

# CDC PUBLIC HEALTH GRAND ROUNDS

## Time for Public Health Action on Infertility



**August 19, 2014**



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

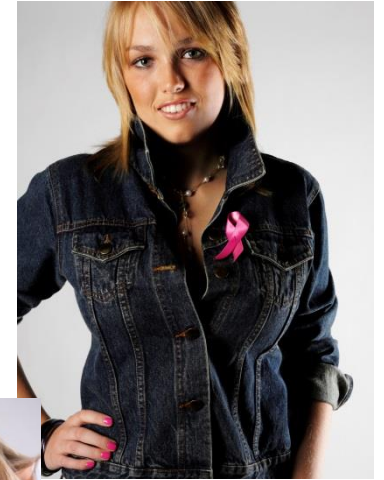
# Infertility and the National Public Health Action Plan



## Lee Warner, PhD, MPH

*Associate Director for Science, Division of Reproductive Health*  
National Center for Chronic Disease Prevention and Health Promotion

# Infertility Can Affect Anyone



# Infertility is a Disease

- ❑ **Infertility is more than a quality-of-life issue**
  
- ❑ **Infertility is considered a disease of the reproductive system according to**
  - World Health Organization (WHO) in 2009
  
  - American Society for Reproductive Medicine (ASRM) in 2013

# Reproduction is a Major Life Activity

## SUPREME COURT OF THE UNITED STATES

Syllabus

BRAGDON *v.* ABBOTT ET AL.

CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR  
THE FIRST CIRCUIT

No. 97–156. Argued March 30, 1998—Decided June 25, 1998



(c) The life activity upon which respondent relies, her ability to reproduce and to bear children, constitutes a “major life activity” under the ADA. The plain meaning of the word “major” denotes comparative importance and suggests that the touchstone is an activity’s significance. Reproduction and the sexual dynamics surrounding it are central to the life process itself. Petitioner’s claim that Congress

# Infertility is a Public Health Concern

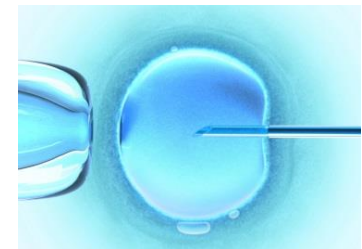
- ❑ **Disparities in access to care and treatment**
- ❑ **More infants born from use of infertility treatments**
  - ~ 6% infants from ovarian stimulation treatments
  - 1.5% infants from assisted reproductive technologies (ART)
- ❑ **Long-term outcomes of treatment are unknown**



Intrauterine insemination



Ovulation medications



In vitro fertilization

# Infertility is a Marker of Past, Present, and Future Health

Original Article

## Increased Risk of High-Grade Prostate Cancer Among Infertile Men

Thomas J. Walsh, MD, MS<sup>1,2</sup>; Michael Schembri, BS<sup>3</sup>; Paul J. Turek, MD<sup>4</sup>; June M. Chan, ScD<sup>2,5</sup>; Peter R. Carroll, MD, MPH<sup>2,6</sup>; James F. Smith, MD, MS<sup>2</sup>; Michael L. Eisenberg, MD<sup>2</sup>; Stephen K. Van Den Eeden, PhD<sup>7</sup>; and Mary S. Croughan, PhD<sup>3,5</sup>

## Semen quality, infertility and mortality in the USA

**Michael L. Eisenberg<sup>1,2,\*</sup>, Shufeng Li<sup>3</sup>, Barry Behr<sup>2</sup>, Mark R. Cullen<sup>4</sup>, Deron Galusha<sup>5</sup>, Dolores J. Lamb<sup>6</sup>, and Larry I. Lipshultz<sup>6</sup>**

<sup>1</sup>Department of Urology, Stanford University School of Medicine, Stanford, CA, USA <sup>2</sup>Department of Obstetrics/Gynecology, Stanford University School of Medicine, Stanford, CA, USA <sup>3</sup>Departments of Urology and Dermatology, Stanford University School of Medicine, Stanford, CA, USA <sup>4</sup>Department of Internal Medicine, Stanford University School of Medicine, Stanford, CA, USA <sup>5</sup>Yale Occupational and Environmental Medicine Program, Yale University School of Medicine, New Haven, CT, USA <sup>6</sup>Scott Department of Urology and the Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA

## Significant medical pathology uncovered by a comprehensive male infertility evaluation

Honig SC<sup>1</sup>, Lipshultz LI, Jarow J.

# Many Factors Contributing to Infertility Can Be Prevented

## Infectious Diseases



## Environmental and Workplace Exposures



## Genetic and Physical Abnormalities



- ❑ **Sexually transmitted infections can lead to pelvic inflammatory disease (PID) and tubal factor infertility (TFI)**
  - TFI accounts for 10%–40% of infertility
  - About 30% of PID is associated with gonorrhea and chlamydia
  
- ❑ **Environmental and workplace exposures can affect sperm quality and disrupt menstrual function**



# Many Factors Contributing to Infertility Can be Prevented



**Chronic  
Conditions  
and  
Diseases**



**Medication  
-induced**



**Behavioral factors**

- ❑ **Certain medications (e.g., chemotherapy) can result in infertility**
  - Fertility preservation methods should be considered
  
- ❑ **Modifiable lifestyle factors are potential causes of infertility**
  - Obesity
  - Smoking

# Hurdles in Defining Infertility

- ❑ **Varying case definitions used across settings and populations**
  - Reproductive outcome (e.g., absence of pregnancy or live birth)
  - Length of time without conception (e.g., 1, 2, or 5 years)
  - Type of infertility (e.g., primary or secondary)
  
- ❑ **Clinical definitions**
  - *Infertility* — Inability to conceive after 12 months of trying
  - *Impaired fecundity* — Difficulty getting pregnant or carrying a pregnancy to a live birth

# Infertility Affects Both Women and Men

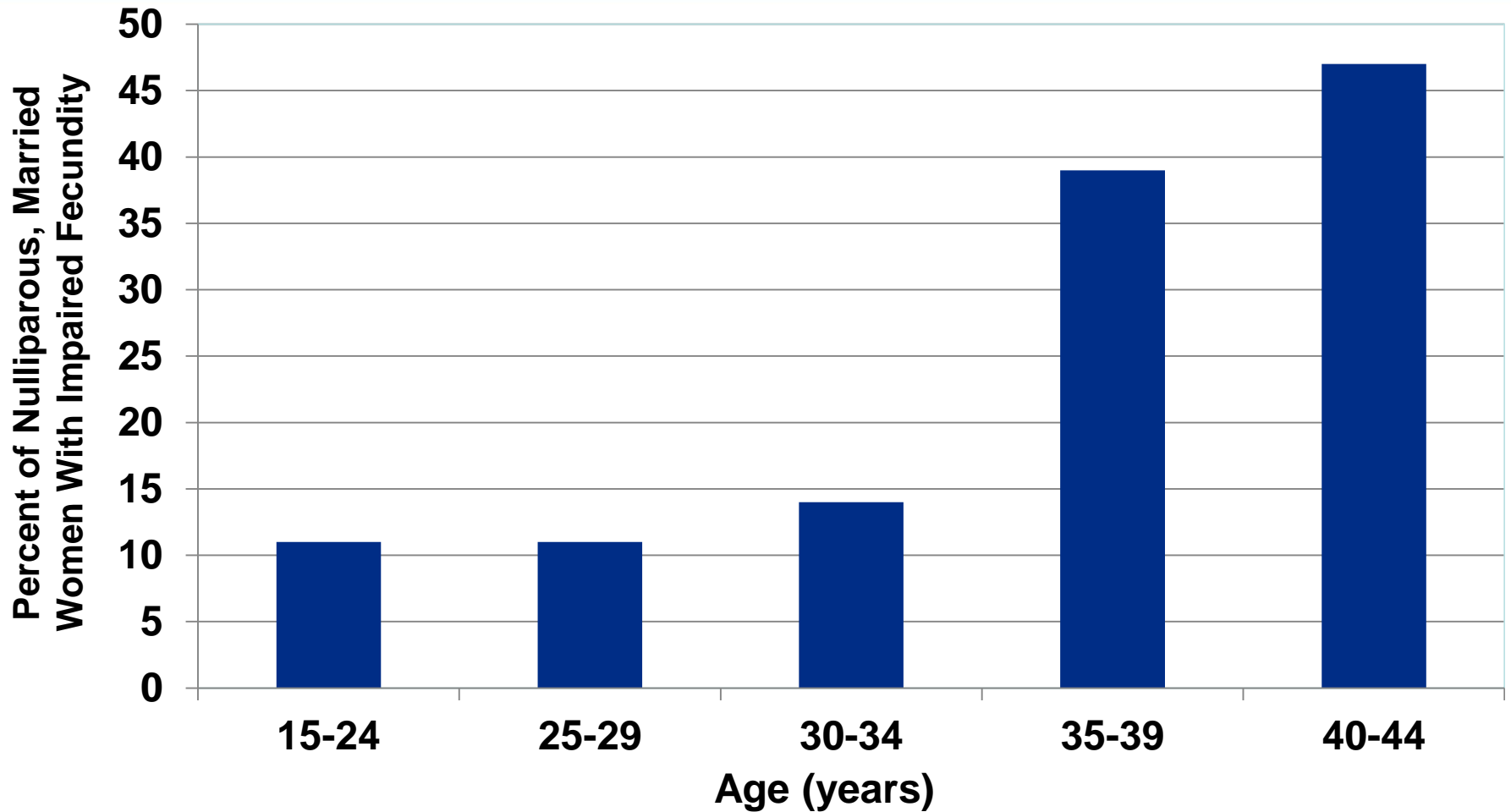
## ❑ Couple-based impairment affecting males and females

