Medical Management of Ectopic Pregnancy

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Introduction

- **Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy.**
- **Currently, a high index of suspicion, serial hormone assays, and TVS facilitate the diagnosis and ttt of ectopic pregnancy before rupture occurs.**

Introduction

- **Early diagnosis and timely treatment have resulted in a dramatic decline in mortality due to ectopic pregnancy.**
- **Treatment with (MTX), achieves results comparable to surgery for the treatment of appropriately selected ectopic pregnancies .**

History

- Ectopic pregnancy was first described in 963 Ad by Albucasis.
  - 1884 -- Robert Lawson Tait of Birmingham performed the first successful Salpingectomy operation.
  - 1953 -- Stromme – Conservative surgery of Salpingostomy.
  - 1973 -- Shapiro & Adller – Laparoscopic Salpingectomy.
  - 1991 -- Young et al – Laparoscopic Salpingotomy.

Definition

Any pregnancy where the fertilised ovum gets implanted & develops in a site other than uterine cavity.

PREVALENCE

- The incidence of ectopic pregnancy is approximately 2% of all pregnancies, and it remains the leading cause of death in early pregnancy.
- Over 95% of ectopic pregnancies are tubal pregnancies, and the remainders are non tubal pregnancies.

PREVALENCE

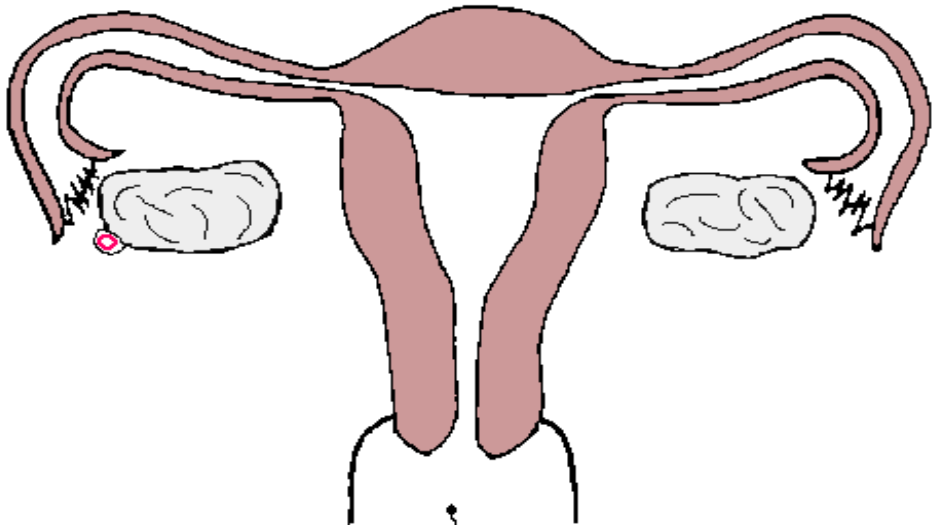
- **Recent evidence indicates that the incidence of ectopic pregnancy has been rising in many countries.**
  - **USA-5 fold – UK-2 fold**
  - **France 15/1000 pregnancies**
- **Recurrence rate - 15% after 1st, 25% after 2 ectopics.**

RISK FACTORS

- **Any pregnant woman potentially can have an ectopic pregnancy.**
- **Damage to the fallopian tubes predisposes a woman to ectopic pregnancy.**
- **Knowledge of risk factors can help identify women who may benefit from close monitoring and early treatment.**

Risk Factor	Risk %
High Risk	
PID	**25**
Tubal corrective surgery	21.0
Tubal sterilization	9.3
Previous EP	8.5
IUD	4.2-45
Documented tubal pathology	3.8-21
Moderate Risk	
Infertility	2.5-21
Previous genital infection	2.5-3.7
Slight risk	
Previous pelvic or abdominal surgery	0.93-3.8
Smoking	2.3-2.5
Intercourse before 18 years	1.6

Pathology of Ectopic Pregnancy



- Zygote reaches the muscular wall
- Trophoblastic cells at zygote periphery proliferate, invade, and erode adjacent muscularis
- Maternal blood vessels disrupted leading to hemorrhage

DIAGNOSIS

- **Timely diagnosis of ectopic pregnancy is important to reduce risk of rupture and improve the success of medical management.**
- **Diagnosis of all women at risk for ectopic pregnancy should be prompt but is not always an emergency and should occur before rupture in a hemodynamically stable woman.**

