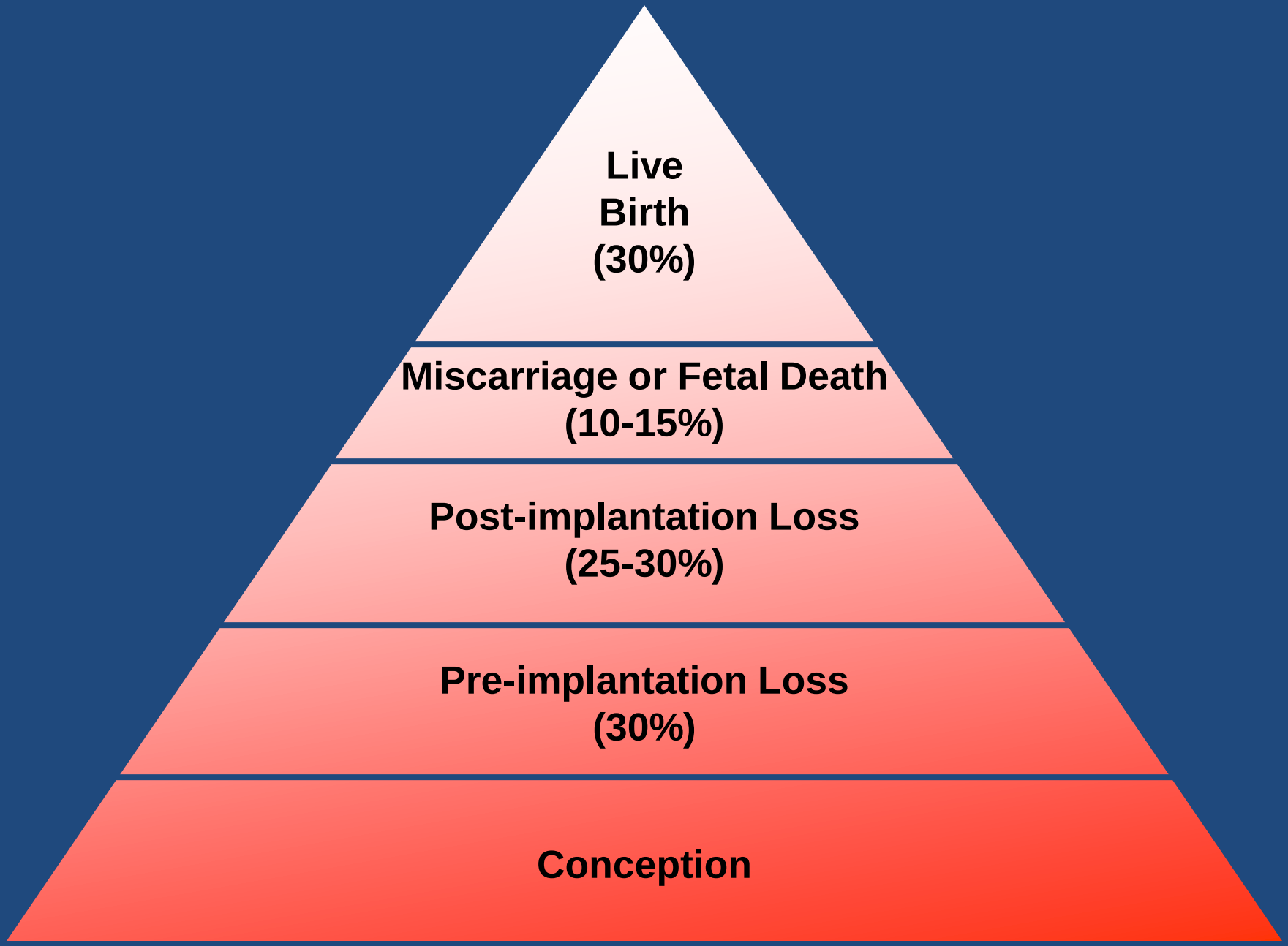
Dr. Branch has no commercial affiliations or conflicts of interest to disclose


Live
Birth
(30%)
Miscarriage or Fetal Death
(10-15%)
Post-implantation Loss
(25-30%)
Pre-implantation Loss
(30%)
Conception