- Female 33%
- Male 20%
- Mixed 39%
- Unexplained 8%

## ❑ U.S. National Survey of Family Growth, 2006–2010

- Women (married)
  - Infertility 6%
  - Impaired fecundity 12%
- Men
  - Infertility 9%

# Impaired Fecundity Increases with Age



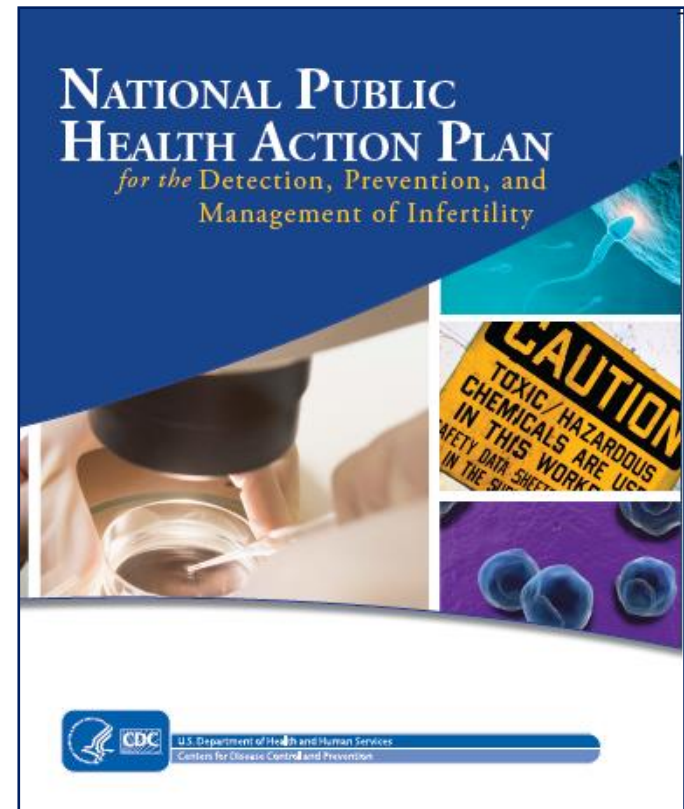
# White Paper and National Action Plan for Detection, Prevention and Management of Infertility

## A public health focus on infertility prevention, detection, and management

*Maurizio Macaluso, M.D., Dr.P.H.,<sup>a</sup> Tracie J. Wright-Schnapp, M.P.H.,<sup>a</sup> Anjani Chandra, Ph.D.,<sup>b</sup> Robert Johnson, M.D., M.P.H.,<sup>c</sup> Catherine L. Satterwhite, M.S.P.H., M.P.H.,<sup>c</sup> Amy Pulver, M.A., M.B.A.,<sup>c</sup> Stuart M. Berman, M.D., Sc.M.,<sup>c</sup> Richard Y. Wang, D.O.,<sup>d</sup> Sherry L. Farr, M.S.P.H., Ph.D.,<sup>a</sup> and Lori A. Pollack, M.D., M.P.H.<sup>f</sup>*

<sup>a</sup> Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>b</sup> Division of Vital Statistics, National Center for Health Statistics, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>c</sup> Division of Sexually Transmitted Disease Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and Tuberculosis Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; <sup>d</sup> Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia; and <sup>f</sup> Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Published July 2014



Macaluso, *Fertil Steril* 2010.

Centers for Disease Control and Prevention. National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, July 2014.

Available at <http://www.cdc.gov/reproductivehealth/Infertility/PublicHealth.htm>

# Improving the Outcome of Infertility Therapy A Clinical Perspective



**Eli Y. Adashi, MD, MS, CPE, FACOG**

*Professor of Medical Science*

The Warren Alpert Medical School

Division of Biology and Medicine

Brown University



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# Goal of Infertility Therapy

The BESST Outcome is a...

**B**irth **E**mphasizing a  
**S**uccessful  
**S**ingleton at **T**erm

# Services Ever Used by Infertile U.S. Women

| Category      | Service                  | Respondents (%) |
|---------------|--------------------------|-----------------|
| Pre-Treatment | Advice                   | 29              |
|               | Infertility Testing      | 27              |
| Non-ART       | Ovulation-Inducing Drugs | 20              |
|               | Artificial Insemination  | 7               |
|               | Surgery                  | 3.4             |
| ART           | IVF                      | 3.1             |

ART: Assisted Reproductive Technology

IVF: In vitro fertilization

Infertility Service Use in the United States: National Health Statistics Report; no 73, 2014.



# Controlled Ovarian Stimulation with Timed Intrauterine Insemination (IUI)

- ❑ Available in the U.S. since 1987
- ❑ Indicated for women diagnosed with Unexplained Ovulatory Subfertility

## Stimulation

Gonadotropins  
Clomiphene  
Letrozole

## Ovulation

hCG

## Timed IUI (within 48 hours)

IUI

# The Process of In Vitro Fertilization (IVF)

- ❑ Available at approximately 500 clinical sites
- ❑ Indicated for
  - Anatomic Pathology
  - Male Factor
  - Age-related Infertility
  - Unexplained Ovulatory Subfertility

Stimulation

Gonadotropins

Ovulation

hCG

Retrieval

Oocytes

Fertilization

IVF

Transfer

Embryo  
Transfer

# A Brief History of IVF

- ❑ **Actualized in the UK in 1978**
- ❑ **Introduced into the US in 1981**
- ❑ **Over 5 million babies born worldwide as a result of IVF**

Louise Brown, the world's first "test tube baby" with her mother Lesley.  
Photo taken 9 October, 1978.



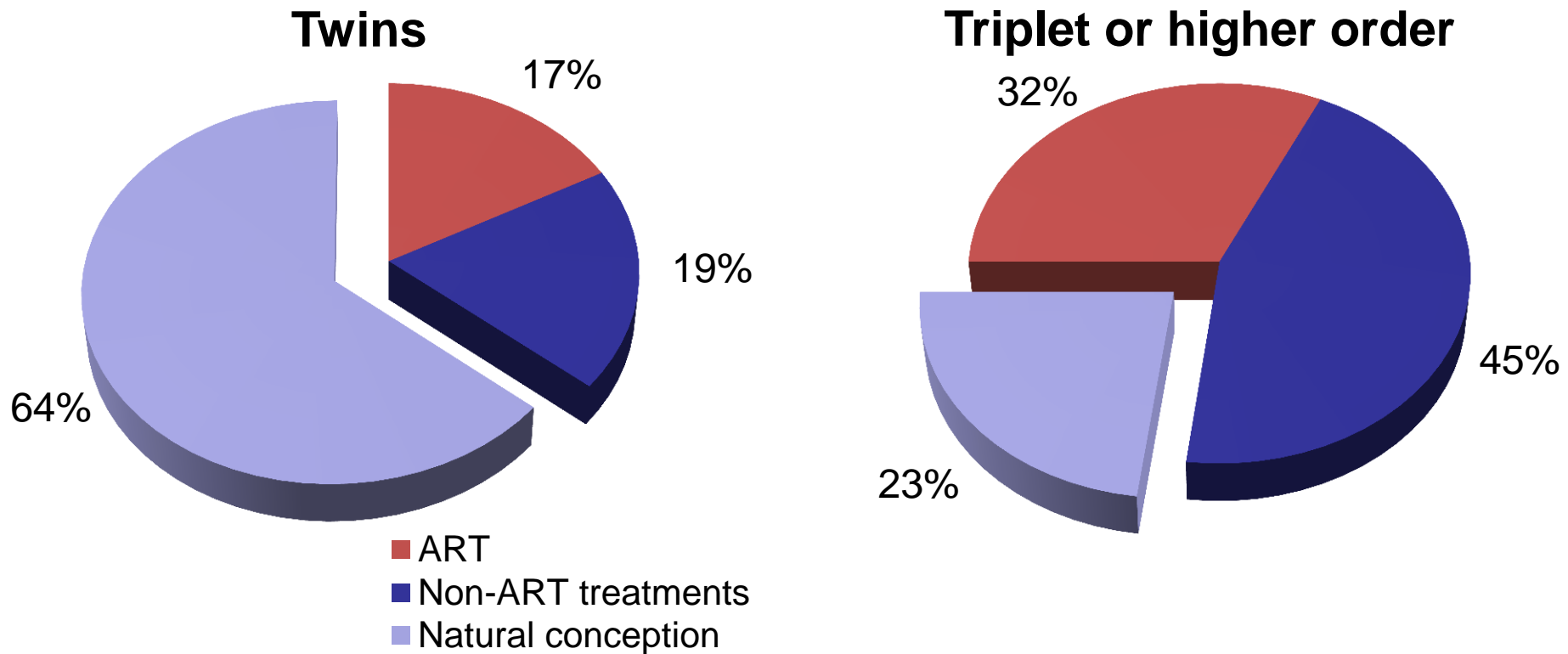
# The 2010 Nobel Prize In Physiology or Medicine



