Elective Single Embryo Transfer (eSET)

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Disclosures

- Industry
  - Research Funding/Consulting
    - Auxogyn
    - Bayer
    - LabCorp
    - Ziva
  - Shareholder in: Advanced Reproductive Care
- Professional Organizations
  - ASRM: Past President
  - FIGO: Chair, Committee on Reproductive Medicine
  - ICMART: Chair
  - IFFS: Board of Directors
  - WERF: President

- Will not be discussing or referring to unlabeled/unapproved uses of drugs, devices, products, protocols, or therapeutic strategies

Learning Objectives

- To apply knowledge of ART procedure outcomes to laboratory and clinical decision making
- To explain actions that can be implemented to reduce the multiple birth rate
- To identify challenges associated with implementation of elective SET and reduction of the multiple birth rate

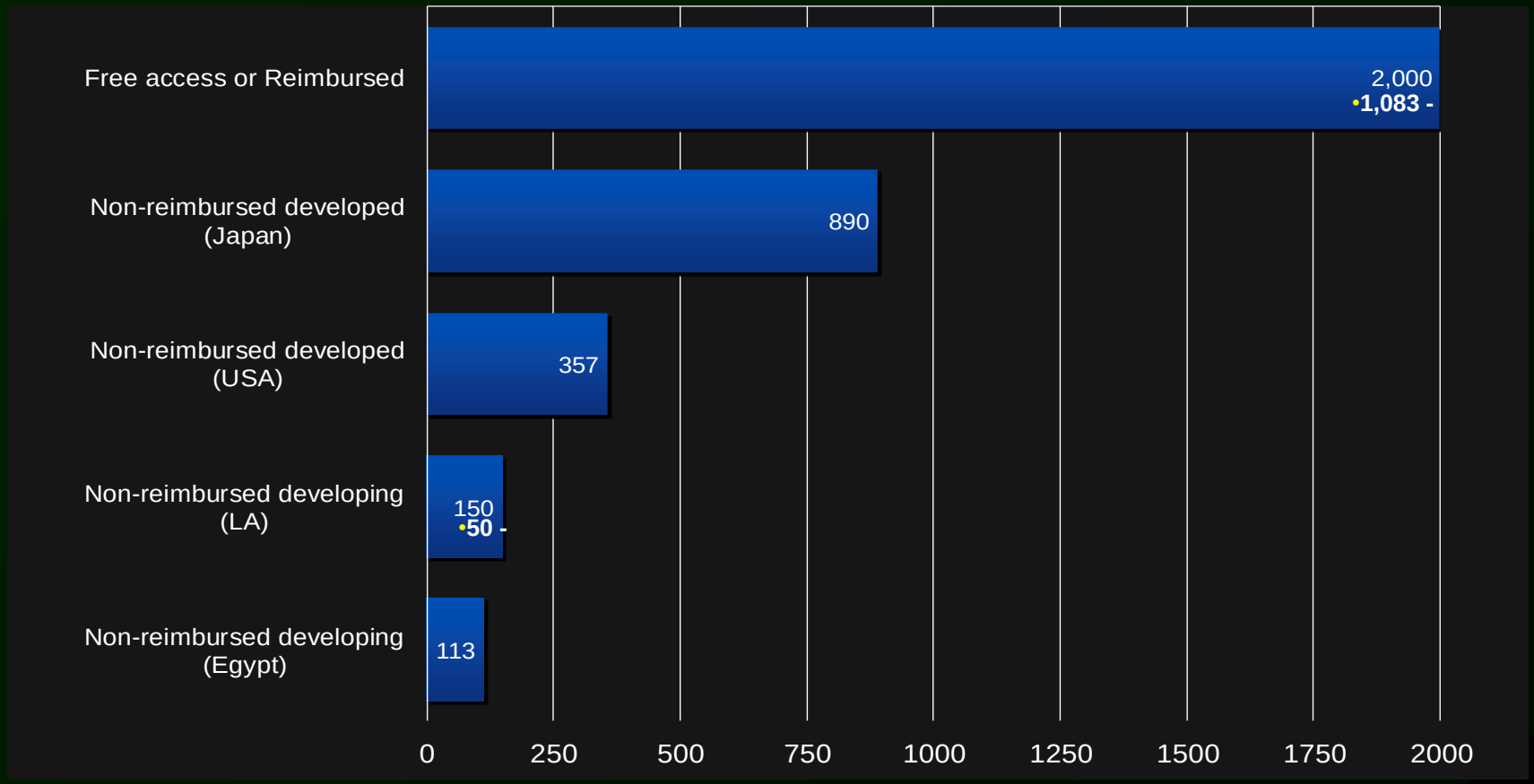
Many Causes of Multiple Births

- Number of embryos transferred
  - eSET vs. DET vs. >DET
- Reproductive potential of embryos
  - Quality
  - Stage at transfer
  - Screened vs. unscreened embryos
  - Fresh vs. frozen cycle
- Elective fetal reduction
- Societal factors
  - Health system
    - Access limitations
    - Patient cost/fertility coverage
    - Quality of clinical and laboratory care
    - Other factors (e.g. reporting, competition)
  - Social values
    - Religious
    - Effectiveness vs. safety

- Adamson, GD. Womens Health. 2009 Jul;5(4):351-8.

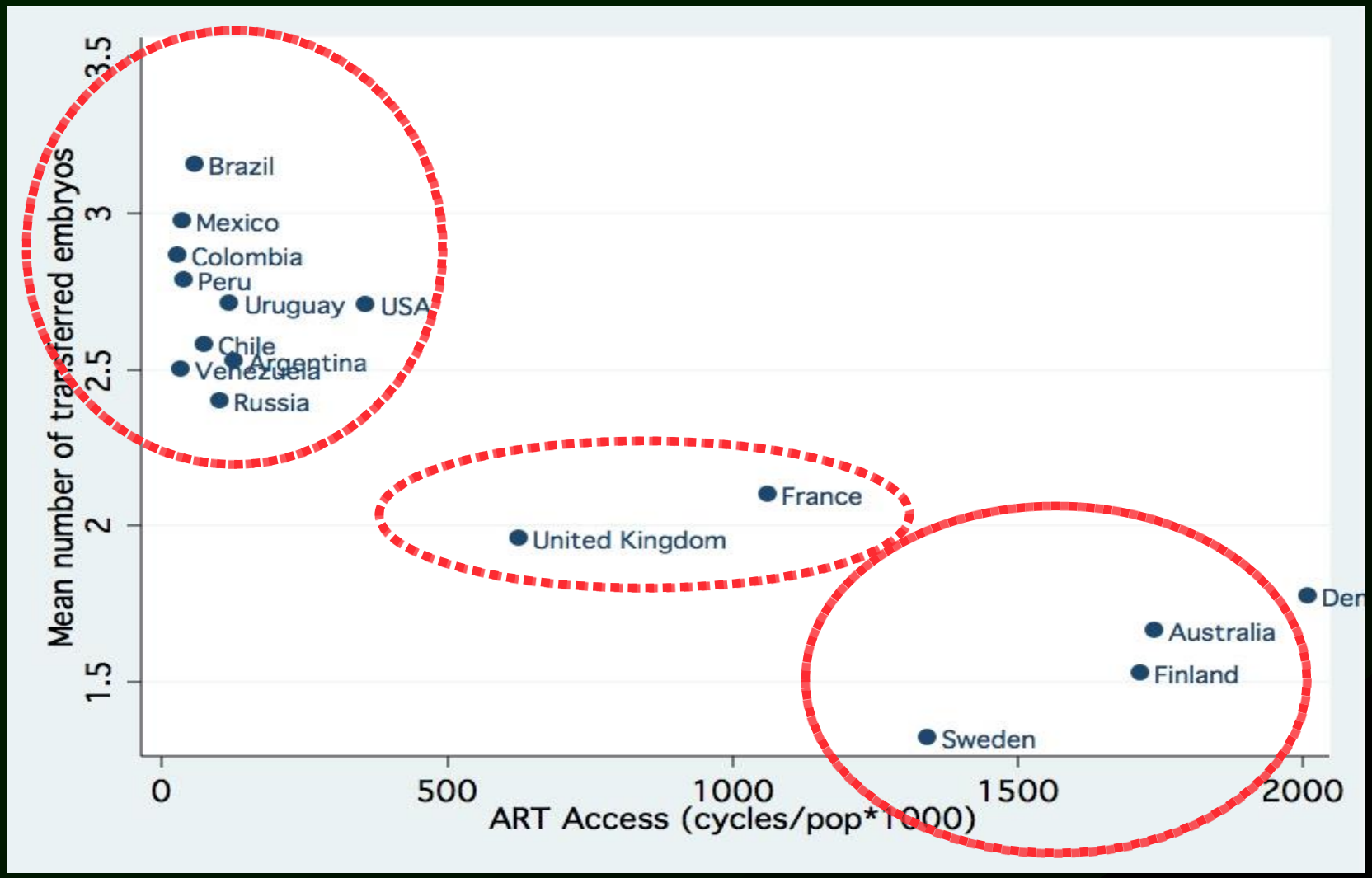
Access to ART

Access to ART Treatment According to Funding



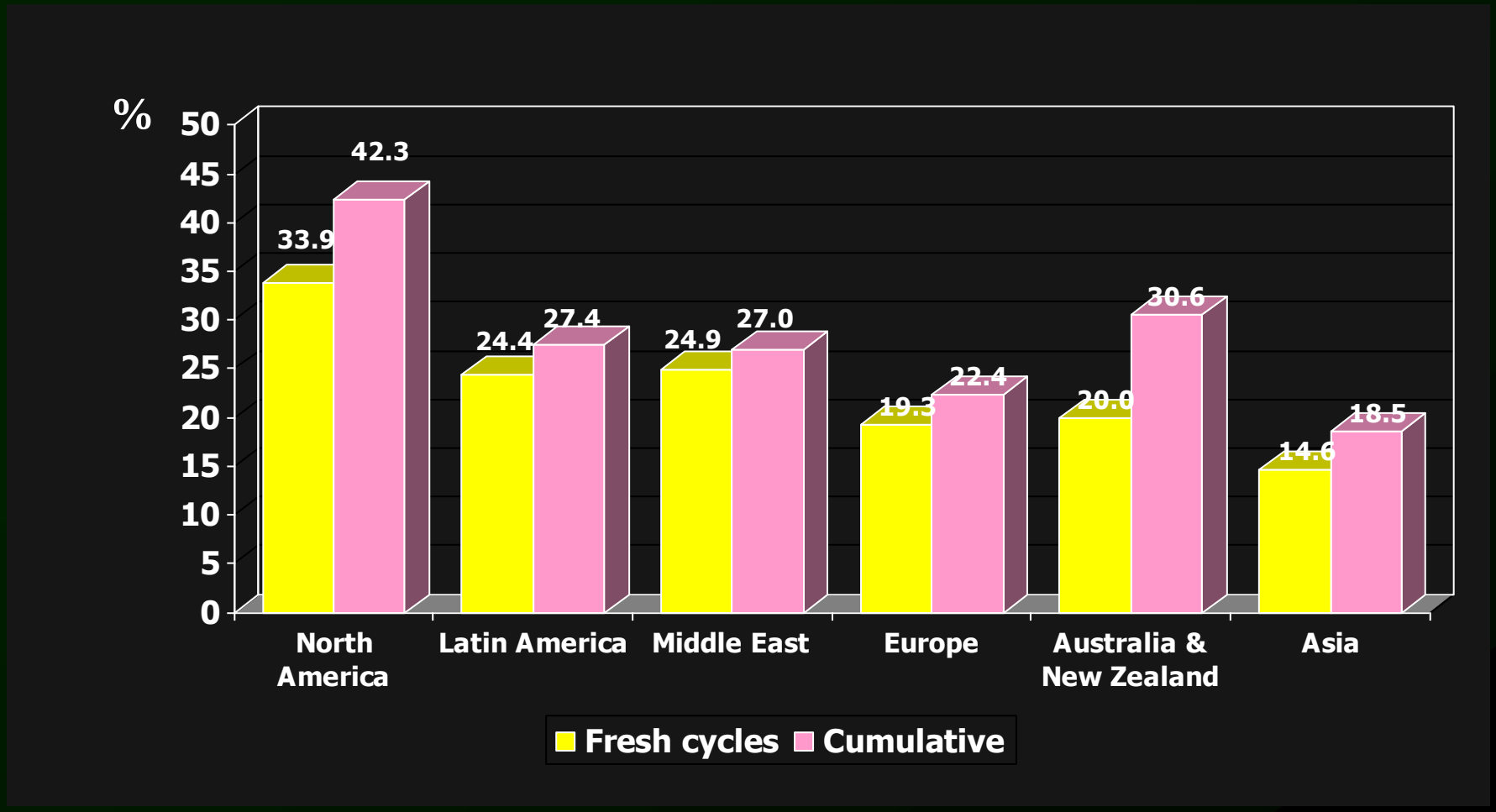
Courtesy Fernando Zegers, MD and ICMART

Relationship Between Access to ART And Number of Embryos Transferred



Effectiveness of ART

Delivery Rates per Aspiration According to Region (IVF & ICSI) 2008



ARS Question 1: With good antenatal care, risk for abnormal outcomes in singleton and twin pregnancies are:

