

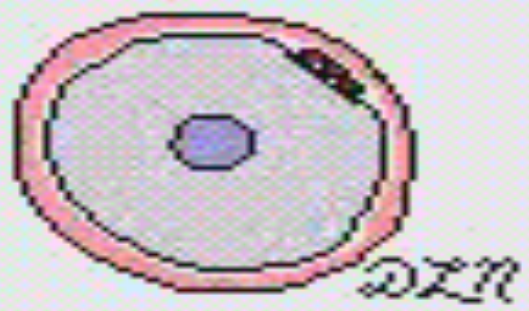
# Early Pregnancy

## - evaluating the signs and signals

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# Declaration of Interests

- Chair elect, European Society of Human Reproduction and Embryology (ESHRE) (2015 -2017)
- NICE Guideline Development Group (CG 154, 2010-2013)  
NICE Evidence Update Advisory Group, 2014
- Chair, Association of Early Pregnancy Units, UK (2006-2011)
- ESHRE Co-ordinator, Special Interest Group for Early Pregnancy (2007-2010), Executive Committee (2011-2015)
- Associate Editor, Human Reproduction Update (2010-2014)

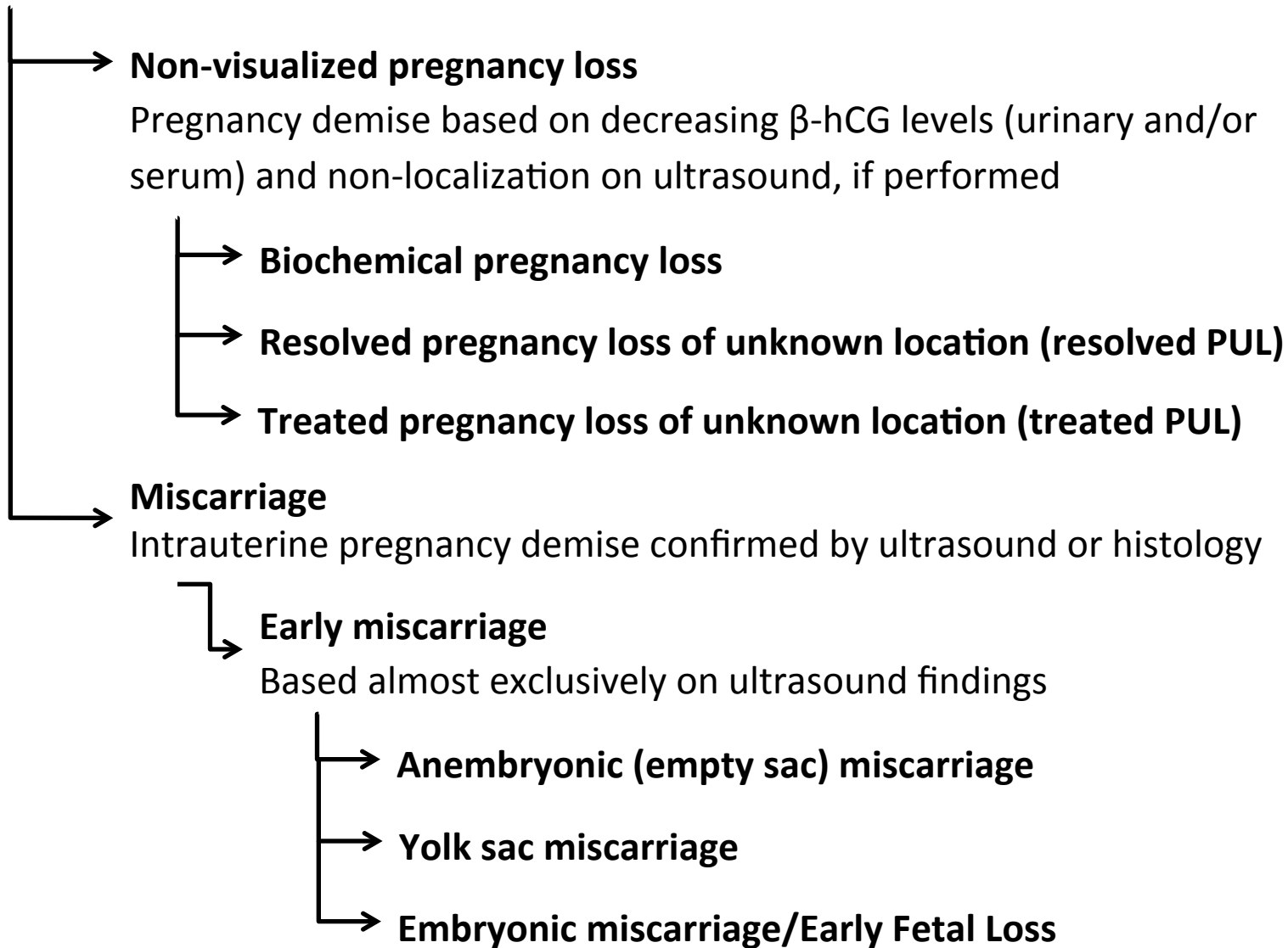


# Predictive Modelling for Early Pregnancy

<b>Area of Interest</b>	<b>Best Diagnostic Utility</b>	<b>Parameter(s)</b>
Ovulation	Biomarker	D21 Progesterone
Pregnancy of Unknown Location (PUL)	Transvaginal (TVU) Scan and Biomarker	TVU Scan + HCG ratio +/- Progesterone
Pregnancy of Uncertain Viability (PUV)	Scan Scan Exclusively Scan	Fetal heart action plus Crown-rump length

# Early pregnancy loss – the Timeline Transition

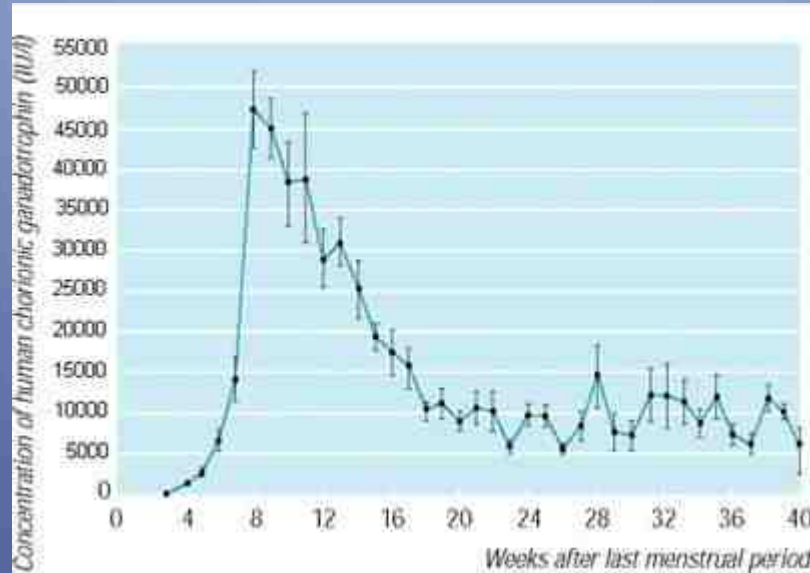
Spontaneous pregnancy loss *from 0 to <10 weeks'* gestation



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



# HCG changes in normal pregnancy



- Mean (SE) serum concentrations of human chorionic gonadotropin (adapted from Braunstein et al 1976)



**Positive hCG = pregnancy**

## **Pregnancy loss**

Spontaneous pregnancy demise

### **Ectopic pregnancy**

A pregnancy outside the endometrial cavity

### **Early pregnancy loss**

Pregnancy demise <10 weeks' gestation

### **Fetal miscarriage**

Pregnancy loss  $\geq 10$  weeks' size and a fetus ( $\geq 33$  mm) on ultrasound

### **Still birth**

Birth of a dead child after threshold of viability (22-28 weeks' gestation)



# PUL

Haemodynamically stable

Pain free

Expectant management

Serum hCG levels  
at 0 and 48 hrs +/-  
progesterone

Intra-uterine Pregnancy

Ectopic Pregnancy

Failing PUL or  
Non-visualised  
Pregnancy Loss  
(NVPL, 2015)

Haemodynamically stable

Pain

? Serum hCG

Consider laparoscopy

Haemodynamically unstable

Pain

Consider laparoscopy/  
laparotomy

# Serum hCG Levels

Single Levels

Serial Levels

Change over 48hrs  
(hCG ratio)

Intrauterine Pregnancies (IUPs)

- Kadar et al. (1981) first to describe the minimal rate of rise for an IUP to be 66% over 48hrs

# Serum hCG Levels

Single Levels

Serial Levels

Change over 48hrs  
(hCG ratio)

NVP Loss 2015 (Failing PULs)

- A decline of 21-35% at 48 hours depending on initial hCG level (*Barnhart et al. 2004*)(*Condous et al., 2006*)

# Serum hCG Levels

Single Levels

Serial Levels

Change over 48hrs  
(hCG ratio)

Ectopic Pregnancy (EP)

- 'No single way to characterize the pattern of serum hCG behaviour' as hCG profile mimicked IUP in 21% and a spontaneous miscarriage in 8% (*Silva et al., 2006*)

# Predicting outcome

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

# Serum Progesterone Levels

Serum Progesterone

< 20 nmol/L

PPV > 95% to predict pregnancy failure  
(*Banerjee et al., 2001*)

