Adverse obstetric outcome after early pregnancy complications

Roy Farquharson (on behalf of SIG Early Pregnancy)

ESHRE Joint SIG meeting

Valencia, December 2010

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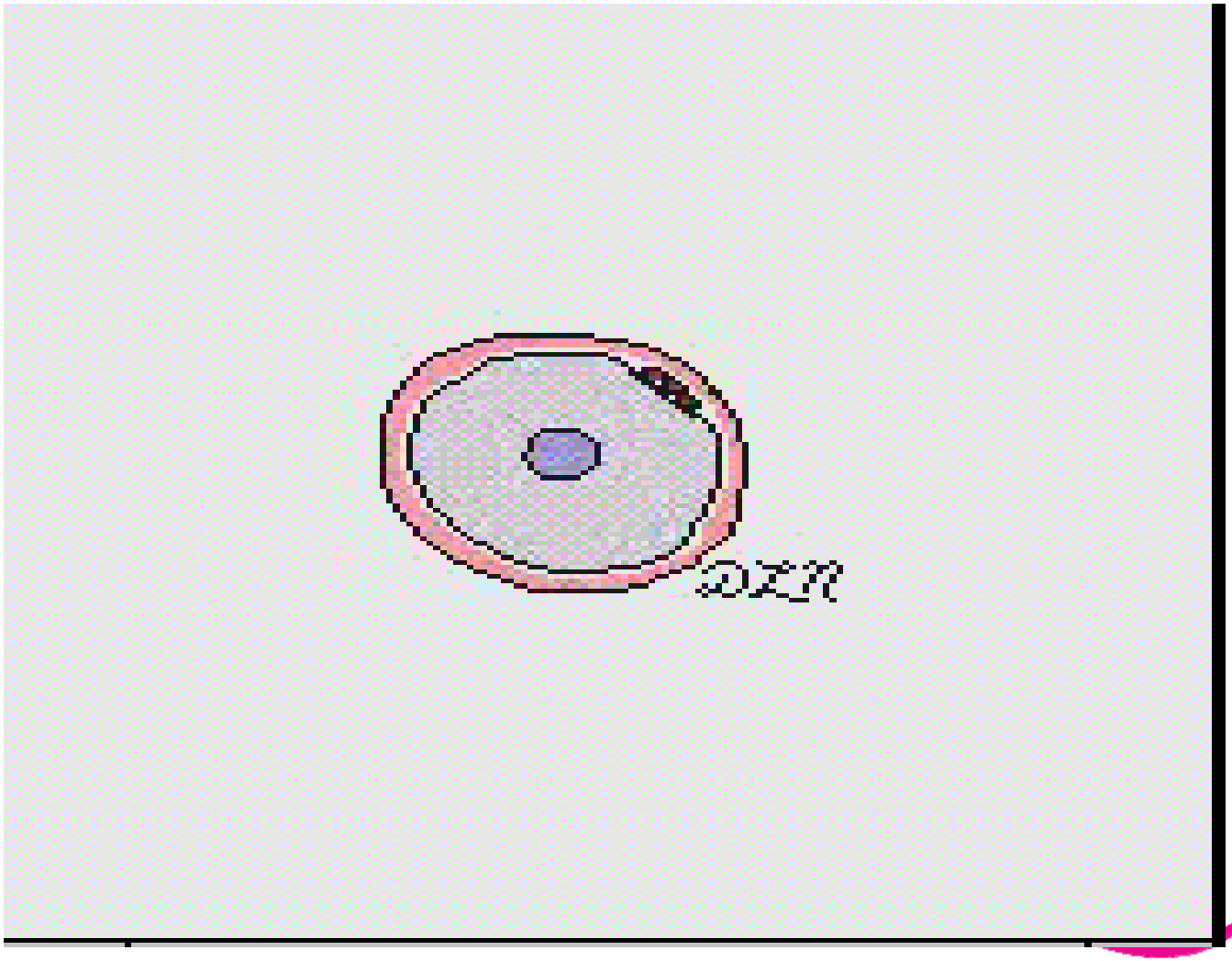

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First trimester complications

- Common
- Distressing
- ?portent of miscarriage?

- Clinician
  - TVU to confirm viability (FH at 8/40= 95% success rate)
  - Reassuring and supporting the couple

- Short term consequences
- Late consequences?

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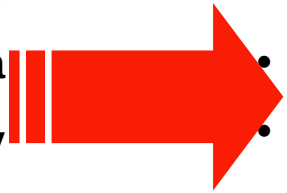
LITERATURE REVIEW

Complications 1st trimester → Adverse obstetric outcome

- Miscarriage
  - Recurrent miscarriage
- Termination of pregnancy
  - Threatened miscarriage
  - Intra-uterine hematoma
    - CRL – discrepancy
      - Vanishing twin
- Hyperemesis gravidarum



- Preeclampsia
- Placental abruption
- Placenta previa
- Preterm delivery <37 weeks / <34 weeks
- SGA p<10 / Growth restriction p<5
- Low birth weight <2500g / <1500g
- Congenital malformation
- Low Apgar score <7 at 5 minutes
- Intrauterine fetal death/ Neonatal death

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Previous Miscarriages

- Single miscarriage
  - Incidence ~ 11%[1]
  - Incidence in subsequent pregnancy ~ 16%[2]

- Recurrent miscarriage
  - 3 or more miscarriages[3]
  - Incidence ~1%[3]

- Risk of adverse obstetric outcome in the subsequent pregnancy

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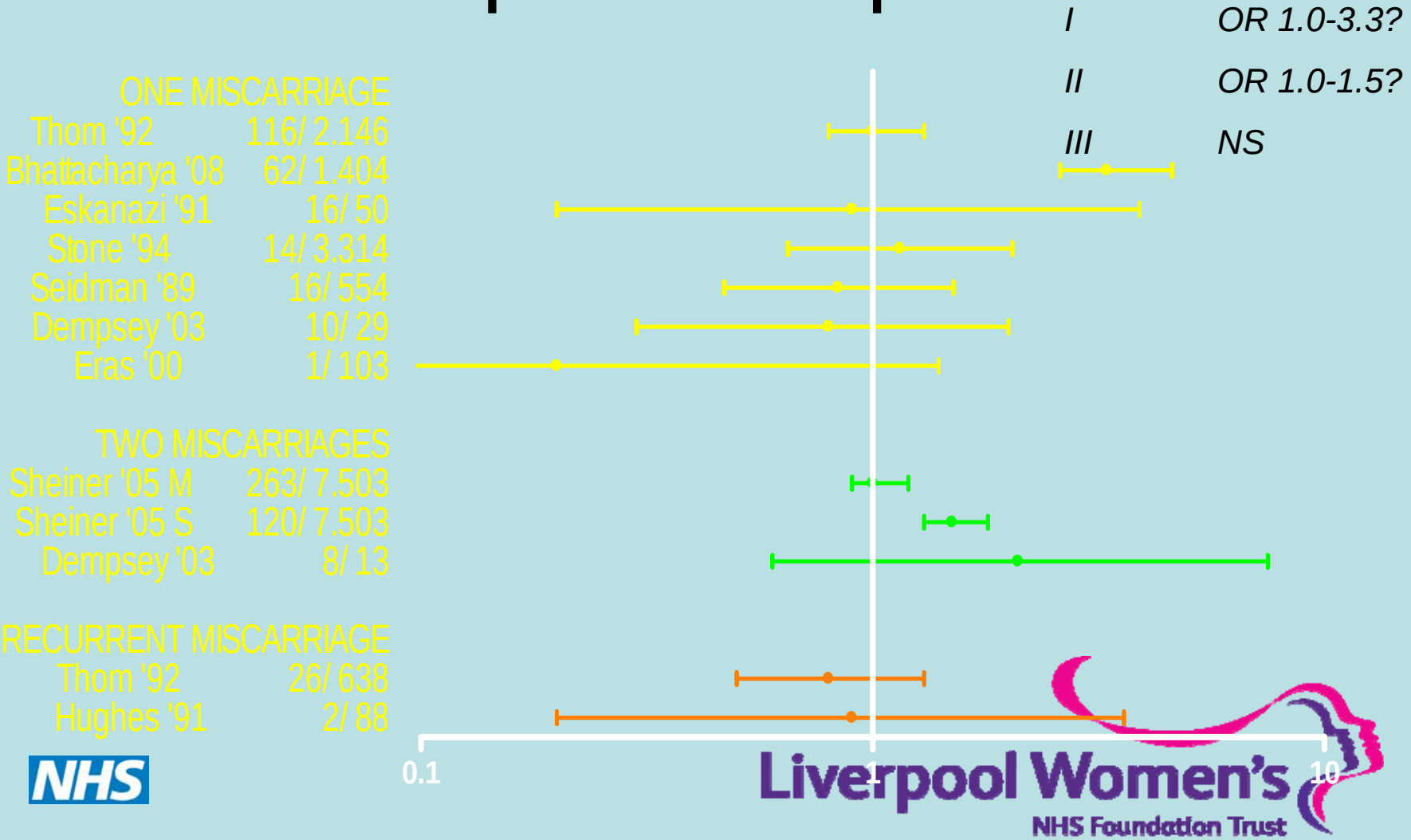
1 Farquharson et al., 2005; 2 Knudsen et al., 1990; 3 Jauniaux et al., 2006

