



Threatened Miscarriage

H.J.A. Carp

Sheba Medical Center, Tel Hashomer
& Tel Aviv University, Israel



Plan of Lecture

- Definition of threatened miscarriage
- Natural History
- Prognosis
- Sub groups
 - Recurrent miscarriage
 - Subchorionic hematoma
 - Late obstetric complications
- Confounding Factors
- Treatment
 - Progestogens
 - hCG
 - Bed Rest



Threatened Miscarriage: Definition

- Bleeding during the first 20 weeks of pregnancy
- Commonest complication in pregnancy, occurring in 20% of pregnancies
- Definition includes anything from spots of blood to potentially fatal shock.
- No therapy can resuscitate a dead embryo. Question is whether treatment can affect threatened miscarriage with a live embryo, or bleeding before viability can be determined.



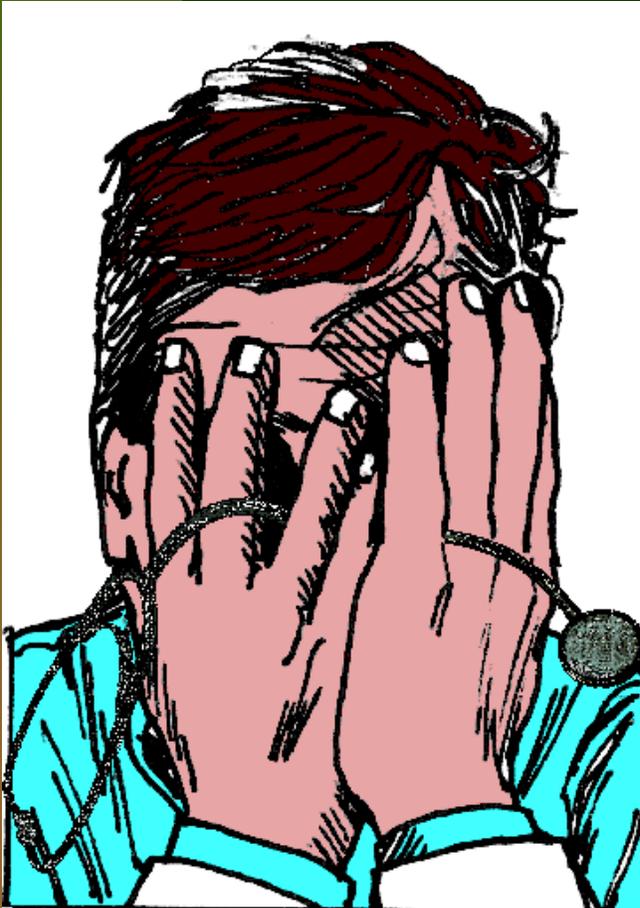
Prognosis with Fetal Heartbeat

Series	Threatened	Controls	RR
Gerhard et al, (1987) RCT Progesterone	5/26 (19.2%)		
Tongsong et al, (1995) RCT	14/255 (5.6%)	5/265 (1.8%)	2.91 (p=0.05)
Tannirandorn et al, (2003) Observational	3/87 (3.4%)		
Farco et al, (1996) Observational	23/149 (15.4%)		
Bennet et al, (1996) Subchorionic hematoma	48/516 (9.3%)		
Total	93/1033 (9.0%)		

91% of pregnancies continue developing



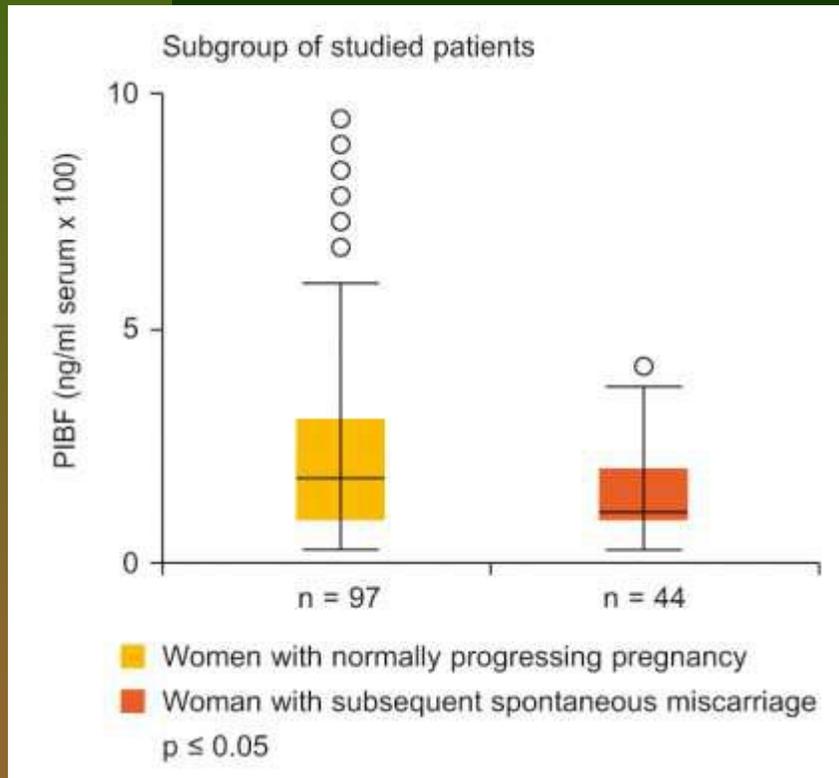
Pitfalls of Using Progesterone Level



- Various authors have assessed progesterone levels, (Stovall et al, 1992; Al-Sebai et al, 1995; Arck et al, 2008; Lek et al, 2017))
- Progesterone secretion pulsatile. Blood may be drawn at a pulse peak or nadir. (Abraham et al, 1974)
- Hormone levels may be normal, but may be deficiency of progesterone receptors
- Abnormal embryo – low hCG leading to low progesterone levels. Low progesterone may be mechanism rather than cause of abortion
- Therefore progesterone levels may be unreliable



