

Autonomy: Who Decides What?

Multiple Pregnancies

David Adamson, MD

Director

Fertility Physicians of Northern California

Clinical Professor

Stanford University School of Medicine

Associate Clinical Professor

University of California at San Francisco

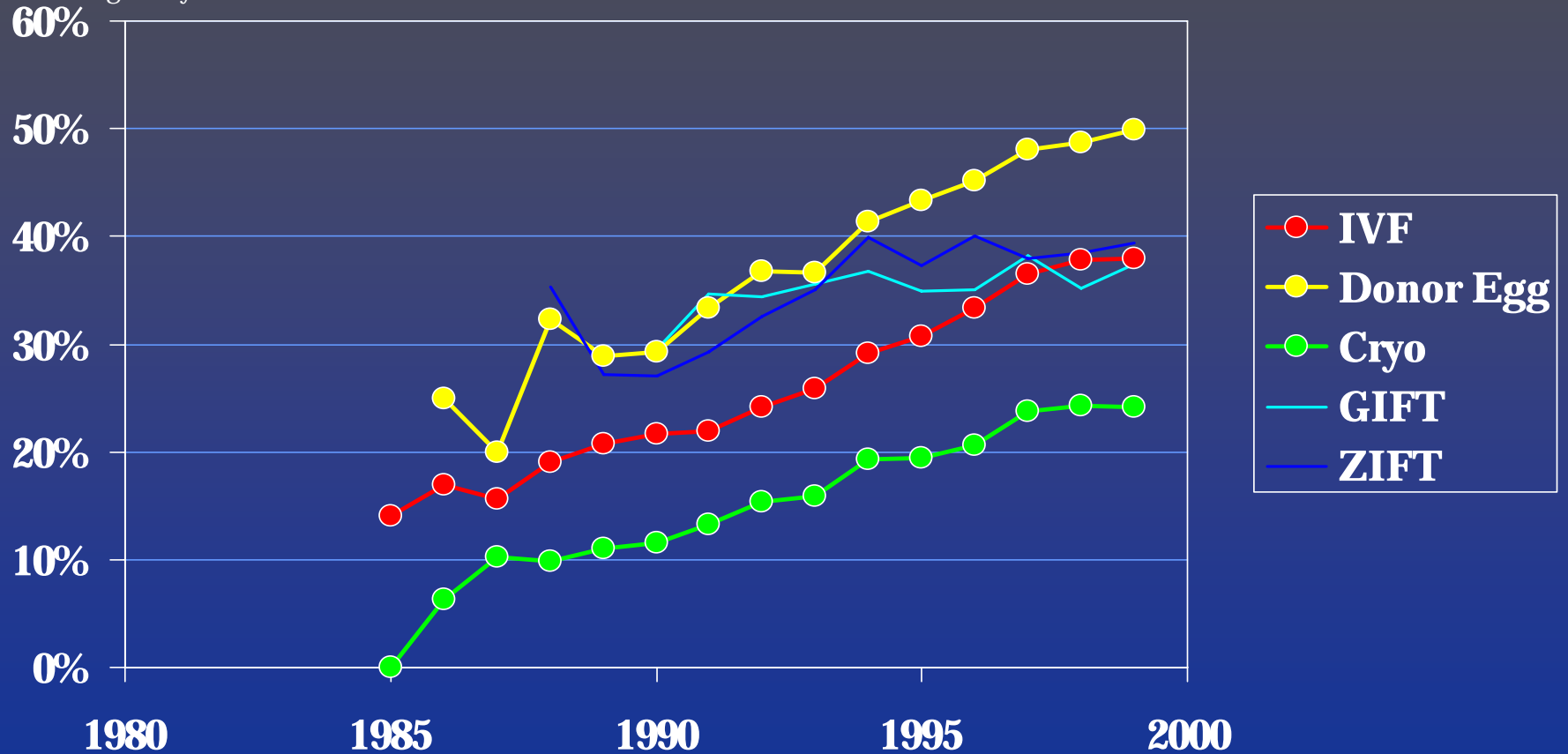
Disclosures

- **Research funding**
 - Serono (anastrozole study)
 - IBSA (gonadotropin study)
- **Management and ownership**
 - Advanced Reproductive Care (ARC)
- **Professional organizations**
 - American Society for Reproductive Medicine (ASRM)
 - International Committee Monitoring ART (ICMART)
 - International Federation of Fertility Societies (IFFS)

CURRENT ART IN UNITED STATES

USA Clinical Pregnancy Rate Per Transfer 1985-2000

Clinical Pregnancy / Transfer



USA Live Birth/Embryo Transfer (%) 2005

	<35	35-37	38-40	41-42
Fresh	43.3	35.8	25.4	14.9
Cryo/thaw	31.9	27.9	23.1	15.6
Donor Egg	52.1	--	--	--
Donor/thaw	31.1	--	--	--

www.SART.org; May 24, 2005

Multiples from ART vs Non-ART Treatment

1997 to 2000

- Total US Births 15,856,809 live-born infants
- ART live-born infants 105,519
- Twin rate increased to 444.7/1000 live ART births
- Triplet rate decreased: 134.3 to 98.7/1000 live ART births
- Proportion multiple births caused by ART increased: 11.2 to 13.6%

In 2000 Triplet/+ Births

- ART 42.5%
- Natural 17.7%

Reynolds. Pediatrics 2003;111(5 Part 2):1159-62.

