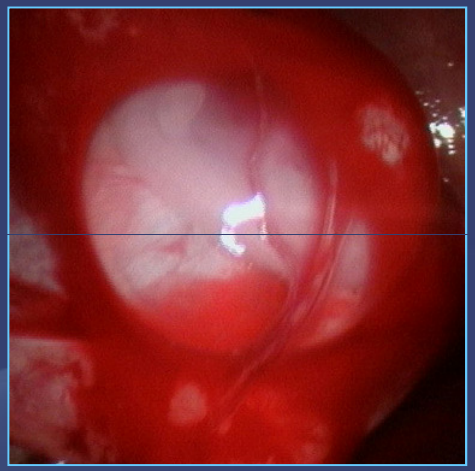
ESHRE Campus Leuven 20100226

Ectopic pregnancies

Patrick Puttemans
LIFE, Leuven, Belgium



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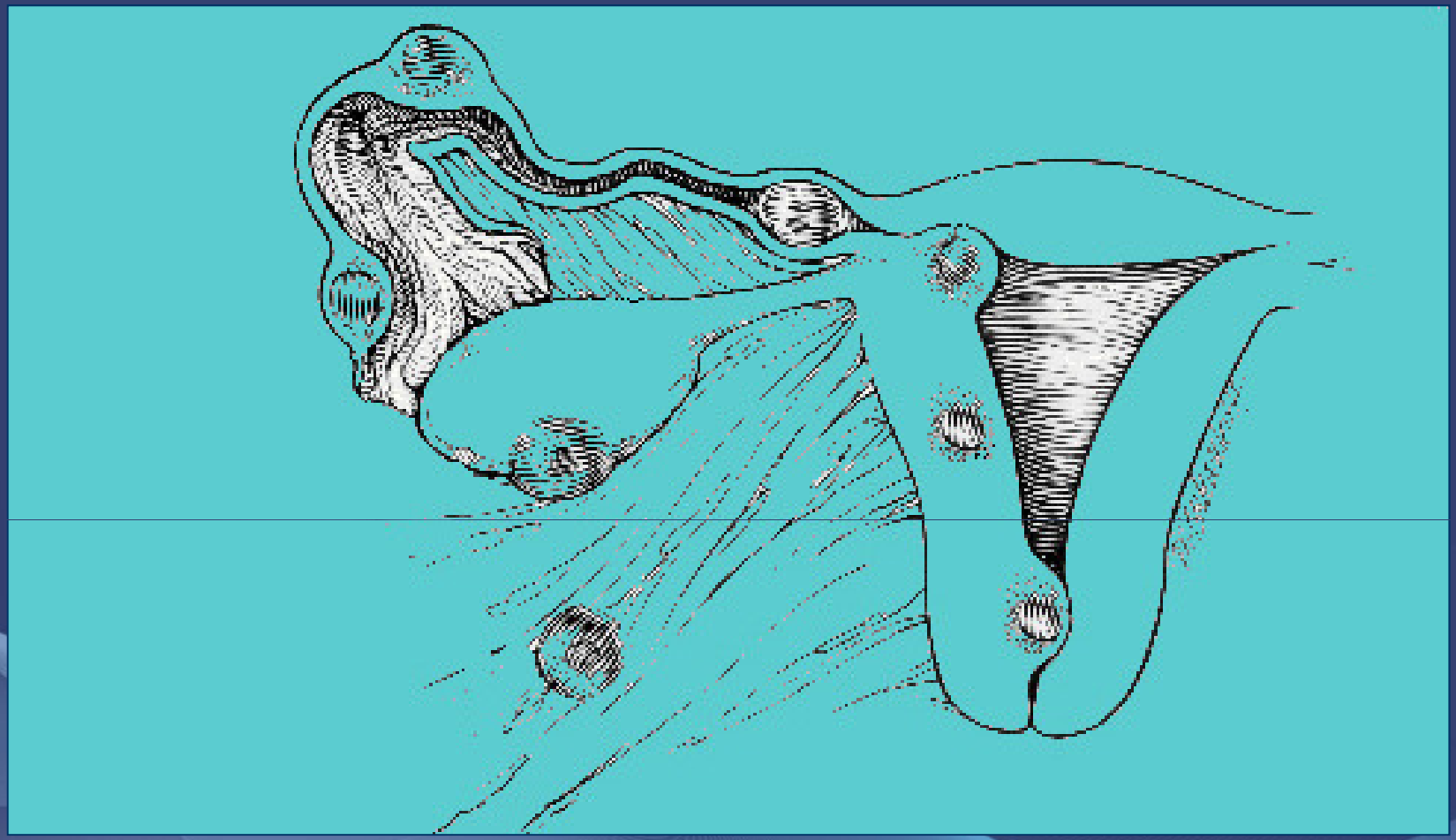
"ectopic" means "out of place"

outside the 'eutopic'
endometrial lining
of the uterine cavity
incidence 0,96 – 1,15%
of all spontaneous pregnancies

- Tubal (98,3%)
  - ampullary (80-90%)
  - isthmic (5-12%)
  - fimbrial (5-6%)
- Extratubal (<2%)
  - intramural (within serosal lining of the uterus)
    - cornual (0,5%)
    - in endocervical canal, e.g. in a previous caesarean section scar
    - intramyometrial, e.g. inside an area of adenomyosis
  - extramural (outside serosal lining of the uterus)
    - ovarian (0,15%)
    - abdominal (1,4%)

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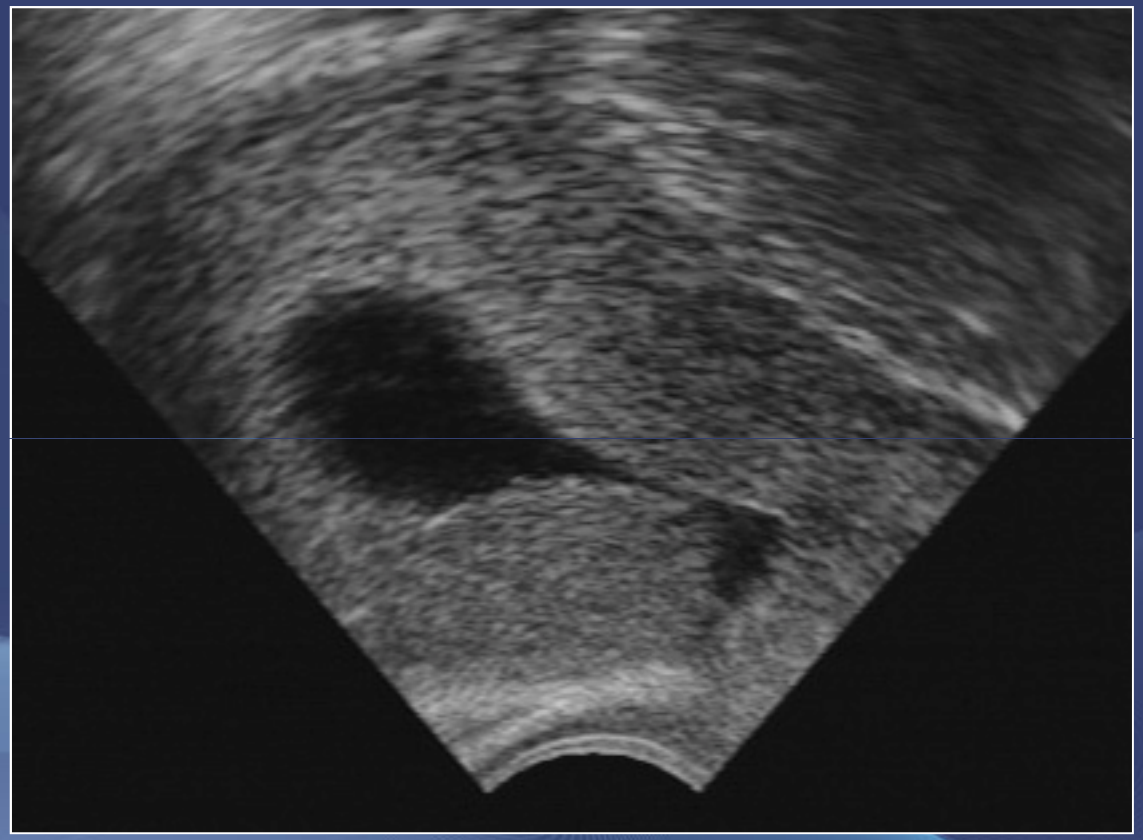
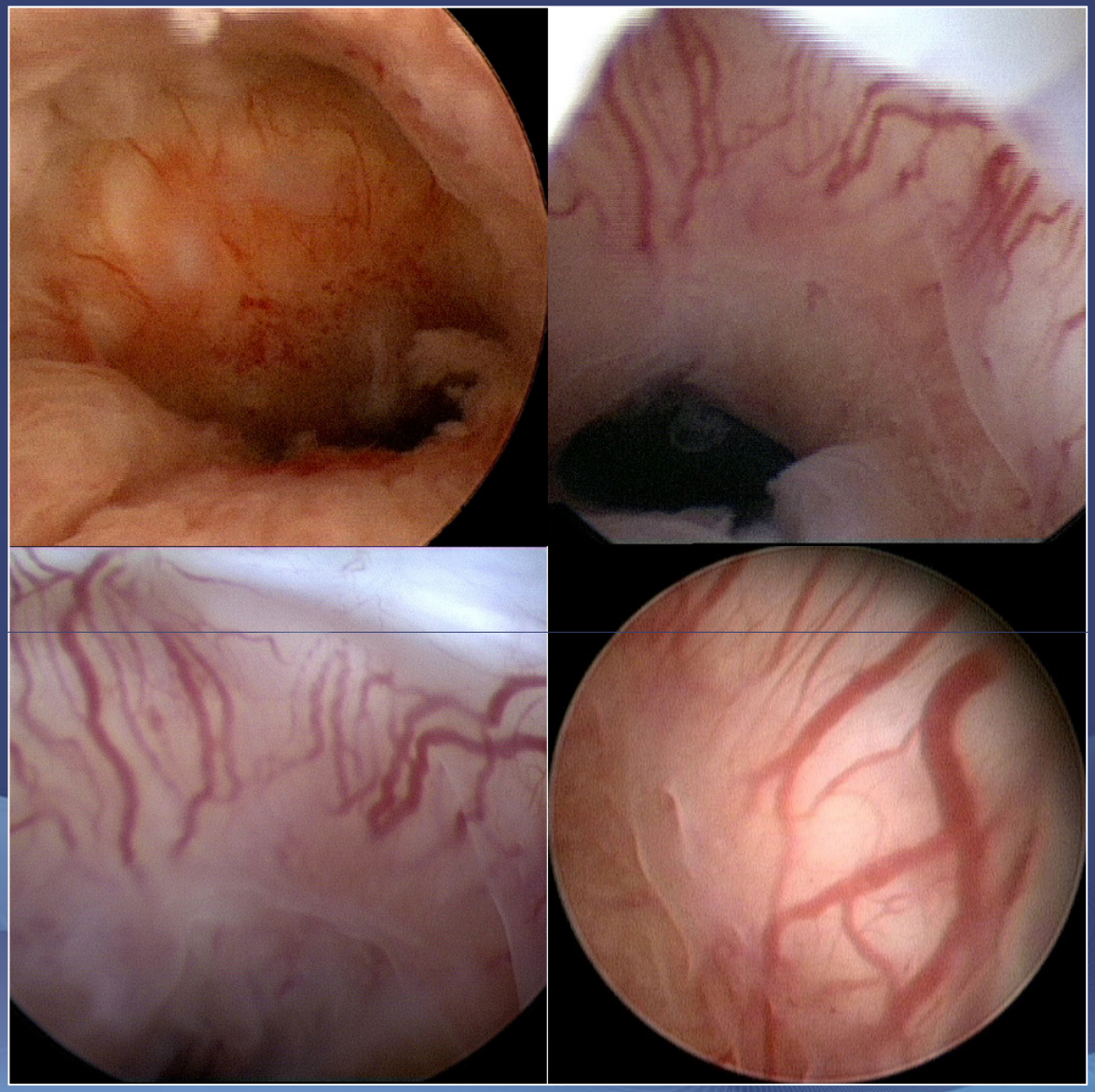
SIS following SC