PIBF



PIBF lower in women with subsequent miscarriage (Arck et al 2008)

- Produced by T-lymphocytes when treated with progesterone.
- Production rises with trophoblast invasion. (Lachmann et al, 2004)
- PIBF blocks NK cell cytotoxic activity (Szekeres-Bartho et al, 1997; Faust et al, 1999).
- Increases production of IL10, IL3 and IL4 (Th2) (Szekeres-Bartho et al, 1996).
- Mediates progesterone induced suppression of decidual lymphocyte cytotoxicity (Laskarin et al, 2002).
- Hence, PIBF related to anti-abortive effects of progesterone (Szereday et al, 1997).



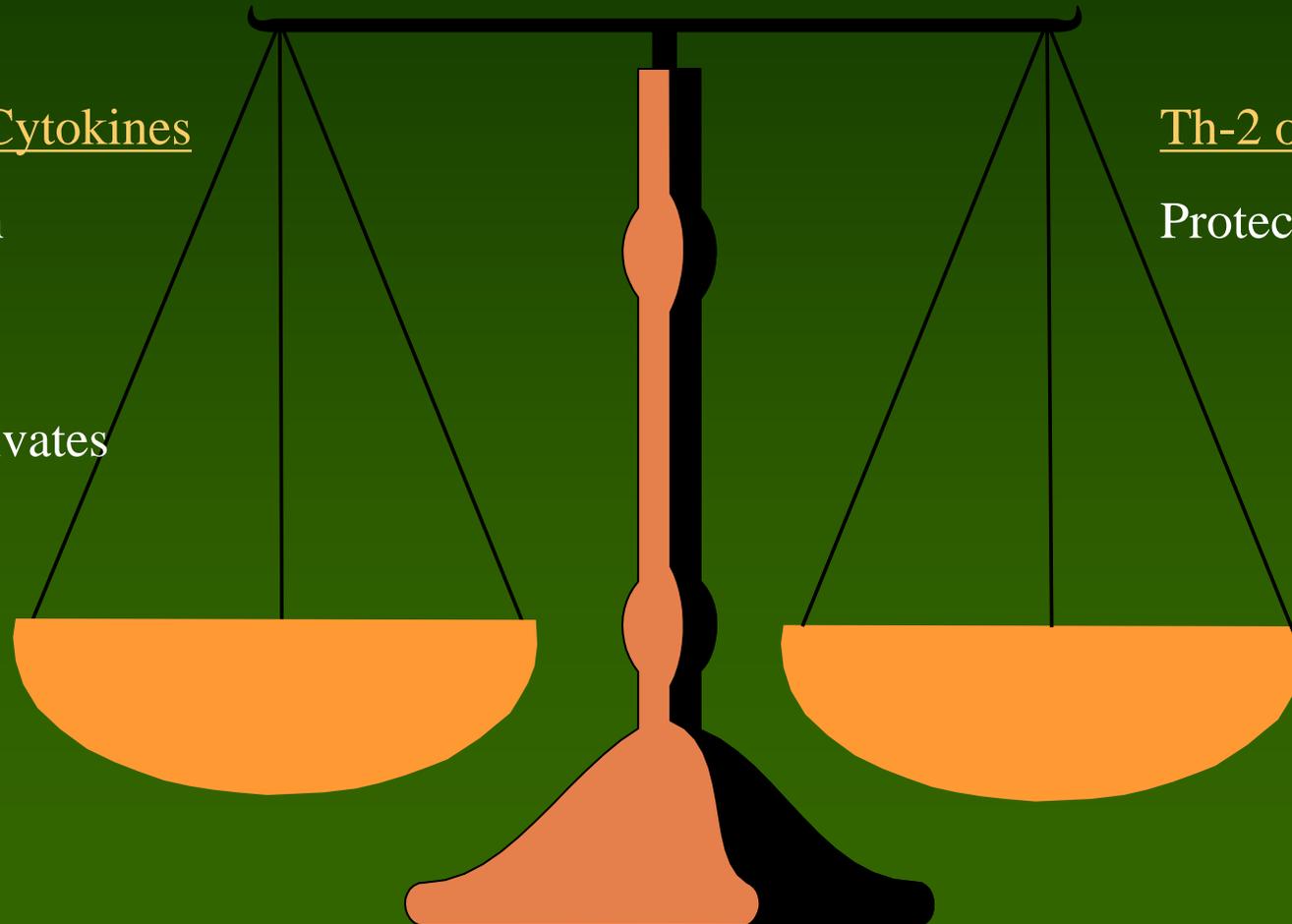
Th-1/Th-2 Concept



Th-1 or Th-17 Cytokines

Associated with
miscarriage

TNF- α leads to
thrombosis, activates
NK cells



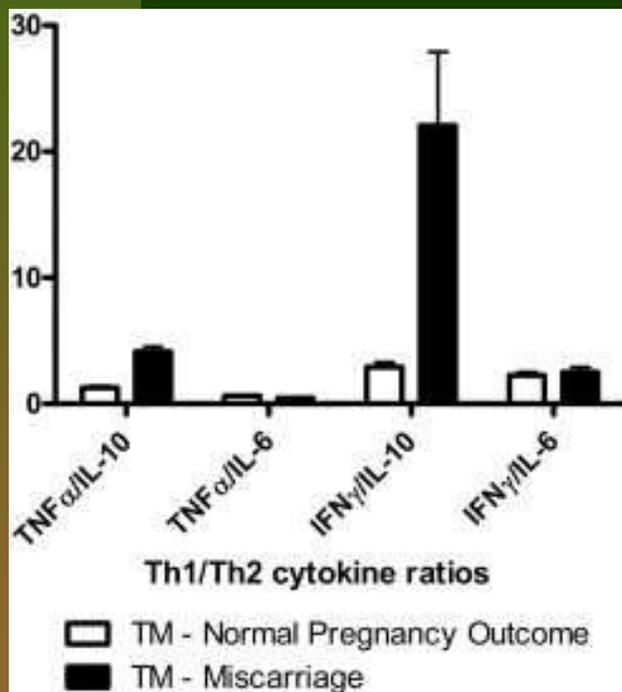
Th-2 or Treg

Protect pregnancy



Th1/Th-2 Ratios in Threatened Miscarriage

(Calleja-Agius et al, 2015)



- Plasma levels of TNF-R1 &2, TNF α , IFN γ , IL -6 & 10 measured by flow cytometry in 80 women with TM:
- 53 women with normal outcome and 27 who miscarried.
- Significantly higher Th-1/Th-2 ratios in patients who subsequently miscarried
 - TNF- α /IL-10,
 - TNF- α /IL6,
 - IFN γ /IL-10



Subgroups

- Recurrent miscarriage
- Subchorionic hematoma
- Late obstetric complications



Subchorionic Hematoma



- Prognostic significance disputed
- Large haematoma associated with 3x increased of risk of miscarriage (19% v 71%) (Bennet et al, 1996)
- Presence or the size of haematoma did not affect miscarriage rate (10% v 11%) (Pedersen & Mantoni, 1990; Dickey et al, 1992)
- Hematoma may become infected leading to contractions
