Methotrexate

guideline

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early pregnancy unit

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Zeven doden door verkeerd gebruik methotrexaat

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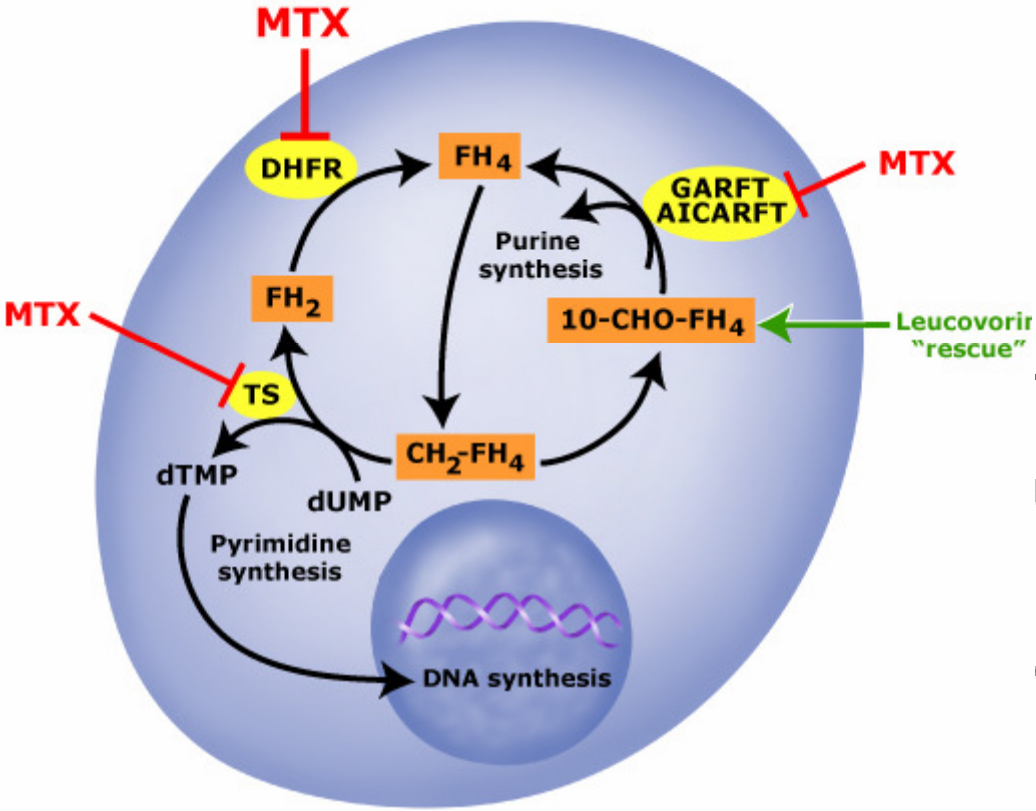
Door een onzer redacteuren

Utrecht, 21 sept. Sinds 2007 hebben dertien ongelukken met het medicijn methotrexaat plaatsgehad, waarvan zeven met fatale afloop. Dat meldde de KNMP, de brancheorganisatie van apothekers, dit weekeinde.

Methylaminopterin (MTX) is cell specific chemotherapy

Methotrexate



MTX	Methotrexate
DHFR	Dihydrofolate reductase
GARFT	Glycinamide ribonucleotide transformylase
AICARFT	Aminoimidazole carboxamide ribonucleotide transformylase
TS	Thymidylate synthetase
FH_2	Dihydrofolate
FH_4	Tetrahydrofolate
10-CHO-FH_4	10-Formyl tetrahydrofolate
CH_2-FH_4	Methylenetetrahydrofolate
dUMP	Deoxyuridine monophosphate
dTMP	Deoxythymidine monophosphate

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Pharmacology

- Im injection: 70-100% bio-availability
- T_{peak} 1-5 hr, $T_{1/2}$ 8-10 hr
- In serum 36-53% albumen binding
- Transport cell membrane
  - active ≈ pH, T, O_2, other drugs
  - perfusion with high [MTX] extracellular
- Cytotoxicity ≈ [free MTX] intracellular
- Production of metabolites
  - 7-OH MTX
  - DAMPA
  - polyglutamyl derivates
- Excretion via kidneys (< 24 hr 55-95%), bile and faeces

Verduijn *et al.* Ned Tijdschr Geneeskd 2009

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Clinical use

- Malignancy
  - leukemia
  - lymfoma
  - gestional trophoblastic disease
- Auto immune disease
  - juvenile rheumatoid artritis
  - systemic lupus erythematosus
- Dermatology
  - psoriasis
- Termination of intra uterine pregnancy
- Ectopic pregnancy

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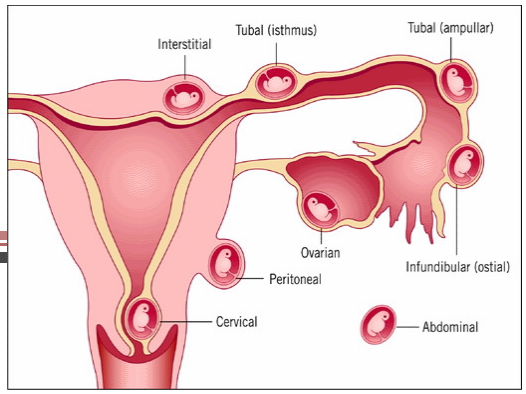
Systemic MTX for EP



