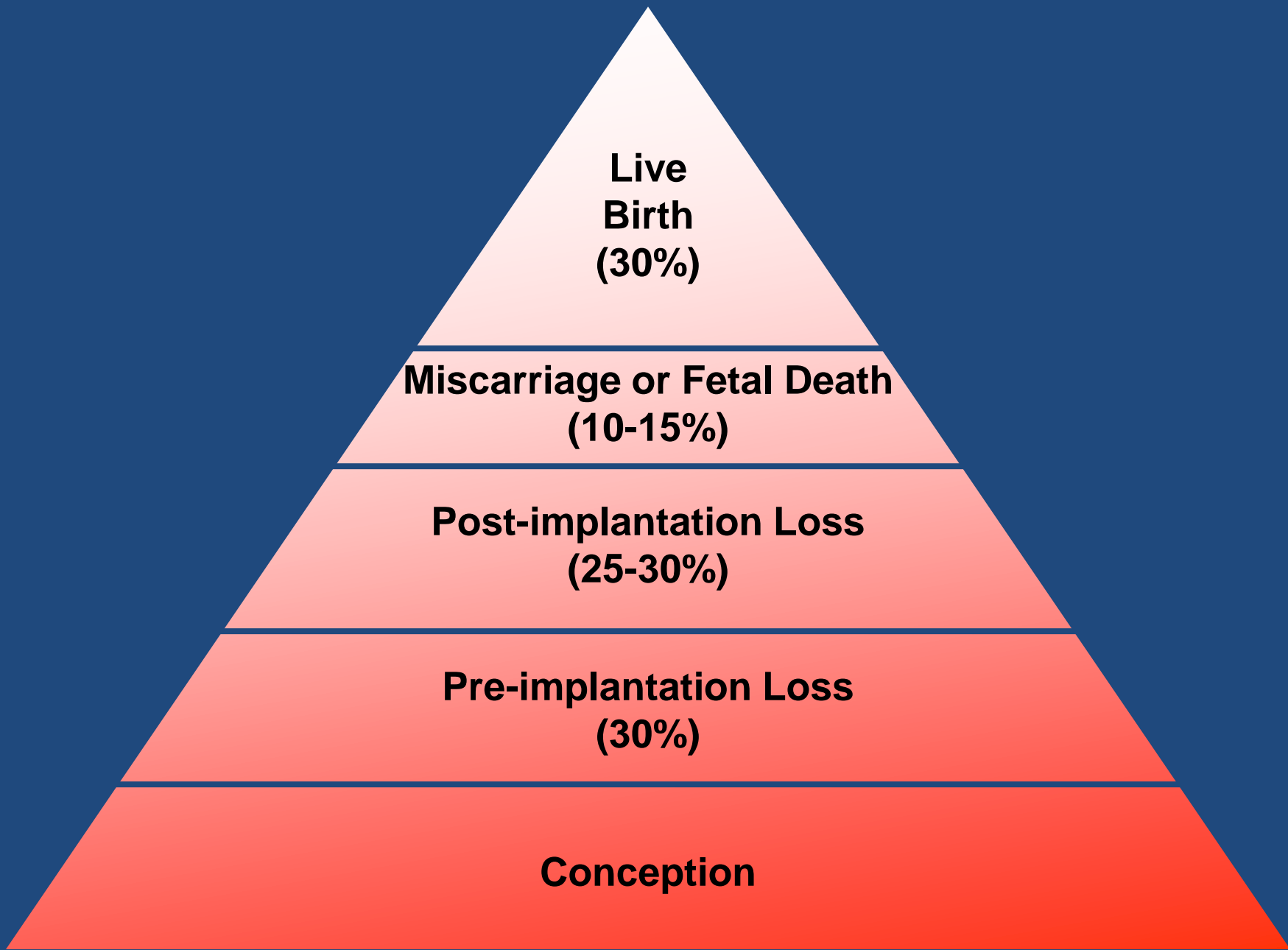


**Dr. Branch has no
commercial affiliations or
conflicts of interest to
disclose**



**Live
Birth
(30%)**

**Miscarriage or Fetal Death
(10-15%)**

**Post-implantation Loss
(25-30%)**

**Pre-implantation Loss
(30%)**

Conception

Recurrent Pregnancy Loss

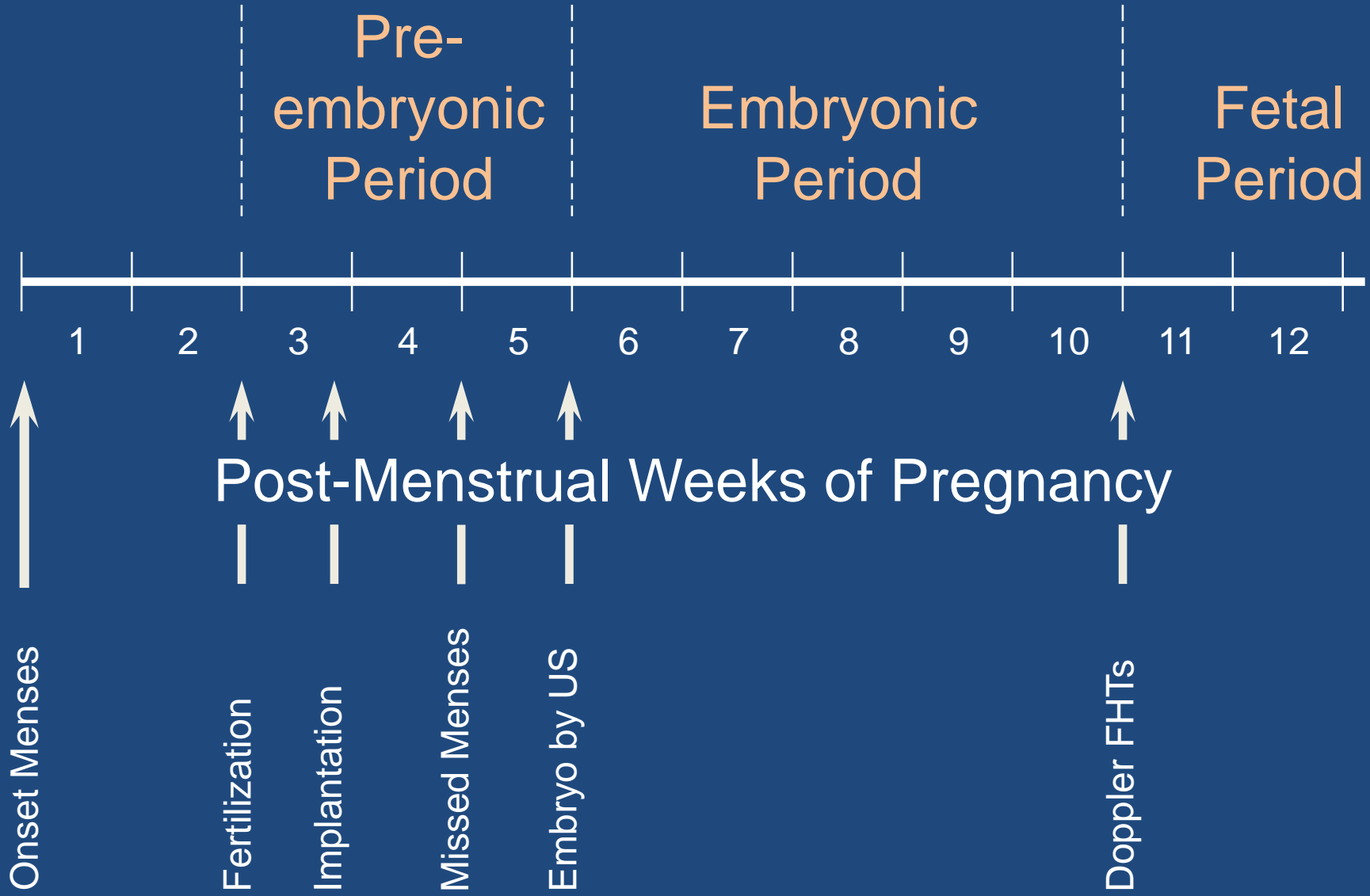
