

The US Multiple Births Epidemic
1967-2013
iatrogenic and Demographic Forces in Action

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NEOGS 2015

April 29, 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

**Fertility Treatments and Multiple Births
in the United States**

Aniket D. Kulkarni, M.B., B.S., M.P.H., Denise J. Jamieson, M.D., M.P.H.,
Howard W. Jones, Jr., M.D., Dmitry M. Kissin, M.D., M.P.H., Maria F. Gallo, Ph.D.,
Maurizio Macaluso, M.D., Dr.P.H., and Eli Y. Adashi, M.D.

New Engl J Med 363 (23)2218-2225: December 2013

Dimensions

Directionality

Drivers

Introduction

- **An Epidemic?**
- **50 Years of Fertility Promotion**
- **CDC Databases Used**

American Journal of Obstetrics and Gynecology (2004) 190, 894-8

ELSEVIER

AMERICAN JOURNAL
of
OBSTETRICS
and
GYNECOLOGY
www.elsevier.com/locate/ajog

**The multiple gestation epidemic: The role of the assisted
reproductive technologies**

Allan Templeton, FRCOG*

*Department of Obstetrics and Gynecology, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen, United
Kingdom*

Calendar Year 1998: Height of the Epidemic

- 27% of twin infants born (~30,000/111,000) were deemed iatrogenic in origin.
- 84% of higher-order infants born (~6,400/7,600) were deemed iatrogenic in origin.
- 627 Quadruplets (~6 expected) and 79 Quintuplets+ (~1-2 expected)

Introduction

- **An Epidemic?**
- **50 Years of Fertility Promotion**
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<p><u>Phase I</u> <u>1967-1980</u></p> <p>Ovulation Induction (Clomiphene - 1967) (HMG - 1970)</p>	<p><u>Phase II</u> <u>1981-1986</u></p> <p>Ovulation Induction + IVF</p>	<p><u>Phase III</u> <u>1987-Present</u></p> <p>Ovulation Induction + IVF + Superovulation & IUI</p>
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Introduction

- **An Epidemic?**
- **50 Years of Fertility Promotion**
- **CDC Databases Used**

**I. Annual NCHS Natality Reports*
1962-2012**

II. Annual ART Success Reports
1997-2012**

*National Center for Health Statistics

**Assisted Reproductive Technology

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1962-2012**

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*National Center for Health Statistics

**Assisted Reproductive Technology

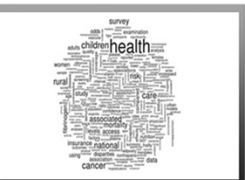
A-Z Index: [A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [Q](#) [R](#) [S](#) [T](#) [U](#) [V](#) [W](#) [X](#) [Y](#) [Z](#)

National Center for Health Statistics...Monitoring the Nation's Health

Link Up With the NCHS RDC
In their latest blog posting, NCHS Research Data Center staff examine major themes covered in 2012 publications which utilized data through the RDC.

[Learn More >](#)

1 2 3 4 5

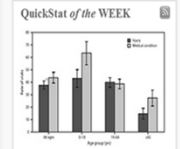


FEATURED TOPICS

Nosologists: What do they do and why is it important?
"How many causes of death are there?" The question makes experts from the Division of Vital Statistics (DVS) share looks and smiles as they point towards enormous binders. A death certificate often includes a series of conditions that led to the death of an individual. This detailed work is collected as part of our national vital registration system.

NEXT TOPIC >

QuickStat of the WEEK



CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

A-Z Index: [A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [Q](#) [R](#) [S](#) [T](#) [U](#) [V](#) [W](#) [X](#) [Y](#) [Z](#)

National Vital Statistics System

Birth Data

In the United States, state laws require birth certificates to be completed for all births, and Federal law mandates national collection and publication of birth and other vital statistics data. The National Vital Statistics System, the Federal compilation of this data, is the result of the cooperation between the National Center for Health Statistics (NCHS) and the States to provide access to statistical information from birth certificates.

