Ultrasound diagnosis and clinical management of ectopic pregnancy

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Ultrasound Diagnosis of Ectopic Pregnancy

- Transvaginal sonography (TVS) is an accurate diagnostic test for ectopic pregnancy with a high sensitivity (87.0-99.0%) and specificity (94.0-99.9%)

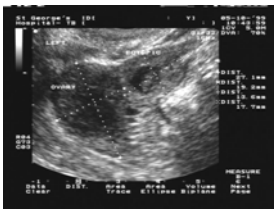
  Braffman et al., 1994, Shalev et al., 1998, Atri et al., 2003, Condous et al., 2005

- Diagnosis based on positive visualisation of an extra-uterine pregnancy, rather than the inability to visualise an intra-uterine pregnancy

Appearance of an Ectopic Pregnancy on TVS

<u>Tubal</u>

Gestational sac and CRL

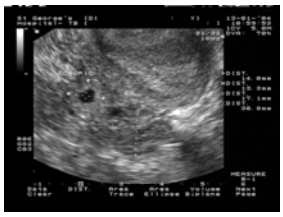


Visible cardiac activity

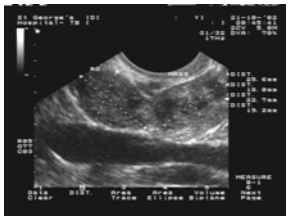
Appearance of an Ectopic Pregnancy on TVS

Tubal

'Bagel Sign'



Inhomogeneous Mass



Appearance of an Ectopic Pregnancy on TVS

Non - Tubal

Cervical

- An empty endometrial cavity, with a gestational sac present below the level of the uterine arteries.
- An absent "sliding sign".
- Visible blood flow around the gestation sac using colour Doppler

Appearance of an Ectopic Pregnancy on TVS

Non - Tubal

Interstitial

- An empty endometrial cavity with products of conception located outside of the endometrial echo, surrounded by a continuous rim of myometrium, within the interstitial area.

Appearance of an Ectopic Pregnancy on TVS

Non - Tubal

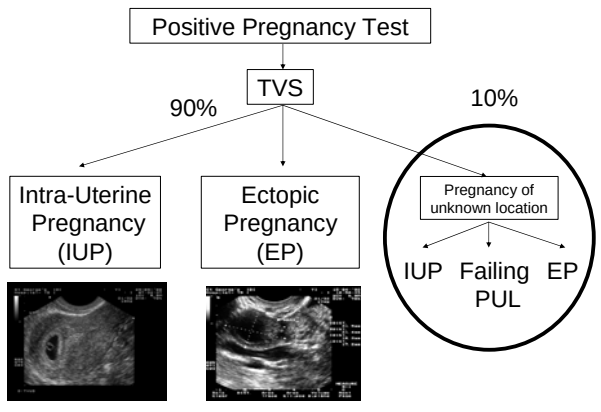
Caesarean Section Scar

- An empty endometrial cavity and cervical canal with a gestational sac implanted within the lower anterior segment of uterine wall
- Evidence of myometrial dehiscence

Diagnosis on the initial TVS examination?

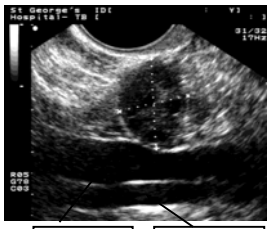
- Studies reporting high sensitivities examined women using TVS immediately prior to laparoscopy, and correlated sonographic features to surgical findings

- Results are therefore possibly misleading as not all ectopic pregnancies would have been visualised on the initial TVS examination



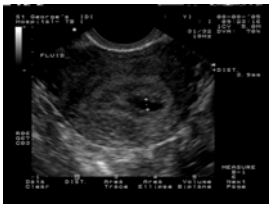
Pregnancy of Unknown Location (PUL)

- Positive pregnancy test
- No pregnancy visualised on scan
- Not interchangeable with 'ectopic pregnancy'