DIAGNOSIS

- **Any woman of reproductive age experiencing abnormal vaginal bleeding with or without abdominal pain is at risk for ectopic pregnancy.**

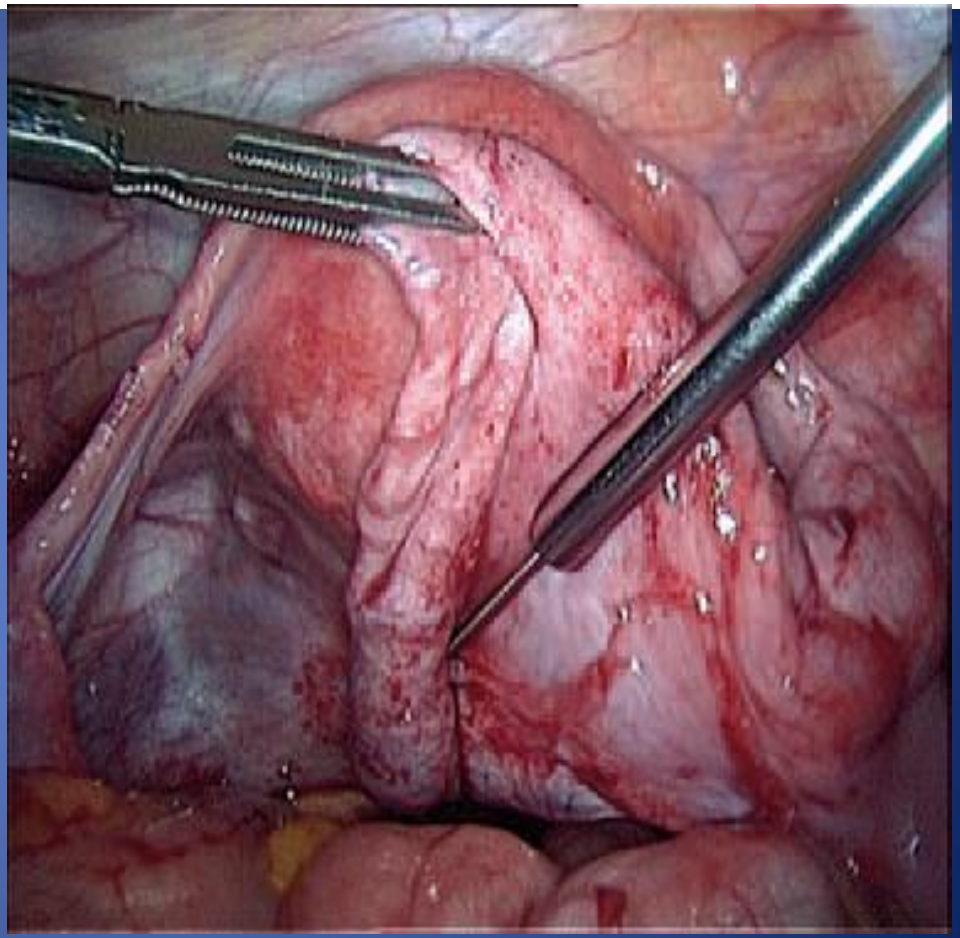
- **Such women should be followed closely until a diagnosis is made.**

DIAGNOSIS

- **Diagnostic approaches that use**
- **Serial (hCG) assays,**
- **Ultrasonography &**
- **Laparoscopy.**

Treatment

- Local (SAM)
- Systemic



SAM TREATMENT

- Aim- trophoblastic destruction without systemic side effects
- Technique- Injection of trophotoxic substance into the ectopic gestational sac or into the affected tube by-
  - Laparoscopy or
  - Ultrasonographically guided
    - Transabdominal (Porreco, 1992)
    - Transvaginal (Feichtingar, 1987)
  - With Falloposcopic control (Kiss, 1993)

Trophotoxic substances

- Methotrexate (Pansky, 1989)
- Potassium Chloride (Robertson, 1987)
- Mifepristone (RU 486)
- PGF2 (Limblom, 1987)
- Hyper osmolar glucose solution
- Actinomycin D

Advantage of local MTX

- Increase tissue concentration at local site .
- Decrease systemic side effects .
- Decrease hospitalization .
- Greater preservation of fertility.