Professor Robert Edwards at his desk at Bourn Hall Clinic, England.  
Photo taken in 1989. Nobel Prize “for the development of *in vitro* fertilization”

# Downsides of ART and Non-ART Technologies

**Both treatments increase the incidence of multiple births, thereby increasing maternal morbidity and mortality**



# The Maternal Burden of Plurality

## Incidence (%) of major maternal complications in pregnancy

| Complication                 | Singleton | Twin  | Triplet | Quadruplet |
|------------------------------|-----------|-------|---------|------------|
| <b>Preeclampsia</b>          | 6         | 10-12 | 25-60   | >60        |
| <b>Gestational diabetes</b>  | 3         | 5-8   | 7       | >10        |
| <b>Preterm birth</b>         | 15        | 40    | 75      | >95        |
| <b>Delivery &lt;37 weeks</b> | 10        | 50    | 92      | >95        |
| <b>Delivery &lt;32 weeks</b> | 2         | 8     | 26      | >95        |

# The Fetal and Neonatal Burden of Plurality

| Outcome                         | Singleton  | Twin       | Triplet     |
|---------------------------------|------------|------------|-------------|
| Average Gestational Age (weeks) | 39.1       | 35.3       | 32.2        |
| Average Birth Weight (gm)       | 3,358      | 2,347      | 1,687       |
| Average Birth Weight            | 7 lbs 8 oz | 5 lbs 4 oz | 3 lbs 12 oz |
| Fetal Death (%)                 | .03        | .09        | .14         |
| Neonatal Death (%)              | .35        | 1.9        | 4.9         |

# Improving Controlled Ovarian Stimulation: Recommended Prudent Practice Patterns

## □ American Society for Reproductive Medicine (ASRM)

### recommendations

- Use of low-dose gonadotropin regimens
- Use of Clomiphene
- Use of Letrozole (Off-label)
  - Reduced birth plurality rates
  - Comparable per cycle pregnancy rates



# Moving Towards Single Embryo Transfers

- ❑ **Improvements in Embryo Selection**
- ❑ **Pre-implantation Genetic Screening (PGS)**
  - Normal chromosomes or euploidy
  - Considered invasive
- ❑ **Embryonic division analysis or morphokinetics**
  - Assessing embryonic cellular fission
  - Considered non-invasive

# The Future?

# An “IVF-Dominant” Future?

- ❑ **A more direct path (“fast track”) to IVF**
  - Without antecedent controlled ovarian stimulation
  - With a focus on Single Embryo Transfers
  
- ❑ **Limited Use of Controlled Ovarian Stimulation**
  
- ❑ **Indicated Ovulation Induction**

# What the “BESST” Future Should Look Like

- ❑ **Infertility treatments resulting in fewer higher order (twins or greater) births**
- ❑ **Mothers receiving treatments face fewer medical risks**
- ❑ **Neonates and infants born to mothers receiving recommended procedures also have a better prognosis**
- ❑ **Alignment of the goals of clinical medicine with the goals of public health**

# Infertility from Both Male and Female Patients' Perspective



**Barbara Collura**

*President/CEO*

RESOLVE: The National Infertility Association



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Centers for Disease  
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# The Profound Impact of the Diagnosis of Infertility

**“For years I struggled with infertility. The physical and emotional toll of infertility, the monthly hope then heartbreak, the appointments with doctors and specialists, the shame and sadness, impacted our lives in ways big and small.**

**I lost count of how many times I cried and prayed, beseeching God to ‘fix’ me so that Nate and I could be parents.**

**For months, I felt broken and alone.”**



# The Profound Impact of the Diagnosis of Infertility



**“I was feeling sad, and hopeless and the 3 ½ years of trying, miscarriages and IVF had really taken its toll. I had even told my husband that I was ready to stop trying all together.**

**Infertility is so lonely and isolating.”**



# Providing Support through the Journey

## ❑ RESOLVE Support Groups

- Each month, 194 peer-led support groups in 42 states

## ❑ Blogs and Social Media

- 3,100 blogs on infertility, adoption, and pregnancy loss
- People use social media to connect and get support

## ❑ Meeting the growing needs of the infertility community

- 25<sup>th</sup> Anniversary of National Infertility Awareness Week
  - April 20-26, 2014
- Walks of Hope increase awareness within communities



# Public Awareness About Infertility

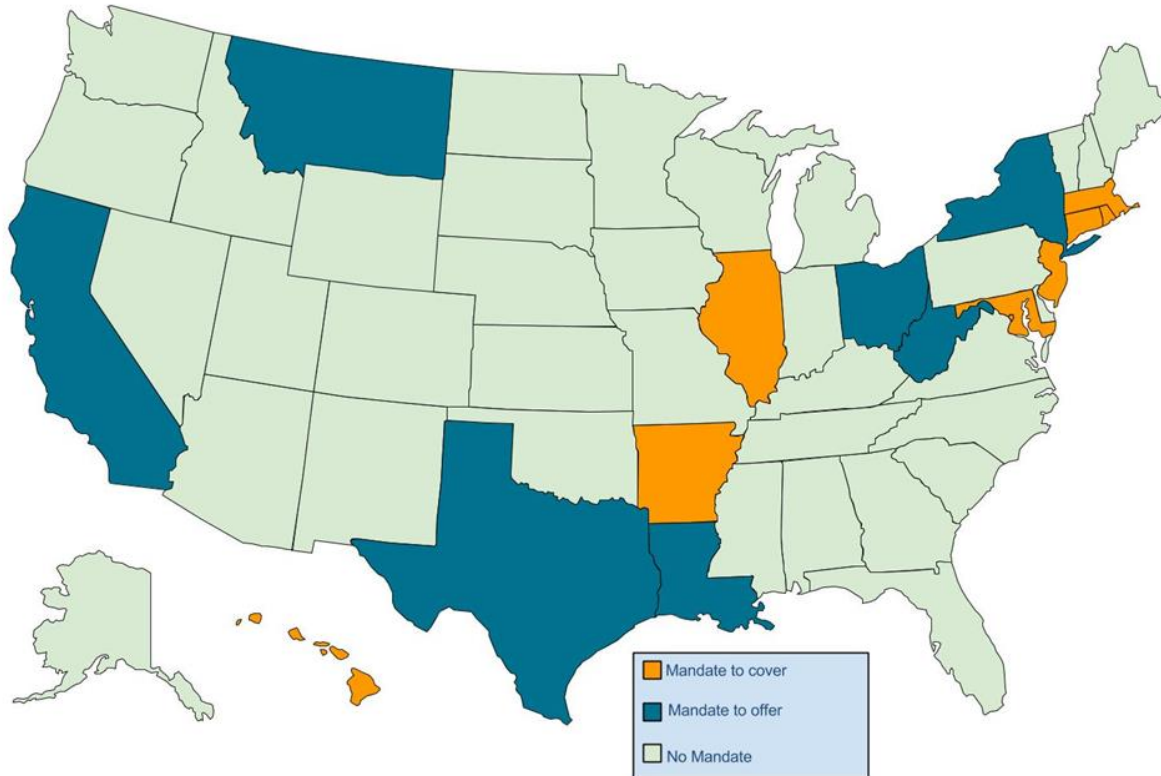


# Infertility Treatment and Insurance Coverage

- ❑ **Infertility is a disease, diagnosed by a physician**
- ❑ **Most insurance plans, including Medicare and Medicaid, do not offer coverage, especially for IVF**
  - Pre-requisites vary from plan to plan
- ❑ **Affordable Care Act may not expand coverage for infertility care**

# Insurance Coverage at the State Level

Pre-requisites vary from state to state



❑ **Only 8 states have an IVF insurance mandate**

➤ AR, CT, HI, IL, MA, MD, NJ, RI

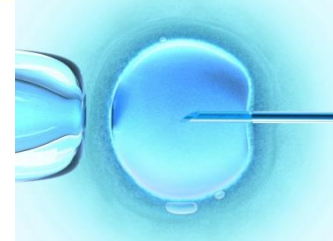
❑ **Another 7 states mandate coverage for some infertility treatment but do not cover IVF**