- 1982 interstitial pregnancy

  Goldstein protocol trophoblastic disease: MTX 1 mg/kg im day 0,2,4,6 / CF 0.1 mg/kg im day 1,3,5,7

- 1985 tubal pregnancy

- 1986 cervical pregnancy

- 1986 case series of six patients tubal pregnancy

- 1989 single dose regimen

Goldstein *et al*. Obstet Gynecol 1976, Tanaka *et al*. Fertil Steril 1982, Chotiner Obstet Gynecol 1985, Cheng *et al*. J Formos Med Assoc 1986, Ory *et al*. AJOG 1986, Stovall *et al*. Fertil Steril 1989

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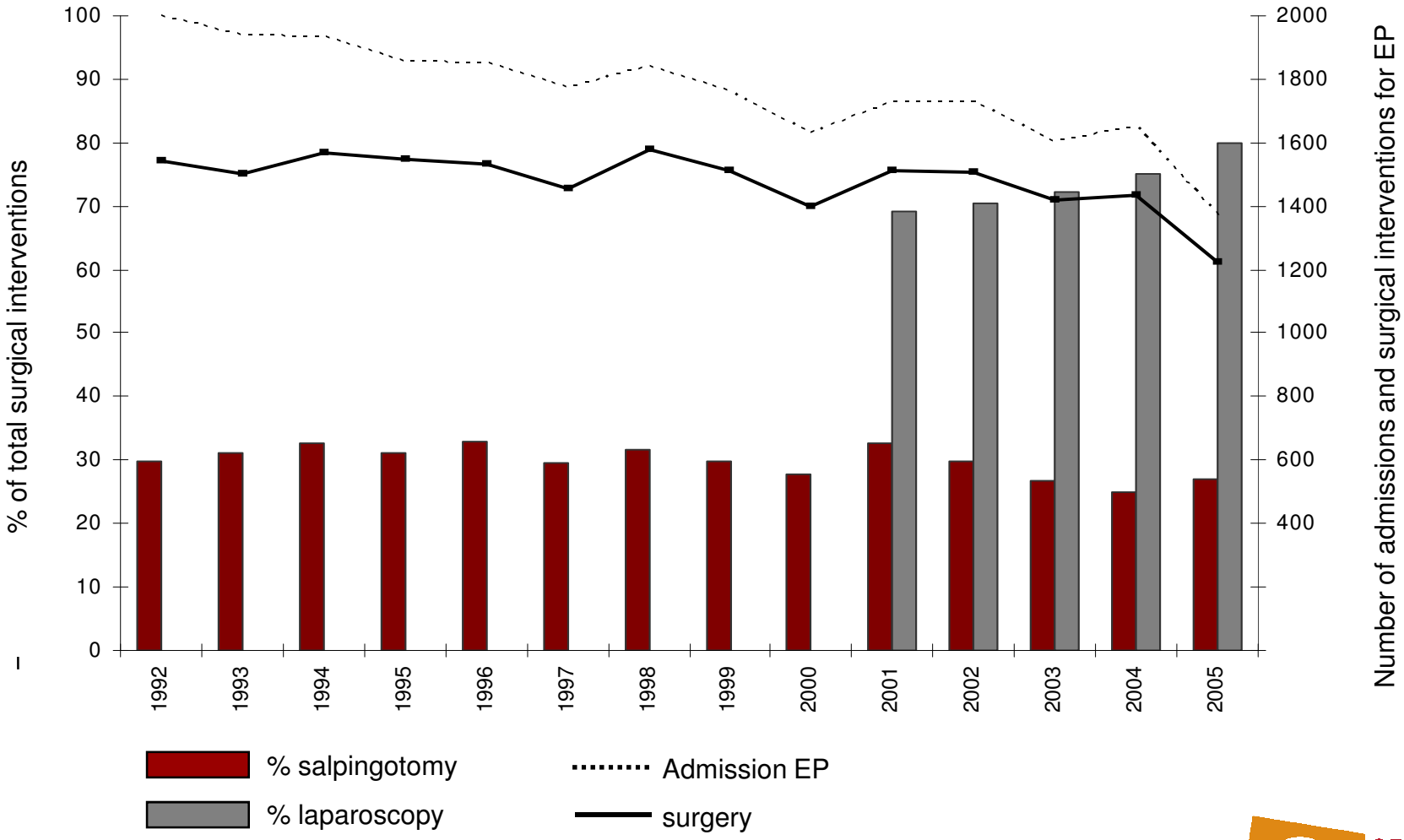
Treatment EP in NL (1991-2005)