Recurrent Pregnancy Loss

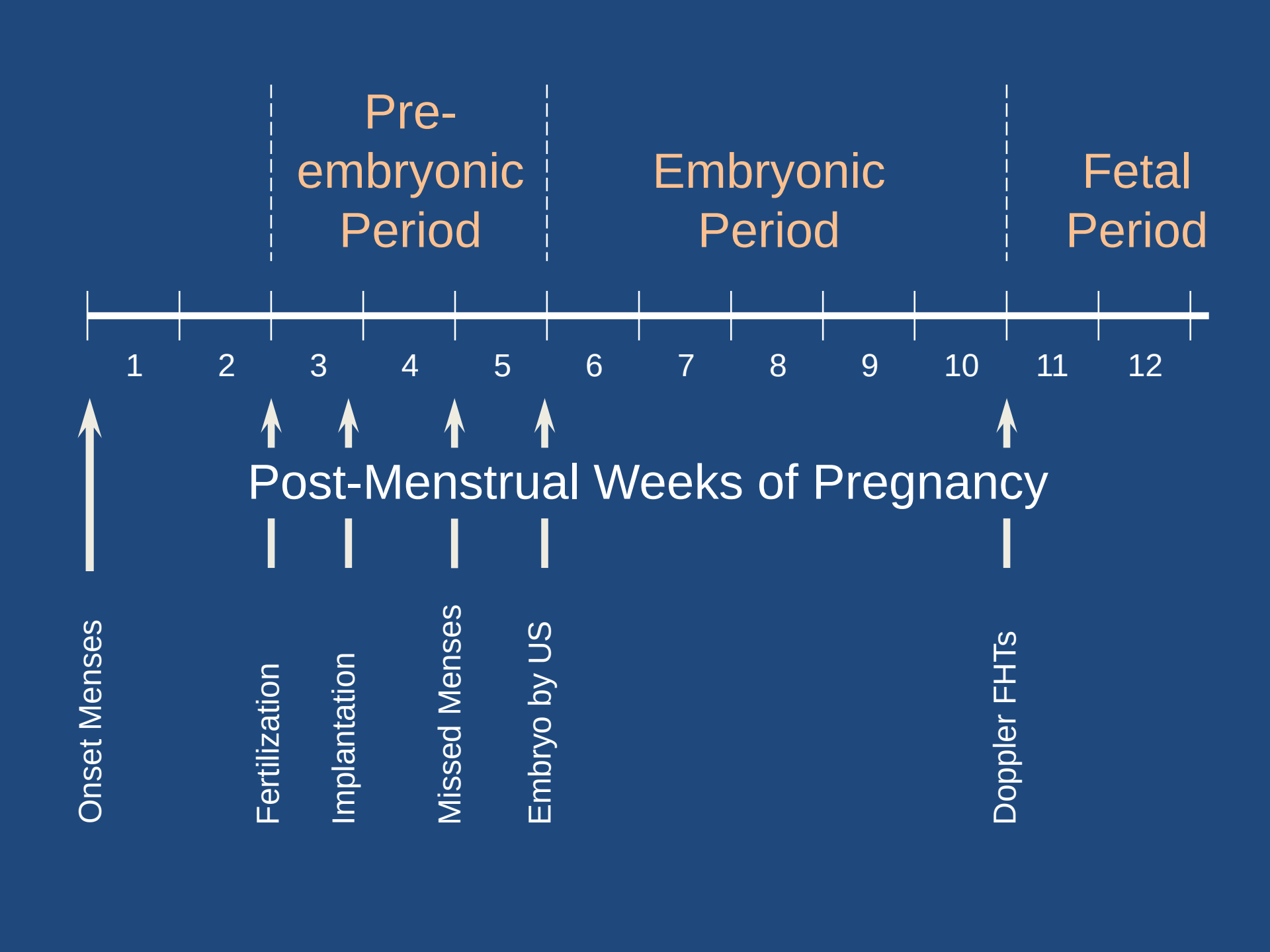
Contemporary Views

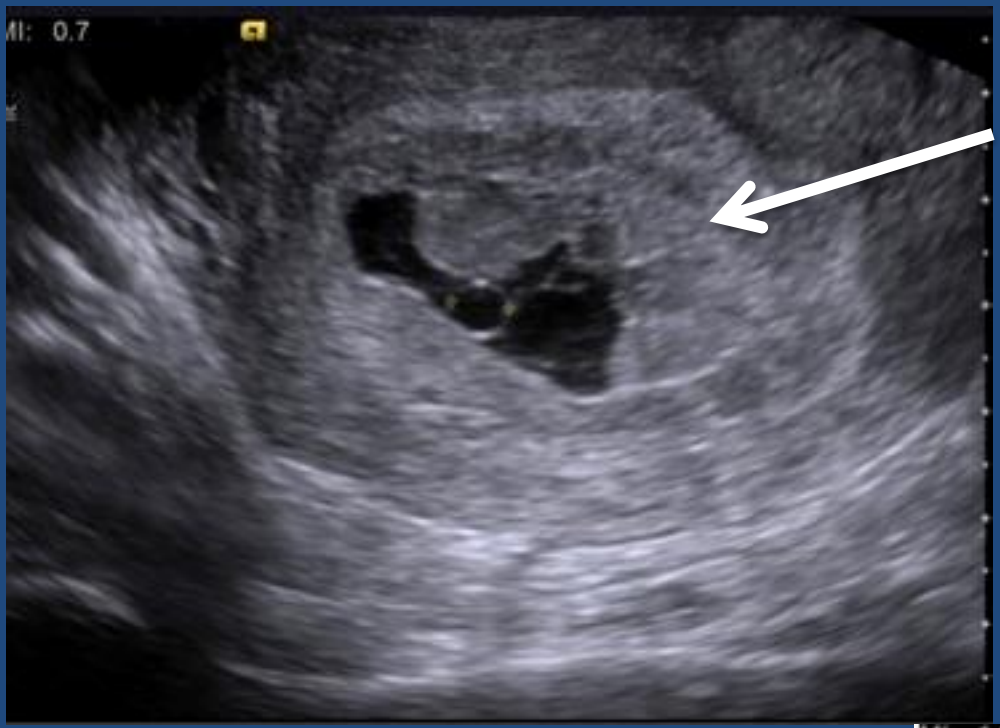
- 2 or more consecutive losses
  2 or 3 non-consecutive losses
  - degree of concern tempered by patient age and other factors
- Categorization of pregnancy loss
  - biochemical
  - pre-embryonic
  - embryonic
  - fetal death

Silver RM, Branch DW, Goldenberg R, Iams JD, Klebanoff MA.

Nomenclature for pregnancy outcomes. Time for a change.

Obstet Gynecol 2011;118:1402-8


Pre-embryonic Period
Embryonic Period
Fetal Period
1
2
3
4
5
6
7
8
9
10
11
12
Post-Menstrual Weeks of Pregnancy
Onset Menses
Fertilization
Implantation
Missed Menses
Embryo by US
Doppler FHTs

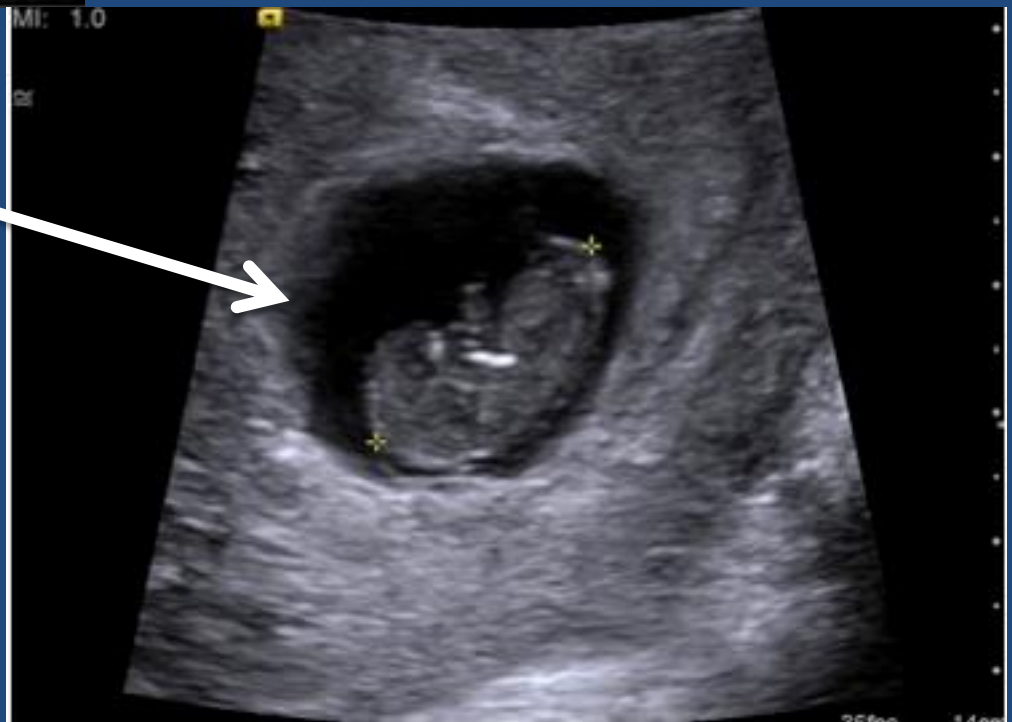


Pre-embryonic demise (anembryonic pregnancy)

