Research Article

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Increased Risk Of Ovarian Cysts With Compound Norethindrone Enanthate Immediately After Abortion

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1. Abstracts

1.1. Objective:
To assess the effect of compound norethindrone enanthate injections immediately after abortion on ovarian cyst formation and post-abortion recovery in women who have had an abortion.

1.2. Methods:
Data were collected from January 2023-June 2023 from patients who were injected with compound norethindrone enanthate immediately after abortion and patients who were not injected in our department, and clinical data and short-term post-abortion recovery of patients who were injected with compound norethindrone enanthate immediately after abortion and patients who were not injected were retrospectively analyzed.

1.3. Results:
The number of days of post-abortion bleeding was mainly 1-3 days in patients who were injected with norethindrone enanthate immediately after abortion, while the number of days of post-abortion bleeding was mainly 4-7 days in patients who were not injected; the amount of post-abortion bleeding in the injected group was significantly less than that in the non-injected group, and the injected group did not see any patients suffering from post-abortion bleeding in large quantities (total amount of >10 ml). The injection of compound norethindrone enanthate immediately after abortion did not affect HCG conversion after abortion. Moreover, the use of exogenous hormone (norethindrone enanthate) allowed patients in the injection group to return to menstruation at a median of 17 days after the abortion. Although patients in the injection group were more likely to develop ovarian cysts than those in the non-injected group, there were no significant differences in the number of days of post-abortion bleeding, the amount of bleeding, the rate of urinary HCG conversion, the time to return to the first menstrual period, the duration of menstruation, the amount of menstruation, or the thickness of the uterine endometrium between the patients who developed an ovarian cysts and those who did not develop ovarian cysts in patients who accepted injection of norethindrone enanthate.

1.4. Conclusion:
The injection of compound norethindrone enanthate immediately after abortion can increase the occurrence of functional ovarian cysts in abortion patients, but it can significantly reduce the time and amount of vaginal bleeding after abortion, and due to the effect of hormone withdrawal, the time of the first menstrual period after abortion was significantly earlier than that of patients in the non-injected group.

2. Key words:
Post-abortion contraception; Compound norethindrone enanthate; ovarian cyst

3. Background

Negative pressure aspiration is a common surgical procedure used in abortion to remove the embryo and its appendages through medical intervention. Estrogen and progesterone decline rapidly in women after the removal of the embryo and its appendages from the uterine cavity. A study evaluated the trend of serum progestational hormone levels in medicated abortion patients after 36-48 hours of mifepristone and misoprostol administration and found that serum progestational hormone levels

decreased rapidly after misoprostol administration [1]. The rapid decline of estrogen and progesterone will inevitably lead to a significant increase in the secretion of gonadotropin-releasing hormone and gonadotropin through the negative feedback regulation of the hypothalamic-pituitary-ovarian axis. Is it possible then that the follicles in the ovaries of aborted patients are stimulated to grow by the flare-up actio¬¬¬n of gonadotropin-releasing hormone, and then, due to rapid pituitary suppression, the follicles do not develop and ovulate, resulting in the formation of functional cysts? This process is similar to the formation of functional ovarian cysts in infertile patients following the use of gonadotropin-releasing hormone agonists [2]. Starting an effective method of contraception at the time of abortion is critical because approximately half of women ovulate within 2-3 weeks after termination of pregnancy early in gestation [3-4]. Estrogen and progesterone injections such as compounded norethindrone enanthate can be given immediately after abortion [5-6]. Does the use of norethindrone enanthate immediately after abortion increase the role of the hypothalamic-pituitary-ovarian negative feedback axis and thus increase the probability of functional ovarian cysts in abortion patients? This paper investigates whether the use of norethindrone enanthate immediately after abortion affects the occurrence of functional ovarian cysts in patients and whether it affects the decline of HCG and vaginal bleeding in patients after abortion.