Previous miscarriage(s)
At risk of preeclampsia?



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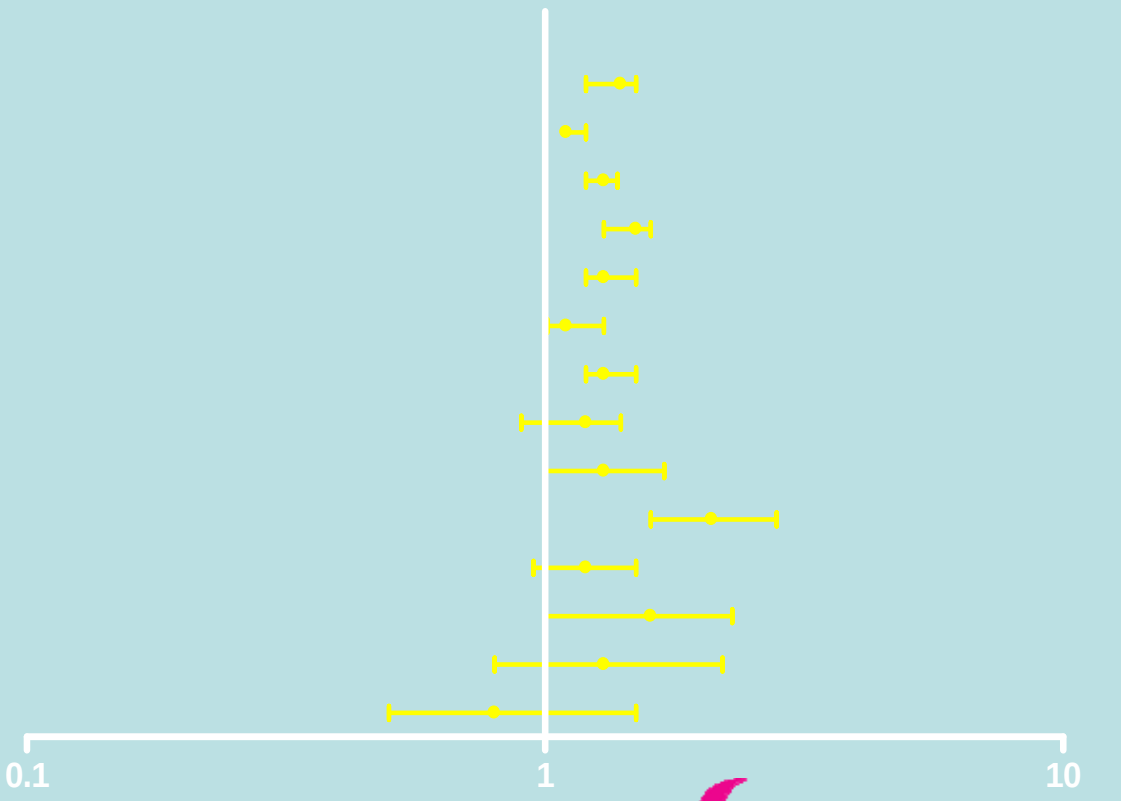
Previous single miscarriage
Risk of preterm delivery <37 weeks

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



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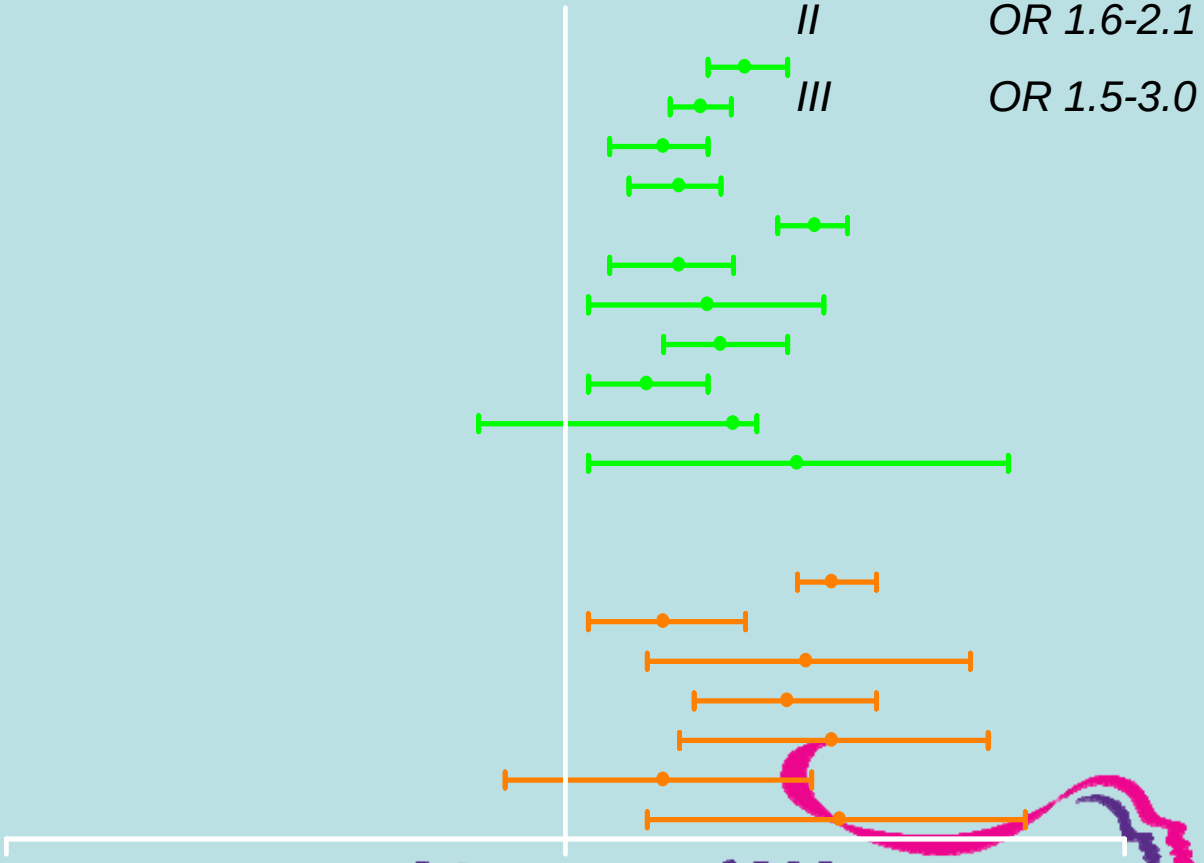
Previous two or more miscarriages
Risk of preterm delivery <37 weeks