1. Similar maternal and higher fetal
2. Similar maternal and fetal
3. Higher maternal and similar fetal
4. Higher maternal and higher fetal
5. None of the above

Safety of ART

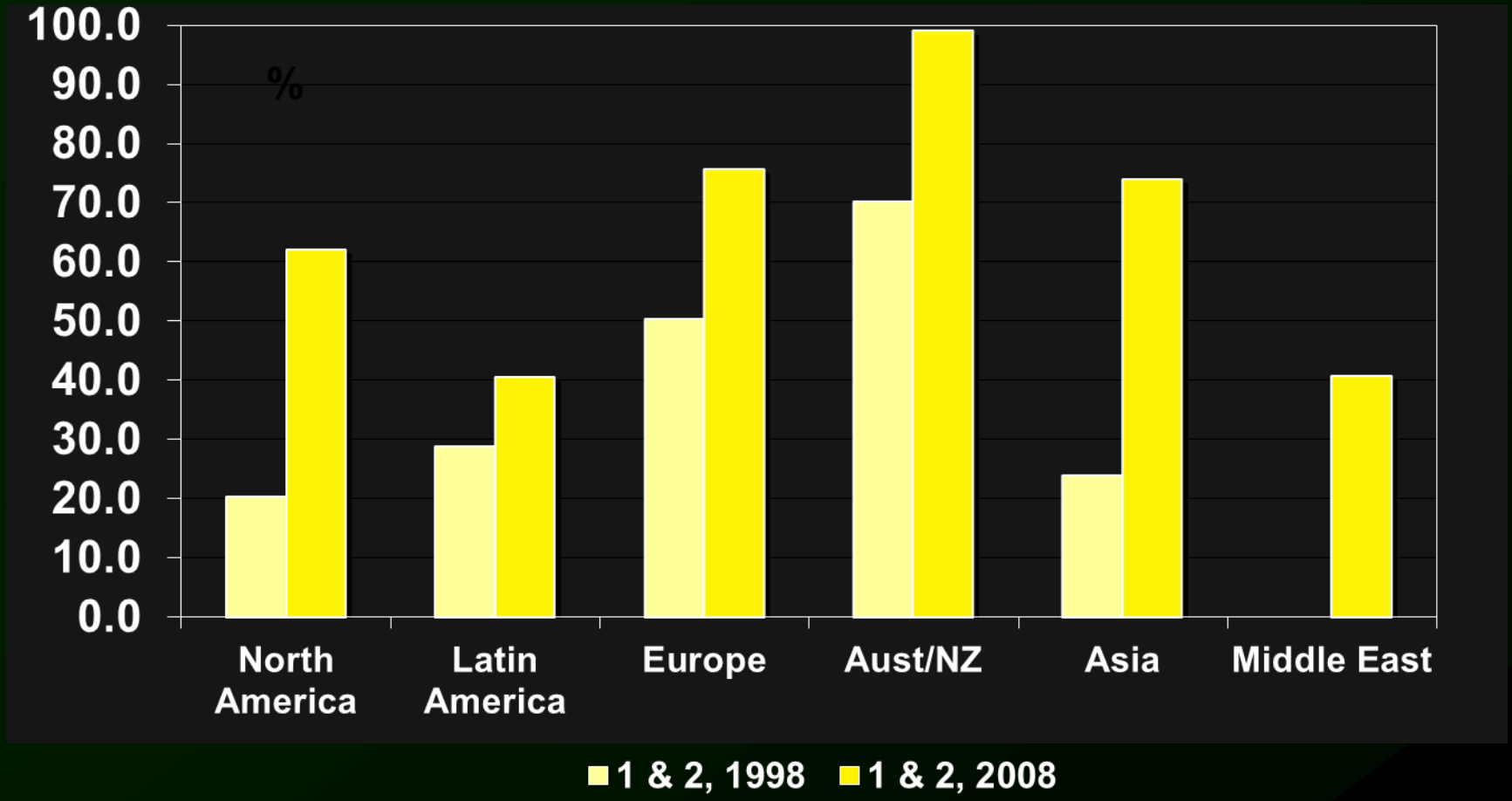
Risks of Multifetal Gestation

NUMBER	FETAL LOSS (%)	AVERAGE DELIVERY	MORTALITY (%)	MORBIDITY (%)
6	90%	26	20%	30% per fetus
5	50%	28	15%	25% per fetus
4	25%	29	6%	15% per fetus
3	15%	32	3%	5% per fetus
2	8%	35	2%	3% per fetus
1	3%	39	1%	2%

2008 Data

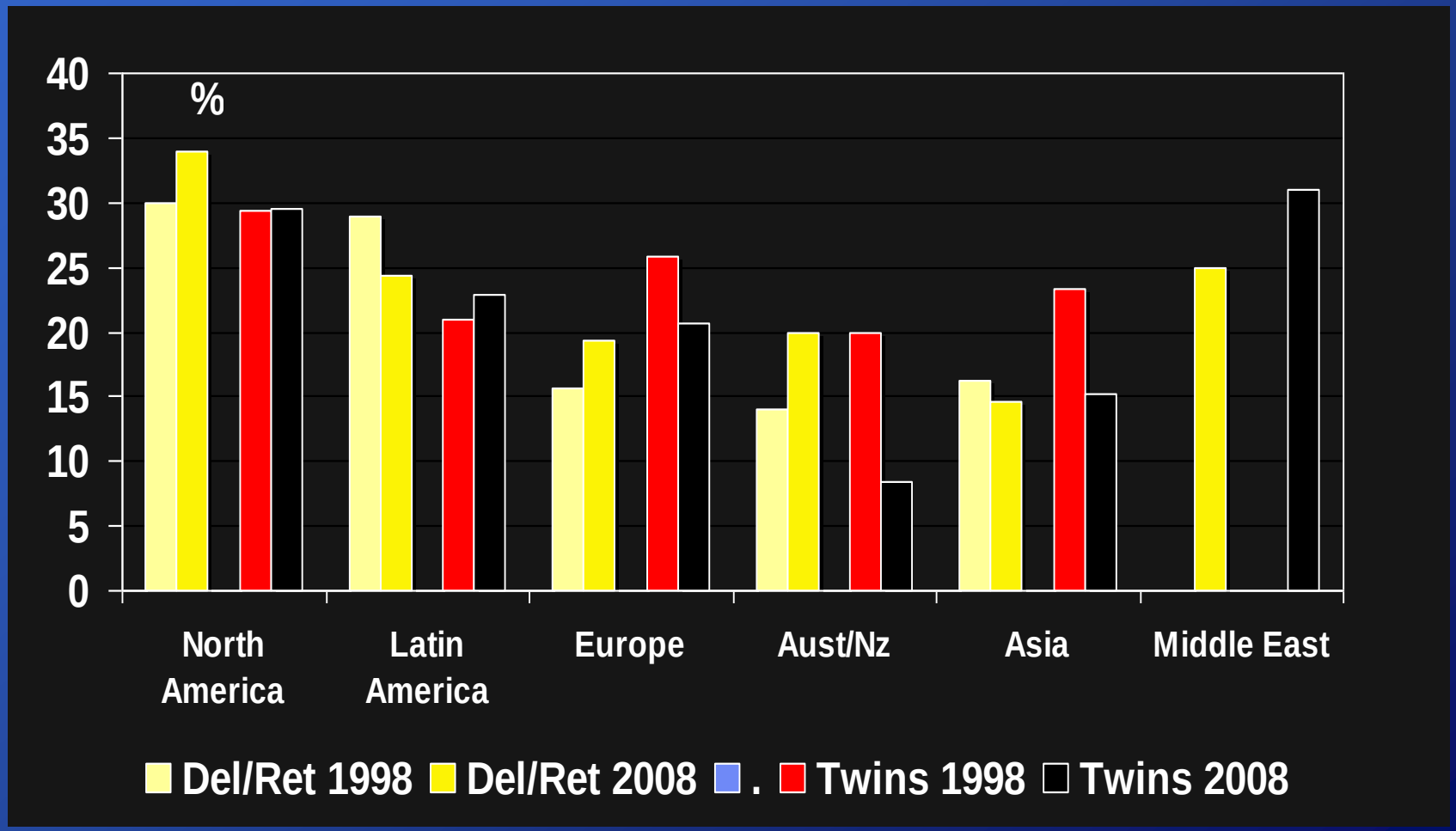
Courtesy Mark Evans, MD

Percentage of Transfers With 1-2 Embryos By Region 1998 & 2008

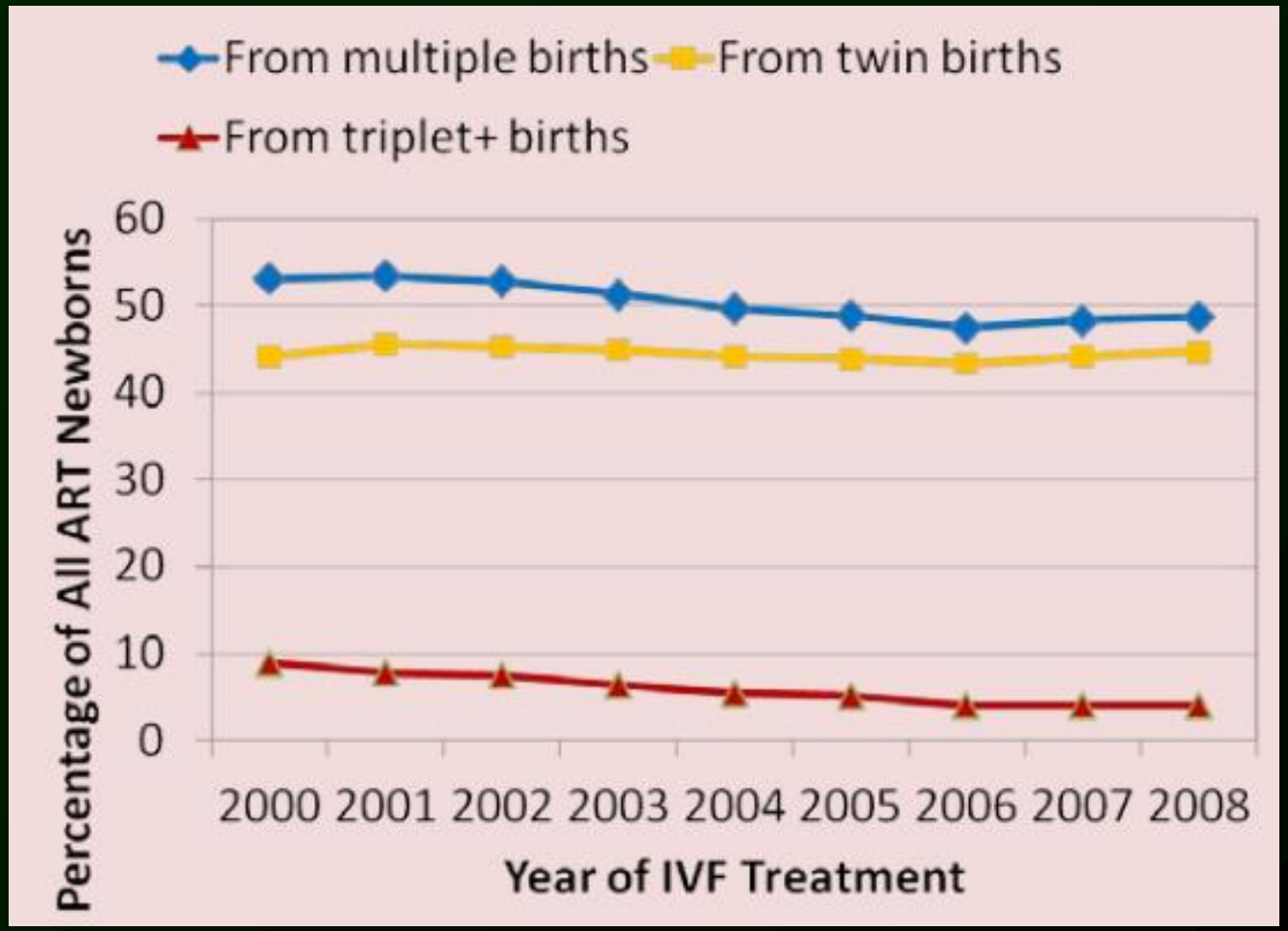


ICMART Preliminary World Report for 2008

Delivery Rate per Retrieval and Twin Pregnancies By Region 1998 & 2008



Proportions of All Liveborn Children Resulting from ART in the US That Were Members of Multiple Births



ASRM Practice Committee eSET. 2011.

