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A Comparative Study between Vaginal versus Oral Administration of Levonorgestrel as A Method of Emergency Contraception

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ABSTRACT

Background: Levonorgestrel-only Emergency Contraception (EC) prevents fertilization by inhibiting ovulation. Using Emergency Contraception within five days of intercourse may prevent more than eighty-five percent of pregnancies.
Aim: This study aimed to evaluate the effectiveness of levonorgestrel administered orally vs. vaginally as an emergency contraceptive.
Patients & methods: This comparative, possible, randomized research has been conducted on one hundred women with regular cycles at Damanhur Medical National Institute from September 2023 until February 2024. Women were split into two groups: First group included 50 women who took 1.5 mg of levonorgestrel orally (two Contraplan II tablets). Second group contained 50 women who received 1.5 mg of levonorgestrel vaginally (two Contraplan II tablets).
Results: No statistically significant variances were found among the examined groups regarding general characteristics, general assessments, anthropometrics, CBC, and profiling of coagulation. A statistically significant variance had been demonstrated among the examined groups regarding the plasma levels of levonorgestrel, platelets, BT, CT, PT, nausea, stomach discomfort, headaches, and vomiting. The vaginal group had a lower pregnancy rate.
Conclusion: We concluded that levonorgestrel vaginal administration is more suitable, effective, and safer as an emergency contraceptive compared to oral administration. So, we suggest using levonorgestrel vaginal administration as an EC rather than oral administration.
Keywords: Emergency contraception (EC), levonorgestrel, Pregnancy.

INTRODUCTION

Emergency contraception (EC) is the brief administration of medications. EC can be used to prevent pregnancy where contraception has not been used, or there has been contraceptive misuse or failure [(1)]. It is capable of preventing more than ninety-five percent of pregnancies when administered within five days of intercourse. The following situations may necessitate the utilization of EC: Unprotected intercourse, concerns regarding potential contraceptive failure, incorrect contraceptive utilization, & sexual assault in the absence of contraceptive coverage [(2, 3)].

The EC pill regimens suggested by the World Health Organization are ulipristal acetate, levonorgestrel, or combined oral contraceptives (COCs) that are composed of ethinyl estradiol & levonorgestrel [(4)]. EC comes in two different forms: Two hormonal approaches; one that uses solely progestins, and the other is the Yuzpe regimen. It has been established that EC is most successful 72–120 hours after an unprotected sexual encounter. Teenagers are currently advised to utilize the progestin-only form of EC since it is more efficient & has fewer adverse impacts than the combination method [(5)].

The levonorgestrel-only pill is frequently utilized as an EC, a backup plan in the event of a failed contraceptive that a woman may employ this method to avoid an unwanted pregnancy within a few days of an unprotected intercourse [(6)].

Levonorgestrel (LNG) is a synthetic hormone-like substance. When administered within seventy-two hours of having unprotected sexual activity, it effectively prevents around eighty-four percent of predicted pregnancies. It isn't guaranteed to prevent pregnancy, &it is more efficient when administered promptly following unprotected sexual intercourse. It is preferable to consume it within twelve hours rather than delaying it till the third day [(7)].

Levonorgestrel-containing oral contraceptives reduce gonadotropins, which prevent ovulation. LNG specifically binds androgen & progesterone receptors & inhibits the production of GnRH from the hypothalamus. This procedure suppresses the LH spike that normally happens physiologically before ovulation. It prevents the release of fertile eggs from the ovaries and the rupture of follicles. When taken before ovulation, levonorgestrel is more effective [(8)]. Levonorgestrel has an elimination half-life of 20 to 60 hours after a 0.75 mg dosage of 1.5 mg [(9)]. The current research's objective was to evaluate the effectiveness of levonorgestrel administered orally vs. vaginally as an emergency contraceptive.