F Mol *et al*. accepted EJOG

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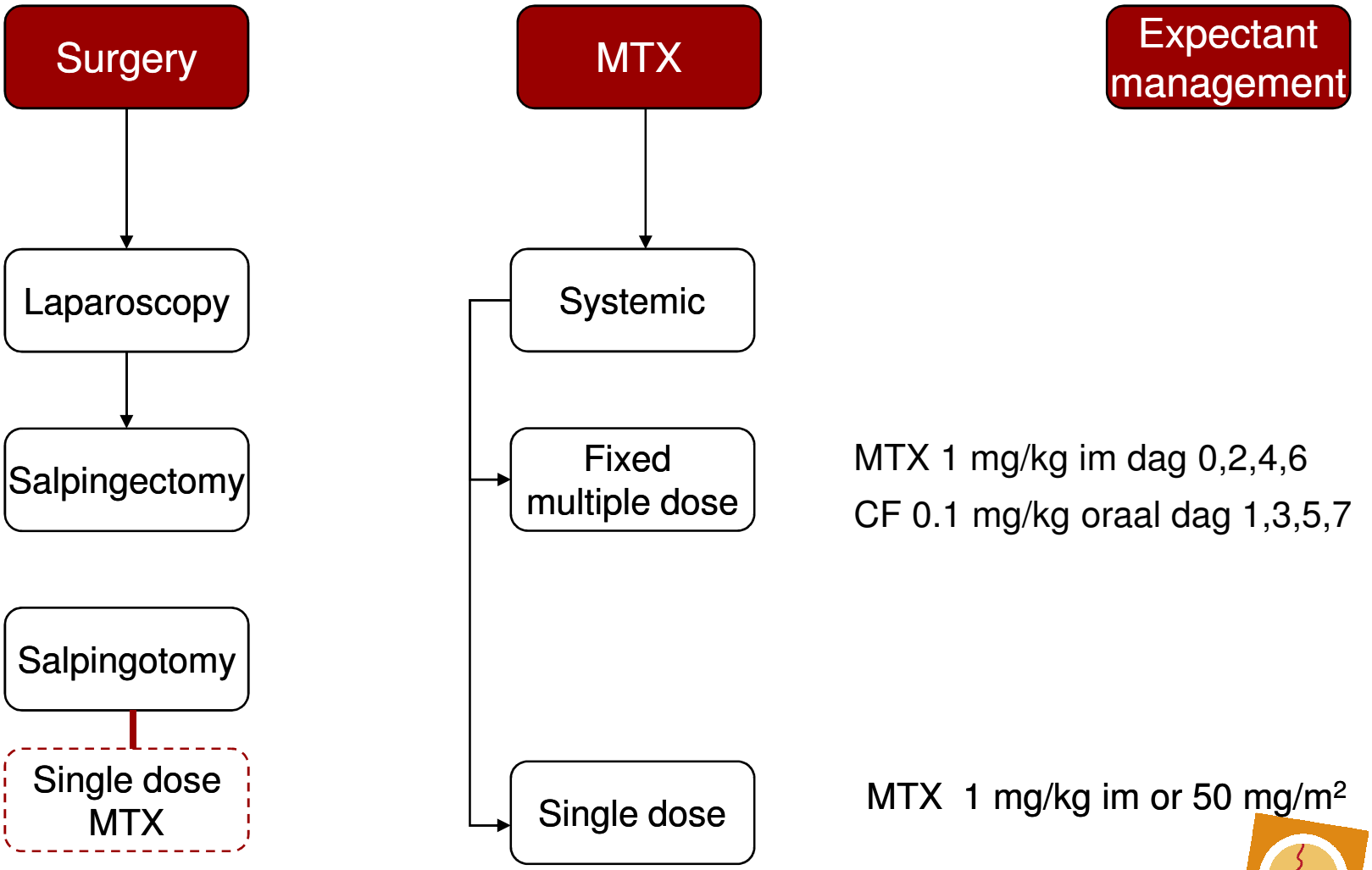
Evidence and clinical practice tubal EP



Hajenius *et al*. Cochrane review, update Jan 2007, F Mol *et al*. Hum Reprod Update 2008

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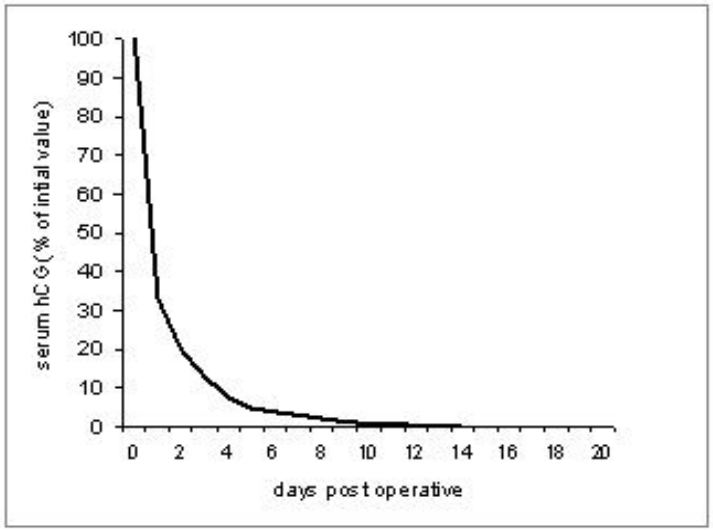
Salpingotomy and single dose MTX im

Review: Interventions for tubal ectopic pregnancy
Comparison: 04 salpingostomy alone versus combined with medical treatment
Outcome: 01 primary treatment success