- Pprospective study of 6675 women found that 1st trimester haematoma increases risk of severe obstetric complications, irrespective of external bleeding.(Nagy et al, 2003)



Late Obstetric Complications:

Hematoma (Nagy et al, 2003)

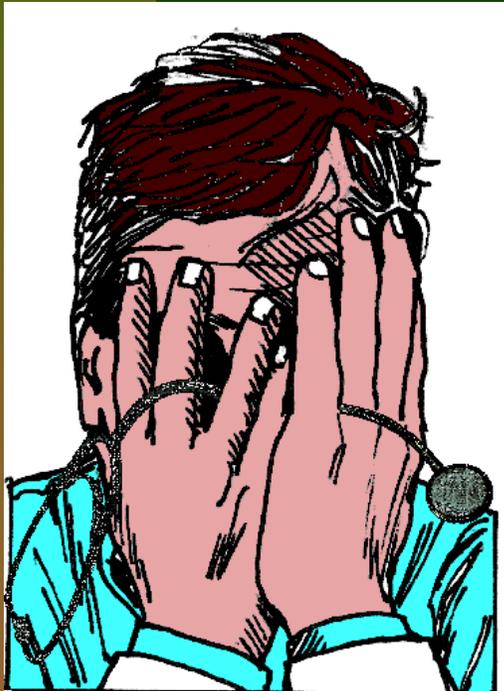


- Instrumental delivery, RR 1.9; CI 1.1- 3.2)
- LSCS (RR 1.4; CI 1.1-1.8),
- PIH (RR 2.1; CI 1.5, 2.9)
- PET(RR 4.0; CI 2.4, 6.7),
- Placental abruption (RR 5.6; CI 2.8, 11.1)
- Retained Placenta (RR 3.2; CI 2.2, 4.7)
- Preterm delivery (RR 2.3; CI 1.6, 3.2),
- IUGR (RR 2.4; CI 1.4, 4.1),
- Fetal distress (RR 2.6; CI 1.9, 3.5),
- Admission to NICU (RR 5.6; CI 4.1, 7.6)



Late Obstetric Complications of Threatened Miscarriage (Ahmed et al, 2012)

- Retrospective case–controlled on 134 women



Outcome measure	Controls cases (n=45)	Studied cases (n=89)	P value
Abortion	1(2.2%)	15(16.9%)	0.001a
Preterm birth	1(2.2%)	14(15.7%)	0.001 a
Fetal mean birth weight(kg)	3.1±0.36709	2.4 ±1.13851	0.01 a
Fetal birth weight range9kg)	1.3-3.2	1.9-4.4	
PROM	2(4.45)	3(6.7%)	0.4837a
Hypertensive disorders	2(4.4%)	5(5.6%)	>0.05 b
Placenta praevia	1(2.2%)	3(3.4%)	>0.05 b
IUGR	1(2.2%)	5(11.2%)	>0.05 b
Caesarian section	10(22.2%)	20(22.5%)	>0.05b



Confounding Factors

- Abnormal embryo
 - Anatomic anomalies incompatible with life
 - Chromosomal anomalies
- Hostile maternal environment



Fetal Causes of Miscarriage

Structural Malformations

- Most miscarriages - blighted ova. Empty sac on ultrasound
- Embryoscopy - developmental defects in 200/233 missed abortions (85%) (Philipp et al, 2003), - anencephaly, encephalocele, spina bifida, syndactyly, pseudosyn-dactyly, polydactyly, cleft hand & cleft lip