TWO MISCARRIAGES	
Basso '98	432/ 5.268
Martius '98	309/ 2.788
Smith '06	178/ 1.792
Buchmayer '04	146/ 1.742
Pickering '91	?/ 1.524
Hammoud '07	88/ 908
Lang '96	?/ ?
Pickering '85	?/ 689
Lekea '90	73/ 439
El-Bastawissi '03	31/ 57
Nguyen '04	8/ 33
RECURRENT MISCARRIAGE	
Martius '98	151/ 639
Thorn '92	63/ 638
Lang '96	?/ ?
Hammoud '07	36/ 225
Lekea '90	?/ ?
Hughes '91	11/88
Jivraj '01	7 /61

I *OR 1.1-1.4*

II *OR 1.6-2.1*

III *OR 1.5-3.0*



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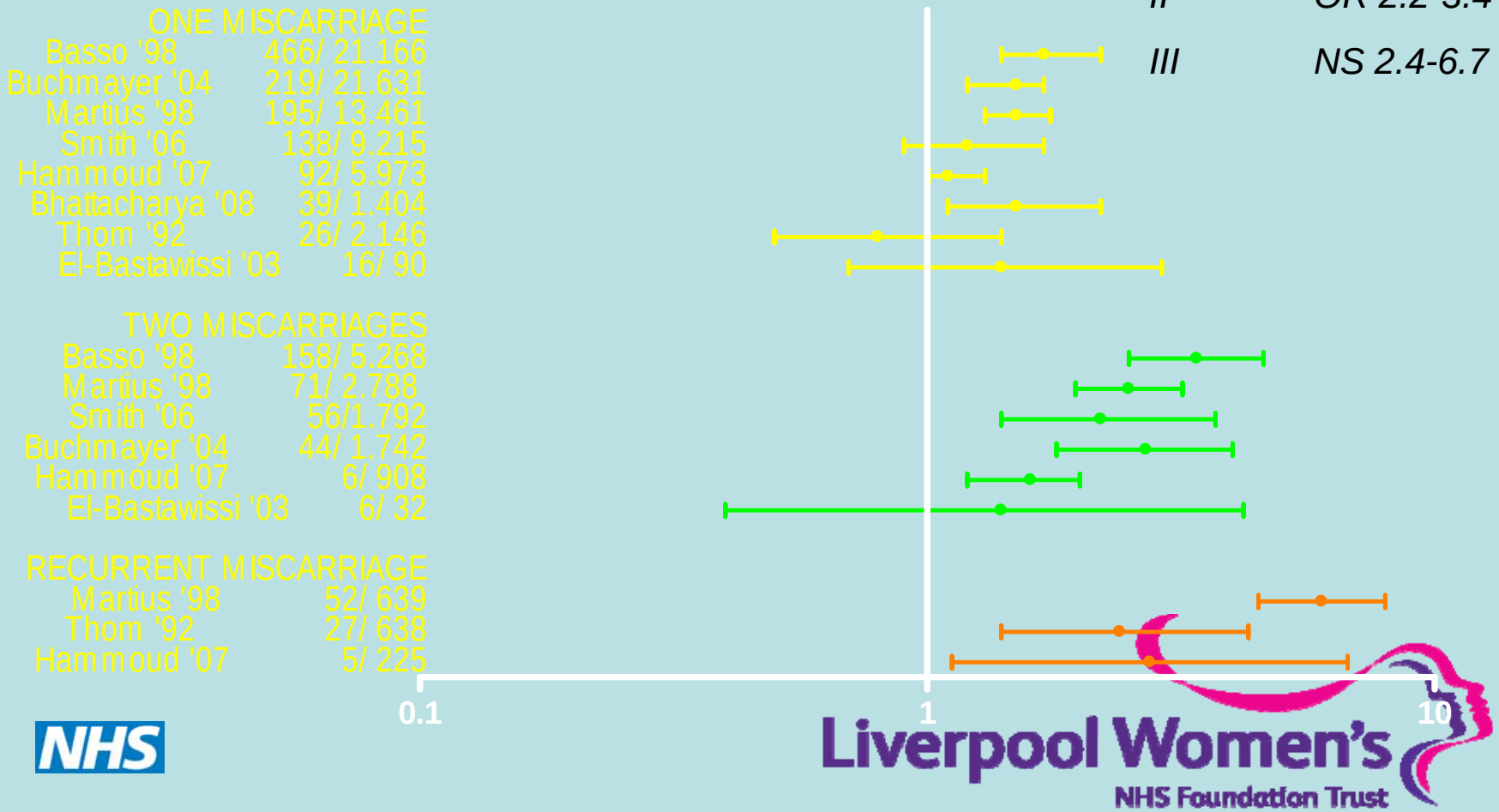
Previous miscarriage(s)
Risk of very preterm delivery <34 weeks