Conclusions Regarding Global Access, Effectiveness and Safety

Conclusions

- Access
  - Much lower than needed worldwide
  - Even in most developed countries
- Effectiveness
  - Highest in US, stabilized at
    - Fresh LBR/Retrieval ~ 35%
    - FET LBR/Transfer ~ 25%
    - Donor Egg LBR/Transfer ~ 55%
- Safety
  - Much improved, BUT
  - Triplet rate needs further reduction by DET
  - Twin rate reduction requires SET

“Twin Pregnancy, Contrary to Consensus, is a Desirable Outcome in Infertility”

- Most risk assessments after fertility treatment use spontaneous conceptions
- IVF twins have 40% lower outcome risks
- Correct outcome is born children, not pregnancy
- Two children born with twins effectively halves the risk for babies and mothers
- For infertile women who want more than one child, twin pregnancies are favorable and cost-effective and should be encouraged

Gleicher. doi:10.1016/j.fertnstert.2008.02.160

How To Meet The Challenge

1. Reduce the Number of Embryos Transferred

- Fewer embryos can be transferred to obtain equivalent pregnancy rates
- Multiple pregnancy rates can be reduced
- Expert physician knowledge and experience is needed
- Individualized patient decision making and treatment is required

LBR by Number of Embryos Transferred, Age and Presence of Embryos to Cryopreserve

Age	Number of Embryos Transferred				
	2	3	4	5	
20-29(-)	17.9	34.3*			* p<0.01
(+)	42.7	41.1			
30-34(-)	17.2	30.4*			
(+)	36.0	41.5			
35-39(-)	13.3	19.9*	30.8*		
(+)	24.7	33.0	37.6*		
40-44(-)	5.1	7.7	13.8*	19.6*	
(+)	-	18.8	17.5	24.0	

(-) = NO embryos to cryopreserve (Poorer prognosis)

(+) = Extra embryos to cryopreserve (Good prognosis)

Schieve. JAMA. 1999 Nov 17;282(19):1832-8.

Relationship of Multiple Gestation and Age

- Risk decreases with age (1)
  - Still high through age 40
- Multiple birth with DET (+ Cryo = TOP)
  - < 35 40%
  - 35-37 33%
  - 38-40 28%
- Maternal risk increases with age
- Blastocyst lower rate, similar IR and PR (2)
- Single blast PR late 30's ~ 50% (1)

1. SART/ASRM Practice Committees. eSET. 2011.

2. Shapiro. Fertil Steril 2002;77:700-5.

2. Don’t Transfer Two Blastocysts!

- Cumulative live birth rates
  - not very different
  - with Blastocyst eSBT vs. DBT
- Twin rates
  - extremely high
- Monozygotic twins
  - more frequent
- ? Increased risks
  - Blastocyst compared with cleavage stage
  - e.g. imprinting disorders
  - ? Increased proportion abnormal babies

Blastocyst Transfer
RCT of eSBT vs. eDBT

n=48	IR	PR	Twins
eSBT	61%	61%	0%
eDBT	56%	76%	47%

Gardner. Fertil Steril 2004;81:551-5.

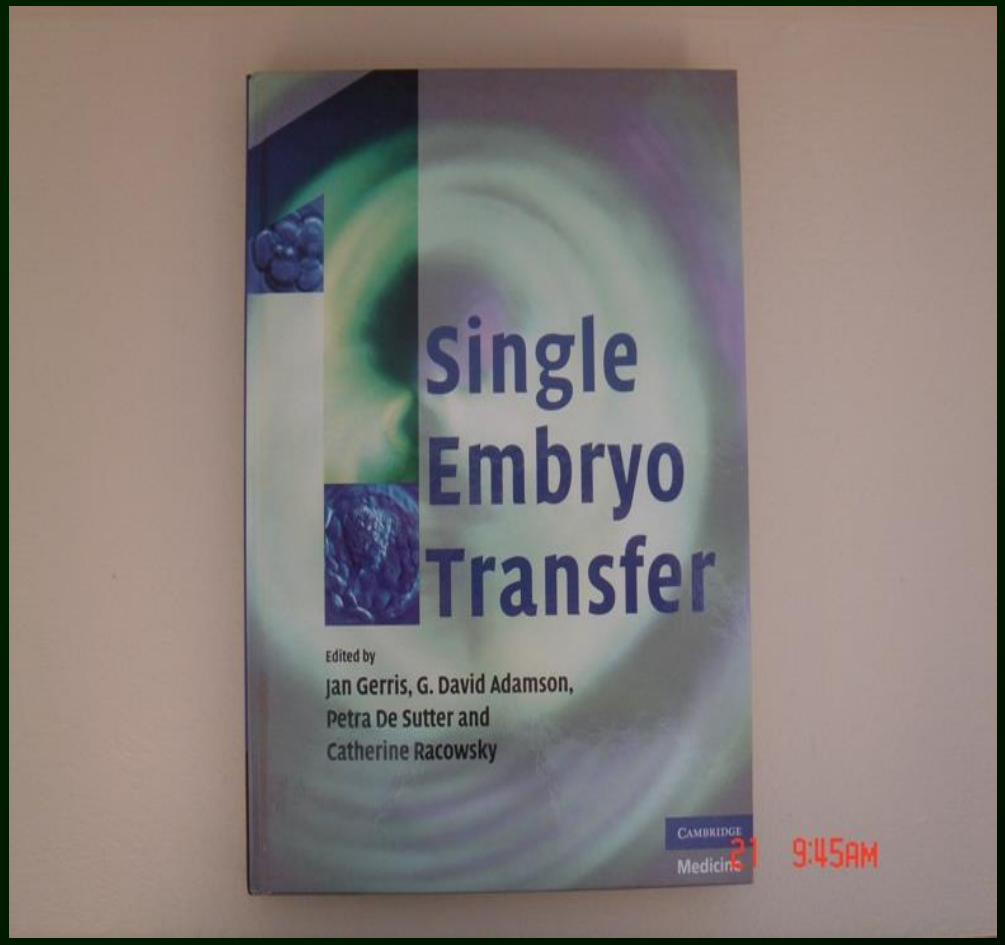
ARS Question 2: Which of the following is the most effective way to reduce the twin rate?

- Reduce the average number of embryos transferred
- Perform more frozen/thaw embryo transfers
- Perform PGS on all patients
- Perform PGS on selected patients
- Do more elective single embryo transfers

3. Increase Use of eSET

- It is the only way to reduce the twin rate
- Live birth rates are reduced only slightly, if at all

“As many babies as you want, but one at a time”

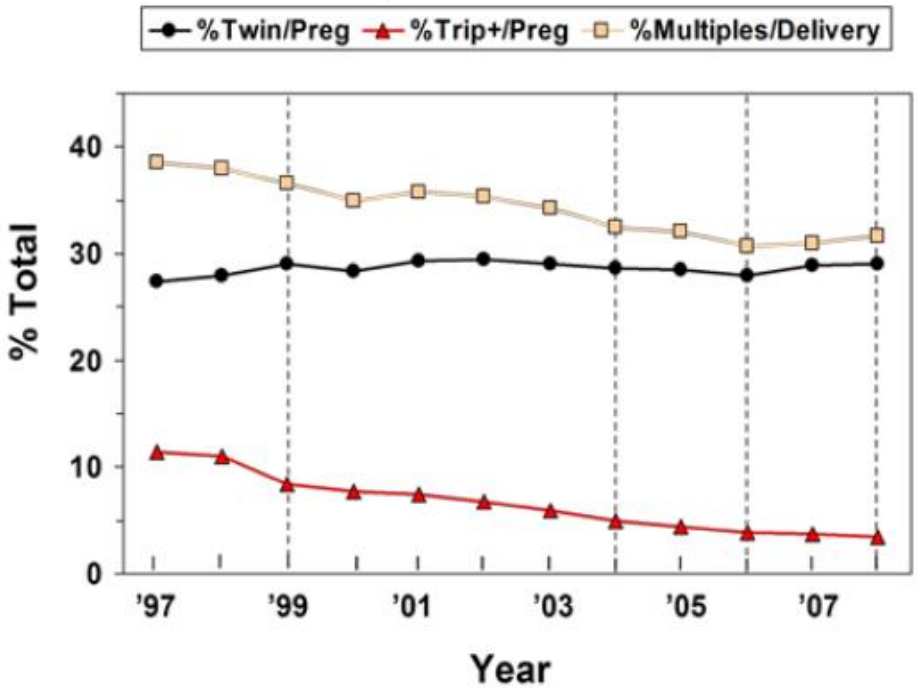


“eSET should be considered for every patient, every time, but is not the best treatment for every patient every time”

Adamson, 2012

ART Outcomes in Relation to Number of Embryos Transferred

Fig. 1. ART Outcomes in US: Relationship with SART/ASRM Guidelines for Number of Embryos to Transfer



Data derived from http://www.cdc.gov/ART/ARTReports.htm
Dashed lined indicated years at which SART/ASRM guidelines were introduced (1998) and subsequently revised (1999, 2004, 2006 and 2008).
Multiple births are expressed per delivery; twin and triplet + pregnancies are expressed per clinical pregnancy.

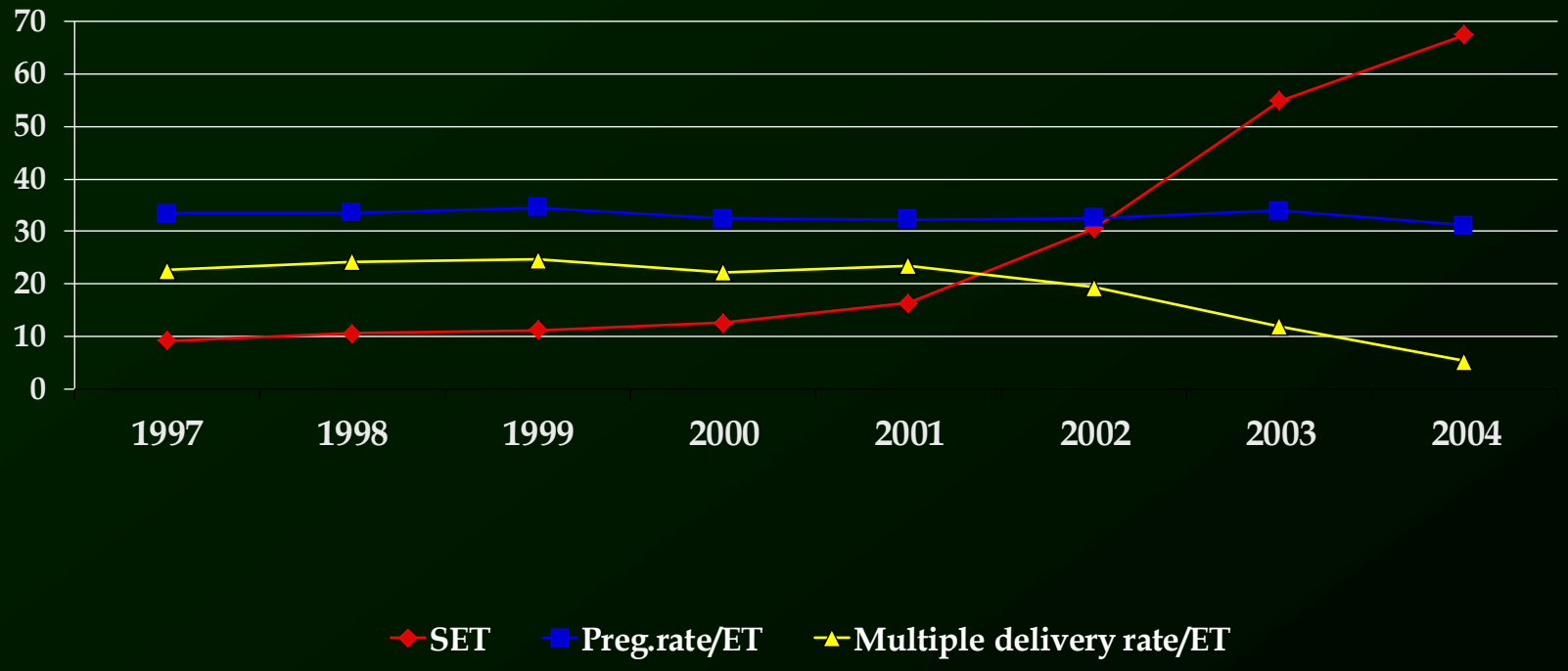
ASRM Practice Committee. Multiple Gestation. 2011.