Study	Alone n/N	with medication n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 with single dose MTX im					
Elmoghazy 2000	19/24	22/23		44.7	0.23 [0.04, 1.28]
Graczykowski 1997	56/62	53/54		55.3	0.25 [0.06, 1.17]
Subtotal (95% CI)	86	77		100.0	0.25 [0.08, 0.76]

Total events: 75 (Alone), 75 (with medication)
Test for heterogeneity chi-square=0.00 df=1 p=0.94 I^2 =0.0%
Test for overall effect z=2.43 p=0.02



Hajenius *et al*. Hum Reprod 1995

NNT = 10 ⇒ serum hCG monitoring

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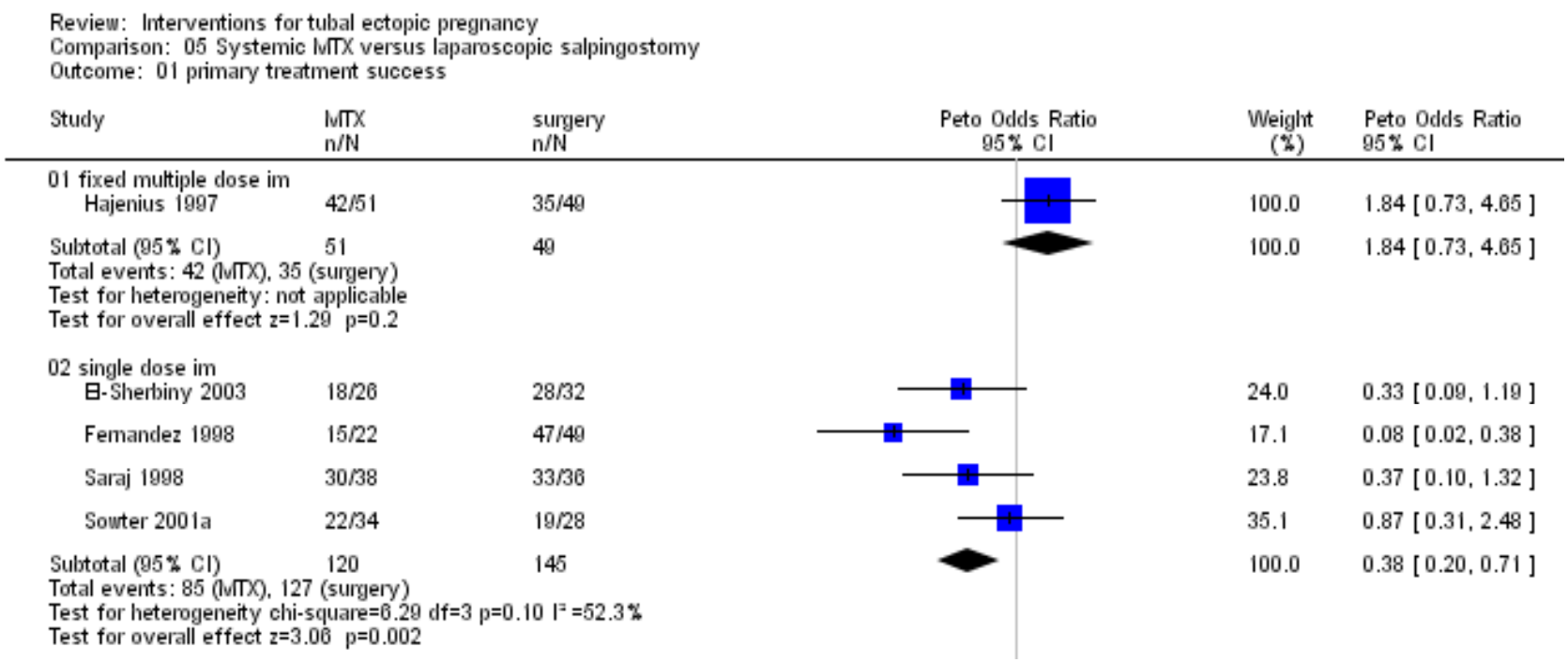
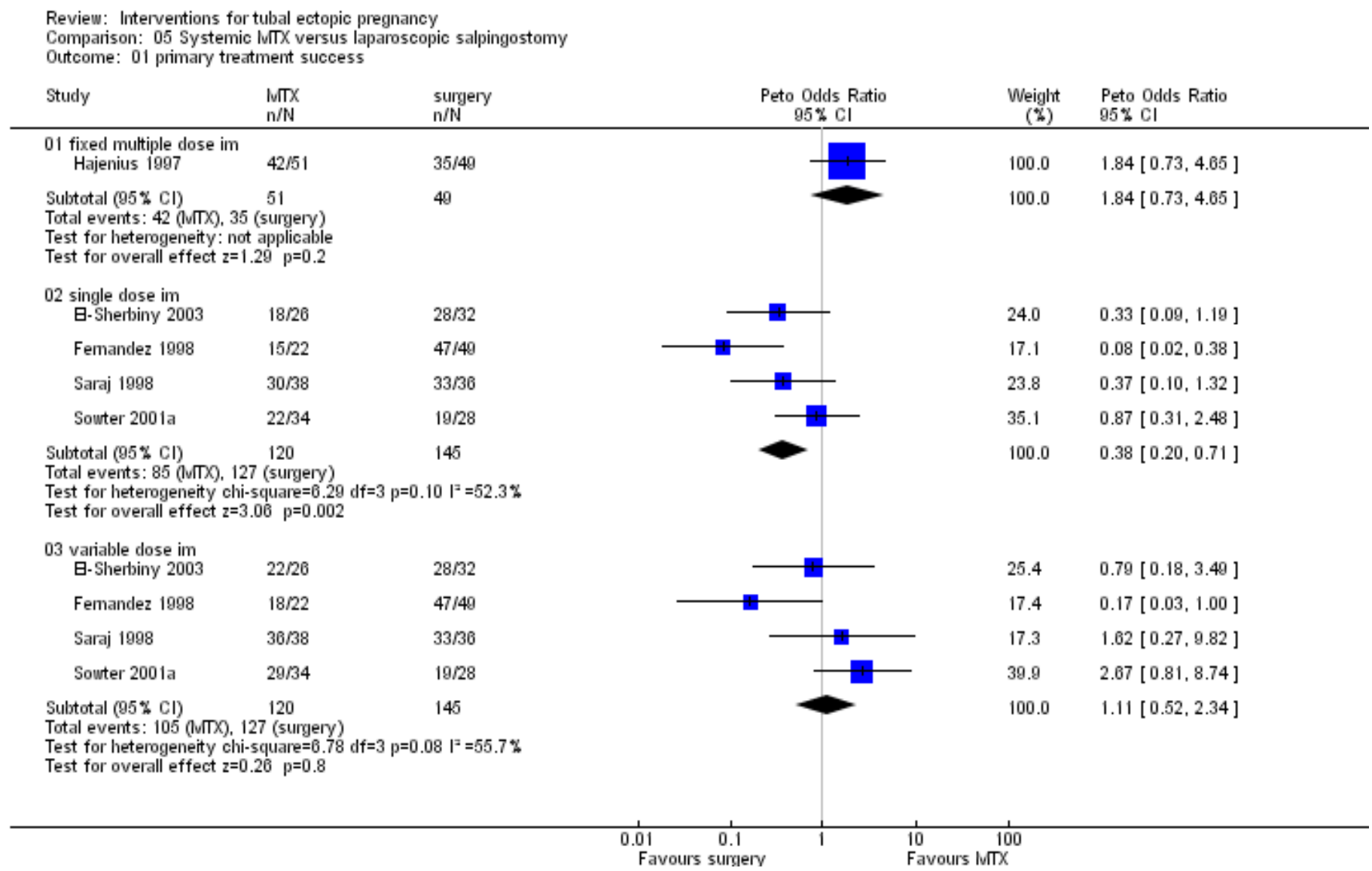
Salpingotomy versus systemic MTX im