➤ CA, LA, MT, NY, OH, TX, WV

# Impact of Lack of Insurance Coverage on Decision-Making



**Non-ART: \$200-\$5,000**



**IVF: \$10,000-\$15,000**

- ❑ **Out-of-pocket costs can be substantial and impact patient decision-making and risk-taking**
  - Less effective treatments are pursued to lower costs
  - Precious time is wasted
  - Risks are ignored
  - Decisions not based on “best medical advice”
  - Maximize “return on investment”
  - Twins are perceived to be “less costly”

# Dealing with Infertility Shouldn't Have to Be a Life Crisis

- ❑ **Access to emotional support and a sense of community can be life-changing**
- ❑ **Patients who receive education and information have increased awareness and manage better**
- ❑ **The current state of insurance coverage for infertility treatment can create incentives that lead to poor outcomes for both individual patients and for public health**
  - Inequities in who gets care and who does not
  - Increased adverse health outcomes for mother and baby
- ❑ **The ASRM and SART standard of care should determine insurance coverage**

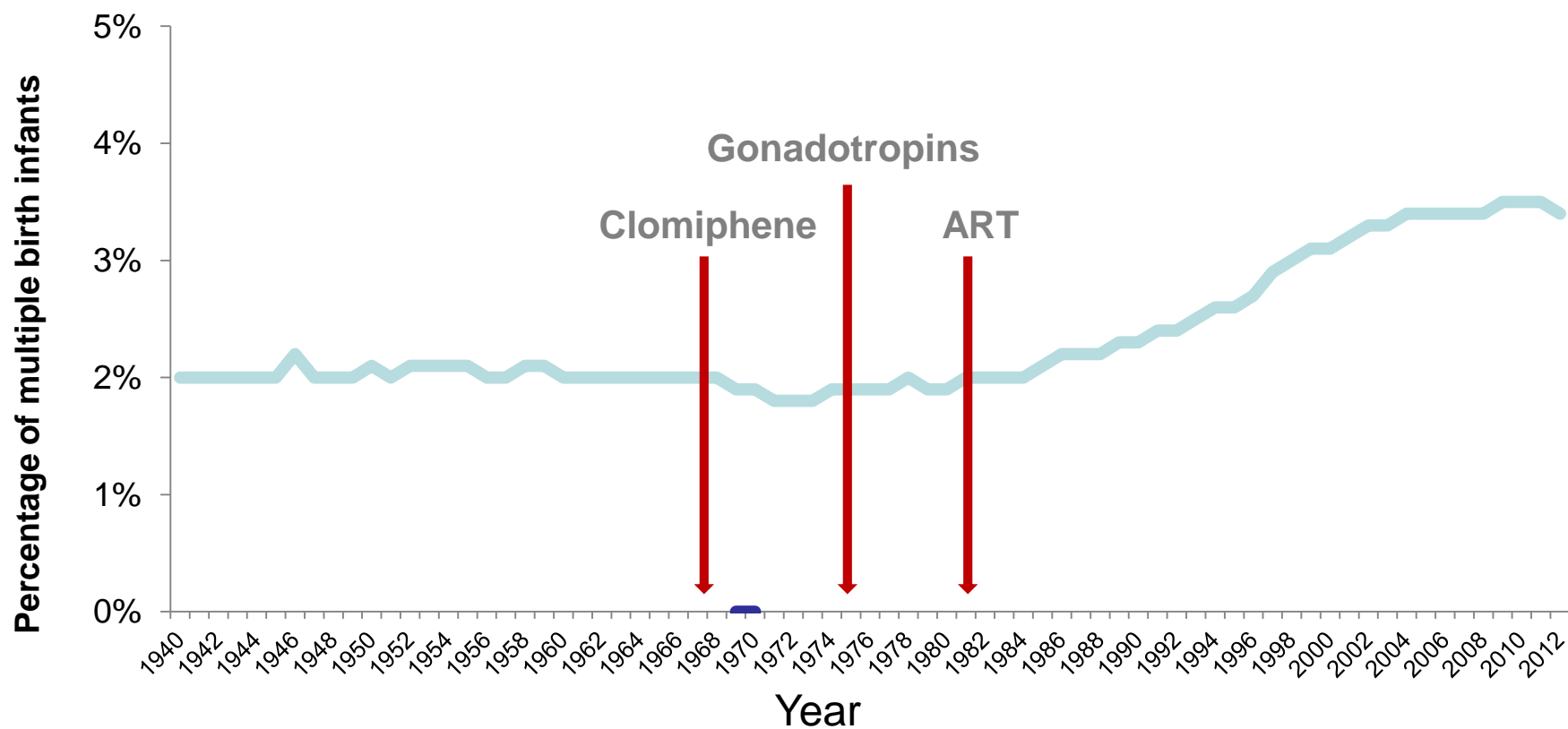
# Infertility Treatments from a Public Health Perspective



**Dmitry Kissin, MD, MPH**

*Team Lead, Assisted Reproductive Technology Surveillance  
and Research Team, Division of Reproductive Health  
National Center for Chronic Disease Prevention and Health Promotion*

# Multiple Birth Infants, United States, 1940-2012



# Public Health Surveillance for ART

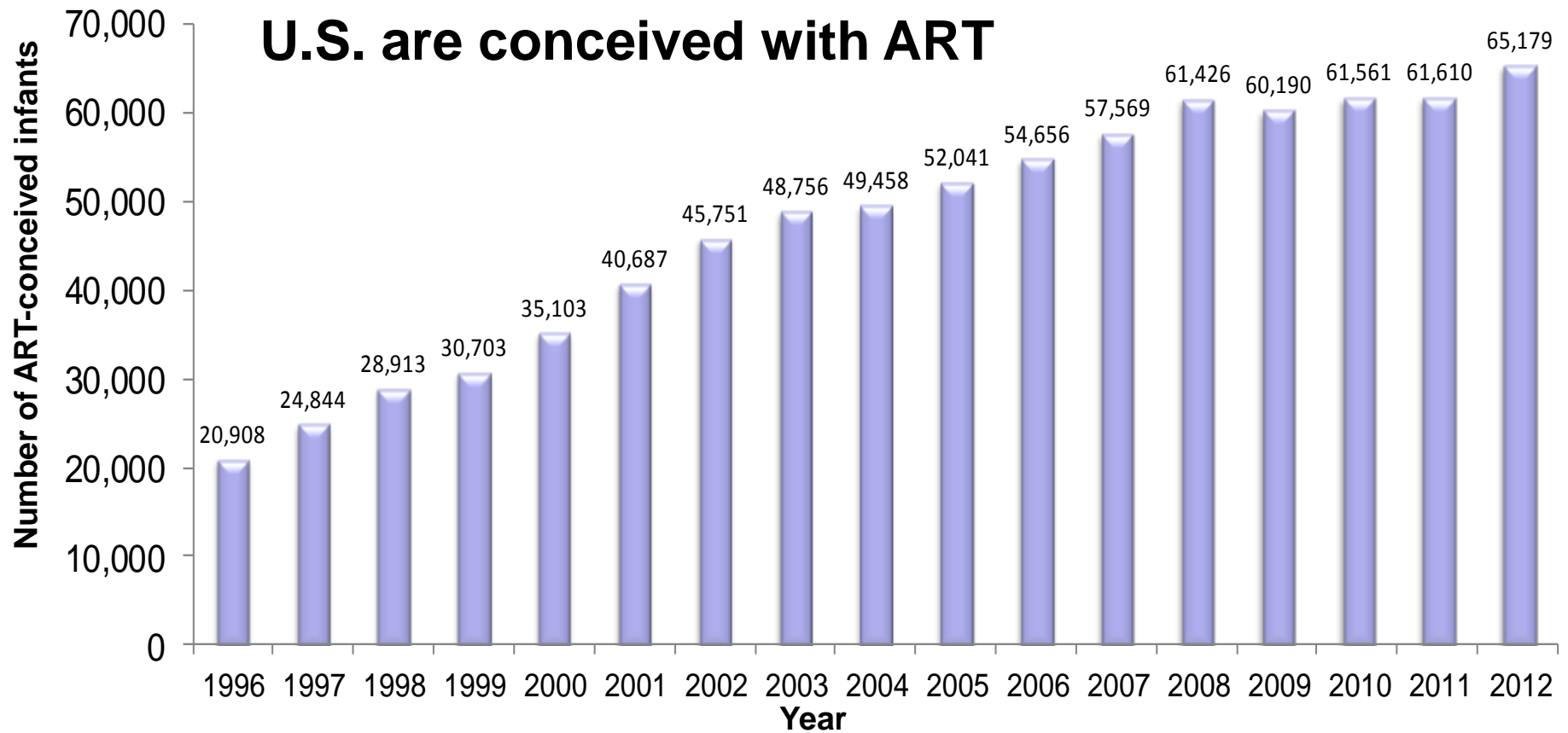


- ❑ **1981: First ART-conceived infant born in the United States**
- ❑ **1992: U.S. Congress passed the Fertility Clinic Success Rate and Certification Act**
- ❑ **1995: CDC initiated National ART Surveillance**
- ❑ **All ART cycles are reported; non-ART fertility treatments are not reportable**