Standard forms for the collection of the data and **model procedures** for the uniform registration of the events are developed and recommended for State use through cooperative activities of the States and NCHS. Material is available to assist persons in completing the death certificate. NCHS shares the costs incurred by the States in providing vital statistics data for national use.

Key Birth Statistics

Data for United States in 2010

- Number of births: 3,999,366
- Birth rate: 13.0 per 1,000 population
- Fertility rate: 64.1 births per 1000 women aged 15-44 years
- Percent born low birthweight: 8.1%
- Percent unmarried: 40.9%
- Source: Births: Final Data for 2010

What's New

Publications

- Recent Trends in Births and Fertility Rates Through June 2012 (12/2012)
- Births: Preliminary Data for 2011 (PDF) (12/10)
- Births: Final Data for 2010 (PDF - 1.3 MB) (8/2012)
- Estimated Pregnancy Rates and Rates of Prepregnancy Outcomes for the United States

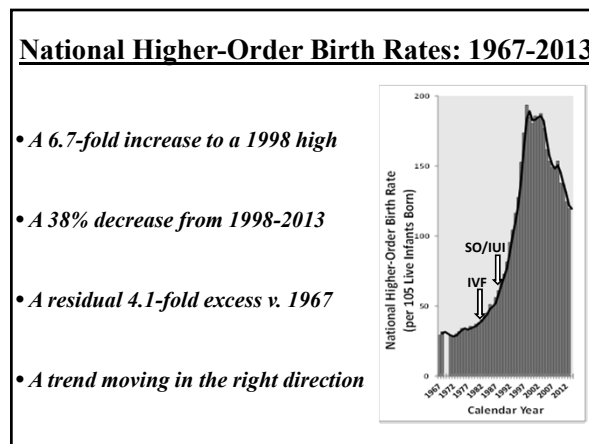
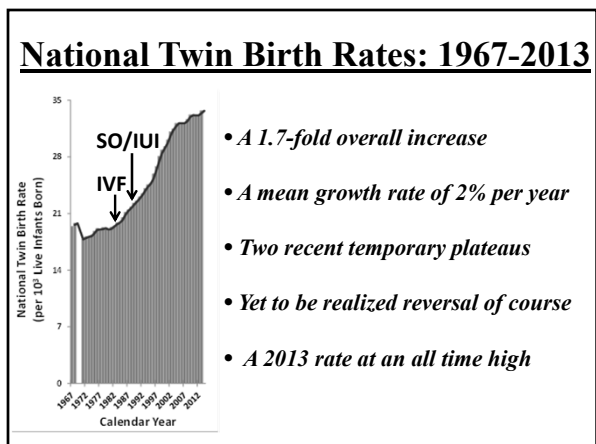
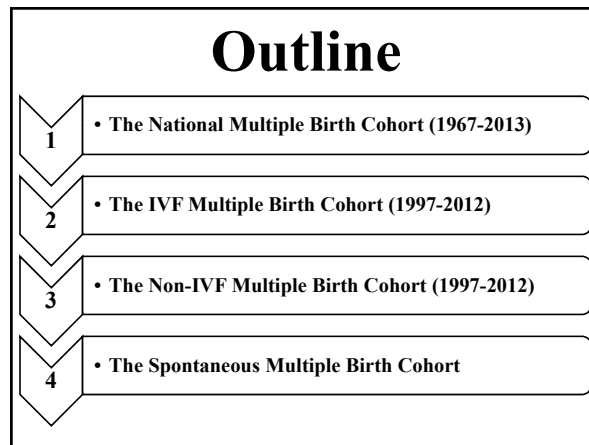
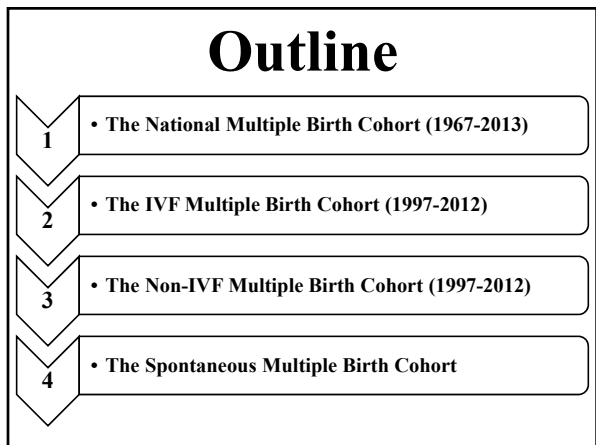
**I. Annual NCHS Natality Reports*
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* National Center for Health Statistics

