens. The presence of EE (Yuzpe) or its absence (Plan B) in emergency contraception did not result in a further alteration in serum androgen levels, consistent with similar degree of LH suppression in all regimens. Moreover, all observed trends in androgen levels appeared to be transient and reversible, with serum values returning to baseline within 24 hours among all treatment groups.

Our study was limited by the small number of subjects enrolled. When present, lack of statistically significant differences in levels of suppression of gonadotropins, hepatic globulins, and androgens achieved with oral and vaginal Plan B and Yuzpe regimens may be a function of inadequate power. As such, larger scale studies are necessary to affirm with certainty the superiority, or lack thereof, of one particular route and regimen over the others.

In conclusion, administration of the Yuzpe and Plan B regimens of emergency contraception results in suppression of circulating gonadotropins, suggesting inhibition of ovulation as a possible mechanism of action. Vaginal administration of double the standard dose of emergency contraception leads to a similar suppression of circulating gonadotropins as the oral route, suggesting a similar effectiveness in ovulation suppression to the oral route. Oral and vaginal administration of both emergency contraception regimens results in a similar transient and reversible suppression of hepatic globulins and androgens, attesting to their safety and tolerability. The enhanced absorption of steroids from the vagina into the endometrium suggests that the vaginal route may actually have an advantage in this regard. Therefore, our preliminary observations suggest that the vaginal route of administration of emergency contraception regimens, at double the standard dose, appears to be a viable alternative to the oral route and may prove to be equally efficacious in future clinical trials.

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