Research Article

Medical Treatment of Undisturbed Ectopic Pregnancy in Minia Maternity University Hospital a Randomized Controlled Study

Kamal El-Deen Abd El-Hameed, Ahmed R. Abd El-Reheim and Ahmed H. Ahmed
Department of Obstetrics & Gynecology, El-Minia Faculty of Medicine

Abstract

Background: Ectopic pregnancy, a high-risk condition in which a fertilized ovum implants outside the uterine cavity, affects 1% to 2% of all pregnancies and poses a significant threat to women of reproductive age. It is the leading cause of maternal death during the first trimester of pregnancy and is responsible for 9% of pregnancy-related deaths in the United States (Creanga et al., 2011). Clinicians should consider the diagnosis of ectopic pregnancy in any woman in the first trimester of pregnancy that has abdominal or pelvic pain, vaginal bleeding or both (ACOG, 2009). After a definitive diagnosis has been made, treatment options include medical, surgical, or expectant management (Hajenius et al., 2007). **Aim of the work:** The aim of our study was to evaluate the efficacy and safety of medical treatment of undisturbed ectopic pregnancy either by Methotrexate, or by Aromatase inhibitors "Letrozole" in comparison to laparoscopic treatment for the same purpose in well selected cases of undisturbed ectopic pregnancy at Minia Maternity University Hospital during period from January 2018 to December 2018. **Patients and Methods:** 400 candidates for the study were diagnosed with ectopic pregnancy either through the outpatient clinics or admitted through the emergency department. These candidates were subjected to full work up. Following this workup, only 200 candidates were diagnosed with undisturbed ectopic pregnancy. From these 200 cases of undisturbed ectopic pregnancy 34 cases of them were eligible to be in our study according our strict inclusion criteria: These 34 cases which fulfilled our inclusion criteria were randomized by closed sealed envelopes into 3 groups: ***Group I (Laparoscopy group)*** It included 10 patients, who had laparoscopic salpingostomy as a first line of treatment for undisturbed ectopic pregnancy. ***Group II (Methotrexate group):*** It included 10 patients, who had given a single dose of Methotrexate (1 mg/kg IM in a single injection) as a first line of treatment for undisturbed ectopic. ***Group III (Letrozole group):*** It included 14 patients, who had given Letrozole 2.5mg, in combination with Norethisterone 5 mg as an adjuvant therapy for 10 days both twice daily as a first line of treatment for undisturbed ectopic. **Results:** The Success rate of the first line of treatment in each group and it was in laparoscopy group (90%), methotrexate group was (80%) and in Letrozole group was (78.6%), therefore the Letrozole can be used in the treatment of undisturbed ectopic in well selected cases. **Conclusion:** Laparoscopy remains the gold standard first line modality for diagnosis and treatment of undisturbed ectopic pregnancy. It is also the modality of choice in case of failure of medical treatment. Medical treatment with methotrexate for undisturbed ectopic pregnancy has its definite role as an alternative to laparoscopy. Letrozole has the advantage of easy administration and high safety profile when compared to methotrexate and laparoscopy.

Introduction

Ectopic pregnancy, a high-risk condition in which a fertilized ovum implants outside the uterine cavity, affects 1% to 2% of all pregnancies and poses a significant threat to women of reproductive age. It is the leading cause of maternal death during the first trimester of pregnancy and is responsible for 9% of pregnancy-related deaths in the United States (Creanga et al., 2011).

The most logical explanation for the increasing frequency of ectopic pregnancy is previous pelvic infection; however, most patients presenting with an ectopic pregnancy have no identifiable risk factor (Bouyer et al., 2003)

Ectopic pregnancy is a considerable cause of maternal morbidity, causing acute symptoms such as pelvic pain and vaginal bleeding and long-term problems such as infertility (Varma and Gupta, 2009).