Viable IUPs reported with levels < 16nmol/L egMAR

> 60 nmol/L

'Strongly' associated with viable pregnancies

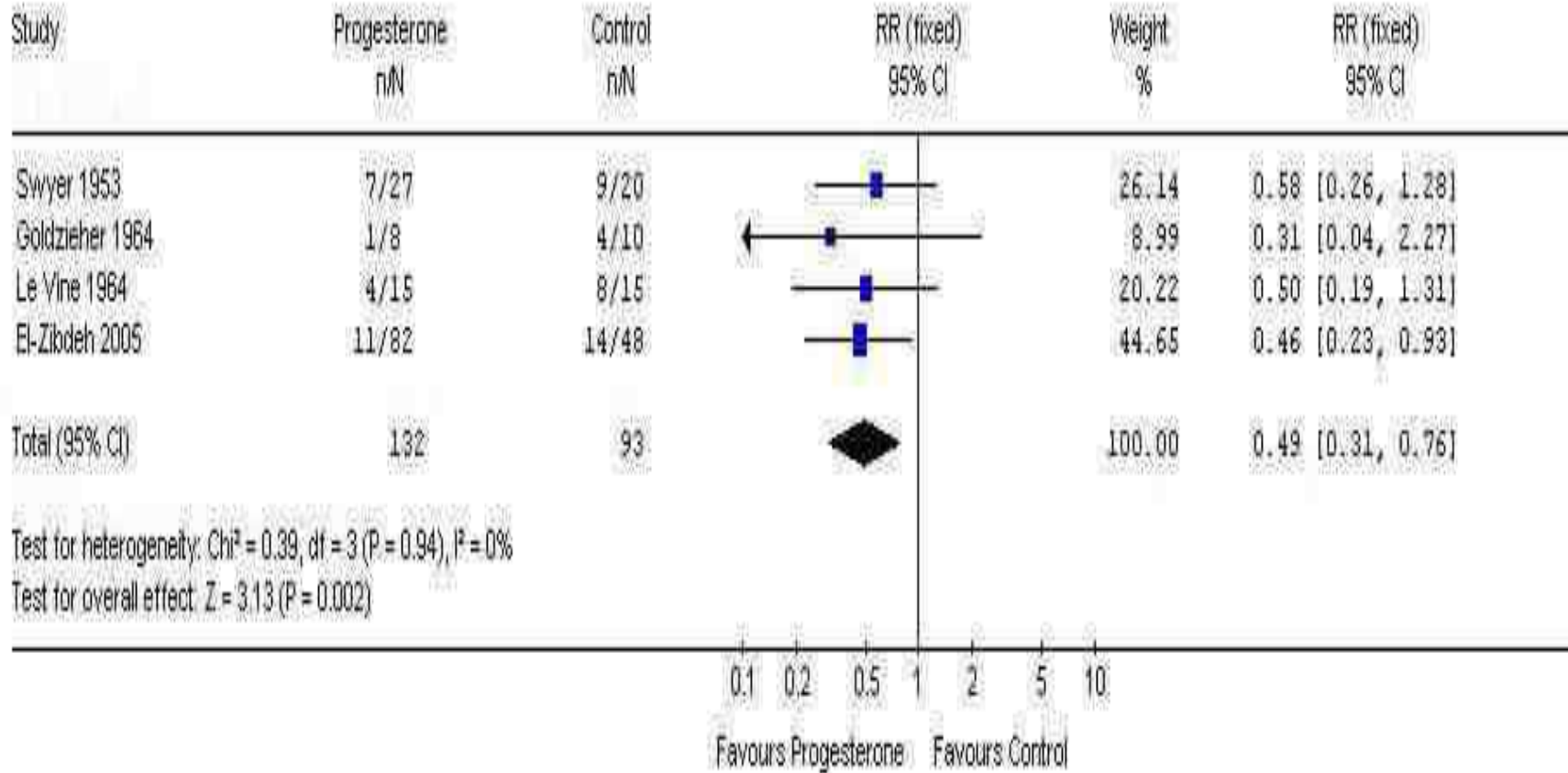
Discriminative capacity insufficient to diagnose ectopic pregnancy with certainty (*Mol et al., 1998*)

Good at predicting viability but not location

# Physiological properties of endogenous Progesterone

Site of action	Effect
Endometrium and uterus	<ul style="list-style-type: none"> <li>• converts the <a href="#">endometrium</a> to its secretory stage to prepare the uterus for implantation.</li> <li>• Anti-mitogenic effects in endometrial epithelial cells</li> <li>• decreases the maternal <a href="#">immune</a> response to allow for the acceptance of the pregnancy</li> <li>• decreases contractility of the uterine <a href="#">smooth muscle</a>.</li> <li>• induces myometrial quiescence by suppressing cytokines, prostaglandins, response to oxytocin and prevents formation of gap junction</li> </ul>
Ovaries	<ul style="list-style-type: none"> <li>• autocrine regulation of ovarian function and ovulation</li> <li>• involved in modulating the morphology and physiology of the oviduct, providing an optimal environment for oocyte maturation, sperm capacitation, fertilization and bi-directional transport of gametes and embryos</li> </ul>
Mammary glands	<ul style="list-style-type: none"> <li>• inhibits lactation during pregnancy. The fall in progesterone levels following delivery is one of the triggers for milk production.</li> </ul>
Cervix	<ul style="list-style-type: none"> <li>• possible role in preserving cervical length</li> </ul>

# Progesterone supplementation in RPL – Cochrane review (2005)





# PROMISE RCT 2015 – primary outcomes

*(Largest RCT in RPL; New England Journal of Medicine, 2015, 373, 2141-8)*

Outcome	Progesterone n (%)	Placebo n (%)	Relative risk (95% confidence interval)	P value
Pregnancy outcomes				
<i>Number of participants</i>	<b>398</b>	<b>428</b>		
Clinical pregnancy 6 to 8 weeks	326 (81.9)	334 (78.0)	1.05 (0.98 to 1.12)	0.16
Ongoing pregnancy 12 weeks	267 (67.1)	277 (64.7)	1.04 (0.94 to 1.14)	0.47
Ectopic pregnancy	6 (1.5)	7 (1.6)	0.92 (0.31 to 2.72)	0.88
<b>Miscarriage</b>	<b>128 (32.2)</b>	<b>143 (33.4)</b>	<b>0.96 (0.79 to 1.17)</b>	<b>0.70</b>
Stillbirth	1 (0.3)	2 (0.5)	0.54 (0.05 to 5.92)	0.61
<b>Live births (<math>\geq 24^{+0}</math>)</b>	<b>262 (65.8)</b>	<b>271 (63.3)</b>	<b>1.04 (0.94 to 1.15)</b>	<b>0.45</b>

# HCG in practice (NICE 2012 )

- Clinical symptoms more important than HCG results
- HCG levels do not 'locate' the pregnancy nor assess viability
- 2 levels 48 hours apart are useful for **'risk stratification'** and act as best evidence for subsequent management
- Limitations of prediction should be shared and **acknowledged to patients** (eg ectopic pregnancy HCG levels mimic viable IUP in 21% and EPL in 8%)
- *Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy. (NICE Clinical guideline 154; 2012; [www.nice.org.uk](http://www.nice.org.uk))*



# Sites of ectopic pregnancies

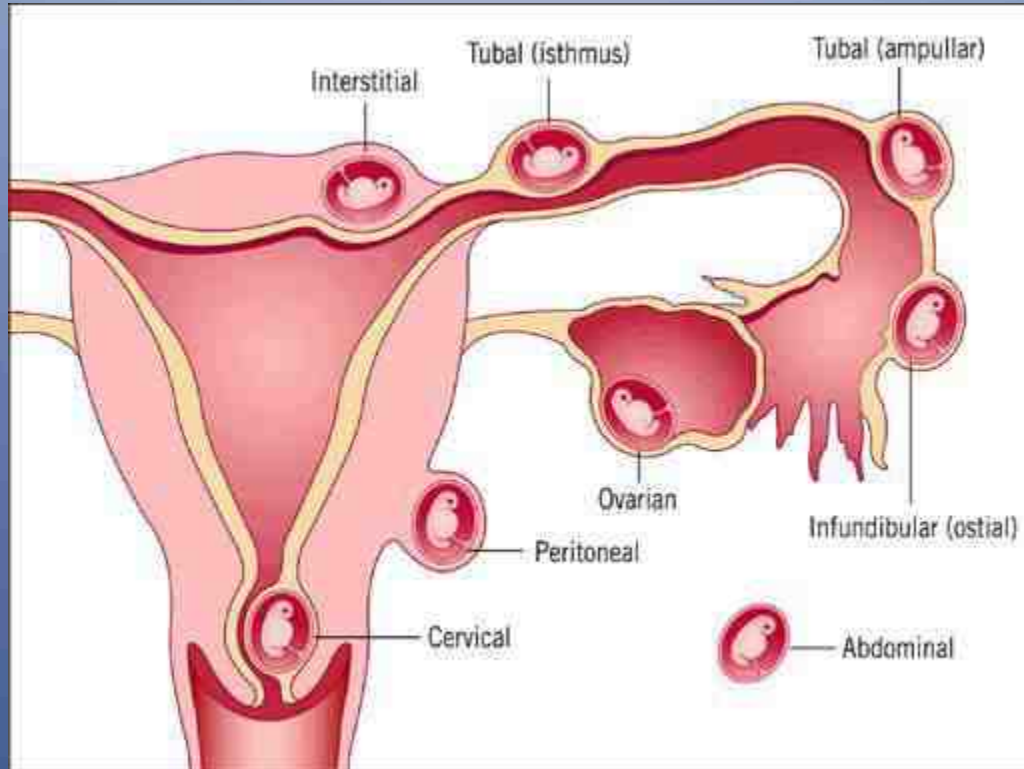


Illustration: John Yanson. Seeber. *Suspected Ectopic Pregnancy. Obstet Gynecol* 2006.