Contemporary Views

- **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

Post-Menstrual Weeks of Pregnancy

Onset Menses

Fertilization

Implantation

Missed Menses

Embryo by US

Doppler FHTs

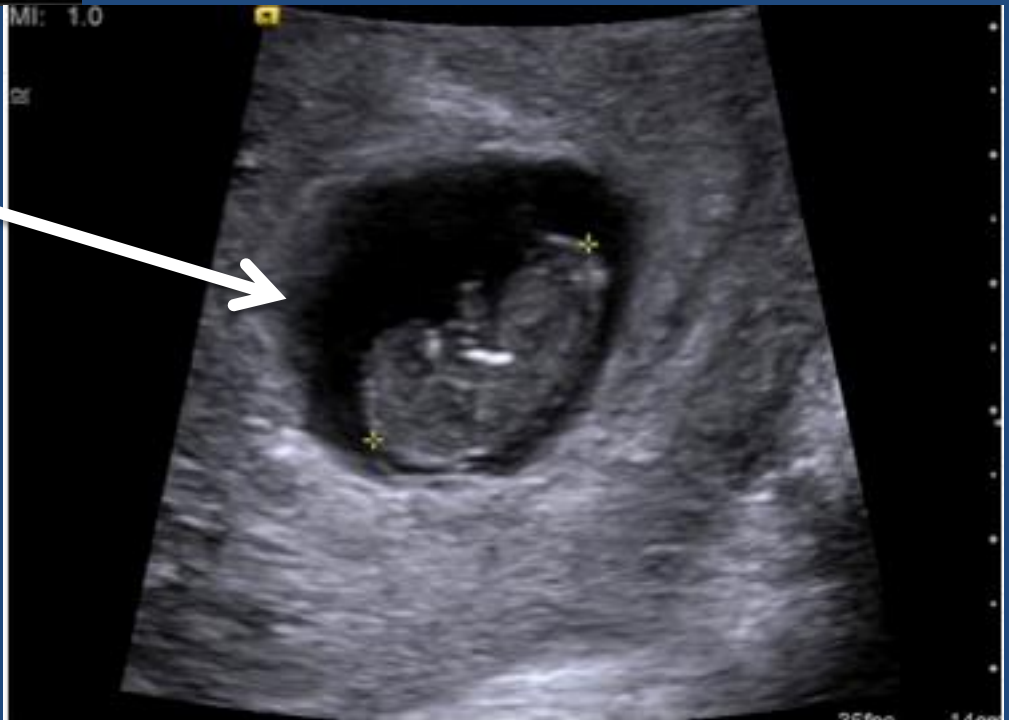


Pre-embryonic demise (anembryonic pregnancy)

- 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 Recurrs 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 1 st fetal death	721	268 (37%)	230 (32%)	200 (28%)
First pregnancy after 1 st fetal death	230	62 (27%)	64 (28%)	99 (43%)
All pregnancies after fetal death	839	202 (24%)	209 (25%)	372 (44%)

CONTEMPORARY OVERARCHING PRINCIPLE:

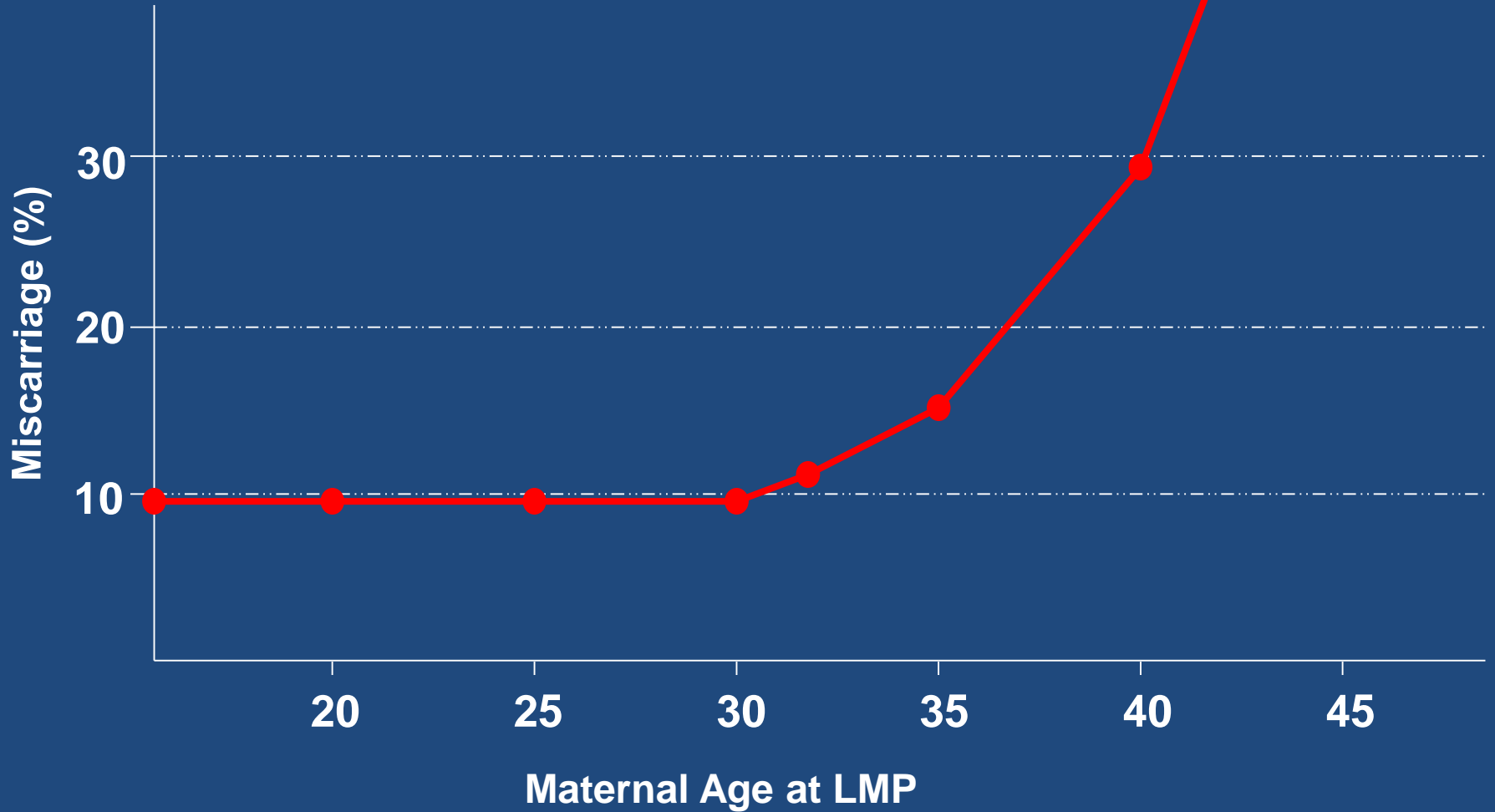
Pregnancy loss is multifactorial in nature, like most medical conditions, *and this should influence counseling and management.*

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	Range
All Women	0	10%	6%-15%
(data from 12 studies)	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)

Maternal Age (years)	Number of Previous Miscarriages			
	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

**Reproductive
Age Women
with
Recurrent
Miscarriage
(RM)**

**Analytic
validity
of test**



**Test
Result(s)**

**Clinical
validity
of test**



**Strength of
Association
with
RM**

**Clinical
utility
of test**



**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 stillbirths 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)

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

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 (%)
1 st 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%)