PATIENTS AND METHODS

This comparative, possible, randomized research has been conducted on one hundred women with regular cycles at Damanhour Medical National Institute from September 2023 until February 2024. Women were split into two groups: First group included 50 women who took 1.5 mg of levonorgestrel orally (two contraplan II tablets). Second group contained 50 women who received 1.5 mg of levonorgestrel vaginally (two contraplan II tablets).

Inclusion criteria: Women of reproductive age had a normal body mass index & had false pregnancy result tests.

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Exclusion criteria: Women who desired to become pregnant, women who had any contradictory factors to the hormonal contraceptive method, including impaired hepatic function, clotting problems, or otherwise who had a family or personal history of thromboembolic disorders & women who were using levonorgestrel contraindications (Undiagnosed vaginal bleeding, high-risk vascular disease in the past or present, or undiagnosed vaginal bleeding were not associated with hypersensitivity to the active substances).

Method of randomization: A closed, sealed envelope was used to assure randomization, with the letter "O" standing for oral contraplan II and the letter "V" for vaginal contraplan II.

Sample size calculation: This study is based on the research conducted by **Ashraf *et al.*** [10]. Clinicalc was utilized to determine the sample size, taking into account the subsequent assumptions: - A power of 80% & a two-sided confidence level of 95% & an α error of 5%. An unwanted side effect of levonorgestrel is abdominal pain, which occurred at a ratio of 66.7% and 36.7% after oral and vaginal levonorgestrel, respectively. 84 was the final maximum sample size obtained from the clincalc output. Consequently, the sample size was raised to one hundred participants in anticipation of any dropout cases that may occur during the follow-up period.

$$N_1 = \left\{ z_{1-\alpha/2} * \sqrt{\bar{p} * \bar{q} * (1 + \frac{1}{k})} + z_{1-\beta} * \sqrt{p_1 * q_1 + (\frac{p_2 * q_2}{k})} \right\}^2 / \Delta^2$$

$$q_1 = 1 - p_1$$

$$q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + k p_2}{1 + K}$$

$$\bar{q} = 1 - \bar{p}$$

$$N_1 = \left\{ 1.96 * \sqrt{0.517 * 0.483 * (1 + \frac{1}{1})} + 0.84 * \sqrt{0.667 * 0.333 + (\frac{0.367 * 0.633}{1})} \right\}^2 / 0.3^2$$

$$N_1 = 42$$

$$N_2 = K * N_1 = 42$$

All women were subjected to the following : Complete history-taking involving complaints & particular biographies of every woman in the research [The duration of sterility, the nature of the condition (secondary or otherwise principal), hirsutism, & acne]. Obstetric history [A record of a comparable circumstance (repeated abortion)]. Contraceptive history (The type & duration of use). Medical history (Any current or past complications & infertility or consanguinity in the family unit's past).

Clinical examination: The physical examination comprised general (height, BMI & weight), abdominal and local (pelvic) examinations.

Investigations: A comprehensive evaluation of the patient's blood, urine, & coagulation profile (involving prothrombin time, bleeding time & CT). Kidney function examinations consist of serum creatinine & blood urea, while liver function tests comprise serum bilirubin, HBV, liver enzymes, & HCV. And **Periodic ultrasound assessments**.

Follow-up: A pregnancy test was conducted 2 weeks subsequent to the levonorgestrel administration.

Ethical consideration: The medication utilized in the investigation, LNG (commercial name Contra Plan II 0.75 mg/tablet), is confirmed by the Egyptian Ministry of Health. The Ethics Committee of the GOTHI Research Centre approved the research protocol (ID of ethical approval: HD000173). Prior to enrollment, written informed consents were gathered from individuals or their legal representatives in accordance with the individual's condition. The purpose of this study was to perform research on humans in compliance with the Declaration of Helsinki, the code of ethics of the World Medical Association.

Statistical analysis

Version twenty of the Statistical Programmed for the Social Sciences (SPSS Inc., Chicago, IL, USA) was used in order to examine the data. The mean and standard deviation were utilized to characterize quantitative variables. Numbers & percentages were utilized to describe qualitative factors. The student t-test was utilized in order to contrast quantitative parametric factors across two groups. When frequencies fell below five, the Chi-square (X^2) test or Fisher's exact test had been employed for comparing qualitative variables. A p-value of 0.05 or below is significant when a variable is not normally distributed.

