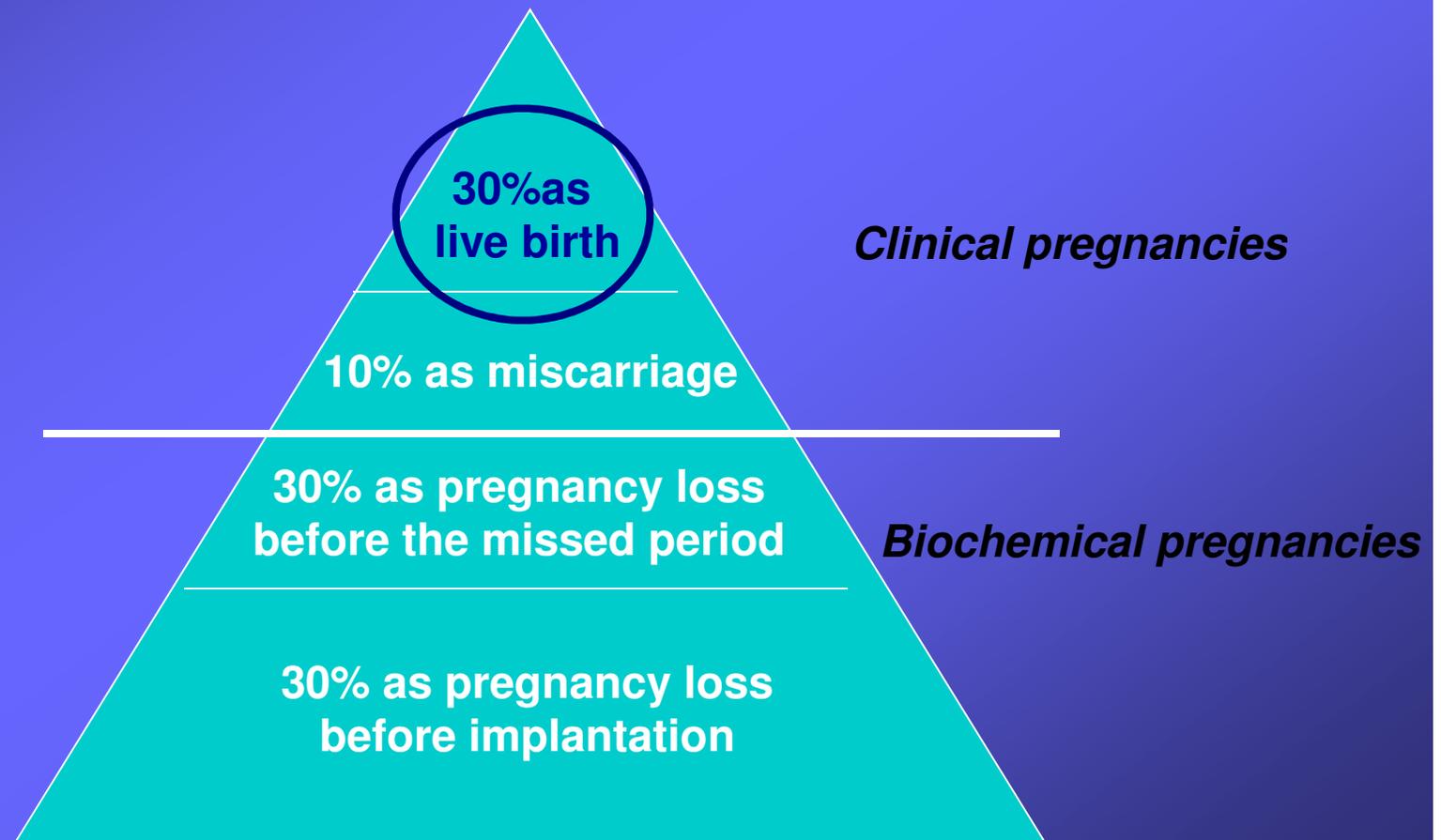# Evidence based practice in miscarriage

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Literature search

- Systematic literature search using Medline and Cochrane Database from 1980-2009

- Limited number of prospective, randomized, comparable studies

- No clear recommendations are developed by national obstetrics and gynecologist societies concerning diagnosis and management of early pregnancy events

Proportion of unrecognized pregnancies, lost to recognized miscarriages and live birth

30%as live birth

Clinical pregnancies

10% as miscarriage

30% as pregnancy loss before the missed period

Biochemical pregnancies

30% as pregnancy loss before implantation

Chard 1991

Early pregnancy complications

- Indications for diagnostic management
- Laboratory tests
- Ultrasound examination
- Prognosis for normal pregnancy development
- Differential diagnosis
- Risk factors
- Management options in diagnosed miscarriage
- Role of EPAU service

Indications for diagnostic management in early pregnancy

- Clinical symptoms

- Obstetric history

- ART pregnancies

Pain & Bleeding (7-24%)

- Colour of blood – no statistically important
- Heaviness - any bleeding and heavy bleeding (OR 3.0,95%CI 1.9-4.6)
- Duration - <2 days low risk (OR 1.5) and >2 days high risk (OR 2.1-4.5)
- *Heavy painful bleeding lasting 3 days or longer (OR 4.79,95%CI 2.97-7.73)*
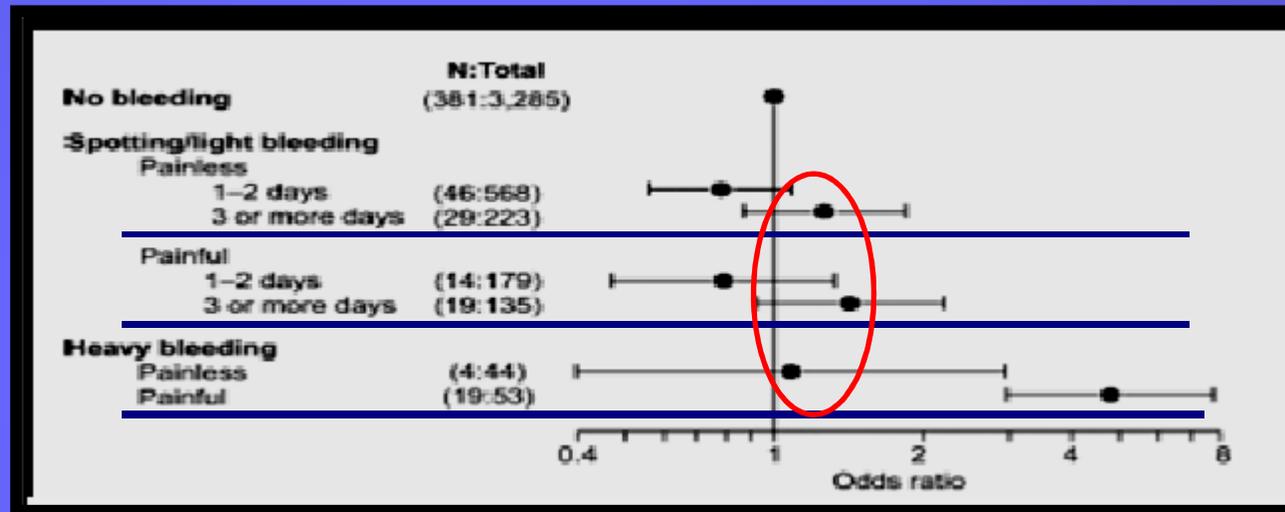
Risk of miscarriage and obstetric history

-for primigravida and for women
 who has delivered a live neonate Blohm 2008

5%

- for women with a single pregnancy
 loss Regan 1989

20%

- for women with 3 or more
 miscarriages Brigham1999

58%

Pregnancy outcome after ART

- 10-30% of pregnancies after ART will result in miscarriage (Westergaard 2000)

- ICSI procedure is associated with higher incidence of chromosomal de novo aberrations Tarlatziz and Grimbisis 1999

- In 30% of MGP vanishing twin phenomenon will occur and in <10% will result in empty sac Dickey 2002, Pinborg 2005

- Gives the most accurate dating of pregnancy

Early pregnancy complications

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Biochemical assesment

None of the current methods combines accuracy, reproducibility and simplicity to become a universal predictive marker of early pregnancy

- β hCG, hCG-H
- Progesterone, 17-α-OH Progesterone
- Inhibin A, Inhibin pro-α C
- Insulin Growth Factor Binding Protein-1
- α-fetoprotein
- PAPP-A
- Activin A
- Estradiol
- Free testosterone

β-hCG

- Detected from the 7th day after fertilization in serum and in 10-11 days after fertilization in urine Shutt and Lopata 1981,Lopata and Hay 1989, McCready et al.1978, Wilcox et al.1985

- Double in maternal serum over 1.4-1.6 days until 35th day and 2.0-2.7 from 35th -42nd day

- At 4 weeks – βhCG 1500IU/L – IUP should be visible in TVS ultrasound

- A cut-off of 200IU/L for serum free β-hCG allows to differentiate between viable and abnormal pregnancies (88.3%sensitivity and 82.6%positive predictive value) Al.-Sebai 1996