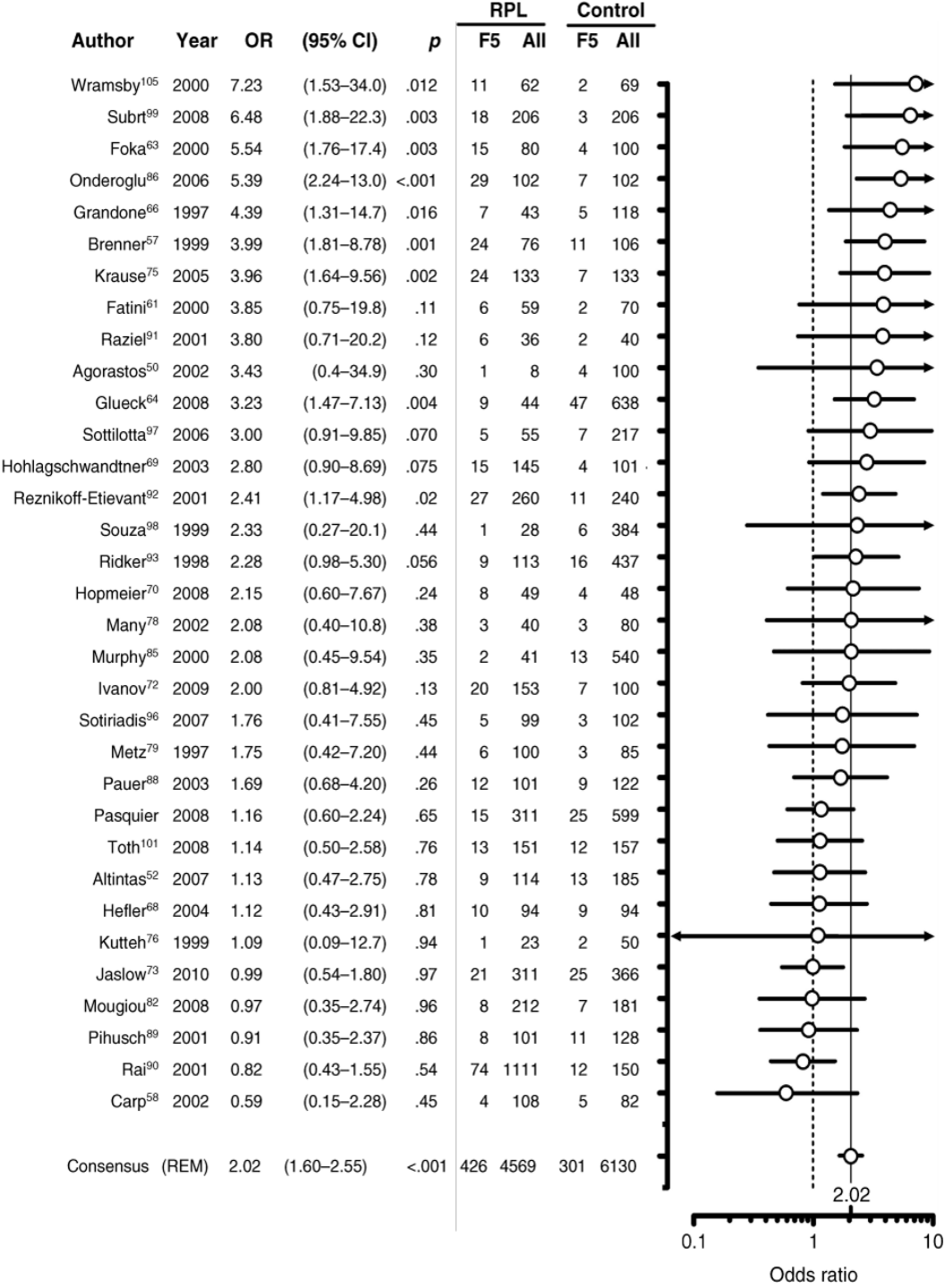
Reproductive Outcomes in Couples with ≥ 2 Miscarriages