Mean serum hCG concentrations 927-3,162 IU/l

Salpingotomy versus systemic MTX im



Single versus multiple dose MTX

- Meta-analysis

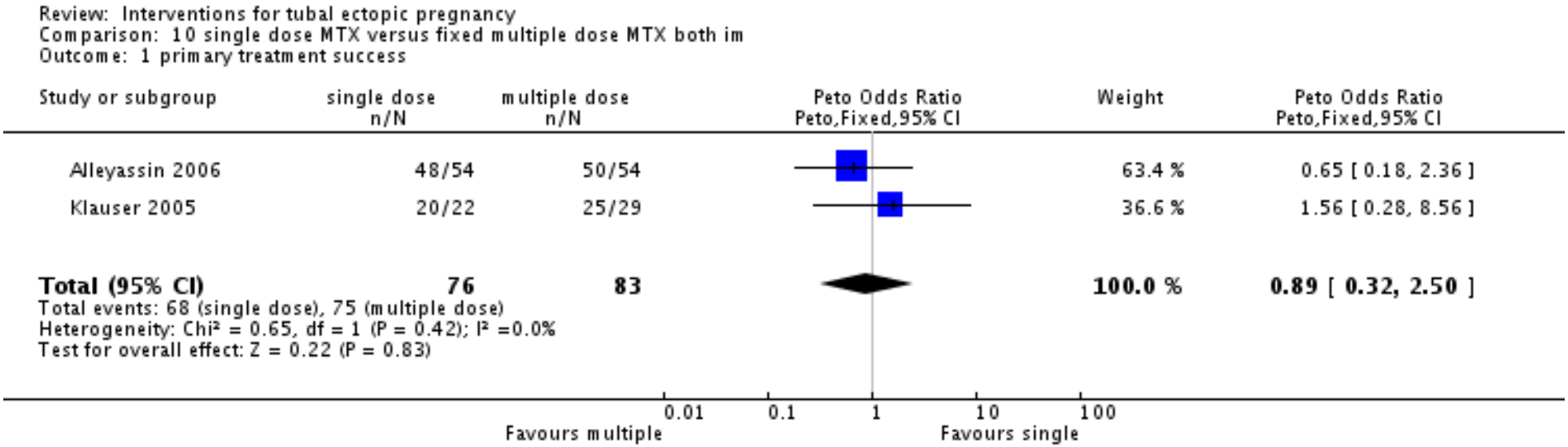
  26 articles, n=1327

- MTX success rate 89%

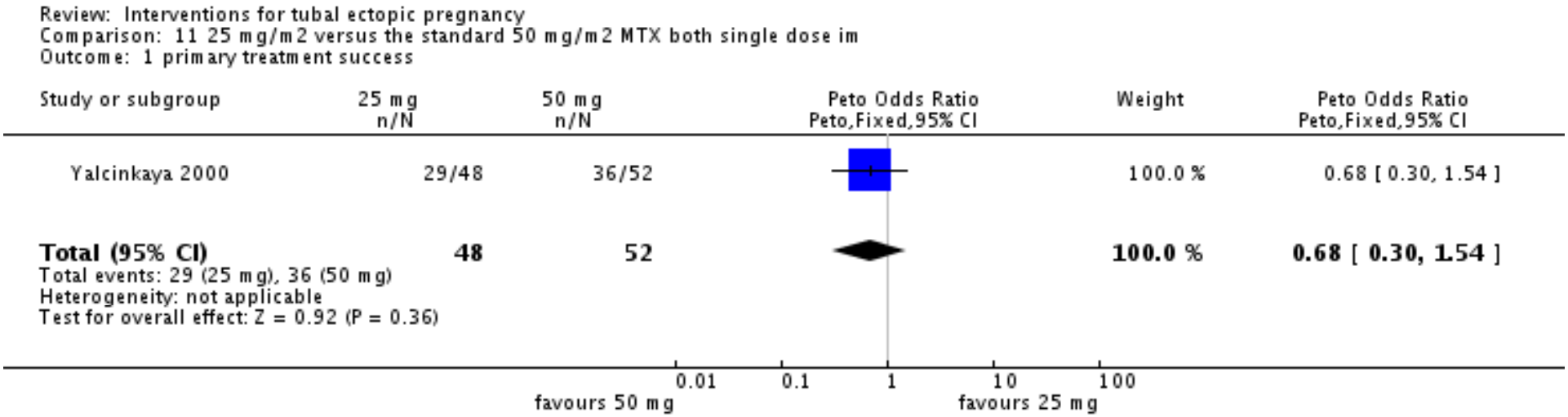
  single dose 88.1% (95% CI 86-90)

  multiple dose 92.7% (95% CI 89-96)

Barnhart *et al*. Obstet Gynecol 2003



Low dose versus standard dose MTX



Systemic MTX regimens still area of research !

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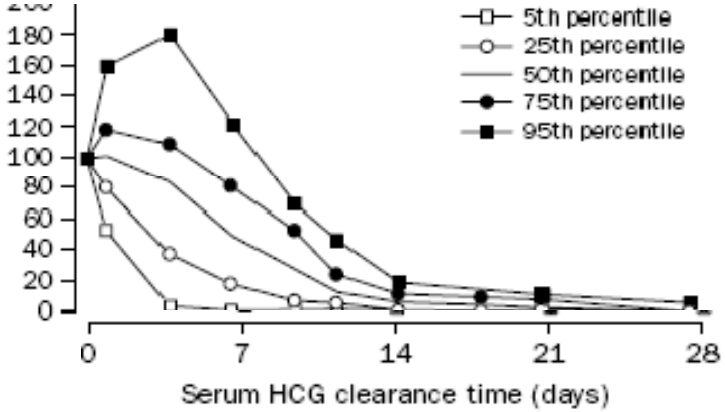
Guideline systemic MTX for tubal EP

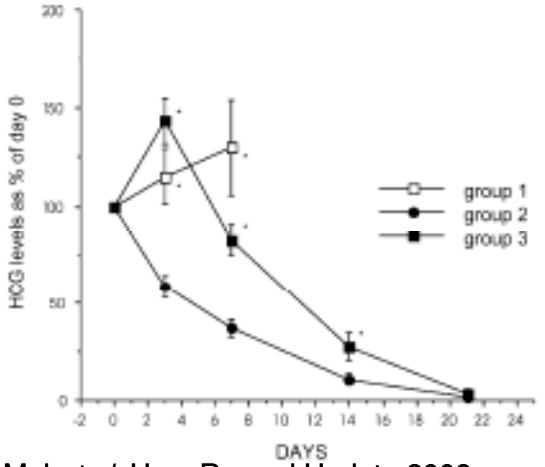
Multiple dose regimen

- 1 mg/kg day 0,2,4,6 im alternated with CF 0.1 mg/kg
- serum hCG < 3,000 IU/l
- Second course if serum $hCG_{day\ 14}$ > 40% of the initial value

Variable dose regimen

- 1 mg/kg or 50 mg/m^2 im
- serum hCG < 1,500 IU/l
- Additional injection if serum hCG days 4 and 7 < 15% decline





Hajenius *et al.* Lancet 1997, Hajenius *et al.* Cochrane review, update Jan 2007, F Mol *et al.* Hum Reprod Update 2008, Natale *et al.* Eu J Obstet Gynecol Reprod 2002

Patient selection

- Hemodynamically stable
- No signs of (tubal) rupture
- Low serum hCG level
- EP < 3.5- 4 cm
- No fetal cardiac activity
- No contra-indications to MTX
- Patient consent and compliance

ACOG Practice Bulletin 2008; No.94, Practice committee ASRM 2008, Van Mello *et al*. Best Practice Research Clinical Obstetrics and Gynaecology 2009