Chromosomal Aberrations

- 60% sporadic miscarriages due to chromosomal aberrations (Boue, et al 1975; Stein, 1975), 29-60% of recurrent miscarriages (Carp et al, 2009)
- Aberrations include trisomies, Monosomy X, Triploidy & structural aberrations e.g. translocations & inversions



Difficulties in Diagnosing Structural Anomalies



- In blighted ova, unknown if rudimentary embryo may have been structurally abnormal.
- Embryoscopy is advanced technique, not usually available.
- Ultrasound misses most anomalies

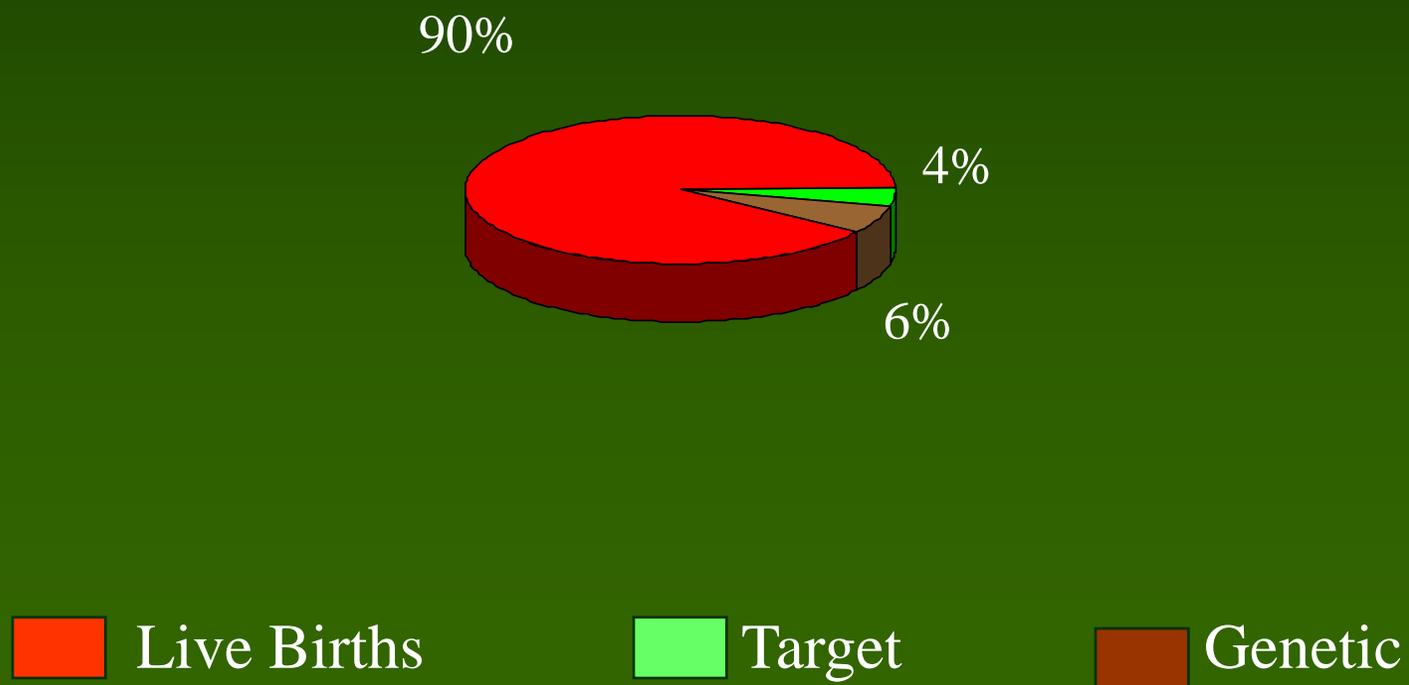




Treatment



Can Progesterone Work In Viable Pregnancies?