- Amniotic sac and yolk sac seen
- No visible embryo
- Pregnancy failure < 6 weeks

Embryonic demise

- Amniotic sac and yolk sac seen
- Visible embryo with no cardiac activity
- CRL c/w 8 weeks 6 days



Idiopathic Recurrent Pregnancy Loss Recurs at Similar Gestational Ages

Heuser et al, Am J Obstet Gynecol, 2010

Timing of QP Loss	<6 weeks (N=81)	6-10 weeks (N=122)	>10 weeks (N=50)	Livebirths (N=81)
Anembryonic (<6 wks) (N=109)	45 (41.3%)	30 (27.5%)	11 (10.1%)	23 (21.1%)
Embryonic (6-10 wks) (N=131)	18 (13.7%)	70 (53.4%)	12 (9.2%)	31 (23.7%)
Fetal loss (>10 wks) (N=94)	18 (19.2%)	22 (23.4%)	27 (28.7%)	27 (28.7%)

Pregnancy Outcomes in 230 Women with Fetal Death

Frias et al, Obstet Gynecol 2004

Pregnancies	Total Pregnancies	Live Births	Fetal Deaths	Miscarriages
Before and including 1st fetal death	721	268 (37%)	230 (32%)	200 (28%)
First pregnancy after 1st fetal death	230	62 (27%)	64 (28%)	99 (43%)
All pregnancies after fetal death	839	202 (24%)	209 (25%)	372 (44%)

CONTEMPORARY OVERARCHING PRINCIPLE:

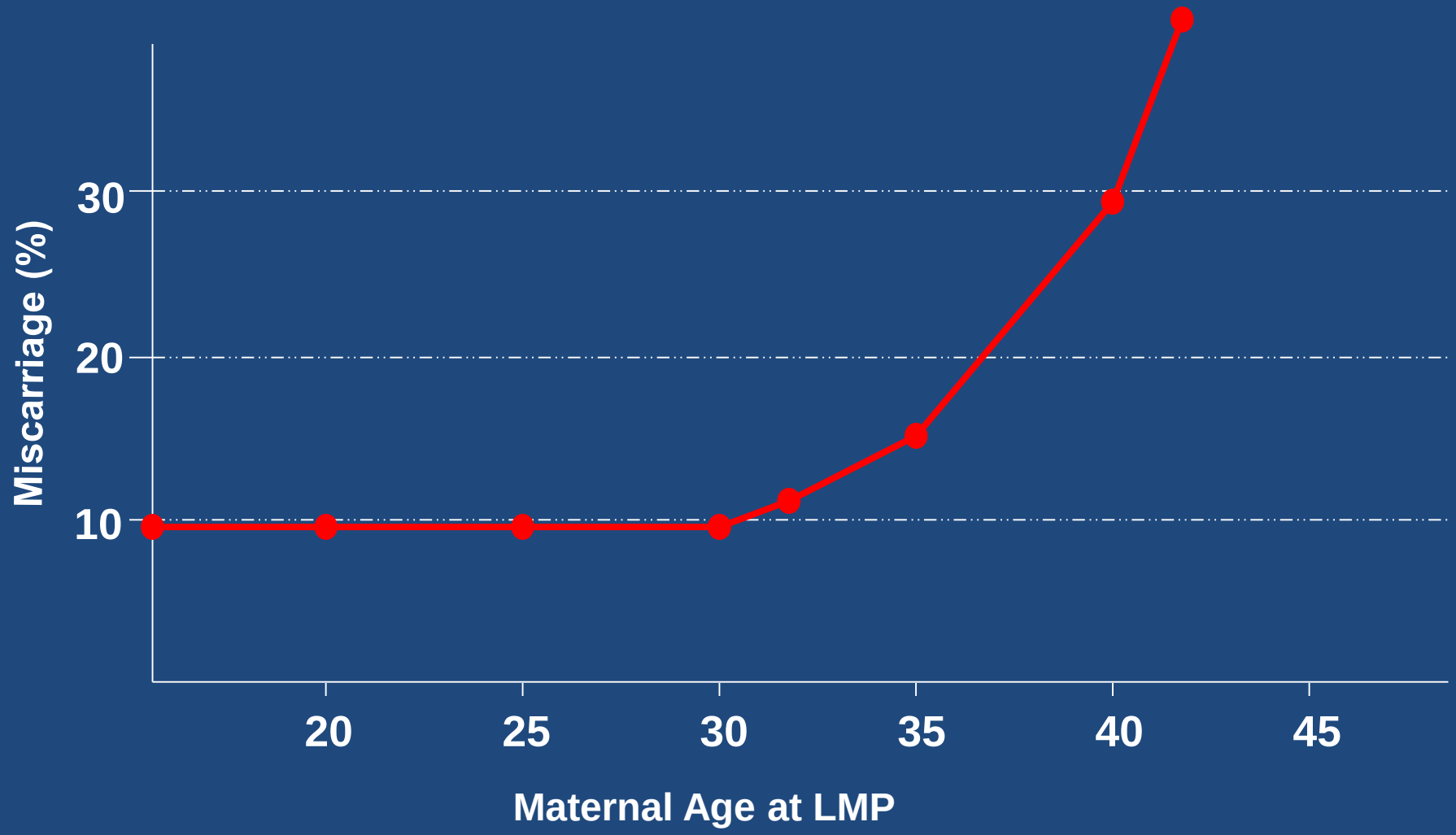
Pregnancy loss is multifactorial in nature, like most medical conditions, *and this should influence counseling and management*.