RESULTS

Regarding demographic information and general exams, there were no statistically significant variances among the analyzed groups (Table 1).

Table (1): Comparison of general characteristics & general assessments among the groups examined

	Oral (n=50)		**Vaginal (n=50)**		**p**
Age (years):					
Range	25-37		23-36		0.421
(mean ± SD)	30.97±3.04		30.86±3.1		
Parity					
(N %)	10	20	8	16	0.602
nulliparous	40	80	42	84	
Multiparous					
Previous abortion:					
Yes (N %)	8	16	11	22	0.444
Surgical history:					
CS (N %)	27	54	31	62	0.417
Comorbidity:					
(N %)					
Diabetes	4	8	3	6	0.823
Hypertension	3	6	2	4	
Systolic BP					
Range	108-138		109-148		0.714
Mean ± SD	124.37±13.02		125.24±12.81		
Diastolic BP:					
Range	69-91		71-90		0.726
Mean ± SD	74.7±6.4		74.92±5.4		
Pulse					
Range	71-96		70-97		0.237
Mean ± SD	81.73±8.02		80.94±7.11		
Temp					
Range	36-38		37-38		0.211
Mean ± SD	37±0.31		36.01±0.34		

We observed no statistically significant variances among the examined groups regarding anthropometrics & CBC (Table 2).

Table (2): Comparison of anthropometrics & baseline CBC among the examined groups

	Oral (n=50)	**Vaginal(n=50)**	**p**
Weight:			
Range	57.8-85	60-85	0.819
Mean ± SD	70.7±4.9	71.21±5.74	
Height:			
Range	153-172	152-173	0.232
Mean ± SD	162.5±5.72	163.73±3.8	
BMI:			
Range	24.1-29.5	23.4-29.1	0.221
Mean ± SD	25.21±1.76	24.93±1.67	
Hb:			
Range	10.5-13.7	10.6-13.8	0.874
Mean ± SD	11.7±0.75	12.1±0.78	
WBCs:			
Range	4.5-7.3	4.6-7.9	0.7
Mean ± SD	6.5±0.85	6.2± 0.6	
Plts:			
Range	152-260	152-267	0.636
Mean ± SD	210.4±36.3	217.07±30.84	

Regarding the profiling of coagulation, it was noted that no statistically significant variance was detected among the tested groups. Concerning the plasma LNG level, there was a statistically significant variation between the examined groups (Table 3).

Table (3): Comparison of baseline coagulation profile & plasma level of levonorgestrel among the re-examined groups

	Oral(n=50)	Vaginal(n=50)	p
Coagulation profile:			
BT (mins):			
Range	1.1-1.4	1-1.4	0.913
Mean ± SD	1.12±0.13	1.21±0.15	
CT (mins):			
Range	4.2-7.5	4.4-7.6	0.735
Mean ± SD	6.22±0.94	5.75±0.81	
PT (Sec):			
Range	10.3-12.4	10.1-12.9	0.451
Mean ± SD	11.81±0.94	11.52±0.78	
Plasma level of levonogestrel (mg):			
• **Peak level 1-4 hours:**	42-101	7-19	<0.001
Range	72.81±20.42	11.81±4.1	
Mean ± SD			
• **Time of peak (mins):**			
Range	61-174	205-318	<0.001
Mean ± SD	105.12±31.7	260..1±34.82	
• **Half-time level:**			
Range	8-30	3-11	<0.001
Mean ± SD	20.82±6.34	6.71±2.13	

A statistically significant variance was found among the analyzed categories regarding platelets, CT, BT, & PT (Table 4).