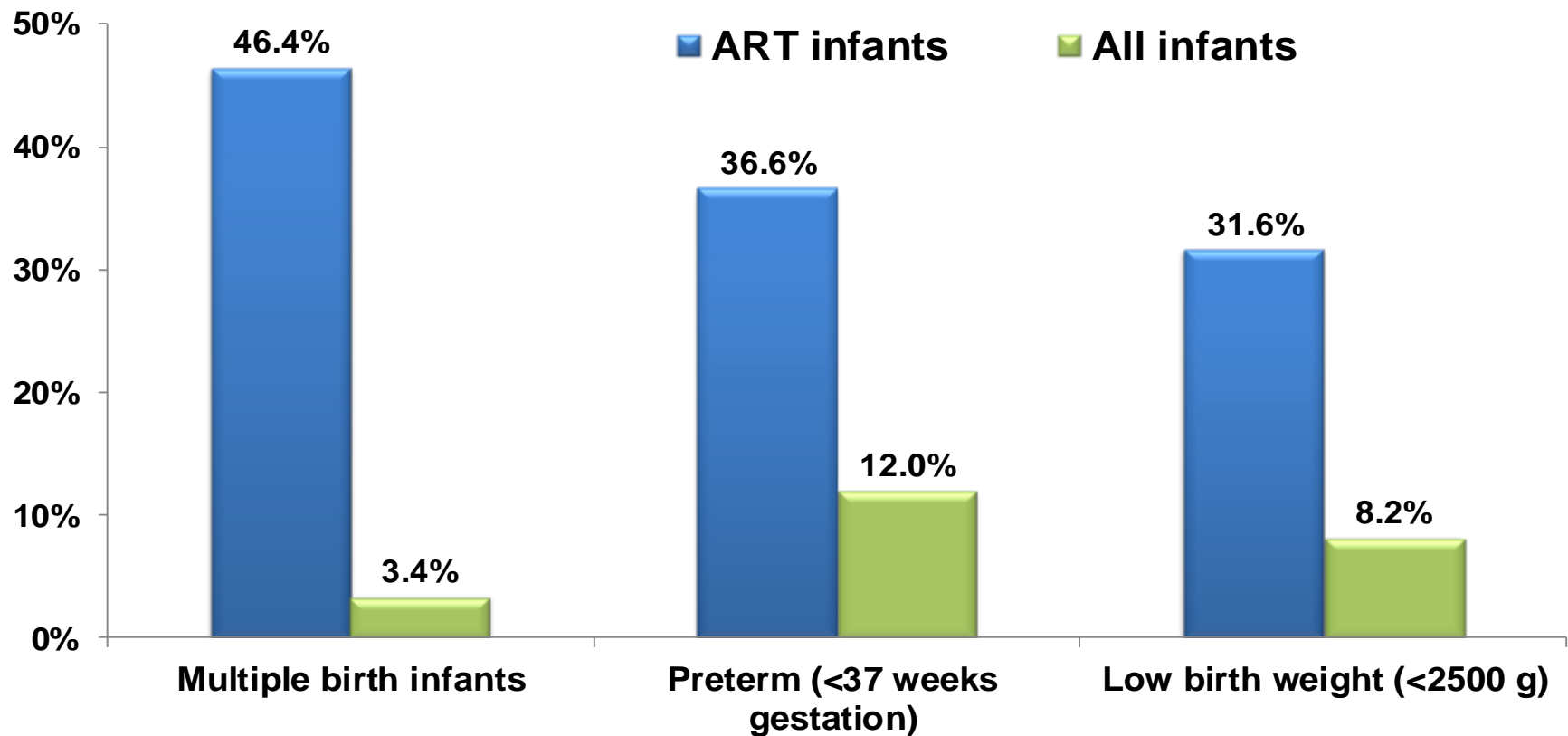


# ART-Conceived Infants, United States, 1996-2012

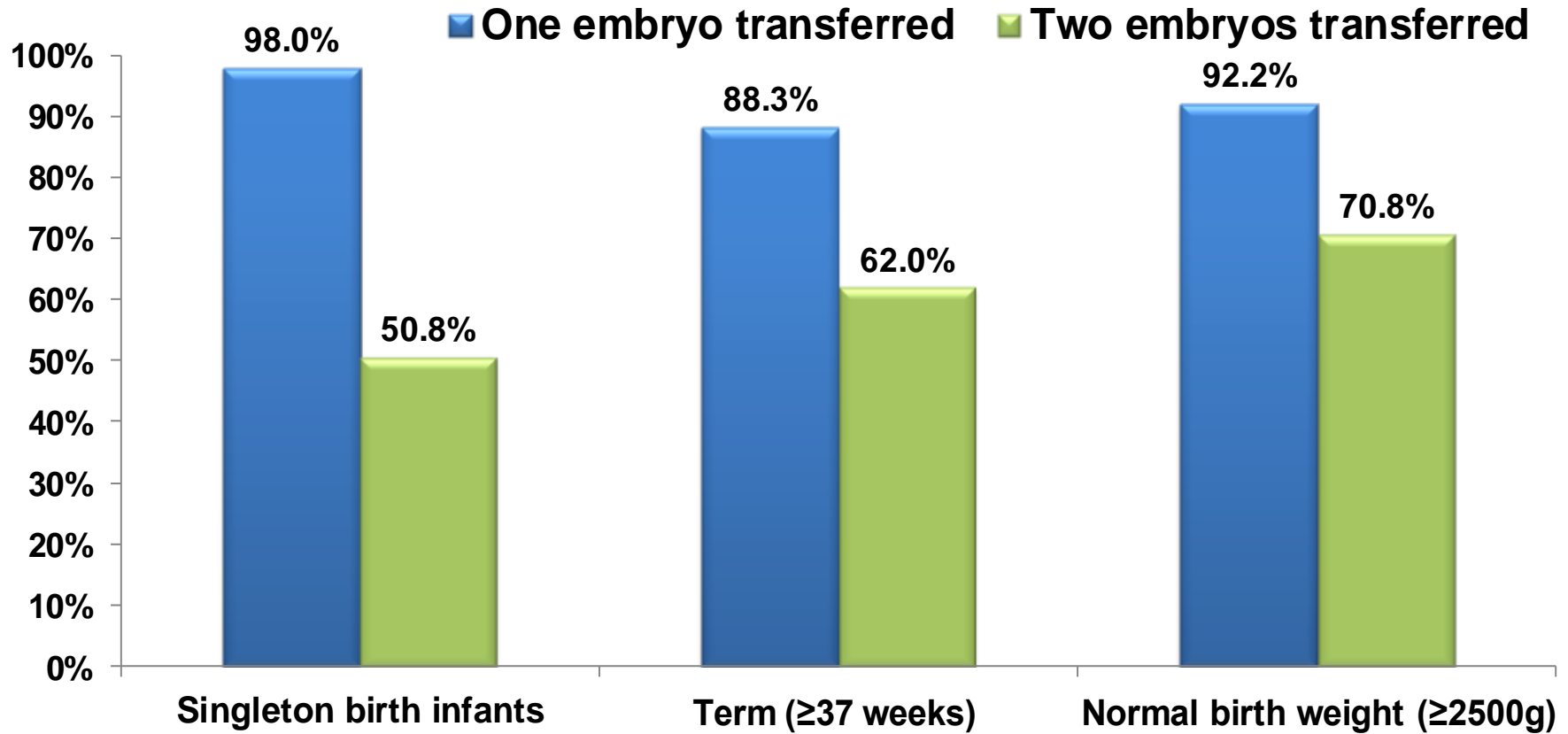
**1.5% of all infants born in the U.S. are conceived with ART**