4. Methods

4.1. Patient data collection:

The 500 subjects came from patients who underwent abortion in the family planning department of Shanghai First Maternity and Infant Hospital from January 2023 to June 2023. Inclusion criteria: age 20-40 years old, regular pre-pregnancy menstruation, patients with uterine singleton pregnancies who underwent negative pressure suction within 6-10 weeks of gestation, all patients did not have symptoms of threatened abortion, such as vaginal bleeding, abdominal pain, etc. Fetal heartbeat was seen on ultrasound one week before the abortion in all patients, and there were no obvious abnormalities in the ovaries bilaterally. The ultrasound of all patients after the first menstrual period after the abortion showed that there was no residue in the uterine cavity. Patients with liver and kidney diseases and sexually transmitted diseases and acute vaginitis and pelvic inflammatory disease were excluded. Patients who used other contraceptive methods immediately after abortion such as intrauterine devices, subcutaneous contraceptive injections, and oral contraceptive pills were excluded. Patients were categorized into two groups according to whether they received compound norethindrone enanthate injection immediately after abortion: injection and non-injection groups, and 250 were included in each of the two groups. Patients' clinical information was collected: age, BMI, pregnancy and childbirth, ordinary menstrual cycle, monthly menstrual flow, number of miscarriages, gestational weeks, number of cesarean sections. Urine HCG was rechecked two weeks after abortion, and ultrasonography was performed three days after the first clean menstruation of the patients. The Medical Ethics Committee of the Shanghai First Maternity and Infant Hospital approved the study. All patients signed an informed consent form.

4.2. Negative pressure suction surgery:

All patients were given misoprostol 400mg vaginally (Senju pharmaceuticals, Zhengjiang, China) before the operation. The patients were placed in the cystotomy position, the vulva and vagina were sterilized, the uterus was examined for position, size, and inclination, and the cervix was sterilized, the depth of the uterus was probed, and the appropriate suction tubes and negative pressures were selected according to the week of gestation of the patients and the size of the cervical os, and the embryos were aspirated by suction tubes under ultrasound guidance and filtered with filters. Under the guidance of ultrasound, the embryo is sucked out with the suction tube, and the sucked out tissue is filtered with a filter to detect whether the embryo and chorionic tissue are intact or not.

4.3. Compound norethindrone enanthate injection:

One ml of compound norethindrone enanthate (Senju pharmaceuticals, Zhengjiang, China) contained 5 mg of estradiol valerate and 50 mg of norethindrone enanthate, and patients receiving compound norethindrone enanthate were injected with 2 ml of compound norethindrone enanthate by intramuscular injection immediately after the abortion.

4.4. Calculation of sample size for both groups of patients:

The primary outcome of this study was the incidence of ovarian cysts, so a non-inferiority design was used to calculate the sample size: the independent sample rate comparison between the two groups was 30% for the injected group and 10% for the non-injected group, and the difference between the two groups with clinical significance was 10%, alpha: 0.05, degree of certainty (1-β): 0.8, and the ratio of sample sizes for injected vs. non-injected group was 1:1. The sample size for each group was 247.

4.5. Statistical analysis and graphing:

SPSS 20 and Graphpad 8 were used for statistics and graphing in this study. Measured variables were described by mean ± standard deviation, count variables were described by the number of cases and percentage, comparisons of measured variables between two groups were analyzed using t-test if they met the conditions of normality and chi-square, otherwise Mann-Whitney U-test, and count variables were analyzed using chi-square test or Fisher's exact test, and $P<0.05$ was considered to have statistical differences.

5. Results

1. Basic clinical data of the group injected with compound norethindrone enanthate immediately after abortion and the group without injection

There was no significant difference in age, BMI, number of pregnancies and births, number of miscarriages, number of cesarean sections, monthly menstrual flow, monthly menstrual period between patients who were injected with compound norethindrone enanthate immediately after the abortion and those who were not injected with the abortion and there was no significant difference in the week of gestation at the time of the abortion between the two groups (Table 1).

Table 1: Baseline characteristics of the two groups

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Variables	Non-injection group	Injection group	p-value
	(n=250)	(n=250)	
Age(y)	30.09±5.25	29.86±5.12	0.63
BMI	20.88±0.93	20.74±0.89	0.09
Gravidity	2.30±1.21	2.39±1.24	0.44
Parity	0.69±0.69	0.67±0.65	0.79
Number of abortions	0.62±0.82	0.71±0.93	0.24
Number of cesarean sections	0.26±0.52	0.29±0.51	0.55
Monthly menstrual volume(ml)			
light(<5ml)			
medium(20-60ml)	10%(25/250)	8.4%(21/250)	0.83
heavy(>80ml)	75.6%(189/250)	76.8%(192/250)	
Menstrual days per month(d)	14.4%(36/250)	14.8%(37/250)	
1-3d			
4-7d	16.4%(41/250)	18%(45/250)	0.85
>7d	76.4%(191/250)	75.6%(189/250)	
	7.2%(18/250)	6.4%(16/250)	
Gestational age at time of abortion(d)	55.46±5.44	54.68±5.39	0.1