FACTORS INFLUENCING THE TENDENCY TO HAVE

~~Causes of Recurrent~~ Pregnancy Loss

- **Maternal age**
- **Pregnancy history – number of prior losses**
- **Genetic abnormalities**
- **Hormonal and/or metabolic abnormalities**
- **Autoimmune disease**
- **Uterine malformations/abnormalities; cervical incompetence**
- **Male factors**

Risk of Miscarriage

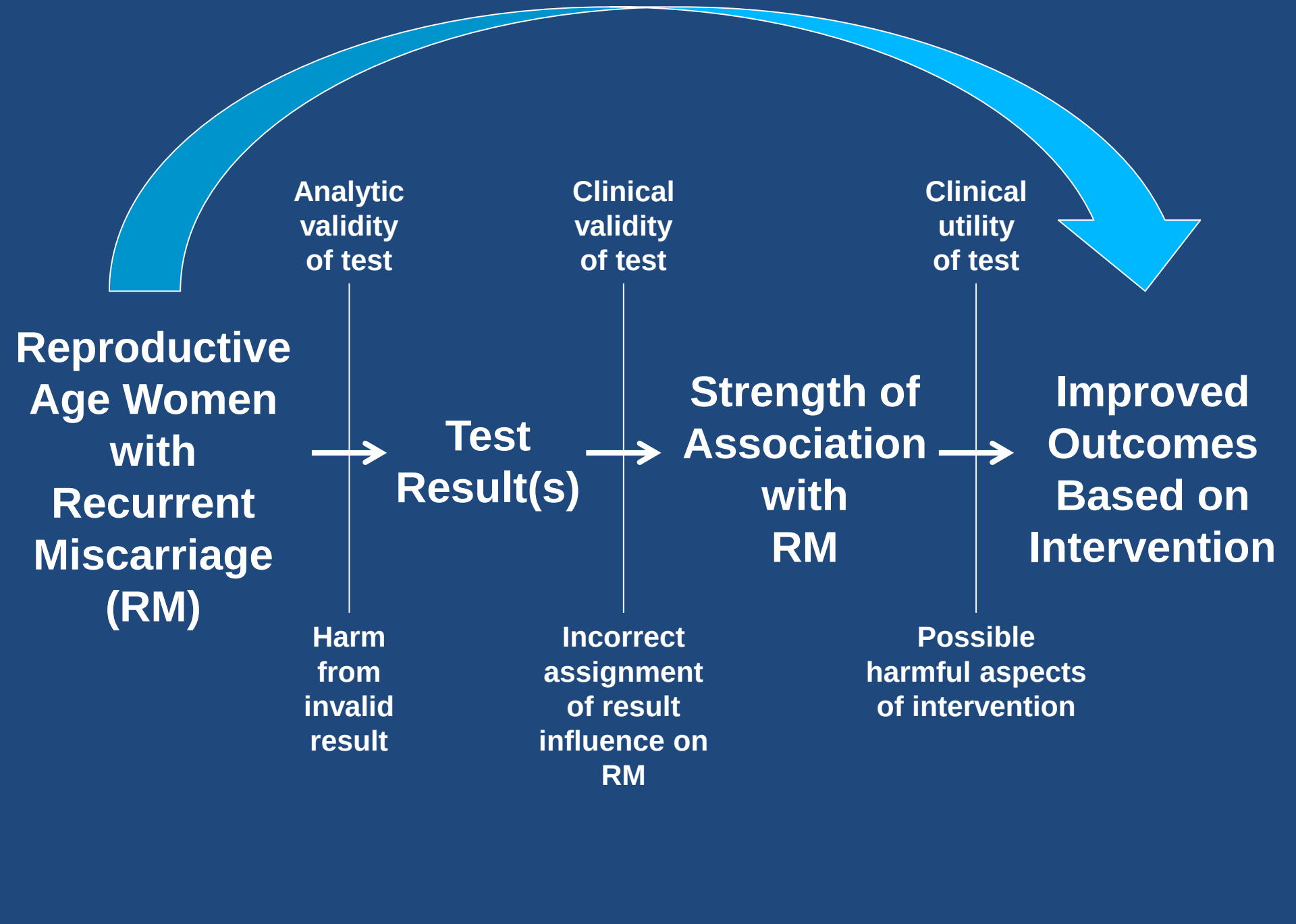


Recurrence Risk for Pregnancy Loss

	Number of Prior Losses	Recurrence Risk Median	Recurrence Risk Range
All Women (data from 12 studies)	0	10%	6%-15%
	1	19%	12%-26%
	2	30%	17%-35%
	3+	33%	25%-47%

Predicted Pregnancy Success in Subsequent Pregnancy by Maternal Age and Previous Miscarriage History (Idiopathic RM)				
	Number of Previous Miscarriages			
Maternal Age (years)	2	3	4	5
20	**92 (86-98)**	**90 (83-97)**	**88 (79-96)**	85 (74-96)
25	**89 (82-95)**	**86 (79-93)**	**82 (75-91)**	79 (68-90)
30	**84 (77-90)**	**80 (74-86)**	**76 (69-83)**	71 (61-81)
35	**77 (69-85)**	**73 (66-80)**	**68 (60-75)**	62 (51-74)
40	69 (57-82)	64 (52-76)	58 (45-71)	52 (37-67)
45	60 (41-79)	54 (35-72)	48 (29-67)	42 (22-62)

S.A. Brigham et al. Hum. Reprod. 1999;14:2868-2871


Analytic validity of test
Clinical validity of test
Clinical utility of test
Reproductive Age Women with Recurrent Miscarriage (RM)
Test Result(s)
Strength of Association with RM
Improved Outcomes Based on Intervention
Harm from invalid result
Incorrect assignment of result influence on RM
Possible harmful aspects of intervention

Genetic Factors

- **Parental Structural Chromosome Abnormalities**
  - **Translocations**
  - **Inversions**
- **Molecular Genetic Abnormalities**
  - **Single gene disorders**

Parental Chromosome Abnormalities in Couples with Recurrent Pregnancy Loss

	Females	Males
All RPL patients	3.3%	2.1%
RPL patients without still-births or anomalous infants	2.4%	1.6%
RPL patients with stillborns or anomalous infants	4.6%	1.7%

Why Consider Obtaining Parental Karyotypes?

- Believable & accepted as cause
- Implications for offspring
- Prognosis
  - Homologous Robertsonian translocations – rare, but normal live birth not possible
- ? Management via IVF-ET with PGS

The Lure Versus the Reality of IVF-ET with PGS for Management of Parental Chromosome Abnormalities

- **IVF-ET with PGS seems a great idea, but combine**
  - **Expense,**
  - **Euploidy rate, and**
  - **ET live birth rate,**

  and what do you get?