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Contra-indications

- Indefinite diagnosis/ probable IUP
- No compliance
- Immunodeficiency
- Hepatic, renal or hematologic dysfunction
- Active pulmonary disease
- Alcoholism
- Known sensitivity to MTX
- Use of anticoagulants
- Morbid adipositas (max dosage MTX 100 mg/injection)

ACOG Practice Bulletin 2008; No.94, Practice committee ASRM 2008, Van Mello *et al*. Best Practice Research Clinical Obstetrics and Gynaecology 2009

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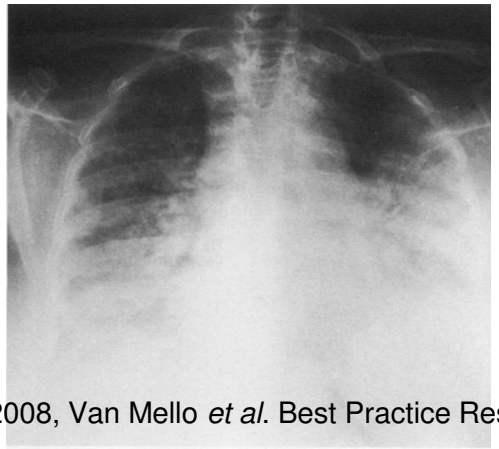
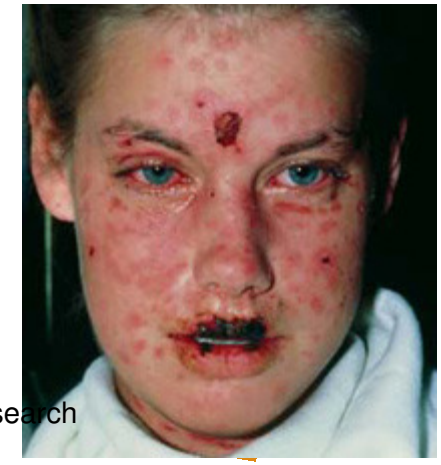
Side-effects

- Vaginal bleeding or spotting
- Minor (incidence 25-28%)
  - nausea, vomiting
  - stomatitis/gastro enteritis
  - conjunctivitis
  - impaired liver function
  - bone marrow depression
  - photosensitivity/dermatits
- Severe (rare)
  - (reversible) alopecia
  - hypersensitivity pneumonitis
  - Stevens Johnson syndrome
  - life threatening pancytopenia





ACOG Practice Bulletin 2008; No.94, Practice committee ASRM 2008, Van Mello *et al*. Best Practice Research Clinical Obstetrics and Gynaecology 2009

Life rules

- No sexual intercourse
- Fluid intake > 1.5 L
- No sunlight exposure
- Mouthwashes with 0.9% saline / Clorhexidin 0.12%
- Avoidance of gas-forming food
- Drug interactions
  - fol(in)ic acid supplements (vitamins)
  - NSAIDs and aspirin
  - antibiotics (trimethoprim, sulfa)
  - omeprazol
  - alcohol
- Folic acid iv if severe side effects

ACOG Practice Bulletin 2008; No.94, Practice committee ASRM 2008, Van Mello *et al*. Best Practice Research Clinical Obstetrics and Gynaecology 2009

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Follow-up

- Serum hCG monitoring until undetectable levels
- Complete blood counts, liver and renal function tests
- 375 IE Anti D im if Rhesus negative
- TVS only if tubal rupture is suspected
- Contraceptive methods for three months*
  - teratogenic effects ?
  - aminopterin syndrome: skeletal and CNS abnormalities
- Early screening next pregnancy

* Lloyd *et al.* QJM 1999, Lewden *et al.* J Reumatol 2004, Matinez Lopez *et al.* Clin Exp Rheumatol. 2009, Svirsky *et al.* Reprod Toxicol 2009

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Ongoing research

Pregnancy of unknown location (PUL)

- (High LR for) EP: inconclusive TVS and high serum hCG levels
  DZ principle (*spontaneous singleton*)
  surgical intervention or systemic MTX treatment in a multiple dose regimen

- Failing PUL: inconclusive TVS and declining serum hCG levels
  expectant management

- Persisting PUL: inconclusive TVS and persisting low serum hCG levels
  10% of women suspected of EP
  expectant management or single dose MTX treatment ? (*two ongoing RCTs*)

Jurkovic *et al.* ISRCTN 95698259, Van Mello *et al.* BMC Womens Health 2008

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METEX study (n=72)

P: persisting PUL < 2,000 IU/l, EP < 1,500 IU/l

I: expectant management

C: MTX single dose 1 mg/kg im

O: Treatment success (serum hCG < 2 IU/l)
quality of life
financial costs
(fertility)

Van Mello *et al*. BMC Womens Health 2008

Current status

- Web based randomisation
- Stratification
  - serum hCG (1,000 IU/l)
  - center
- Inclusions: n= 40 (30/11/09)

www.metexstudy.nl, www.studies-obsgyn.nl

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Follow-up day 7

Expectant management

> 15% decline in serum hCG
→ successful treatment

> 15% rise in serum hCG
→ start systemic MTX

Plateau = < 15% decline and < 15% rise
→ repeat serum hCG after 48 hours

Persistent plateau or serum hCG rise
→ start systemic MTX

Systemic MTX

> 15% decline in serum hCG
→ successful treatment

< 15% decline or rising serum hCG
→ additional MTX injection (4 max)