Multiples from ART vs Non-ART Treatment

2001

- **Twins constitute 46% of babies**
 - (15X natural occurrence of 3%)
- **Triplets constitute 8% of babies**
 - (42X natural occurrence of 0.2%)
- **54% of ART babies come from multiple pregnancies**

Wright. MMWR April 30, 2004/53(SS01);1-20.

Complications of Multiple Pregnancy

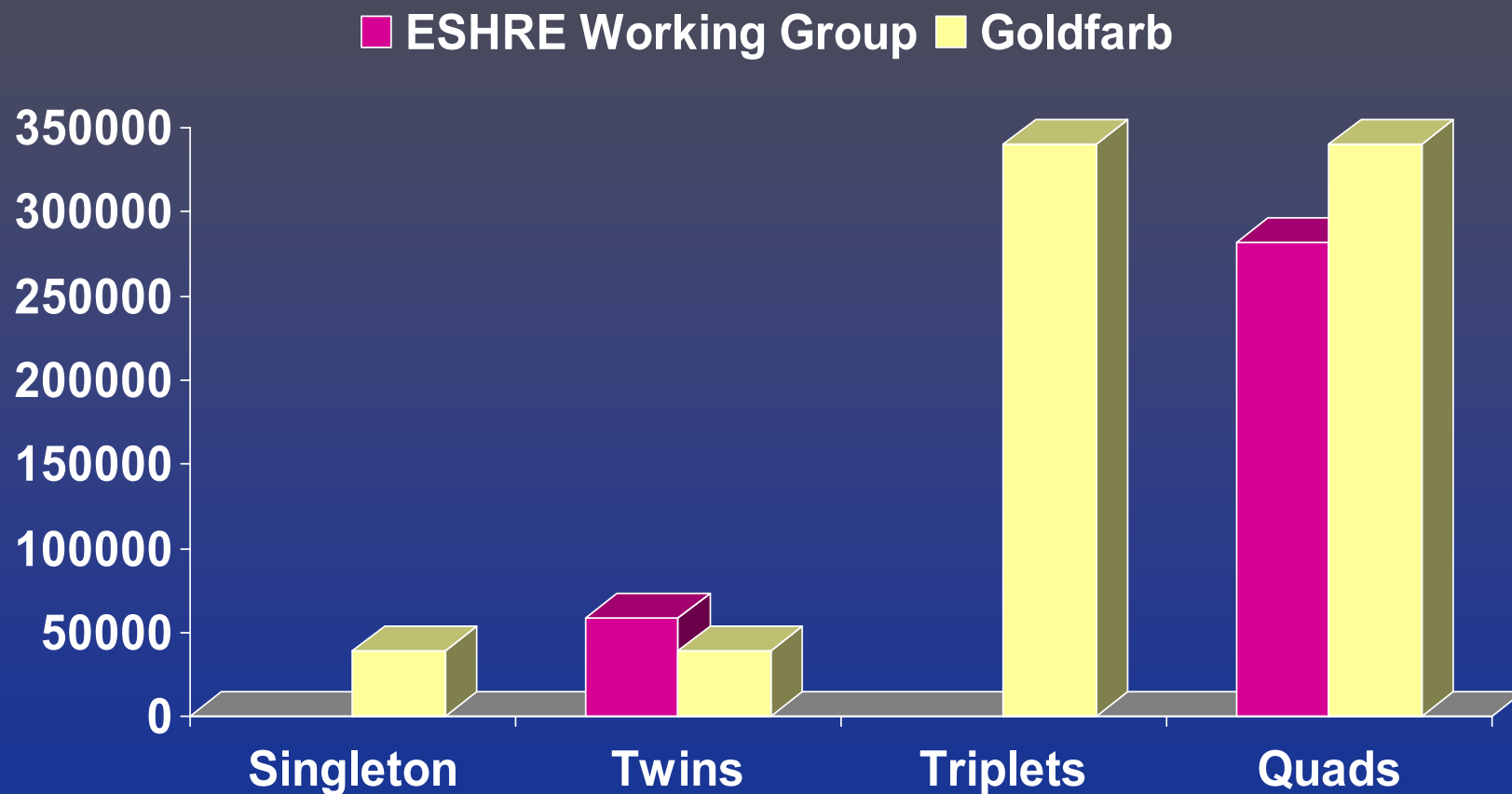
- **Mother (Increased ~2 times)**
 - Pre-eclampsia
 - Gestational diabetes
 - Pre-term labor and delivery
 - Weight gain, anemia, nausea, GI symptoms, dermatoses, other
 - Caesarian delivery
- **Fetuses (Increased 2-4 times)**
 - Premature delivery
 - Fetal growth restriction
 - Caesarian delivery
 - Placental and other obstetrical complications