Clinicians should consider the diagnosis of ectopic pregnancy in any woman in the first trimester of pregnancy that has abdominal or pelvic pain, vaginal bleeding or both (ACOG, 2009).

In the last 20 years, there have been major changes in the management of ectopic pregnancy as a result of earlier diagnosis, the recognition and subsequent intrauterine pregnancy is possible after conservative surgery, and the advent of medical treatment and good laparoscopic surgical equipment. In some centers , more than 90% of ectopic pregnancies are now dealt with laparoscopically, and several authors have shown intra-uterine pregnancy rates of over 50% when conservative surgery as opposed to salpingectomy has been carried out. (Ego et al, 2001).

Recent advances in diagnosis and treatment have led to a 50% reduction in mortality rates since the 1980s. Earlier detection has played a vital role in this reduction, and limited access to care is strongly associated with worse outcomes (Creanga et al., 2007).

After a definitive diagnosis has been made, treatment options include medical, surgical, or expectant management (Hajenius et al., 2007).

Aim of the work

The aim of our study was to evaluate the efficacy and safety of medical treatment of undisturbed ectopic pregnancy either by Methotrexate, or by Aromatase inhibitors "Letrozole" in comparison to laparoscopic treatment for the same purpose in well selected cases of undisturbed ectopic pregnancy at Minia Maternity University Hospital during period from January 2018 to December 2018.

Patients & Methods

400 candidates for the study were diagnosed with ectopic pregnancy either through the outpatient clinics or admitted through the emergency department.

These candidates were subjected to <u>full work up</u>

1- Full history taking including complete medical and surgical history.
2- Thorough general examination of pulse, temperature and blood pressure for assessment of hemodynamic instability, BMI. was calculated,
3- Abdominal and vaginal examinations were also performed.
4- Routine investigations including ABO Rh, CBC, renal function tests.
5- Serum B-HCG level by ELISA.
6- Ultrasound Scan:
   - Abdominal ultrasound: to exclude presence of internal hemorrhage.
   - Vaginal ultrasound: to detect gestational sac either intrauterine or extra uterine.

Following this workup, only 200 candidates were diagnosed with undisturbed ectopic pregnancy as:

1- ***Hemodynamics***:
   Generally stable without/with mild symptoms, with good vital data and no signs of active bleeding.
2- ***US findings***:
   a- Adnexal mass with/without fetal pole ± cardiac pulsation
   b- No or mild pelvic collection.
3- ***B-HCG titre:***
   a- A serum B- HCG level > 2000 IU/L with absence of an intra-uterine gestational sac on trans-vaginal ultrasonography.
   b- A serum B-HCG level of < 2000 IU/L. with an adnexal mass as detected by trans-vaginal ultrasonography.
   c- Abnormal rising (< 66% rise) in serum B-HCG level after 48 hours.

From these 200 cases of undisturbed ectopic pregnancy 34 cases of them were eligible to be in our study according to <u>strict inclusion criteria</u>:-

1- ***Hemodynamics***: Generally stable as regard BP & Pulse with no symptoms or signs of active bleeding.
2- ***US findings***:
   a- Adnexal mass size didn't exceed 4 cm
   b- Absence of fetal pole
   c- Absence of hemo-peritoneum.
3- ***B-HCG titre*** below 3000 IU/mL.

The 34 cases which fulfilled our inclusion criteria were randomized by closed sealed envelopes into 3 groups as follow:

<u>Group I (Laparoscopy group):</u>

It included 10 patients, who had laparoscopic salpingostomy as a first line of treatment for undisturbed ectopic pregnancy.

Laparoscopic salpingostomy (a linear incision was made medial to the swollen part of the tube

with a mono-polar micro diathermy needle. The product of conception was removed by manipulation, hydro dissection, and suction. Once hemostasis was obtained, the tubal incision was left open for spontaneous healing).

Group II (Methotrexate group):

It included 10 patients, who had given a single dose of Methotrexate (1 mg/kg IM in a single injection) as a first line of treatment for undisturbed ectopic.