1 Fresh + 1 Frozen Embryo vs 2 Fresh Embryo Transfer

	eSET N = 350	DET N = 353	Adj. OR (95% CI)
Live birth	38%	42%	0.85 (0.62, 1.15)
Multiple live birth	1%	32%	0.02 (0.00, 0.13)

McLernon. BMJ 2010. 341:c6945

Single Embryo Transfer (SET): The Swedish Experience IVF/ICSI 1997-2004



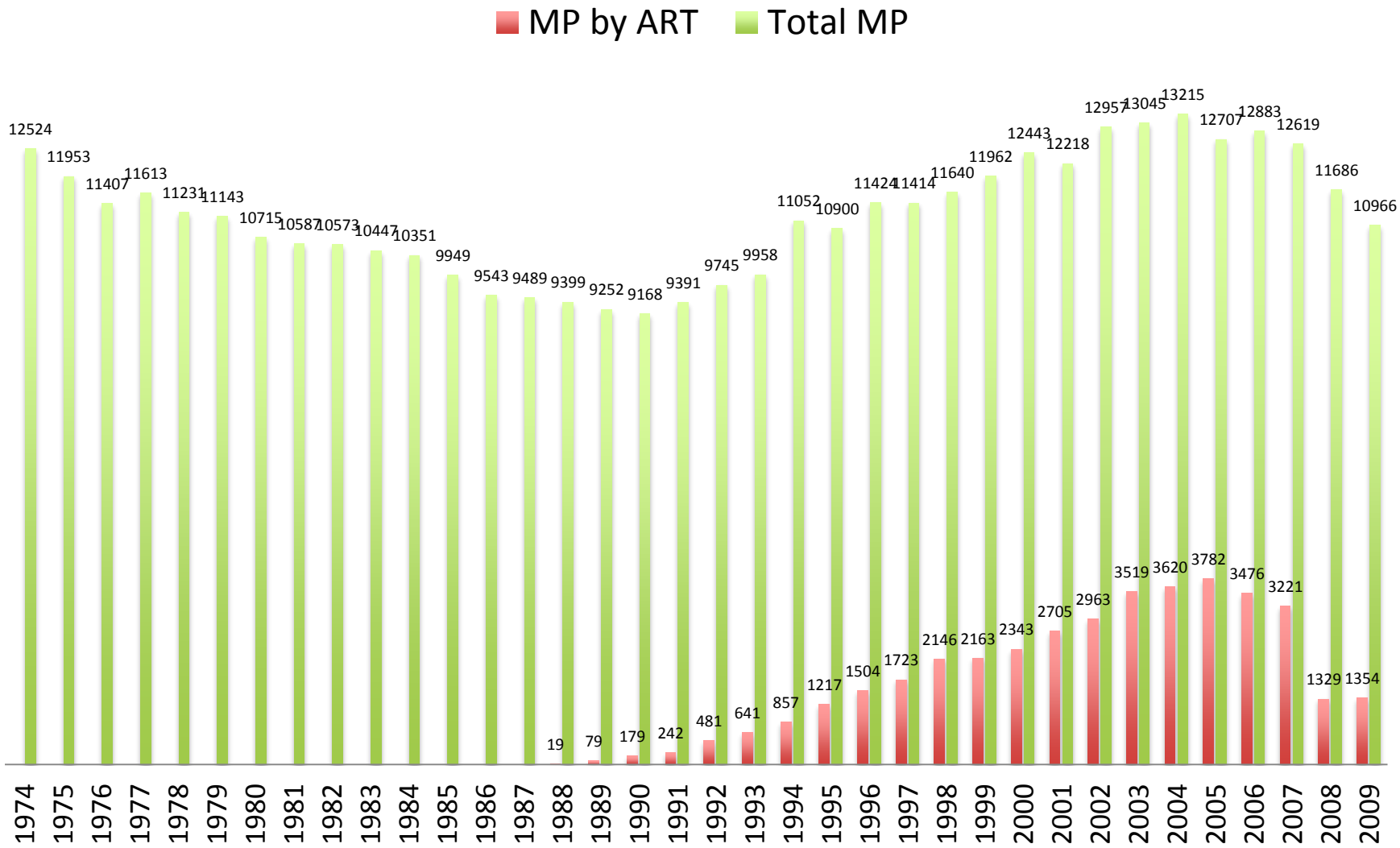
ART Outcomes in Sweden and the US, 2006

Table 4. ART Outcomes in Sweden and the US, 2006 (65, 68)

Country	% per Embryo Transfer		% per Live Birth	
	Live Birth Rate	Singleton Birth Rate	Multiple Birth Rate	Singleton Birth Rate
Sweden	27.2	25.6	5.8	94.2
US	35.4	24.6	30.6	69.4

ASRM Practice Committee. Multiple Gestation. 2011.

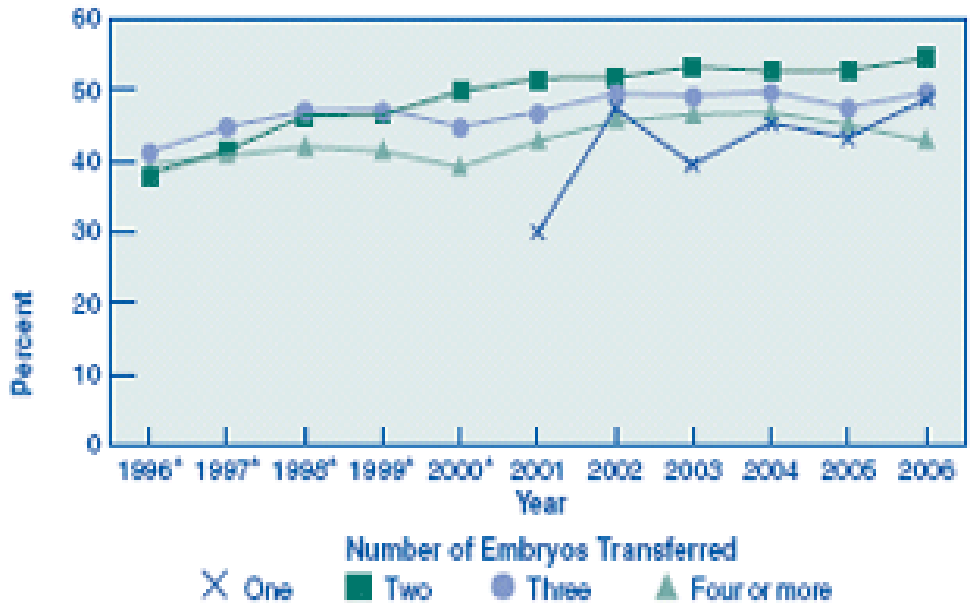
Dramatic Decrease in Annual Number of Multiple Births in Japan



Ishihara. MHLW and JSOG data.

LBR/Fresh Nondonor Transfer <35 + Extra Embryo by Number of Embryos Transferred

Figure 61
Percentages of Transfers That Resulted in Live Births Among Women Who Were Younger Than 35 and Set Aside Extra Embryos for Future Use, by Number of Embryos Transferred, 1996–2006



*Cycles involving the transfer of one embryo were not included because of the small number of cycles where one embryo was transferred and extra embryos were set aside for future use.

http://www.cdc.gov/art/ART2006/sect5_fig49-64.htm#f61

ASRM Practice Guideline October 2011

eSET should be considered seriously for good prognosis patients, assuming the availability of effective cryopreservation protocols that will help to maximize cumulative pregnancy rates.

ASRM Practice Committee. Multiple gestation. October, 2011.

4. Follow SART/ASRM Guidelines (At Least!)

Number of Embryos to Transfer (2008)

Day 3	<35	35-37	38-40	>40
Favorable*	1-2	2	3	5
All Others	2	3	4	5
Day 5				
Favorable*	1	2	2	3
All Others	2	2	3	3

1st cycle, good embryos, # to cryo, or prior IVF success

Updated (2009) SART/ASRM Guidelines on Number of Embryos Transferred

- Based on 2007 ASRM and SART data
- Poor prognosis patients
  - No more than one additional embryo
- Frozen embryo transfer cycles
  - number of good quality thawed embryos transferred
  - not exceed the recommended number of fresh embryos

SART/ASRM Practice Committees. Fertil Steril 2009;92:1518–9.

ASRM Practice Committee Statement

Clinicians have a professional and ethical obligation to optimize the chance of a singleton birth for prospective parents whose preferences and choices may be clouded by feelings of desperation to achieve a pregnancy.

SART/ASRM Practice Committees. eSET. 2011.

5. Use New Technologies To Reduce The Number of Embryos Transferred

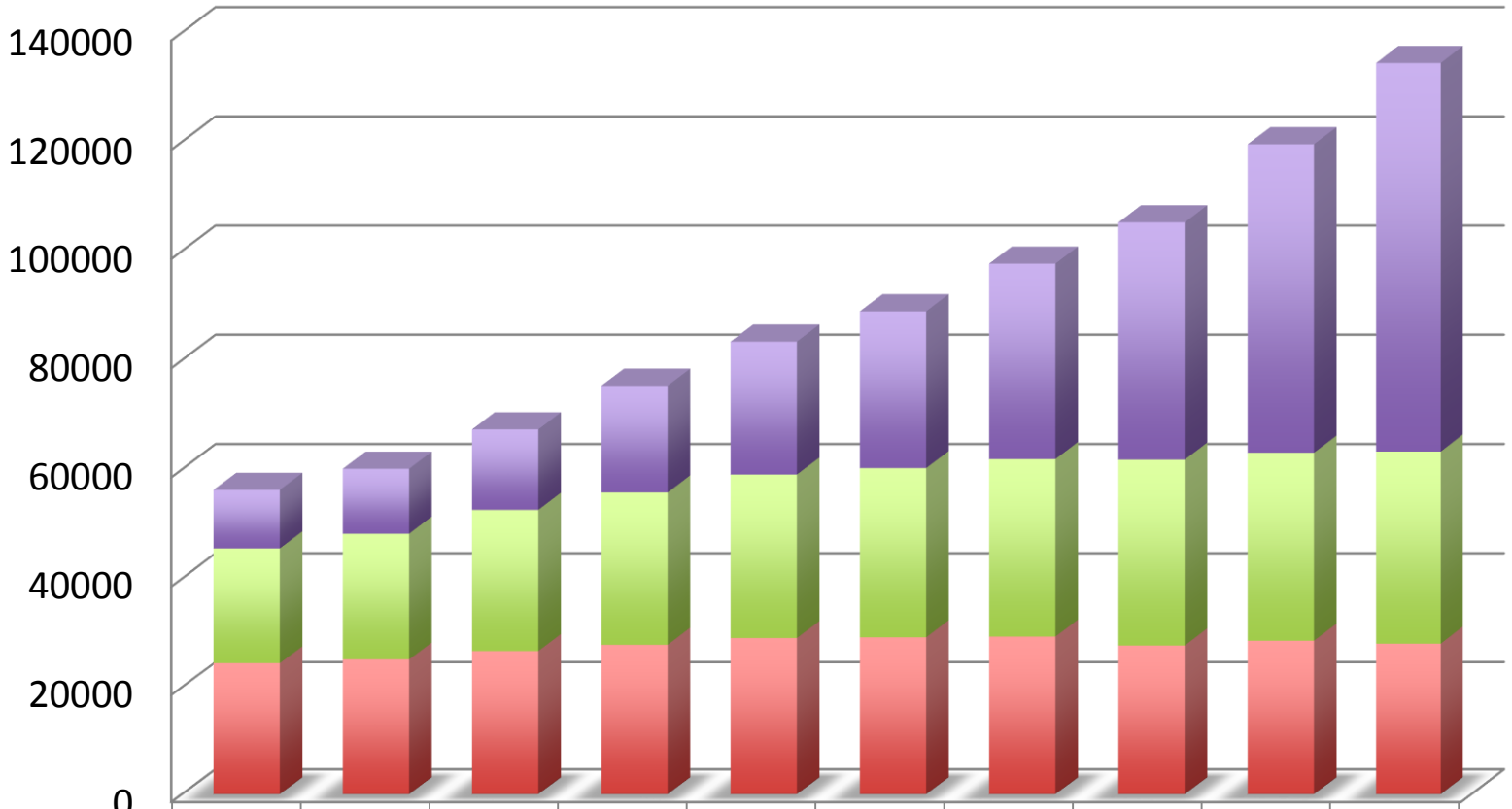
- Embryo cryopreservation
  - Vitrification
- Blastocyst transfer
  - Selected patients
- Assessment of embryo quality
  - PGD/S
  - Complete Genomic Hybridization (CGH)
  - Metabolomics
  - Proteomics
  - Time lapse photography

Risk of Multiple Gestation With Cryopreserved Embryos

- Reduced compared with fresh transfer (1)
- Decisions regarding eSET should consider
  - Prognosis
  - Embryo quality
  - Individual program pregnancy rates (2)

1.Wright. MMWR Surveill Summ 2008;57:1-23
2.SART/ASRM Practice Committees. eSET. 2011.