Hospital Charges by Plurality

Plurality (N)	Maternal	Each Neonate	Total Family
1	\$5,000	\$5,000	\$10,000
2	\$10,000	\$15,000	\$40,000
3+	\$15,000	\$30,000	\$110,000 (\$216,340*)

*Inflation adjusted 2004 dollars

Cost Per Family For Multiple Births Resulting from IVF



Factors Causing Multiple Births

- Patients' sense of urgency
- Less than complete health care coverage (1)
- Competitive marketplace pressures
- Different perspectives of multiple risk (2)
- Infertility MD's lack of involvement in follow-up care
- Focus on LBR/Cycle rather than overall treatment plan
- Underestimate consequences of twin pregnancies(3-6)
- 69% of patients, after education re risks, still prefer twins (4)
- Younger, poorer, prior evaluation, longer & 1* infertility (6)

(1) N Engl J Med 2002;347:661-666

(2) Hartshorne. Hum Reprod 2002;17:1023-1030

(3) Leiblum. J Psychosom Obstet Gynaecol 1990;11:197-210

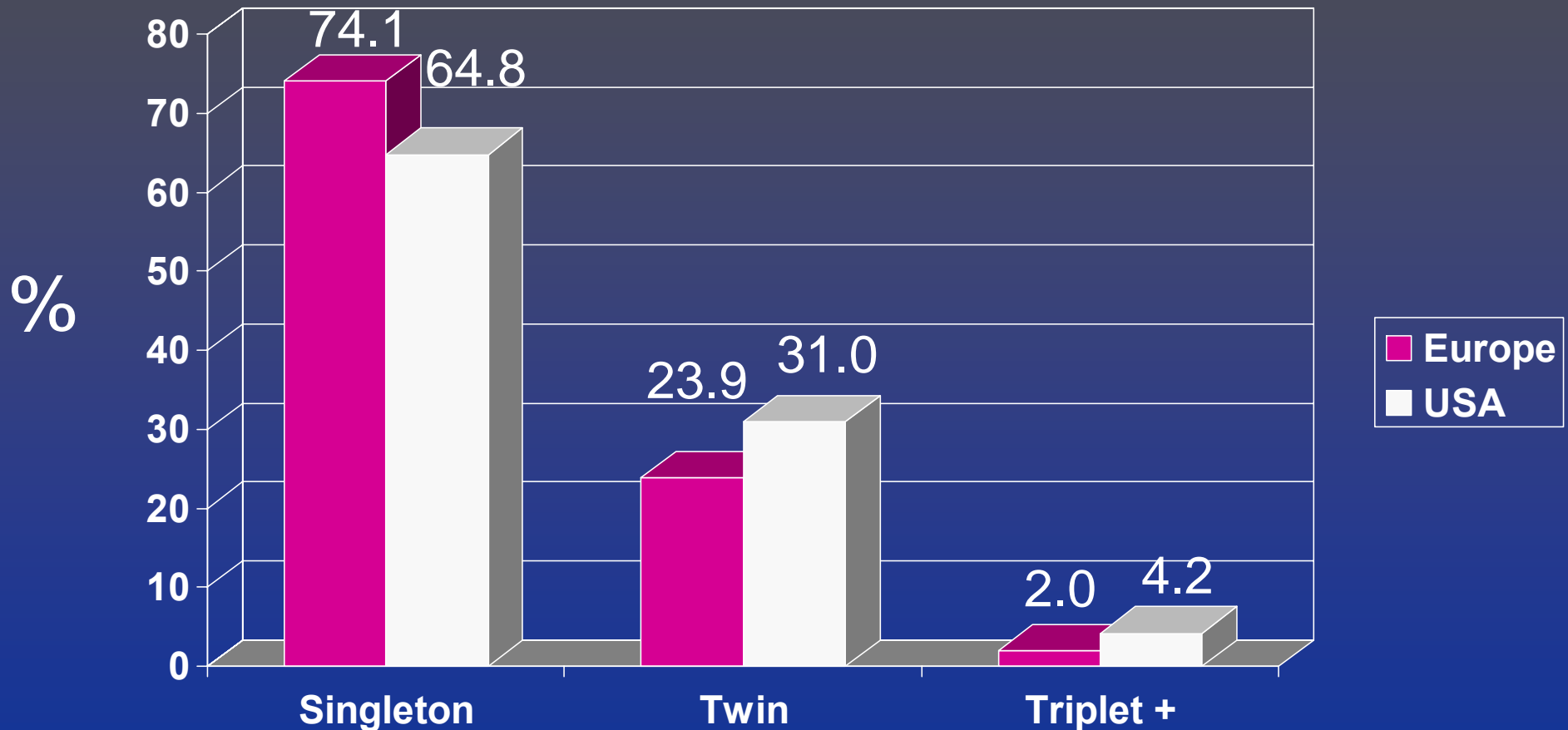
(4) Murdoch. Hum Reprod 1997;12(Nat'l Suppl) 2:88-92