Early Intra-uterine Gestational Sac

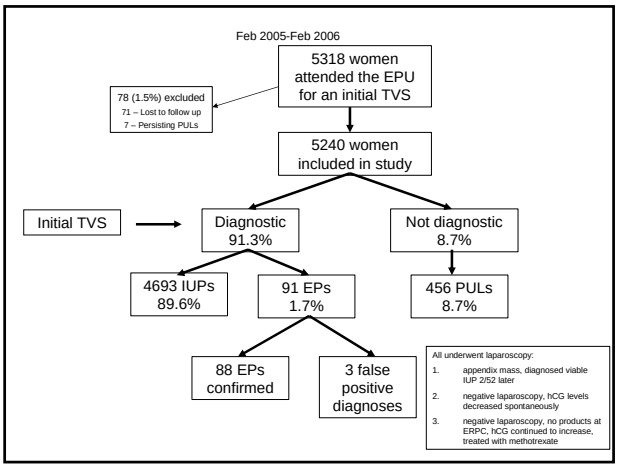
Fluid in the endometrial cavity

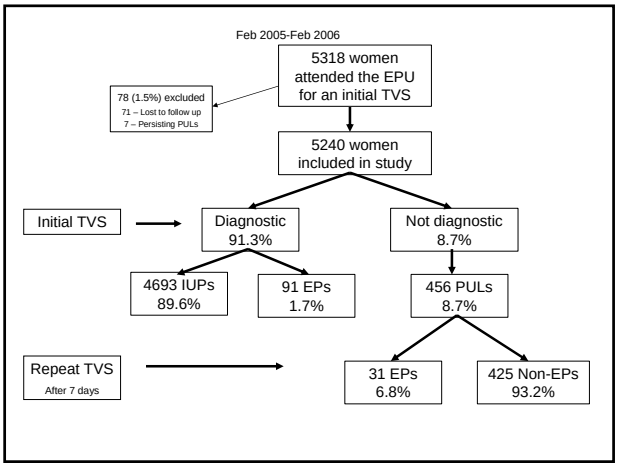


Diagnostic effectiveness of the initial TVS to diagnose ectopic pregnancy

- A prospective observational study including all women attending the Early Pregnancy Unit with a positive pregnancy test over a one-year period
- Outcome measure = ectopic pregnancy
- The sensitivity, specificity, PPV, NPV and likelihood ratio with 95% confidence intervals (CI) for the initial USS to diagnose ectopic pregnancy were calculated

Kirk et al, Hum Reprod 2007





Sensitivity of TVS to detect ectopic pregnancy

- Initial TVS:
  - Sensitivity 73.9% (95% CI: 55.7 – 81.2%)
  - Specificity 99.9% (99.8-100.0%)
  - PPV 96.7% (91.6 – 99.2%)
  - NPV 99.4% (99.1 – 99.6%)
- Overall (including follow-up scans):
  - Sensitivity 98.3% (95% CI: 94.1 - 99.8%)
  - Specificity 99.9% (99.8 - 100.0%)
  - PPV 97.5% (92.9 - 99.5%)
  - NPV 100% (99.9 - 100.0%)

Why are some ectopic pregnancies missed on the initial scan?

	Initial TVS result		p-value
	Ectopic Pregnancy	PUL	
n	353	58	-
Maternal age (years) Mean (SD)	30.4 (5.9)	32.0 (6.3)	0.0551
Bleeding n (%)	216 (61.2)	39 (67.2)	0.4657
Pain n (%)	233 (66.0)	34 (58.6)	0.2997
ET mm Mean (SD)	10.1 (5.7)	11.1 (5.3)	0.098

Why are some ectopic pregnancies missed on the initial scan?

	Initial TVS result		p-value
	Ectopic Pregnancy	PUL	
Gestational age (days) Mean (SD)	45.6 (14.5)	41.4 (13.5)	0.0317
hCG IU/L Median (IQR)	1286 (3384, 478-3826)	635 (1796, 234-2030)	0.0010
Prog nmol/L Median (IQR)	19 (27, 9-36)	30 (26, 19-45)	0.0095

Why are some ectopic pregnancies missed on the initial scan?