Group III (Letrozole group):

It included 14 patients, who had given Letrozole 2.5mg, in combination with Norethisterone 5 mg as an adjuvant therapy for 10 days both twice daily as a first line of treatment for undisturbed ectopic.

Inclusion Criteria:

1. ***Hemodynamics***: Stable as regard BP & Pulse with no symptoms or signs of active bleeding.
2. ***US findings***:
   a- Adnexal mass size didn't exceed 4 cm
   b- Absence of fetal pole
   c- Absence hemoperitoneum.
3. ***B-HCG titre*** below 3000 IU/mL (only for medically treated groups either by methotrexate or by letrozole).

Exclusion criteria:

1. ***Hemodynamics***: Unstable as regard BP & Pulse with symptoms or signs of active bleeding.
2. ***US findings***:
   a- Adnexal mass size exceeded 4 cm
   b- Presence of fetal pole or fetal cardiac activity.
   c- Presence of hemo-peritoneum.
3. ***B-HCG titre*** above 3000 mIU/mL (only for medically treated groups either by methotrexate or by letrozole).
4. Coexistent viable intrauterine pregnancy (heterotopic pregnancy).
5. Non-compliant patient or patient living far away from the hospital.

As regards MTX group:

- Clinically significant renal, hepatic or hematological impairment.
- Known hypersensitivity to methotrexate.
- Breast feeding.
- Immunodeficiency/concurrent use of corticosteroids.

Follow up:

Patients in our study were monitored all through the treatment period as follows

1. Clinical picture: Thorough general examination of pulse, temperature and blood pressure for assessment of hemodynamic instability.
2. Routine investigations including HB & HCT levels.
3. Ultrasound Scan: to detect any change in adnexal mass size or appearance of hemoperitoneum.
4. B-HCG titre on 4^{th}, 7^{th} &14^{th} day and obtain weekly β-HCG levels until they have reached the negative level for the lab.

In addition to specific considerations in each group as follows:

Group I: Laparoscopy group:

During the postoperative period patients were monitored by serial clinical exams, HB levels, and ultrasound scans.

After they were discharged follow up of plasma-B-HCG measurements until the plasma B-HCG concentration was below 5 IU/L.

Group II: Methotrexate group:

After initiation of the treatment patients were monitored as follow:

Day 1

Obtain levels of the following:

- Complete blood count (CBC)
- Blood type, Rh status, and antibody screening are also performed, and all Rh-negative patients were given Rh immunoglobulin.
- B-HCG (the baseline level against which subsequent levels are measured)
- Renal Function test.
- Liver function test.

Methotrexate (1 mg/kg) is administered by IM injection. Advise patients not to take vitamins with folic acid until complete resolution of the ectopic pregnancy. They should also abstain from sexual intercourse for the same period.

Day 4

The patient returns for measurement of her β-HCG level.

Day 7

Draw β-HCG and AST levels and perform a complete blood count (CBC).

Group III: Letrozole group:

After initiation of the treatment patients were monitored as follow:

Day 1

Obtain levels of the following:

- Complete blood count (CBC)
- Blood type, Rh status, and antibody screening are also performed, and all Rh-negative patients are given Rh immune-globulin.
- B-HCG (the baseline level against which subsequent levels are measured)
- Renal function test (RFT)

They should also abstain from sexual intercourse for the same period.

Day 4

The patient returns for measurement of her β-HCG level.