- High levels of serum βhCG are seen in early multiple pregnancies (vanishing twin phenomenon)

hCG-H

- Hyperglycosylated hCG seems to be a predominant form of hCG present in serum and urine samples in early pregnancies

- Significantly lower levels of hCG-H are found in spontaneously aborting and ectopic pregnancies
Kovalevskaya et al.2002, O'connor et al.1998

- Single serum hCG-H measurment test is simple, fast with a higher predictive accuracy and utility Jaime et al.2006

hCG-H

- With a cut-off level of 13mcg/L for both urine and serum samples βHCG-H test has 73% pregnancy failure detection rate in serum (2.9% false positive rate) and 75% failure detection in urine (15% false positive rate)

Week	Serum				Urine			
	Median hCG values	Median hCG-H values	Average % hCG-H ± SD	n	Median hCG values	Median hCG-H values	Average % hCG-H ± SD	n
3rd	22	6.8	89 ± 24	5				
4th	627[a]	25[a]	41 ± 13%	13	529	30[a]	61 = 37%	45
5th	2816	54	31 ± 11%	20	2022	54	40 = 30%	69
6th	12,144	120	21 ± 14%	13	2678	58	32 = 32%	20
7th	19,690	348	16 ± 13%	12	13,050	130	31 = 4%	5
8th	98,615	347	7.0 ± 5.4%	24				
Total				87				139

[a] Logarithms of urine and serum hCG correlate (r^2 = 0.95), 4th–7th weeks of gestation. During this same period, serum hCG-H correlates with urine hCG-H (r^2 = 0.97).

Progesterone

- Is the single most powerful predictor of pregnancy outcome (Phipps 2000)

- Progesterone level <25nmol/L in anembryonic pregnancy – diagnostic of nonviability

- Spontaneous resolution of PUL pregnancy with progesteron level <20nmol/L (93%sensitivity and 95%specificity) Banerje et al. 2001, Hahlin et al.1995

- With serum progesterone level >50nmol/L spontaneously resolving pregnancy is unlikely-with low βhCG ones should wait until βhCG reach the level of 1000IU/L

Progesterone

- Ectopic pregnancies with progesterone level <10nmol/L are successfully treated with metotrexat Ranson et al. 1994

- Only 3% women with progesterone <20nmol/L and 8% with P > 60nmol/L had an ectopic pregnancy

- 10% of ectopic pregnancies when viable have high serum progesterone level Shepherd at al.1990

17 α-OH Progesterone

- A better marker of corpus luteum function in early pregnancy

- Plasma concentration rises from 2.6ng/mL in the 3rd week of pregnancy to 5.8ng/mL at the 5th week and later declines

- 17 α-OHP seems to be lower in nonviable intrauterine pregnancies and ectopic Choe et al.1992

Inhibin A

- Originates from corpus luteum and syncytiotrophoblast production site and peaks at 8th week gestation

- Decreased maternal serum level is observed in missed miscarriages and biochemical pregnancies Muttukrishna et al.2002

- Has shorter half-life than either hCG or progesterone and better reflects throphoblast changes Glennon et al.2000

- Undetectable level is a best predictor of complete miscarriage in a expectant management cases Elson 2005

Inhibin pro-αC

- Corpus luteum is a major source of inhibin pro-αC in early pregnancy

- Has a paracrine and endocrine effect on placental function

- Level of inhibin pro-αC is lower in failed intrauterine pregnacies Lockwood et al. 1997

- Lower levels of pro-αC are associated with an increased success of expectant management Elson 2005

Insulin Growth Factor Binding Protein-1

- Is produced by syncytiotrophoblast in early pregnancy and rapidly rises in the first trimester

- Higher IGFBP-1 in uterine flushings from periimplantation endometrium influence higher miscarriage rate Salim et al. 2004

- Presence of a raised level of IGFBP-1 indicates a better prognosis for spontaneous miscarriage Elson et al.2005

α-fetoprotein

- Elevation >2.5MoM in the absence of chromosomal abnormalities and fetal structural anomalies is suggestive of placental vascular lesions and presence of thrombophilia, gestational hypertension and preterm deliveries Salafia et al.2007,Cusick et al. 1996,Killam et al.1991

- Low maternal AFP <0.25MoM is associated with spontaneous abortion, preterm birth, stillbirth and macrosomia Doran et al.1987,Krause et al.2001

- Higher levels of serum AFP are found in male neonates Caballero et al.1977

Maternal serum pregnancy associated plasma protein-A

- Elevated PAPP-A has no influence on adverse pregnancy outcomes

- Low PAPP-A has a higher risk of spontaneous miscarriages RR 2.5—13.3;95%CI

- Both PAPP-A and SP-1 levels are reduced before fetal death (Al.-Sebai 1996)

Activin A

- Dimeric glycoprotein belonging to the TGF-β superfamily synthetized in the placenta

- Activin A increases progesterone production and GnRH induced relaese of hCG Petrakgia et al.1989

- Serum level of activin A progresively increases throughout pregnancy until delivery

	Cutoff value	Sensitivity (%)	Specificity (%)	LR (+)	LR (−)	AUC
hCG	658 IU/liter	75.0 [63.7–84.2]	76.1 [71.9–79.9]	3.14	0.33	0.806 [0.77–0.839]
Progesterone	5.01 ng/ml	85.5 [75.6–92.5]	66.1 [61.6–70.4]	2.52	0.22	0.622 [0.579–0.663]
Activin A	0.37 ng/ml	99.6 [95.2–100]	99.6 [98.4–99.9]	230.0	0.0	1.0 [0.993–1.00][a]

Numbers in *brackets* refer to lower and upper $CI_{95\%}$.
[a] $P < 0.0001$ *vs.* other AUCs.

Estradiol

- Low level of E2 is seen in missed abortions and anembryonic pregnancies

- 80% of normal pregnancies has E2 level of > 350pg/ml

- High level of E2 >200 pg/ml is associated with a good outcome in early pregnancy (90% probability) Barry et al.1990

Free testosterone

- Low level of fT in normal pregnancy is associated with increase in SHBG levels and E2

- fT ratio >1.05 are present in subsequently miscarrying group Siyami 1996

Early pregnancy complications

- Indications for diagnostic management
- Laboratory tests
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- Risk factors
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- Role of EPAU service

USG assesment of early pregnancy

- The number of sacs, the MSD and the regularity of the outline of the sac
- The presence of a yolk sac
- The presence of an embryo and the CRL measurement
- The presence or absence of heart movements
- The presence of any hematoma
- Endometrial thickness
- Early doppler ultrasound

When death of an embryo is suspected two TV scans at least 7 days apart should be performed

# Ultrasound of normal early pregnancy
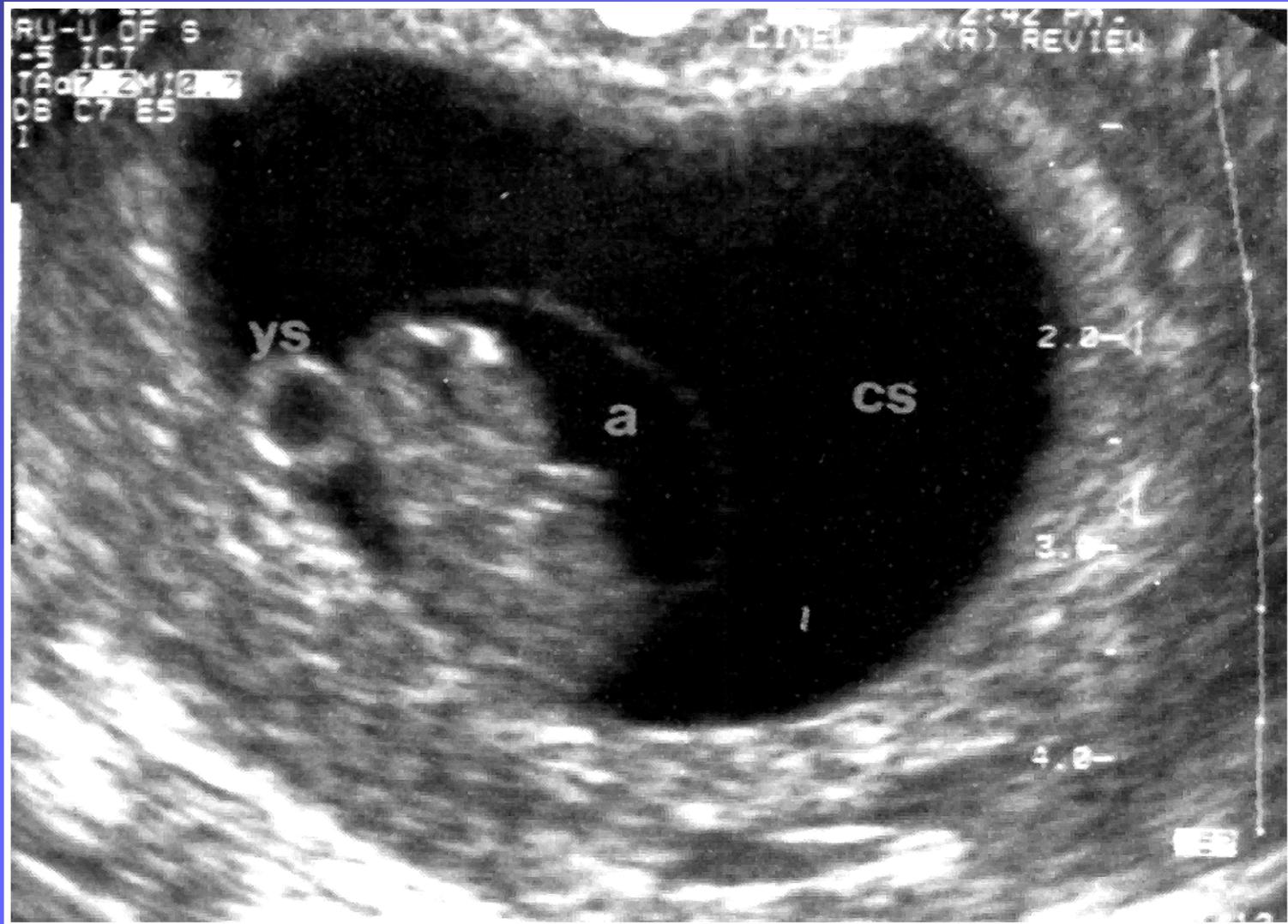
USG assesment of early pregnancy

- After 4 weeks of pregnancy and βhCG level of 1500IU/L gestational sac becomes visible