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

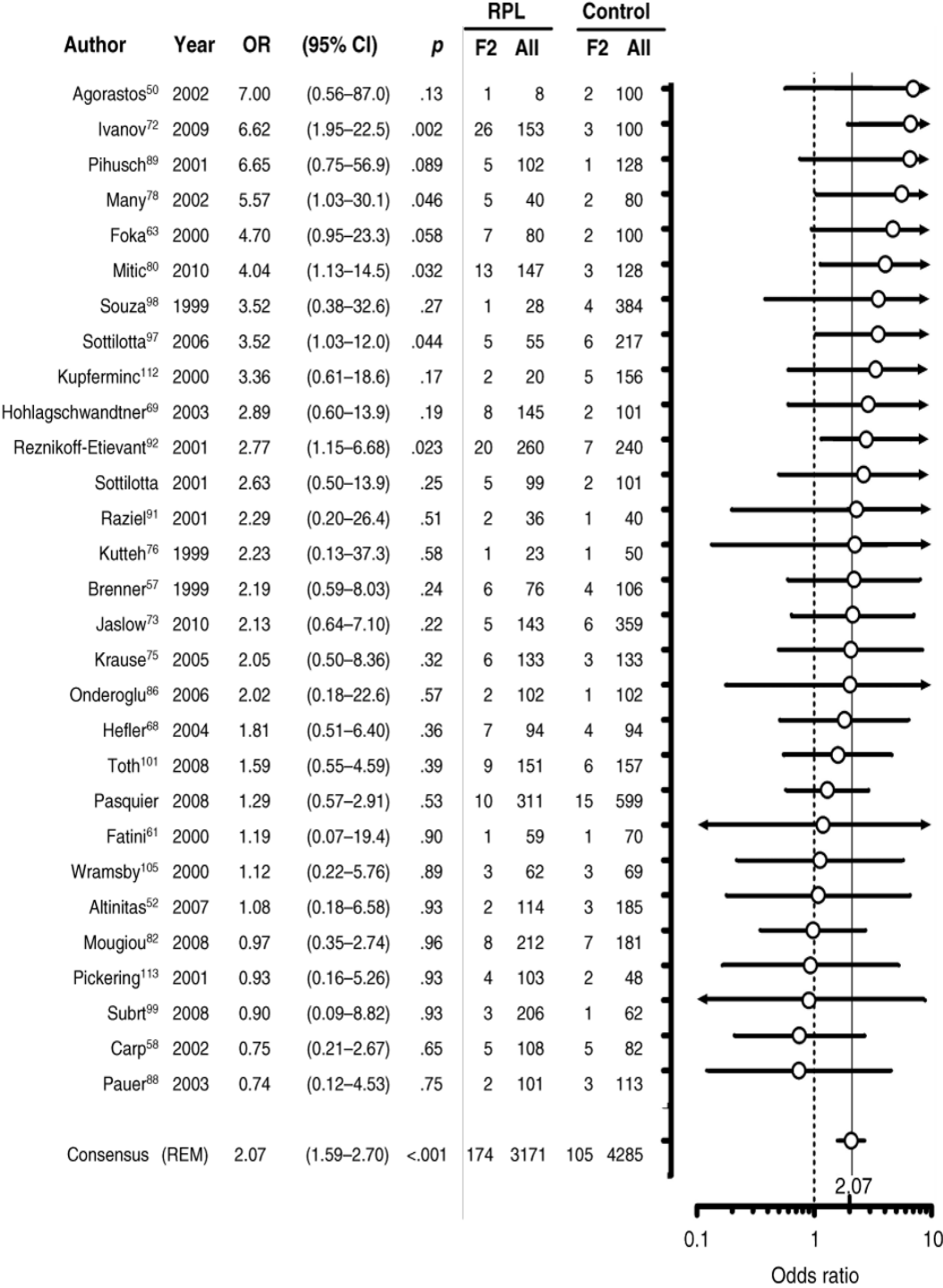
Why You You Might Hesitate to Obtain Parental Karyotypes in Couples with Recurrent Miscarriage

- **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



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

Bradley et al, Genet Med 2012

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

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)