In case of clinical symptoms → surgical intervention

Van Mello *et al*. BMC Womens Health 2008

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Conclusions

NHS National Patient Safety Agency
Patient safety alert
Alert

- Systemic MTX for selected women with (tubal) EP
- Information leaflet
- Informed consent
- Hospital protocol
- Results of ongoing and future research to be awaited

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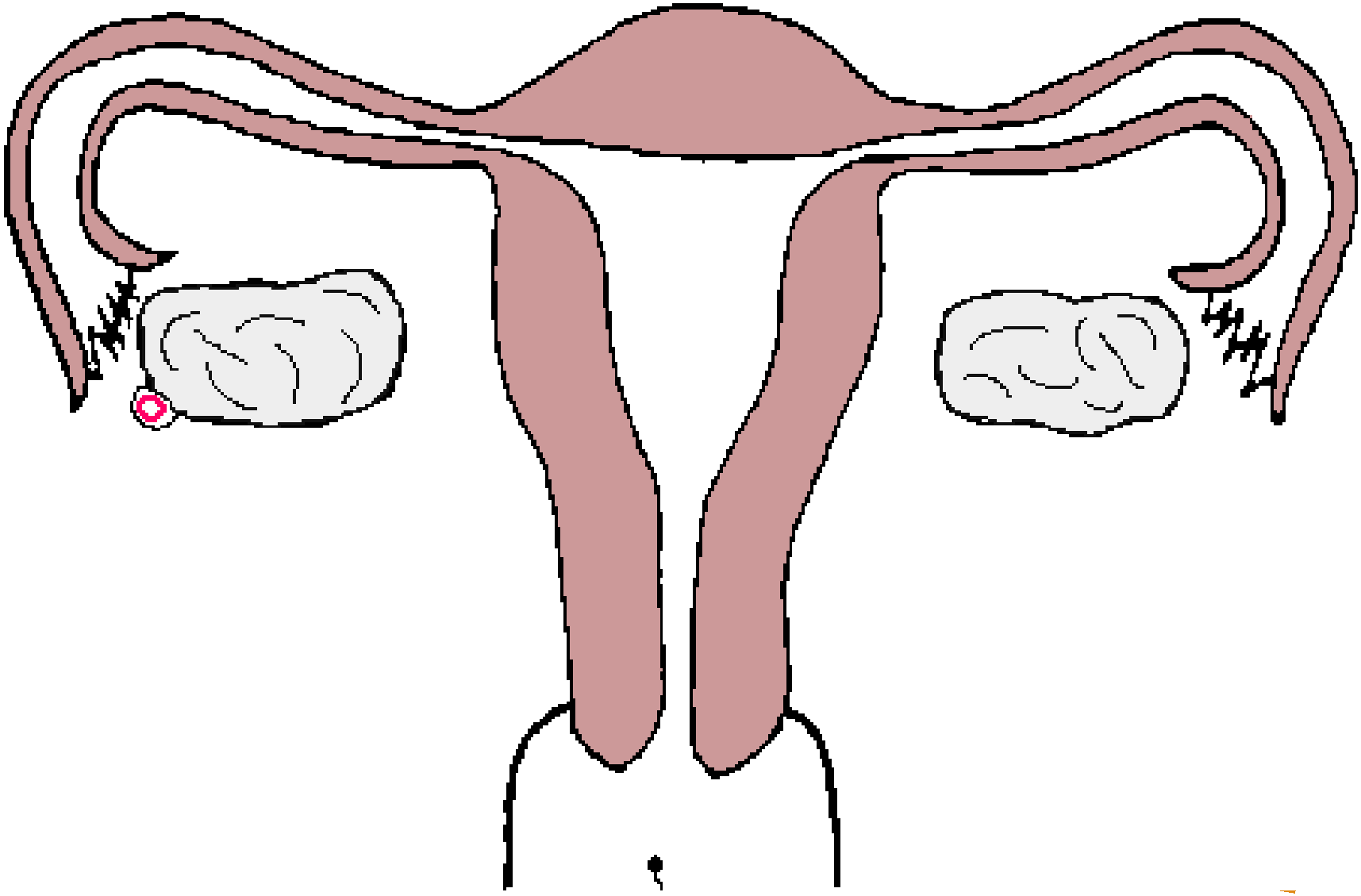
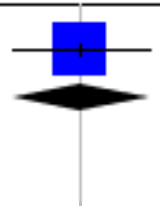


Expectant management *vs* systemic MTX

Review: Interventions for tubal ectopic pregnancy
Comparison: 17 expectant management versus medical treatment
Outcome: 1 primary treatment success

Study or subgroup	expectant management n/N	medical treatment n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 versus oral MTX					
Korhonen 1996	23/30	23/30		100.0 %	1.00 [0.31, 3.28]
Subtotal (95% CI)	**30**	**30**		**100.0 %**	**1.00 [0.31, 3.28]**

Total events: 23 (expectant management), 23 (medical treatment)
Heterogeneity: not applicable
Test for overall effect: Z = 0.0 (P = 1.0)



No clinical significance

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Inclusions n = 40 (30-11-09)