INFERTILITY: A SNAPSHOT OF NATIONAL TRENDS, TREATMENTS, AND OUTCOMES

Jennifer F. Kawwass, MD
Professor, Division Director, Reproductive Endocrinology & Infertility
Medical Director, Emory Reproductive Center
Emory University School of Medicine

EMORY
REPRODUCTIVE CENTER

NO DISCLOSURES

EMORY
REPRODUCTIVE CENTER

LEARNING OBJECTIVES

- Define **infertility and its incidence** over time
- Understand **Preconception Optimization**
  - Collaboration with Primary Ob/Gyn and with MFM specialist
- Detail infertility **treatment options**
  - Ovulation Induction & Superovulation with Intrauterine Insemination
  - *In vitro* fertilization (IVF)
  - Donor oocyte, donor sperm, donor embryo
  - Oocyte and embryo cryopreservation
- Describe national **IVF trends** over time
  - Utilization
  - Practice Patterns
  - Maternal and Neonatal Outcomes

EMORY
REPRODUCTIVE CENTER

INFERTILITY: DEFINITION, INCIDENCE

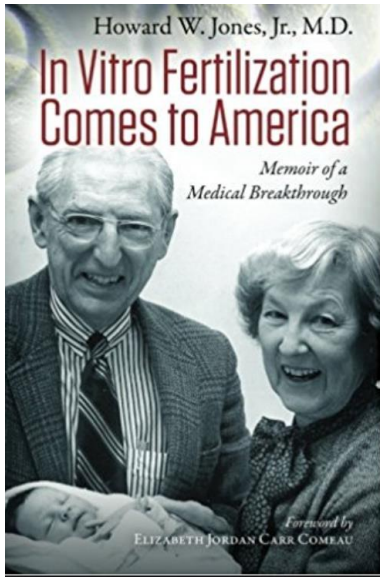
EMORY
REPRODUCTIVE CENTER

BACKGROUND

Infertility: 15.5% of reproductive-aged couples

Until 1978, many infertile couples unable to conceive a biologically related child

Over the past 40 years, improved IVF access and effectiveness



EMORY REPRODUCTIVE CENTER

INFERTILITY: DIAGNOSTIC TESTING

FEMALE

- Preconception Counseling
  - Pan-ethnic carrier screening
  - Health optimization
- Ovarian Reserve
  - AMH, FSH/Estradiol, AMH
- Tubal Status
- Uterine Status
- Ovulatory Status

MALE

- Health Optimization
  - Semen Analysis

EMORY
REPRODUCTIVE CENTER

PRECONCEPTION OPTIMIZATION

- Collaboration with Maternal Fetal Medicine (MFM) if appropriate
- Collaboration with other subspecialists if appropriate

EMORY
REPRODUCTIVE CENTER

MATERNAL RISKS:
PRE-EXISTING CONDITIONS

- **Optimize maternal health before conception**
  - Consider referral to maternal fetal medicine specialist when appropriate
- **Severe Pre-Existing Medical Conditions**
  - Congestive heart failure with a low ejection fraction
  - End-stage renal disease
  - Pulmonary hypertension
  - Considered contraindications to pregnancy
  - Warrant discussion about using gestational carrier
- **More Common Pre-Existing Medical Conditions**
  - Diabetes
  - Hypertension
  - Obesity
  - Warrant counseling and optimization prior to pregnancy

EMORY
REPRODUCTIVE CENTER

MATERNAL RISKS, OBESITY

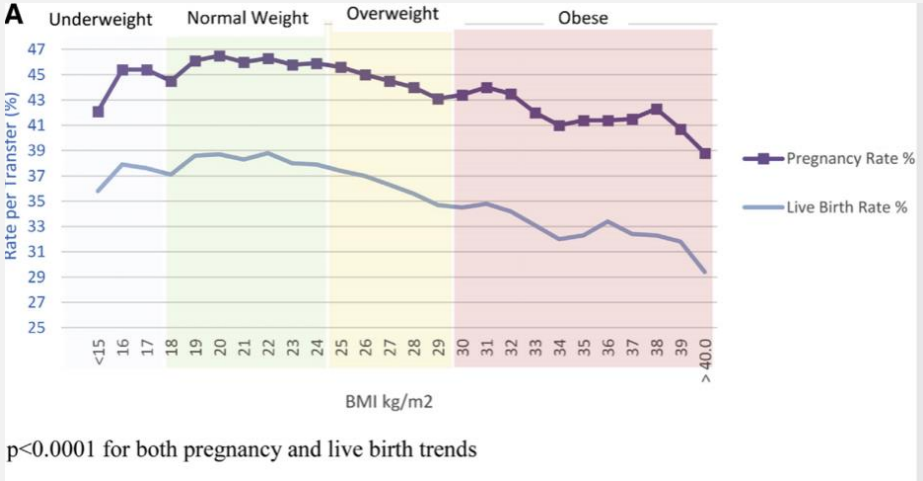
Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States