- Yolk sac appears after 5 completed weeks

- Fetal pole and heart beat is first seen after 6 weeks gestation with GS >20mm

- After 7 weeks fetal pole with a separate amniotic sac and celomic cavity with yolk sac is seen, heart beat visible at 150bpm

- In 15-20% of women with clinical suspicion of early pregnancy failure ultrasound findings are not diagnostic

Gestational sac (GS)
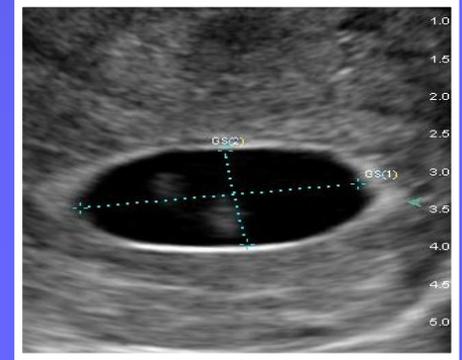
Double Decidual Sac Sign
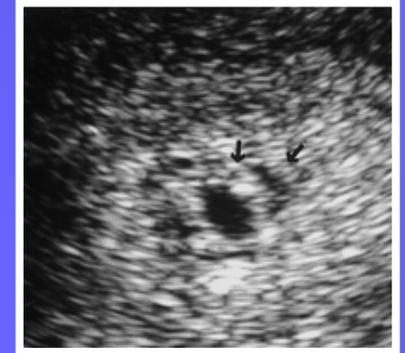
- Once GS is documented on USG subsequent loss of viability is around 11% Goldstein 1994

- 3D assesment of GS volume in the first trimester is a sensitive indicator of pregnancy outcome Babinszki et al.2001

If the GS is less than 15mm a second scan should be carried out at least 7 days later

Sawyer&Jurkovic 2007

GS

- Small GS is more likely to occur in triploid and trisomy 16 pregnancies

- Older women has GS of 0.12 mm larger for each 1 year increase in maternal age Bottomley et al.2009

- No fetal part in GS >20mm – empty sac or early embryonic demise occured Luise 2002

- Pseudogestational sac is seen in 10-20% of ectopic pregnancies
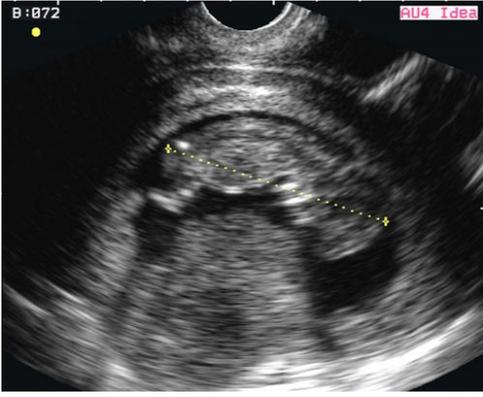
Crown-rump lenght (CRL)

- If an embryo's lenght is 5mm subsequent loss of viability occurs in 7.2% of cases Goldstein 1994
- Loss rate drop to 3.3% for embryos 6-10mm
- Only 0.5% of embryos will be lost when CRL is of 10mm
- In 1/3 of embryos with CRL<5mm, have no cardiac activity Levi et al.1990

If the embryo of more than 5mm is present without FHR scan should be repeated in 7 days

CRL

- Smaller than expected CRL may be present in trisomies 13,18 and triploidies

- Black ethnic origin is accociated with a greater rate of increase in CRL compared with white and asian

- Older women has fetuses with greater increase in CRL (discrepancy of two days) Bottomley et al.2009
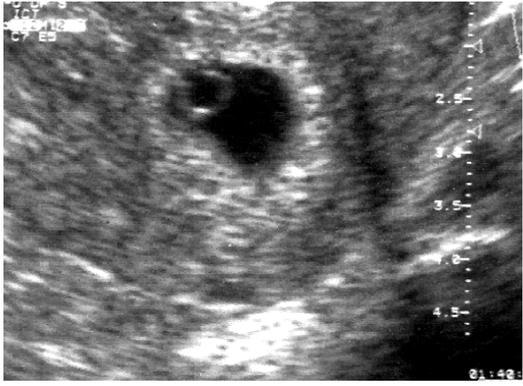
Yolk sac (YS)
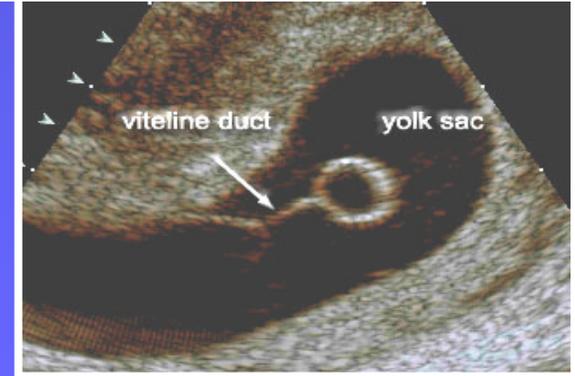
- Absent of YS in MSD of more than 8mm in TVS is always abnormal Levi et al.1988

- A YS diameter of more than 5.6mm in pregnancy of less than 10 weeks, visualization of embryo without YS or abnormally shaped YS is always abnormal Lindsay et al.1992

- In all pregnancies which continue past the I trimester with sonographically abnormal YS, sonographic follow-up before 20 week is recommended Lindsay et al.1992

- Calcification of a yolk sac is associated with fetal demise

- In monochorionic twins the absence of one yolk sac is associated with monoamnionicty

Fetal heart pulsation
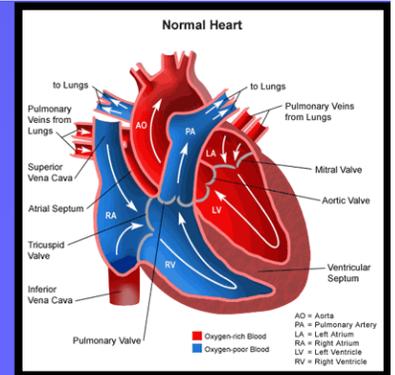
- Is the earliest proof of fetal viability and can be documanted as early as 36 days' MA Tezuka 1991

- In 5-10% of embryos with CRL between 2-4mm cannot be demonstrated Brown 1990

- From 5-9 week of gestation there is a rapid increase in mean heart rate from 110 to 175 bpm that later decreases to around 160-170 bpm Coulam et al.1995,Stefos et al.1998

- FHR below 120bpm in the I trimester is associated with increased pregnancy loss rate (specificity 95%, sensitivity 54%) Chittacharoen et al.2004

- Specificity reaches 100% when the heart rate is below 85bpm Chittacharoen et al.2004

- Bradycardia more likely indicate trisomies 18 and triploidies while tachycardia is present in trisomies 21

Fetal bradycardia

Fetal heart rate	Risk of spontaneous miscarriage
40 – 69	100%
70 – 79	91%
80 – 90	79%

< 90 bpm 86%

Early oligohydramnion

- Oligohydramnion is diagnosed when between 5.5 and 9 th gestational week

$$GS - CRL \leq 5 \text{ mm}$$

- Early oligohydramion is associated with a high risk of spontaneous miscarriage 80-94%
  Dickey et al.1991,Bromley et al.1991

# Early oligohydramnion

Intrauterine hematoma (IUH)
(18-39%)

- Hematoma may be a first sign of incomplete placentation and may be associated with acute oxidative stress Jauniaux 2005

- Presence of IUH has been associated with a 4-33% rate of miscarriage depending on the gestational age when first described (especially <9th week) and its location (under the cord insertion)