ET Cycles in Japan



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
FER	10711	11883	14729	19545	24342	28701	35784	43452	56494	71161
ICSI	21067	23058	25866	27895	29946	30983	32509	34032	34425	35168
IVF	24447	25143	26708	27857	29090	29232	29361	27729	28609	28073

JSOG data

Improve Embryo Quality

- Improve quality of embryos transferred
  - Time-lapse imaging
  - Assessment of embryo morphology and growth dynamics (1)
  - Blastocyst transfer in selected patients
  - Preimplantation Genetic Screening (PGS) (yet to be validated) (2-4)
  - Better technologies to assess embryos: e.g. CGH, proteomics, metabolomics, algorithms, time lapse photography etc. (yet to be validated) (5,6)

1.Holte. Hum Reprod 2006;22(2):548-57.
2.Mastenbroek. N Engl J Med 2007;357(1):9-17.
3.Cohen. Reprod Biomed Online 2007;15(4):365-6.
4.Jansen. In SET, Ed. Gerris, Pub Cambridge Press. 2008.
5.Patrizio. Reprod Biomed Online 2007;15(3):346-53.
6.Barthelery. Stem Cells Dev 2007;16(6):905-19.

ARS Question 3: Day 5 blastocyst transfer has better outcomes than day 3 cleavage stage transfers.

- True
- False

6. Assess Objectively the Benefits and Disadvantages of New Technologies
e.g. Cleavage vs. Blastocyst Transfer & PGS

- Live Birth Rate
  - Blastocyst > Day 3: OR 1.35 (95% CI 1.05-1.74)
  - Especially for
    - Good prognosis patients
    - Equal number of embryos transferred (including SET)
    - Randomization on Day 3 (ability to select patients for blast culture)
- Rates of Embryo Cryopreservation
  - Blastocyst < Day 3: OR 0.45 (95% CI 0.36-0.56)
- Failure to Transfer Any Embryos
  - Failure Blastocyst > Day 3: OR 2.85 (95% CI 1.97-4.11)
  - Good prognosis Pts: OR 1.50 (95% CI 0.79-2.84)
- "Emerging evidence that in selected patients blastocyst culture may be applicable for SET."

Outcome Issues: CD 3 Cleavage vs. CD 5 Blast Transfer

- ? Effects of longer durations of culture
  - Epigenetic issues
  - Some literature creates concern
  - Some literature is reassuring
- Adverse neonatal outcomes vs. natural
  - CD 3 OR, 1.11 (95% CI, 1.02-1.21)
  - CD 5 OR, 1.53 (95% CI, 1.23-1.90)
- Clinical significance unclear (1)

SART/ASRM Practice Committees. eSET. 2011.
ASRM Practice Committee. Multiple Gestation. 2011.

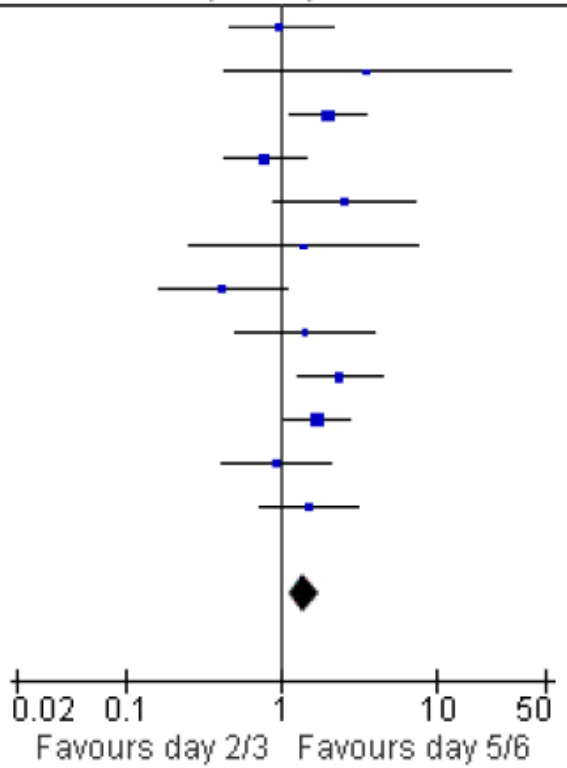
Cleavage vs. Blastocyst Transfer:
Live Birth per Couple (Favors Blastocyst)

Figure 3. Forest plot of comparison: 1 Live birth rate, outcome: 1.1 Live birth per couple.

Study or Subgroup	Day 5/6 Events	Day 5/6 Total	Day 2/3 Events	Day 2/3 Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brugnon 2010	22	55	21	52	7.8%	0.98 [0.46, 2.12]
Devreker 2000	3	11	1	12	1.0%	3.53 [0.43, 29.14]
Elgindy 2011	52	100	35	100	14.8%	1.99 [1.14, 3.48]
Emiliani 2003	33	82	41	89	12.6%	0.79 [0.43, 1.44]
Frattarelli 2003	15	29	8	28	4.2%	2.57 [0.90, 7.35]
Levitas 2004	3	23	3	31	1.6%	1.40 [0.26, 7.65]
Levron 2002	8	46	15	44	5.2%	0.42 [0.16, 1.08]
Livingstone 2002	14	30	11	29	4.4%	1.42 [0.51, 3.96]
Papanikolaou 2005	38	80	23	84	11.6%	2.35 [1.25, 4.43]
Papanikolaou 2006	56	175	38	176	20.7%	1.70 [1.06, 2.72]
Rienzi 2002	24	50	24	48	7.4%	0.92 [0.42, 2.03]
Van der Auwera 2002	24	70	17	66	8.6%	1.49 [0.72, 3.10]
Total (95% CI)		**751**		**759**	**100.0%**	**1.40 [1.13, 1.74]**
Total events	292		237			

Heterogeneity: $Chi^2 = 18.43$, $df = 11$ ($P = 0.07$); $I^2 = 40\%$

Test for overall effect: $Z = 3.07$ ($P = 0.002$)



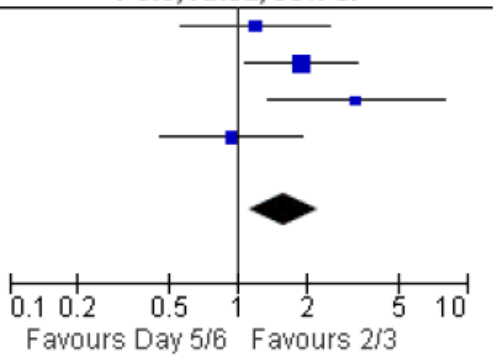
Cleavage vs. Blastocyst. Cochrane 2012 Jul 11;7:CD002118

Cleavage vs. Blastocyst Transfer:
Cumulative Pregnancy Rate From Fresh and Frozen Transfers (Favors Cleavage Stage)

Figure 5. Forest plot of comparison: 3 Cumulative pregnancy rate, outcome: 3.1 cumulative pregnancy rate from fresh and frozen transfers.

Study or Subgroup	Day 5/6 Events	Day 5/6 Total	Day 2/3 Events	Day 2/3 Total	Weight	Peto Odds Ratio (Non-event) Peto, Fixed, 95% CI
Brugnon 2010 (1)	24	55	25	52	21.5%	1.19 [0.56, 2.55]
Emiliani 2003	43	99	56	94	39.0%	1.90 [1.08, 3.34]
Rienzi 2002	31	50	41	48	15.5%	3.28 [1.35, 8.02]
Van der Auwera 2002	24	66	22	63	24.0%	0.94 [0.46, 1.93]
Total (95% CI)		**270**		**257**	**100.0%**	**1.58 [1.11, 2.25]**
Total events	122		144			

Heterogeneity: Chi² = 5.54, df = 3 (P = 0.14); I² = 46%
Test for overall effect: Z = 2.55 (P = 0.01)



(1) Study had policy of single embryo transfer

Cleavage vs. Blastocyst. Cochrane 2012 Jul 11;7:CD002118

Cleavage vs. Blastocyst Transfer:
Multiple Pregnancy Rate/Couple (P=NS)

Analysis 4.1. Comparison 4 Multiple-pregnancy rate, Outcome 1 multiple-pregnancy rate per couple.

Review: Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Comparison: 4 Multiple-pregnancy rate

Outcome: 1 multiple-pregnancy rate per couple

Study or subgroup	Day 5/6 n/N	Day 2/3 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Bungum 2003	13/61	15/57		9.5 %	0.76 [0.33, 1.77]
Coskun 2000	15/100	13/101		10.6 %	1.19 [0.54, 2.65]
Elgindy 2011	12/59	8/61		6.9 %	1.05 [0.39, 2.84]
Emiliani 2003	12/82	8/89		7.8 %	1.72 [0.68, 4.37]
Frattarelli 2003	5/29	7/28		4.2 %	0.63 [0.18, 2.23]
Hreinsson 2004	2/64	4/80		2.5 %	0.63 [0.12, 3.23]
Karaki 2002	9/80	10/82		7.4 %	0.91 [0.35, 2.37]
Kolibianakis 2004	15/226	20/234		14.2 %	0.76 [0.38, 1.52]
Levitas 2004	2/23	3/31		2.0 %	0.89 [0.14, 5.63]
Leveron 2002	4/46	8/44		4.6 %	0.44 [0.13, 1.49]
Livingstone 2002	0/30	4/29		1.7 %	0.12 [0.02, 0.88]
Motta 1998 A % B	3/58	10/58		5.1 %	0.30 [0.10, 0.95]
Papanikolaou 2005	18/80	8/84		9.7 %	2.63 [1.14, 6.06]
Papanikolaou 2006	0/175	2/176		0.9 %	0.14 [0.01, 2.17]
Rienzi 2002	9/50	7/48		5.9 %	1.28 [0.44, 3.72]
Van der Auwera 2002	9/70	9/66		6.9 %	0.93 [0.35, 2.51]
Total (95% CI)	**1233**	**1248**		**100.0 %**	**0.92 [0.71, 1.19]**

Total events: 128 (Day 5/6), 136 (Day 2/3)

Heterogeneity: Chi² = 20.59, df = 15 (P = 0.15); I² = 27%

Test for overall effect: Z = 0.67 (P = 0.50)

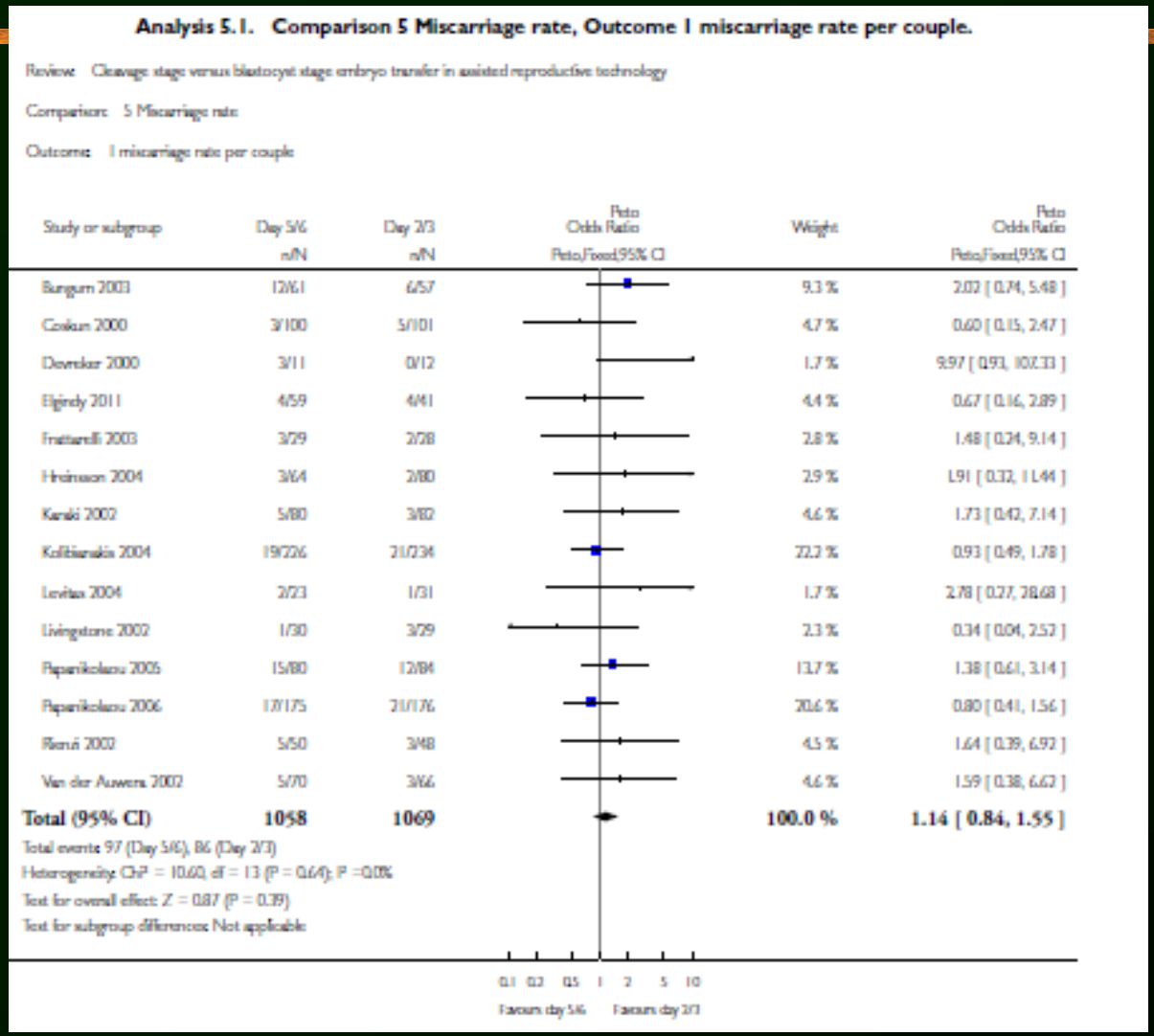
Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours day 5/6 Favours day 2/3

Cleavage vs. Blastocyst. Cochrane 2013.