Jennifer F. Kawwass, M.D.,[a,b] Aniket D. Kulkarni, M.B.B.S., M.P.H.,[b] Heather S. Hipp, M.D.,[a,b] Sara Crawford, Ph.D.,[b] Dmitry M. Kissin, M.D., M.P.H.,[a,b] and Denise J. Jamieson, M.D., M.P.H.[a,b]

[a] Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, School of Medicine, Emory University; and [b] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Obesity

- Known risk factor for many adverse perinatal outcomes[1]
  - Miscarriage, congenital malformations, preeclampsia, gestational diabetes, stillbirth, indicated preterm birth, and cesarean delivery
- Also adversely affects the IVF cycle and perinatal outcomes[2]
  - Lower live birth rates, increased miscarriage rates



(**A**) Pregnancy and live-birth rate per transfer by body mass index, fresh autologous IVF cycles, 2008–2013. (**B**) Miscarriage rate among all pregnancies by body mass index, fresh autologous IVF cycles, 2008–2013.

Kawwass. Extremities of BMI, IVF, and perinatal outcomes. Fertil Steril 2016.

1. Berghella CRC 2017
2. Kawwass F&S 2016

EMORY REPRODUCTIVE CENTER

TREATMENT OPTIONS

Chance of Conception Per Month

- No Infertility: ~15%
- Infertility: <3%

INTRAUTERINE INSEMINATION (IUI)

- Oral Medication + Timed Intercourse
  - 5-8% pregnancy per month, 3-5% twins
- **Oral Medication + IUI (8-12%)**
  - 8-12% pregnancy per month, 3-5% twins
- Oral Medication + Gonadotropins +IUI (15-20)
  - 15-20% pregnancy per month, 15-20% twins

IN VITRO FERTILIZATION (IVF)

- Nationally reported outcomes by age
- Very broadly:
  - 50-60% live birth per euploid embryo transfer, 1.3% chance of twins

EMORY REPRODUCTIVE CENTER

IVF IN THE 1990'S AND EARLY 2000'S

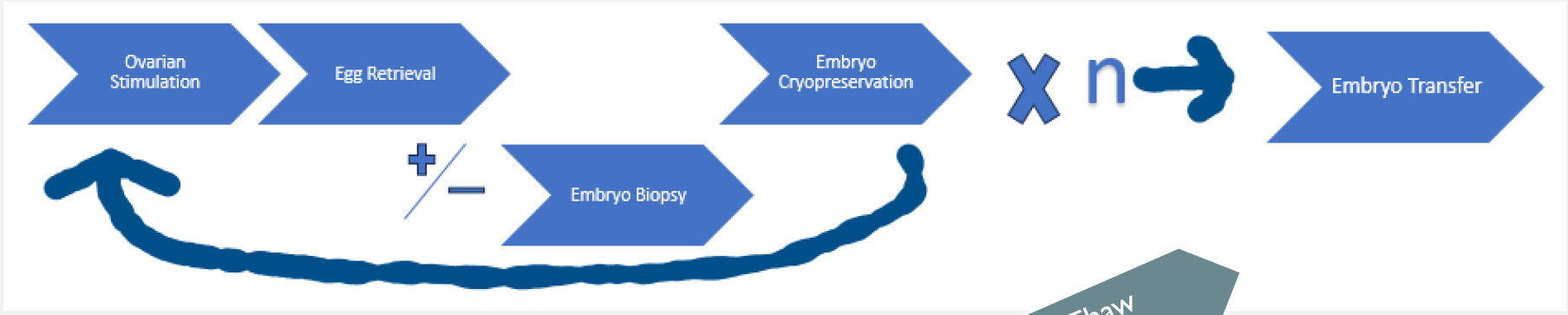
Linear Cycle-Based Outcomes

IVF IN THE 2020'S…

- **Egg Freezing:** batching or for future family building
- **Single Intent:** primary goal is immediate pregnancy
- **Dual Intent: Family Planning for NOW *and* THE FUTURE:** pregnancy now & additional future children
- **Embryo Banking**
- **Future Family Building**
- **IVF for PGT-M as the Primary Indication**
- **IVF in the setting of medical necessity to defer childbearing**