I *OR 1.5-1.7*

II *OR 2.2-3.4*

III *NS 2.4-6.7*



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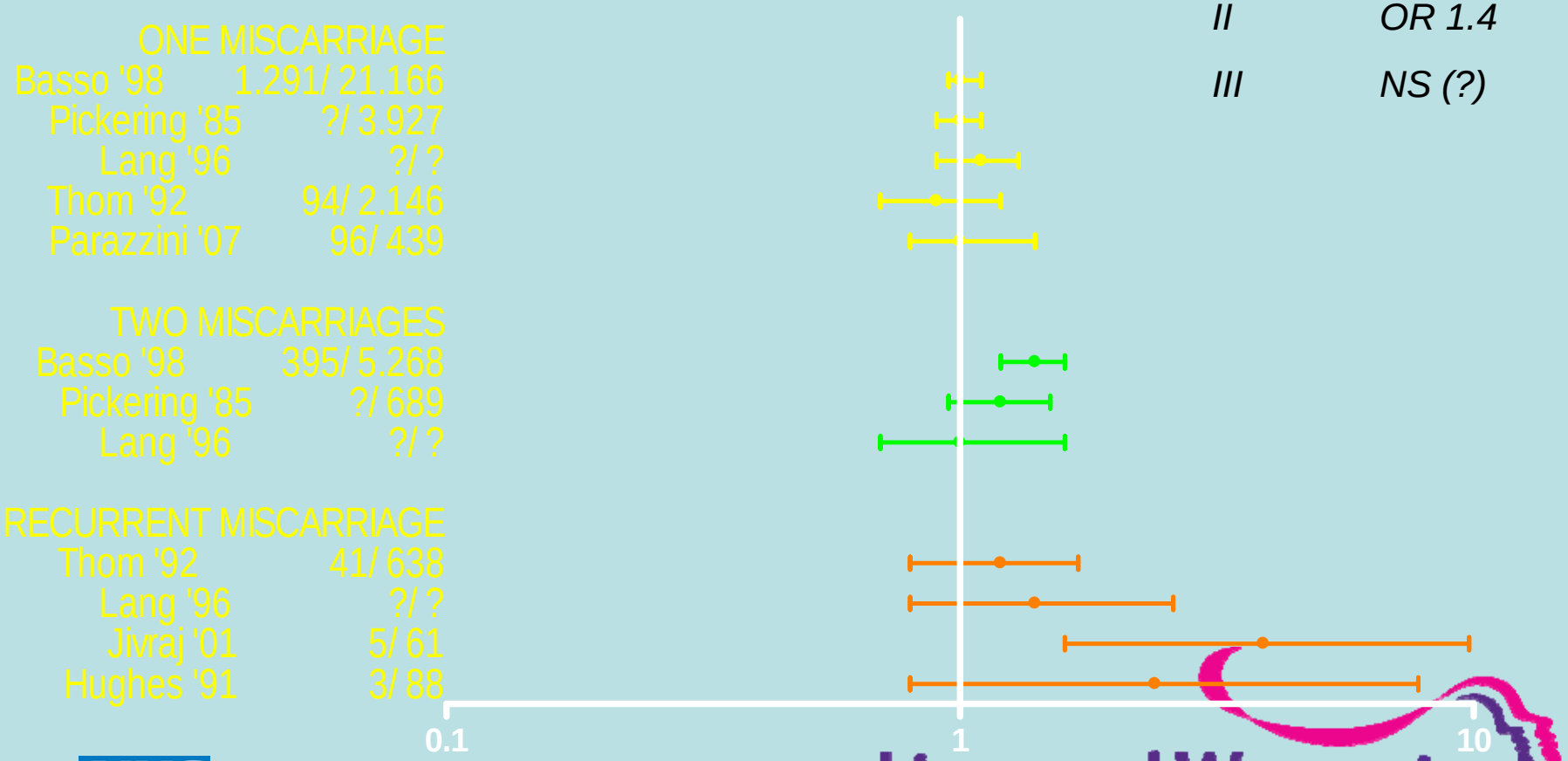
Previous miscarriage(s)
Risk of small for gestational age

I	*NS*
II	*OR 1.4*
III	*NS (?)*



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Risk of adverse outcome in subsequent pregnancy

OR/ *RR	Miscarriage			Termination of pregnancy	
Number	1	≥2	≥3	1	≥2
Preeclampsia	1.0-3.3[1,2]	1.0-1.5[4]	-	ns	ns
Placental abruption	ns	1.5[4]	-	ns	ns
Placenta previa	ns	1.7[4]	*6.0[4]	ns	ns
Preterm <37	1.1-1.4[3,5]	1.6-2.1[3.5]	*1.5-3.0[1,6]	1.1-1.3[6,8]	1.6-2.3[6,8]
Preterm <34	1.5-1.7[3,5]	2.2-3.4[3,5]	*2.4-6.7[1,6]	1.3-1.5[7,8]	1.8-2.9[7,8]
SGA p<10	ns	1.4[5]	?[1]	ns	ns
LBW <2500	ns	?[4,5]	*2.0[4]	ns	ns
LBW <1500	ns	ns	-	?[9,10]	?[9]
Cong. Malformation	ns	ns	*1.8[4]	ns	ns
Low AS	ns	ns	ns	ns	ns
Intrauterine Fetal death	1.9[2]	ns	ns	ns	ns

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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

Threatened miscarriage & Haematoma

- Blood loss first trimester
  - Incidence 14-20%[1,2]
  - ~50% will miscarry[1-3]
  - After confirmation of viability → 2-14% chance of miscarriage[3-5]

- Intrauterine haematoma
  - Incidence 18-39% in women with a threatened miscarriage[6,7]
  - When <9 weeks → the risk of miscarriage 2.5 higher[7-10]

- Risk of adverse obstetric outcome in the ongoing pregnancy

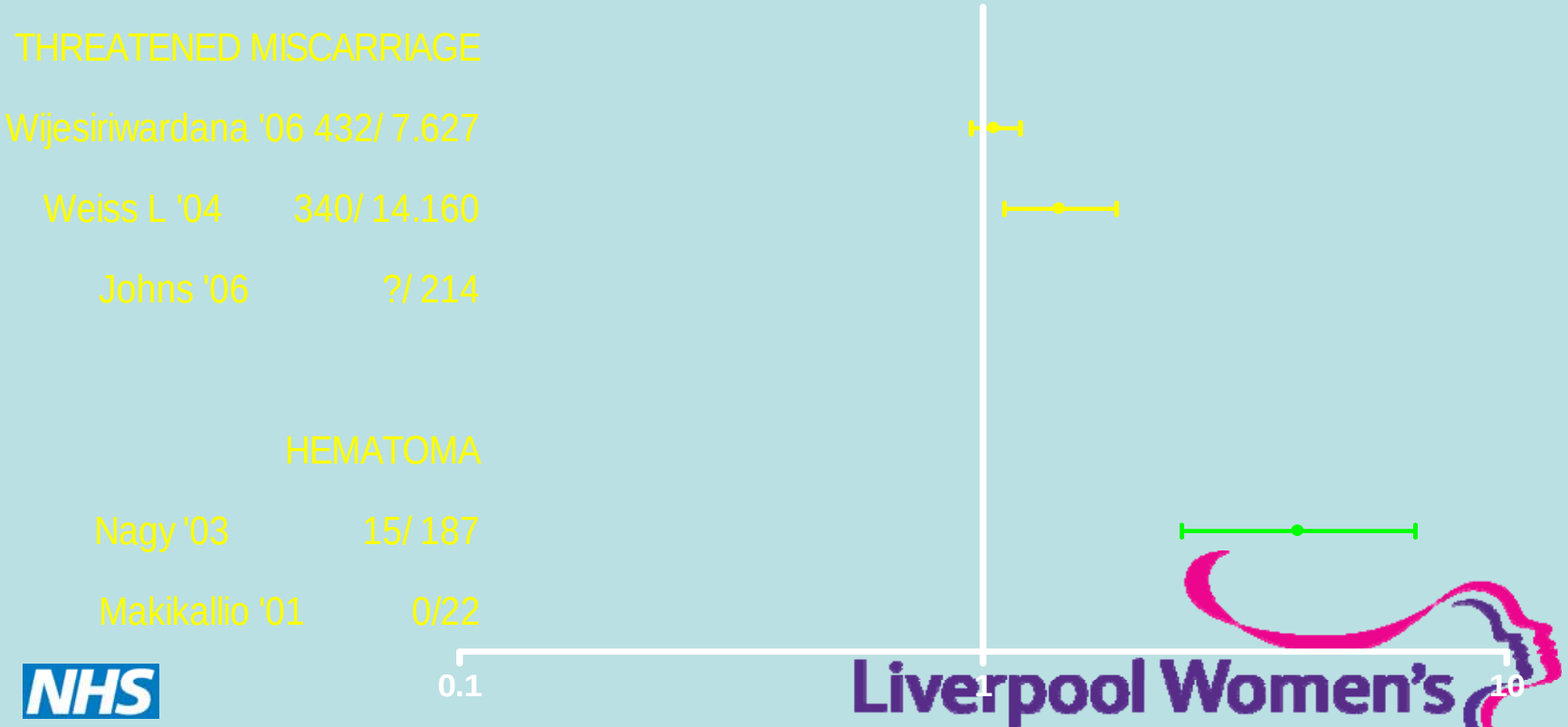
1 Everett 1997; 2 Weiss et al., 2004; 3 Wijesiriwardana et al., 2006; 4 Johns et al., 2006; 5 Schauberger et al., 2005: 6 Johns et al., 2003; 7 Pedersen and Mantoni 1990;8 Leite et al., 2006; 9 Maso et al., 2005; 5 Ball et al., 2005; 10 Nagy et al., 2003