Table (4): Comparison of lab amongst individuals ' data prior & atfollow-up

	Before(n=100)	After (n=100)	p
Hb (g/dl)			
Mean ± SD	12.63±0.92	12.54±0.84	0.432
WBCs × 10^9/L			
Mean ± SD	6.11±0.92	6.22±0.99	0.489
Plts × 10^{11}/unit			
Mean ± SD	213.65±33.82	221.12±33.73	<0.001
BT (mins):			
Range	1-1.1	0.8-1.4	<0.001
Mean ± SD	1.51±0.13	1.21±0.12	
CT (mins):			
Range	4.2-7.6	3.8-7.4	<0.001
Mean ± SD	5.86±0.83	5.72±0.94	
PT (Sec): Range	10.1-12.9	9.92-12.8	<0.001
Mean ± SD	11.42±0.81	11.31±0.82	
AST U/L			
Mean ± SD	26.1±5.74	26.38±5.93	0.971
ALT U/L			
Mean ± SD	27.1±1.1	27.4±3.91	0.311
Serum bilirubin µmol/L			
Mean ± SD	0.91±0.2	0.95±0.21	0.132
Urea mmol/L			
Mean ± SD	18.32±3.91	18.11±2.97	0.401
Serum creatinine (mg/dL)			
Mean ± SD	0.97±0.21	0.96±0.23	0.731

No statistically significant variance was found between both groups, the vaginal group had a lower pregnancy rate. A statistically significant variation was found among the tested groups concerning stomach discomfort, headaches, nausea & vomiting (Table 5).

Table (5): Comparison of pregnancy and complications within the examined groups

	Oral (n=50)		Vagina (n=50)		p
	No.	%	No.	%	
Early pregnancy: Yes	4	8	2	4	0.273
Complications:					
Nausea	26	52	8	16	0.001
Vomiting	11	22	2	4	0.026
Fatigue	16	32	15	30	0.12
Breast tenderness	15	30	20	40	0.305
Abdominal pain	33	66	16	32	0.011
Headache	38	76	15	30	0.002

DISCUSSION

Levonorgestrel-only EC prevents fertilization by inhibiting ovulation. Misconceptions in regards to its mechanism of action contribute to its little utilization in specific situations [(11)]. LNG-containing oral contraceptives inhibit gonadotropins, thereby preventing ovulation. In particular, LNG binds to androgen & progesterone receptors, thereby suppressing the secretion of gonadotropin-releasing hormone from the hypothalamus. This process leads to the inhibition of the typical physiological surge of luteinizing hormone that occurs prior to ovulation [(12)]. It prevents the release of viable eggs from the ovaries & the rupture of follicles. LNG was demonstrated to be more efficient when administered prior to ovulation [(13)]. The elimination half-life of a 0.75 mg dosage of 1.5 mg of LNG is twenty to sixty hours following administration [(14)].

In the current study, regarding demographic information and general exams, there were no statistically significant variances among the analyzed groups. In accordance with our results, **Elnasr *et al.*** [(15)] aimed to evaluate the effectiveness, satisfaction, pregnancy rate, & adverse reactions of EC in women that chose either an oral LNG or copper intrauterine device (IUD). They found that no significant variance was found among the two groups with regard to age & parity. Also, **Ashraf *et al.*** [(10)] who aimed to assess the efficacy of oral versus vaginal LNG administration as an EC. They established that no statistically significant variance was demonstrated among the examined groups regarding general characteristics & general evaluations.

In our results, we observed no statistically significant variances among the examined groups regarding anthropometrics and CBC. In accordance with our results, **Rezk *et al.*** [(16)] documented that no statistically significant variance was found among the examined groups in terms of anthropometrics (weight, height, BMI, & WC). Also, **Hoseini *et al.*** [(17)] purposed to evaluate the acceptability of LNG & the Yuzpe regimen among Iranian women by examining the adverse reactions & the subsequent changes in the quantity & pattern of menstruation. They discovered that no statistically significant variance was obtained among the examined groups regarding weight, height, & BMI. In the research done by, **Singh *et al.*** [(18)], who studied the impacts of LNG-IUS on metabolic parameters, they reported that the anthropometric data from day one was statistically significant when compared to the follow-up data at six & nine months. At six months, there was a significant decline in waist circumference & BMI. However, these values returned to their previous levels by nine months. The other anthropometric parameters didn't demonstrate any significant change ($P < 0.05$).