Bed Rest

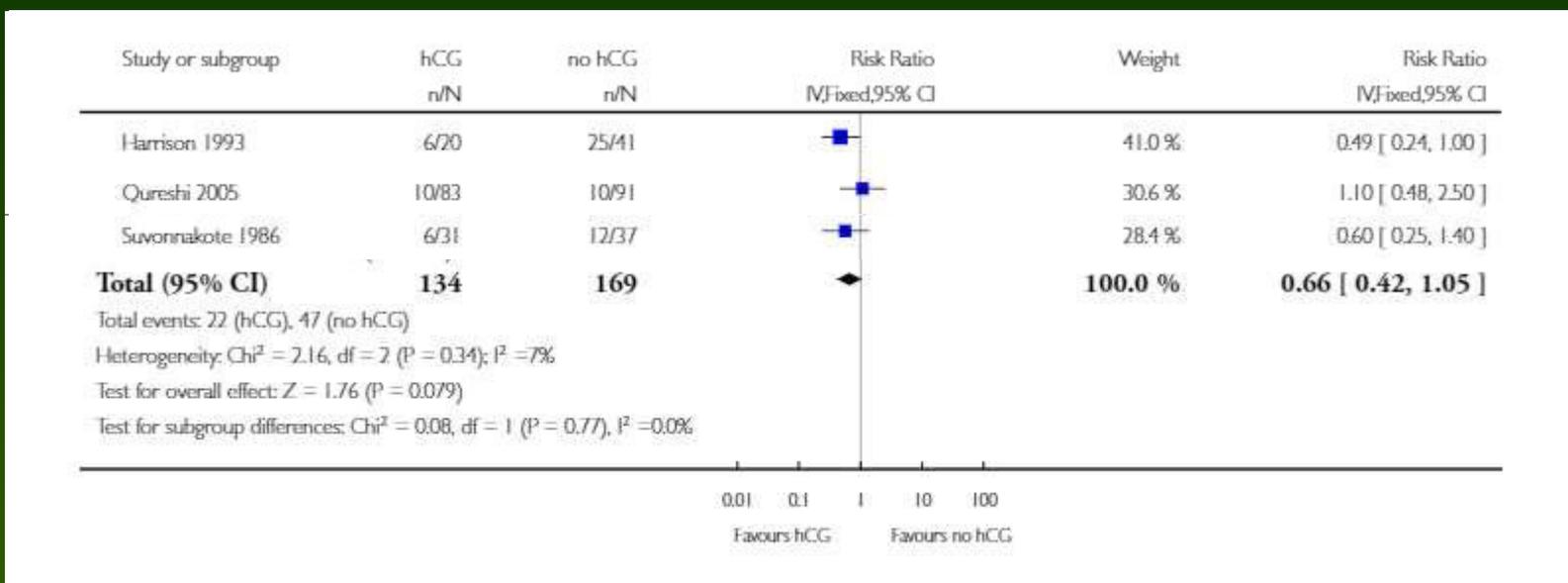


- Often prescribed for bleeding in pregnancy.
- RCT in threatened miscarriage (Harrison et al, 1993) 15/20 miscarried
- "Therapeutic" bed rest in pregnancy: unethical and unsupported by data". (McCall et al, 2003)
- Not Supported by Cochrane systematic review (Aleman et al, 2005)
- Lack of evidence for prescription of antepartum bed rest. (Maloni, 2011)



hCG in Threatened Miscarriage

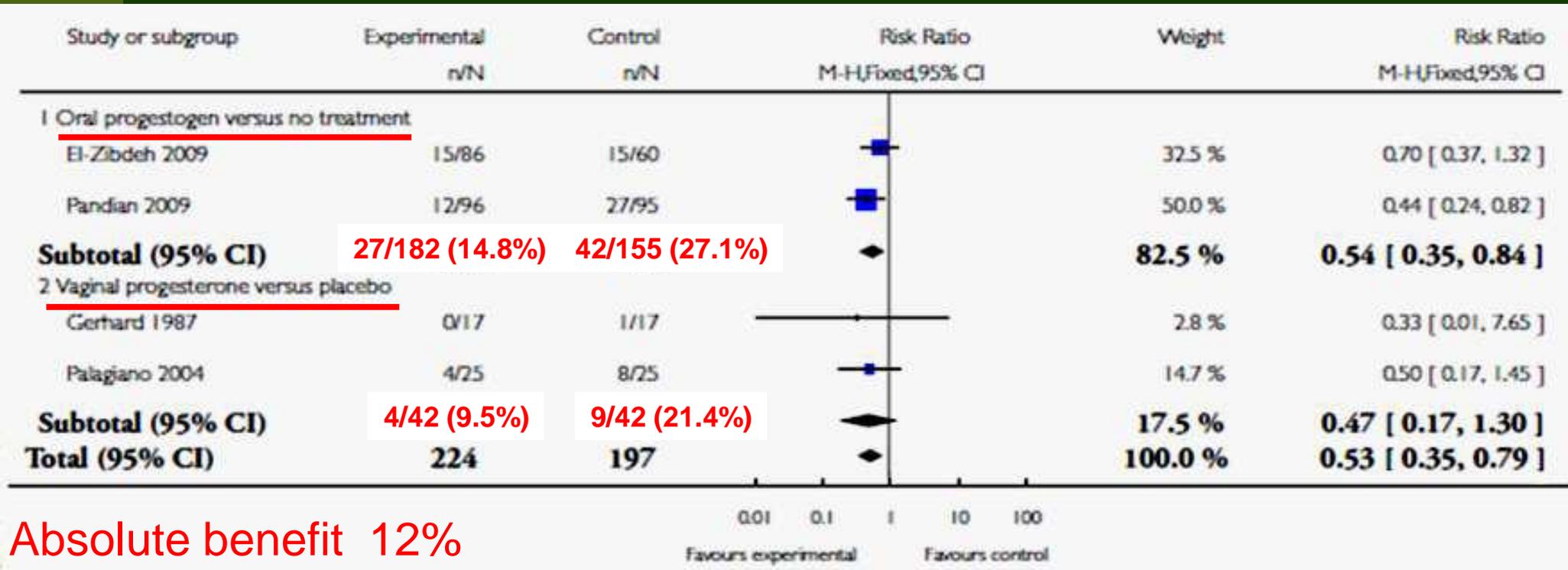
(Devaseelan et al, 2010)



- RCT of hCG, Placebo and bed rest: hCG is significantly better than bed rest. (Harrison et al, 1993)
- The current evidence does not support the routine use of hCG in the treatment of threatened miscarriage. (Devaseelan et al, 2010)



Do Progestogens Work in Threatened Miscarriage? (Wahabi et al, Cochrane Database 2011)





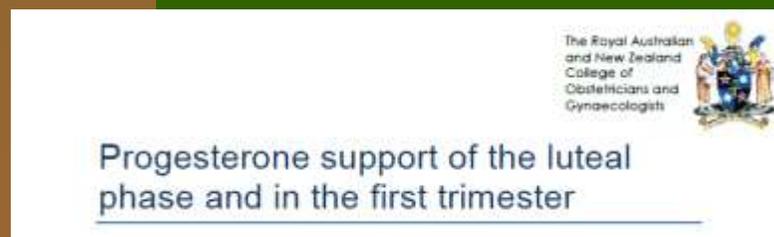
Recent Guidelines

NICE Guideline (2012)



- Data from a meta-analysis of several small studies suggest that progestogens are better than placebo. The lack of strong evidence makes this a priority area for research.