(5) Pinborg. Hum Reprod 2003;18:621-627

(6) Ryan. Fertil Steril 2004;81:500-504

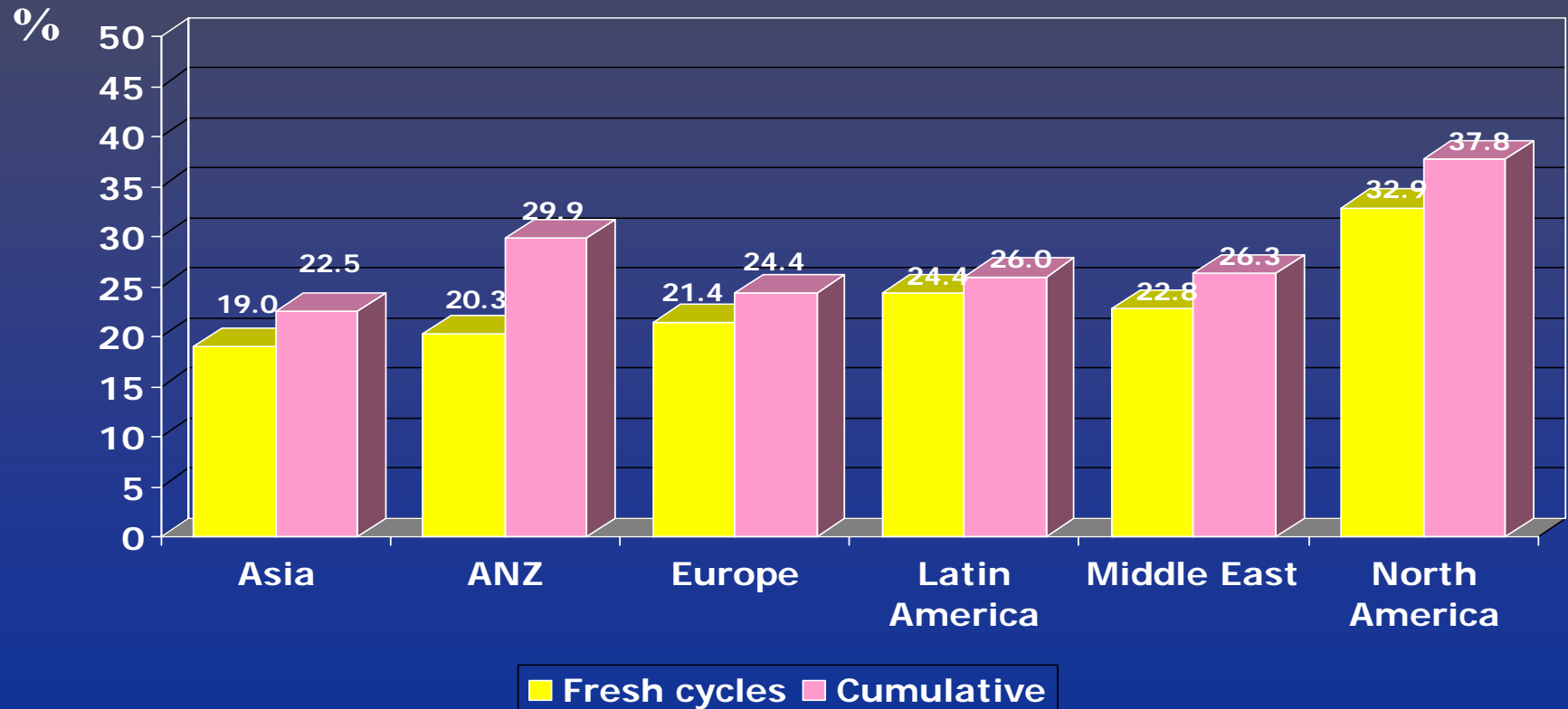
COMPARISON OF ART IN USA AND EUROPE

USA Compared to Europe Multiple Birth Rates, Year 2000

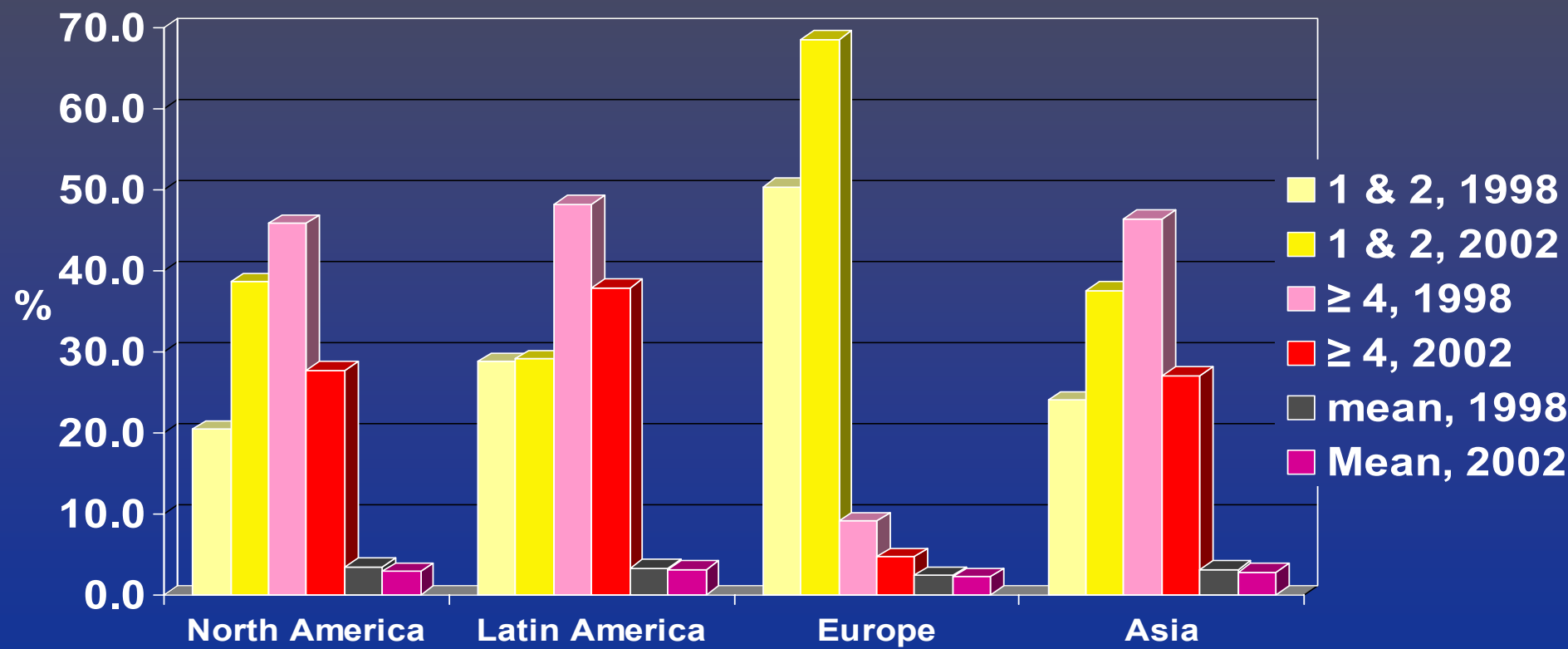


Adamson (ICMART World Report). Fertil Steril 2006;85:1586-622.

Delivery Rate (IVF & ICSI) Per Retrieval By Region 2002



Number of Embryos Transferred By Region 2002



Additional Factors Affecting ART Prognosis That Influence Treatment Decisions

- **Race** (Grainger F&S, 2004)
- **Drop-out rates** (F&S Feb 2004; Daya HR 2005)
- **Co-morbidities**
 - Age
 - Obesity
 - Hypertension
 - Diabetes
- **Life-style** (Hassan. Fertil Steril 2004)
 - Alcohol
 - Smoking
 - Caffeine

General European Perspective on Multiple Birth

- Patients who have a multiple birth could usually have been managed so that they had a singleton.
- The total number of babies eventually born will be approximately the same, even if fewer embryos are replaced, because additional cycles can be performed.
- The costs of managing multiples over their lifetime will dwarf the cost of additional IVF cycles needed to obtain an equivalent number of babies one at a time.