Threatened miscarriage & Haematoma
Risk of preeclampsia

Normal *NS*

Heavy *NS*

Hematoma *OR 4.0*



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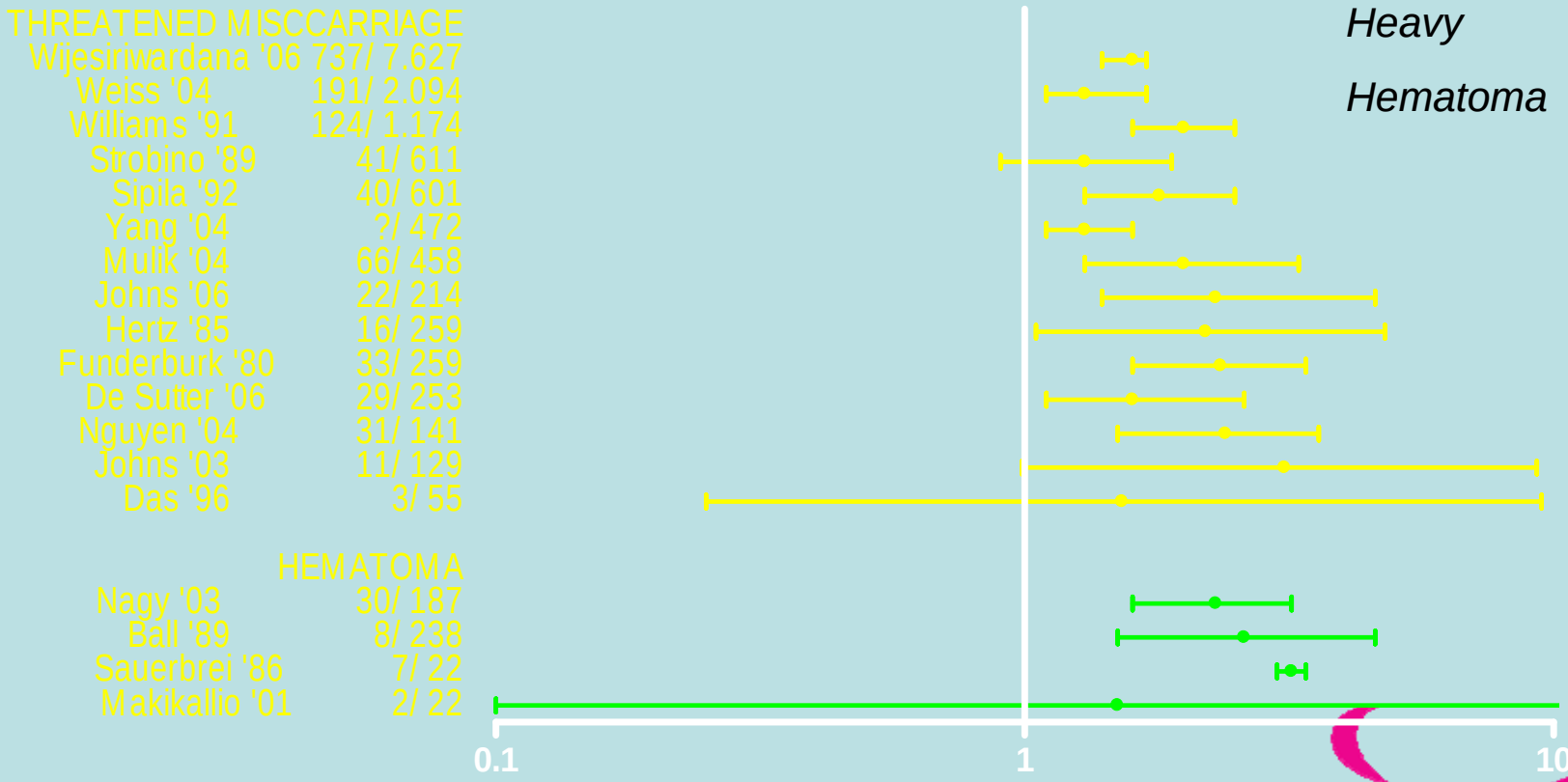
Threatened miscarriage & Haematoma
Risk of preterm delivery <37 weeks

Normal *OR 1.3-1.6*

Heavy *OR 3.0*

Hematoma *OR 2.3-2.6*



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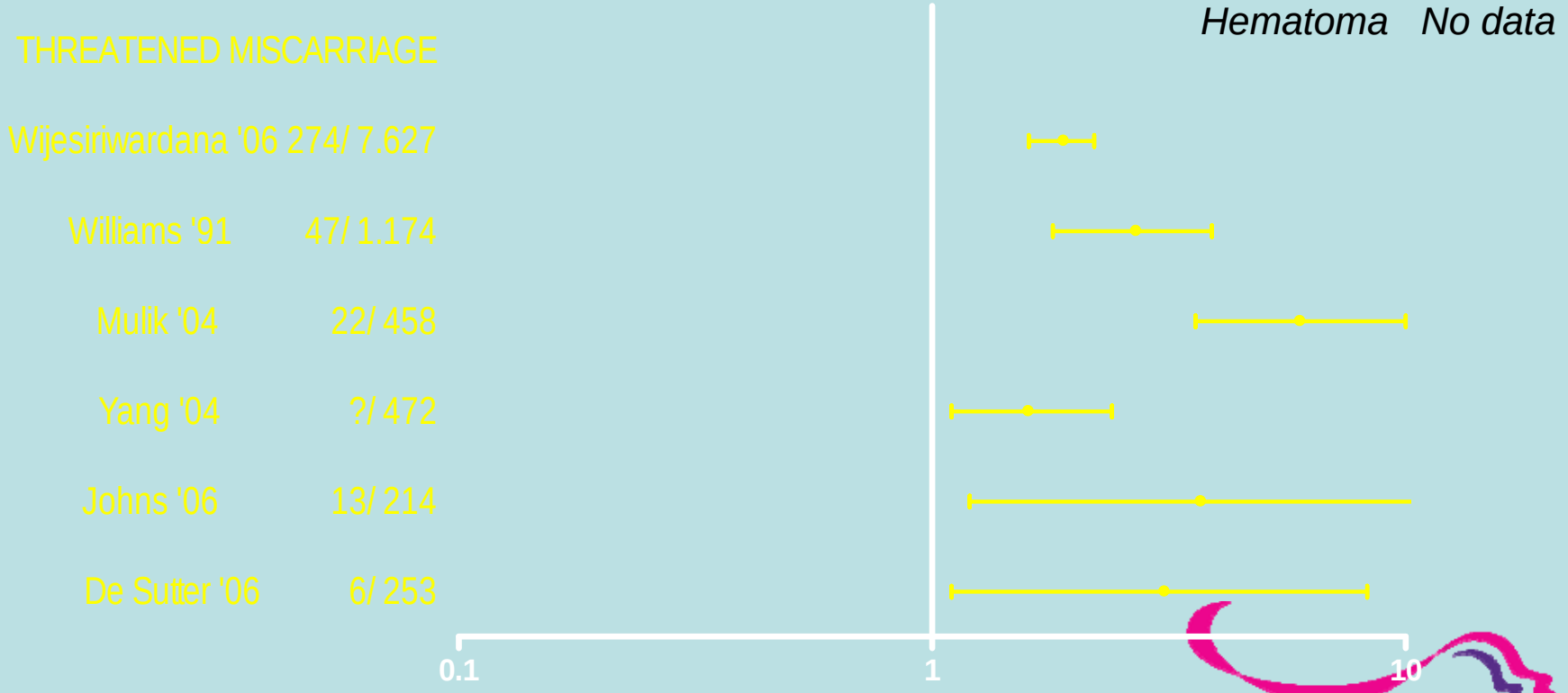
Threatened miscarriage & Haematoma
Risk of very preterm delivery <34 weeks