Ectopic endometrium

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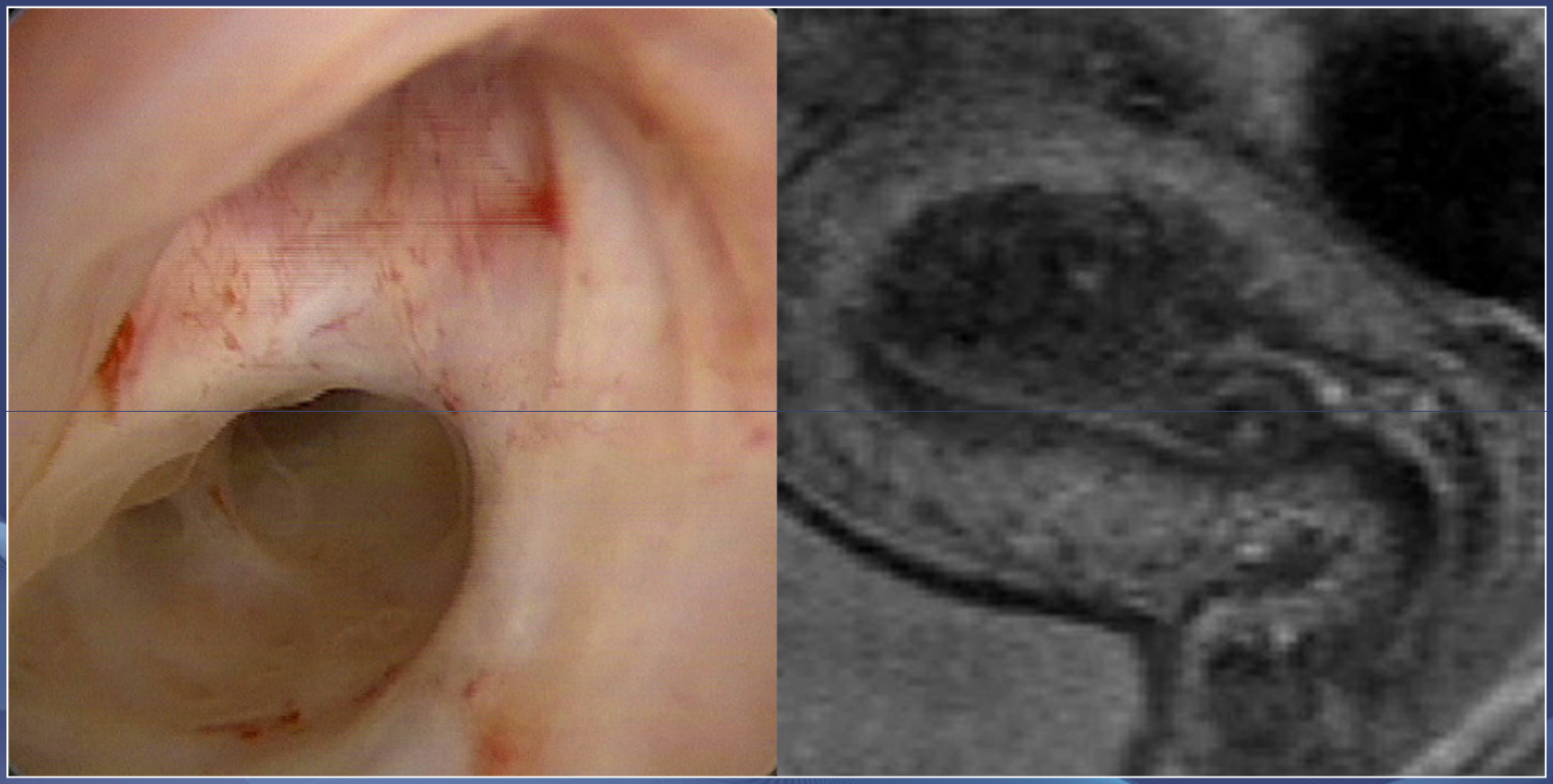
False route in adenomyosis



Intramural pregnancy
following embryo transfer

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US vs UK

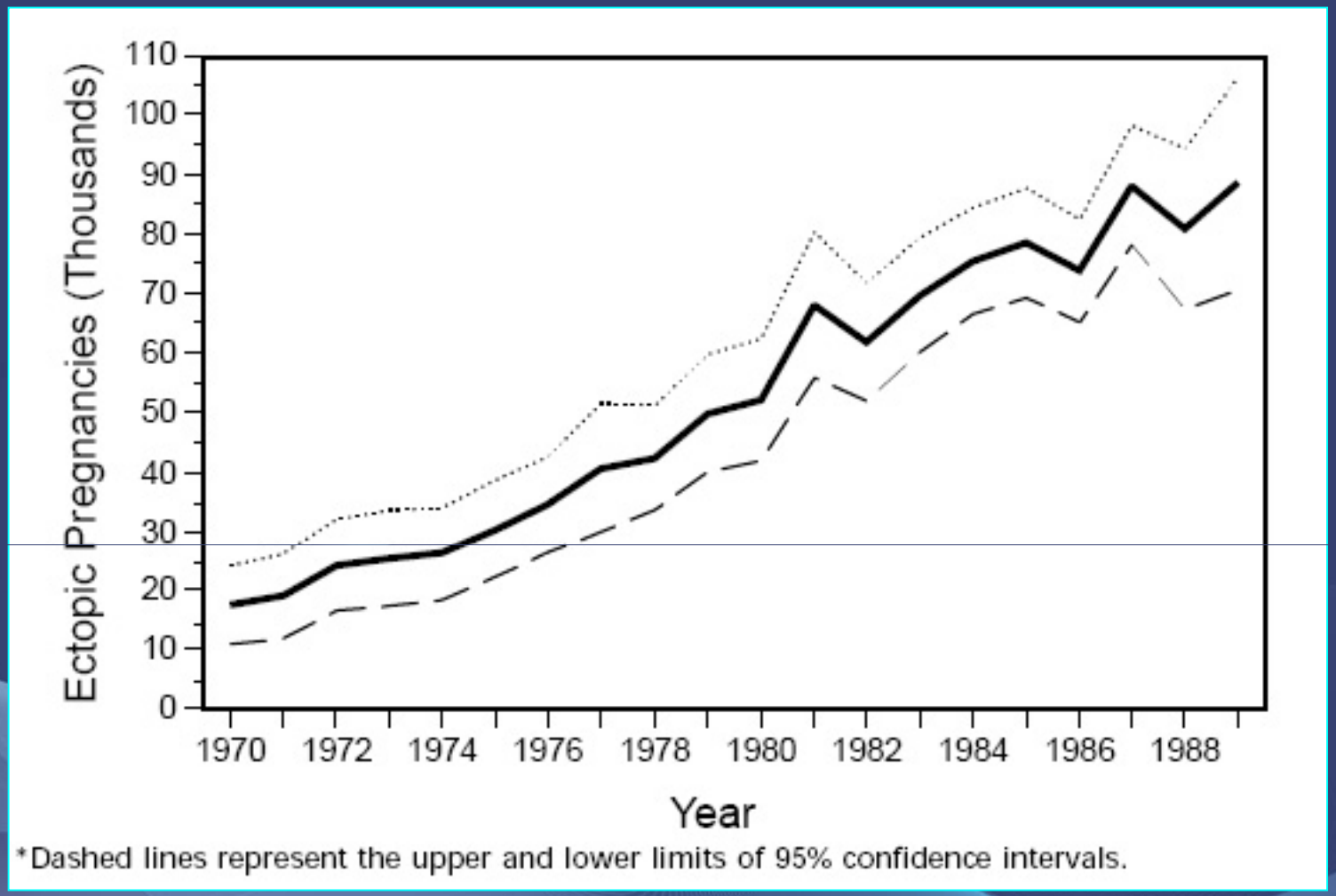
The Centers for Disease Control (CDC) examined ectopic pregnancies occurring during a 19 year period (1970-1989) in the US and noted that:

- the ectopic pregnancy rate increased almost 4-fold mainly due to STD (from 4.5 to 16.8 per 1,000 reported pregnancies)
- the fatality rate from ectopic pregnancies dropped by almost 90% (from 35.5 to 3.8 per 10,000 ectopics, 860 deaths in 1970-1989)
- ectopics were still the 2nd leading cause of maternal mortality in the US (accounting for 12% of all maternal deaths in 1987)

Over more recent years the incidence has remained static in the UK:

- 11.1 per 1,000 pregnancies, i.e. almost 32,000 ectopics annually ~ UK
- still 13 maternal deaths resulting from an ectopic in the UK 1997-1999
- 4th leading cause direct maternal deaths ~ 80% of first trimester deaths

CDC Surveillance Summaries, 17/12/1993, Vol. 42
Condous et al. 2004, Gynecol Surg, 1, 81-86



*Dashed lines represent the upper and lower limits of 95% confidence intervals.

