Treatment of Ectopic Pregnancy

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Tampere University Hospital
24.9.2004
Clinical presentation of ectopic pregnancy

• Change from a life threatening disease to a more benign condition
Epidemiology of ectopic pregnancy

- 13 maternal deaths 1997-1999 in the UK
Implantation sites of ectopic pregnancies
Risk factors for ectopic pregnancy (Pisarska MD et al., 1998)

- Tubal surgery x 21
- Previous ectopic pregnancy x 8
- IUD x 4-45
- Infertility x 3-21
- Previous genital infections x 3-4
- Previous abdominal surgery x 1-4
Diagnosis of ectopic pregnancy

- Early and accurate diagnosis by non-invasive methods
- Symptoms and clinical examination
- Sensitive pregnancy test
- Transvaginal sonography has largely replaced laparoscopy
- Serum markers
- Progesterone
Diagnosis of ectopic pregnancy by vaginal ultrasonography in combination with a discriminatory serum hCG level of 1000 IU/L (Cacciatore et al. 1990)

- Sensitivity 97%
- Specificity 99%
- Positive predictive value 98%
- Negative predictive value 98%
Serum markers

• Creatinine kinase, fetal fibronectin, glycodelin, smooth muscle heavy-chain myosin, leukaemia inhibitory factor, tumor necrosis factor, IL-8

• The ideal marker would be specific for tubal damage or only be present following endometrial implantation
Progesterone

• >25 ng/ml (80 nmol/l) normal intrauterine pregnancy in 98%
• <5 ng/ml (16 nmol/l) identifies a nonviable pregnancy, regardless of location (Stovall T et al., 1992)
Treatment of tubal pregnancy

• Surgical
  – Laparoscopic / open
  – Radical / conservative

• Medical
  – Systemic
  – Local (transvaginally, laparoscopically)

• Expectant
Surgical treatment

• Salpingectomy
  – Uncontrolled bleeding, recurrent EP, severely damaged tube, a large tubal pregnancy
• Salpingostomy
• Fimbrial expression
• Segmental resection
Salpingostomia
Tubal resection
Salpingectomy
Medical treatment

- Methotrexate, prostaglandins, hyperosmolar glucose, potassium chloride, sodium chloride, actinomycin D, etoposide, mifepristone, danazol, anti hCG antibodies
Treatment results

• Short-term outcome
  – Primary treatment success
  – Need for reinterventions

• Long-term outcome
  – Tubal patency
  – Future fertility
Hajenius, PJ; Mol BWJ; Bossuyt, PMM; Ankum, WM; Van der Veen, F:

Interventions for tubal ectopic pregnancy

Cochrane Database of Systematic Reviews
3, 2003
Studies included
(Cochrane Database of Systematic Reviews 3, 2003)

• 39 randomized controlled studies
• 22 comparisons been described
  – 5 in surgical treatment
Surgical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

• **Laparoscopic conservative surgery/open conservative surgery** (Vermesh –89, Lundorff –91, Murphy –92)
  – 3 studies, n=228
  • Higher persistent trophoblast rate in laparoscopic surgery (RR 3.6)
  • No significant differences in tubal patency
  • No significant differences in IUP or EP
  • **Operation time, perioperative blood loss, analgesic requirements, hospital stay and convalescence time were significantly shorter or less in laparoscopic surgery**
Surgical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

• Salpingostomy without tubal suturing/salpingostomy with tubal suturing (Tulandi –91)
  - n = 34
  - No significant differences in postoperative course, IUP, EP
Surgical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

- Salpingostomy combined with a single dose intramuscular methotrexate/salpingostomy alone (Graczykowski –97)
  - n=116
  - Incidence of persistent trophoblast with additional intervention was reduced with methotrexate (RR 0.19)
  - No data of tubal patency or future fertility
  - Mean serum hCG clearance time did not differ
  - 5.5% mild side-effects with methotrexate
Surgical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

• Laparoscopic salpingostomy with use of vasopressin/laparoscopic salpingostomy alone (Ugur –96)
  – N=40
  – Vasopressin reduced the need for electrocoagulation for hemostasis ( RR 0.36) and significantly shorter operation time ( 68 vs 88 minutes)
  – No differences in primary treatment success and tubal preservation or conversions to open surgery
  – No differences in tubal patency
Surgical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

- Laparoscopic salpingotomy with intramesosalpingeal injection of 20 IU oxytocin diluted in 20 ml saline / laparoscopic salpingotomy with intramesosalpingeal injection of 20 ml saline (Fedele –98)
  - N=25
  - Oxytocin reduced significantly intra- and postoperative blood loss with an easier removal of the tubal pregnancy (p<0.05)
  - No differences in primary treatment success
  - No data of tubal patency or future fertility
Surgical treatment

• No randomized controlled trials that specifically compare laparoscopic (or open) salpingectomy and salpingostomy