Pregnancy Outcomes Following 24-chromosome PGD in Couples with Balanced Translocations

- **Retrospective cohort study of 74 couples with balanced translocations who pursued IVF-ET with PGD**
  - **Embryo biopsies underwent 24-chromosome screening with SNP aCGH (microarray)**

Idowu et al. Fertil Steril 2015;103:1037

Population	No. of Embryos	Unbalanced Translocation (%)	Sporadic Aneuploidy (%)	Combined Abnormalities (%)	Total Abnormalities (%)	Euploid (%)
Total	539	18	36	20	74	26
Robertsonian	201	6	55	2	63	37
Reciprocal	338	24	26	31	81	19
Maternal age ≥35 yrs	202	16	34	31	81	19
Maternal age <35 yrs	337	19	38	14	71	29

Idowu et al. Fertil Steril 2015;103:1037

Pregnancy Outcomes Following 24-chromosome PGD in Couples with Balanced Translocations

- **Live birth rate per biopsy cycle 38%**
- **Clinical miscarriage rate 10%**
- **No chromosomally normal embryos in 30%**

Idowu et al. Fertil Steril 2015;103:1037

Reproductive Outcomes after PGD in in Couples with ≥2 Miscarriages and a Parental Structural Chromosome Abnormality

Franssen et al, Hum Reprod 2011

Category, Number of Studies	No. Couples	No. Live Births (%)	No. Miscarriages (%)
1st pregnancy after natural conception, 4	469	249 (range: 33–60%, median 55.5%)	164 (range: 21–40%, median 34%)
All pregnancies after natural conception, 2	299	238 (range: 64–83%, median 73.5%)	131 (range: 21–49%, median 35%)
PGD, 21 (133 cycles started)	126	44 (range: 0–100%, median 31%)	6 (range: 0–50%, median 0%)

Reproductive Outcomes in Couples with ≥2 Miscarriages

Franssen et al, BMJ 2006

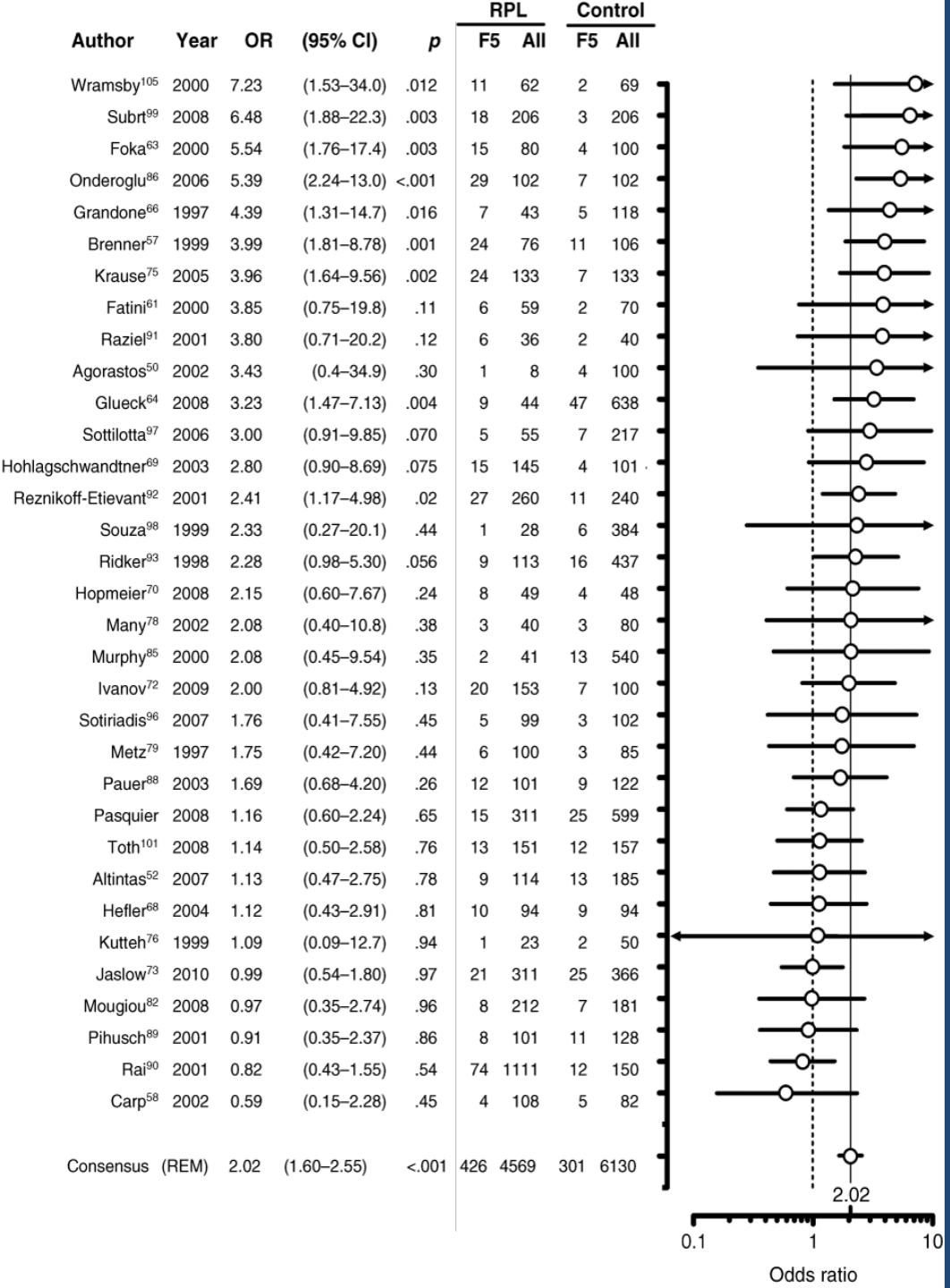
Reproductive outcome	Carrier couples (n=247)	Non-carrier couples (n=409)	Difference in % (95% CI)	P value
Failure to conceive	8 (3.2)	19 (4.6)	−1.4 (−4.4 to 2.0)	0.38
One or more miscarriages	120 (48.6)	122 (29.8)	18.8 (11.1 to 26.3)	<0. 01
One or more ectopics	3 (1.2)	13 (3.2)	−2.0 (−4.3 to 0.7)	0.11
One or more stillbirths	3 (1.2)	6 (1.5)	−0.3 (−2.1 to 2.2)	0.79
One or more children who died postpartum	1 (0.4)	4 (1.0)	−0.6 (−2.1 to 1.4)	0.41
One or more ill or handicapped children	2 (0.8)	11 (2.7)	−1.9 (−4.0 to 0.5)	0.09
One or more healthy children	205 (83.0)	344 (84.1)	−1.1 (−7.2 to 4.6)	0.71