Day 7

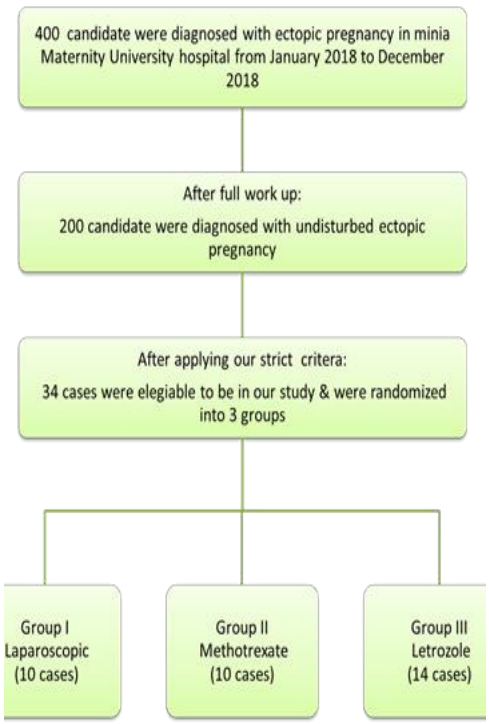
Draw β-HCG and perform a complete blood count (CBC).

Successful treatment:

- Clinically no signs of disturbance of the ectopic pregnancy as hemodynamic inst-ability or decrease in HB & HCT level.
- By Ultrasound there is no increase of adne-xal mass or appearance of hemo-peritoneum.
- If the β-HCG level has dropped 15% or more on day 7.

Unsuccessful treatment:

- Clinically there are signs of disturbance of the ectopic pregnancy as hemodynamic instability.
- By Ultrasound there is increase of adnexal mass or appearance of hemperitoneum.
- If the β-HCG level does not decrease by at least 15% on day 7 after treatment, or if it plateaus or increases after the first week following the initiation of our protocol, treatment failure must be assumed, In this case, second line of treatment was conduc-ted.



Patients flow chart in our study

Results

This study included thirty Four (34) patients of undisturbed ectopic pregnancy who were randomized into three groups, ten (10) cases underwent laparoscopic salpingostomy, ten (10) cases received single dose of Methotrexate (1 mg/kg IM) and the remaining cases (14) received Letrozole 2.5mg, in combination with Norethisterone 5 mg as an adjuvant therapy for 10 days both twice daily.

Table (1) Distribution of the studied patients regarding their descriptive criteria:

	Group I Laparoscopic	Group II Methotrexate	Group III Letrozole	P valu
Age				*0.660*
Range	(17-30)	(17-38)	(19-32)	
Mean ± SD	25.8±4.2	27.8±6.7	26.4±4.2	
BMI				*0.448*
Range	(18-23)	(18-26)	(18.5-24)	
Mean ± SD	21±1.7	21.9±2.6	20.9±1.6	
Obstetric history a-Parity				
NP	5 (50%)	4 (40 %)	4 (28.5%)	
Low Parity (P1orP2)	3 (30%)	4 (40%)	9 (64.3)	
High Parity (≥P3)	2 (20%)	2 (20%)	1 (7.2%)	
b-Previous deliveri				
NP	5 (50%)	4(40%)	4(28.6%)	
SVD	4 (40%)	1(10%)	2(14.3%)	
C/S	1(10%)	5(50%)	8(57.1%)	
c-Previous Abortio				
0	5 (50%)	6 (60%)	7 (50%)	
1	2 (20%)	2 (20%)	3 (21.4%)	
2	1 (10%)	1 (10%)	3 (21.4%)	
3	2 (20%)	1 (10%)	1 (7.2%)	

SVD → Spontaneous Vaginal Delivery C/S → Caesarean Section

Table (2) Distribution of the studied patients regarding their ultrasound findings:

	Group I Laparoscopic	Group II Methotrexate	Group III Letrozole	P value		
Adnexal mass size (cm)				0.096		
Range	2-5 cm	2-4 cm	2.5-4.5 cm	I vs II	I vs III	II vs III
Mean ± SD	3.8 ± 0.9	3.1 ± 0.8	3.3 ± 0.6	0.089	0.252	0.740
Pelvic Collection	Mild to Moderate pelvic collection	No pelvic Collection	No pelvic collection	Non-Significant	Non-Significant	Non-Significant

This table shows that:

The mean adnexal mass size in Laparoscopy group was (3.8), in Methotrexate group was (3.1) & in Letrozole group (3.3) with P value of (0.096).