• The reviews suggest that there is no increase in the subsequent intrauterine pregnancy after salpingostomy compared with salpingectomy
Medical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

  - n=100
  - No differences in primary treatment succes and tubal preservation
  - No significant differences in tubal patency rate or fertility outcome
  - Health related quality of life was more severely impaired after systemic methotrexate
  - Systemic methotrexate less expensive if an initial s-hCG <1500 IU/l
Medical treatment

(Cochrane Database of Systematic Reviews 3, 2003)

• Systemic methotrexate in a single dose intramuscular regimen /laparoscopic salpingostomy (Fernandez -98, Saraj -98, Sowter -99)
  – n=207
  – Methotrexate in a single single dose regimen was significantly less successful (RR 0.83)
  – With additional methotrexate injections no differences in treatment success (RR 1.1)
  – No significant differences in tubal patency rate or fertility outcome
Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies (Lipscomb et al., 1999)

- 81% (283/350) received one dose of methotrexate
- 17% (60/350) received two doses
- 2% (6/350) received three doses
- 1 woman received four doses
- 82% (261/320) of the successfully treated women received only one dose

- S-progesterone concentrations and the frequency of fetal cardiac activity were higher among women who required more than one dose of methotrexate (p<0.001)
Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies (Lipscomb et al., 1999)

<table>
<thead>
<tr>
<th>S-hCG (mIU/ml)</th>
<th>Success rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10000</td>
<td>94</td>
</tr>
<tr>
<td>&gt; 15000</td>
<td>68</td>
</tr>
</tbody>
</table>

- A high S-hCG is the most important factor associated with failure of treatment with a single dose methotrexate protocol
- No relation between women’s age or parity, the size of the conceptus or the presence of fluid in the peritoneal cavity and the efficacy of treatment
- Fetal cardiac activity was present in 12% of the successfully treated cases and 30% of those in which treatment was not successful (p=0.01)
Complications and side effects of methotrexate

- Transient pelvic pain
- Bone marrow suppression
- Hepatotoxicity
- Stomatitis and gastritis/enteritis
- Pulmonary fibrosis
- Alopecia
- Photosensivity
Reproductive outcome after methotrexate treatment of tubal pregnancies

Amélie Gervaise, M.D., Laurent Masson, M.D., Renaud de Tayrac, M.D., René Frydman, M.D., and Hervé Fernandez, M.D.

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Cumulative intrauterine pregnancy rate.

Medical treatment

- Methotrexate-mifepristone (n=113) /methotrexate-plasebo (n=99) (Rozenberg et al., 2003)
  - Methotrexate 50 mg /m² i.m., mifepristone 600mg p.o.

- Success rate 79.6% / 74.2%  RR:1.07
- Interaction between progesterone level and effect of treatment
- Progesterone >10 ng/ml
  - Success rate 83.3% / 38.5%
Expectant management

• The overall efficacy of expectant management was 69.2% in 10 prospective studies (Yao et al., 1997)

• The role of expectant management in those with known ectopic pregnancy is limited because of its risks compared with efficacy and accessibility of methotrexate or surgical treatment
Kohdunulkkoisen raskauden hoitosuositus. Duodecim 1998;114(22):2367-2375
Treatment of ectopic pregnancy in Tampere University Hospital

• Sopanen et al., 1994
  – 1987-1991, n=133 treated by laparoscopy
  – Salpingostomia  112 (84%)
  – 50%-glucose injection  14 (11%)
  – Expression or tubal abortion  7 (5%)
• Success rate  116 (87%)
Treatment of ectopic pregnancy in Tampere University Hospital

- Saarelainen, 2003
  - 2000-2002, n=185, ectopic pregnancy
  - **Operative treatment** n=114 (62%), laparoscopically n=99 (87%)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>N</th>
<th>Success %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salpingectomia</td>
<td>99 (87%)</td>
<td>100</td>
</tr>
<tr>
<td>Salpingostomia</td>
<td>12 (10%)</td>
<td>83,3</td>
</tr>
<tr>
<td>Expression or tubal abortion</td>
<td>3 (3%)</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>41 (22%)</td>
<td>75,6</td>
</tr>
<tr>
<td>Expectant</td>
<td>30 (16%)</td>
<td>87,6</td>
</tr>
</tbody>
</table>
Comparison of treatments

• Surgical treatment
  – Risks of anesthesia
  – Operative complications

• Medical treatment
  – No histological confirmation
  – Follow-up time and examinations
  – Side-effects
  – Impaired quality of life
Conclusion

• A combination of transvaginal ultrasound and serum hCG can reliably diagnose EP in most women
• Surgical treatment: laparoscopic salpingostomy/salpingectomy?
• Intramuscular injection of methotrexate is an alternative to surgical treatment in selected patients
• Expectant management in selected patients
• The choice between the treatments together with the patient