Why You You Might Hesitate to Obtain Parental Karyotypes in Couples with Recurrent Miscarriage

- **Abnormal karyotypes infrequent (~3% of couples with only RM)**
  - **For some of these, miscarriage rates only slightly elevated**
- **Expensive and may be out-of-pocket**
- **Lack of proven utilitarian impact on management?**

Association of FVL genotype and REM in 33 case-control studies

Bradley et al, Genet Med 2012

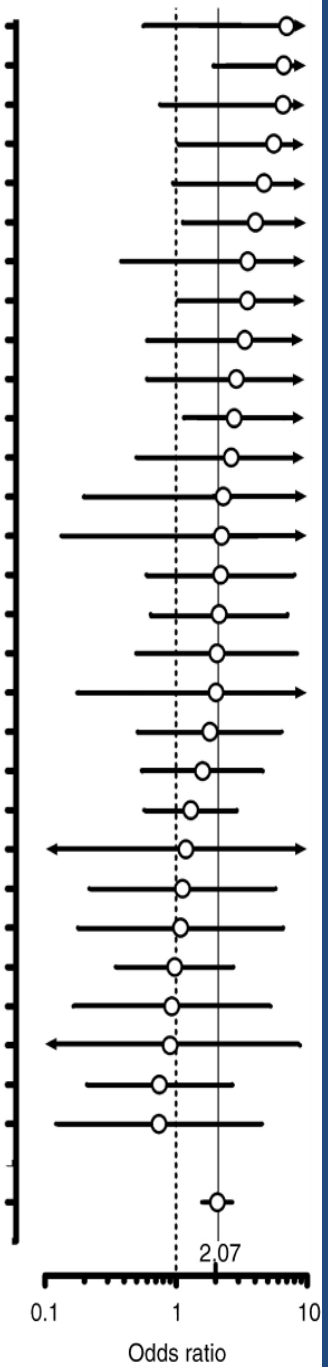


Author	Year	OR	(95% CI)	p	RPL F5	RPL All	Control F5	Control All
Wramsby[105]	2000	7.23	(1.53–34.0)	.012	11	62	2	69
Subrt[99]	2008	6.48	(1.88–22.3)	.003	18	206	3	206
Foka[63]	2000	5.54	(1.76–17.4)	.003	15	80	4	100
Onderoglu[86]	2006	5.39	(2.24–13.0)	<.001	29	102	7	102
Grandone[66]	1997	4.39	(1.31–14.7)	.016	7	43	5	118
Brenner[57]	1999	3.99	(1.81–8.78)	.001	24	76	11	106
Krause[75]	2005	3.96	(1.64–9.56)	.002	24	133	7	133
Fatini[61]	2000	3.85	(0.75–19.8)	.11	6	59	2	70
Raziel[91]	2001	3.80	(0.71–20.2)	.12	6	36	2	40
Agorastos[50]	2002	3.43	(0.4–34.9)	.30	1	8	4	100
Glueck[64]	2008	3.23	(1.47–7.13)	.004	9	44	47	638
Sottilotta[97]	2006	3.00	(0.91–9.85)	.070	5	55	7	217
Hohlagschwandtner[69]	2003	2.80	(0.90–8.69)	.075	15	145	4	101
Reznikoff-Etievant[92]	2001	2.41	(1.17–4.98)	.02	27	260	11	240
Souza[98]	1999	2.33	(0.27–20.1)	.44	1	28	6	384
Ridker[93]	1998	2.28	(0.98–5.30)	.056	9	113	16	437
Hopmeier[70]	2008	2.15	(0.60–7.67)	.24	8	49	4	48
Many[78]	2002	2.08	(0.40–10.8)	.38	3	40	3	80
Murphy[85]	2000	2.08	(0.45–9.54)	.35	2	41	13	540
Ivanov[72]	2009	2.00	(0.81–4.92)	.13	20	153	7	100
Sotiriadis[96]	2007	1.76	(0.41–7.55)	.45	5	99	3	102
Metz[79]	1997	1.75	(0.42–7.20)	.44	6	100	3	85
Pauer[88]	2003	1.69	(0.68–4.20)	.26	12	101	9	122
Pasquier	2008	1.16	(0.60–2.24)	.65	15	311	25	599
Toth[101]	2008	1.14	(0.50–2.58)	.76	13	151	12	157
Altintas[52]	2007	1.13	(0.47–2.75)	.78	9	114	13	185
Hefler[68]	2004	1.12	(0.43–2.91)	.81	10	94	9	94
Kutteh[76]	1999	1.09	(0.09–12.7)	.94	1	23	2	50
Jaslow[73]	2010	0.99	(0.54–1.80)	.97	21	311	25	366
Mougiou[82]	2008	0.97	(0.35–2.74)	.96	8	212	7	181
Pihusch[89]	2001	0.91	(0.35–2.37)	.86	8	101	11	128
Rai[90]	2001	0.82	(0.43–1.55)	.54	74	1111	12	150
Carp[58]	2002	0.59	(0.15–2.28)	.45	4	108	5	82
Consensus (REM)		2.02	(1.60–2.55)	<.001	426	4569	301	6130