Normal *OR 1.9*

Heavy *No data*

Hematoma *No data*



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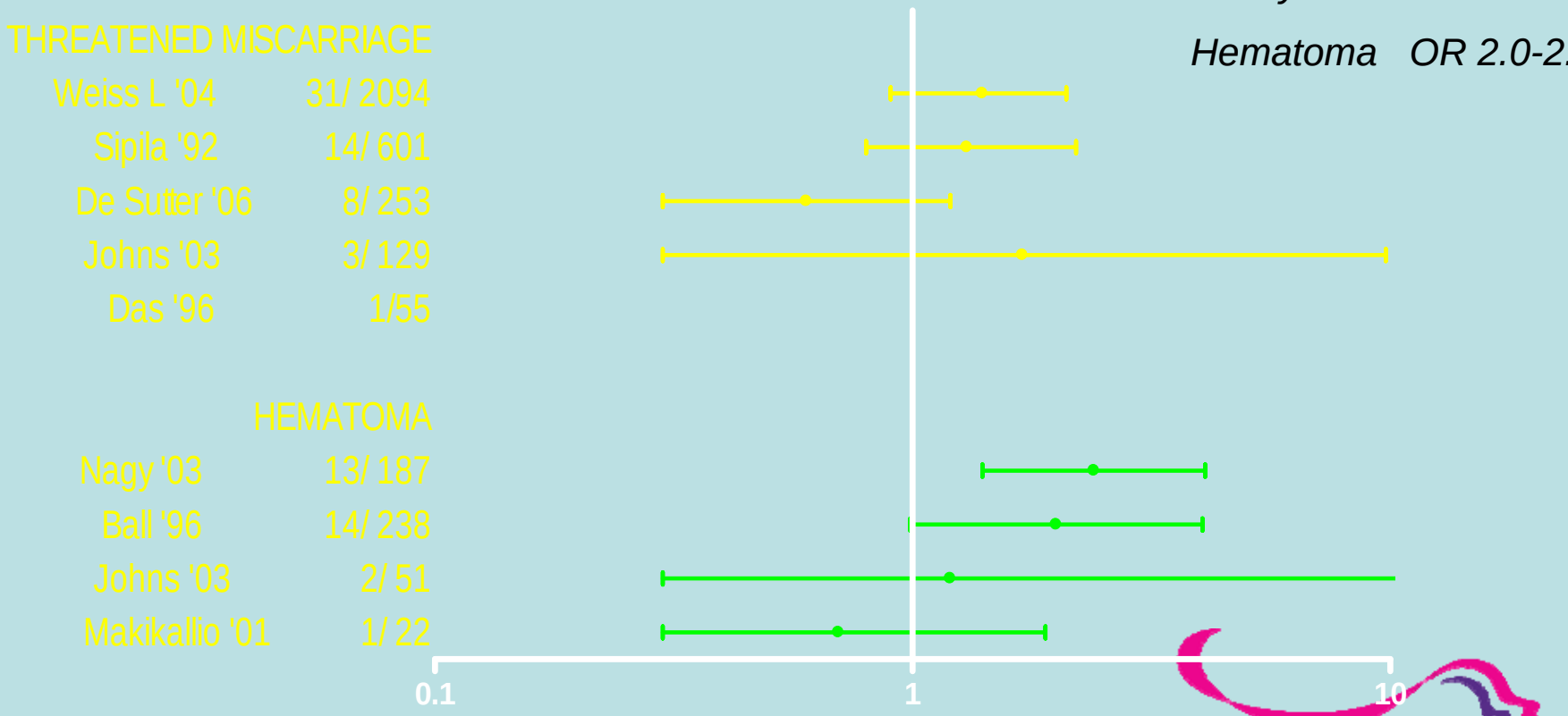
Threatened miscarriage & Haematoma
Risk of small for gestational age

Normal	*NS*
Heavy	*OR 2.6*
Hematoma	*OR 2.0-2.4*



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Risk of adverse outcome in INDEX pregnancy

OR / *RR	Threatened Miscarriage	Intrauterine haematoma	CRL discrepancy	Vanishing twin	Hyperemesis gravidarum
Preeclampsia	ns	*4.0[4]	-	ns	ns
Placental abruption	1.2-1.6[1,2]	*5.6[4]	-	ns	-
Placenta previa	1.8[2]	-	-	ns	-
Preterm <37	1.3-1.6[1,2]	*2.3-2.6[4,5]	-	1.6[9]	*3.0[11]
Very preterm <34	1.9[2]	-	2.0[7]	3.0[9]	-
IUGR p<5	-	-	2.8[7]	-	-
SGA p<10	ns	2.0-*2.4[4,5]	1.1[8]	1.6[10]	1.4-*1.5[11,12]
LBW <2500	*1.2-2.3[2,3]	-	1.7[7]	2.0[9]	1.5-*2.8[11,12]
LBW <1500	*2.2[3]	-	-	3.0[9]	1.4[12]
Cong. Malformation	ns	ns	-	ns	ns
Low Apgar Score	ns	*2.6[4]	-	-	*5.0[11]
Intrauterine Fetal Death	ns	2.8[5]	ns	ns	ns

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1 Weiss et al. 2003; 2 Wijesiriwardana et al, 2006; 3 Williams et al, 1991; 4 Nagy et al. 2003; 5 Ball et al, 1996; 7 Smith et al. 1998; 8 Bukowski et al. 2007; 9 Pinborg et al. 2005; 10 Pinborg et al. 2007; 11 Dodds et al. 2006; 12 Bailit et al. 2005

Conclusion (1)

- Data from our literature review indicate that early pregnancy complications are predictors for subsequent adverse obstetric outcome
- The increased risks are related to the severity of the 1st trimester complication
- Some associations are based on a few small, retrospective series, with poor stratification bias and poor matching of cases and controls
- And some of these associations have a small increased risk and therefore the clinical relevance can be questionable

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Conclusion (2)

- The risk of preeclampsia was increased in women with an intrauterine haematoma and possibly after previous miscarriages
- The risk of preterm birth was increased after any of the early pregnancy complications
- More epidemiologically-based studies, using National Birth Registries, are needed to confirm these findings and this would be especially useful for pregnancy following idiopathic recurrent miscarriage (eg ALIFE and SPIN RCT's)