# Poor Perinatal Outcomes Associated with ART-conceived Infants, 2010

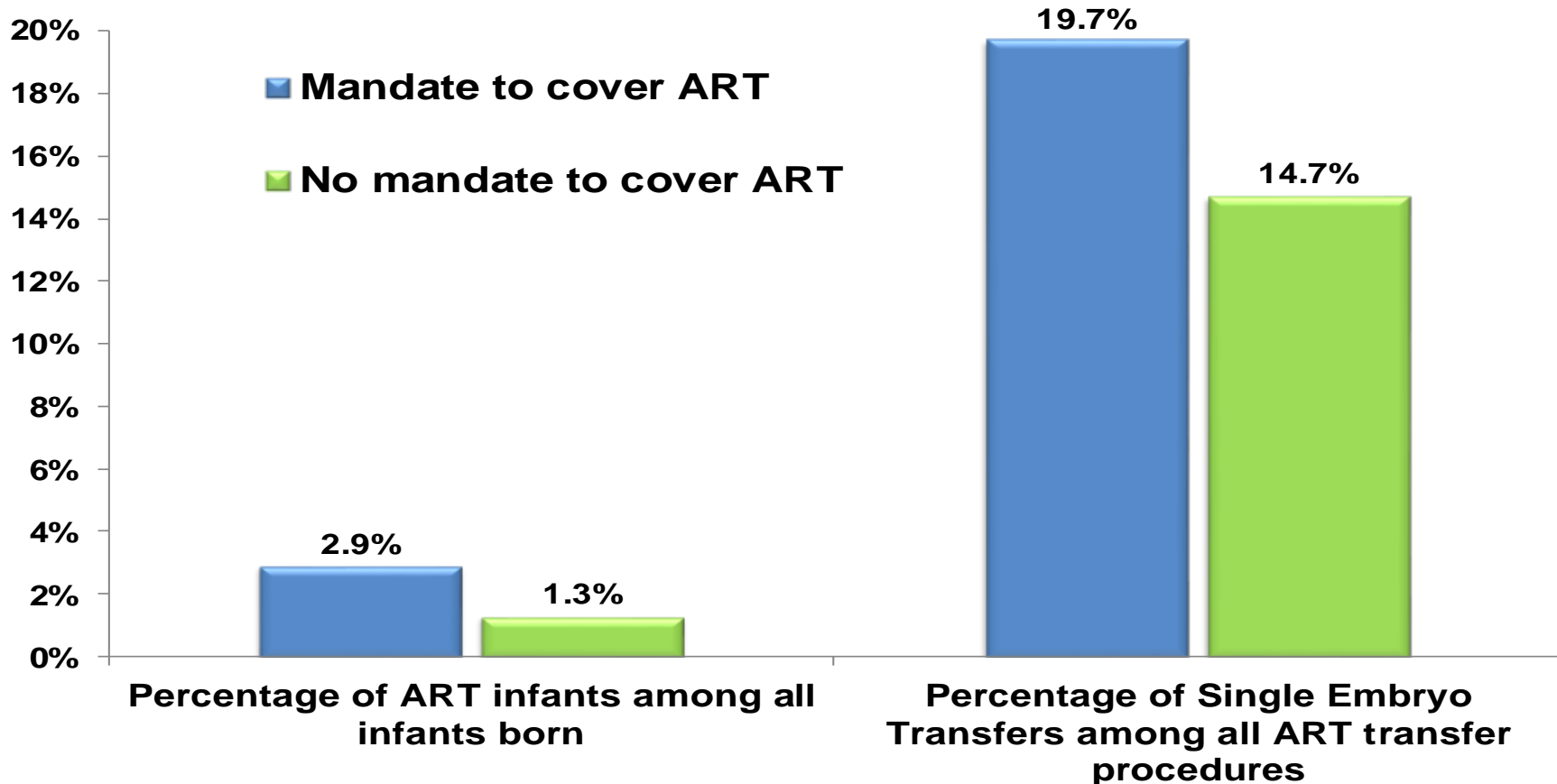


# Good Perinatal Outcomes Associated with Single Embryo Transfers, 2010



**Good Perinatal Outcome – term, normal birth weight singleton**

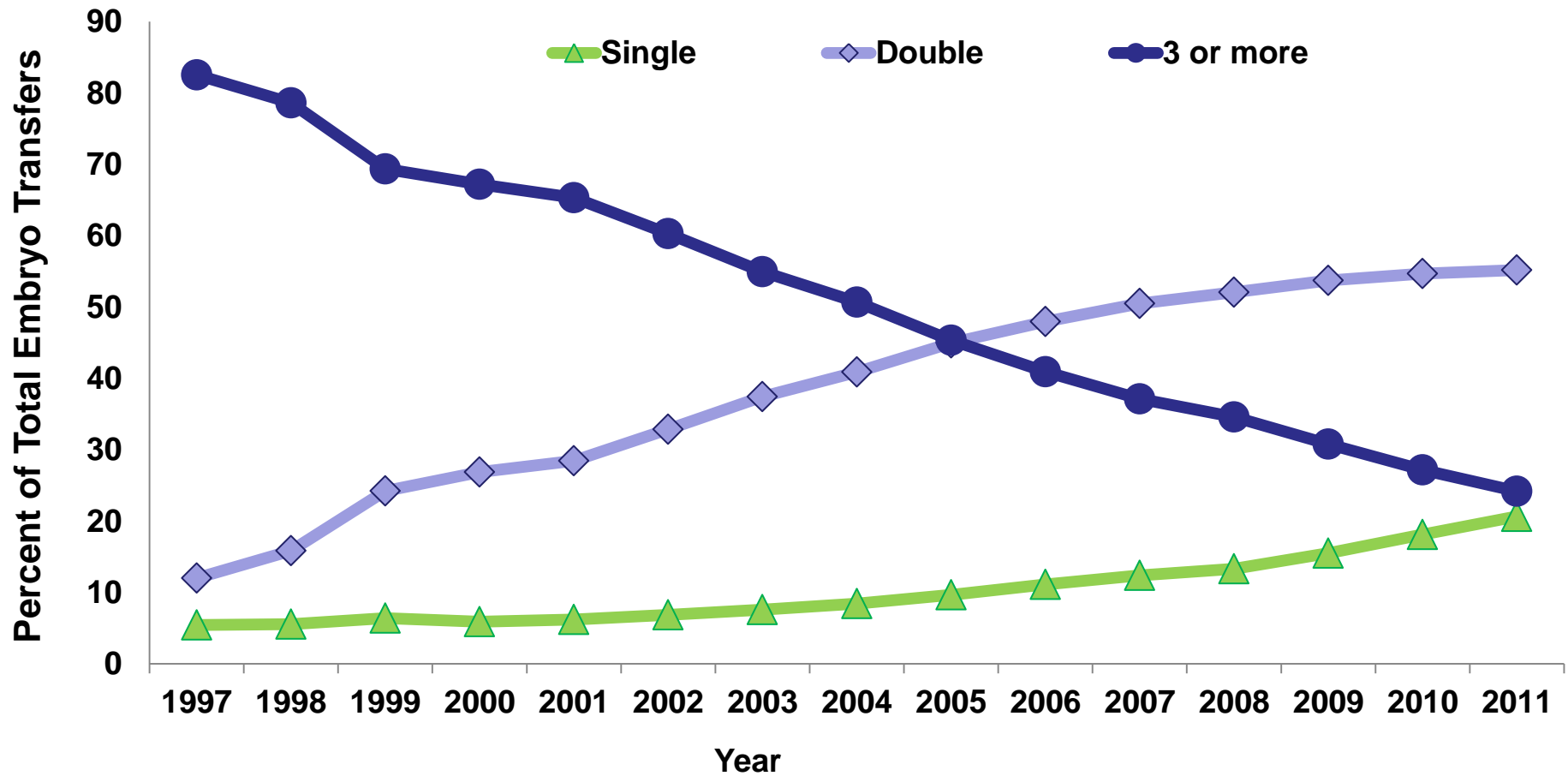
# Increased Use of ART and Single Embryo Transfers with Insurance Coverage, 2011



# ART Practice Guidelines and Good Perinatal Outcomes

- ❑ Issued by American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) since 1998
- ❑ Recommend maximum number of embryos to transfer during ART
- ❑ Contributed to the reduction of number of embryos transferred and number of triplets and higher order multiple births
- ❑ Have not affected twin births after ART