From: Seeber: *Obstet Gynecol*, Volume 107(2, Part 1). February 2006. 399-413



# Ectopic Pregnancy presentation

- **ACUTE (typical)**
- Collapse with lower abdominal pain, tachycardia and hypotension
- Pain, amenorrhoea and sign of pelvic tenderness
- EPU presentation with positive pregnancy test, scan showing empty uterus and adnexal inhomogeneous mass
- **CHRONIC (atypical)**
- Symptoms mimicking gastroenteritis
- Light irregular bleeding
- $>1/3^{\text{rd}}$  of all patients have no risk factors

# Treatment Options –

recent RCT evidence

- Laparoscopic surgery -  
Salpingectomy versus Salpingostomy (ESEP trial 2013)
- Systemic Methotrexate (MTX)
  - acts as folate antagonist and increases cell death in rapidly dividing trophoblast cell groups
  - single or multiple dose injection that still has a small failure rate
  - emerging role of gefitinib (EGFinhibitor:NIHR 2016 RCT)
- Expectant management – essential criteria for patient support and rapid access (DEMETER 2013; METEX 2013)

# It's all about Quality of Care

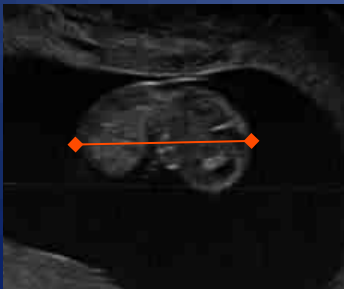


# The Signs of Miscarriage

- Exclusively ultrasound based
- Updated CRL measurements
- Revised **crown rump length** criteria for confirmed diagnosis of early pregnancy loss (>7mm; NICE GDG & RCOG 2012)
- Acknowledgement of inherent, wide biological variation of embryo growth velocities
- Specificity of viability assessment is 99.9%
- **Defining safe criteria to diagnose miscarriage: prospective observational multicentre study. BMJ, 2015 Sep 23;351:h4579. doi: 10.1136/bmj.h4579.**

# Updated Gestational Age Measurement in early pregnancy

- Total number of pregnancies: 6666 (2002-2008)
- No. Excluded = 2956 (uncertain dates, redated, infertility treatment, miscarriage, stillbirth, genetic or congenital abnormalities)
- No. Included = 3710 normal singleton pregnancies dated according to known and recorded last menstrual period (LMP) with confirmed viability at the time of the nuchal scan
- Predominantly transvaginal ultrasound below 10 weeks by contrast with Robinson transabdominal derived CRL curve (BMJ, 1972)
- The gestational age (GA) ranged between 35 and 98 days
- Linear mixed-effects model in order to account for possible co-dependency of multiple CRL measurements in the same patient

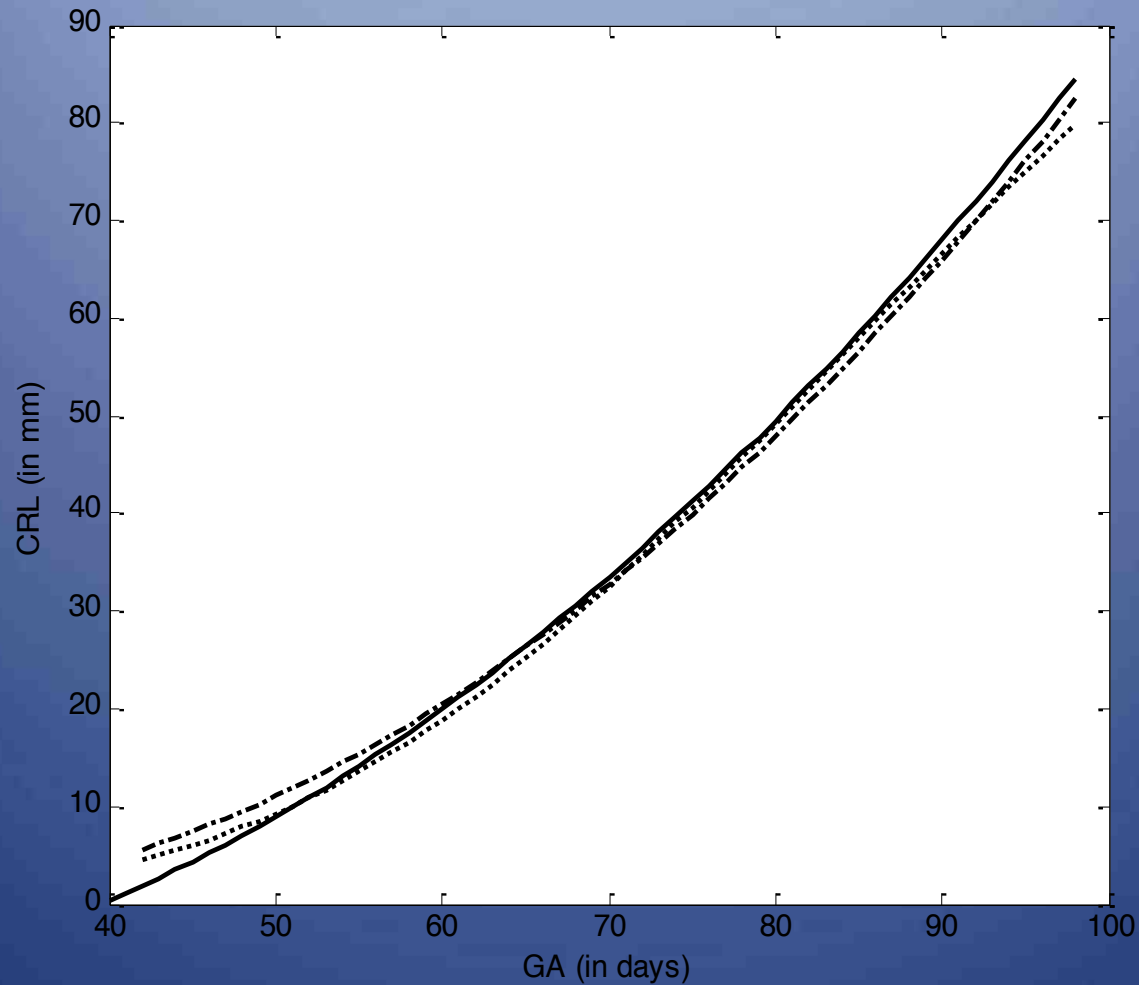


Reference: Abdallah Y, Daemen A, Guha S, Syed S, Naji O, Pexsters A, Kirk E, Stalder C, Gould D, Ahmed S, et al. *Ultrasound Obstet Gynecol.* 2011 Nov; 38(5): 503-9





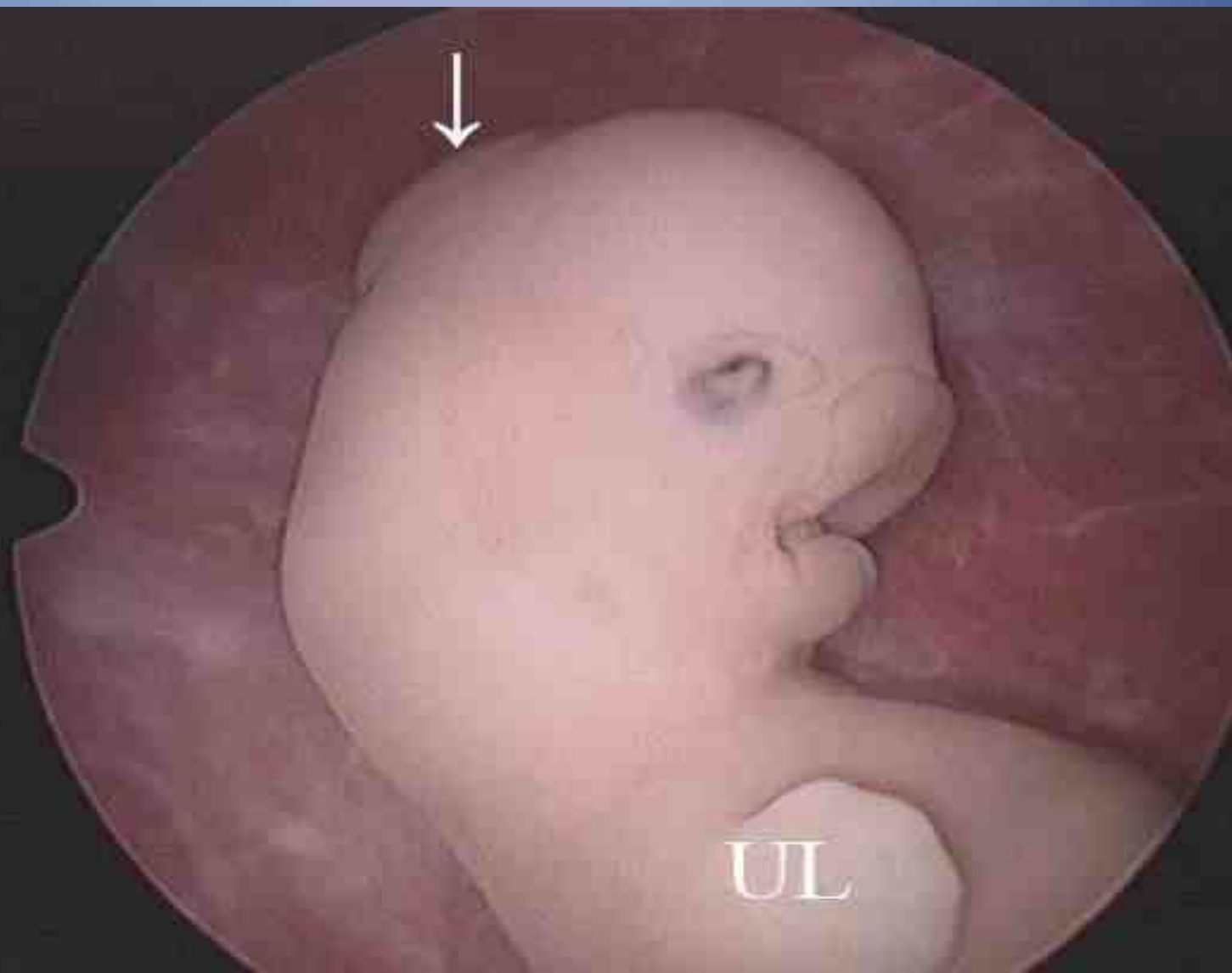
# Comparison of the CRL curve (solid line) with the Robinson curve (dashdotted) and the Hadlock curve (dotted)