Pearlstone et al.1993
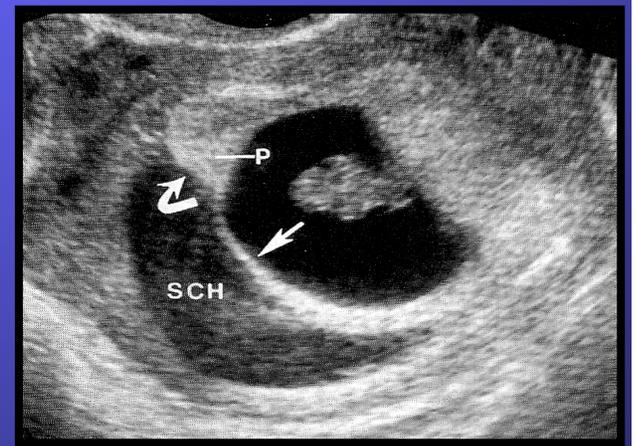
Subchorional hematoma (IUH)

- Recent metaanalysis do not confirm higher incidence of fetal loss in pregnancies complicated with IUH Nagy et al.2003, John and Jauniaux 2006

- Is associated with PPROM and PET Johns 2003

Endometrial thickness

- Endometrial thickness between 12-15mm, negative urinary test and hCG<50IU/L – complete miscarriage Alcazar et al.1995; Condous et al.2005; Jauniaux 2005

- Endometrial thickness measurement cannot be used as a reliable test for diagnosis of RPOC Sawyer et al.2007

| Endometrial parameter	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR +ve (95% CI)	LR −ve (95% CI)
Thickness > 5 mm	0.94 (0.87–0.97)	0.05 (0.01–0.25)	0.85 (0.78–0.90)	0.13 (0.02–0.47)	0.99 (0.88–1.11)	1.22 (0.88–1.11)
Thickness > 8 mm	0.87 (0.8–0.92)	0.21 (0.09–0.43)	0.86 (0.79–0.92)	0.22 (0.09–0.45)	1.10 (0.87–1.41)	0.61 (0.23–1.66)
Thickness > 12 mm	0.75 (0.66–0.82)	0.37 (0.19–0.59)	0.87 (0.80–0.94)	0.80 (0.67–0.93)	1.18 (0.82–1.70)	0.69 (0.35–1.35)
Thickness > 15 mm	0.56 (0.47–0.65)	0.53 (0.32–0.73)	0.87 (0.77–0.93)	0.17 (0.1–0.29)	1.18 (0.72–1.95)	0.84 (0.52–1.35)
Thickness > 25 mm	0.10 (0.06–0.17)	0.89 (0.67–0.97)	0.85 (0.56–0.96)	0.15 (0.09–0.22)	0.96 (0.23–3.99)	1.01 (0.85–1.19)
Volume > 1 mL	0.89 (0.82–0.94)	0.32 (0.15–0.54)	0.88 (0.81–0.93)	0.33 (0.16–0.56)	1.30 (0.95–1.78)	0.35 (0.15–0.82)

LR +ve and LR −ve, positive and negative likelihood ratios; NPV, negative predictive value; PPV, positive predictive value.

Ultrasound Obstet Gynecol 2007; 29: 205–209.
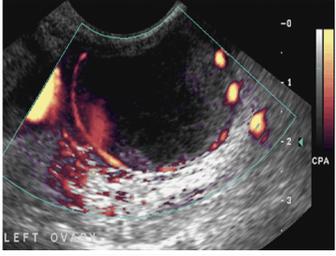
Colour doppler sonography

- Can be used to select the most suitable patients for expectant management Jauniaux et al.1994, Valentin et al.1996

- Presence of blood flow in intervillous space is associated with high likelihood of complete spontaneous abortion within 7 days (80% of cases vs 23%) Schwarzler et al.1999

- Both resistive and pulsatility indices within UtA were higher in patients with incomplete or threatened abortion vs normal pregnancy Salim et al.1994

- In most cases of early pregnancy failure before 12 weeks the placenta contains several large lakes with moving echoes inside Jauniaux et al.2003

3D ultrasound
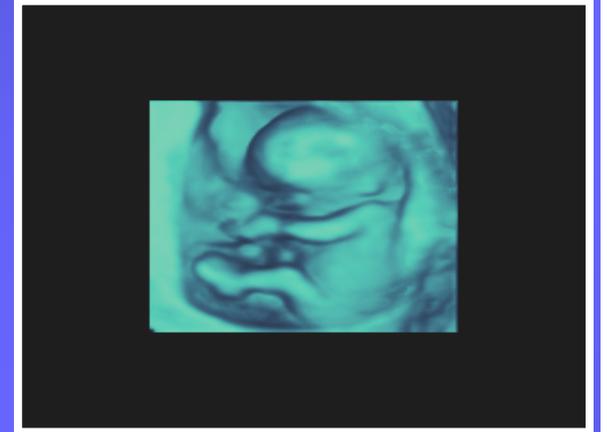
- Vocal – calculate the volume of YS, GS, fetus and chorion

- Volume of YS < 5 centile and > 95 centile and reduced fetal volume corelates well with the number of misscariages Figueras et al.2003

- Intra-uterine-ultrasound provides additional information on the visualization of anatomical structures of the embryo in the early I trimester of pregnancy Toshiyuki 1997

Prognostic factors in case of threatened abortion

Favourable prognostic factors	Adverse prognostic factors
History	
Advancing gestational age	Maternal age > 34 years
	Increasing number of previous miscarriages
Sonography	
Fetal heart activity at presentation	Fetal bradycardia
	Discrepancy between gestational age and crown to rump lenght
	Empty gestational sac > 15 – 17 mm
Maternal serum biochemistry	
Normal levels of these markers	Low β hCG values
	Free β hCG values of 20 ng/ml
	β hCG increase < 66% in 48 hrs
	Bioactive / immunoreactive ratio β hCG < 0.5
	Progesterone < 50 nmol/L in 1st trimester
	Inhibin A < 0.553 mulitples of median
	Ca125 level $\geq$ 43.1 U/mL in 1st trimester

Early pregnancy complications

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Prediction of pregnancy viability

■ *Assesment with multiparameter diagnostic models*

 - logistic regression model

Probability of spontaneous resolution = -2.20 – 0.15*progesterone (nmol/L) + 3.36* bleeding score- 0.0013*serum βhCG (IU/L) + 0.45*endometrial thickness (mm) Banerjee et al.1999

- Hahlin's model

βhCG ratio of <-5% and initial serum progesterone level <20nmol/L

.

Prediction of pregnancy viability

- ***Probability of viability*** $= 1/(1=e^{-z})$

  $z=(6.091 \times \ln \text{progesterone})-(0.159 \times \text{sac diameter})-(0.164 \times \text{maternal age})-17.435$ Elson et al.2003

- Almost identical results could be achieved by using serum progesterone at cut-off of 25nmol/L

Variable	Area under the curve	Standard error	P
Logistic model	0.9693	0.0109	1
Progesterone	0.9493	0.0158	> 0.05
Gestational age	0.83	0.0316	< 0.01
Gestational sac diameter	0.7032	0.04	< 0.01
Maternal age	0.6283	0.0408	< 0.01
β-hCG	0.4906	0.0446	< 0.01

β-hCG, beta-human chorionic gonadotropin.

Early pregnancy complications

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Differential diagnosis

- **Pregnancy related** miscarriage , PULs pregnancy, ectopic, hydatiform mole

- Coincidental to Pregnancy: Gynecologic ruptured corpus luteum of pregnancy, ovarian cyst accident, torsion or degeneration of pedunculated fibroid

- Coincidental to Pregnancy: Nongynecologic appendicitis, renal colic, intestinal obstruction, cholecystitis

- Nor related to Pregnancy, but Gynecologic pelvic inflammatory disease, dysfunctional uterine bleeding, endometriosis

PULs pregnancies

- In women with PUL pregnancies maternal serum activin A levels are the lowest in those with early pregnancy

- 1/3 of PULs are early developing IUP but too small to be visualized

- The pregnancy site cannot be visualized by TVS in 8-31% of women presenting at EPU Hahlin 1995, Cacciatore 1988, Banerjee 2001

- Persisting PUL accounts for 2% of total PUL population Condous 2004

- With a progesterone cut-off of 0.37ng/ml there is 100% sensitivity, 99.6% specificity, 97.4% of PPV and 0% of NPV Pasquale et al.2007

Management of PUL's pregnancies

- Majority of PULs fail to resolve spontaneously (44-69%)
  Condous 2004

- „Wait and see" approach is safe, reduce the need for surgical intervention and has no serious adverse outcomes

- 9-29% of women with PUL still require surgical intervention due to worsening clinical condition or non-declining serum hCG Hahlin 1995

- Prevelane of ectopic pregnancies in PULs population varies between 8.7-42.8% Ankum et al.1993, Banerjee et al.1999

- Evaluation of serum hormone levels at defined times in PULs can be used reliably to predict viability of a PUL but cannot predict its location

Management of PUL's pregnancies

- 15% of normal IUPs screened in this way will be abnormal and 13% of ectopic will give contradictory results and delay diagnosis Kadar 1981

- Serum hCG ratio of 1.66 (hCG at 48h/hCG at 0h) correlates well with devoloping IUP