Cleavage vs. Blastocyst Transfer:
Miscarriage Rate per Couple (P=NS)



Analysis 5.1. Comparison 5 Miscarriage rate, Outcome 1 miscarriage rate per couple.

Review: Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Comparison: 5 Miscarriage rate

Outcome: 1 miscarriage rate per couple

Study or subgroup	Day 5/6 n/N	Day 2/3 n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Bungum 2003	12/61	6/57		9.3 %	2.02 [0.74, 5.48]
Coskun 2000	3/100	5/101		4.7 %	0.60 [0.15, 2.47]
Devreker 2000	3/11	0/12		1.7 %	9.97 [0.93, 107.33]
Elgindy 2011	4/59	4/41		4.4 %	0.67 [0.16, 2.89]
Frattarelli 2003	3/29	2/28		2.8 %	1.48 [0.24, 9.14]
Hreinsson 2004	3/64	2/80		2.9 %	1.91 [0.32, 11.44]
Karaki 2002	5/80	3/82		4.6 %	1.73 [0.42, 7.14]
Kolibianakis 2004	19/226	21/234		22.2 %	0.93 [0.49, 1.78]
Levitas 2004	2/23	1/31		1.7 %	2.78 [0.27, 28.68]
Livingstone 2002	1/30	3/29		2.3 %	0.34 [0.04, 2.52]
Papanikolaou 2005	15/80	12/84		13.7 %	1.38 [0.61, 3.14]
Papanikolaou 2006	17/175	21/176		20.6 %	0.80 [0.41, 1.56]
Rienzi 2002	5/50	3/48		4.5 %	1.64 [0.39, 6.92]
Van der Auwera 2002	5/70	3/66		4.6 %	1.59 [0.38, 6.62]
Total (95% CI)	**1058**	**1069**		**100.0 %**	**1.14 [0.84, 1.55]**

Total events: 97 (Day 5/6), 86 (Day 2/3)

Heterogeneity: Chi² = 10.60, df = 13 (P = 0.64); I² = 0.0%

Test for overall effect: Z = 0.87 (P = 0.39)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours day 5/6 Favours day 2/3

Cleavage vs. Blastocyst.

Cochrane 2013.

Cleavage vs. Blastocyst Transfer:
Embryo Freezing per Couple (Favors Cleavage)

Analysis 6.1. Comparison 6 Embryo freezing rate, Outcome 1 embryo freezing per couple.

Review: Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Comparison: 6 Embryo freezing rate

Outcome: 1 embryo freezing per couple

Study or subgroup	Day 5/6 n/N	Day 2/3 n/N	Peto Odds Ratio(Non-event) Peto,Fixed,95% CI	Weight	Peto Odds Ratio(Non-event) Peto,Fixed,95% CI
Brugnon 2010	42/55	51/52		3.2 %	6.63 [2.17, 20.30]
Bungum 2003	36/61	54/57		5.6 %	7.08 [3.04, 16.48]
Hreinsson 2004	15/64	34/80		8.4 %	2.32 [1.16, 4.64]
Karaki 2002	72/80	35/82		9.7 %	1.94 [1.02, 3.69]
Kolibianakis 2004	114/226	145/234		29.5 %	1.60 [1.10, 2.31]
Lewron 2002	12/46	25/44		5.7 %	3.51 [1.52, 8.09]
Motta 1998 A % B	15/58	45/58		7.6 %	7.80 [3.77, 16.10]
Pantos 2004	16/81	79/162		13.4 %	3.37 [1.95, 5.81]
Rienzi 2002	18/50	42/48		6.1 %	8.56 [3.81, 19.22]
Tan 2011	20/28	26/27		2.0 %	5.95 [1.44, 24.53]
Van der Auwera 2002	26/70	35/66		8.8 %	1.89 [0.96, 3.71]
Total (95% CI)	**819**	**910**		**100.0 %**	**2.88 [2.35, 3.51]**

Total events: 336 (Day 5/6), 571 (Day 2/3)

Heterogeneity: Chi² = 35.44, df = 10 (P = 0.00011); I² =72%

Test for overall effect: Z = 10.35 (P < 0.00001)

Test for subgroup differences: Not applicable

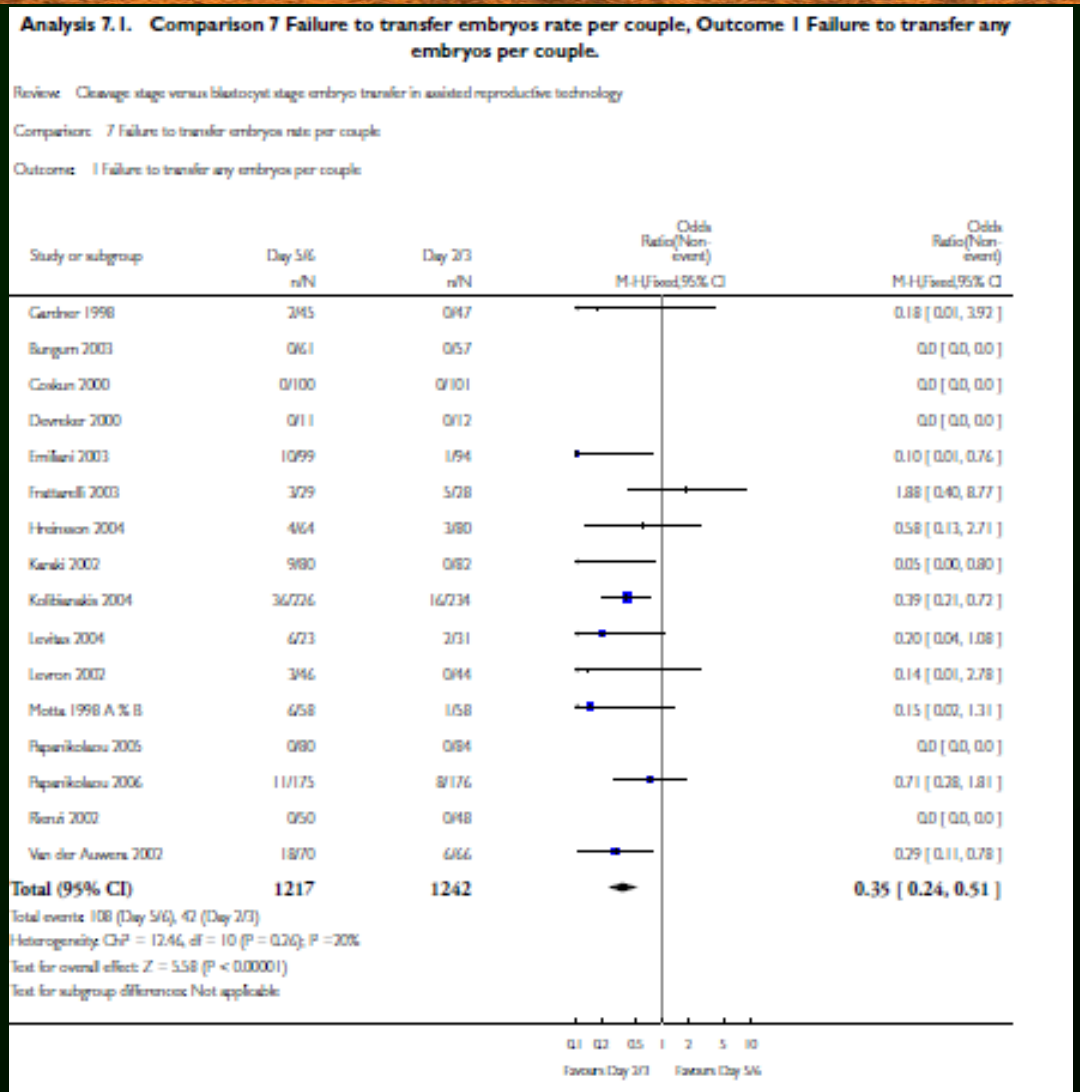
OR=2.88

P=0.00001

Cleavage vs. Blastocyst.

Cochrane 2013.

Cleavage vs. Blastocyst Transfer:
Failure to Transfer Embryos (Favors Cleavage)



Analysis 7.1. Comparison 7 Failure to transfer embryos rate per couple, Outcome 1 Failure to transfer any embryos per couple.

Review: Cleavage stage versus blastocyst stage embryo transfer in assisted reproductive technology

Comparison: 7 Failure to transfer embryos rate per couple

Outcome: 1 Failure to transfer any embryos per couple

Study or subgroup	Day 5/6 n/N	Day 2/3 n/N	Odds Ratio(Non-event) M-H,Fixed,95% CI	Odds Ratio(Non-event) M-H,Fixed,95% CI
Gardner 1998	2/45	0/47		0.18 [0.01, 3.92]
Bungum 2003	0/61	0/57		0.0 [0.0, 0.0]
Coskun 2000	0/100	0/101		0.0 [0.0, 0.0]
Devroker 2000	0/11	0/12		0.0 [0.0, 0.0]
Emiliani 2003	10/99	1/94		0.10 [0.01, 0.76]
Frattarelli 2003	3/29	5/28		1.88 [0.40, 8.77]
Hreinsson 2004	4/64	3/80		0.58 [0.13, 2.71]
Karaki 2002	9/80	0/82		0.05 [0.00, 0.80]
Kolibianakis 2004	36/226	16/234		0.39 [0.21, 0.72]
Levitas 2004	6/23	2/31		0.20 [0.04, 1.08]
Levron 2002	3/46	0/44		0.14 [0.01, 2.78]
Motta 1998 A % B	6/58	1/58		0.15 [0.02, 1.31]
Papanikolaou 2005	0/80	0/84		0.0 [0.0, 0.0]
Papanikolaou 2006	11/175	8/176		0.71 [0.28, 1.81]
Rienzi 2002	0/50	0/48		0.0 [0.0, 0.0]
Van der Auwera 2002	18/70	6/66		0.29 [0.11, 0.78]
Total (95% CI)	**1217**	**1242**		**0.35 [0.24, 0.51]**

Total events: 108 (Day 5/6), 47 (Day 2/3)

Heterogeneity: Chi^2 = 12.46, df = 10 (P = 0.26); I^2 =20%

Test for overall effect: Z = 5.58 (P < 0.00001)

Test for subgroup differences: Not applicable

0.1 0.2 0.5 1 2 5 10

Favours Day 2/3 Favours Day 5/6

OR = 0.35

P=0.00001

Cleavage vs. Blastocyst.

Cochrane 2013 ▪

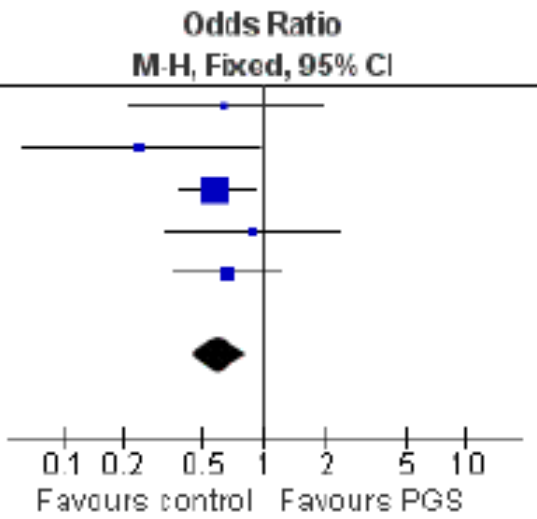
PGS for Aneuploidy:
Advanced Maternal Age
LBR Per Woman Randomized (Favors Control)

Figure 3. Forest plot of comparison: 1 advanced maternal age, outcome: 1.1 live birth rate per woman randomised.

Study or Subgroup	PGS group Events	PGS group Total	Control group Events	Control group Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Debrock 2010	6	44	10	50	7.5%	0.63 [0.21, 1.91]
Hardarson 2008	3	56	10	53	9.1%	0.24 [0.06, 0.94]
Mastenbroek 2007	49	206	71	202	50.9%	0.58 [0.37, 0.89]
Schoolcraft 2009	16	32	16	30	7.7%	0.88 [0.32, 2.37]
Staessen 2004	21	199	29	190	24.7%	0.65 [0.36, 1.19]
Total (95% CI)		**537**		**525**	**100.0%**	**0.59 [0.44, 0.81]**
Total events	95		136			

Heterogeneity: $Chi^2 = 2.39$, $df = 4$ ($P = 0.66$); $I^2 = 0\%$

Test for overall effect: $Z = 3.35$ ($P = 0.0008$)



Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005291.