RANZCOG Guideline (2013)



- Miscarriage was significantly less likely to occur on progestins than placebo or no treatment (risk ratio 0.53; 95% CI 0.35 to 0.79), The evidence remains preliminary and additional well designed studies are required to confirm these findings.



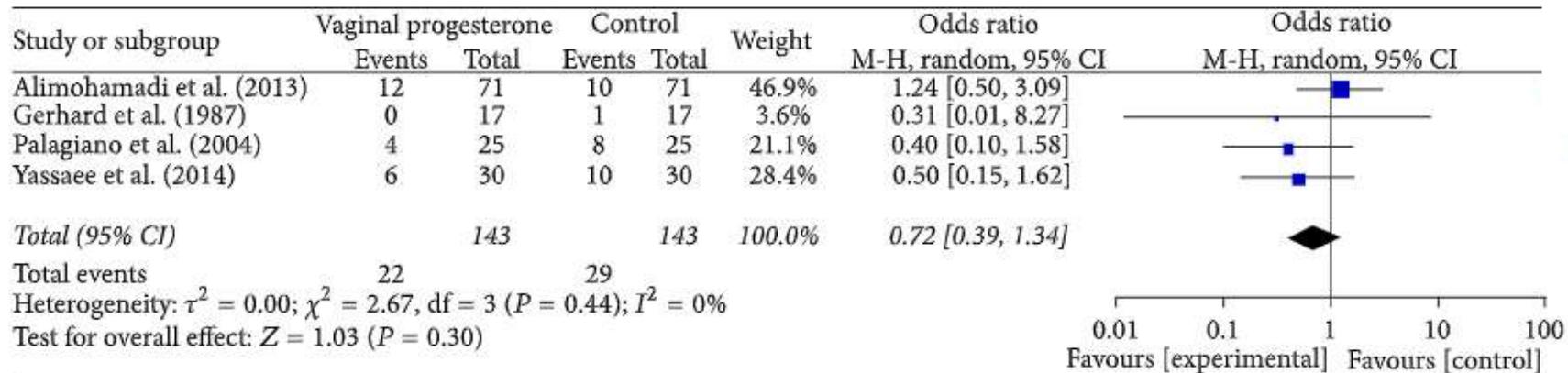
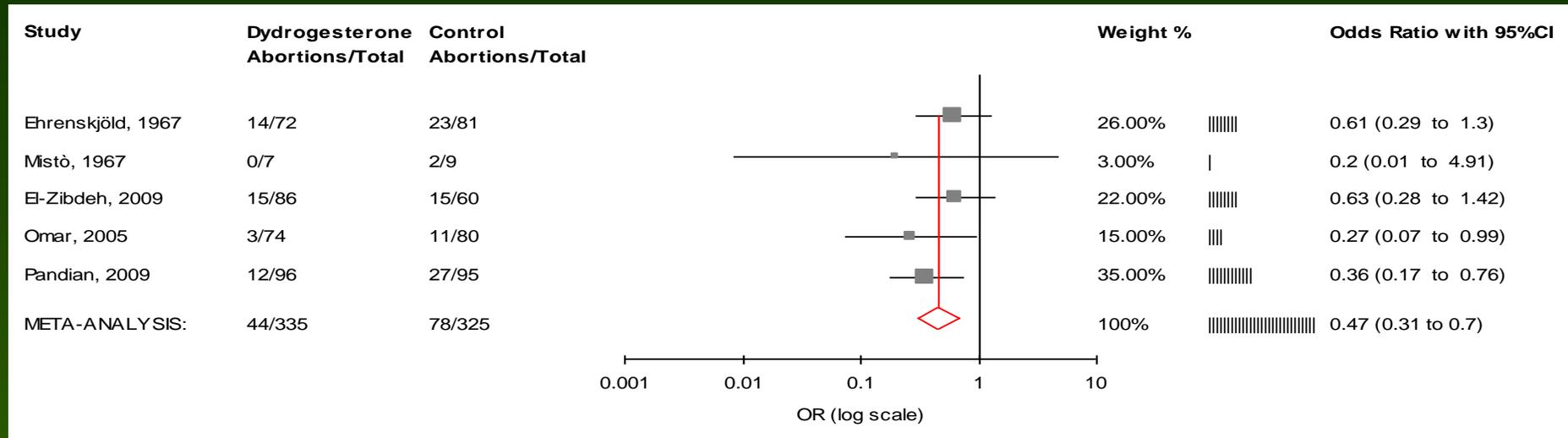
Author's Meta-analysis

- Literature search performed for all papers in EMBASE and Ovid MEDLINE[®] using search terms – Progestogens, Micronised progesterone, 17-OH Progesterone, Duphaston or dydrogesterone
- Metaanalysis only performed on RCT's
- 1 additional on micronised progesterone to those in Wahabi's metaanalysis
- No reports on 17-OHP
- 23 publications retrieved from the literature on Dydrogesterone.
- 5 reports eligible for inclusion in the metaanalysis, two double blind studies, 3 open label randomized studies, summarizing 660 patients



Progestogens in Threatened Miscarriage (Fixed effects Model)