P-value<0.05 means statistic difference

2. Post-abortion situation in the group injected with compound norethindrone enanthate immediately after the abortion and in the group without injection The number of post-abortion bleeding days was significantly shorter in the patients who were injected with compound norethindrone enanthate immediately after abortion than in the non-injected group, and the majority of patients in the injected group had post-abortion bleeding for 1-3 days, while most of those in the non-injected group had post-abortion bleeding for 4-7 days, and the number of patients with post-abortion bleeding for 1-3 days in the injected group was significantly higher than that in the non-injected group (89.2% vs. 28.4%), and the proportion of those who had post-abortion bleeding for 4-7 days in the injected and non-injected groups were 10.8% and 67.2%, respectively. and we found that none of the abortion patients in the injection group had bleeding for more than 7 days after abortion. The amount of post-abortion bleeding in patients who were injected with norethindrone enanthate immediately after abortion was also significantly less than that in the non-injected group, with the proportion of small amount of bleeding (total amount less than 5 ml) in the injected group and small amount of bleeding in the non-injected group accounting for 35.6% and 3.6%, respectively, and the proportion of those who had large amount of bleeding (total amount more than 10 ml) in the non-injected group accounting for 67.6%, while the proportion of those who had large amount of bleeding in the injected group accounted for only 5.2%. Urine HCG testing 2 weeks after abortion we found that there was no significant difference in the number of patients in the two groups who turned negative for urine HCG, and the patients in the two groups who were positive for urine HCG on the 14th day after abortion were negative for urine HCG after one week of retesting. The time to resume menstruation after abortion was significantly shorter in patients who were injected with norethindrone enanthate immediately after abortion than in the non-injected group, and although there was no significant difference in the amount of the first menstrual period after abortion, the duration of menstruation, and the thickness of the endometrium on the third day after menstruation was cleaned up in the injected and non-injected groups. But we found that the rate of ovarian cyst formation in the injected group of patients undergoing abortion was significantly higher than that of the non-injected group (21.2% VS 3.2%) (Table 2). To determine the association of ovarian cysts with the use of norethindrone enanthate, we followed up the abortion patients who developed ovarian cysts with the use of norethindrone enanthate and reviewed the ultrasound 3 months after discontinuation of norethindrone enanthate, and all of the patients who developed ovarian cysts had no abnormal anechoicity of the ovaries 3 months after discontinuation of the use of norethindrone enanthate.

Table 2: Post-abortion situation in two groups

Variables	Non-injection group	Injection group	p-value
	(n=250)	(n=250)	
Days of bleeding after abortion(d)	28.4%%(71/250)	89.2%(223/250)	0
1-3d			
4-7d			
>7d	67.2%(168/250)	10.8%(27/250)	
	4.4%(11/250)	0%(0/250)	
The amount of blood lost after abortion(ml)			
light(<5ml)			
medium(5-10ml)	3.6%(9/250	35.6%(89/250	0
heavy(>10ml)	28.8%(72/250)	59.2%(148/250)	
	67.6%(169/250)	5.2%(13/250)	
Urine HCG two weeks after abortion			
positive			
negative	9.2%(23/250)	10.4%(26/250)	0.76
	90.8%(227/250)	89.6%(224/250)	
Time to menstruation after abortion(d)	43.6±5.56	16.33±2.03	<0.001
Amount of menstruation after abortion(ml)			
light(<5ml)			
medium(20-60ml)			

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heavy(>80ml)	27.6%(69/250)	31.2%(78/250)	0.43
	64.8%(162/250)	63.6%(159/250)	
	7.6%(19/250)	5.2%(13/250)	
Number of days of menstruation after abortion(d)			
1-3d			
4-7d			
>7d	20.4%(51/250)	18.8%(47/250)	0.8
	64.4%(161/250)	67.2%(168/250)	
	15.2%(38/250)	14%(35/250)	
Endometrial thickness(mm)	5.93±0.83	6.05±0.68	0.07
ovarian cysts occur	3.2%(8/250)	21.2%(53/250)	0

P-value<0.05 means statistic difference

3. Basic clinical data of patients who developed cysts and those who did not develop cysts in the injection group. We collected basic clinical data between patients with and without cysts who were injected with norethindrone enanthate immediately after abortion and found that there were no differences in age, BMI, number of deliveries, and number of cesarean sections between the 53 patients with cysts and the 197 patients without cysts; however, patients with cysts had more pregnancies and more miscarriages than patients without cysts, and patients with cysts had a significantly greater number of gestational days at the time of abortion than patients without cysts. Therefore, we believe that patients with more pregnancies and miscarriages and those with a large gestational week at the time of abortion have a higher probability of developing cysts when injected with norethindrone enanthate immediately after abortion (Table 3).