Association of PT mutation genotype and REM in 29 case-control studies

Bradley et al, Genet Med 2012

Author	Year	OR	(95% CI)	p	RPL F2	RPL All	Control F2	Control All
Agorastos[50]	2002	7.00	(0.56–87.0)	.13	1	8	2	100
Ivanov[72]	2009	6.62	(1.95–22.5)	.002	26	153	3	100
Pihusch[89]	2001	6.65	(0.75–56.9)	.089	5	102	1	128
Many[78]	2002	5.57	(1.03–30.1)	.046	5	40	2	80
Foka[63]	2000	4.70	(0.95–23.3)	.058	7	80	2	100
Mitic[80]	2010	4.04	(1.13–14.5)	.032	13	147	3	128
Souza[98]	1999	3.52	(0.38–32.6)	.27	1	28	4	384
Sottilotta[97]	2006	3.52	(1.03–12.0)	.044	5	55	6	217
Kupferminc[112]	2000	3.36	(0.61–18.6)	.17	2	20	5	156
Hohlagschwandtner[69]	2003	2.89	(0.60–13.9)	.19	8	145	2	101
Reznikoff-Etievant[92]	2001	2.77	(1.15–6.68)	.023	20	260	7	240
Sottilotta	2001	2.63	(0.50–13.9)	.25	5	99	2	101
Raziel[91]	2001	2.29	(0.20–26.4)	.51	2	36	1	40
Kutteh[76]	1999	2.23	(0.13–37.3)	.58	1	23	1	50
Brenner[57]	1999	2.19	(0.59–8.03)	.24	6	76	4	106
Jaslow[73]	2010	2.13	(0.64–7.10)	.22	5	143	6	359
Krause[75]	2005	2.05	(0.50–8.36)	.32	6	133	3	133
Onderoglu[86]	2006	2.02	(0.18–22.6)	.57	2	102	1	102
Hefler[68]	2004	1.81	(0.51–6.40)	.36	7	94	4	94
Toth[101]	2008	1.59	(0.55–4.59)	.39	9	151	6	157
Pasquier	2008	1.29	(0.57–2.91)	.53	10	311	15	599
Fatini[61]	2000	1.19	(0.07–19.4)	.90	1	59	1	70
Wramsby[105]	2000	1.12	(0.22–5.76)	.89	3	62	3	69
Altinitas[52]	2007	1.08	(0.18–6.58)	.93	2	114	3	185
Mougiou[82]	2008	0.97	(0.35–2.74)	.96	8	212	7	181
Pickering[113]	2001	0.93	(0.16–5.26)	.93	4	103	2	48
Subrt[99]	2008	0.90	(0.09–8.82)	.93	3	206	1	62
Carp[58]	2002	0.75	(0.21–2.67)	.65	5	108	5	82
Pauer[88]	2003	0.74	(0.12–4.53)	.75	2	101	3	113
Consensus (REM)		2.07	(1.59–2.70)	<.001	174	3171	105	4285



Comparative incidence of pregnancy outcomes in thrombophilia-positive women from the NOH-APS observational study

Outcome	Thombophilia, N=93	No Thrombophilia, N=483	P
Recurrent early Sab <10 wks	13 (14.0%)	92 (19.2%)	0.2584
Fetal death ≥10 wks (% of ongoing pregnancies)	7 (8.8%)	9 (2.3%)	0.0063
Ongoing pregnancies ≥20 wks (% of all pregnancies)	75 (80.6%)	384 (80.0%)	0.9073
Live births (% of all pregnancies)	73 (77.4%)	379 (79.0%)	0.6639

Heparin for the Prevention of Recurrent Miscarriage

Group	LMWH + LDA	LDA	Placebo
Clark et al (SPIN)			
Live Births	77.6%	NA	79.3%
Kaandorp et al			
Live Births	69.1%	61.6%	67.0%
Visser et al			
Live Births	65.0%	61.0%	NA

FACTORS INFLUENCING THE TENDENCY TO HAVE

~~Causes of Recurrent~~ Pregnancy Loss

- **Maternal age**
- **Pregnancy history – number of prior losses**
- **Genetic abnormalities**
- **Hormonal and/or metabolic abnormalities**
- **Autoimmune disease**
- **Uterine malformations/abnormalities; cervical incompetence**
- **Male factors**

Hormonal and Metabolic Factors

- **Hormonal**
  - Luteal phase defect
  - Poorly-controlled diabetes
  - Symptomatic thyroid disorders
  - PCOS/hyperandrogenism
  - Hyperprolactinemia
- **Metabolic**
  - Metabolic syndrome?
  - Obesity?

Progesterone Insufficiency / Luteal Phase Defect

A Factor in Recurrent Miscarriage?

- Progesterone required for maintenance of early pregnancy
- LPD reported in up to 40% of women with RM

Progesterone Insufficiency / Luteal Phase Defect

A Factor in Recurrent Miscarriage?

- Studies lack concurrently tested controls
- Endometrial biopsy
  - High rate of abnormal endometrial histology among normal women
  - High rate of inter- & intra-observer variation
- Luteal phase progesterone levels
  - Vary from hour-to-hour
  - Do not correlate well with histology

A Randomized Trial of Progesterone in Women with Recurrent Miscarriages

- **Multicenter RCT of progesterone to prevent recurrent miscarriage**
  - **BID vaginal micronized progesterone, 400 mg**
  - **From positive pregnant test through 12 weeks**

Coomarasamy et al. N Engl J Med. 373:2141-2148 November 26, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Outcome	Progesterone N=398	Placebo N=428	RR (95% CI)
Clinical pregnancy at 6-8 wks	326 (81.9%)	334 (78.0%)	1.05 (0.98-1.12)
Ongoing pregnancy at 12 wks	267 (67.1%)	277 (64.7%)	1.04 (0.94-1.14)
Ectopic	6 (1.5%)	7 (1.6%)	0.92 (0.31-2.72)
Miscarriage	128 (32.2%)	143 (33.4%)	0.96 (0.79-1.17)
Stillbirth	1 (0.3%)	2 (0.5%)	0.54 (0.05-5.92)
Live birth after 24 wks	262 (65.8%)	271 (63.3%)	1.04 (0.94-1.15)
Live birth before 37 wks	27 (10.3%)	25 (9.2%)	1.12 (0.67-1.87)

Coomarasamy et al. N Engl J Med. 373:2141-2148

The NEW ENGLAND JOURNAL of MEDICINE

Progesterone Insufficiency / Luteal Phase Defect

A Factor in Recurrent Miscarriage?