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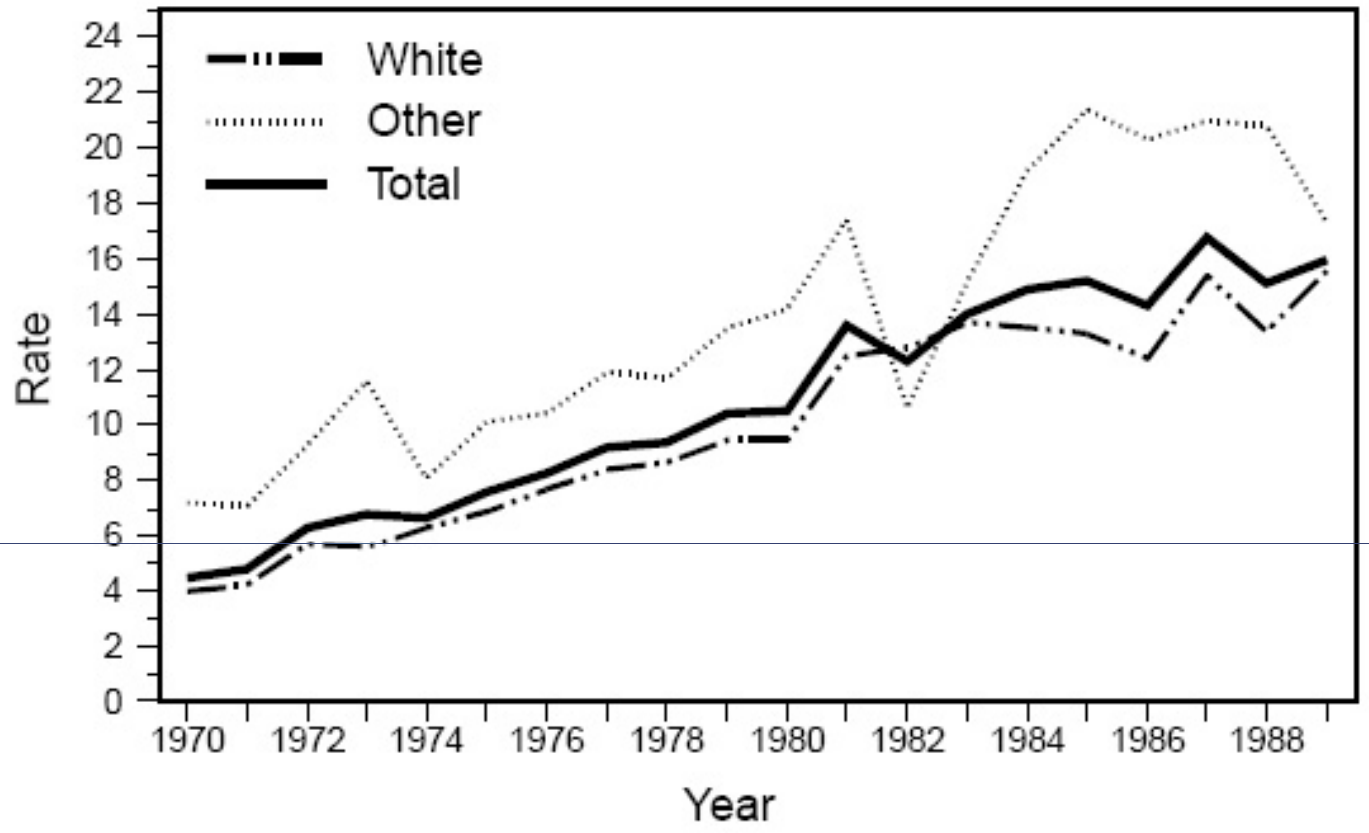
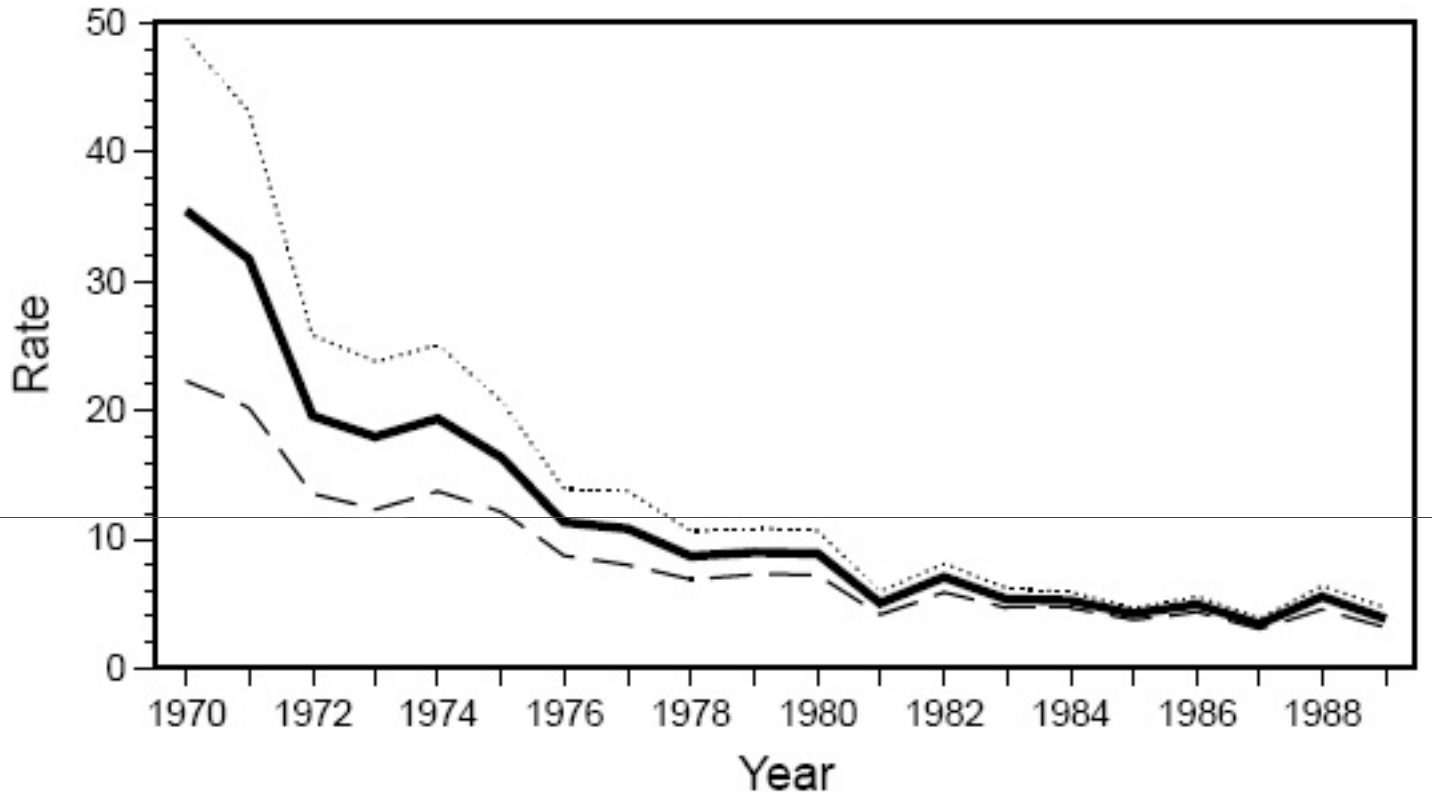
FIGURE 2. Rates* of ectopic pregnancy, by race —United States, 1970–1989



*Per 1,000 reported pregnancies (live births, legal abortions, and ectopic pregnancies).

FIGURE 5. Rates* of ectopic pregancy mortality — United States, 1970–1989



*Per 10,000 ectopic pregnancies. Dashed lines represent the upper and lower limits of 95% confidence intervals.

US vs UK

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CDC Surveillance Summaries, 17/12/1993, Vol. 42
Condous et al. 2004, Gynecol Surg, 1, 81-86

Risk factors

- a prior history of ectopic pregnancy
  (recurrence rate ~ 15% in case of 1 earlier EUP, ~ 25% in case of 2)
- a history of surgery on the fallopian tubes or within the pelvis
- a history of pelvic infection, i.e. salpingo-oophoritis or PID
- a history of infertility & the use of assisted reproductive technology
- a history of IUD use (cupper >> hormone IUD)
- a history of destruction of the cavity lining (e.g. Ashermann)
- a history of DES exposure in utero
- a history of non-infectious pelvic inflammation (e.g. endometriosis)
- salpingitis isthmica nodosa

Symptoms

- Asymptomatic (± 15%)
- Amenorrhea
- Abdominal Pain (30%)
- Vaginal Bleeding (13%)
- Pain and bleeding (37%)
- Syncope
- Shock
- Pelvic Mass

ß-hCG - Romero et al. 1986

- ß-hCG levels double every 48 hrs
- < 66% rise/48 hrs consistent with ectopic

  ⇨ PPV 80.7%, false positive rate 12.5% ⇦
- single determination not helpful enough
- reliable if done within same laboratory
- never rules out an ectopic

ß-hCG - Cacciatore et al. 1990

- In patients with an initial ß-hCG level exceeding 1000 IU/L, an intrauterine sac was found in all the intrauterine pregnancies but in none of the ectopic pregnancies.
- PUL + ß-hCG ≥1000 IU/L, a normal IUP can be ruled out.
- The use of this threshold in combination with sonographic detection of an adnexal mass is pathognomonic for an ectopic pregnancy.