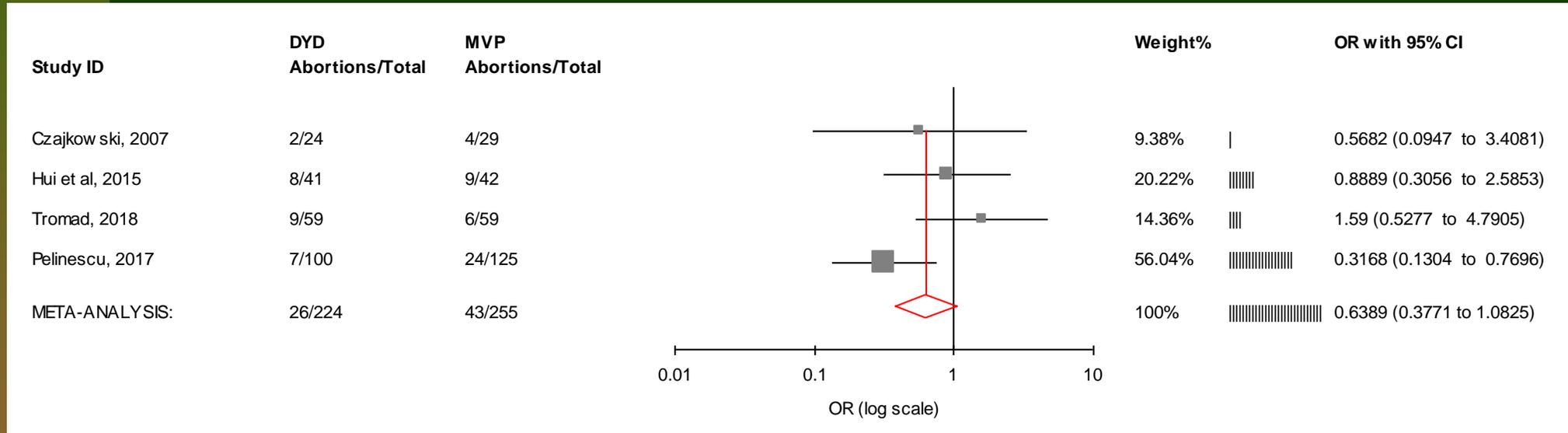
Carp, 2012



Lee et al,
2017



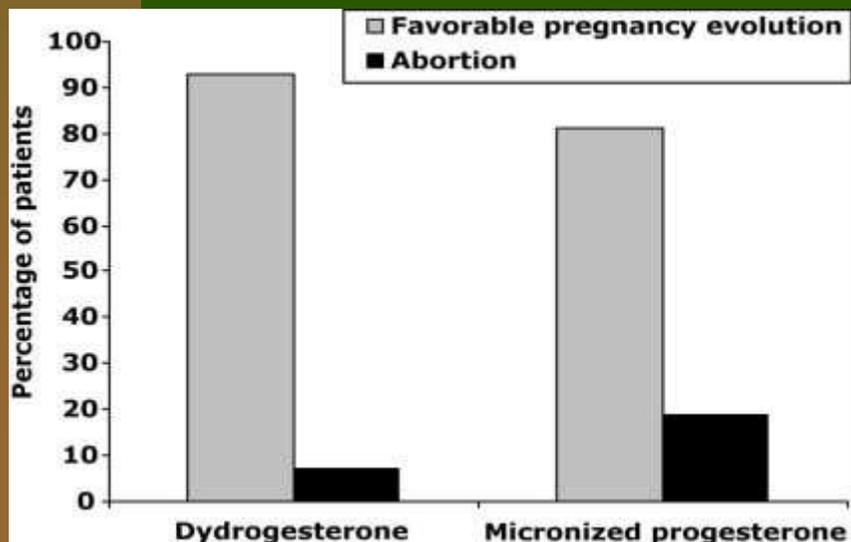
DYD vs MVP (Fixed effects Model)





Progestogens in Retro-placental Hematoma

(Pelinescu-Onciul, 2007)



- Non randomized comparative cohort study
- 100 women, threatened miscarriage & viable embryo received DYD 40mg/d. 93 live births, 7 miscarriages (93% births)
- 125 women – micronized progesterone 600mg/d. (81.3% births)
- RR=2.04 (1.05-3.97)