General American Perspective on Multiple Birth

- **Singleton pregnancy is the best outcome.**
- **Infertile patients want a baby, and many prefer or accept a twin pregnancy.**
- **The financial and/or psychological barriers are such that obtaining the highest possible pregnancy rate each cycle is important.**
- **While triplets should be avoided, the outcome of twin pregnancies is not that much worse than singleton pregnancies.**
- **It is reasonable for patients to participate in determining the amount of risk they wish to accept in undergoing treatment.**

SOLUTIONS TO MULTIPLE BIRTH PROBLEM IN ART

“Solutions” to Multiple Birth Problem in ART

- ***Improve quality of embryos transferred***
 - *Embryo assessment problematic*
 - *? Blastocyst*
 - *Preimplantation Genetic Screening (PGS)*
- ***Reduce number of embryos transferred***
 - *Reduce patient demand through education and insurance*
 - *Have physicians implement lower transfer number guidelines*
 - *Change voluntary professional guidelines*
 - *Be regulated by government*
- **Induced reduction of multi-fetal pregnancy**

Multiple Birth: SART Guidelines

November, 1999

- Age ≤ 34

Good Prognosis (e.g. sufficient embryos to cryopreserve): No more than **2 good embryos**

Average Prognosis: No more than **3 good embryos**

- Age 35-39: No more than **4 good embryos**
- Age ≥ 40 : No more than **5 good embryos**

Profession Is Responding to the Problem

Average Number of Embryos Transferred

Age	1996	1997	1998	1999	2000	2001	2002....2005*	
≤ 34	3.9	3.7	3.4	3.0	2.9	2.8	2.7	2.4
35-37	(3.9)	3.8	3.6	3.3	3.2	3.1	3.0	2.6
38-40	(4.0)	3.9	3.7	3.5	3.5	3.4	3.3	3.0
≥ 41	(4.0)	4.0	3.9	3.7	3.7	3.7	3.5	3.3
All	4.0	3.8	3.6	3.2	3.2	3.1	3.0	2.6

P < 0.001

Jain et al. N Eng J Med 2004;350(16):1639-45.

IVF 1995-2005

Year	Ret	Deliv/ Ret	Mult/ Deliv	Trips/ Deliv	Triplet Fetuses
1995	35,269	22.5%	37%	5.8%	---
1996	38,432	26.0%	39%	6.9%	---
1997	44,170	27.9%	39%	6.5%	11.4%
1998*	53,154	28.9%	38%	6.0%	10.6%
1999	56,835	29.2%	37%	4.9%	8.4%
2000	64,280	29.6%	35%	4.3%	7.7%
2001	66,786	32.3%	36%	4.2%	7.6%
2002	71,402	33.8%	36%	3.9%	7.0%
2003	79,717	33.7%	34%	3.2%	5.9%
2004	82,612	32.6%	33%	2.6%	4.9%
2005	83,935	32.7%	33%*	2.3%*	4.4%

Patients Need Individual Treatment

- Age
- Ovarian Reserve
- Diagnosis
- Number of Previous Cycles
- Quality of embryos
- Cryopreservation
- Value system/religious beliefs
- Multiple other individual characteristics
- Program characteristics

Fertil Steril 1999, 71(5),Suppl 2:12S-13S.

Major Factors Influencing Success Rates

- Patient (egg source) age (1,2)
- Embryo quality (probably most important) (3)
- Number of embryos transferred (1,2)

(1) Bassil. J Reprod Med 1997;42:761-766.

(2) Roseboom. Hum Reprod 1995;10:3035-3041.

(3) Terriou. Fertil Steril 2001;75:525-531.

The Question Regarding Reducing from 2 to 1 Embryo Transfer Is:

Can the reduction from 3 to 2 embryo transfer (which has largely been accepted and occurred successfully) be extrapolated to a 2 to 1 embryo transfer?

This is clearly not the case in an indiscriminating and linear way.

**ELECTIVE SINGLE
EMBRYO TRANSFER
(eSET)**

eSET vs. eDET in IVF

A Prospective Randomized Controlled Study

- Live birth rate 38.8% (eSET) vs. 42.9% (eDET)
- Multiple births 0.8% vs. 33.1% ($p < 0.001$)
- Study Participation
 - 7,839 cycles with fresh embryo transfer
 - 2,698 eligible cycles (+209 already in study = 37.1%)
 - 661 participate
- Patient Characteristics
 - Average age 30.9 years
 - Duration of infertility 3.7 years
 - Male factor 48.3%
 - Prior pregnancy 29.2%

Economics of eSET vs. DET

- Cost to obtain each child does NOT differ for eSET vs. DET *in selected populations* (1,2)
- Twins increase indirect and long term costs
 - NICU
 - Hospitalization
 - Special education
 - Other costs, e.g. disability pay, day care, incremental health cost
- Psychological consequences
- Family consequences

(1) De Sutter. Hum Reprod 2002;17:2891-2896.

(2) Lukassen. Hum Reprod 2005;20:702-8.