Systemic Methotrexate

- Resolution of tubal pregnancy by systemic administration of Methotrexate was first described by Tanaka et al (1982) .
- Then, become widely accepted as primary treatment for ectopic pregnancy .
- Methotrexate is a folic acid antagonist .
- Folic acid normally is reduced to tetrahydrofolate by the enzyme dihydrofolate reductase (DHFR), a step in the synthesis of DNA and RNA precursors.

TREATMENT

- **Methotrexate inhibits DHFR, causing depletion of cofactors required for DNA and RNA synthesis.**

- **Folinic acid (leucovorin) is an antagonist to MTX that can help reduce otherwise prohibitive side effects, particularly when higher doses of MTX are used.**

CANDIDATES FOR MEDICAL TREATMENT

- ***Inclusion Criteria :***
- **Haemodynamically stable.**
- **Indications**

1. **Unruptured tubal or other ectopic pregnancy.**
2. **Persistent trophoblast after salpingotomy.**

- **Serum quantitative βHCG < 5000 IU/L**
- **Size of ectopic mass < 3.5cm**
- **Normal LFT's, KFT's, and FBC.**
- **Patient compliance for regular follow up (average follow up 35 days).**
- **No severe or persistent abdominal pain,**

Contraindications to MTX therapy

Absolute contraindications :

- Intrauterine pregnancy
- Evidence of immunodeficiency
- Moderate to severe anemia, leukopenia, or thrombocytopenia
- Sensitivity to MTX
- Active pulmonary disease
- Active peptic ulcer disease
- Clinically important hepatic dysfunction
- Clinically important renal dysfunction
- Breastfeeding
- Ruptured ectopic pregnancy
- Hemodynamically unstable patient

Relative contraindications

- Embryonic cardiac activity detected by TVS.
- High initial hCG concentration (>5,000 IU/L).
- Ectopic pregnancy >4 cm in size by TVS.
- Inability to participate in follow-up.

Predictors of MTX treatment failure

Adnexal fetal cardiac activity.

- Size of the gestational mass (>4 cm).
- High initial hCG concentration (>5,000 IU/L).
- Presence of free peritoneal blood(100-300)
- Rapidly increasing hCG concentrations (>50%/48 h) before MTX.
- Continued rapid rise in hCG concentrations during MTX.

PRE-TREATMENT CHECKS

- Discuss the options for treatment.
- CBC,LFT,KFT, βHCG,US.
- Satisfy inclusion and exclusion criteria.
- Obtain written consent.
- Calculate the Patient Body Surface Area from height and weight.
- Prescribe methotrexate as per the dosage regimen.

DOSAGE REGIMEN

- Day 1 is the day of MXT treatment.
- On Days 4 and 7, a serum HCG concentration is checked and if the decrease in HCG is less than 15 percent between Days 4 and 7, a 2nd dose of MXT is administered.
- A 15% decrease in serum HCG between day 4 and day 7 is a very good indicator of the likely success of MXT.

Calculate body surface area (BSA) using the formula:

$$\sqrt{\frac{\text{height (cms)} \times \text{weight (kgs)}}{3600}}$$

(ie. Commence the calculation inside the brackets & then calculate the square root to reach the BSA)

(Eg) A women 165cm & 60kg = 165 x 60 = 9900 ÷ 3600 = 2.75
square root of 2.75 = 1.65
which gives a BSA of 1.65m^2

Weight (kg)	Height (cm)													
	70	80	90	100	110	120	130	140	150	160	170	180	190	200
10	0.42	0.46	0.50	0.54										
15	0.49	0.54	0.59	0.64	0.69	0.73	0.77							
20	0.56	0.62	0.67	0.72	0.78	0.83	0.87	0.92	0.97					
30	0.66	0.73	0.80	0.86	0.92	0.98	1.04	1.10	1.15	1.21	1.26			
40					1.04	1.11	1.17	1.24	1.30	1.37	1.43	1.49		
50							1.29	1.36	1.43	1.50	1.57	1.63	1.70	
60							1.40	1.47	1.55	1.62	1.69	1.77	1.84	1.91
70								1.57	1.65	1.73	1.81	1.89	1.96	2.04
80									1.75	1.83	1.92	2.00	2.08	2.15
90										1.93	2.01	2.10	2.18	2.27
100										2.02	2.11	2.20	2.28	2.37
110											2.19	2.29	2.38	2.47
120											2.28	2.37	2.47	2.56
130											2.35	2.45	2.55	2.65