- Serum hCG ratio <0.87 predicts PUL which resolve spontaneously with no intervention. Sensitivity 93.1%, specificity 90.8% (95%CI82.2-95.7)

- Serum progesterone of less than 20nmol/L correlates well with a failing PUL-PPV >95% Banerjee 2001

- D&C can be safely performed after non-viable pregnancy has been documented by either serum hCG after 2 days (ratio <1.50) or with serum progesterone <15.9nmol/L

PUL
One day visit strategy

```
                        ┌──────────────────┐
                        │       PUL        │
                        └──────────────────┘
        ┌───────────────────────┼────────────────────────────┐
┌─────────────────┐    ┌─────────────────────┐      ┌─────────────────────────┐
│ Progesterone    │    │ Progesterone        │      │ Progesterone 10-50      │
│ <10 nmol/L      │    │ >50 nmol/L          │      │ nmol/L                  │
│ or              │    │ and                 │      │ hCG >25 IU/L            │
│ hCG <25 IU/L    │    │ hCG >25IU/L         │      │                         │
└─────────────────┘    └─────────────────────┘      └─────────────────────────┘
┌─────────────────┐    ┌─────────────────────┐      ┌─────────────────────────┐
│ Resorbtion PUL  │    │ IUP                 │      │ EP ?                    │
└─────────────────┘    └─────────────────────┘      └─────────────────────────┘
┌─────────────────┐    ┌─────────────────────┐      ┌─────────────────────────┐
│ Low risk PUL    │    │ Low risk PUL        │      │ High risk PUL           │
└─────────────────┘    └─────────────────────┘      └─────────────────────────┘
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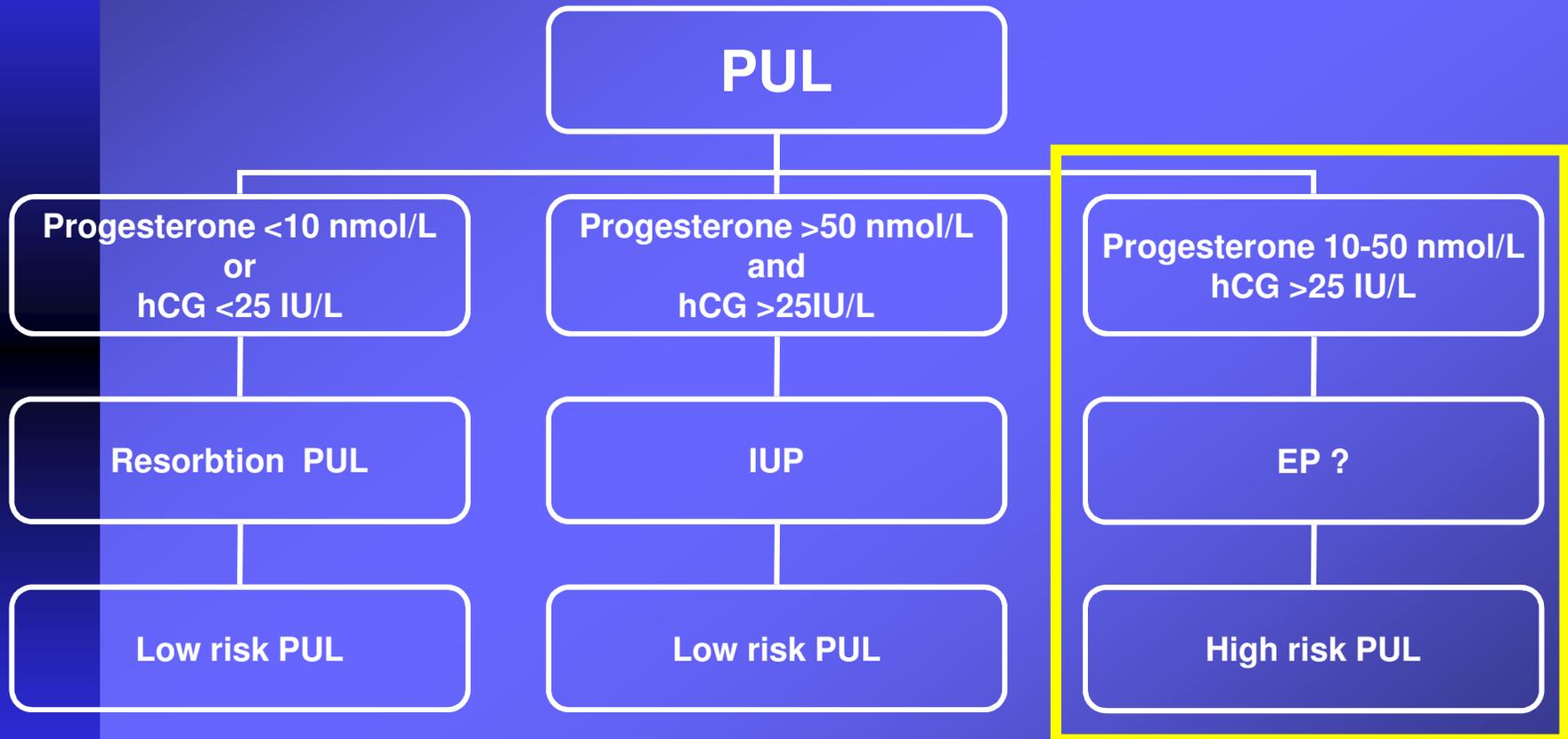
Ectopic pregnancy

- Is a leading cause of maternal mortality in early pregnancy

- The incidence is about 1% of all pregnancies

- Predisposing risk factors are:
  - Infertility
  - Increased Chlamydia antibody titer
  - Tubal sterilization and reconstruction
  - Intrauterine contraceptive device
  - Endometriosis

Ectopic pregnancy

■ Management options:

Expectant management

– βhCG less than 1000 IU/L (monitored every 3-4 days)

- No visible GS on TVS

- Progesterone level of less than 20 nmol/l

Trio et al.1995, Banerjee et al.2001

■ Management options:

Medical treatment

- Methotrexate single dose of 1mg/kg or 50mg/m^2 (rarely giving rise to side effects) + folinic acid Fernandez 1994

- For hCG values of 2000 to 5000 IU/L the likelihood of success is 92%;95%CI Lipscomb et al.1999

- Success rate with metotrexate treatment of ectopic is only 30% when hCG rises >10000IU/L Sowter et al.2001

- Better reproductive outcome after Metotrexate treatment – higer rate of IUP and lower of ectopic

■ Management options:

Surgical treatment

- Laparoscopic salpingectomy is the preferred method of treatment RCOG 1999

- Higher sucess rate after laparotomy Hajenius et al.2003
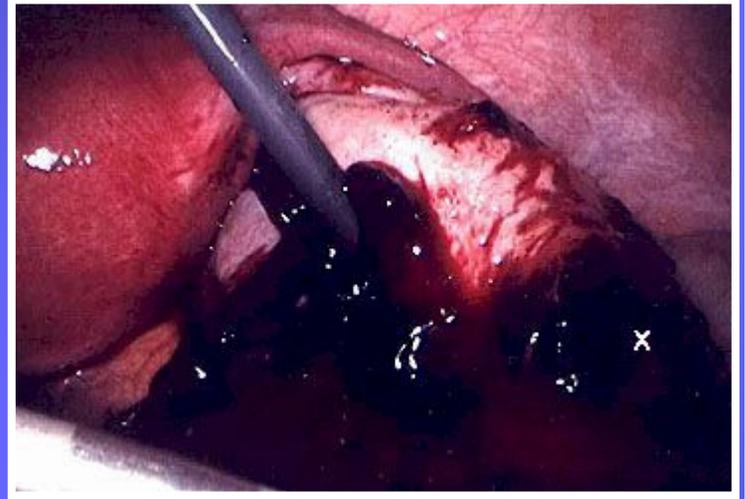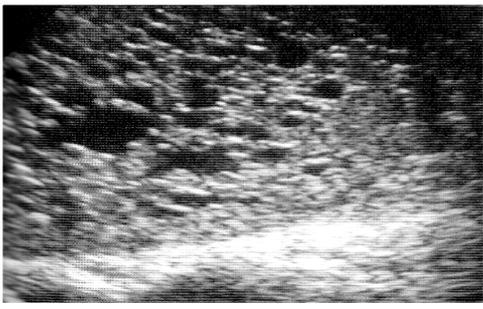
Gestational Trophoblastic Disease

- The incidence of GTD is 0.6-2.3 per 1000 pregnancies

- Persistent trophoblastic disease or malignant complication are much more common with complete molar pregnancy with a risk of 8%

- Symptoms and signs of molar pregnancy
  - Irregular first-trimester vaginal bleeding
    - Enlarge uterus
      - Pain from theca-lutein cysts
        - Exaggerated pregnancy symptoms: hyperemesis, hyperthyroidism, preeclampsia