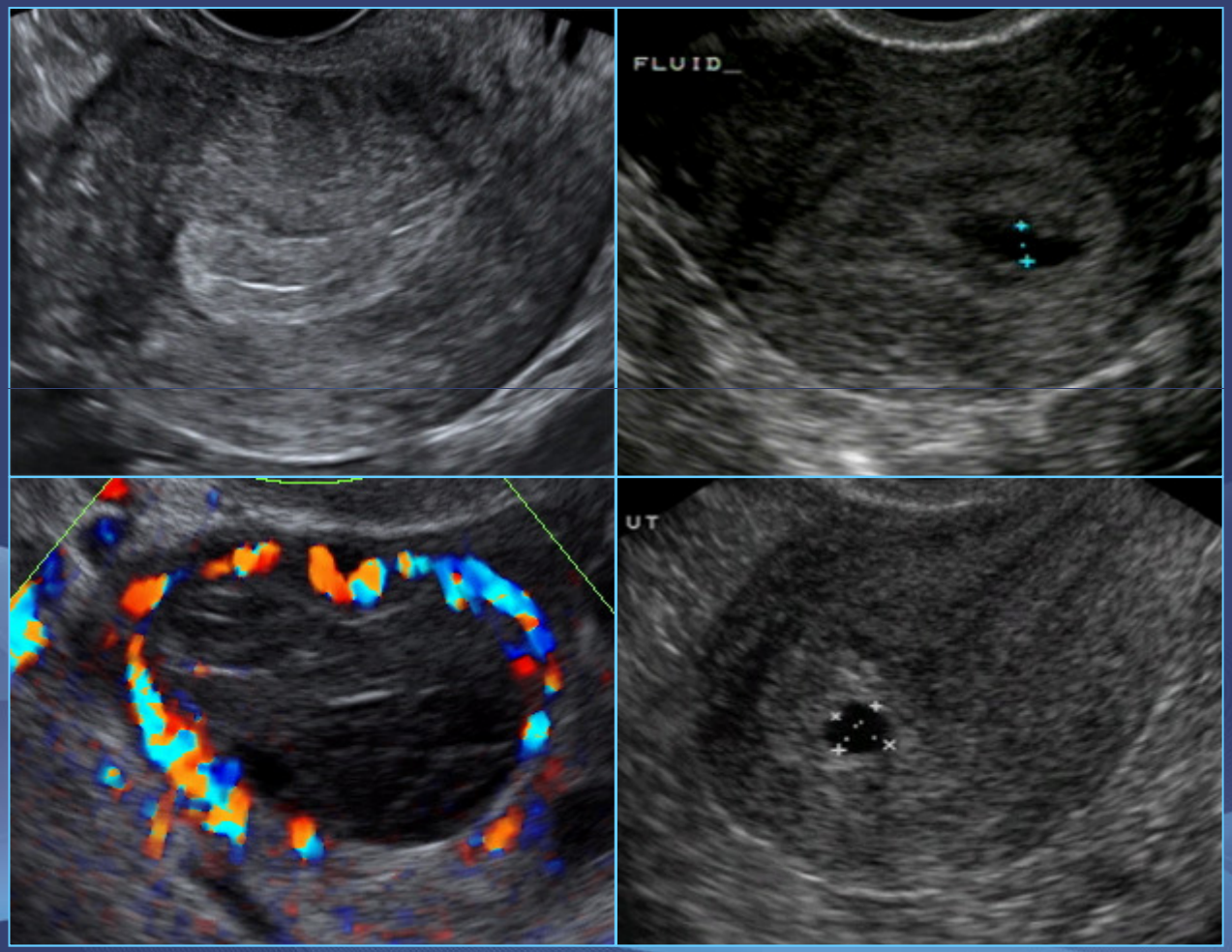
sensitivity 97%, specificity 99%, PPV 98%, NPV 98%

IUP at TvS

	$T_{vag}S$	$T_{abd}S$
Amniotic sac	4 - 5	5 - 6
Yolk sac	5 - 6	6 - 7
Embryo	5 - 6	6 - 7
Heart beat	5 - 6	6 – 7

weeks of pregnancy

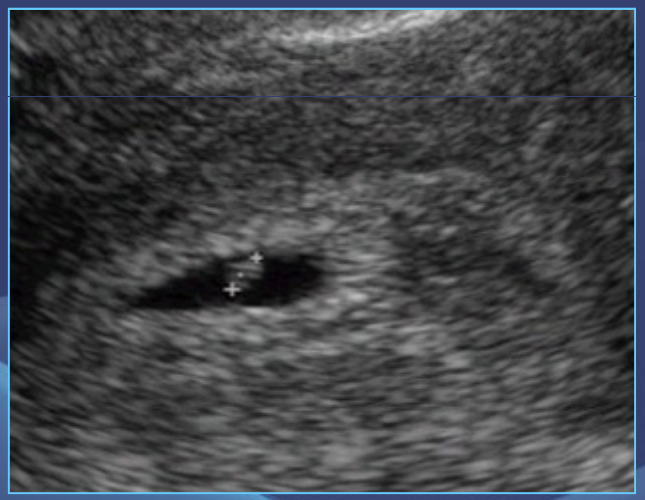
IUP at TvS - week 4 (32-34d)



images courtesy of Dirk Timmerman

IUP at TvS - week 5

- Amniotic sac grows 1 mm/day
- Yolk sac confirms IUP
- CRL 2 mm at the end of the 5th week
- positive heart beat



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How good is TvS in the detection of an ectopic pregnancy?

- Cacciatore et al. 1990, Br J Obstet Gynaecol
  - Sensitivity 93%, Specificity 99%, PPV 98%, NPV 96%
- Shalev et al. 1998, Fertil Steril
  - Sensitivity 87%, Specificity 94%, PPV 92,5%, NPV 90%
- Condous et al. 2005, Hum Reprod
  - Sensitivity 90,5%, Specificity 99,8%, PPV 92,1%, NPV 99,8%

Condous et al. 2004, Gynecol Surg

The diagnosis of ectopic pregnancy should not be based on an inability to visualise an IUP, but **on the positive visualization of an adnexal mass using high-resolution probes at TvS**. This should in turn result in **a decrease in the number of false positive laparoscopies**. If a pregnancy cannot be seen using TvS, then it is classified as a PUL, **10% of which are ectopic**. Misdiagnosis should be a rare event with the use of TvS. An EPU standard of care **can be judged by its false-positive and false-negative rates** for the diagnosis of an ectopic

Condous et al. 2005, Hum Reprod

The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery

George Condous[1,4], Emeka Okaro[1], Asma Khalid[1], Chuan Lu[2], Sabine Van Huffel[2], D Timmerman[3] and Tom Bourne[1]

- 6621 consecutive TvS
- 5840 (88,2%) ~ IUP
- 581 (8,8%) ~ PUL
- 200 (3,0%) ~ EUP
- 48 excluded ~ no AP
- leaving n=152 EUP/TvS

- 58% “blob sign”
- 7% viable EUP
- 6% non viable EUP
- 20% “bagel sign”
- i.e. 91% correct TvS
- 7,2% PUL
- 1,3 % IUP

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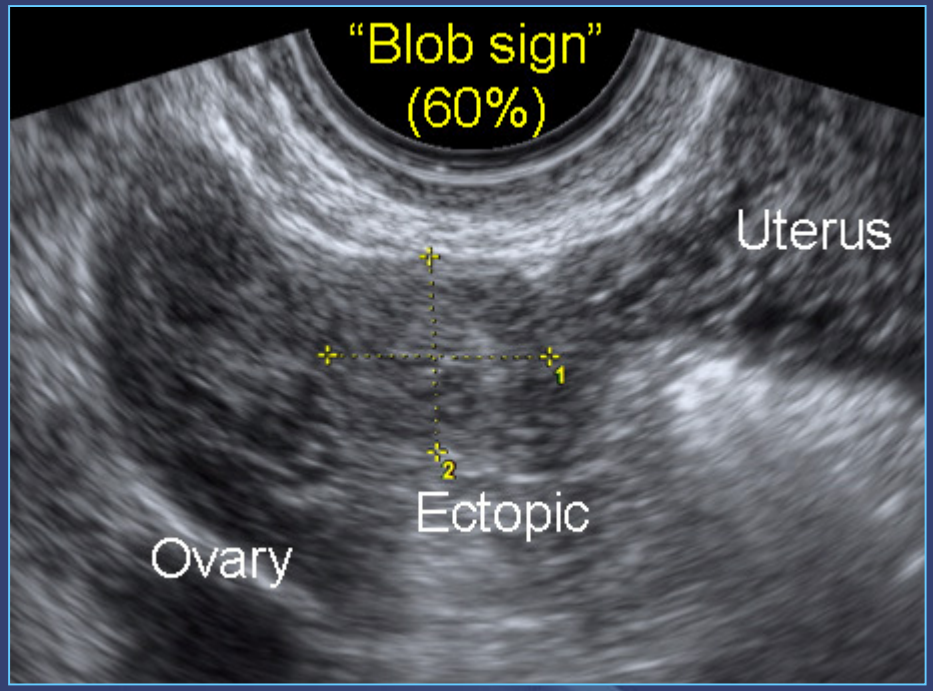