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

NS = not significant

“Treatments” Patients with RM Ask About

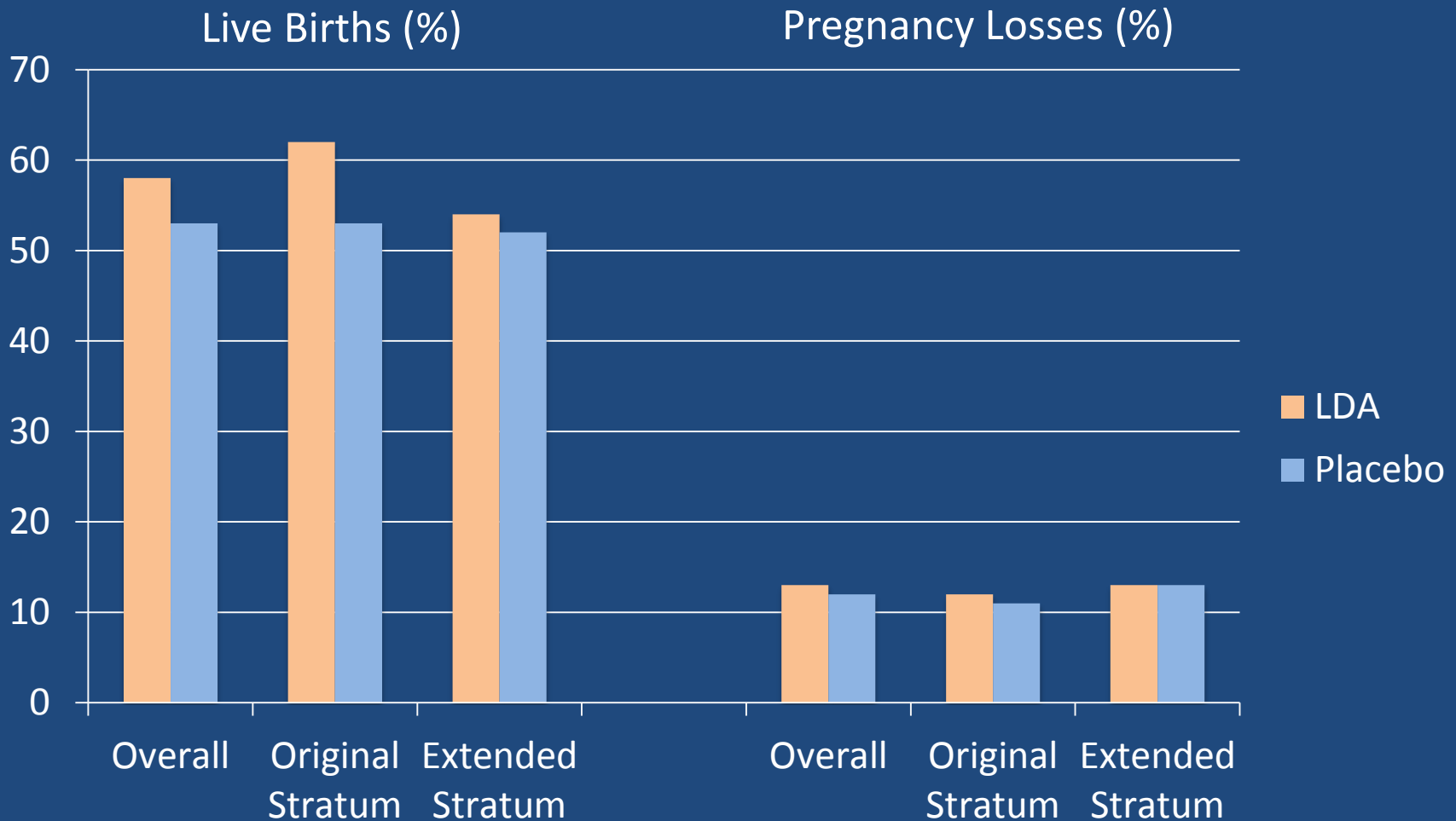
- **LDA**
 - **Progesterone**
 - **Heparin**
 - **IVIG**
 - **Prednisone**
 - **Intralipid**
-

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 ≤ 1 prior live birth
 - 586 with ≤ 2 prior losses and ≤ 2 prior live births

Preconception LDA and Pregnancy Outcomes (EAGeR Trial)

Schisterman et al. Lancet, 2014





**THANK
YOU
FOR
LISTENING**

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