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Vanishing Twin phenomenon

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

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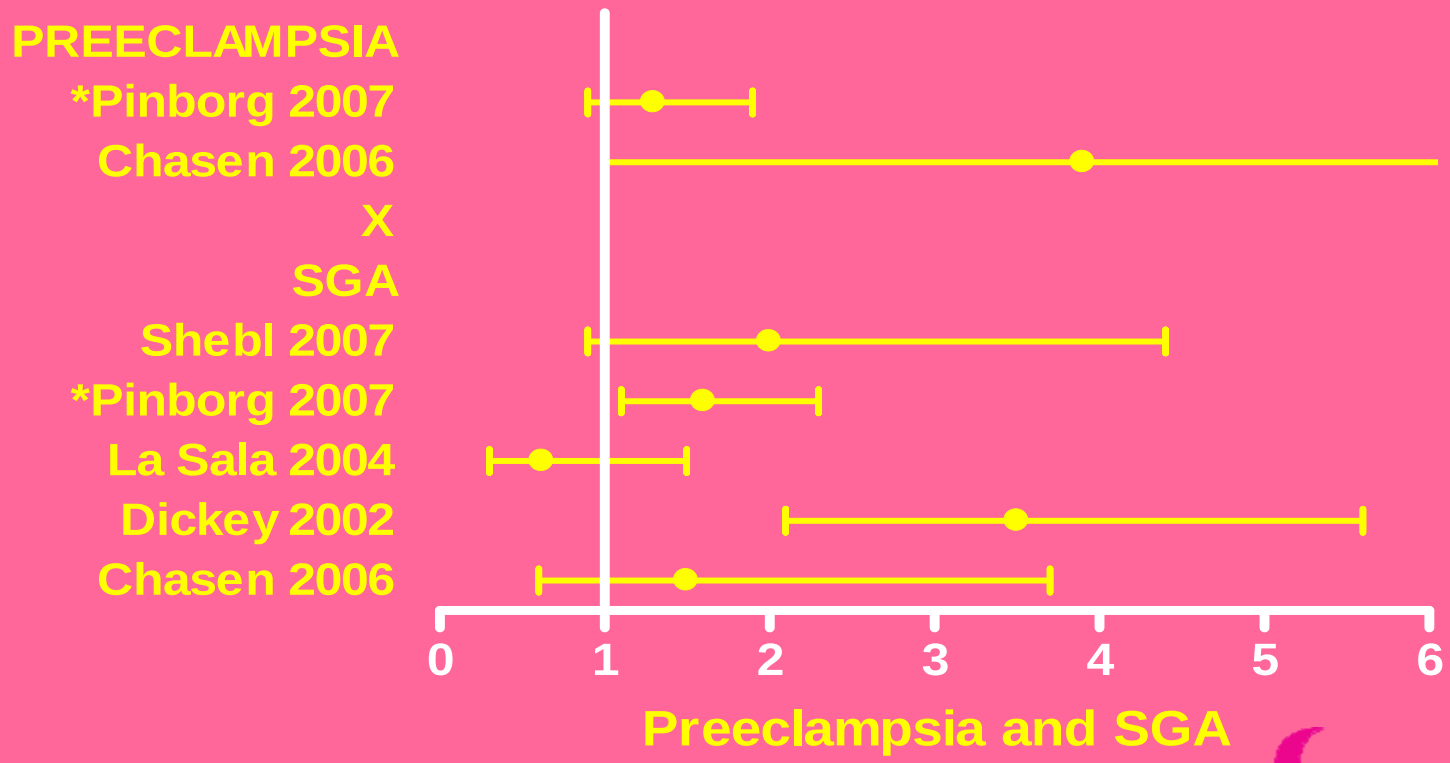
1 Dickey et al., 2002; 2 Landy and Keith 1998; 3 Pinborg et al., 2005

Vanishing Twin: Risk of Preeclampsia and SGA



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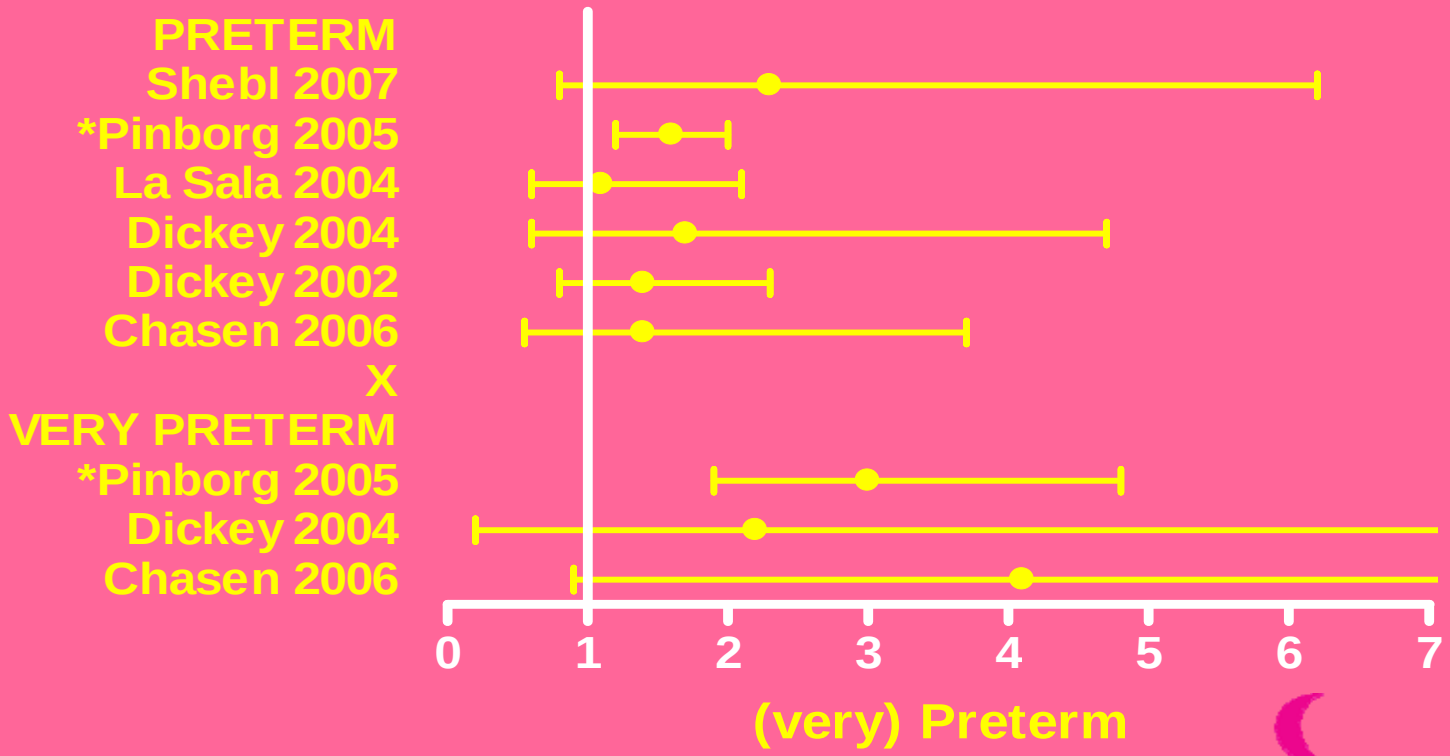
Vanishing Twin:
Risk of Preterm <37 weeks and very Preterm <34 weeks



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Vanishing twin; Preterm

Preterm delivery <37 weeks			Case	Control	OR	95% CI	%Case	%Control	Signi
Chasen et al	2006	Retrospective	55	168			12,7%	8,9%	NS
Dickey et al	2002	Retrospective	140	4.683			11,4%	8,3%	0,05
Dickey et al	2004	Retrospective	41	261			12,2%	7,3%	NS
La Sala et al	2004	Retrospective	62	437			19,3%	17,7%	NS
Pinborg et al	2005	Retrospective	642	5.237	1,6	1,2-2,0	13,2%	9,0%	0,001
Shebl et al	2007	Retrospective	46	92			19,6%	8,7%	0,067
Very preterm delivery <32 weeks									
Chasen et al	2006	Retrospective	55	168			7,3%	1,8%	0,04
Dickey et al	2004	Retrospective	41	261			2,4%	1,1%	NS
Pinborg et al	2005	Retrospective	642	5.237	3,0	1,9-4,8	3,3%	1,3%	0,001

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Vanishing Twin; SGA-LBW

Low birth weight <2500g			Case	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
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	
Very low birth weight <1500g										
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	
Small for gestational age <10th										
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
Shebl et al	2007	Retrospective	46	92			32,6%	16,3%	0,029	

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Acknowledgements

- Erasmus University Medical Center, Rotterdam
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- University College London
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Questions

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Unresolved Questions

- Would screening early pregnancy events help in pregnancy management?
- Would risk assessment at antenatal booking improve our detection of adverse pregnancy outcome?
- Should scanning assessment of early pregnancy be extended beyond just viability and growth data?