Table 3: Basic clinical data of patients with and without cysts in the injection group

Variables	With cyst (n=53)	Without cyst (n=197)	p-value
Age(y)	31.08±5.12	29.54±5.17	0.06
BMI	20.75±0.85	20.74±0.91	0.98
Gravidity	2.79±1.31	2.28±1.21	0.01
Parity	0.81±0.59	0.63±0.66	0.08
Number of abortions	0.98±1.10	0.63±0.88	0.04
Number of cesarean sections	0.32±0.51	0.28±0.51	0.6
Gestational age at time of abortion(d)	56.06±4.53	54.30±5.55	0.02

P-value<0.05 means statistic difference

4. Post-abortion situation of patients with and without cysts in the injection group. So how does the occurrence of cysts and the absence of cysts from compound norethindrone enanthate injections immediately after an abortion affect the post-abortion situation? By analyzing the post-abortion data of patients with and without cysts in the injection group, it was found that there was no significant difference in the number of days of post-abortion bleeding, the amount of post-abortion bleeding, the rate of post-abortion urinary HCG negativity, the time of the first menstrual period after abortion, the duration of menstruation, the amount of menstruation, and the thickness of the uterine endometrium on the third day after menstrual cleansing between the two groups with and without cysts (Table 4). Immediate post-abortion injection of compound norethindrone enanthate did not adversely affect post-abortion recovery even if ovarian cysts occurred.

Table 4: Post-abortion situation of patients with and without cysts in the injection group

Variables	With cyst (n=53)	Without cyst (n=197)	p-value
Days of bleeding after abortion(d)			
1-3d			
4-7d	88.7%(47/53)	89.4%(176/197)	0.89
>7d	11.3%(6/53)	10.6%(21/197)	
	0%(0/53)	0%(0/250)	
The amount of blood lost after abortion(ml)			
light(<5ml)			
medium(5-10ml)	35.8%(19/53)	35.5%(70/197)	0.98
heavy(>10ml)	58.5%(31/53)	59.4%(117/197)	
	5.7%%(3/53)	5.1%(10/197)	
Urine HCG two weeks after abortion			
positive			
negative	11.3%(6/53)	10.2%(20/197)	0.8
	88.7%(47/53)	89.8%(177/197)	
Time to menstruation after abortion(d)	16.62±1.64	16.25±2.12	0.17
Amount of menstruation after abortion(ml)			
light(<5ml)			
medium(20-60ml)			
heavy(>80ml)	30.2%(16/53)	31.5%(62/197)	0.97
	64.2%(34/53)	63.4%(125/197)	
	5.6%(3/53)	5.1%(10/197)	

Number of days of menstruation after abortion(d)			
1-3d			
4-7d			
>7d	18.9%(10/53)	18.8%(37/197)	0.88
	66.0%(35/53)	67.5%(133/197)	
	15.1%(8/53)	13.7%(27/197)	
Endometrial thickness(mm)	6.07±0.72	6.05±0.67	0.81

