

Aromatase inhibitor letrozole: a novel treatment for ectopic pregnancy

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Ectopic pregnancy:

- ▶ Estimated rate between
 - ▶ 1% to 2% of all pregnancies
 - ▶ 2% to 5% of pregnancies achieved after assisted reproduction
- ▶ mortality 6% of all maternal deaths

Cont.

- ▶ Treating include:
 - ▶ surgery
 - ▶ medical management with methotrexate
- ▶ Methotrexate:
 - ▶ more cost effective than surgical management while maintaining similar treatment success and future fertility
- ▶ adverse effects and contraindications:
 - ▶ increased failure rates, with high beta human chorionic gonadotropin (b-hCG) and progesterone levels

Cont.

- ▶ Methotrexate is associated with:
 - ▶ long interval until resolution of the ectopic pregnancy
 - ▶ the need to wait for several weeks before another attempt at pregnancy.
 - ▶ negative effects on ovarian reserve and future fertility potential are not unexpected

*hypothesized :
inhibiting the estrogen synthetase progesterone
would not exert its physiological role in
maintaining early pregnancy*

*studied:
the use of the aromatase letrozole for the
treatment of ectopic pregnancy in comparison
with methotrexate*

MATERIALS AND METHODS

- ▶ nonrandomized prospective cohort study
- ❖ women with undisturbed ectopic pregnancy who had no contraindications to methotrexate or letrozole treatment
- ▶ The study had three groups:
 - ▶ control group (surgical treatment in the form of laparoscopic salpingectomy)
 - ▶ two study groups
 - ▶ methotrexate (group 1)
 - ▶ letrozole (group2)
- ❖ Each patient chose her own treatment

Participants

- ▶ 42 consecutive women with undisturbed tubal ectopic pregnancy
 - ▶ Surgical treatment (control group)
 - ▶ medical treatment with methotrexate (group 1)
 - ▶ medical treatment with letrozole (group 2)
- ▶ Each group included 14 patients

▶ **The inclusion criteria included:**

- ▶ spontaneously achieved pregnancies in women between 18 and 40 years old
- ▶ ectopic pregnancy diagnosis confirmed by the admitting physician

▶ **The diagnosis of ectopic pregnancy:**

- ▶ the absence of an intrauterine gestational sac on vaginal ultrasound examination
- ▶ associated with b-hCG titers beyond the discrimination zone of at least 2,000 mIU/mL
- ▶ and/or gestational age of at least 6 weeks confirmed by positive pregnancy test at least 2 weeks before the diagnosis of ectopic pregnancy

▶ **The exclusion criteria:**

- ▶ b-hCG levels >3,000 mIU/mL
- ▶ hemoglobin level <10 g/dL
- ▶ platelets count <150,000/mL
- ▶ elevated liver enzymes, blood urea, or serum creatinine
- ▶ presence of a fetal heartbeat in a gestational sac detected outside the uterine cavity

Treatments

- ▶ **methotrexate treatment group:**

- ▶ women received one intramuscular injection of 50 mg per square meter of body surface area

- ▶ **letrozole treatment group:**

- ▶ letrozole was administered as two 2.5-mg tablets every day for 10 days

- ❖ The b-hCG levels were measured on the day of treatment and then 4, 7, 14 days after treatment.
- ❖ Complete blood count, liver enzymes, blood urea, and serum creatinine levels were obtained on the day of treatment and 7 days after treatment.
- ❖ Levels of AMH were measured on the first day of treatment and 3 months after treatment

Outcomes

- ▶ The primary outcome:
 - ▶ was a complete resolution of the ectopic tubal pregnancy as determined by serum b-hCG levels below laboratory immunoassay detection

- ▶ The secondary outcome:
 - ▶ included changes in the biochemical parameters of ovarian reserve, AMH level, hemoglobin levels, blood platelets count, and liver enzymes—aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

RESULTS

- ▶ There was no statistically significant difference among the three groups (the control and two study groups) with regards to age, body mass index, or parity

TABLE 1

Demographic data between the three ectopic pregnancy groups.

Characteristic	Laparoscopy (n = 14)	Methotrexate (n = 14)	Letrozole (n = 14)	P value
Age, y	25.7 ± 3.8 (18–30)	26.7 ± 5.2 (18–35)	26.4 ± 4.2 (19–32)	.832
BMI, kg/m ²	21.1 ± 2.3 (18–25)	21.5 ± 2.1 (19–25)	20.9 ± 2.1 (18–25)	.782
Parity	1 (0–2.3)	1.5 (0–2)	1 (0–2)	.925

Note: Values are mean ± standard deviation (range) unless stated otherwise. BMI – body mass index.

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- ▶ Complete resolution of the ectopic pregnancy occurred in an equal number of patients, 12 out of 14 (86%), in each of the two medication treatment groups
 - ▶ The two patients who failed methotrexate treatment had to undergo surgery after becoming hemostatically unstable
 - ▶ In the letrozole group, one patient became hemodynamically unstable, in the second patient, the decision to perform surgery was made when the b-hCG levels had failed to decline 4 days after letrozole treatment

- ▶ There was no statistically significant difference in b-hCG levels on the day of treatment
- ▶ The decline in b-hCG levels was faster in the letrozole group when compared with the methotrexate group, but the difference was not statistically significant

TABLE 2

Level of β -hCG at different times between the three ectopic pregnancy groups.