# Fetal loss at 7 weeks CRL = 19mm

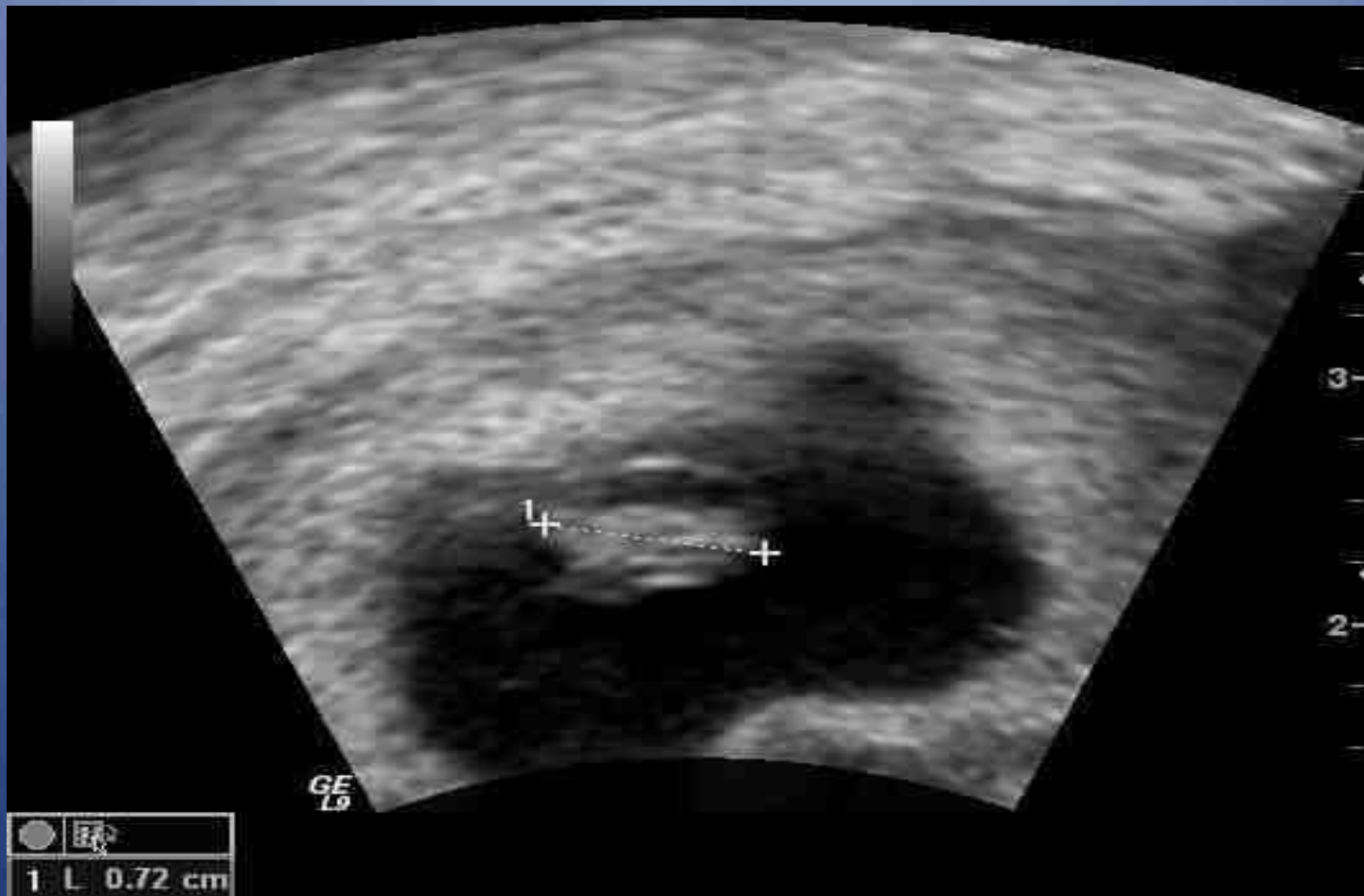


**Karyotype and Phenotype Characteristics can be different** ie normal chromosomes, developmental anomaly



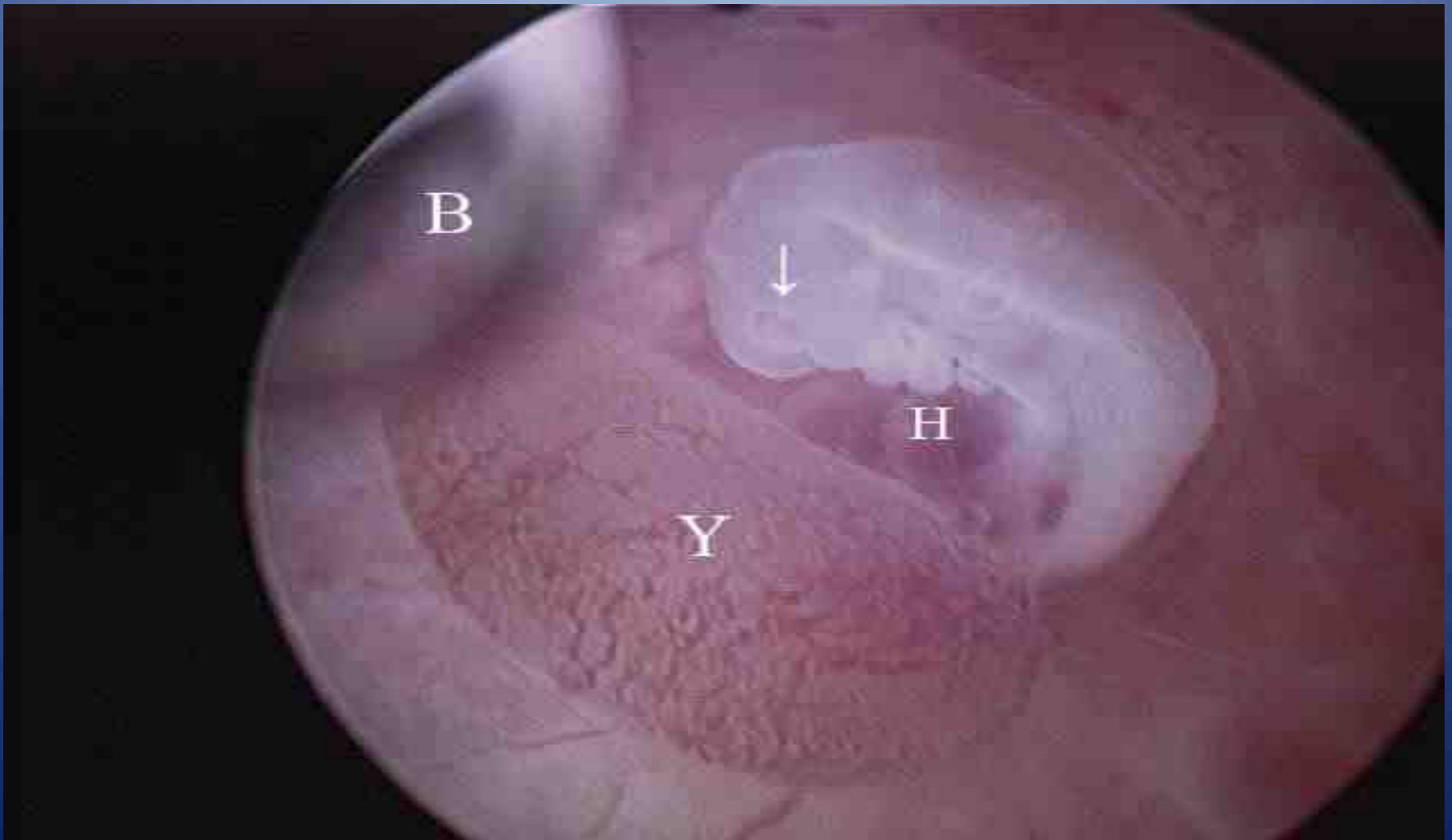
# TV Ultrasound

## Fetal loss with CRL = 7mm



# Embryoscopy – the close-up

H=head/heart prominence, Y=yolk sac, B=bubble



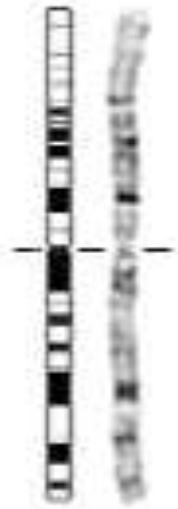
Opportunity is now where

# microarrays

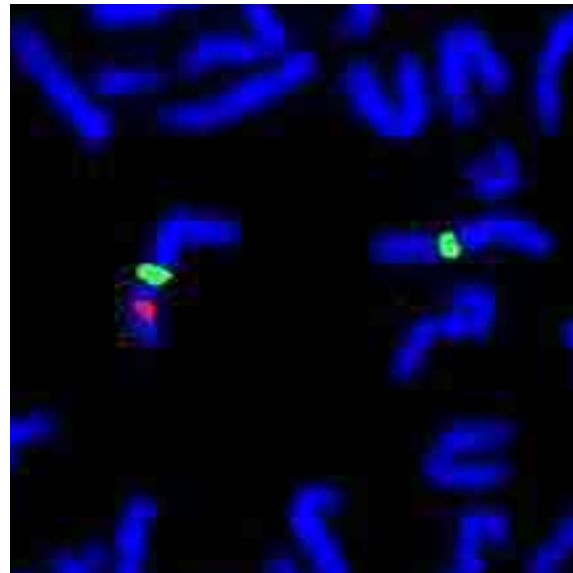
- technique

high resolution WHOLE genome scan with **NGS**

cytogenetics



FISH



arrays

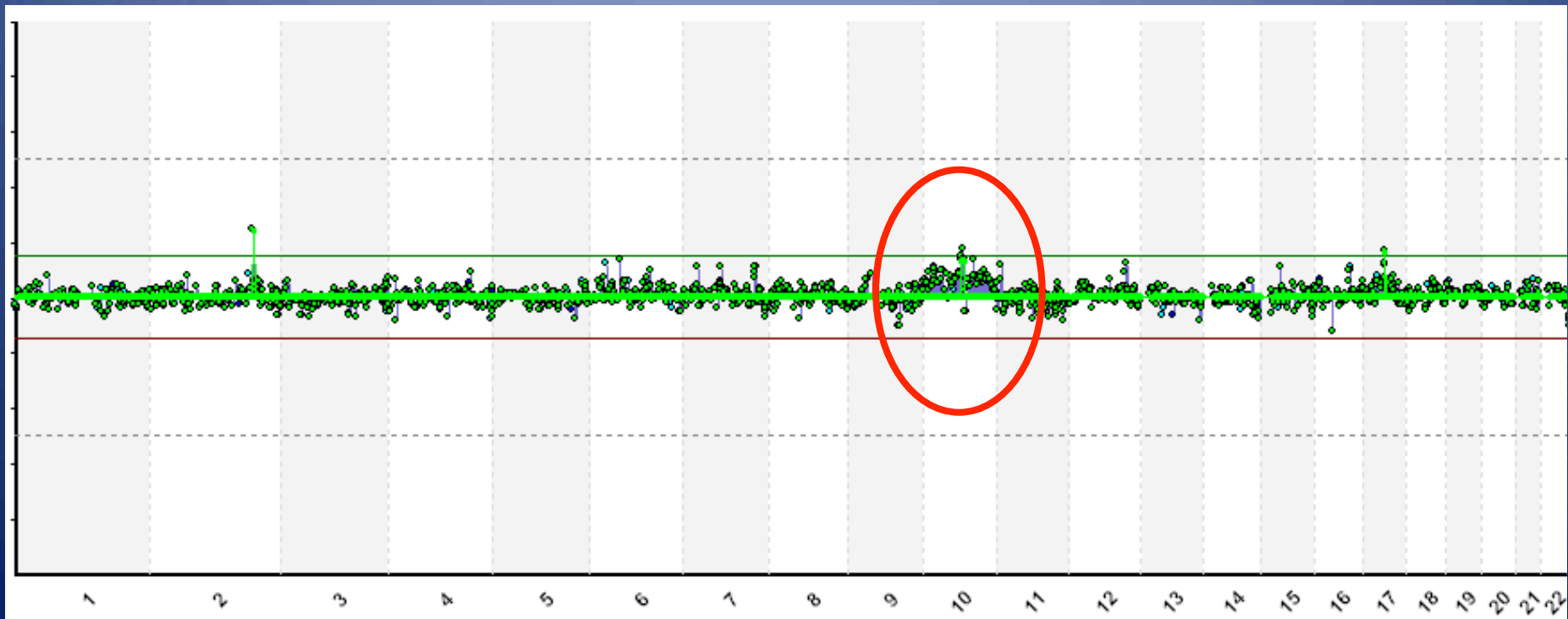


# • Trisomy 10 - TR

Karyotype = Normal Female