Table (3): The Pre therapeutic (Basal) B-HCG titre in the different groups:

Pre therapeutic B-HCG titre (mIU/ML)	Group I Laparoscopic	Group II Methotrexate	Group III Letrozole	P value		
Median	1515	1328	865	0.391		
IQR	(558.3-5565.8)	(734.5-1647.3)	(485.5-1416.3)	I vs. II	I vs. III	II vs. III
				0.520	0.242	0.320
Significance				Non-Significant	Non-Significant	Non-Significant

This table shows that:

The median pre therapeutic B-HCG titre (MIU/ML) of laparoscopic group (1515), of methotrexate group was (1328) and of letrozole group (865) with P value of (0.391), which is not statistically significant.

Table (4): Comparison of the serum B-HCG titre in group II (Methotrexate) at different times:

Group II Methotrexate	Day 1	Day 4	Day 7	Day 14
Median IQR	1328 (734.5-1647.3)	640 (335-869.5)	314.5 (181.3-398.5)	39.5 (30.8-53)
P value				
Day 1		0.093*	0.152	0.012*
Day 4			0.101	0.012*
Day 7				0.012*

This table shows that

There was a statistically significant difference regarding decrease in B-HCG titre in group II at days 4, 7, &14 following successful treatment with Methotrexate.

Table (5): Percentage of decrease in serum B-HCG titre in group II:

% of decrease in titre	Day 4	Day7	Day 14
Range	43.6-58.2%	66-77.9%	90-97.6%
Mean ± SD	47.9±4.2%	71±4.2%	95.5±2.8%

This table shows that:

The Percentage of fall in serum B-HCG titre after successful treatment with methotrexate on day four was (47.9%), on day seven was (71%) and on day fourteen was (95.5%).

Table (6): Comparison of the serum B-HCG titre in group III (Letrozole) at different times:

Group III Letrozole	Day 1	Day 4	Day 7	Day 14
Median IQR	865 (485.5-1416.3)	405 (256.5-1020)	180 (95.5-440)	29 (19-50)
P value				
Day 1		0.093	0.152	0.003*
Day 4			0.101	0.003*
Day 7				0.003*

This table shows that

There was a statistically significant difference regarding decrease in B-HCG titre in group III at days 4, 7, &14 following successful treatment with Letrozole**.**

Table (7): Percentage of decrease in serum B-HCG titre in group III:

% of decrease in titre	Day 4	Day7	Day 14
Range	33.6-56.5%	62.7-91.7%	90-100%
Mean ± SD	46±8.7%	80.3±5.6%	96.3±2.9%

This table shows that:
The Percentage of fall in serum B-HCG titre after successful treatment with letrozole on day four was (46%), on day seven was (80.3%) and on day fourteen was (96.3%).

Table (8): Comparison of percentage of decrease in serum B-HCG titre between groups II& III at different times:

% decrease in the titer	Day 4	Day 7	Day 14	P value		
				4 vs 7	4 vs 14	7 vs 14
Group II (M) **Range** **Mean ± SD**	(43.6-58.2%) 47.9±4.8	(66-77.9) 71 ±4.2	(90-97.6%) 95.5±2.8	<0.001*	<0.001*	<0.001*
Group III (L) **Range** **Mean ± SD**	(33.6-56.5%) 46±8.7	(62.7-91.7%) 80.3±5.6	(90-100%) 96.3±2.9	<0.001*	<0.001*	<0.001*

This table shows that:
There was no statistically significant difference regarding percentage of decrease in serum the B-HCG titre between the groups II & III at days 4, 7&14.