- **Progesterone**
  - **No clear proof of efficacy**
  - **At best controversial, at worst ineffective**
  - **Luteal phase support yet to be studied in RM**

Recommended Hormonal / Metabolic Assessments in RM

ASRM Guidelines, 2012

- **Prolactin**
- **TSH**
- **Hgb A1c**

RM and Hyperprolactinemia

Hirahara et al. Fertil Steril 1998

Group	No. of conceptions	No. (%) of live births	No. (%) of miscarriages
Bromocriptine (n = 24)	21	18 (85.7%)	3 (14.3%)
No bromocriptine (n = 22)	21	11 (52.4%)	10 (47.6%)

Obesity is Associated with Miscarriage and Recurrent Miscarriage

Lashen et al, Hum Reprod 2004

- **Retrospective analysis of UK maternity database comparing obese (BMI>30) with 1:2 age-matched controls of normal BMI**
  - **1633 obese – 3288 normal weight controls**

Obesity is Associated with Miscarriage and Recurrent Miscarriage

Lashen et al, Hum Reprod 2004

Patient Category	N	Previous miscarriage	Recurrent miscarriage
BMI> 30	1644	12.5%	0.4%
Normal	3288	10.5%	0.1%

ORs for obese women having previous miscarriage or recurrent miscarriage 1.2 (1.01-1.46) and 3.51 (1.03-12.01)

Effect of BMI on Pregnancy Outcome

Lo et al, J Family Community Med 2012

Variable	Category	Pregnancy outcome		*P* value	Odd ratio (95% Confidence interval)
		Live birth	Miscarriage		
BMI	Obese (*n* = 90)	41%	59%	0.028	1.73, 1.06 – 2.83
	Overweight (*n* = 190)	49%	51%	NS	1.27, 0.89 – 1.83
	Normal (*n* = 406)	56%	44%		Comparator
	Underweight (*n* = 10)	90%	10%	NS	0.12, 0.15 – 1.00
Ethnicity	Caucasian (*n* = 542)	56%	44%		Comparator
	Asian (*n* = 53)	32%	68%	0.001	2.87, 1.52 - 5.39
	Black, Afro-Carribean (*n* = 41)	41%	59%		1.82, 0.93 – 3.55
	Oriental (*n* = 7)	43%	57%		1.86, 0.39 – 8.79
	Other (*n* = 1)	0%	100%		0
	Not stated (*n* = 52)	48%	52%		1.44, 0.80 – 2.61
Maternal age	<35 (n = 369)	60%	40%		Comparator
	≥35 (*n* = 327)	45%	55%	<0.0001	1.99, 1.45 – 2.73
Number of previous miscarriages	3 – 4 (*n* = 542)	57%	43%		Comparator
	≥5 (*n* = 154)	39%	61%	<0.0001	2.08, 1.42 - 3.06

NS = not significant

“Treatments” Patients with RM Ask About

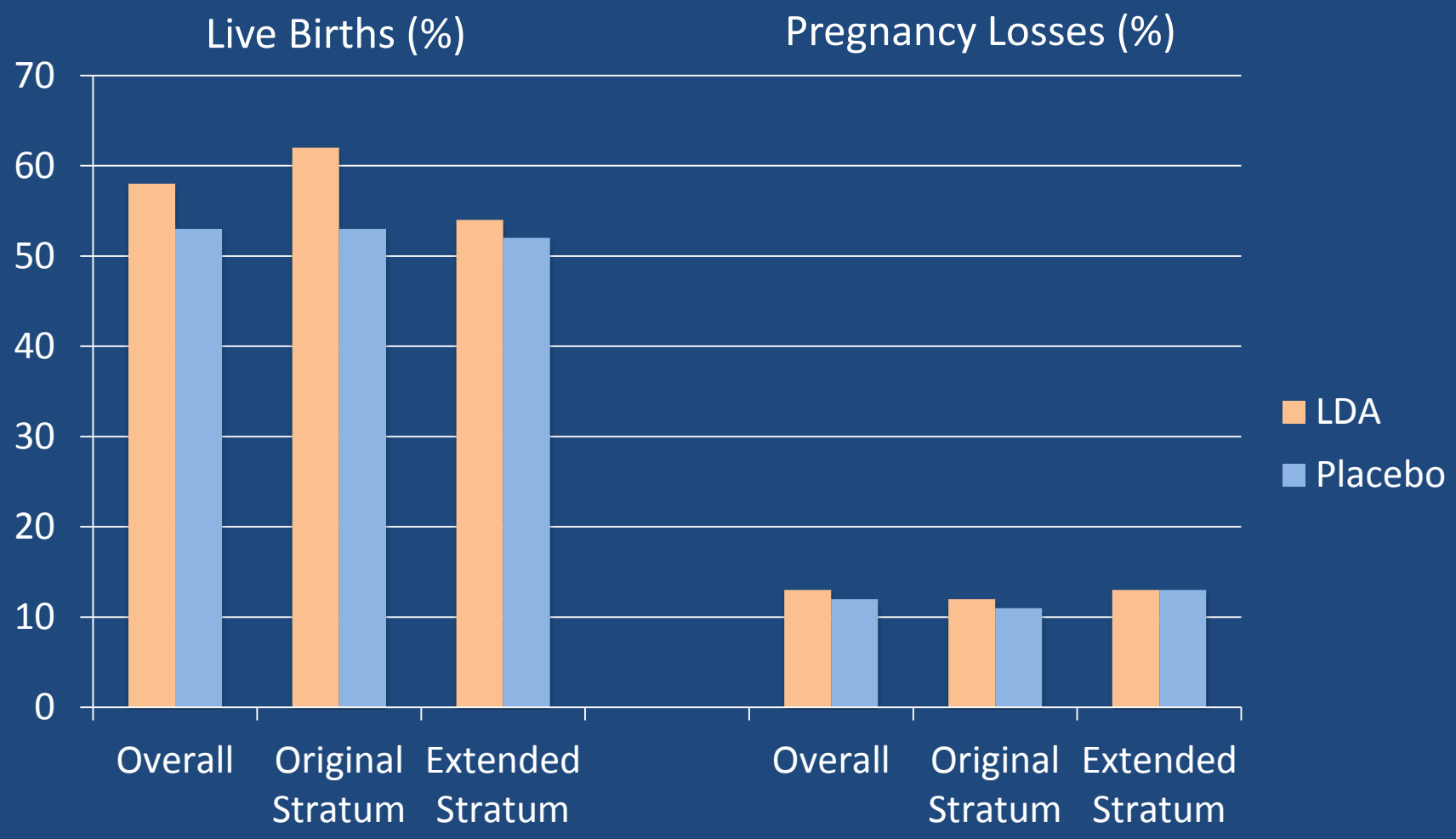
- LDA
- Progesterone
- Heparin
- IVIG
- Prednisone
- Intralipid

EAGeR Trial

- **Prospective, double-blind, placebo controlled, RCT**
  - **healthy women (18-39 yrs) attempting pregnancy**
  - **1-2 prior pregnancy losses**
  - **no diagnosis of / or treatment for infertility**
- **1,078 women completed trial**
  - **492 with ≤1 prior loss and ≤1prior live birth**
  - **586 with ≤2 prior losses and ≤2 prior live births**

Preconception LDA and Pregnancy Outcomes (EAGeR Trial)

Schisterman et al. Lancet, 2014

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