	TVS to visualise ectopic pregnancy		**p-value**
	Initial TVS	**Subsequent TVS**	
hCG IU/L Median (IQR)	**1286 (3384, 473-3826)**	**1259 (2657, 340-2997)**	**0.2431**
Prog nmol/L Median (IQR)	**19 (27, 9-36)**	**20 (17, 11-28)**	**0.7334**
Appearance on TVS:			
Inhomogeneous mass n (%)	**222 (62.9)**	**25 (71.4)**	**0.1029**
Empty gestational sac n (%)	**77 (21.8)**	**9 (25.7)**	
Gestational sac with yolk sac/fetal pole n (%)	**54 (15.3)**	**1 (2.9)**	
Mean size of ectopic mass mm (SD)	**22.2 (9.3)**	**15.4 (5.3)**	**<0.0001**

Why are some ectopic pregnancies missed on the initial scan?

- Compared to ectopic pregnancies visualised on the initial TVS, ectopic pregnancies initially classified as PULs had:
  - Lower mean gestational age
  - Lower mean initial hCG,
  - Higher mean progesterone level at presentation
- However, at the time of visualization: serum hCG, serum progesterone levels and the appearance were not significantly different between the two groups

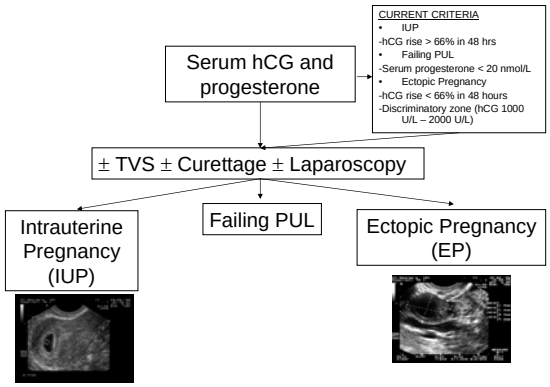
Why are some ectopic pregnancies missed on the initial scan?

- Failure of visualization of the ectopic pregnancy on the initial TVS may be due to the fact that they are too small and probably too early in the disease process

Diagnosis of ectopic pregnancies in PUL population

1. Hormones
2. Surgical intervention
3. Mathematical models

PUL Management



1. Hormones

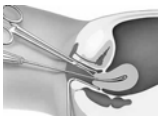
- Human chorionic gonadotrophin (hCG)
- Progesterone
- Other:
  - CA 125
  - Creatine kinase
  - Activin A
  - Inhibin A

2. Surgical Intervention

- Laparoscopy

- The combination of a positive pregnancy test and the absence of an IUP on TVS is an accepted indication for laparoscopy

- Curettage

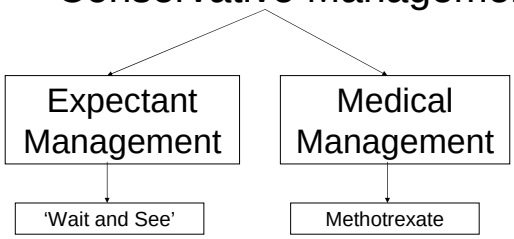


- Serial measurements of hCG and progesterone, TVS and uterine curettage have been combined into various diagnostic algorithms when a pregnancy cannot be seen on TVS

3. Use of mathematical models

- Mathematical models have been developed to predict the outcome of PULs
- They do not require any understanding of the behaviour of serum biochemistry in early pregnancy and could possibly lead to more standardised management protocols

Conservative Management

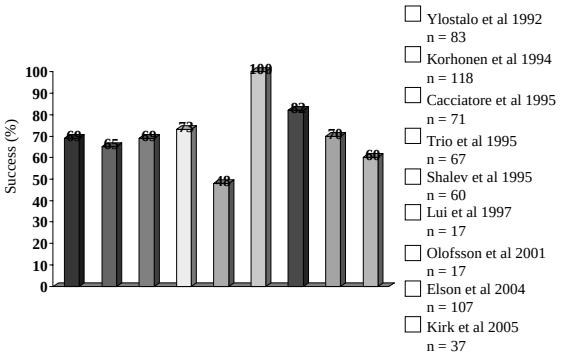


Expectant Management

- In select women it is safe and effective
- Close follow up and out-of-hours emergency back up is essential
- Some units offer expectant management to > 60% of their EPs
  Elson et al 2004