Table (9): Distribution of the studied patients regarding the results after treatment:

	Group I Laparoscopic	Group II Methotrexate	Group III Letrozole	P value		
Outcome				0.749		
Success	9(90%)	8(80%)	11(78.6%)	**I vs II**	**I vs III**	**II vs III**
Failed	1(10%)	2(20%)	3(21.4%)	1	0.615	1

This table shows that:
Success rate of the first line of treatment in each group and it was in laparoscopy group (90%), methotrexate group was (80%) and in Letrozole group was (78.6%).

Table (10): B-HCG titre on day 4 & 7 as a prediction of failure treatment after using Letrozole:

	On day 4	On day 7
Optimal cutoff of B-HCG	>1190	>600
AUC	1	1
95% CI	0.753-1	0.753-1
P value	**<0.001***	**<0.001***
Sensitivity	100	100
Specificity	100	100
PPV	100	100
NPV	100	100
Accuracy	100	100

This table shows that:
Day 4 & 7 B-HCG titre is a good indicator for prediction of failure of treatment after using letrozole.. As If B-HCG titre on day 4 and day 7 is more than 1190 and 600 respectively, then the failure rate of the treatment will be 100%

Discussion

The incidence of ectopic pregnancy increased almost epidemically to a level of 2% in developed countries during the past decades. Now Approximately 1% of all pregnancies are extra-uterine (Farquhar, 2005; Bakken, 2008).
Using data from 1997 to 2002, the World Health Organization (WHO) estimated that ectopic pregnancy was the cause of 4.9% of pregnancy-related deaths in the industrialized world. (Khan et al., 2006).

Thanks to the new modalities off diagnosis available nowadays and the growing knowledge of ectopic pregnancy made medical treatment of ectopic in an outpatient setting is now a realistic option. (Wedderburn et al., 2009).

Conservative surgical treatment of ectopic pregnancy is well established, and laparoscopic surgery seems to be feasible even in poor surgical candidates including morbidly obese patients (Mitwally et al., 2004).

Laparoscopic salpingostomy is the preferred operative method in un-ruptured cases. Non-surgical therapy for ectopic pregnancy, however, may prevent undesired postoperative adhesions that often result from surgical manipulation of the fallopian tubes (Wolf et al, 1991)

Methotrexate has been used in treatment of undisturbed ectopic however being a chemo-therapeutic drug its use is associated with deleterious effects like liver and renal function affection moreover its hazardous effect on the ovarian reserve (Uyar, Ibrahim et al., 2013)

This modality was introduced in 1991 by Stovall et al., (Stovall et al., 1991). In 1997, the first randomized clinical trial on MTX versus laparoscopic salpingostomy was published, 1997 (Hajenius et al., 1997).

Letrozole is a third generation aromatase inhibitor drug which has been advocated for medical treatment of undisturbed ectopic (Mitwally & Casper, 2005)

Mitwally and Casper hypothesized that the use of aromatase inhibitors prevents the establishment of ectopic pregnancy and destruction of the early trophoblastic tissues as a result of two mechanisms:
First: by a direct mechanism involving local estrogen withdrawal by inhibition of blastocyst and trophoblastic aromatase and local estrogen production.
Second: by a direct or indirect intra-ovarian effect resulting from steroid precursor substrate failure (i.e. androgens and progestin) to be converted into estrogen by reduced aromatase levels (Mitwally & Casper 2005)

Medical treatment has many advantages over laparoscopic treatment, as it requires less hospital stay and is more economic (Bachman et al., 2012).

These 34 cases which fulfilled our inclusion criteria were randomized by closed sealed envelopes into 3 groups

Group I (Laparoscopy group):
It included 10 patients, who had laparoscopic salpingostomy as a first line of treatment for undisturbed ectopic pregnancy.
9 (90%) cases underwent laparoscopic salpingostomy, 1 case had another set of laparoscopy was indicated due to persistence of trophoplastic tissue evidenced by Transvaginal ultrasound & inappropriate decrease of decreasing of B-HCG titre after treatment.