# Single, Double and Three or More Embryo Transfers, United States, 1997-2011



Kulkarni AD, *N Engl J Med* 2013.  
All tests for trend  $P < 0.001$

# Insurance Coverage and Practice Standards

## ❑ Insurance coverage

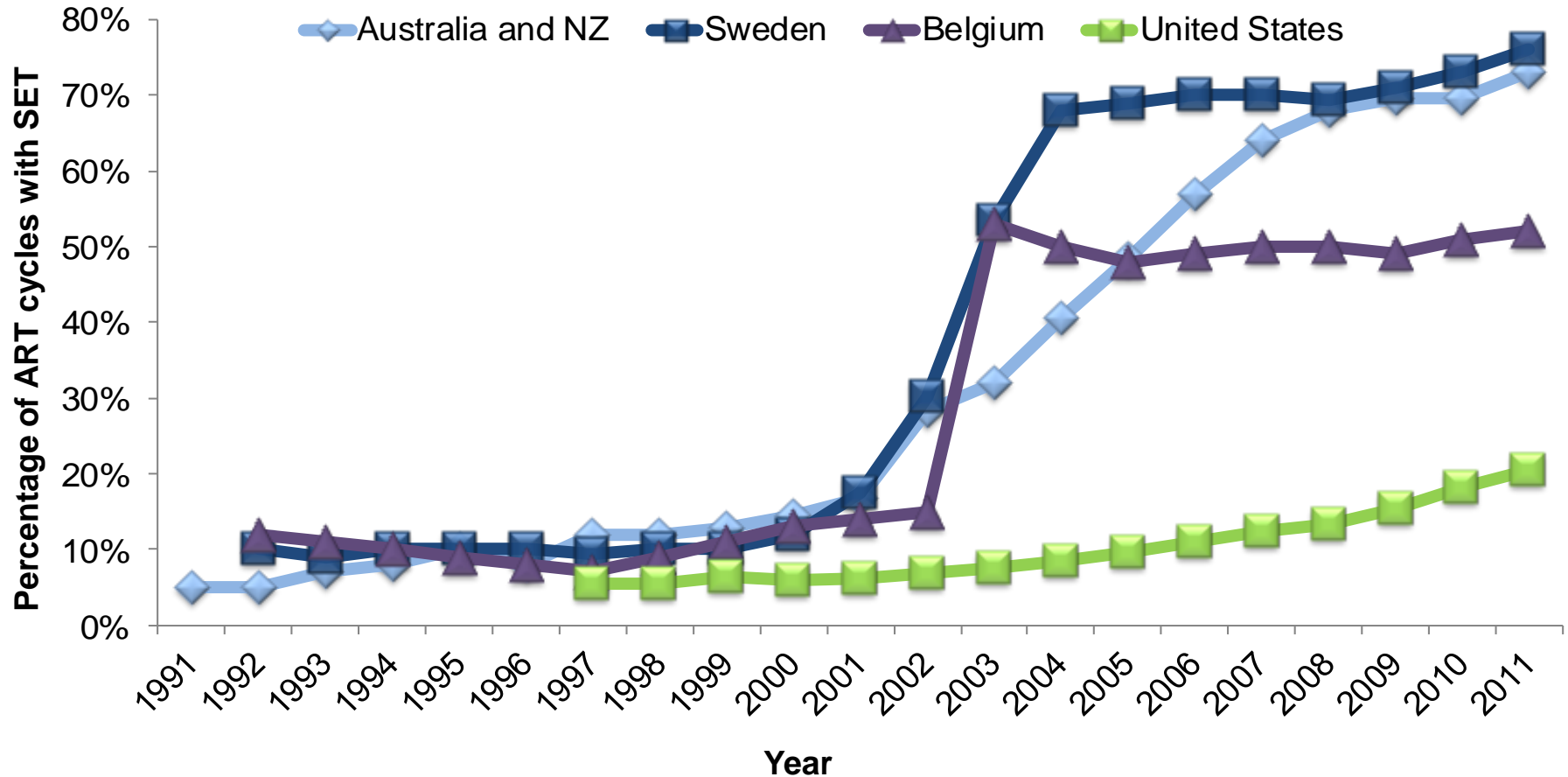
- Increased use of ART
- Increased the percentage of elective single embryo transfers, but only 1 in 5 chose single embryo transfer, even with coverage

## ❑ Practice Guidelines

- Reduced the number of three or more embryos transferred
- Have not reduced the number of twin gestations

## ❑ Other countries have been able to successfully implement the restrictions on the number of embryos to transfer by offering insurance coverage

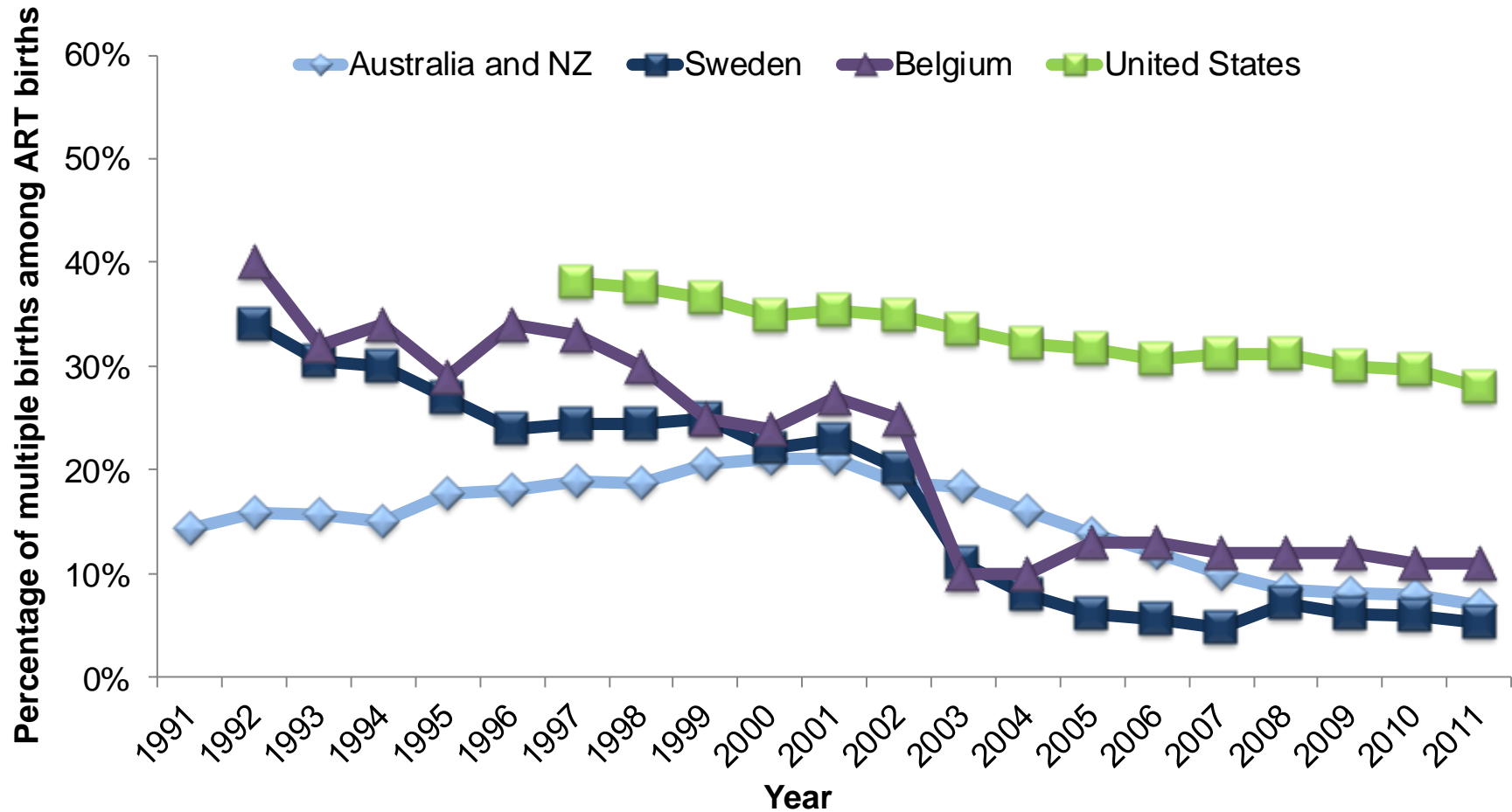
# Single Embryo Transfer (SET) in the United States and Other Countries



Chambers, *Med J Aust* 2011. De Neubourg, *Hum Reprod* 2013. Karlström, *Hum Reprod* 2007.  
Information from National ART Surveillance Systems in Belgium, Sweden, United States, Australia and New Zealand, including unpublished data.



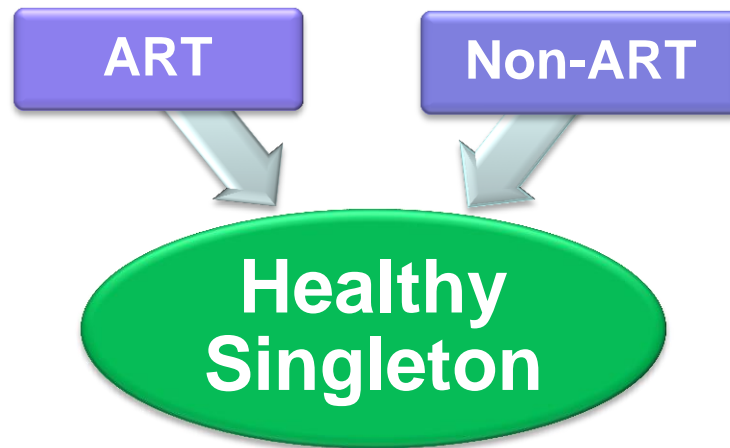
# ART-Related Multiple Births in the United States and Other Countries