β -hCG level (mIU/mL)	Treatment group			P value
	Laparoscopy (n = 14)	Methotrexate (n = 14)	Letrozole (n = 14)	
Treatment day	1,255 (670–1,665)	1,415 (710–1,722.5)	1,065 (491.5–1,438)	.443
Day 4	516 (277.3–967)	710.5 (424–937)	512.5 (275.3–900)	.748
Day 7	188 (111.3–314)	344 (172.5–484.8)	191.5 (97.3–414.3)	.232
Day 14	18 (7.3–36.5)	35.5 (19.5–46)	22.5 (16–30.5)	.096

Note: Values are median (interquartile range) unless stated otherwise. β -hCG = β -human chorionic gonadotropin.

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Cont.

- ▶ It is important to mention:
 - ▶ we wish we could present data on the trajectory of the b-hCG levels to illustrate patterns of response to the studied treatments
- ▶ the b-hCG assays were performed at different laboratories, which would limit the conclusions due to known interlaboratory variability
- ▶ the small sample size of patients included in the study would add to the limitation

Cont.

- ▶ no statistically significant difference in:
 - ▶ Hemoglobin levels among the three patient groups when they started treatment
- ❖ the hemoglobin levels statistically significantly dropped in the methotrexate treatment group after 7 days when compared with the surgery and letrozole treatment groups

Treatment with methotrexate = higher levels of liver enzymes
 lower blood platelets count

❖ statistically significant

TABLE 3

Platelets and liver enzymes at different times between the three ectopic pregnancy groups.

Laboratory test	Laparoscopy (n = 14)	Methotrexate (n = 14)	Letrozole (n = 14)	P value
Platelets count ($\times 10^3$)				
Treatment day	233.3 \pm 58.4 (151–326)	251.5 \pm 70.7 (152–387)	214.9 \pm 71.4 (147–382)	.363
Day 7	213.7 \pm 74.6 (40–310)	162 \pm 48.4 (101–277)	213.9 \pm 66.2 (152–367)	.058
P value	.022 ^a	<.001 ^a	.747	
AST level (U/L)				
Treatment day	19.3 \pm 2.8 (15–24)	19.8 \pm 2.5 (17–24)	18.1 \pm 2.6 (15–24)	.223
Day 7	20.3 \pm 2.9 (16–25)	44.1 \pm 5.8 (35–56)	19.9 \pm 3.1 (16–28)	<.001 ^a
P value	<0	<.001 ^a	.056	
ALT level (U/L)				
Treatment day	27.4 \pm 4.7 (21–36)	29.5 \pm 5.2 (21–36)	20.7 \pm 4.7 (12–28)	<.001 ^a
Day 7	29 \pm 4.6 (22–38)	52 \pm 6.1 (39–63)	22.7 \pm 3.7 (17–28)	<.001 ^a
P value	<.05	<.001 ^a	<.05	

Note: Values are mean \pm standard deviation (range) unless stated otherwise. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

^a Statistically significant ($P < .05$).

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Three months after treatment

- ▶ the AMH levels were lower in the :
 - ▶ methotrexate group when compared with the letrozole and surgery groups
- ❖ not statistically significant

TABLE 4

AMH level at different times between the three ectopic pregnancy groups.

AMH level (ng/mL)	Laparoscopy (n = 14)	Methotrexate (n = 14)	Letrozole (n = 14)	P value
Treatment day	1.7 ± 0.5 (1–2.6)	1.8 ± 0.6 (1–2.8)	2 ± 0.7 (0.9–3.5)	.548
Day 7	1.7 ± 0.5 (1–2.5)	1.7 ± 0.6 (1–2.8)	1.9 ± 0.7 (1–3.5)	.712
P value	.991	.035 ^a	.061	

Note: Values are mean ± standard deviation (range) unless stated otherwise. AMH = antimüllerian hormone.

^a Statistically significant ($P < .05$).

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DISCUSSION

is the first report in the literature on the success of letrozole for the medical treatment of ectopic pregnancy

estrogen
plays a
substantial role in
establishing and
maintaining early
pregnancy
remains
controversial

- ▶ only progesterone is needed to rescue a pregnancy after corpus luteum removal
- ▶ successful pregnancies in conditions with very low estrogen levels, such as aromatase deficiency
- ▶ the failure to consistently demonstrate estrogen receptors in the trophoblast and early pregnancy placenta suggests the lack of a crucial role for estrogen in early pregnancy

Estrogen effect:

- ▶ estrogen is produced by several tissues other than the corpus luteum
- ▶ progesterone can be converted to estrogen but not the reverse
- ▶ substantial estrogen-receptor saturation occurs with very low estrogen levels

Estrogen effect:

- ▶ substantial estrogen-receptor saturation occurs with very low estrogen levels
- ▶ In cases with aromatase deficiency:
 - ▶ low levels of locally synthesized estrogen are still produced so
 - ▶ low estrogen levels may be enough to mediate estrogen actions in maintaining early pregnancy
 - ▶ the placenta should not be affected
- ▶ different type of estrogen receptor
- ▶ expression of the aromatase enzyme in the corpus luteum, embryo, and trophoblast has been established

limitations

- ▶ small sample size and nonrandomized design of the study
- ▶ almost half of patients with ectopic pregnancy with b-hCG levels <2,000 mIU/mL had spontaneous resolution with expectant management

secondary outcome

- ▶ longer follow-up period may be needed to show whether a negative effect exists
- ▶ Decline in the AMH levels was greater in the methotrexate group