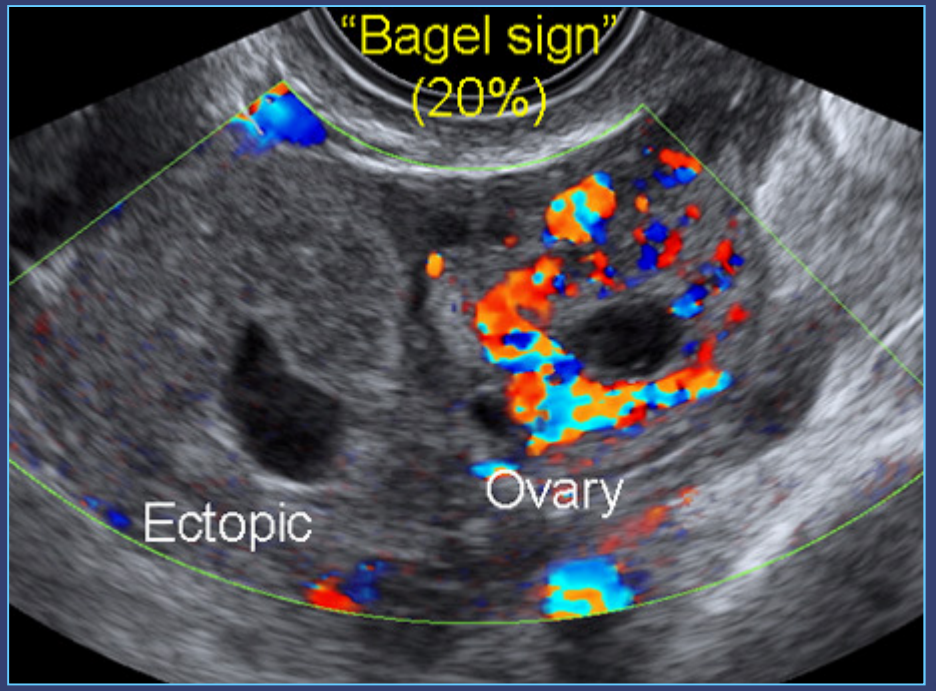

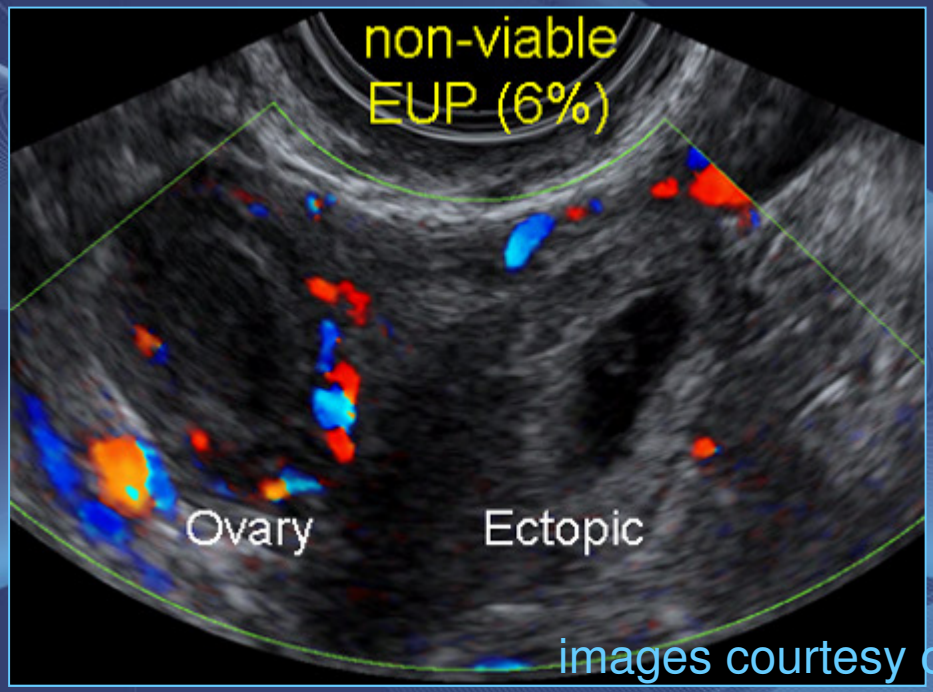

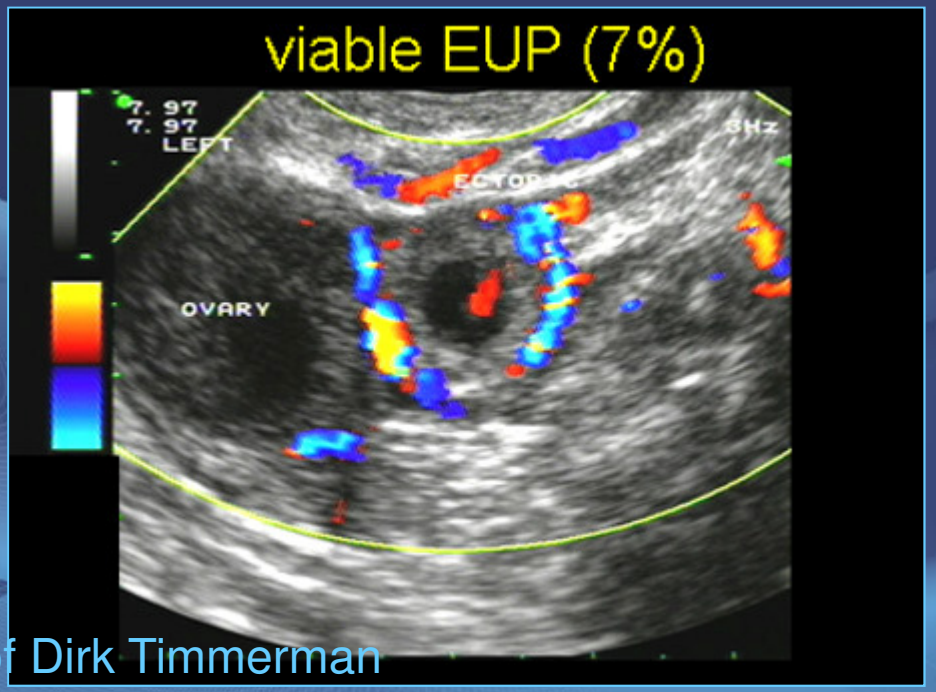

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Pregnancies of unknown location: consensus statement

G. CONDOUS*, D. TIMMERMAN†, S. GOLDSTEIN‡, L. VALENTIN§, D. JURKOVIC¶ and T. BOURNE**

% of PUL

Quality of TvUS is crucial:

- with experience the # of early IUP & EUP diagnoses will increase significantly
- % of PUL is inversely proportional to the quality of the TvS
- PUL rates must remain below 15%

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Culdocentesis … ? an old slide

- Highly specific if performed and interpreted correctly: presence of free-flowing, NON-clotting blood …
- A negative tap however is inconclusive …
- May obviate, i.e. render unnecessary, the use of sonography …
- Is most helpful in emergent situations to confirm a suspected diagnosis; remains controversial in literature …

Human Reproduction Vol.21, No.10 pp. 2706–2710, 2006
Advance Access publication June 21, 2006.

doi:10.1093/humrep/del223

There is no role for uterine curettage in the contemporary diagnostic workup of women with a pregnancy of unknown location

G.Condous[1,4], E.Kirk[1], C.Lu[2], B.Van Calster[2], S.Van Huffel[2], D.Timmerman[3] and T.Bourne[1]

Single hormonal markers

Single hormone measurement 0 h	PUL outcome	Area Under ROC Curve	Sensitivity	Specificity
Prog < 20 nmol/L	Failing PUL	0.952	87.2%	89.6%
hCG > 1000 IU/L	Ectopic	0.666	21.6%	87.3%
hCG > 1500 IU/L	Ectopic	0.666	18.9%	93.4%
hCG > 2000 IU/L	Ectopic	0.666	13.5%	95.2%

Condous et al., Hum Reprod 2004

& Ultrasound Obstet Gynecol 2005

Condous et al. 2004, Int J Gynaecol Obstet

- Serum hCG and progesterone levels at defined times can be used to predict the immediate viability of a PUL, but cannot be used reliably to predict its location.
- Clinical experience does not significantly improve the ability to assess PUL outcome

Hum. Reprod. Advance Access published April 10, 2009

Human Reproduction, Vol.0, No.0 pp. 1–7, 2009

doi:10.1093/humrep/dep084

human reproduction

ORIGINAL ARTICLE *Early pregnancy*

The optimal timing of an ultrasound scan to assess the location and viability of an early pregnancy

C. Bottomley[1,5], V. Van Belle[2], F. Mukri[1], E. Kirk[3], S. Van Huffel[2], D. Timmerman[4], and T. Bourne[1,3,4]

- The ability to confirm viability or non-viability is significantly related to gestational age.
- In asymptomatic women with no previous ectopic pregnancy TvS should be delayed ~ 49 days.
- Their data suggest that this would reduce the number of inconclusive scans, without an associated increase in morbidity from missed ectopic pregnancies.