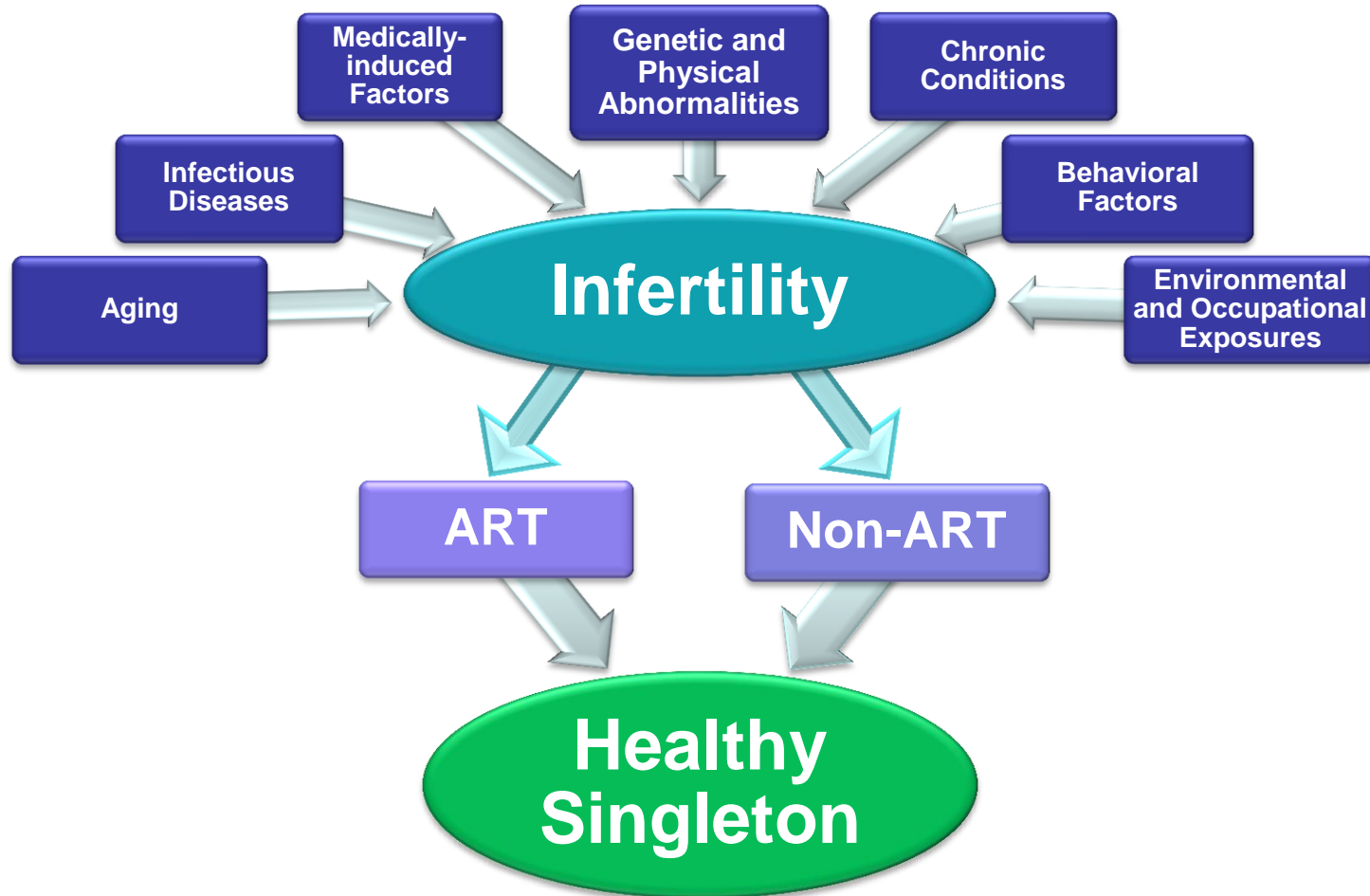
Chambers, *Med J Aust* 2011. De Neubourg, *Hum Reprod* 2013. Karlström, *Hum Reprod* 2007.

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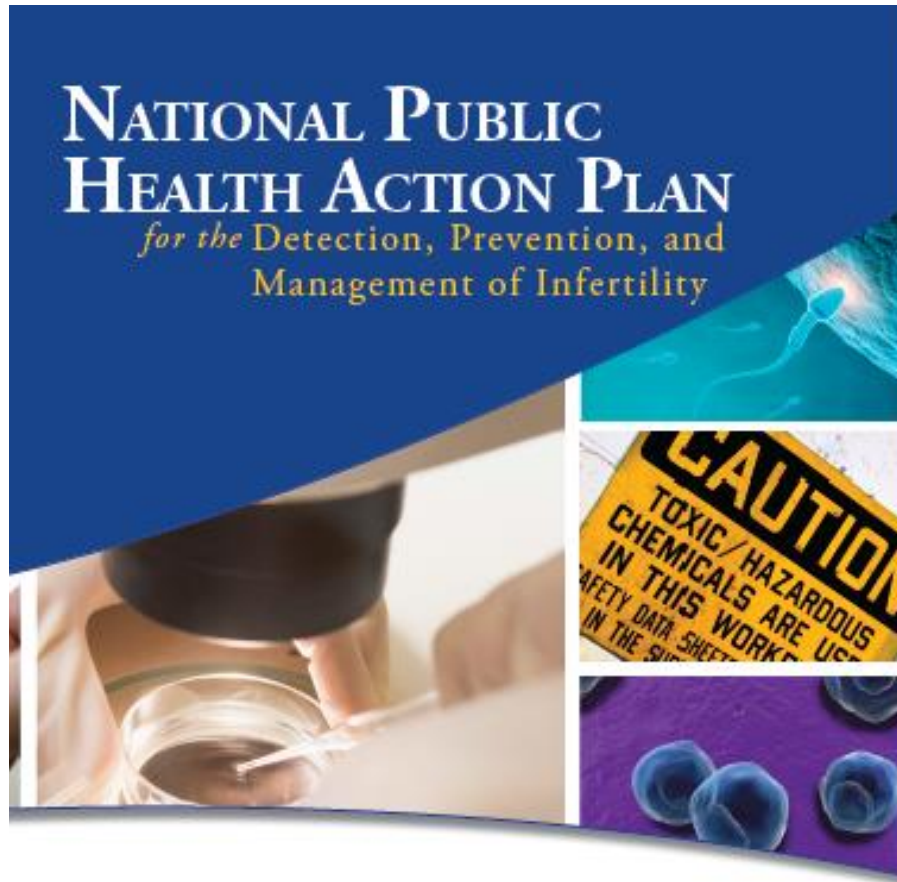
# Infertility, Infertility Treatments, and Good Perinatal Outcomes



# Infertility, Infertility Treatments, and Good Perinatal Outcomes



# A Call to Action



Centers for Disease Control and Prevention. National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, July 2014. Available at <http://www.cdc.gov/reproductivehealth/Infertility/PublicHealth.htm>

# National Public Health Action Plan

## ❑ Public health strategies can

- Promote healthy behaviors to preserve fertility
- Emphasize the prevention and treatment of medical conditions that lead to infertility
- Reduce exposures to hazardous agents that affect fertility



<http://www.cdc.gov/reproductivehealth/Infertility/PublicHealth.htm>

# Detection of Infertility: Public Health Opportunities

- ❑ **Develop standardized case definitions**
  
- ❑ **Improve surveillance for infertility and related factors**
  - Enhance information collected in existing surveillance systems
  - Expand surveillance efforts
    - Collect information about non-ART use and outcomes



# Prevention of Infertility: Public Health Opportunities

## ❑ Improved understanding of the risks and causes of infertility

- Infectious diseases
- Chronic conditions and diseases
- Environmental/Workplace
- Medication-induced
- Modifiable behavioral factors
- Genetic and physical abnormalities

## ❑ Increase public awareness of causes of infertility and the importance of prevention



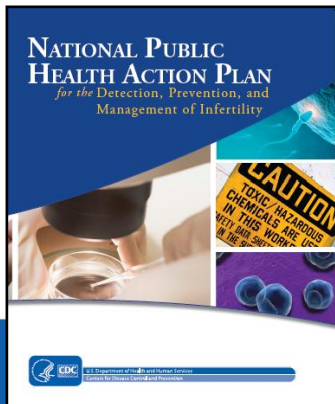
# Management of Infertility: Public Health Opportunities

- ❑ **Monitor safety and effectiveness of infertility treatments**
  - ART: long-term outcomes unknown
  - Non-ART: short-term and long-term outcomes unknown
- ❑ **Promote evidence-based guidelines and recommendations**
- ❑ **Increase public awareness of and eliminate disparities in access to affordable infertility services**





# In the End, It's About Families



**E-mail questions, comments  
or concerns to:**  
**[drhinfo@cdc.gov](mailto:drhinfo@cdc.gov)**



National Public Health Action Plan for the Detection, Prevention, and Management of Infertility, July 2014. Available at:  
<http://www.cdc.gov/reproductivehealth/Infertility/PublicHealth.htm>