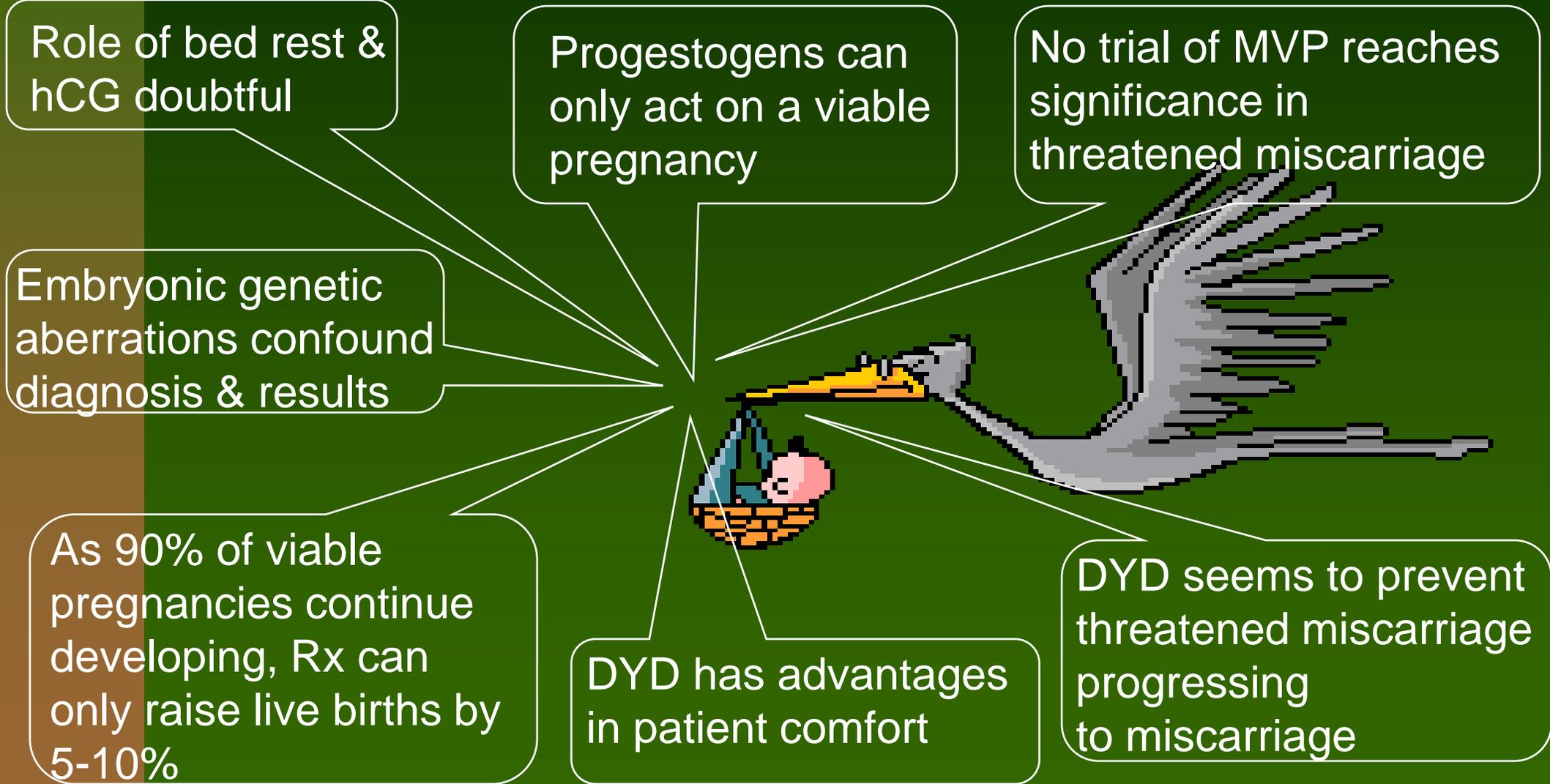
What Should Our Policy Be?



- Only evidence – where no evidence - don't treat
- This is physicians approach
- However, even if little evidence of efficacy, patient wants treatment
- No way to exclude chromosomal aberrations in threatened abortion
- Should non evidence based therapy be used? Does patient have autonomy to decide?



Thank You for Listening





Serum Markers in Threatened Miscarriage



(1)

- Lower hCG values in miscarriage compared to continuing pregnancy (La Marca et al 1998)
- Free BhCG <20ng/ml 88.3% sensitivity (Al –Sebai et al, 1996)
- Inhibin A, activin A, & hCG much lower in miscarriage; inhibin A, 0.553 MOM best predictor (Florio et al, 2004).
- CA125, constant or increases in miscarriage In ongoing pregnancy, low or steeply declining CA125 concentration (Schmidt et al, 2000).
- Single CA125 ≥ 43.1 IU/ml associated with increased risk of miscarriage (Fiegler et al, 2003).



Serum Markers in Threatened Miscarriage



(2)

- Systematic review of 1253 women with threatened miscarriage (Pillai et al, 2016), assessing: Progesterone, hCG, PAPP-A estradiol & CA-125).
- CA 125, most sensitive marker (648 women in 7 studies) sensitivity 90% (CI, 83-94%), specificity 88% (CI, 79-93%), positive likelihood ratio 7.86 (CI, 4.23-14.60). Negative likelihood ratio 0.10 (CI, 0.06-0.20). Negative test likely to identify those who are likely to continue pregnancy.
- Estradiol, next best marker, sensitivity of 45% (CI, 6-90%), specificity 87% (CI, 81-92%), positive likelihood ratio of 3.72 (95% CI 1.01-13.71), negative likelihood ratio of 0.62 (CI 0.20-1.84).

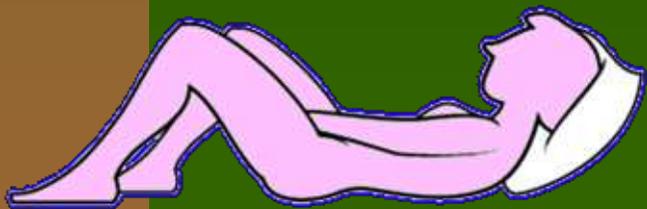


Patient Comfort

It's time for my
progestogen



It's time for my
progestogen





Bed Rest

(Bigelow et al, 2011)

Author(s), Year	N	Study Design	Study Group	Control Group	Efficacy of Bed Rest
Diddle <i>et al.</i> , 1953	9742	Prospective observational	Bed rest +/- sedation	Normal activity	No difference
Hamilton <i>et al.</i> , 1991	23	RCT	Bed rest	Normal activity	3 patients miscarried, does not report which study group; trial was stopped
Harrison, 1993	61	Double-blind RCT	Bed rest	hCG injection	hCG significantly better than bed rest to prevent abortion
Ben-Haroush <i>et al.</i> , 2003	230	Nonrandomized retrospective analysis	Compliant with bed rest	Noncompliant	Patients adherent to bed rest had fewer SABs ($P = 0.006$) and higher rate of term pregnancy ($P = 0.004$)