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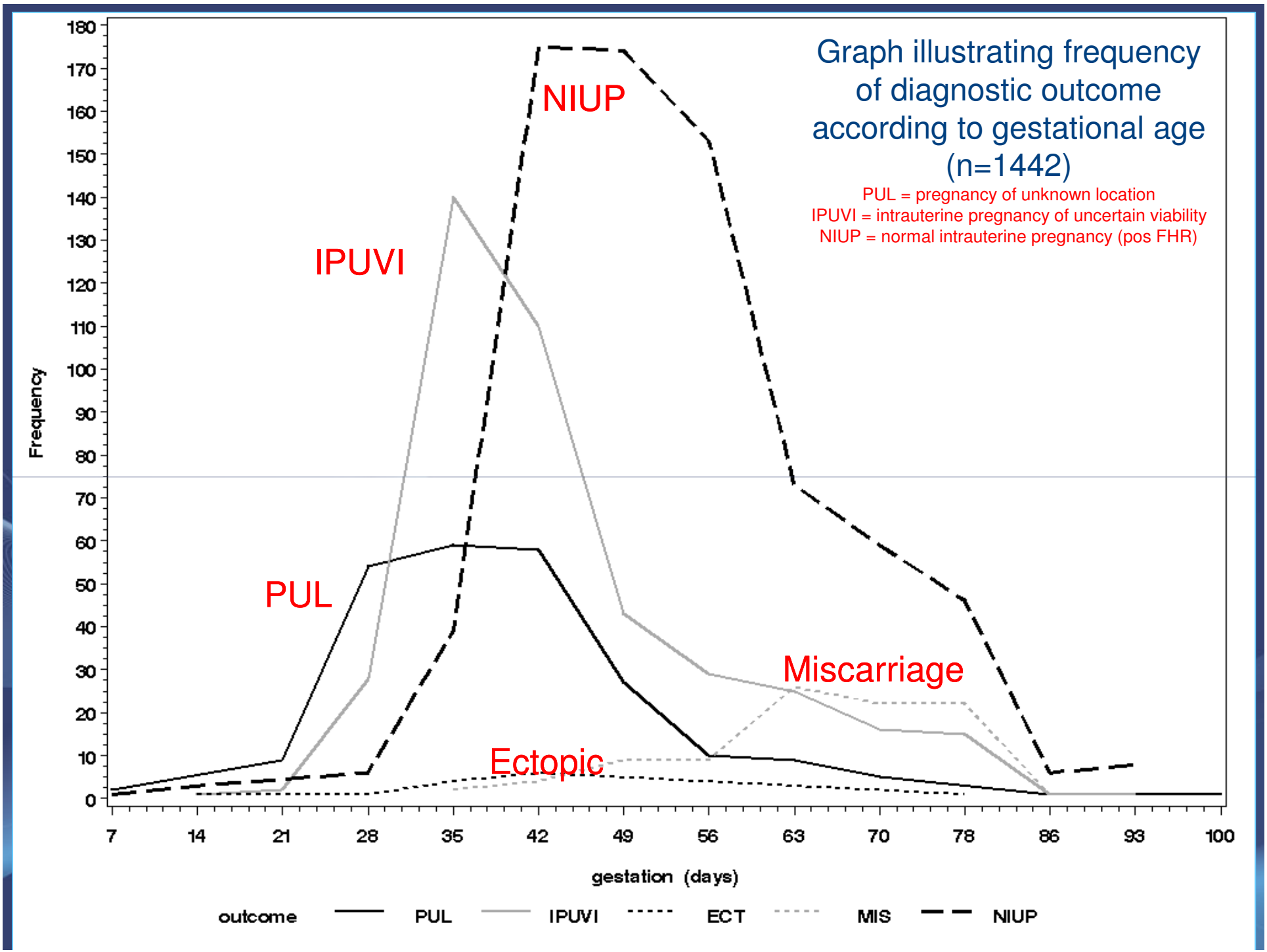
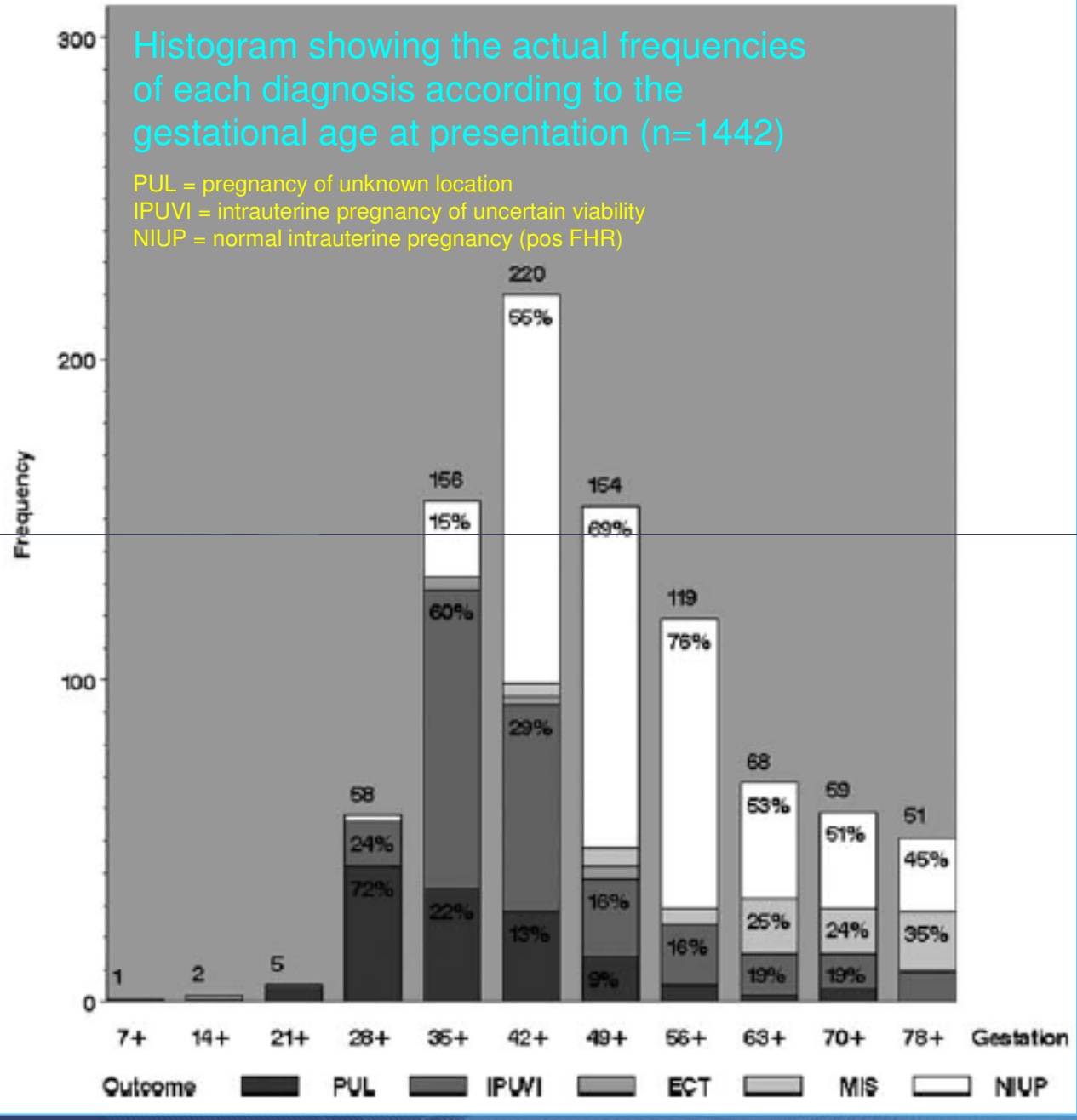

Graph illustrating frequency of diagnostic outcome according to gestational age (n=1442)
PUL = pregnancy of unknown location
IPUVI = intrauterine pregnancy of uncertain viability
NIUP = normal intrauterine pregnancy (pos FHR)
NIUP
IPUVI
PUL
Miscarriage
Ectopic
Frequency
gestation (days)
outcome
PUL
IPUVI
ECT
MIS
NIUP

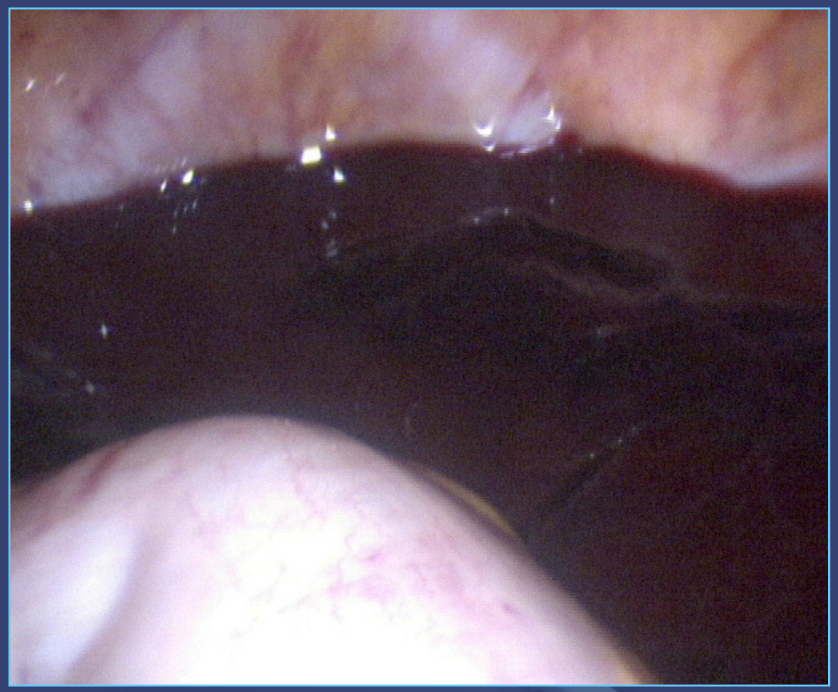
Histogram showing the actual frequencies of each diagnosis according to the gestational age at presentation (n=1442)

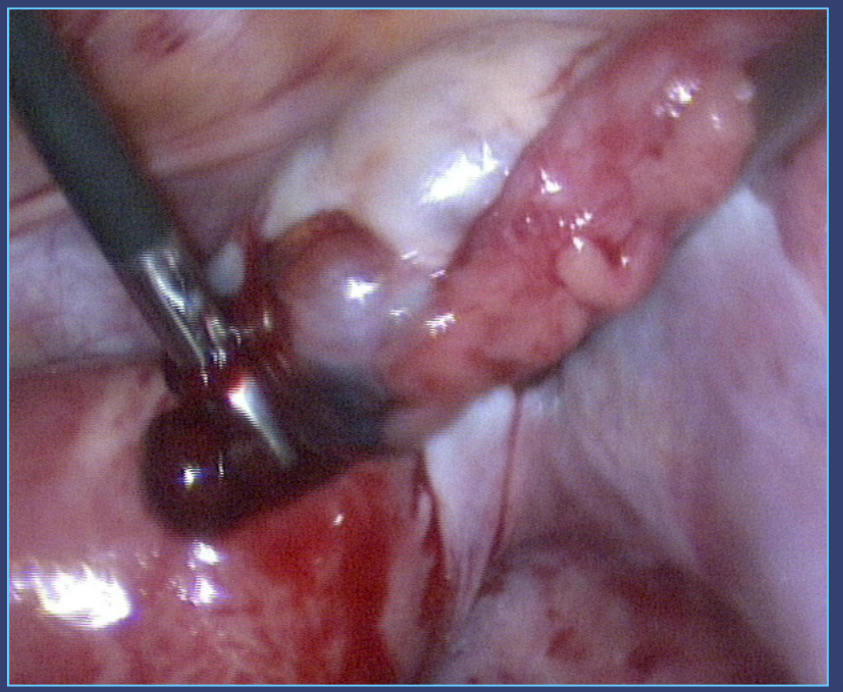
PUL = pregnancy of unknown location
IPUVI = intrauterine pregnancy of uncertain viability
NIUP = normal intrauterine pregnancy (pos FHR)