Value of A Human Life

- Litigation Analytics (humanlifevalue.com)
35 y.o. male, \$75K income **\$1,952,658**
- humanforsale.com
24 y.o. female, IQ 119 **\$2,363,228**
- National Center for Policy Analysis
13 year old boy died auto **\$200,000**
- Pw1.netcom.com/~drpauls/value
Alcohol and drug control stds **\$400,000**
- 9/11 Government fund **\$2M (.25--7.1)**

***ALL VALUES ARE MUCH GREATER THAN THE
COST OF NEONATAL CARE FOR TRIPLETS***

Economic Analysis of Costs AND Benefits

A Model

- **Assumptions (1,2)**

- Handicaps included
- eDET E\$7,000 more expensive than eSET per live birth
- Therefore, for 100 live births is E\$ 700,000 more expensive
- Multiples: eSET = 1%; eDET = 33%: Difference = + 32 twins

- **Value of extra baby**

- If Baby = $E\$700,000/32 = E\$ 21,875$; then eSET E\$ = eDET E\$
- If baby is worth more than this (? E\$ 400,000), then
- NET BENEFIT of eDET = $(E\$ 400,000 - E\$ 21,875) \times 32 =$
~E\$ 12,100,000

(1) Lukassen. Hum Reprod 2005;20:702-8.

(2) Bergh. Hum Reprod 2005;20:323-7.

Patient Drop-out Rates Are 37 – 68%: What is the Impact on Cumulative eSET?

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

(1) Fertil Steril 2004;81:258-78.

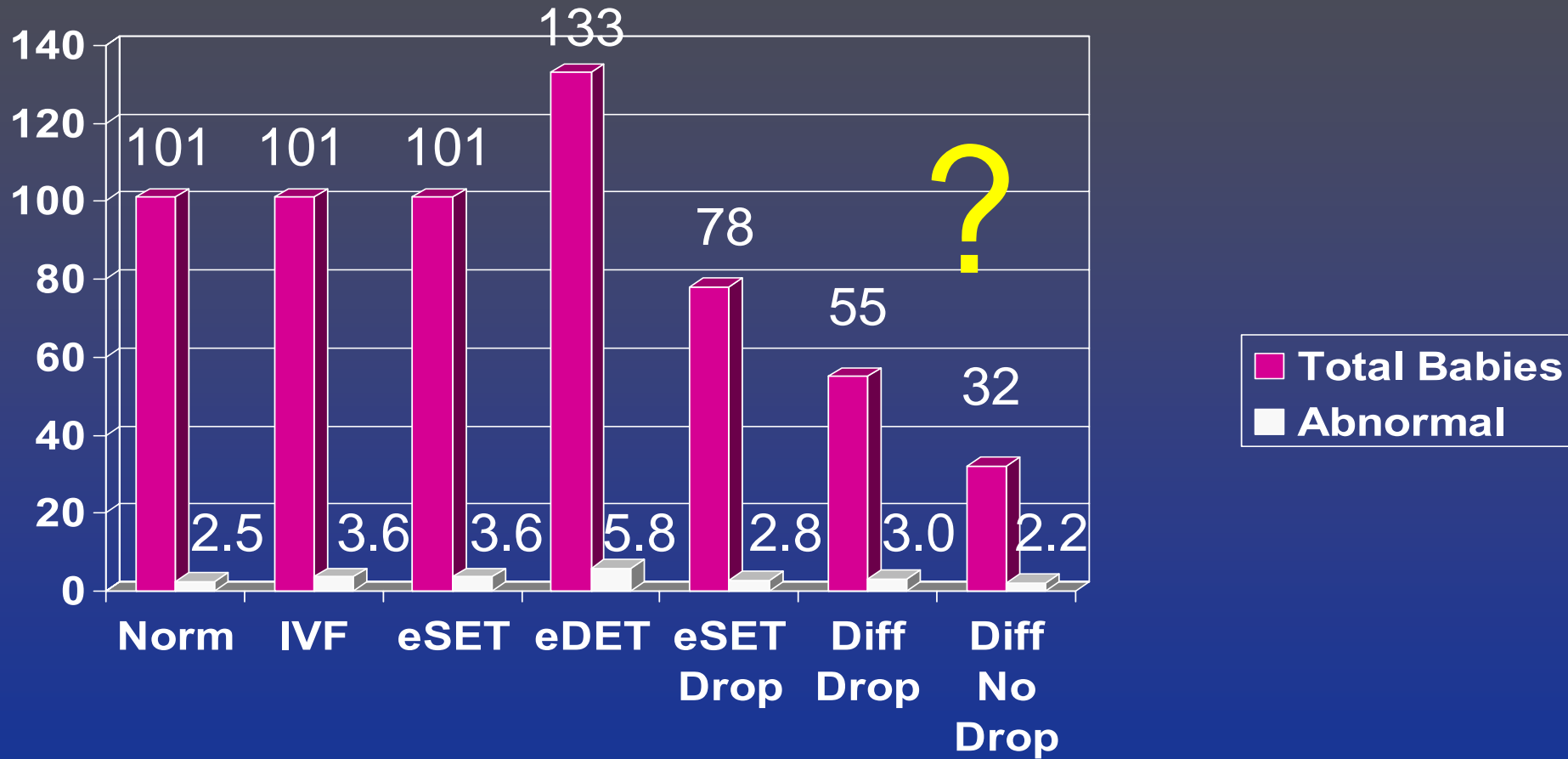
(2) Daya. Hum Reprod 2005;20:1135-43.