Array = **Abnormal MALE result +10**

FISH = confirmed +10 (70% MCC)



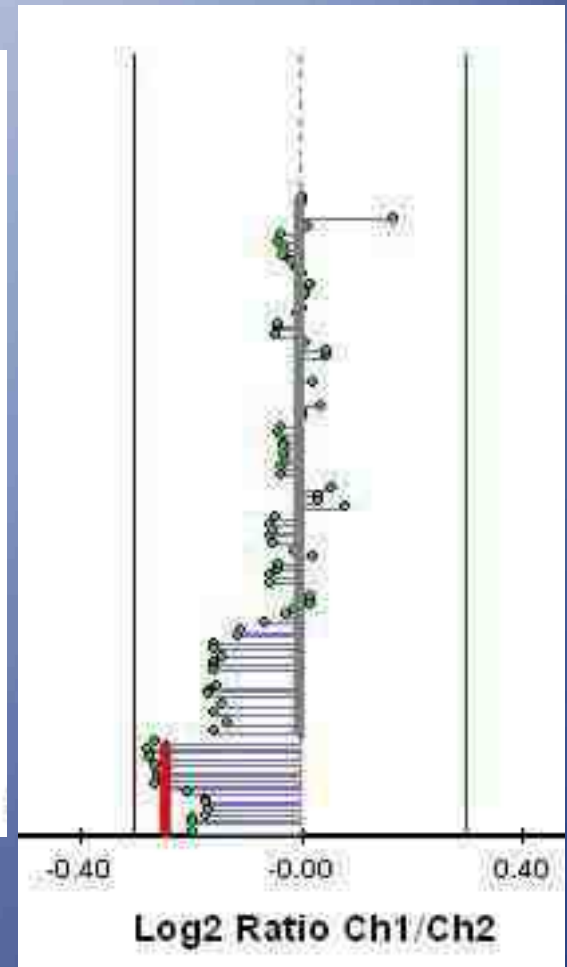
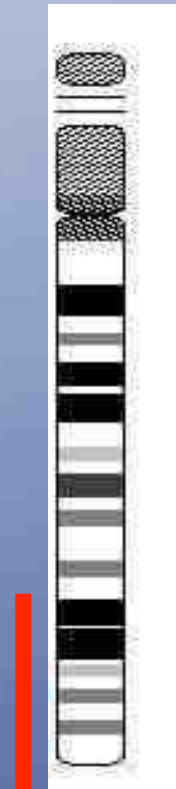


- 14q deletion - JS

Karyotype = Normal  
Female

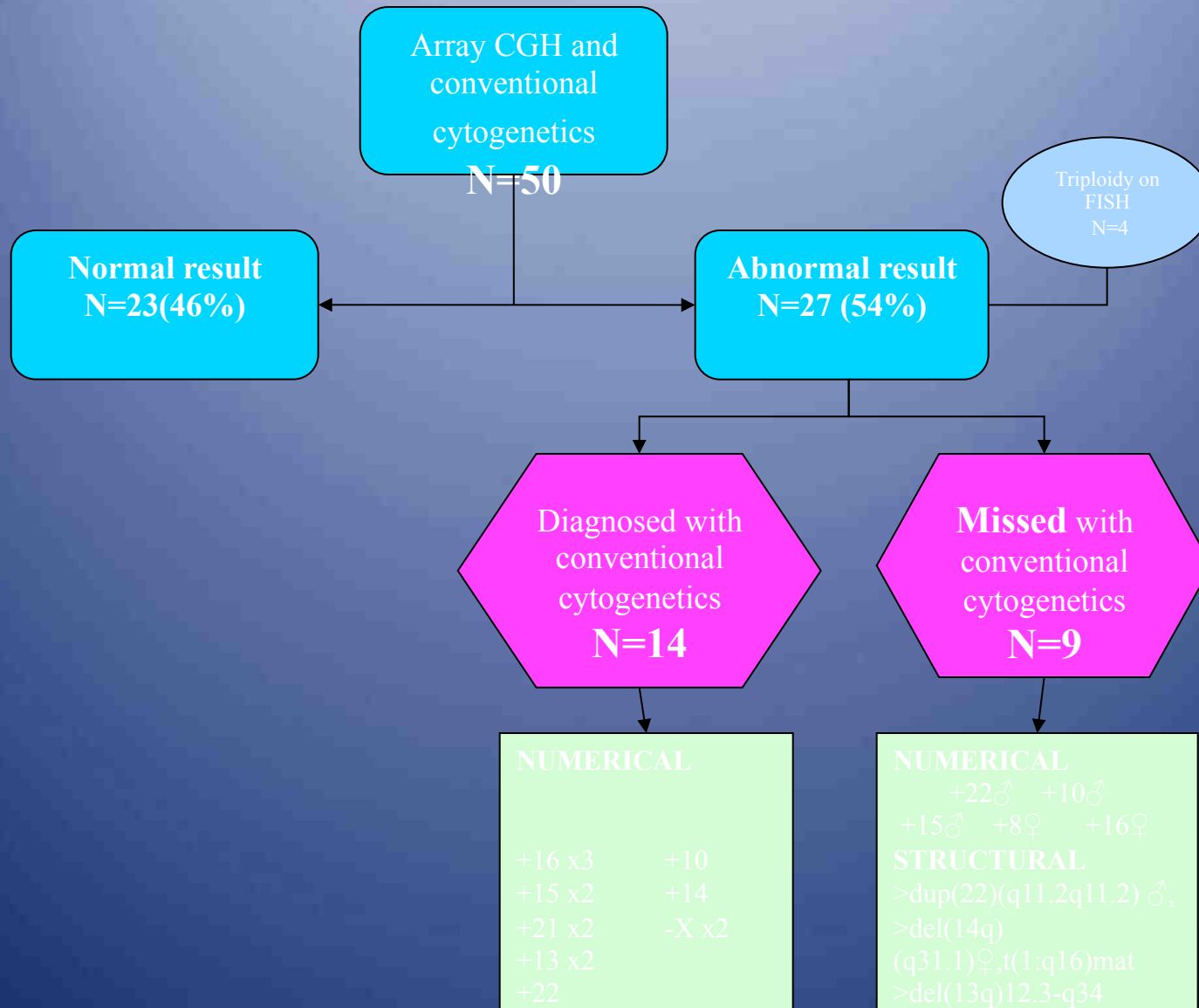
Array = **Abnormal Female –  
deletion 14q**

FISH = confirm deletion in 11%  
of cells (89% MCC)



# RM – Evaluation of Array CGH v Conventional Cytogenetics

(McNamee et al, British Journal of Hospital Medicine, 2013, 74, 36-40 )



# Pregnancy Success Prediction Matrix

Following idiopathic RM, the predicted probability (%) of successful pregnancy is determined by age and previous miscarriage history ( 95% confidence interval <20% in bold).