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Further Research Questions

- Would larger prospective observational studies help in risk assessment following EP events eg haematoma visualisation?
- Are patient symptoms reliable witnesses?
- Is there a place for treatment interventions?

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Hyperemesis gravidarum

- Incidence 0.3-1.5%
- Exact etiology remains unknown and therefore the treatment remains symptomatic
- Decreased risk of miscarriage OR 0.3, (95% CI 0.2-0.3)[1]

- No increased risk of preeclampsia[2,6]

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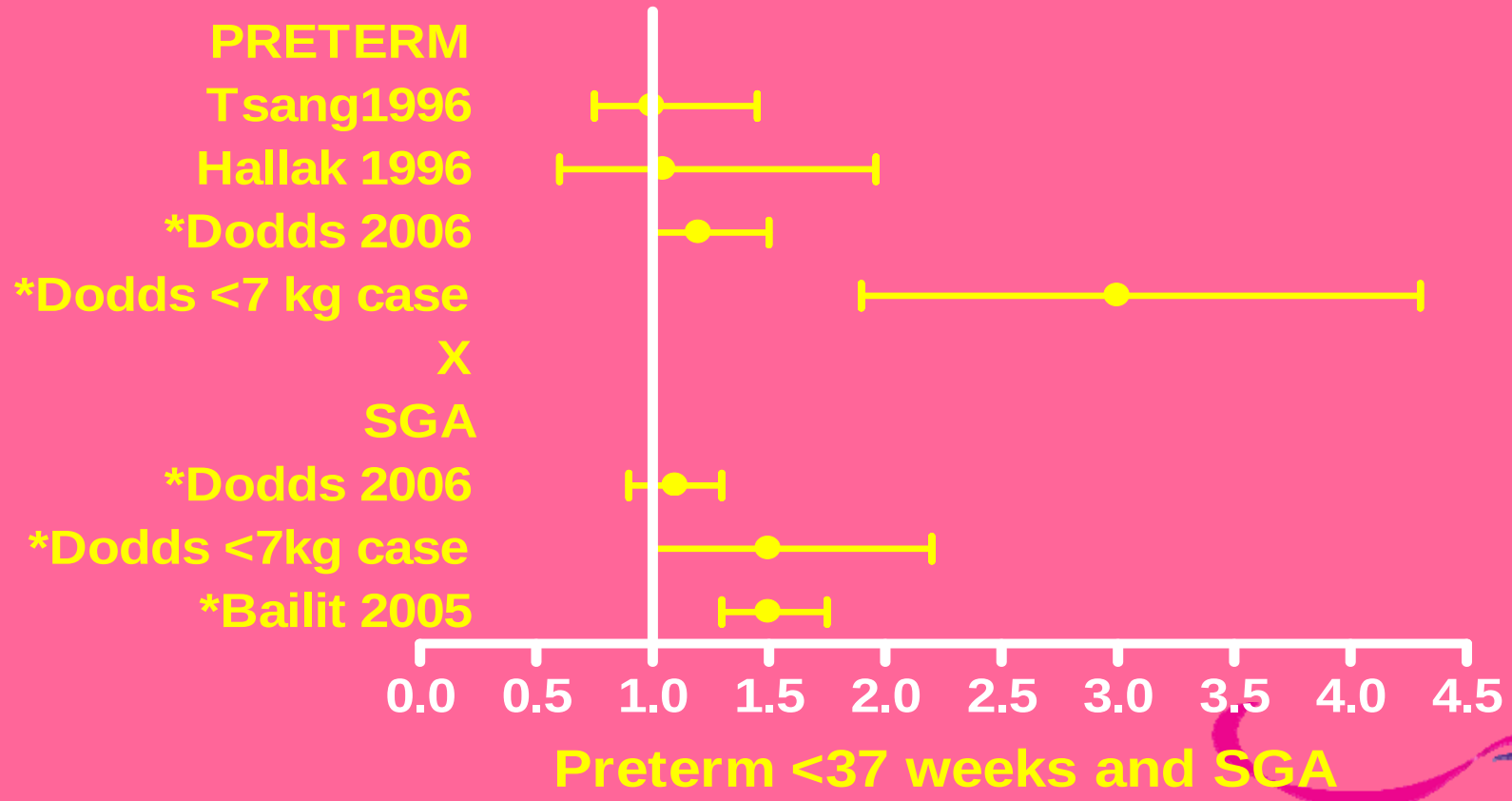
1 Maconochie et al 2007; 2 Dodds et al 2006; 3 Hallak et al 1996; 4 Tsang et al 1996; 5 Bailit et al 2005; 6 Bashiri et al 1995; 7 Hod et al 1994; 8 Gross et al 1989; 9 Kawamura et al 2008

Hyperemesis: Preterm < 37 weeks and SGA



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CRL discrepancy

- If measured Crown-Rump Length (CRL) is smaller then expected (2-6 days)

- Associated with higher risk of miscarriage[1]
- Associated with aneuploidy[2-6]
- Related to birthweight[7,8]

- If there is a CRL discrepancy: Dating issue or very early growth restriction?

1 Reljic 2001; 2 Kuhn et al 1995; 3 Schermer et al 1997; 4 Bahado-Sing et al 1997; 5 Falcon et al 2005; 6 Goldstein et al 1996; 7 Bukowski et al 2007; 8 Leung et al 2008; 9 Smith et al 1998

Hyperemesis Gravidarum

Preterm	Jaar	Opzet	Case	Control	OR	95% CI	%Case	%Cont	Sign	
Dodds et al	2000	Retrospective	1.270	154.821	1,2	1,0-1,5	6,5%	5,4%	S	
			144	127.835	3,0	1,9-4,3	13,9%	4,9%	S	Weight gain < 7kg
			144		1,4	0,9-2,1			NS	Weight gain < 7kg in Case and controls
Hallak et al	1996	Retrospective	98	12.335			11,2%	10,7%	NS	
Tsang et al	1996	Retrospective	193	12.857			23,0%	22,0%	NS	
Low birth weight <2500g										
Bailit et al	2005	Retrospective	2.270	486.505			7,8%	5,1%	0,01	
Dodds et al	2006	Retrospective	1.270	154.821	1,3	1,0-1,7	5,7%	4,6%	S	
			144	127.835	2,8	1,7-4,3	12,5%	4,2%	S	Weight gain < 7kg
			144		1,3	0,8-2,0			NS	Weight gain < 7kg in Case and controls
Very low birth weight <1500g										
Bailit et al	2005	Retrospective	2.270	486.505			1,5%	1,1%	0,04	
Small for gestation p<10										
Bailit et al	2005	Retrospective	2.270	486.505			29,2%	20,8%	0,01	
Dodds et al	2006	Retrospective	1.270	154.821	1,1	0,9-1,3	10,8%	10,0%	NS	
			144	127.835	1,5	1,0-2,2	14,6%	10,0%	S	Weight gain < 7kg
			144		1,1	0,7-1,5			NS	Weight gain < 7kg in Case and controls