** Assisted Reproductive Technology

The screenshot shows the CDC website page for Assisted Reproductive Technology (ART). The page includes a navigation menu with letters A-Z, a search bar, and a main heading "Assisted Reproductive Technology (ART)". Below the heading, there are sections for "ART Reports and Resources" and "ART Success Rates". The "ART Reports and Resources" section lists various reports such as "ART 2010 Fertility Clinic Success Rates Report", "ART 2009 Report", and "ART 2008 Report". The "ART Success Rates" section provides information about the data and how to use it. There are also links to "More Related Links" and "Publications".



Conclusions: Four Decades of Multiples

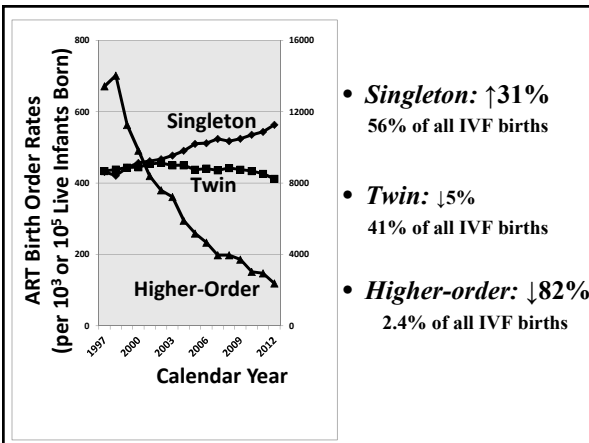
1. The dimensions of the multiple births epidemic remain substantial
2. The directionality of the epidemic suggests that it **may** be cresting:
 - Twin birth rate growth may be slowing down
 - Higher-order birth rate has clearly been receding

Outline

- 1 • The National Multiple Birth Cohort (1967-2013)
- 2 • The IVF Multiple Birth Cohort (1997-2012)
- 3 • The Non-IVF Multiple Birth Cohort (1997-2012)
- 4 • The Spontaneous Multiple Birth Cohort

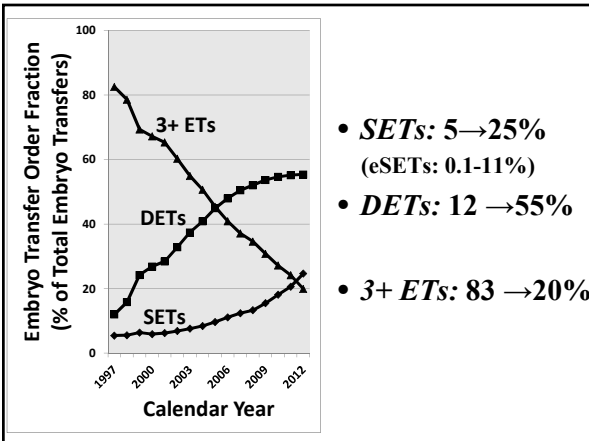
IVF Birth Rate Trends

1997-2012



Embryo Transfer Trends

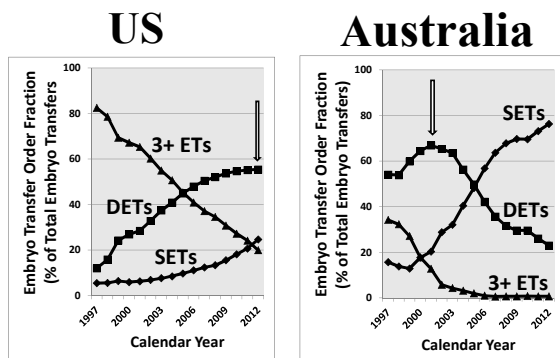
1997-2012



Future of SETs in the US?