- **USG – no fetus, presence of tecalutein cysts, ,,snow storm apearence'', low doppler resistance in uterine arteries after 9th week gestation (Jauniaux 1998)**

# Gestational Trophoblastic Disease

- **Management options**

  - Evacuation with suction curettage or medical termination in partial molar pregnancy

- **Follow-up**

  - Clinical

  - βhCG surveillance (<5IU/L)

  - Adjuwant chemotherapy may be required in 10% of women after uterine evacuation

  - βhCG testing 6 weeks after any subsequent pregnancy-risk of throphoblastic disease

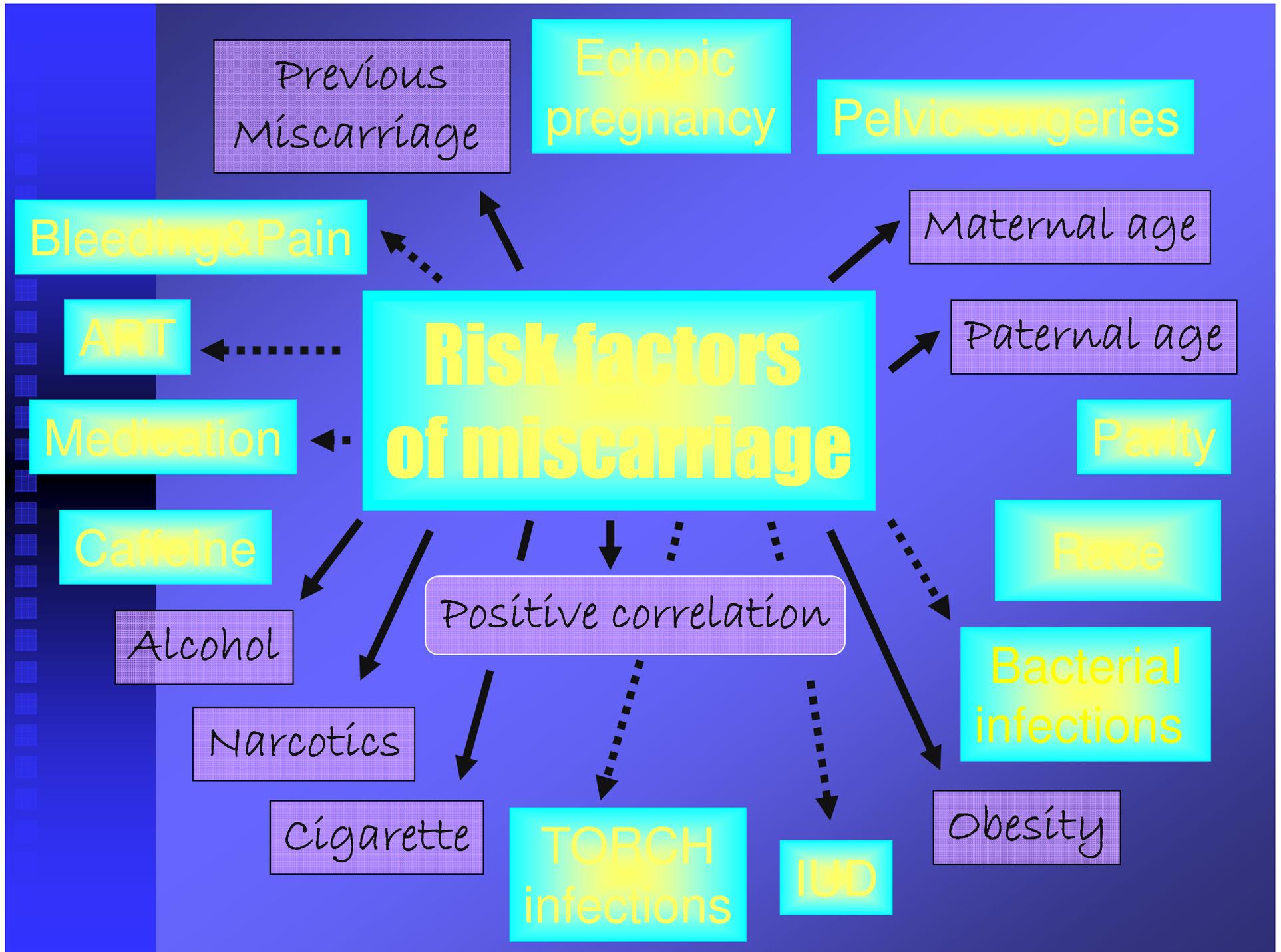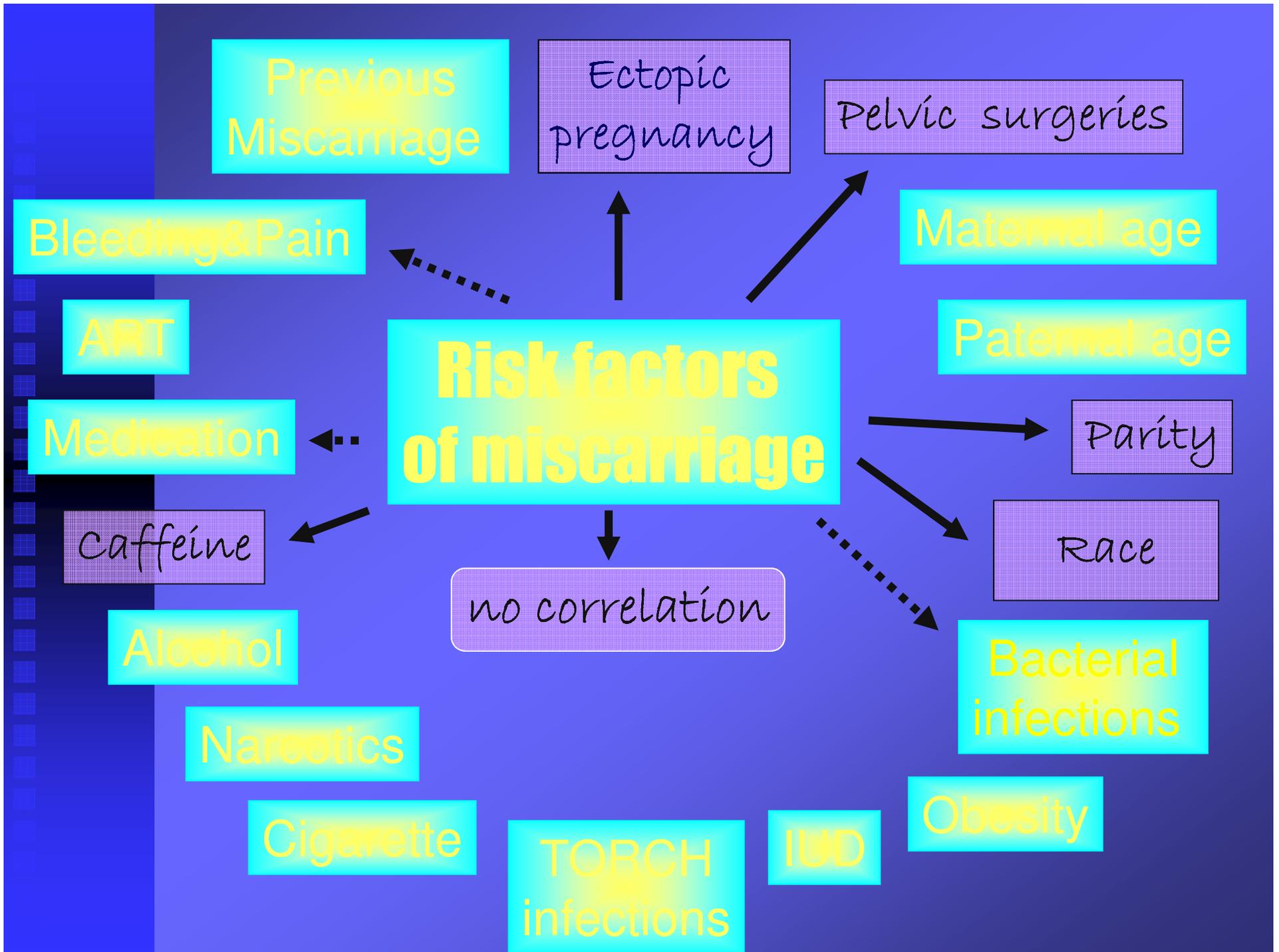   Curry et al.1975, Hancock et al.2002
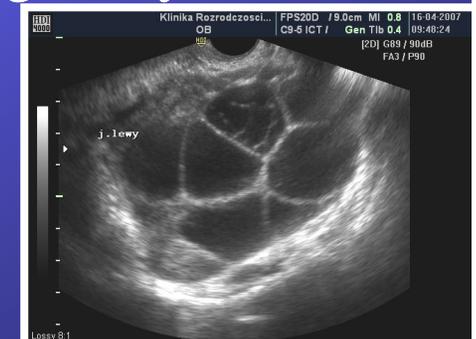
Adnexal masses in early pregnancy

- The incidence of adnexal pathology in first trimester varies from 0.17-2.94%

- Expectant management is advocated at least until pregnancy is beyond 14 week's gestation Caspi et al.2000

- Only 1.2% of lesions persisted beyond 16 weeks Czekierdowski et al.2001

- It should be differenciated between germ cell tumors and placental site trophoblastic tumors Condous 2003

Early pregnancy complications

- Indications for diagnostic management
- Laboratory tests
- Ultrasound examination
- Prognosis for normal pregnancy development
- Differential diagnosis
- Risk factors
- Management options in diagnosed miscarriage
- Role of EPAU service

Risk factors of miscarriage

Previous Miscarriage
Ectopic pregnancy
Pelvic surgeries
Maternal age
Paternal age
Parity
Race
Bleeding&Pain
ART
Medication
Caffeine
Alcohol
Narcotics
Cigarette
Positive correlation
TORCH infections
IUD
Bacterial infections
Obesity

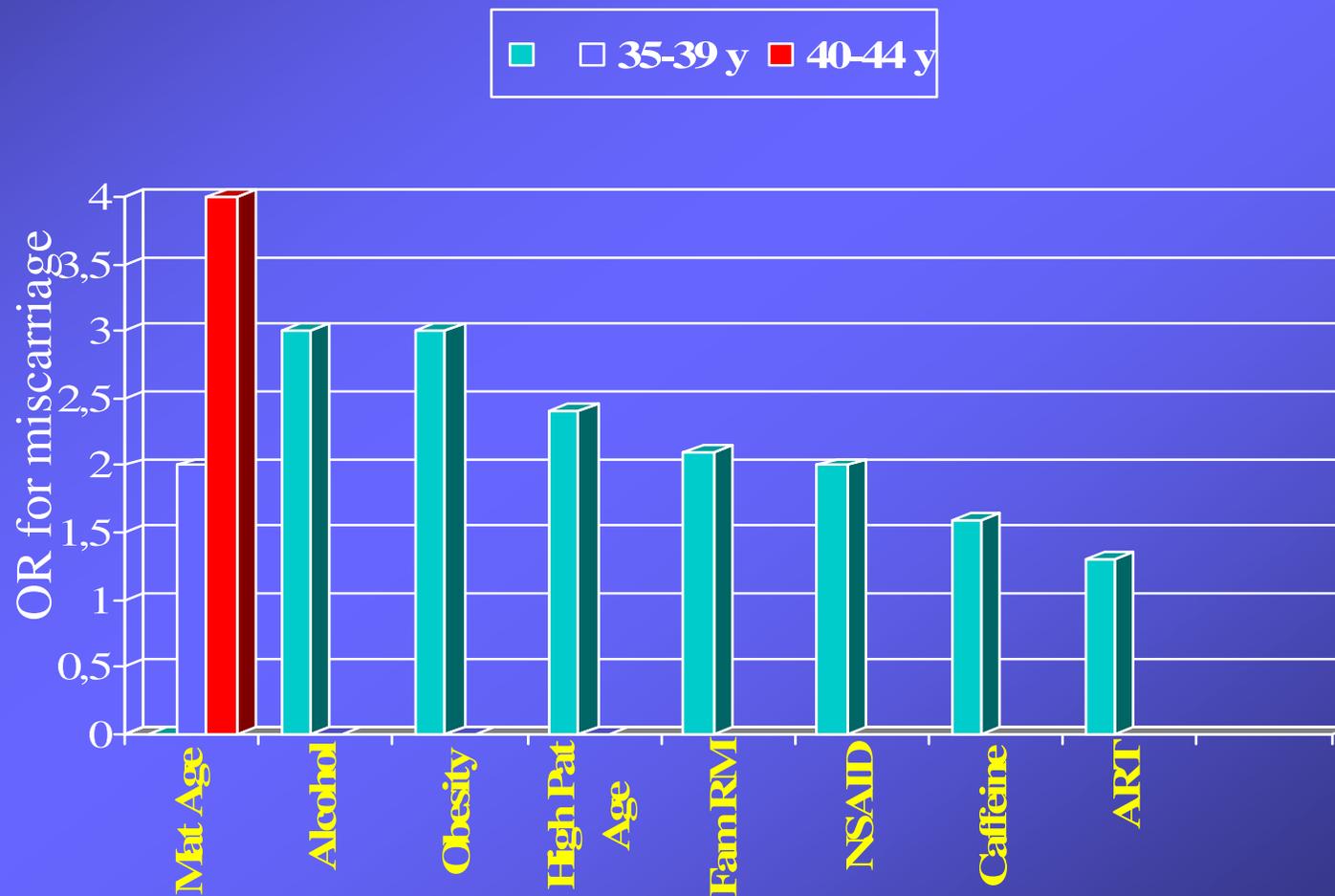# Clinical risk factors for miscarriage ranked according to strength

Early pregnancy complications

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- Conclusion

Management options in diagnosed miscarriage

- Expectant management

- Medical management

- Surgical intervention

- Infection prevention

- Rhesus prophylaxis

- Psychological support

Expectant management
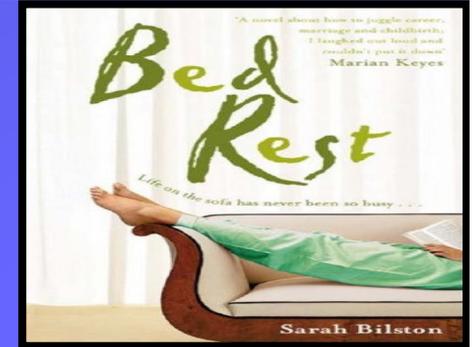
- There is no increased risk of complications for women who underwent expectant management of incomplete miscarriage to a surgical approach Neilsen and Halin 1995 *(complication rate in expectant group 3% and in surgical group 11%)*

- Is method of choice if the products of conception have mean diameter of less than 15mm Nielsen et al.1999

- There is no difference in psychological morbidity between expectant and surgical management Neilsen et al.1996

- Succes rate within this approach is 25-96% Jurkovic et al.1998;Sairam et al.2001

- Sucess rate of expectant management is variable across studies with completion rate of 80-96% within 2 weeks in incomplete miscarriage Luise et al.2002, Sairam et al.2001

- 76% of missed miscarriage and 66% of anembryonic pregnancies resolve without intervention Luise et al.2002

- Neither the presence of a GS within uterine cavity nor the thickness of endometrium is clinically useful in determining the outcome of expectant management Luise 2002

- The need for surgery can be based on the presence or absence of pain, bleeding, infection endometrium thickness > 15mm and patient's will

The conservative management of early pregnancy complications: a review of the literature

G. CONDOUS, E. OKARO and T. BOURNE

Early Pregnancy, Gynaecological Ultrasound and Minimal Access Surgery Unit, St George's Hospital Medical School, London, UK

Group classification at diagnosis	Patients	Complete miscarriage		Successful outcome by day 46