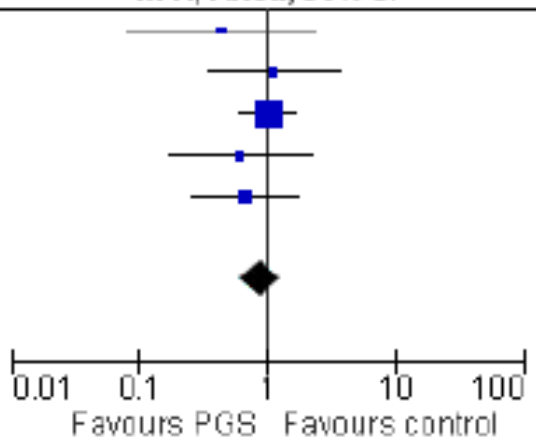
PGS for Aneuploidy:
Advanced Maternal Age
Miscarriage Rate (P=NS)

Figure 9. Forest plot of comparison: 1 advanced maternal age, outcome: 1.7 miscarriage rate per woman randomised.

Study or Subgroup	PGS group Events	Total	Control group Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Debrock 2010	2	44	5	50	8.0%	0.43 [0.08, 2.33]
Hardarson 2008	7	56	6	53	9.7%	1.12 [0.35, 3.58]
Mastenbroek 2007	37	206	36	202	53.6%	1.01 [0.61, 1.68]
Schoolcraft 2009	5	32	7	30	11.0%	0.61 [0.17, 2.18]
Staessen 2004	7	199	10	190	17.7%	0.66 [0.24, 1.76]
Total (95% CI)		**537**		**525**	**100.0%**	**0.87 [0.59, 1.27]**
Total events	58		64			

Heterogeneity: Chi² = 1.80, df = 4 (P = 0.77); I² = 0%

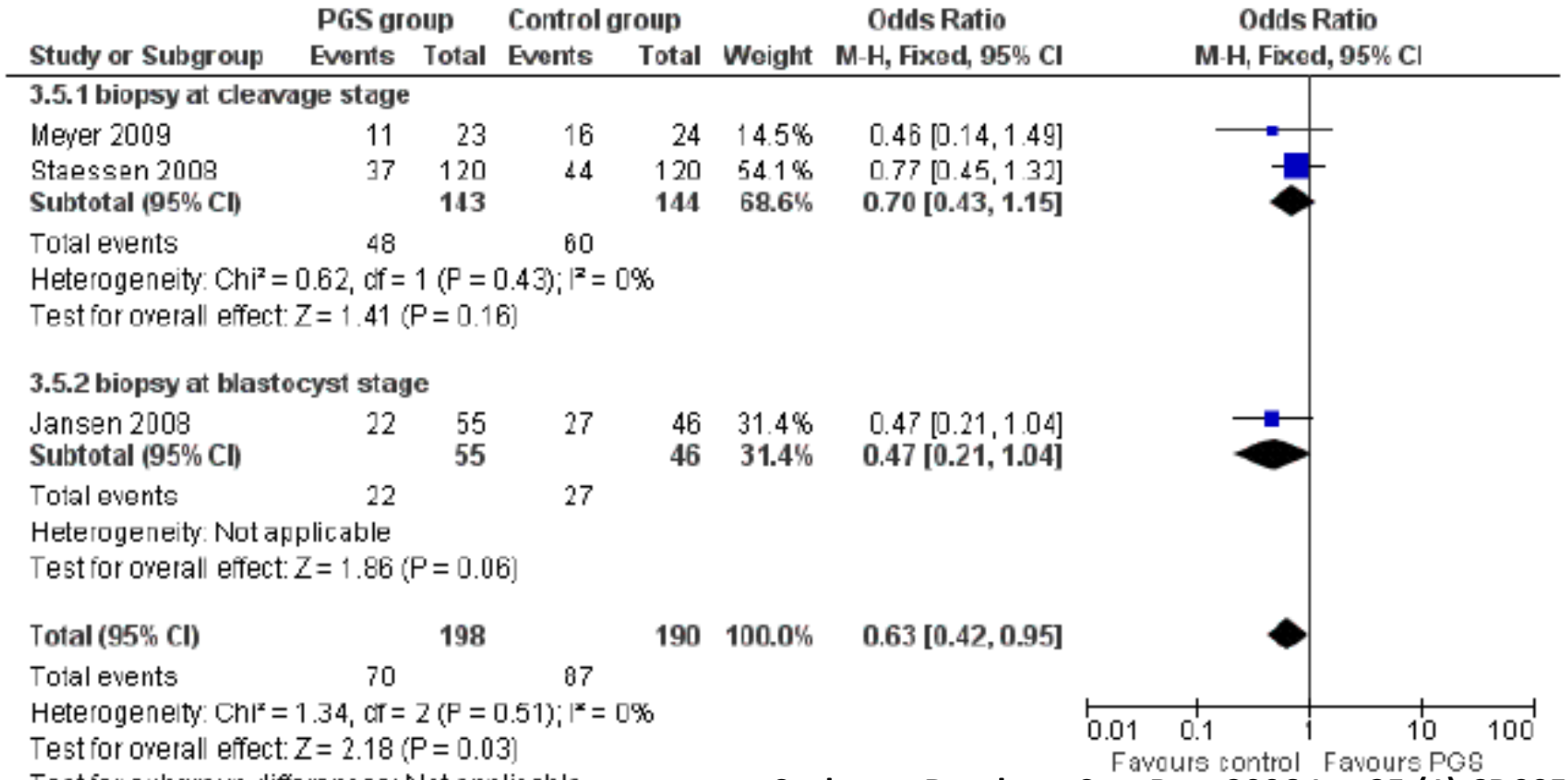
Test for overall effect: Z = 0.73 (P = 0.47)



Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005291.

PGS for Aneuploidy:
Good Prognosis
Clinical Pregnancy Rate (Favors Control)

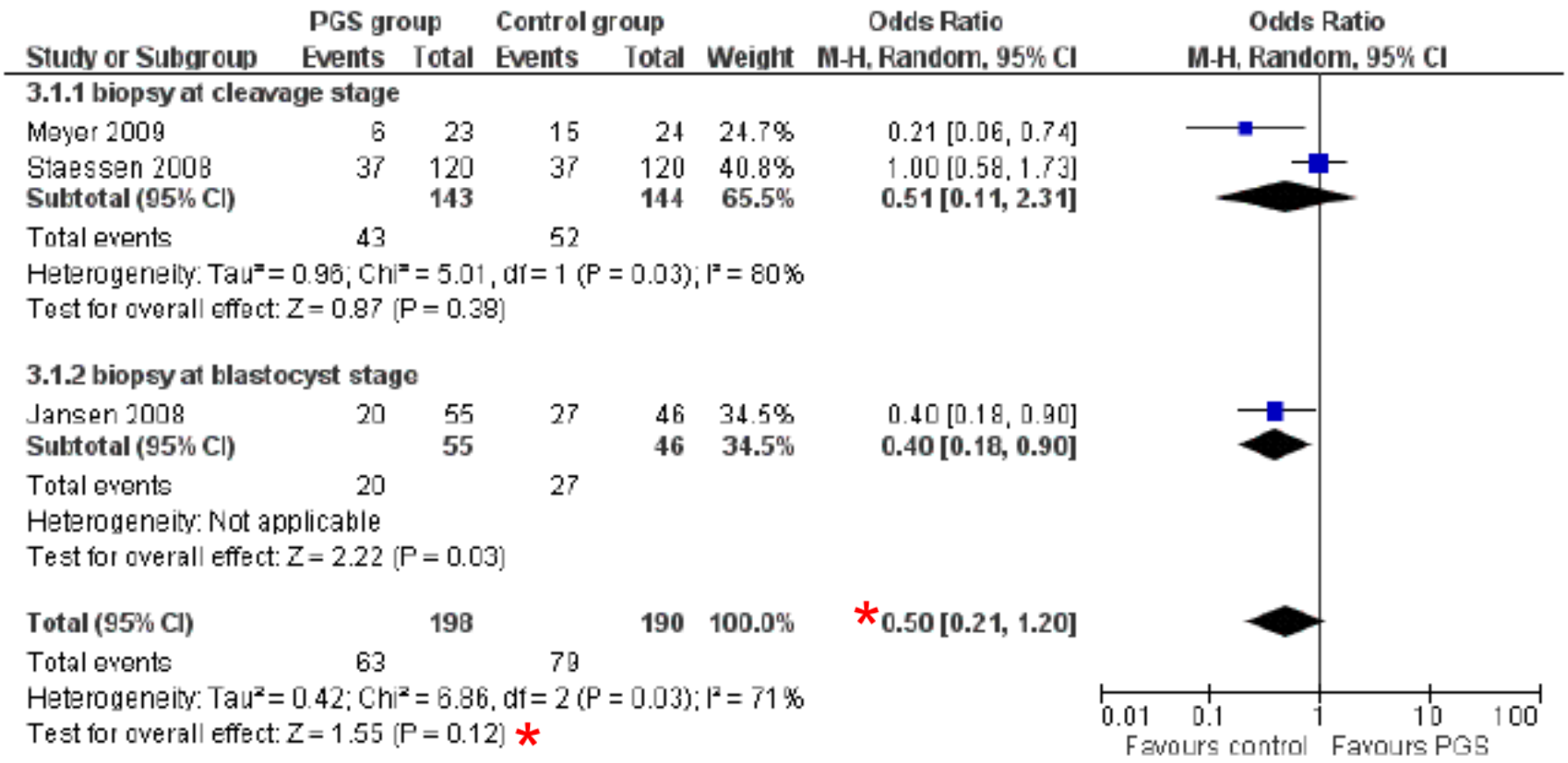
Figure 12. Forest plot of comparison: 3 good prognosis patients, outcome: 3.5 clinical pregnancy rate per woman randomised.



Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005291.

PGS for Aneuploidy:
Good Prognosis
Live Birth Rate (P=NS*)

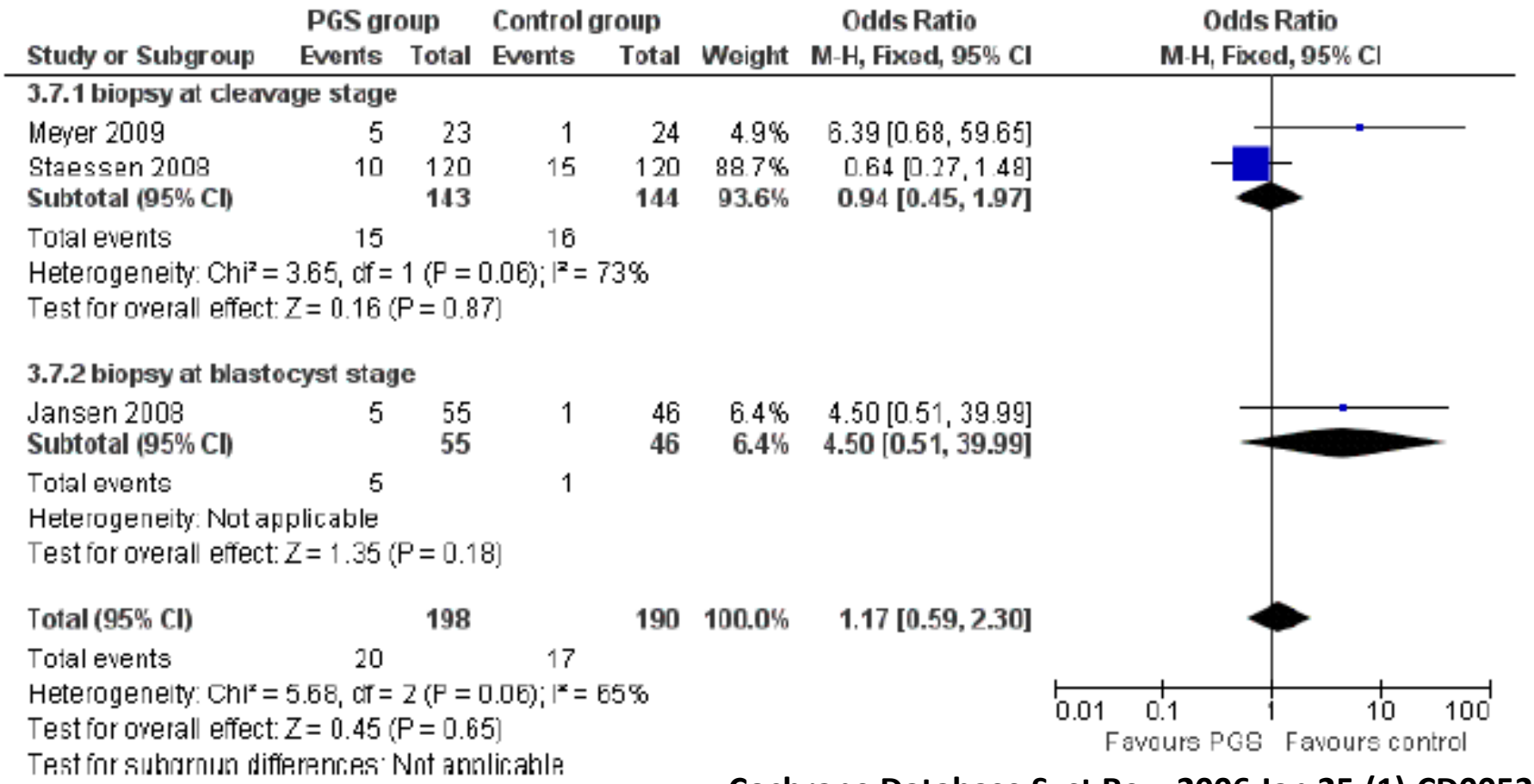
Figure 10. Forest plot of comparison: 3 good prognosis patients, outcome: 3.1 live birth rate per woman randomised.



Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005291.

PGS for Aneuploidy:
Good Prognosis
Miscarriage Rate (P=NS)

Figure 13. Forest plot of comparison: 3 good prognosis patients, outcome: 3.7 miscarriage rate per woman randomised.



Cochrane Database Syst Rev. 2006 Jan 25;(1):CD005291.

7. Recognize Patient Choice, But Make It Informed Choice

- Majority of patients desire twins
- This is understandable
- BUT this is BEFORE they have to take care of twins, ESPECIALLY if the baby is not healthy
- Patients (and physicians) underestimate risks and family burden
  - Babies and Mothers
  - Short term
  - Long term
- Informed choice is essential

Factors Causing Multiple Births

- Patients' sense of urgency
- Inadequate health care coverage
- Competition from marketplace pressures
- Different perspectives of multiple risk (1)
- Infertility specialists' lack of involvement in follow-up care
- Focus on LBR/Cycle rather than cumulative LBR (2)
- Patients and physicians underestimate negative consequences of twin pregnancies(3-5)

1.Hartshorne. Hum Reprod 2002;17:1023-1030.
2.Ryan. Fertil Steril 2004;81:500-4.
3.Leiblum. J Psychosom Obstet Gynaecol 1990;11:197-210.
4.Murdoch. Hum Reprod 1997;12(Nat'l Suppl) 2:88-92.
5.Pinborg. Hum Reprod 2003;18:621-627.

Physician Attitudes

- Factors affecting patients' attitudes towards single- and multiple embryo transfer (1)
  - Physicians' attitudes matter
- Attitudes towards and management of single embryo transfer among Nordic IVF doctors (2)

(1) Newton. Fertil Steril 2007;87:269-78.

(2) Bergh. Acta Obstetrica Gynecol Scand 2007;86:1222-30.

Patient Education

- Increased patient education makes eSET more acceptable (1,2)
  - Preference for twins reduced by half
  - eSET became preferred option
  - Written patient education materials tripled eSET rate in 1 year
  - RCT of DVD vs. Written Brochure
    - eSET vs. DET
    - DVD significantly better

1. SART/ASRM Practice Committees. eSET. 2011.
2. Ryan. Fertil Steril 2007;88(2):354-60.

ASRM Practice Committee Conclusions 2011

Conclusions

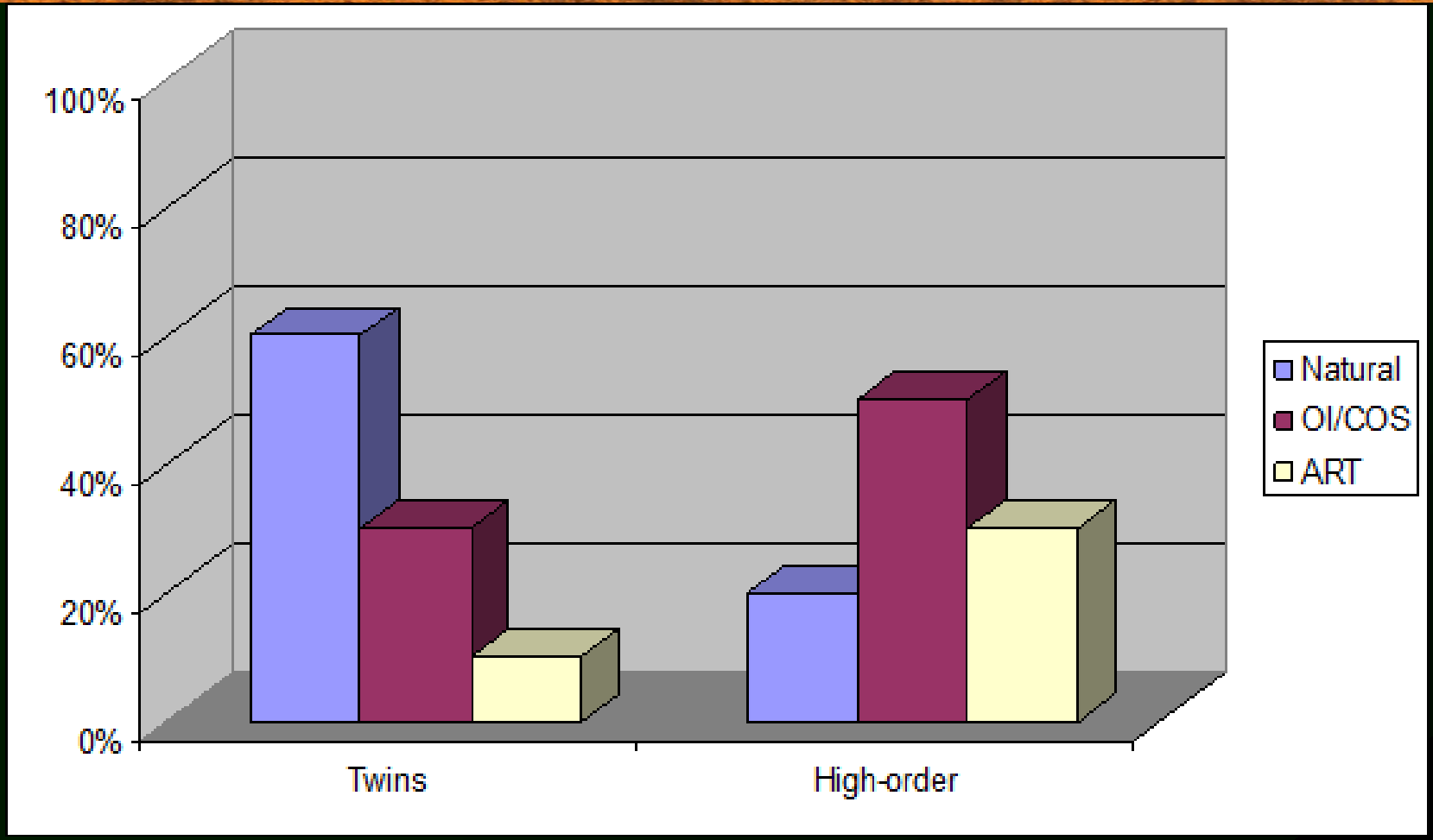
- Elective SET should be offered to patients with a good prognosis and to recipients of embryos from donated eggs.
- IVF centers should promote eSET when appropriate through provider and patient education.
- Improvements in embryo selection should further increase the application of eSET.

SART/ASRM Practice Committees. eSET. 2011.

8. Discuss Fetal Reduction

- A technology that is successful
  - Ethical issues
  - Personal and societal value issues
- Controversial for many
  - Know your patient's perspective
- Be especially conservative if unacceptable to patient(s)

9. Reduce Multiple Births With COS/IUI, Not Just With ART



https://www.asrm.org/Guidelines/ Accessed December 22, 2011.

10. Reduce Financial Disincentives

- Reduce risk of the cost of multiple cycles
- Educate patients(2)
  - Long term costs of twins
  - Especially if unwell
- Insurance coverage (2)
  - Reduces number of embryos transferred
- Financial programs (2)
  - Increase eSET 50%

1.Ryan. Fertil Steril 2004;81:500-4.
2.SART/ASRM Practice Committees. eSET. 2011.

11. Reduce Drop-out Rates

- Patient drop-out rates are 37-68%
- A major unknown confounding variable on the overall success of eSET (1,2)
  - Cost
  - Physician-recommended
  - Sweden: 65% not pregnant did not pursue covered treatment (3)
    - Psychological –26%
    - Poor Prognosis – 25%
    - Spontaneous pregnancy – 19%
    - Physical burden – 6%
    - Serious disease – 2%
    - Other –7%

1.Olivius. Fertil Steril 2004;81:258-78.
2.Daya. Hum Reprod 2005;20:1135-43.
3.Olivius. Fertil Steril 2002;77:505-10.

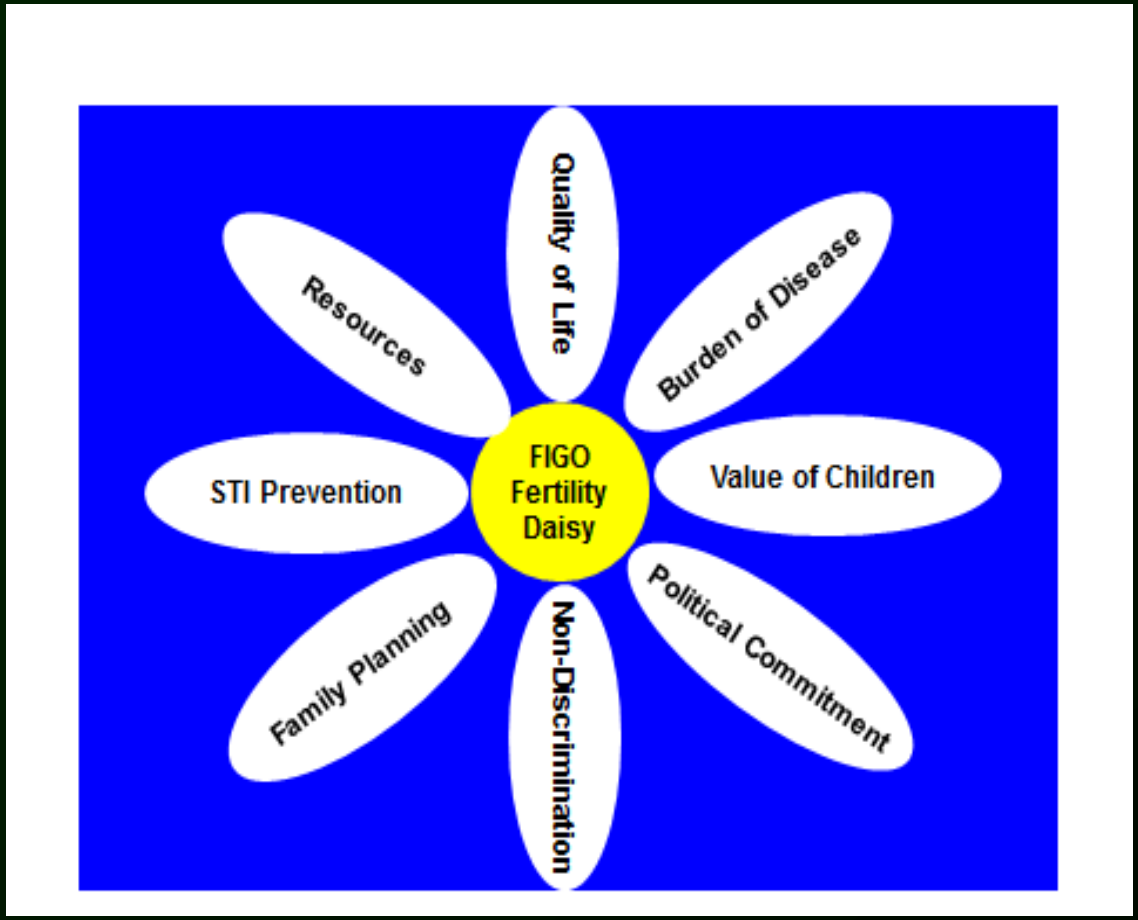
Emotional Support and Mind-Body Programs

The pain and burden
of infertility
is real.

12. Create Systematic Change To Reduce Multiple Births

- Professionals
  - Associations
    - Change guidelines
    - Change reporting of outcomes (e.g. % eSET, %eSBT, %DBT)
  - Individual physicians transfer fewer embryos/blastocysts
- Other stakeholders can initiate change
  - Professional colleagues (e.g. MFM)
  - March of Dimes
  - WHO
- Government can regulate
- Change perspectives
  - Patients
  - Society

Why Does Infertility Matter?
The FIGO Fertility Tool Box™



www.arcfertility.com/figo

Thank You!