Other National Models?

Embryo Transfer Trends



How did they do it?

What Was the Australian Solution?

- **Commitment to SET**
- **“Dream” ART Benefits**

- 80% of all outpatient IVF costs covered subject to a deductible and a cap
- Unlimited number of ART cycles covered
- Eligibility independent of:
 - Parental age
 - Number of previous attempts
 - Existing children

Underwriting
+
Commitment to SET
=
Plurality Risk Reduction

America is not Australia

Underwriting of Infertility Tx in US

- Limited (under- or uninsured)
- Exclusively private (non-governmental)
- Largely self-funded (out-of-pocket)
- Partially State-mandated (15 of 50 States)
- At times employer-sponsored

Dismal
Socially Unjust

Elective single embryo transfer: A 6-year progressive implementation of 784 single blastocyst transfers and the influence of payment method on patient choice

Robert J. Stillman, M.D.,^a Kevin S. Richter, Ph.D.,^a Nicole K. Banks, M.D.,^b and James R. Graham, M.S.^a

^aShady Grove Fertility Reproductive Science Center, Rockville, Maryland; and ^bDepartment of Obstetrics and Gynecology, Georgetown University, Washington, D.C.

Objective: To evaluate efforts to reduce twin pregnancies through progressive implementation of elective single embryo transfer (eSET) among select patients over a 6-year period.

Design: Retrospective review.

Setting: Private practice IVF center.

Patient(s): Infertile women undergoing 15,418 consecutive IVF-ET cycles.

Intervention(s): IVF-ET, including blastocyst-stage eSET among select patients with good prognosis and high risk of multiple pregnancy.

Main Outcome Measure(s): Pregnancy, multiple pregnancy, method of payment.

Result(s): Pregnancy rates were similar for autologous eSET versus double-blastocyst transfer (65% vs. 63%), while twin rates were much lower (1% vs. 44%). For recipients of donor oocytes, pregnancy rates were slightly lower with eSET (63% vs. 74%), while twin rates were much lower (2% vs. 54%). There was no decrease in overall pregnancy rates, despite a dramatic rise in eSET use over time (1.5% to 8.6% of all autologous transfers and 2.0% to 22.5% of all transfers to donor oocyte recipients between 2002 and 2007). Overall singleton pregnancy rates increased, while twin pregnancy rates declined significantly over time. Use of eSET was significantly more common among patients with insurance coverage or who were participating in our Shared Risk money-back guarantee program.

Conclusion(s): Selective eSET use among good-prognosis patients can significantly reduce twin pregnancies without compromising pregnancy rates. Patients are more likely to choose eSET when freed from financial pressures to transfer multiple embryos. (Fertil Steril® 2009;92:1895-906. ©2009 by American Society for Reproductive Medicine.)

The American Solution?
(Cost-Independent)