(3) Olivius. Fertil Steril 2002;77:505-10.

Effect of 1/3 Patient Dropout on Eventual Live Birth Rate: A Model

	eSET (27.6%/16.4%)		eDET (42.9%)	
Fresh	27.6		42.9	
Frozen/Thaw	11.2	38.8	--	
Fresh	16.9		24.5	
Frozen/Thaw	7.3	63.0	--	67.4
Fresh	--		14.0	
Frozen/Thaw	--		--	81.4
TOTAL		63.0%		81.4%

Effect of eSET With Dropout vs. eDET A Model



Assumptions: 1. LBR: Thurin, 2005. 2. Abnormalities: Van Steirteghem, Congress 2005. 3. Dropout Rate: Olivia 2002 Daya 2005, Fertil Steril 2004.

RCT of *Single Day 3 Embryo Vs. Single Day 5 Blastocyst Transfer*

	Clinical Pregnancy/ Transfer	Delivery/ Transfer
Day 3	23.3%	21.6%
Day 5	33.1%	32.0%

Papanikolaou et al. N Engl J Med 2006;354:1139-46.

RCT of *Single Day 3 Embryo Vs. Single Day 5 Blastocyst Transfer*

- It would seem obvious to do Blastocyst transfer instead of Day 3
- **BUT: personal communication with Andre Van Steirteghem**
 - Reduction of embryo number with blastocyst culture
 - Lower cryopreservation results with blastocysts
- *They do day 3 transfer with eSET*
- Each IVF Clinic must choose best approach

Papanikolaou et al. N Engl J Med 2006;354:1139-46.

Multiple Birth: ASRM/SART Guidelines Number of Embryos to Transfer (2006)

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

CONCLUSIONS

Public Policy

“Continuing the high rates of multiple pregnancies is a threat to reproduction technologies, since policymakers and the public are not pleased with the implications.”

Peter A. Van Dop, MD, PhD

The Netherlands

Professional Assessment

“Because of the number of variables and the repetitiveness with which these variables change, the selection of a rigid number of embryos to transfer.... would greatly handicap many, many patients....”

Jones and Cohen, IFFS Surveillance 98, Fertil Steril 1999, 71(5)Suppl 2:12S-13S

CDC Recommends Guidelines

“...efforts are needed ...to limit the number of embryos transferred for patients receiving ART. These approaches ...should follow guidelines issued by organizations such as the American Society for Reproductive Medicine...”

MMWR. July 19, 2000;49;535-538

Conclusion: NO To Absolute Limits

- Problem is improving
- Profession is responding
- Patients need individual treatment
- Guidelines are working
- Net economic benefit is positive
- Technology outdates legislation
- Social advances outdate legislation

Conclusion: NO To Absolute Limits

- **Cause reproductive tourism**
- **Are discriminatory**
- **Involve medicine in politics**
- **Have unintended consequences**
- **May be illegal**
- **Criminalize medicine**
- **Recommended against by many experts**
- **Other management approaches**

Implementation of eSET

- **Not all patients are favorable prognosis**
- **Quality of data for individual decision-making**
 - Embryology data
 - Clinical data
- **Patient selection criteria**
- **Patient dropout rates**
- **Patient autonomy vs. social consequences**
- **Day 3 vs. Day 5 transfer**
 - Efficacy vs. safety (monozygotic twins and epigenetics)
 - Cryopreservation success rates
- **Multiple birth complications vs. value of additional babies**

eSET

An American Perspective

- **Decrease in number of embryos transferred from two to one**
 - Reasonable option in one-third of patients
 - Reduces twin incidence to half its original
 - No decline in ongoing pregnancy rate overall
- **The proportion of patients for whom this is appropriate will vary from program to program, depending on individual patient characteristics.**
- **Implement the program gradually**
 - Distinct clinical phases
 - Judicious patient selection
- **Cryopreservation**

Multiple Births from ART: A Challenge That Must Be Met

- **Recognize tension between individual rights/desires and social good**
- **Acknowledge real risks of multiple pregnancy**
- **Individual treatment to avoid adverse outcomes**
- **Specialist care**
- **Report outcomes by healthy singletons**
- **Improve basic and clinical science**
- **Improve education and informed consent**

Or Face Regulation

THANK YOU!