Group II (Methotrexate group):
It included 10 patients, who had given a single dose of Methotrexate (1 mg/kg IM in a single injection) as a first line of treatment for undisturbed ectopic.
8(80%) cases were given single dose of Methotrexate with a success, 1 case underwent abdominal exploration due to homodynamic instability and a case underwent laparoscopic salpingostomy due to increasing β –HCG level.

Group III (Letrozole group):
It included 14 patients, who had given Letrozole 2.5mg, in combination with Norethisterone 5 mg as an adjuvant therapy for 10 days both twice daily as a first line of treatment for undisturbed ectopic.

11 (78.6%) cases were given Letrozole for 10 days with a success, 1 case underwent abdominal exploration due to homodynamic instability, 1 case underwent laparoscopic salping-

ectomy due to increasing β –HCG level with appearance of moderate amount of abdominal collection and 1 case was given Methotrexate due to increasing β-HCG titre.

There were no significant differences between the three study groups in the baseline characteristics (age, gravidity, parity, abortions and BMI).

The success rate following laparoscopic surgery was 90% (1/10 patients), neither significantly different from that in the Methotrexate group 80% (8/10 patients) nor significantly different from that in the Letrozole group 78.6% (11/14 patients).

Our results of conservative management of ectopic pregnancy either by laparoscopic salpingostomy or using single dose methotrexate agreed with:

Kayatas et al., 2014 who reported that of 403 patients were treated conservatively. These conservative managements consist of 334 (82.8%) salpingostomy performed by laparoscopy and 69 by laparotomy. Because of persistent ectopic pregnancy, 16 patients underwent medical treatment. In total, 387 (96%) patients were treated successfully with conservative surgical management compared to 90% in our study.

Berretta et al., 2015 who reported their findings on diagnosis and treatment of 402 retrospectively collected tubal ectopic pregnancy. Systemic Methotrexate (MTX) was effective in 56 out of 65 patients (failure rate 13.8%) compared to 20% in our study.
They concluded that single-dose MTX is safe and effective in eligible patients; surgery represents the treatment of most of the ectopic pregnancies, mainly through laparoscopic approach.

Moeller et al., 2009 found that the success rate following laparoscopic surgery was 87% (46/53 patients) "90% in our study" and not significantly different from that in the MTX group 74% (39/53 patients) "80% in our study".

Our results of successful conservative surgical management of ectopic pregnancy using laparoscopic salpingostomy was 90% and this is in agreement with: Song et al., 2014 who reported that of 20 cases managed by laparoscopy, 19 cases (95%) were successfully performed without any additional intervention and 1 case was switched to salpingectomy during the initial surgery. During the mean β-human chorionic gonadotropin resolution time of 17.9±6.4 days, postoperative complications or persistent trophoblasts did not occur.

Our results of conservative non-surgical management of ectopic pregnancy using single dose methotrexate agreed with:

Mirbolouk et al., 2015 who reported that of 370 patients, 285(77.1%) were successfully treated with MTX, compared to 80% in our study, 85 patients (22.9%) required surgery after a mean of 5.4 (range 2-15) days. Day-1 beta- human chorionic gonadotropin (β-HCG) and fall in β-HCG between day 1 and day 4 were the best predictors for single dose MTX treatment success. The cutoff value of initial β-HCG with the success treatment results was found to be 1375 IU/mL

In our study we found the median B-HCG titre on day 1 in Methotrexate group was 1328 IU/mL which is very similar to that found by Mirbolouk et al., Van Mello et al., 2013 who reported that they included 41 women of whom 31 were success-fully treated with single-dose MTX management, compared to 80% in our study. In nine women (22%), additional MTX injections were needed. One woman (2%) underwent surgery.

Our results of conservative non-surgical management of ectopic pregnancy by using Letrozole we found that:

To the best of our knowledge, this is first study in the literature performed on the use of letrozole as a medical treatment of undisturbed ectopic pregnancy. The hypothesis of this study was based on the invention created by M.F. Metwally 2005

There was no difference as regard patients clinical presentation or their past medical history in our three groups.