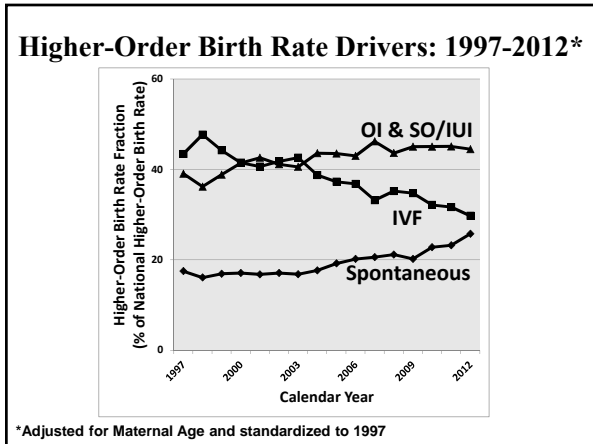
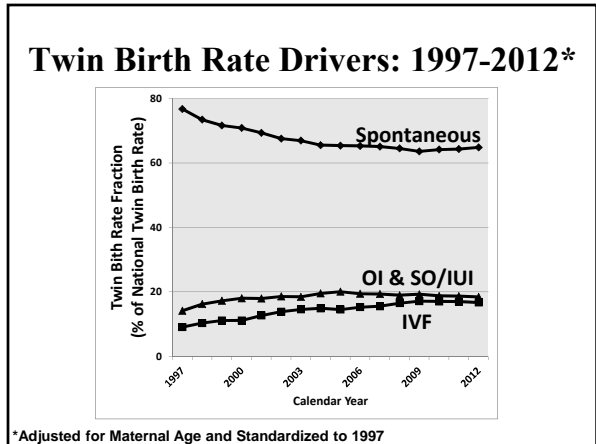
- Optimizing embryo selection & implantation
- Increasing confidence in & acceptance of SET
- “Carrots and Sticks” by commercial payers
- Increased oversight by SART
- Education, education-it got us this far!

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- ## If Not IVF Than Who?
- Ovulation Induction (OI)
 - Ovarian Stimulation/IUI (OS)

- ## OI/OS
- Are not as “controlled” as IVF
 - Are offered consecutively ≥ 6 times
 - Are offered by generalists & REIs alike
 - Are linked to significant birth plurality



Outline

1

- The National Multiple Birth Cohort (1967-2013)

2

- The IVF Multiple Birth Cohort (1997-2012)

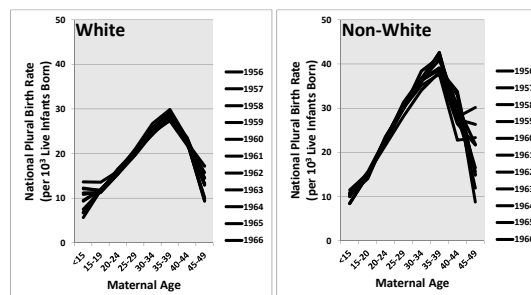
3

- The Non-IVF Multiple Birth Cohort (1997-2012)

4

- The Spontaneous Multiple Birth Cohort

Spontaneous Birth Plurality Effect of Maternal Age & Race



Spontaneous Births Plurality is a Function of Maternal Age and Race

The Future?

An “IVF-Dominant” Future?

- A more direct path to IVF absent SO/IUI
- SO/IUI for those who cannot afford IVF
- Ovulation Induction for anovulation

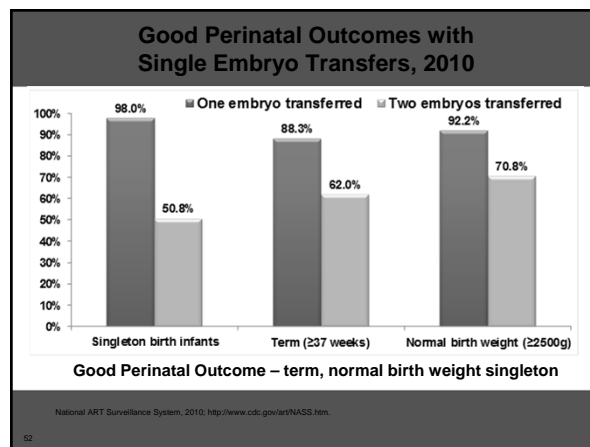
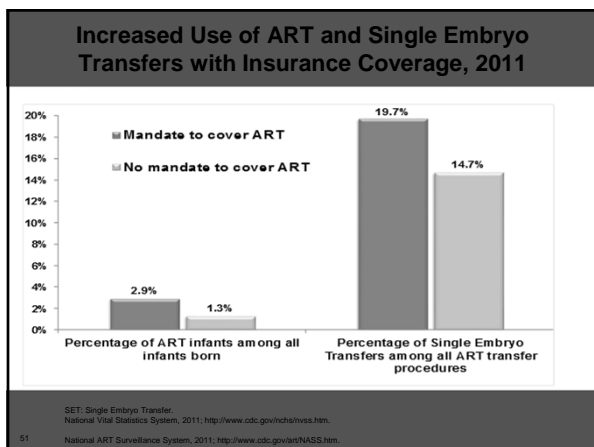
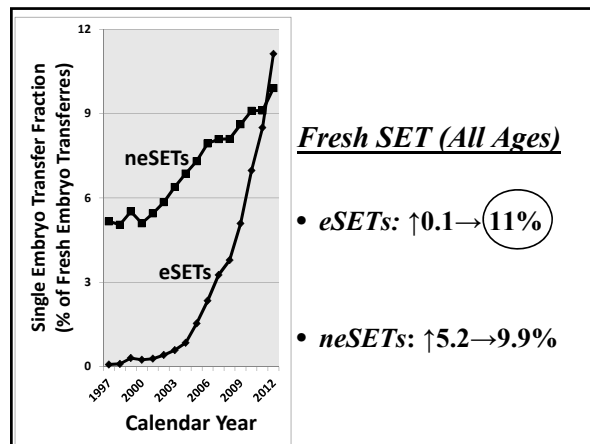
Current Payer Policies: Massachusetts