P-value<0.05 means statistic difference

6. Discussion

The formation of functional ovarian cysts is considered to be one of the adverse effects of gonadotropin-releasing hormone agonist therapy in infertile women [7]. The reasons for the formation of functional ovarian cysts in pituitary down regulation: direct action of gonadotropin-releasing hormone agonists on the ovaries or elevated action of gonadotropins on the ovaries [8]. The rapid increase in gonadotropin-releasing hormone and gonadotropins due to the rapid decrease in estrogen and progesterone after abortion due to the removal of the embryo and its appendages is similar to the endocrine alterations in women undergoing gonadotropin-releasing hormone agonist therapy. In this study, we found that the probability of functional ovarian cysts was 3.2% in patients who were not injected with norethindrone enanthate for contraception after abortion, and the probability of functional ovarian cysts was 21.2% with norethindrone enanthate immediately after abortion. The probability of functional cysts occurring in the ovaries of patients who used compound norethindrone enanthate injections immediately after abortion was higher than that of patients who did not use it, and the probable reason for this is that the removal of intrauterine gestational material in patients with abortion caused a sharp drop in estrogen and progesterone in the body, which caused an elevation in gonadotropins through the action of the negative feedback axis of the hypothalamus-pituitary-ovary resulting in the beginning of the development of follicles in the ovaries, and as pituitary down-regulation occurs, the gonadotropins are maintained at a the low level of gonadotropins, coupled with the negative feedback regulation of compound norethindrone enanthate (topical estrogen and progesterone) will make the level of endogenous gonadotropins even lower, resulting in a significant increase in the probability of non-growth and non-ovulation of follicles grown under the action of gonadotropin flare-up, leading to an increase in the occurrence of ovarian cysts.

There was no significant difference in the urinary HCG conversion rate two weeks after abortion between the injection group and the non-injection group, probably because there was no difference in the basic clinical data between the two groups of patients, and the time of abortion was 6-10 weeks of gestation, and the negative-pressure suction operation was completed by clinically experienced physicians in our department. This result of ours is the same as that of a previous study that showed that compounded norethindrone enanthate did not affect HCG clearance after abortion[9]. The duration of vaginal bleeding was shorter in the patients who were injected with norethindrone enanthate immediately after the abortion than in the control patients, probably because the endometrium was thicker in the patients than in the control group due to the exogenous use of estrogen and progesterone after the abortion, which in turn reduced the duration of vaginal bleeding. Although the duration of vaginal bleeding in the control group was more than that in the patients who were injected with norethindrone enanthate immediately after the abortion, the amount of vaginal bleeding after an abortion is less than the usual monthly menstrual flow in non-injected group.

The average time to the first menstrual period in patients who were injected with norethindrone enanthate immediately after abortion was half a month, which was significantly shorter than that in the control group. The possible reasons for this are that patients who were injected with norethindrone enanthate immediately after abortion further inhibited the hypothalamo-pituitary-ovarian axis because of the negative feedback effect of exogenous estrogen and progesterone, and that the endometrium was thicker than that of control patients under the effect of exogenous estrogen and progesterone after abortion, which led to the faster onset of menstruation in the patients who were injected with compound norethindrone enanthate immediately after abortion. However, the number of days of menstruation and the amount of bleeding were not significantly different from those of the control group, and there was no difference in endometrial thickness between the two groups as indicated by ultrasound on the third day after the first menstrual period. There was no significant difference in the duration of vaginal bleeding after abortion, the time of menstrual flow after abortion, the number of days of menstruation, the amount of menstruation, and the thickness of the endometrium in the first post-abortion ultrasound in the two groups that developed functional cysts of the ovary and did not develop ovarian cysts in the injection group. Therefore, we believe that although the use of compound norethindrone enanthate immediately after abortion may cause an increase in the occurrence of ovarian cysts, the ovarian cysts can be absorbed after discontinuing the use of the hormone, so we believe that these ovarian cysts are caused by the use of hormones, and they are not pathologic cysts. The use of norethindrone enanthate immediately after abortion reduces the amount of vaginal bleeding after abortion, and because the hormonal withdrawal of bleeding is very short after the abortion, it reduces the patient's anxiety about the fear of uterine adhesions, so the use of norethindrone enanthate immediately after abortion is an excellent contraceptive for abortion patients who need contraception. To the best of our knowledge, this is the first study on the effects and recovery of compounded norethindrone enanthate medication injected immediately after abortion. This study only retrospectively analyzed and compared the short-term postoperative situation of patients who received one injection of norethindrone enanthate immediately after abortion with those who did not receive an injection of norethindrone enanthate after abortion, and future studies could focus on analyzing the advantages and disadvantages of long-term use of norethindrone complex enanthate as a method of contraception for postabortion patients.

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7. Conclusion

The injection of compound norethindrone enanthate immediately after abortion increased the incidence of functional ovarian cysts in patients with abortion, but significantly reduced the amount of post-abortion vaginal bleeding and resulted in a significantly earlier onset of the first menstrual period after abortion than in patients in the non-injected group due to the effect of hormonal withdrawal.

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