		By day 7	By day 14	
Incomplete miscarriage	221 (49)	117 (53)	185 (84)	201 (91)
Missed miscarriage	138 (31)	41 (30)	81 (59)	105 (76)
Anembryonic pregnancy	92 (20)	23 (25)	48 (52)	61 (66)
Total	451 (100)	181 (40)	314 (70)	367 (81)

*Values are numbers with percentages given in parentheses. Table reprinted with permission[7].

Expectant management of miscarriage—prediction of outcome using ultrasound and novel biochemical markers

J.Elson[1], A.Tailor[1], R.Salim[1], K.Hillaby[1], T.Dew[2] and D.Jurkovic[1,3]

Variable	Expectant (n = 37)	Surgical (n = 17)	P-value
Maternal age (years)[a]	32.3 (7.8)	32.2 (5.25)	>0.05
Gestational age (days)[a]	74 (13.6)	67.2 (26.2)	>0.05
Vaginal bleeding (%)[b]	95	76	>0.05
Diameter of products of conception (mm)[c]	18.6 (16–44)	24.7 (22–35.5)	<0.05
βHCG (IU/l)[c]	918 (254–2755)	5290 (2070–11 742)	<0.001
Progesterone (nmol/l)[c]	7 (5–16)	18 (9–39)	<0.05
17-αOH progesterone (ng/l)[c]	1.6 (0.9–2.1)	2.5 (1–2.9)	>0.05
IGFBP-1 (μg/l)[c]	30.9 (2.9–23.9)	29.2 (6.8–23.9)	>0.05
Inhibin A (pmol/l)[c]	24.6 (5.8–21.1)	74.8 (7.1–47.3)	<0.001
Inhibin pro α C-RI (pmol/l)[c]	259 (139–192)	499 (168–419)	<0.05

[a]Data distributed normally with values given as the mean and SD.

[b]Discrete data given as a percentage of a feature for each final outcome.

[c]Data distributed non-parametrically with values given as the median (25th to the 75th interquartile range).
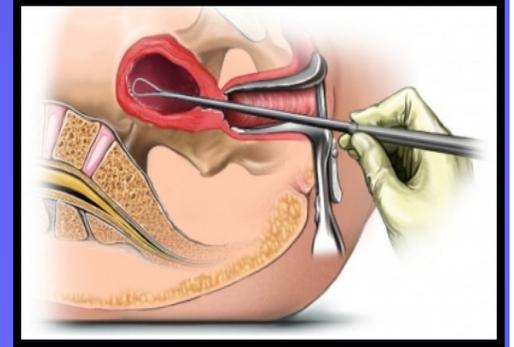
Medical management

- Treatment regimens include: misoprostol, sulprostone and gameprost (<9w.g.800-400mcg; >9w.g.400-400-400-400mcg)

- There is greater analgesic needs and vaginal bleeding Johnson et al.1997

- In 50-80% of women ERPC is still required Chung et al.1999, Ngai et al.2001

- Medical management of miscarriage has only benefit in early embryonic or fetal demise Nielsen et al.1999

- No differences are found in the number of days of bleeding, pain scores, blood loss or complication rate between pateints managed expectantly and medically Nielsen et al.1999

- Is indicated when the tissue mass is between 15-50mm Nielsen et al.1999

- Women choosing medical treatment appear to have better mental health score subsequently Wieringa-de Waard et al.2002
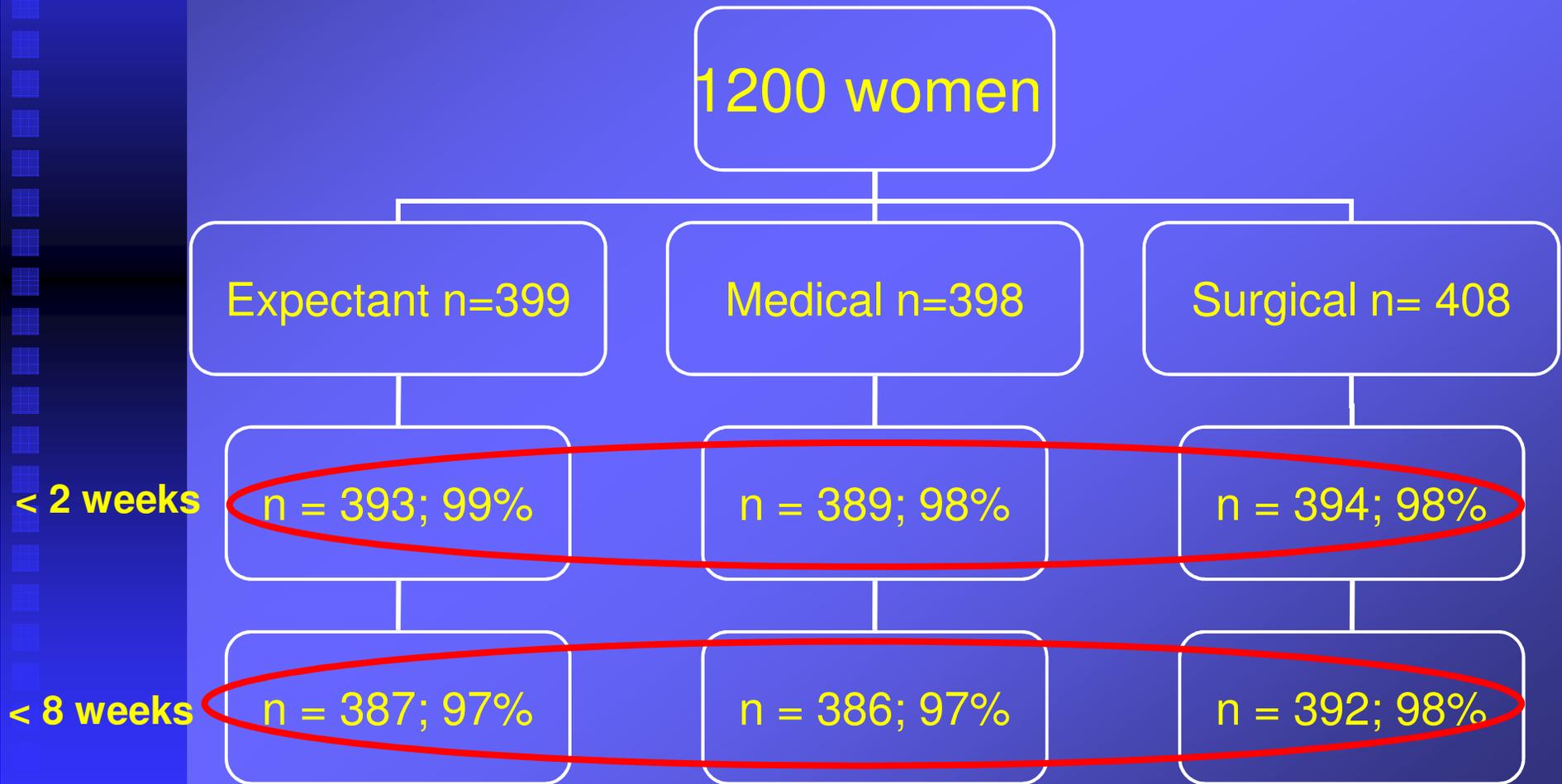
Surgical management

- Vacuum aspiration is preferred over surgical curettage (quicer, safer and less painful) Forna et al.2003

- Women of high parity are more likely to have a complete abortion after surgical management Child et al.2001

- ERCP is necessary if the tissue diameter exeeds 50mm and/or heavy bleeding is present Nielsen et al.1999

Miscarriage treatment *MIST trial*

Result of randomized, controlled studies
Including initially 3909 women from EPU

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                           ┌─────────────────┐
                           │   1200 women    │
                           └─────────────────┘
                ┌──────────────────┼──────────────────┐
        ┌───────────────┐  ┌───────────────┐  ┌───────────────┐
        │ Expectant     │  │ Medical n=398 │  │ Surgical n=408│
        │ n=399         │  │               │  │               │
        └───────────────┘  └───────────────┘  └───────────────┘
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< 2 weeks | n = 393; 99% | n = 389; 98% | n = 394; 98%

< 8 weeks | n = 387; 97% | n = 386; 97% | n = 392; 98%

Trinder et al. BMJ 2006, 332,1235-1240

Infection rate