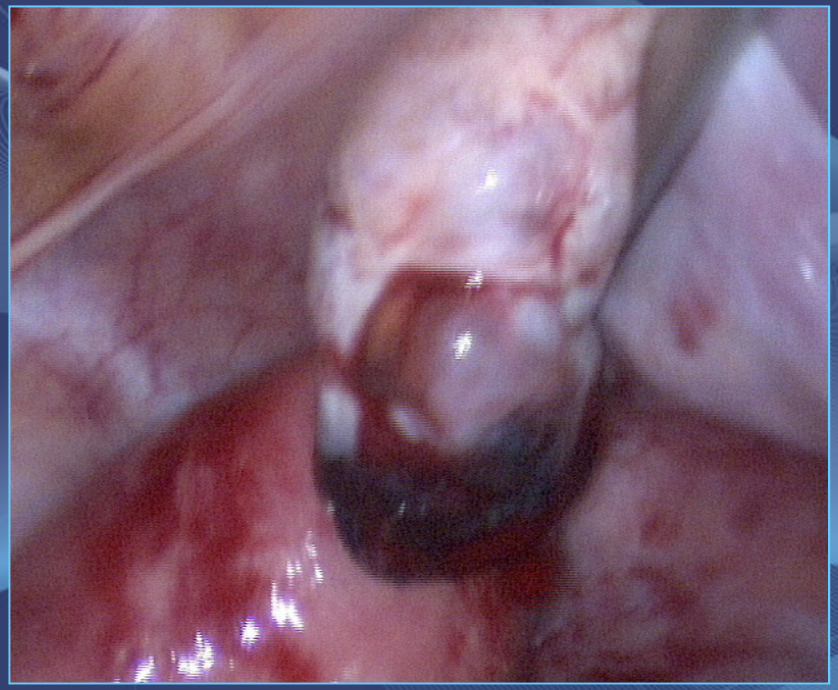


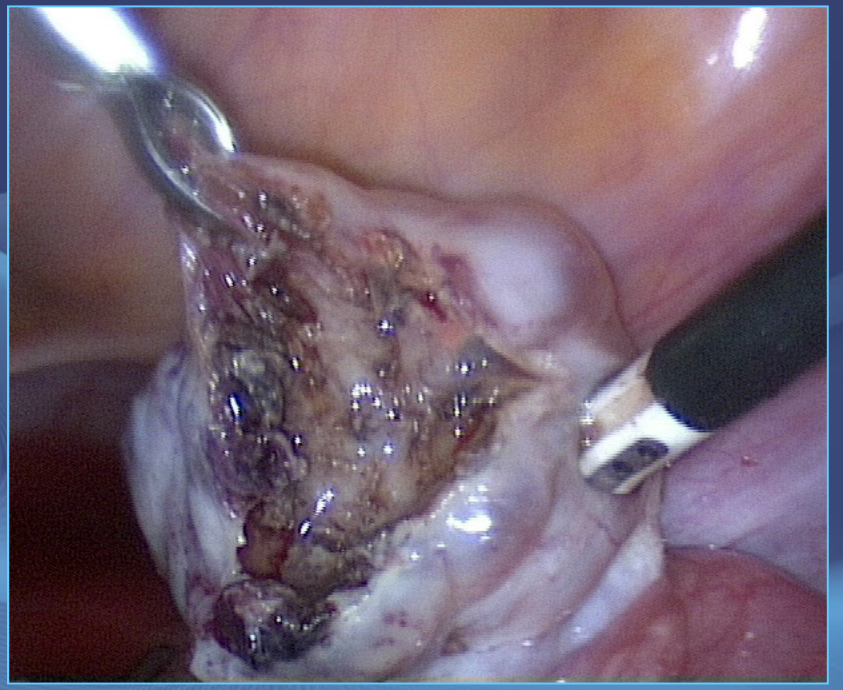
PUL … during 1 day

- cryotransfer of 2 embryos 06/11/2009
- β-hCG 1620 mIU/ml & prog 9,88 ng/ml 18/11/2009
- acute pain & hemoperitoneum 19/11/2009
- emergency laparoscopy reveals an ovarian pregnancy at the right side
- treated conservatively by aqua- or hydrodissection & bipolar coagulation









Management of ectopic pregnancy either … or … (1)

strict follow-up of evidence based guidelines

- Dutch Society 2001
- RCOG 2004
- Cochrane 2007
- ACOG 2008

versus

individualized patient care based on personal clinical experience & the clinical experience of our peers

Management of ectopic pregnancy either … or … (2)

What is the best guarantee of a complete removal of all trophoblast, a "blood"proof hemostasis and a recurrence rate at least at that site of 0%

?

versus

What is the best guarantee of an intact tubal integrity, a preserved fertility potential despite the risk of persistent bleeding and/or trophoblast

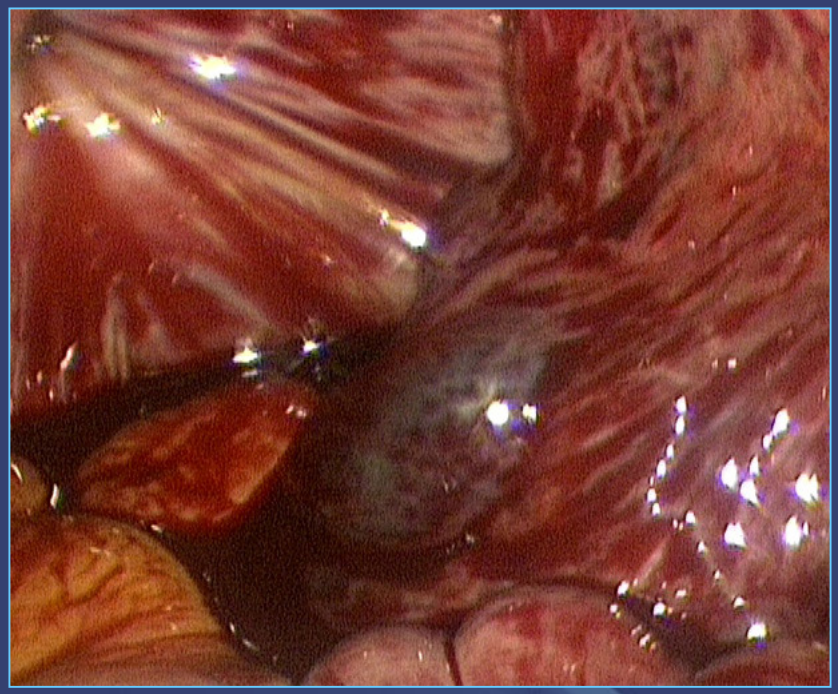
?

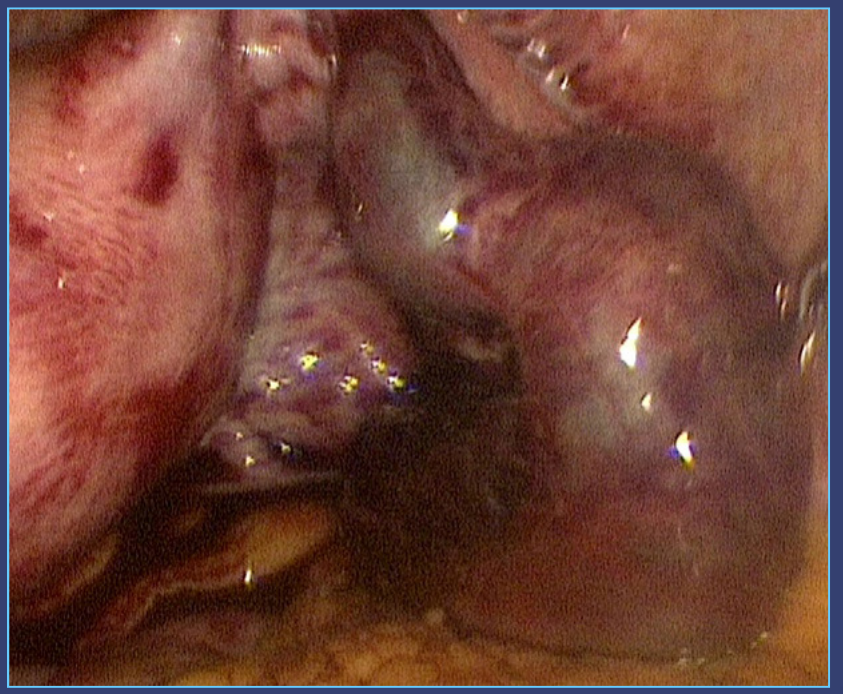
Management of ectopic pregnancy

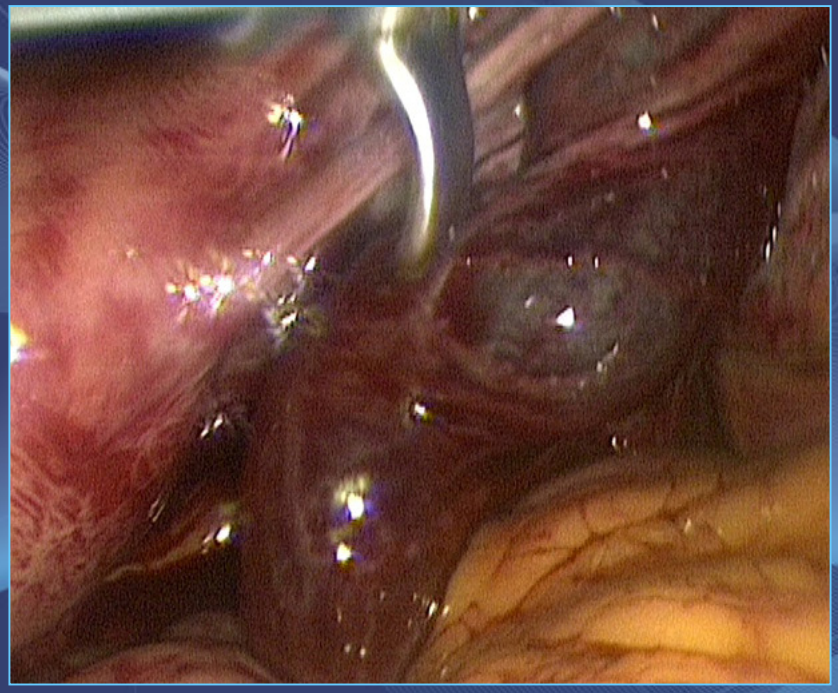
- ß-hCG monitored expected management unless CV unstable, moderate/severe pelvic pain, +HR inside ectopic, or hemoperitoneum: 95% success if ß-hCG is < 175 vs. 66% if b-hCG 176 to 1500
- Methotrexate (MTX) is a folic acid antagonist. It inhibits DNA synthesis and cell reproduction, primarily in actively proliferating cells such as trophoblast ~ ACOG but what about fertility patients ?
- Surgical management: laparoscopy is superior to and cheaper then laparotomy and salpingotomy is preferred over salpingectomy
- Salpingectomy indicated if uncontrolled bleeding from implantation site, recurrent ectopic in the same tube, severely damaged tube, large tubal pregnancy (>5cm) or if completed childbearing.
- Persistent ectopic can occur in 4-15% of women after a salpingotomy: ß-hCG should be followed weekly until it is negative.