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Age (yrs)	Number of Previous Miscarriages			
	2	3	4	5
20	<b>92</b>	<b>90</b>	<b>88</b>	85
25	<b>89</b>	<b>86</b>	<b>82</b>	79
30	<b>84</b>	<b>80</b>	<b>76</b>	71
35	<b>77</b>	<b>73</b>	<b>68</b>	62
40	69	64	58	52
45	60	54	48	42

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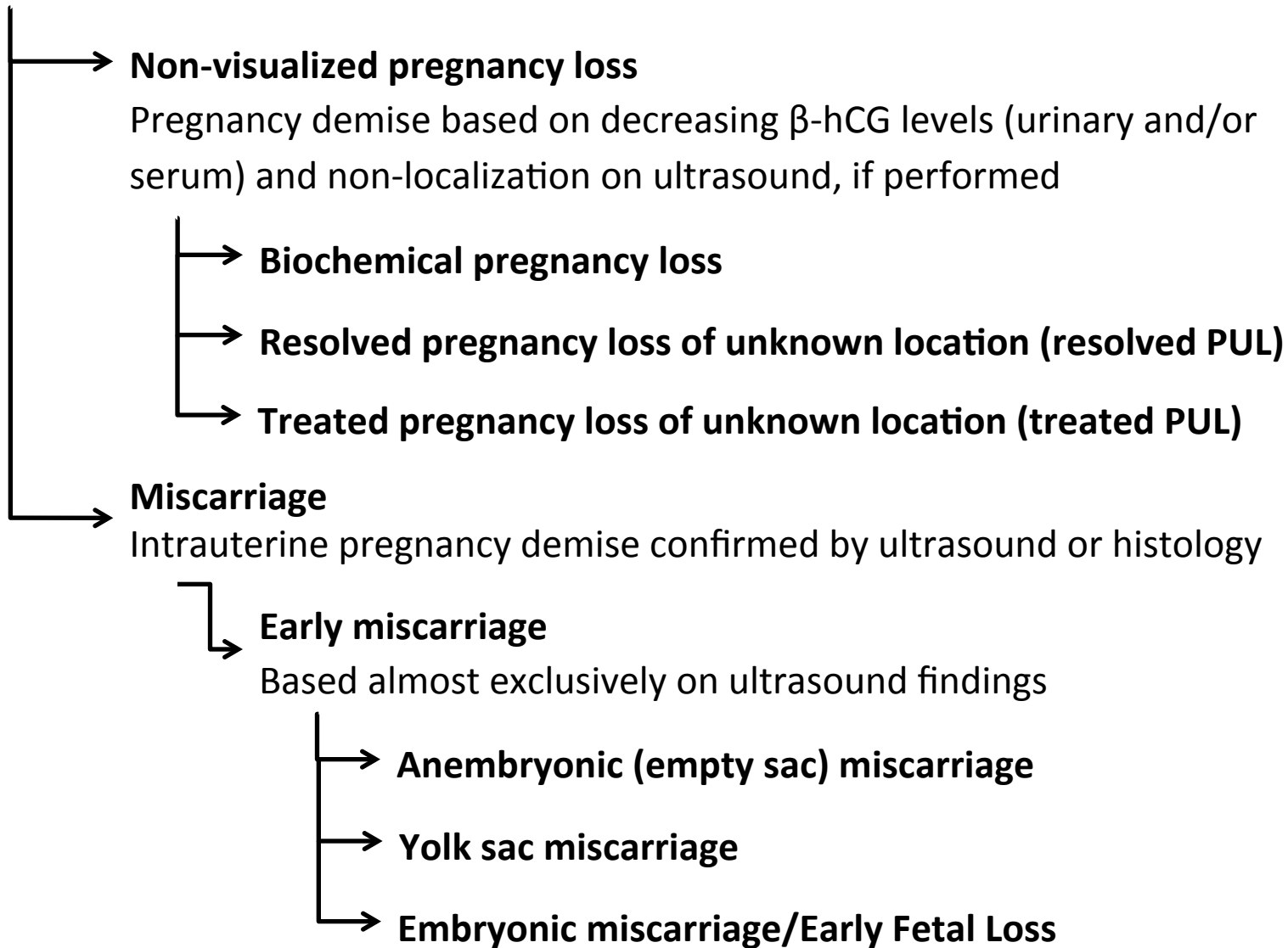
Brigham et al, Hum Rep, 1999, 14, 2868-2871; Lund et al, O&G, 2012, 119, 43-47

# Summary

- Following diagnosis of early pregnancy loss, all 3 management options are available for implementation and patient choice
- PUL and PUV should be evaluated over time and ectopic pregnancy excluded whenever possible
- If CCS is available in your unit, consider using CGH/NGS for all pregnancy losses....

# Early pregnancy loss

Spontaneous pregnancy loss **<10 weeks'** gestation



# Prediction or Patience?

- “There are events in the womb of time, as yet, undelivered “

from **Othello** (Act 1 Scene 2)

William Shakespeare

# ***Definition of pregnancy loss prior to viability***

**on behalf of the ESHRE Special Interest Group for Early Pregnancy**

**(Kolte A et al, Hum Rep, 2015, 30, 495-8)**

<b>Type of pregnancy loss</b>	<b>Definition</b>
<b>Early pregnancy loss</b>	Spontaneous pregnancy demise before 10 weeks of gestation age (before 8 <sup>th</sup> developmental week)
<b>Non-visualised pregnancy loss</b>	Spontaneous pregnancy demise based on decreasing serum or urinary hCG levels and non-localization on ultrasound, if performed
-Biochemical pregnancy loss	Spontaneous pregnancy demise based on decreasing serum or urinary hCG levels, without an ultrasound evaluation
-Resolved pregnancy loss of unknown location (resolved PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum hCG after expectant management or after uterine evacuation without chorionic villi on histology
-Treated pregnancy loss of unknown location (treated PUL)	Pregnancy demise not visualized on transvaginal ultrasound with resolution of serum hCG after medical management
<b>Miscarriage</b>	Intrauterine pregnancy demise confirmed by ultrasound or histology
-Anembryonic (or empty sac) miscarriage	Intrauterine pregnancy loss with a gestational sac but without a yolk sac or an embryo on ultrasound
-Yolk sac miscarriage	Intrauterine pregnancy loss with a gestational sac and yolk sac, without an embryo on ultrasound
-Embryonic miscarriage	Intrauterine pregnancy loss with an embryo without cardiac activity on ultrasound
-Fetal miscarriage	Pregnancy loss $\geq 10$ weeks size with a fetus ( $\geq 33$ mm) on ultrasound
<b>Ectopic pregnancy</b>	Ultrasonic or surgical visualization of a pregnancy outside of the endometrial cavity



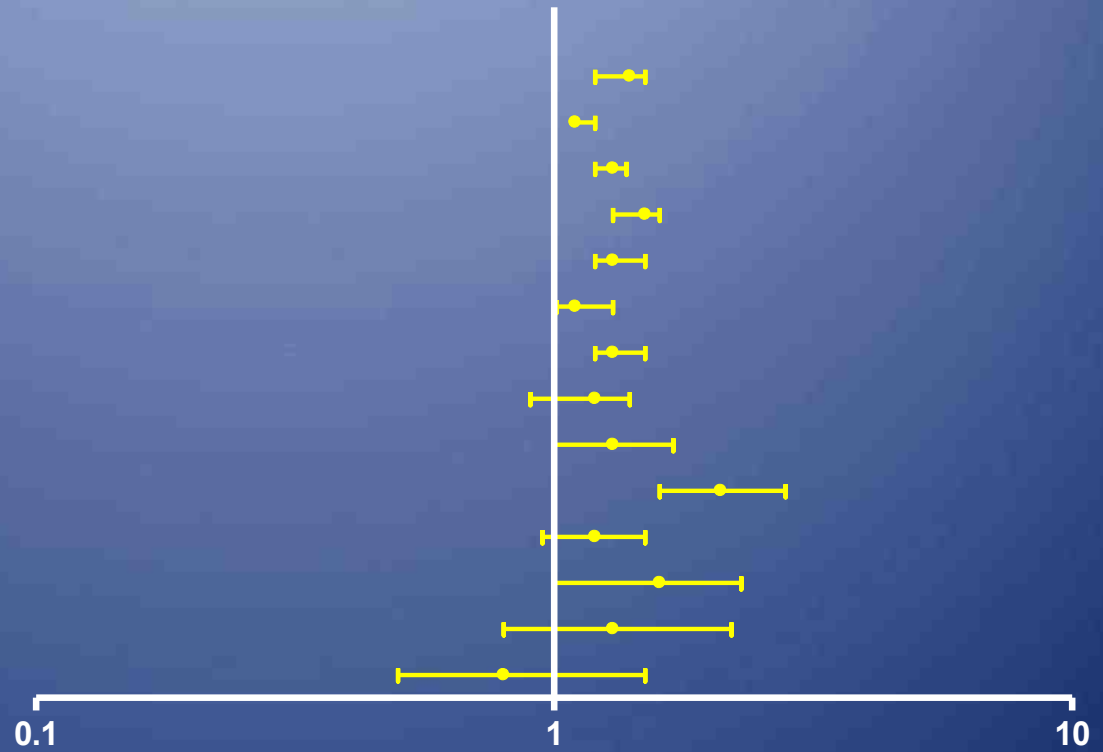


# Previous single miscarriage Risk of preterm delivery <37 weeks

OR 1.1-1.4

ONE MISCARRIAGE

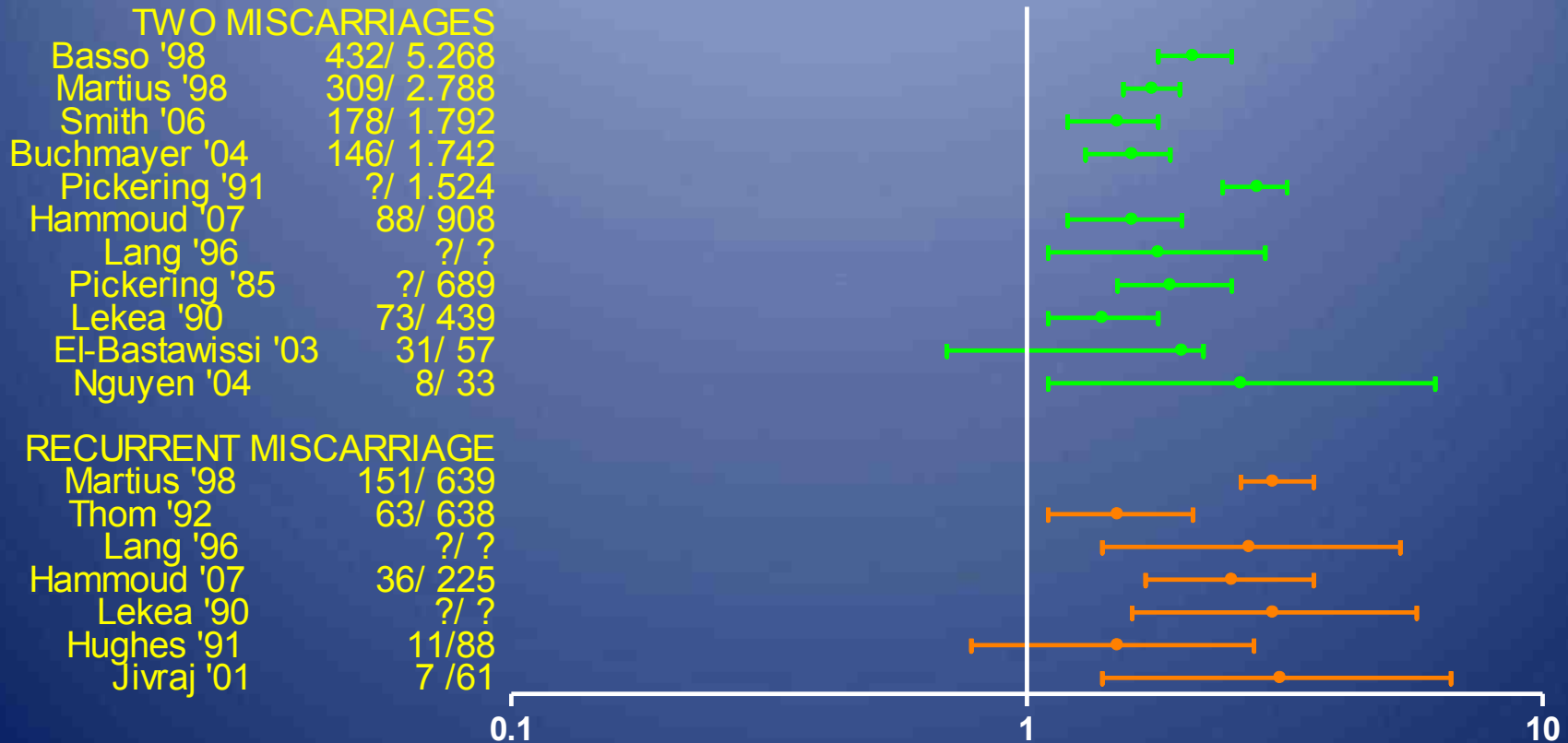
Basso '98	1.333/ 21.166
Buchmayer '04	1.293/ 21.631
Martius '98	1.069/ 13.461
Pickering '91	?/ 8.589
Smith '06	673/ 9.215
Hammoud '07	369/ 5.973
Pickering '85	?/ 3.927
Thom '92	174/ 2.146
Lang '96	?/?
Bhattacharya '08	128/ 1.404
Lekea '90	117/ 1.291
El-Bastawissi '03	69/ 143
Schoenbaum '80	17/189
Nguyen '04	16/164