Weight (kg)	Height (cm)									
	70	80	90	100	110	120	130	140	150	160
10	21	23	25	27						
15	24.5	27	29.5	32	34.5	36.5	38.5			
20	28	31	33.5	36	39	41.5	43.5	46	48.5	
30	33	36.5	40	43	46	49	52	55	57.5	60.5
40					52	55.5	58.5	62	65	68.5
50							64.5	68	71.5	75
60							70	73.5	77.5	81
70								78.5	82.5	86.5
80									87.5	91.5
90										96.5
100										101
110										
120										
130										

TABLE 3

Single-dose MTX treatment protocol (33).

Treatment day	Laboratory evaluation	Intervention
Pretreatment	hCG, CBC with differential, liver function tests, creatinine, blood type, and antibody screen	Rule out spontaneous abortion Rhogam if Rh negative
1	hCG	MTX 50 mg/m^2 IM
4	hCG	
7	hCG	MTX 50 mg/m^2 IM if β-hCG decreased <15% between days 4 and 7

Note: CBC = complete blood count; MTX = methotrexate; IM = intramuscularly.

Practice Committee. Medical treatment of ectopic pregnancy. Fertil Steril 2013.

TABLE 2

Multiple-dose MTX treatment protocol (28, 29).

Treatment day	Laboratory evaluation	Intervention
Pretreatment	hCG, CBC with differential, liver function tests, creatinine, blood type, and antibody screen	Rule out spontaneous abortion RhoGAM if Rh negative
1	hCG	MTX 1.0 mg/kg IM
2		LEU 0.1 mg/kg IM
3	hCG	MTX 1.0 mg/kg IM if <15% decline day 1–day 3 If >15%, stop treatment and start surveillance
4		LEU 0.1 mg/kg IM
5	hCG	MTX 1.0 mg/kg IM if <15% decline day 3–day 5 If >15%, stop treatment and start surveillance
6		LEU 0.1 mg/kg IM
7	hCG	MTX 1.0 mg/kg IM if <15% decline day 5–day 7 If >15%, stop treatment and start surveillance
8		LEU 0.1 mg/kg IM

Note: Surveillance every 7 days (until hCG <5 mIU/mL). Screening laboratory studies should be repeated every week after the last dose of MTX. CBC = complete blood count; MTX = methotrexate; IM = intramuscularly; LEU = leucovorin.

Hybrid protocol

- It involving two equal doses of MTX (50mg/m2) administered on days 1 and 4 without leucovorin rescue and follow-up as described previously for the single dose protocol, may offer a more optimal balance between convenience and efficacy.
- The protocol also allows for more than two doses of MTX when hCG values do not decrease 15% between days 4 and 7.

	Single Dose	Two Dose	Multi-Dose
Dosing	One dose; repeat if necessary	Days 0 and 4	Up to four doses of both drugs until serum -hCG declines by 15%
Methotrexate	50mg/m^2 BSA [day 1]	50 mg/m2 BSA	1 mg/kg, days 1, 3, 5, and 7
Leucovorin	-	-	0.1 mg/kg days 2, 4, 6, and 8
B hcg	Days 0, 4, 7	Days 0 , 4 and 7. Days 11 and 14 if repeat dose is given	Days 0 (baseline), 1, 3, 5, and 7
Additional dose	○ If serum -hCG level does not decline by 15% from day 4 to day 7 ○ Less than 15% decline during weekly surveillance	○ If serum -hCG does not decline by 15% from day 4 to day 7 ○ If serum -hCG does not decline by 15% from day 7 to day 11 ○ Maximum of four doses	If serum -hCG declines <15%, give additional dose; repeat serum -hCG in 48 hours and compare with previous value; maximum four doses
Surveillance	Weekly until serum -hCG undetectable	Weekly until serum -hCG undetectable	Weekly until serum -hCG undetectable

SINGLE VERSUS MULTIPLE DOSE REGIMEN

- Similar success rates for single dose and multiple dose regimens.
- More side effects/ less patient satisfaction with multiple dose regimens.
- No difference in future tubal patency/intrauterine pregnancy/or recurrent ectopic pregnancy.