Expectant Management

1. Published studies



Expectant Management

2. Success rates

- Rates vary due to different inclusion criteria:
  - Some include PULs rather than sonographically or laparoscopically visualised EPs
  - Some select women on the basis of serum hCG and progesterone levels which is likely to affect overall success rates

Expectant Management

3. Predictors of success

- Lower serum hCG levels
- Low serum progesterone
- Decrease in trend of hCG levels
- Absence of an ectopic gestation sac
- Longer time from LMP
- TVS monitored decrease in size of the EP

Trio et al 1995, Atri et al 2001, Cacciatore et al 1995

Expectant Management

4. Reproductive Outcome

- 93% tubal patency on hysterosalpingogram
- Subsequent IUP rates 63-88%
- Repeat EP in 4-5%
- Similar subsequent IUP rates in those undergoing delayed surgery due to failed expectant management compared to those undergoing primary surgery

Rantala 1997, Fernandez 1991, Zohav 1996, Stobelt 2000

Expectant Management

5. Comparison to other treatments

- One randomised trial comparing expectant management to oral methotrexate
- No significant difference in primary success

Korhonen et al 1996

Medical Management

Methotrexate first used in the 1980s for management of ectopic pregnancy

Systemic	Single Dose Multiple Dose IV Oral
Local	TVS guided injection Laparoscopic injection

Medical Management

1. Single Dose Protocol

- Single intramuscular dose of 50mg/m^2

Day 1- hCG,FBC, U+Es, LFTs
Methotrexate administration
Day 4 - hCG
Day 7 - hCG, FBC, U+Es, LFTs

- If hCG decrease < 15 % day 4-7 - repeat dose
- If hCG decrease > 15 % day 4-7 - repeat hCG weekly until < 15 U/L

Stovall et al 1993

Medical Management

2. Inclusion Criteria

- Asymptomatic
- ? Cutoff hCG level
  - Success reported when hCG > 10,000
- ? Fetal cardiac activity
  - 12% had FH in those treated successfully

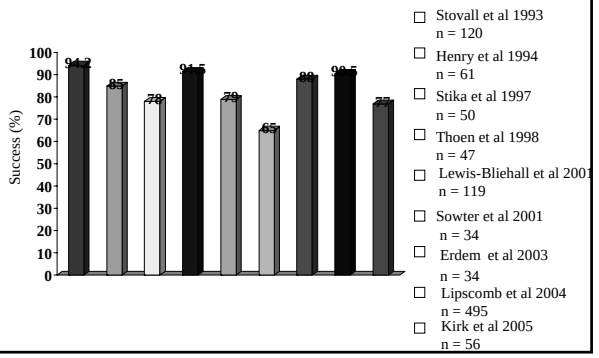
Lipscomb et al 1999

- ? Haemoperitoneum
  - 62% success rate in those with haemoperitoneum

Kumtepe et al 2004

Medical Management

3. Published Studies



Medical Management

4. Predictors of Success

- Initial Serum hCG
- Initial Serum Progesterone
- Trend in hCG levels
- TVS Findings
- Previous history of EP

Medical Management

5. Reproductive outcome

- 77-82% tubal patency on hysterosalpingogram
- > 80% subsequent pregnancy rates
- 13-24% EP rate

Glock 1994, Stovall 1993, Tolaymat 1999, Gervaise 2004

Medical Management

6. Comparison to other treatments

- Multiple dose methotrexate similar to salpingostomy
- Single dose methotrexate less effective than salpingostomy
- Lower direct costs with systemic methotrexate with low hCG levels compared to surgery

Hajenius 1997, Fernandez 1998, Saraj 1998, Mol 1999,Sowter 2001