There was no difference in adnexal mass size in ultrasonography findings for successful treatment in our three groups with mean mass size was 3.3cm for letrozole, 3.1cm for methotrexate and 3.8cm for laparoscopy.

The median pre-therapeutic B- HCG titre (MIU/ ML) for successful treatment using letrozole was (865), which was less than that for methotrexate (1328) and for laparoscopy (1515).

Day 4 & Day 7 B-HCG titre is a good predictor of failure of treatment of letrozole. The optimal cut off value of B-HCG titre for successful treatment with letrozole was on day 4 less than (1190) and on day 7 less than (600)

The percentage of decrease in B-HCG titre in successful treatment using letrozole was 44.9% on day 4, 78.8% on day 7 and 96.5% on day 14.

There was no difference in percentage of decrease in B-HCG titre in successful treatment either by using letrozole or using methotrexate.
Out of 14 cases, 11 were treated successfully with letrozole (78.6%). 2 cases needed surgery and 1 case needed single dose of methotrexate.

Conclusion & Recommendation

Laparoscopy remains the gold standard first line modality for diagnosis and treatment of undisturbed ectopic pregnancy. It is also the modality of choice in case of failure of medical treatment.
Medical treatment with methotrexate for undisturbed ectopic pregnancy has its definite role as an alternative to laparoscopy.
Letrozole has the advantage of easy administration and high safety profile when compared to methotrexate and laparoscopy.
We recommend further & bigger studies on the use of letrozole in treatment of undisturbed ectopic pregnancy to establish its role.
We recommend further studies on the use of letrozole as an adjuvant treatment With Methotrexate or laparoscopy.

References

1. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980- 2007. Obstet Gynecol. 2011; 117(4):837-843.
2. American College of Obstetricians and Gynecologists (ACOG) ACOG Practice Bulletin No. 101: Ultrasonography in pregnancy. Obstet Gynecol. 2009 Feb. 113(2 Pt 1): 451-61.
3. Hajenius PJ, Mol F, Mol BW, Bossuyt PM, Ankum WM, van der Veen F. Interventions for tubal ectopic pregnancy. Cochrane Database Syst Rev. 2007 Jan 24. CD000324.
4. Bouyer J, Coste J, Shojaei T, et al., Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. Am J Epidemiol. 2003; 157:185–194.
5. Varma R, Gupta J. Tubal ectopic pregnancy. Clin Evid (Online) 2009; 1406. Pii
6. Ego A, Subtil D, Cosson M, Legoueff F, Houfflin – Debarge V, Querleu D. [Survival analysis of fertility after ectopic pregnancy.] Fertil Steril. 2001; 75:560 – 6.
7. Creanga AA, Shapiro-Mendoza CK, Bish CL, Zane S, Berg CJ, Callaghan WM. Trends in ectopic pregnancy mortality in the United States: 1980- 2007. Obstet Gynecol. 2011; 117(4):837-843.
8. Bakken IJ. Chlamydia trachomatis and ectopic pregnancy: pecent epidemiological findings.Curr Opin Infect Dis.2008;21:77–82.
9. Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006 Apr 1. 367(9516):1066-74.
10. Mohamed F. M. Mitwally, Michael P. DiamondRobert F. Casper Use of aromatase inhibitors for the treatment of ectopic pregnancy 2005
11. Stovall T G, Ling F W, Cope B J, et al.,: Preventing ruptured ectopic pregnancy with single serum progesterone Am J. Obstet. Gynecol.1989; 60:1425- 1431.
12. Hajenius PJ, Engelsbel S, MOL BWJ, Vander Veca F, Ankum WM, Bossuyt POM M et al.,: Randomized trial of Systemic MTX. Versus Laparoscopic Salpingostomy in Patients with tubal Pregnancy. Lancet, 2000; 350; 774-9.