SINGLE VERSUS MULTIPLE DOSE REGIMEN

- Single dose regimen is less expensive, needs less intensive monitoring and does not require folinic acid rescue.

Caveats for physicians & patients regarding the use of MTX

- Avoid pelvic examinations and ultrasound during surveillance of MTX therapy.
- Avoid sun exposure to limit risk of MTX dermatitis.
- Avoid foods and vitamins containing folic acid.
- Avoid gas-forming foods because they produce pain.
- Avoid new conception until hCG is undetectable.NSAI

Methotrexate Embryopathy

microcephaly,
skull bone hypoplasia,
wide fontanels,
craniosynostosis,
broad nasal bridge,
shallow supraorbital ridges, prominent eyes, low set ears, maxillary hypoplasia, epicanthal folds, short limbs, talipes, and syndactyly

EFFICACY

- Overall success is 88-90% with a single dose regimen.
- 14% of patients on single dose regimen will require a second dose and less than 1% of women will require more than two doses.

Randomized trials of single-dose or multidose MTX for ectopic pregnancy (evidence I)

Authors	No. of patients	Results
Alleyassin et al, 2006	***108***	Comparable success rate between single dose (88.9%) and multidose MTX (92.6%; odds ratio 5 0.64; 95% confidence interval, 0.17–2.4)
Guvendag et al, 2010	***120***	Comparable success rate between single dose (80.6%) and multidose MTX (89.7%; odds ratio 5 0.90; 95% confidence interval, 0.77–1.05) No significant difference in side effects
Roshdy et al,2012	***157***	Comparable success rate between 2-dose (88.6%) and single-dose MTX (82.0%) No significant difference in side effects

Treatment & drug side effects associated with MTX

Treatment side effects :

- Increase in abdominal girth.
- Increase in hCG during initial therapy.
- Vaginal bleeding or spotting.
- Abdominal pain.

Separation pain

- Up to 75% of patients may complain of pain on days 2-7 after receiving the medication.
- The pain may be due to tubal miscarriage or tubal distension from haematoma formation and can usually be managed with simple analgesia.

Drug side effects

- Gastritis, enteritis,nausea, and vomiting.
- Stomatitis. Conjunctivitis.
- Dizziness.
- Elevated liver enzyme.
- Severe neutropenia (rare).
- Reversible alopecia (rare).
- Pneumonitis (rare).

SUBSEQUENT REPRODUCTIVE PERFORMANCE

- There is no evidence of adverse effects of MXT treatment of ectopic pregnancy on future pregnancies.
- Treatment with MXT does not appear to compromise ovarian function.

SUBSEQUENT REPRODUCTIVE PERFORMANCE

- The incidence of recurrent ectopic pregnancy is approximately 15% and rises to 30% following two ectopic pregnancies.
- The risk of recurrence appears to be the same for both medical and surgical treatments.
- Observational studies have shown a subsequent intrauterine pregnancy rate of 58 –89 %.

MEDICAL VERSUS SURGICAL TREATMENT

- Approximately 35% of women with ectopic pregnancy will satisfy the criteria for medical management.
- In these women, systemic treatment with variable dose MTX regimen is as effective as laparoscopic salpingotomy (82 – 95% MTX Vs 80-92% Salpingotomy).

MEDICAL VERSUS SURGICAL TREATMENT

- Similar Post treatment tubal patency and intrauterine pregnancy rates.
- Similar risk of recurrent ectopic pregnancy.
- Side effects are more with medical treatment especially so with multiple dose regimen.

CONCLUSIONS

- Both conservative surgery and medical therapy may be viewed as appropriate first-line therapies in many early unruptured ectopic pregnancies.
- Multiple-dose MTX treatment has a lower failure rate than single-dose MTX.
- Single-dose MTX is sufficient to treat persistent trophoblastic tissue after salpingostomy and ectopic pregnancies associated with low initial hCG values.

CONCLUSIONS

- Postoperative, prophylactic, single-dose systemic MTX may reduce the incidence of persistent ectopic pregnancy after salpingostomy.
- Medical therapy appears more cost-effective than surgery except when the initial hCG level is high and/or embryonic cardiac activity is observed.