- **BCBS**: Allows a direct path to IVF absent SO/ IUI
- **HPHC**: Requires TWO cycles of SO/IUI prior to IVF
- **Tufts**: Allows a direct path to IVF or a MAXIMUM of TWO cycles of SO/IUI prior to IVF
- **Fallon**: Requires TWO cycles of SO/IUI prior to IVF

“Sufficient unto the day is one baby. As long as you are in your right mind don’t you ever pray for twins. Twins amount to a permanent riot; and there ain’t any real difference between triplets and an insurrection.”

Mark Twain, The Baby Speech, 1879

The End



2013 ASRM Criteria

NUMBER OF EMBRYOS TO BE TRANSFERRED

Recommended limits on the numbers of embryos to transfer.

Prognosis	Age (y)			
	< 35	35-37	38-40	41-42
Cleavage-stage embryos ^a				
Favorable ^b	1-2	2	3	5
All others ^c	2	3	4	5
Blastocysts ^d				
Favorable ^b	1	2	2	3
All others ^c	2	2	3	3

^a See text for more complete explanations. Justification for transferring one additional embryo more than the recommended limit should be clearly documented in the patient's medical record.
^b Favorable = first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.
^c Practice Committee. Pharmacogenetic approach to male infertility. *Fertil Steril* 2013.

Prudent Practice Patterns (OS/IUI)

Multiple gestation associated with infertility therapy: an American Society for Reproductive Medicine Practice Committee opinion

Practice Committee of the American Society for Reproductive Medicine
 American Society for Reproductive Medicine, Birmingham, Alabama

Fertil Steril 97:825-34, 2012

Prudent Practice Patterns (OS/IUI)

- Limiting the use of high-dose (≥ 150 IU) gonadotropin regimens whenever possible in favor of alternatives.
- Encouraging the use of low-dose (≤ 75 IU) gonadotropin, clomiphene, or off label letrozole regimens which outperform high-dose (≥ 150 IU) gonadotropins in the birth plurality category while maintaining comparable per cycle pregnancy rates.

Estimating the Contribution of OI/OS

$$\text{Total}_{\text{Twins}} - \text{ART}_{\text{Twins}} - \text{Spontaneous}_{\text{Twins}} = 0$$

Or

$$\text{Total}_{\text{Twins}} - \text{ART}_{\text{Twins}} - \text{Spontaneous}_{\text{Twins}} \neq 0$$

Ergo: An Unexplained Contributor

Future Underwriting of Infertility Tx

- National health insurance is unlikely to take hold in the US in our lifetime
- Even if it were, it is unlikely to underwrite infertility Tx given the pro-choice/pro-life divide
- At best, infertility Tx may be the subject of federal tax credits courtesy of *The Family Act* if enacted

WOMEN AND INFANTS' DIVISION OF REPRODUCTIVE MEDICINE AND INFERTILITY
PROVIDENCE, RHODE ISLAND

A comparison of clinic success rates may not be meaningful because patient medical characteristics and treatment approaches vary from clinic to clinic. For more details about this, along with information on how to interpret the statistics in this table, see Introduction to Fertility Clinic Success Rates.