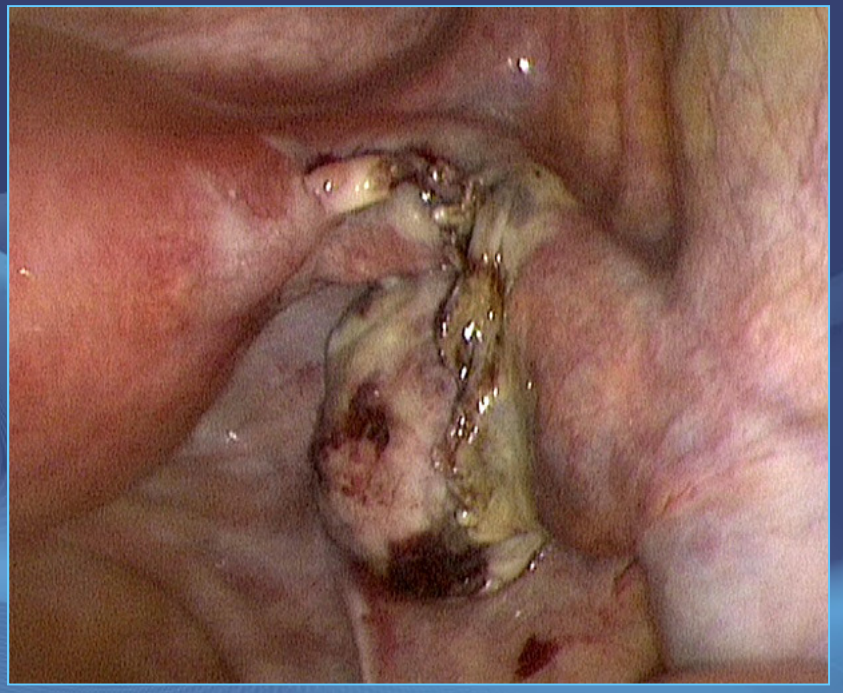
Expectant management

Date	ß-hCG	E_2	Prog
07/09/2009	36	165	26,61
11/09/2009	31	148	25,49
16/09/2009	116	< 30	1,30
21/09/2009	96	65	0,96
24/09/2009	165	92	1,68
28/09/2009	171	120	5,16
01/10/2009	251	136	9,47









- If the patient is shocked or hemodynamically compromised, treatment should be immediate resuscitation and laparotomy without delay, even before blood and fluid losses have been completely replaced.
- However, in some emergency situations if prompt haemostasis and a clear surgical field of view can be achieved, and provided the surgeon is experienced, laparoscopic treatment may still be considered first line.

Persistent trophoblast … ?

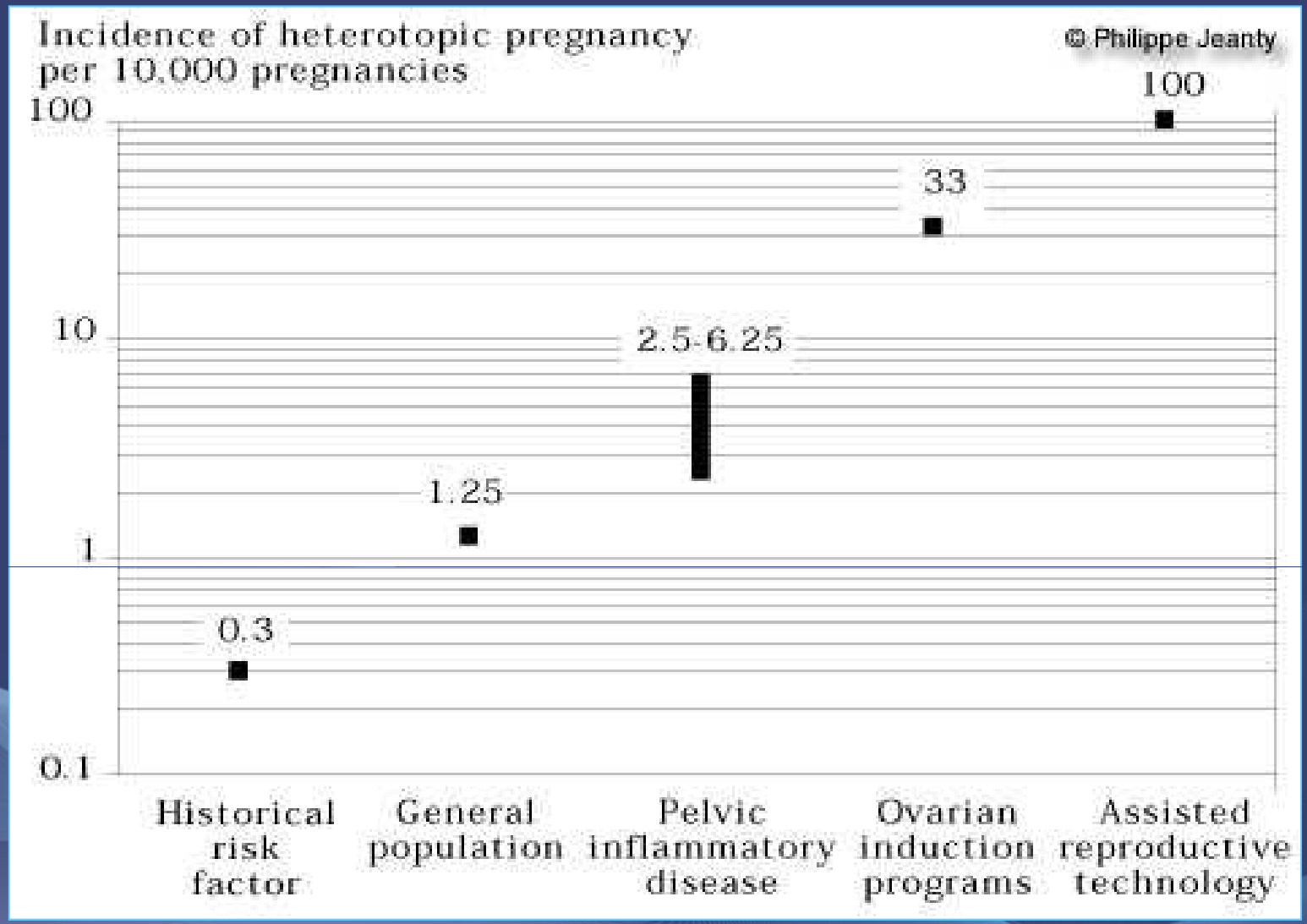
Hajenius et al. 1995, Hum Reprod 10, 683-687

Clearance curves of serum human chorionic gonadotrophin for the diagnosis of persistent trophoblast

- There was no difference in the post-operative clearance of serum hCG after successful conservative surgery compared to radical surgery.
- However, persistent trophoblast occurred in 8 pts (29%) after laparoscopic salpingotomy and in only 1 pt (6.3%) who had a salpingotomy by open surgery.
- Serum HCG clearance curves allow early identification of patients with persistent trophoblast after conservative surgical treatment.
- Moreover, monitoring of post-operative serum HCG until it becomes undetectable is mandatory in order to reveal late-onset types of persistent trophoblast

"ectopic" as part of “heterotopic"

- Simultaneous development of a gestation inside AND outside the uterine cavity (heterotopic = eutopic + ectopic).
- Prevalence: historically 0,3/10.000 pregnancies, now 1,25-2,50/10.000 spt. pregnancies, 0.1% in assisted conceptions
- Aetiological factors:
  - increase in the incidence of PID;
  - prevalent use of cupper IUCD’s;
  - increase in tubal surgery, notably microsurgery;
  - ovulation induction & superovulation;
  - assisted reproductive technologies like IVF & GIFT
- Risk factors: delayed diagnosis, hemoperitoneum, acute abdomen, tubal rupture


Incidence of heterotopic pregnancy
per 10,000 pregnancies
© Philippe Jeanty
100
10
1
0.1
100
33
2.5-6.25
1.25
0.3
Historical risk factor
General population
Pelvic inflammatory disease
Ovarian induction programs
Assisted reproductive technology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!!!

- 2,8 - 5,7 % of all pregnancies following assisted reproductive technology are indeed ectopic …
- 0,7 - 1,3 % of all pregnancies following assisted reproductive technology are indeed heterotopic …

Diagnosis of heterotopic pregnancy

- a high index of suspicion, esp. following ART !!!
- despite normal ß-hCG values (due to the normal IUP)
- at TvS the presence of an intrauterine gestational sac lowers the suspicion of another (i.e. ectopic) pregnancy
- the visualization of an IUP may result in less rigorous sonographic evaluation of the adnexae and a delayed or missed diagnosis of a heterotopic gestation
- an adnexal mass is seen sonographically in 80% of ectopic pregnancies; this also means that potentially the diagnosis of an heterotopic pregnancy can be made in 80% of the cases with rigorous sonographic evaluation of the adnexae

Doppler & trophoblast ?

- Taylor et al. (1989, Radiology 173:93) have described a high velocity, low resistance Doppler signal that is associated with the developing trophoblast
- Transvaginal identification of this type of flow pattern in an adnexal mass raised the sensitivity for the diagnosis of an ectopic pregnancy to 96% and a specificity of 93% using transvaginal color Doppler
- These encouraging results however were not confirmed by other authors

Management of heterotopic pregnancy

- Surgical removal of the ectopic gestation by salpingotomy or salpingectomy is the treatment of choice.
- In patients in whom the diagnosis of ectopic pregnancy can be made without laparoscopy and who sonographically demonstrate an unruptured gestation and a persistent downward trend of the ß-hCG, expectant management has been successfully applied.
- Fine needle aspiration with the injection of methotrexate or KCl (potassium chloride) into the gestational sac is still investigational at this time.