- There is no increased incidence of infection between women managed surgically, medically or expectantly Tinder et al. (Mist trial) 2006

- In women undergoing surgical evacuation Metronidazol 1g supp. and Doxycycline 100mg/7 days are recommended Nanda et al.2006

- According to randomized trial Chlamydia screening and antibiotic treatment reduce infection rate in induce miscarriages only Prietto et al.1995

- No advantage of prophylactic Doxycycline in postoperative febrile morbidity in patients with incomplete abortion Jose 1995

Rhesus prophylaxis

- Complete spontaneous miscarriage without surgical intervention below 12 weeks do not require anti-D prophylaxis

- Anti-D prophylaxis is recommended in threatened miscarriage after 12 weeks and when heavy bleeding and abdominal pain are present

- 250IU anti-D immunoglobulin is required after surgical evacuation even before 12 weeks' gestation

- Women who have miscarriaged after 12 weeks' gestation require anti-D (250IU anti-D immunoglobulin)

- Anti-D immunoglobulin should be given within 72 hours of the sensitizing episode and when neccesary repeated at intervals of no more than 6 weeks (the half-life is 2 weeks)
  Robson et al.1998; Murphy et al.1994

Psychological support

- Specific antenatal councelling and psychological support increase pregnancy success rate of 86% compared to 33% Clifford et al.1997

- The combination of information with medical and psychological care is superior in reducing women's distress over benefits obtained solely through medical care Nikcevic 2003

Early pregnancy complications

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EPAU service
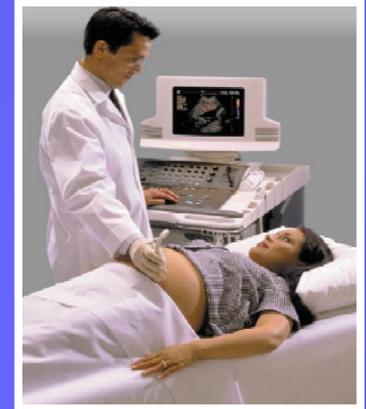
- Availability of rapid access to serum βhCG measurement same-day βhCG estimation

- Good quality ultrasound machines with high resolution TVS

- Introduction of fast-track referrals to early pregnancy assessment units or clinics experienced medical and nursing staff

Early pregnancy complications

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Conclusion

- In asymtomatic women without previous history of ectopic pregnancy the initial scan can be delayed until 49 days in order to reduce number of inconclusive scans and need for unnecessary blood test and TVS examinations Bottomley et al.2009

- Fetuses with slow heart rate (<120bpm) and empty GS>20mm in I trimester threatened abortion are at high risk for pregnancy loss

- Endometrial thickness <15mm and negative urinary test or hCG level<50IU/l are characteristic of complete miscarriage

Conclusion

- A cut-off of 200IU/L for serum β-hCG allows to differentiate between viable and abnormal pregnancies

- Progesterone level <25nmol/L in anembryonic pregnancy is diagnostic of nonviability

- Serum inhibin A levels are the most powerful predictor of successful expectant management of miscarriage

- High level of E2 >200pg/ml in early pregnancy is associated with a good outcome

Conclusion

- Following up patients with a combination of hCG and ultrasonography remains so far the optimal diagnostic strategy to evaluate patients with symptomatic early pregnancy

- Recent studies suggest that traditional early pregnancy growth curves developed by Robinson (1973) and Hadlock (1992) may not be optimal for various ethnic populations and maternal age. Only accurate individualized dating of all pregnancies in first trimester may help to predict several complications in later pregnancy

Thank You for Your attention