2010 ART CYCLE PROFILE			
Type of ART*	100%	Procedural Factors	
IVF	0%	With ICSI	59%
ZIFT	0%	Unstimulated	2%
Combination	0%	Used gestational carrier	11%
		Used PGD	6%
		With eSET	2%

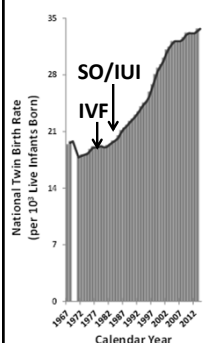
2010 PREGNANCY SUCCESS RATES		Data Verified by Bhagavath Balesubramanian, MD			
Type of Cycle	Age of Women	Type of Cycle			
		<35	35-37	38-40	41-42 43-44*
Fresh Embryos From Nondonor Eggs					
Number of cycles		216	119	115	78
Percentage of embryos transferred resulting in implantation*		29.9	17.4	10.3	10.1
Percentage of cycles resulting in pregnancies*		46.8	30.3	25.2	21.8
Percentage of cycles resulting in live births**		31.2	26.1	17.4	12.6
(Confidence Interval)		(34.6-48.1)	(18.4-34.9)	(11.0-25.6)	(6.3-22.3)
Percentage of retrievals resulting in live births**		12.4	25.5	19.8	14.5
Percentage of transfers resulting in live births**		44.3	29.5	20.8	18.4
Percentage of transfers resulting in singleton live births*		32.8	23.8	15.6	11.5
Percentage of cancellations*		2.8	1.7	12.2	11.5
Average number of embryos transferred		2.1	2.4	2.8	3.2
Percentage of pregnancies with twins*		27.7	25.0	17.2	2/17
Average number of pregnancies with triplets or more*		0.0	0.0	0.0	2/17
Percentage of live births having multiple infants**		25.8	19.4	25.0	5/10
Freeze Embryos From Nondonor Eggs					
Number of transfers		46	31	15	5
Percentage of transfers resulting in live births**		22.9	22.6	3/13	0/3
Average number of embryos transferred		1.9	1.9	2.3	2.3
		All Ages Combined*			

Impact of Monozygotic Twinning*

- SETs account for 0.5% of IVF twins
- DETs account for 29% of IVF triplets
- DETs + TETs account for 65% of IVF quadruplets

*Gee et al. Am J Obstet Gynecol 210:468e1-6, 2014

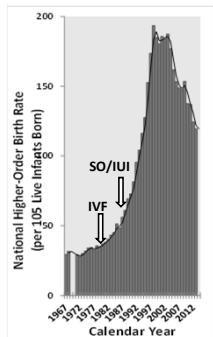
National Twin Birth Rates: 1967-2013



- A 1.7-fold overall increase
- A mean growth rate of 2% per year
- Two temporary plateaus
- Resumption of growth in 2013 (1.8%)
- Yet to be realized reversal of course

National Higher-Order Birth Rates: 1967-2013

- A 6.7-fold increase to a 1998 high
- A 38% decrease from 1998-2013
- A residual 4.1-fold excess in 2013
- A trend moving in the right direction



The Patient Outlook on SET

- Given the high upfront cost, my preference is to transfer two embryos to maximize the likelihood of conception.
- I am not concerned about the risks associated with a plural birth. "I can handle it."
 - Variable appreciation of the risks involved
 - Youthful invincibility
 - Abandon

Conclusions

IVF does not fully account for the iatrogenically derived multiple infants

<p>Since 1997, IVF was not the leading contributor of <i>Twin Infants</i></p>	<p>Since 2004, IVF was not the leading contributor of <i>Higher-Order infants</i></p>
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