# miscarriages

## Risk of preterm delivery <37 weeks

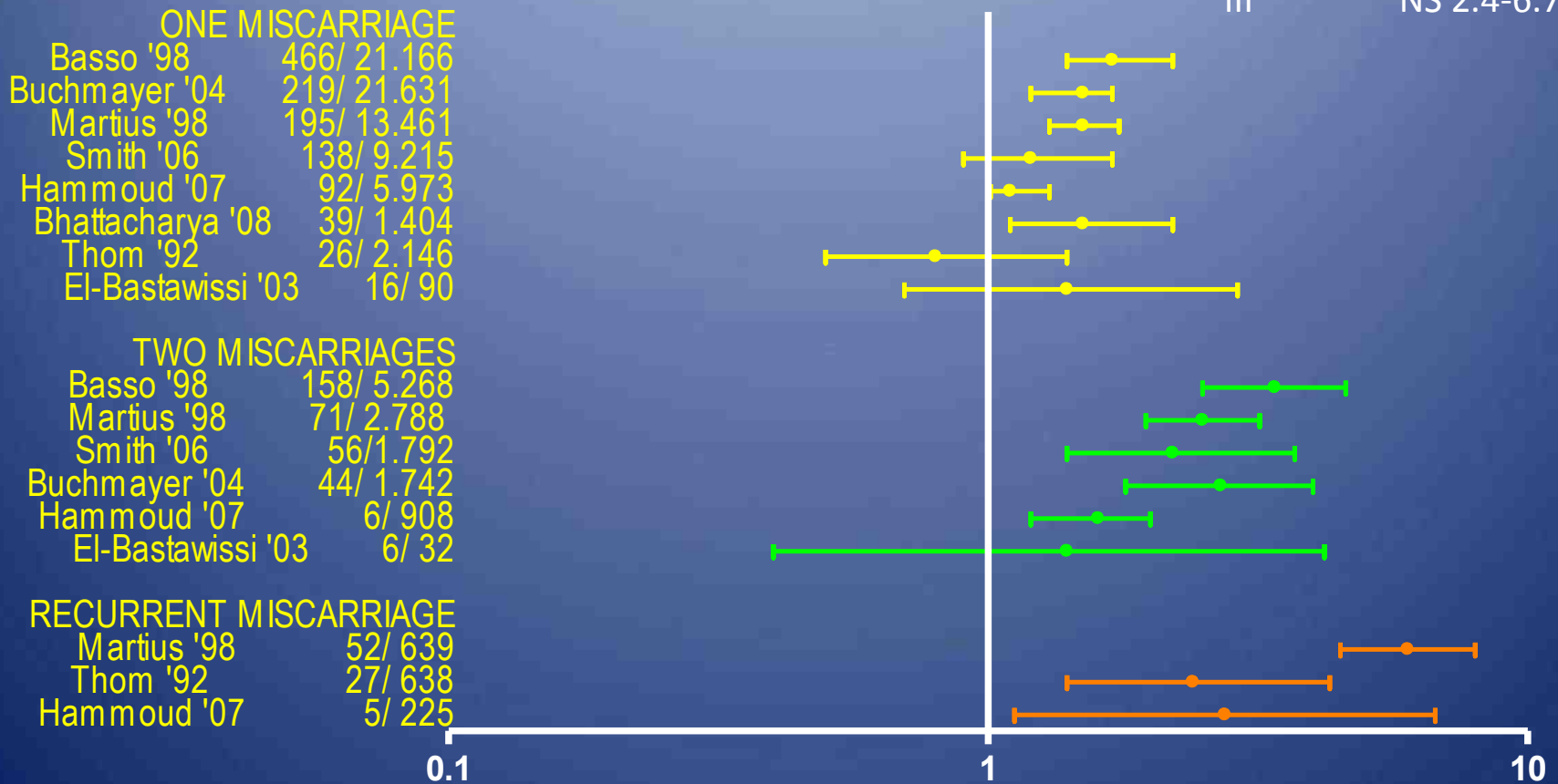
- I OR 1.1-1.4
- II OR 1.6-2.1
- III OR 1.5-3.0



# Previous miscarriage(s)

## Risk of very preterm delivery <34 weeks

I OR 1.5-1.7  
 II OR 2.2-3.4  
 III NS 2.4-6.7



# Previous miscarriage(s)

## Risk of small for gestational age

I NS  
II OR 1.4  
III NS (?)

### ONE MISCARRIAGE

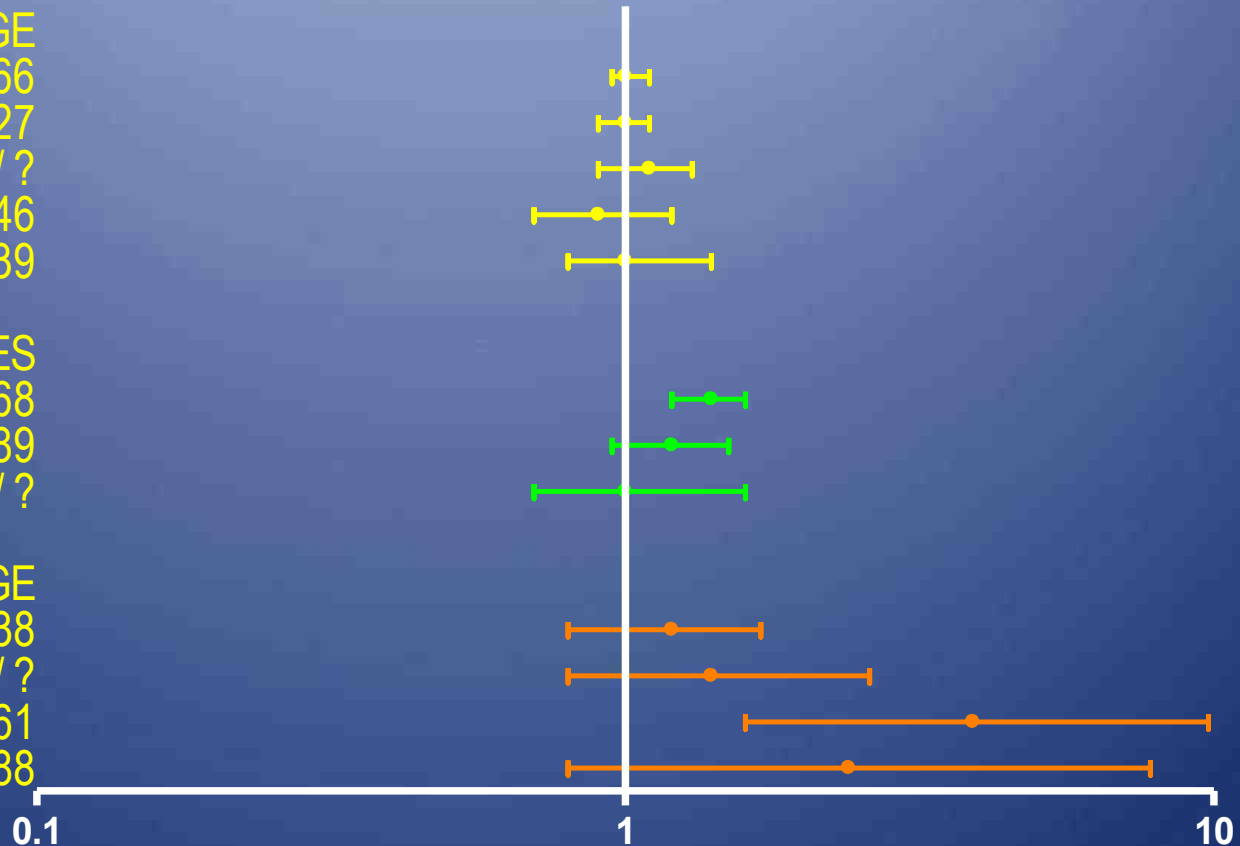
Basso '98 1.291/ 21.166  
Pickering '85 ?/ 3.927  
Lang '96 ?/ ?  
Thom '92 94/ 2.146  
Parazzini '07 96/ 439

### TWO MISCARRIAGES

Basso '98 395/ 5.268  
Pickering '85 ?/ 689  
Lang '96 ?/ ?