In our study as regards the profiling of coagulation, there was no statistically significant variance between the tested groups. Regarding plasma level of levonorgestrel, a statistically significant variation was detected among the examined groups. In support with our findings, **Kives *et al.*** [(19)] aimed to evaluate the pharmacokinetics of the Yuzpe (500 Ag LNG, 100 Ag EE) & levonorgestrel (750 Ag LNG) regimens of EC when administered orally & vaginally. They examined the mean plasma LNG concentrations (± SD) over 24-hour period following the oral & vaginal administration of the LNG regimen in four individuals. They discovered that the intrasubject variability in LNG concentrations was reduced for both oral & vaginal administrations in comparison to the Yuzpe regimen. The average LNG values for C max, T max, & AUC0–24. In comparison with oral administration, vaginal administration of double the dosage caused a lower peak reaction of 9.8 ng/mL (95% CI = 5.5 to 14.1; p =.006, paired t test), a delayed time-to-peak reaction of 6.1 h (95% CI = 0.7 to 11.6; p =.037, paired t test), & a lower AUC of 46.9 ng/mL (95% CI = 17.2 to 111.0; p =.102, paired t test). The mean relative bioavailability (AUC0–24 vaginal/oral) of LNG for the LNG regimen was 62%, with a coefficient of variation of 41%. The relative bioavailability was 31% after adjusting for dosage.

In our findings, a statistically significant variance was found among the analyzed categories regarding platelets, BT, CT & PT. In accordance with our results, **Ashraf *et al.*** [(10)] discovered that a statistically significant variance was found among the examined groups as regard platelets, CT, BT, & PT. Also, **Mor *et al.*** [(20)], who aimed to evaluate the physiological impacts of EC that is administered orally & vaginally. They showed that the transient direct inhibition of gonadotropin, hepatic globulin, & androgen levels is caused by the great doses of LNG identified in emergency contraception regimens.

This impact is consistent with the administration of EC orally & vaginally. Consequently, the oral administration of EC regimens might be equally effective as the vaginal route.

In the present study, we found that although there was no statistically significant variance among both groups, the vaginal group had a lower pregnancy rate. A statistically significant variation was obtained among the tested groups concerning nausea, stomach discomfort, headaches, & vomiting. In accordance with our study, **Ashraf *et al.*** [(10)], they found that in the vaginal group, the pregnancy rate was lower, but no statistically significant variance was found among both groups. The examined groups showed a statistically significant variance in terms of nausea, abdominal pain, headaches, & vomiting. Contrary to our study, **Mor *et al.*** [(20)] who aimed to evaluate the physiological impacts of emergency contraception that is administered orally & vaginally, reported that each participant experienced sleepiness following the oral & vaginal administration of both regimens, which is reliable with the concurrent dimenhydrinate administration. Vomiting, headaches, vaginal irritation, or vaginal discharge weren't reported by any of the participants.

CONCLUSION

We revealed that, although no statistically significant variance was obtained among both groups, the vaginal group had a lower pregnancy rate. A higher statistically significant variation was obtained in the oral group compared to the vaginal group concerning nausea, stomach discomfort, headaches, & vomiting. Accordingly, we concluded that levonorgestrel vaginal administration is more suitable, effective, and safer as an emergency contraceptive compared to oral administration. So, we suggest utilizing LNG vaginal administration as an EC rather than oral administration.

DECLARATIONS

- **Consent for publication:** All author granted permission for the work to be submitted.
- **Funding:** No fund.
- **Availability of data and material:** Available.
- **Conflicts of interest:** No conflicts of interest.
- **Competing interests:** None.

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