### RECURRENT MISCARRIAGE

Thom '92 41/ 638  
Lang '96 ?/ ?  
Jivraj '01 5/ 61  
Hughes '91 3/ 88



## Risk of adverse outcome in subsequent pregnancy

OR/ *RR	Miscarriage			Termination of pregnancy	
	1	≥2	≥3	1	≥2
Preeclampsia	1.0-3.3 <sup>1,2</sup>	1.0-1.5 <sup>4</sup>	-	ns	ns
Placental abruption	ns	1.5 <sup>4</sup>	-	ns	ns
Placenta previa	ns	1.7 <sup>4</sup>	*6.0 <sup>4</sup>	ns	ns
Preterm <37	1.1-1.4 <sup>3,5</sup>	1.6-2.1 <sup>3,5</sup>	*1.5-3.0 <sup>1,6</sup>	1.1-1.3 <sup>6,8</sup>	1.6-2.3 <sup>6,8</sup>
Preterm <34	1.5-1.7 <sup>3,5</sup>	2.2-3.4 <sup>3,5</sup>	*2.4-6.7 <sup>1,6</sup>	1.3-1.5 <sup>7,8</sup>	1.8-2.9 <sup>7,8</sup>
SGA p<10	ns	1.4 <sup>5</sup>	? <sup>1</sup>	ns	ns
LBW <2500	ns	? <sup>4,5</sup>	*2.0 <sup>4</sup>	ns	ns
LBW <1500	ns	ns	-	? <sup>9,10</sup>	? <sup>9</sup>
Cong. Malformation	ns	ns	*1.8 <sup>4</sup>	ns	ns
Low AS	ns	ns	ns	ns	ns
Intrauterine Fetal death	1.9 <sup>2</sup>	ns	ns	ns	ns

1 Thom et al. 1992; 2 Bhattacharya et al., 2008; 3 Buchmayer et al., 2004; 4 Sheiner et al., 2005; 5 Basso et al., 1998; 6 Martius et al., 1998; 7 Moreau et al 2005; 8 Ancel et al., 2004; 9 Lumley 1985; 10 Reime et al 2008

# Vanishing Twin phenomenon

- Spontaneous reduction of a multiple pregnancy
- IVF-population (~5%)
- Incidence 10-30%<sup>1-3</sup>
- Studies: IVF population
- Vanishing twin IVF pregnancies, which were spontaneously reduced from twin to single pregnancies, were compared to single IVF pregnancies



# Vanishing Twin: Risk of Preeclampsia and SGA

## PREECLAMPSIA

\*Pinborg 2007

Chasen 2006

X

## SGA

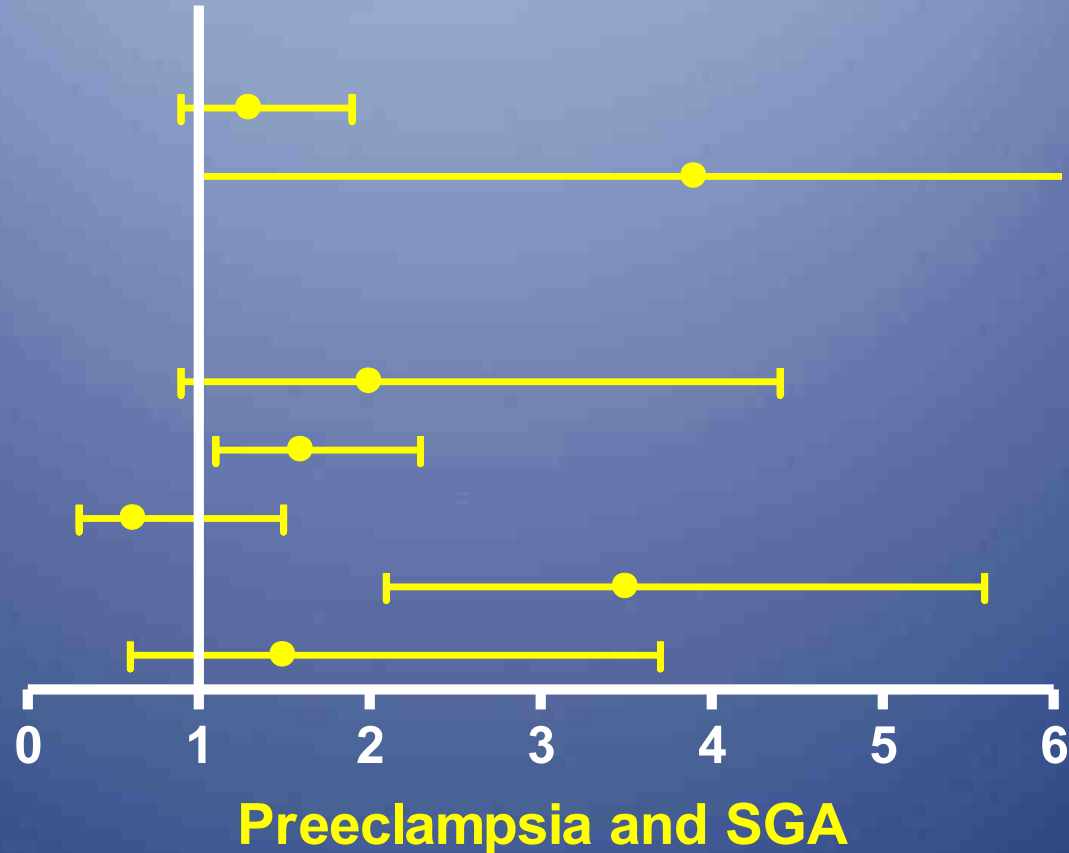
Shebl 2007

\*Pinborg 2007

La Sala 2004

Dickey 2002

Chasen 2006



# Vanishing Twin; SGA-LBW

<b>Low birth weight &lt;2500g</b>			Cas e	Control	OR	95%CI	%Case	%Control	Signi	
La Sala et al	2004	Retrospective	62	437			9,7%	8,9%	NS	
Pinborg et al	2007	Retrospective	642	5.237	1,7	1,1-2,7			S	
			187	424	2,8	1,1-7,1			S	vanishing twin > 8 wks vs <8 wks
Pinborg et al	2005	Retrospective	642	5.237	2,0	1,5-2,6	11,7%	6,3%	0,001	
Shebl et al	2007	Retrospective	46	92			26,1%	12,0%	0,036	
<b>Very low birth weight &lt;1500g</b>										
La Sala et al	2004	Retrospective	62	437			3,2%	2,7%	NS	
Pinborg et al	2005	Retrospective	642	5.237	3,0	1,9-4,7	4,1%	1,5%	0,001	
<b>Small for gestational age p&lt;10</b>										
Chasen et al	2006	Retrospective	55	168			14,5%	9,6%	NS	
Dickey et al	2002	Retrospective	140	4.683			15,7%	4,5%	NS	
La Sala et al	2004	Retrospective	62	437			9,7%	15,6%	NS	
Pinborg et al	2007	Retrospective	642	5.237	1,6	1,1-2,3			S	
			187	424	2,1	0,99-4,4			NS	Vanishing twin > 8 wks vs. <8 wks
Shebl et al	2007	Retrospective	46	92			32,6%	16,3%	0,029	



# The Sound of Life - Greetings From Liverpool!!



# Questions





# Sites of ectopic pregnancies

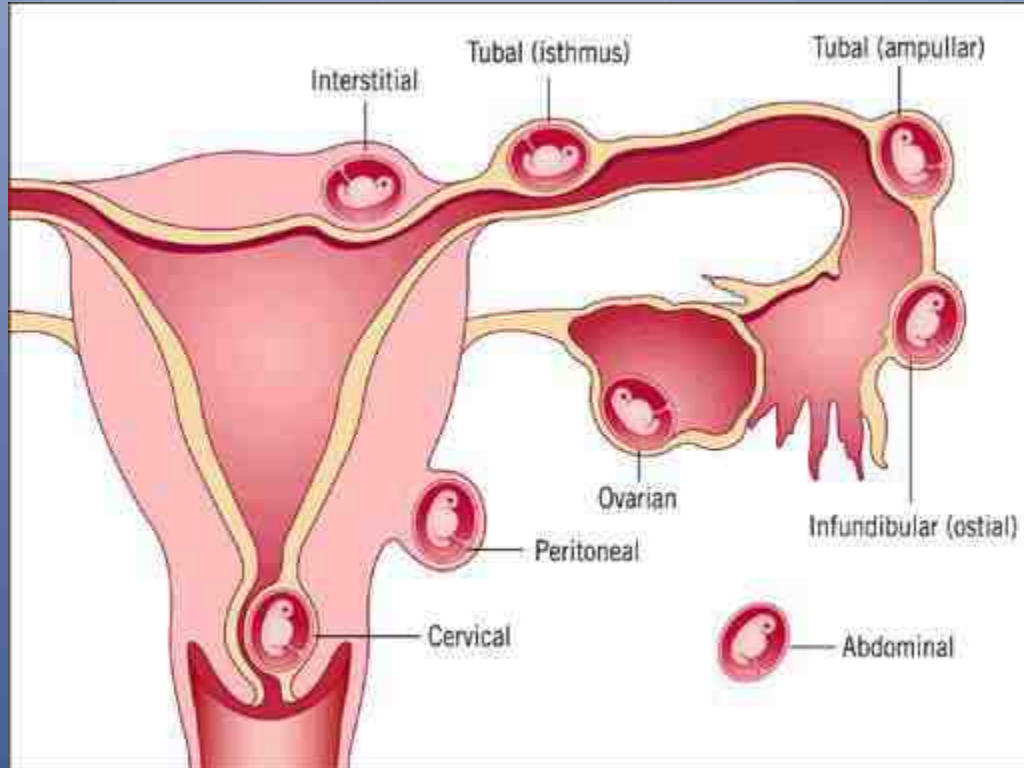


Illustration: John Yanson. Seeber. *Suspected Ectopic Pregnancy. Obstet Gynecol* 2006.

From: Seeber: *Obstet Gynecol*, Volume 107(2, Part 1). February 2006. 399-413



# TVU – small embryonic structure in disproportionately large sac



**Embryoscopy** – short body stalk with 6mm CRL  
- cytogenetics = 47XY+7