IVF IN THE 2020'S…

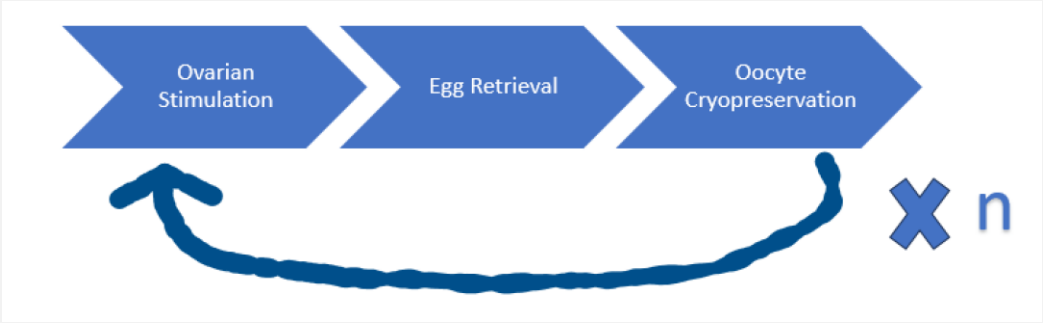
Embryo Creation



Embryo Transfer

Oocyte Thaw Fertilization

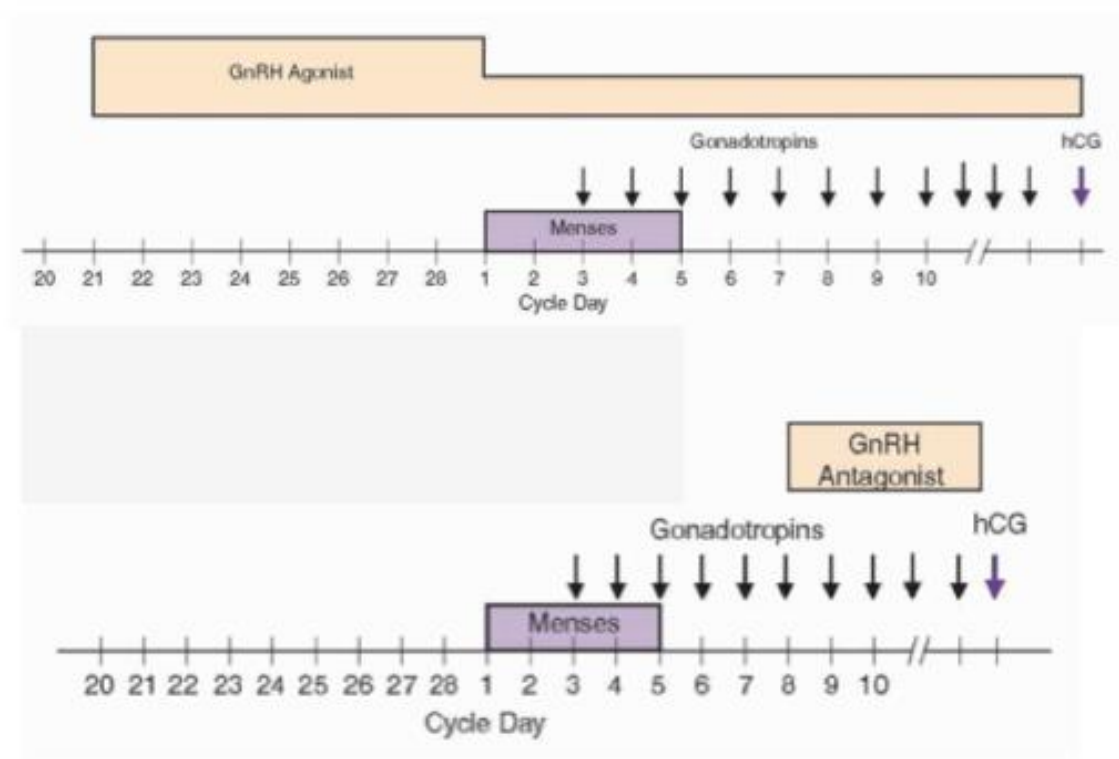
Oocyte Cryopreservation



Countless variations based on unique patient situations

CONTROLLED OVARIAN HYPERSTIMULATION

- Injectable gonadotropins (FSH/ LH) daily for 9-12 days
  - GnRH agonist or antagonist to prevent ovulation

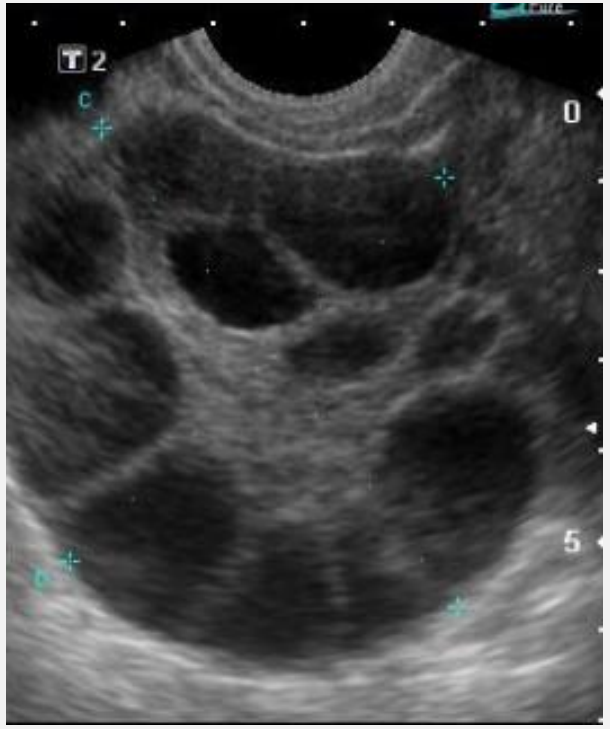


EMORY REPRODUCTIVE CENTER

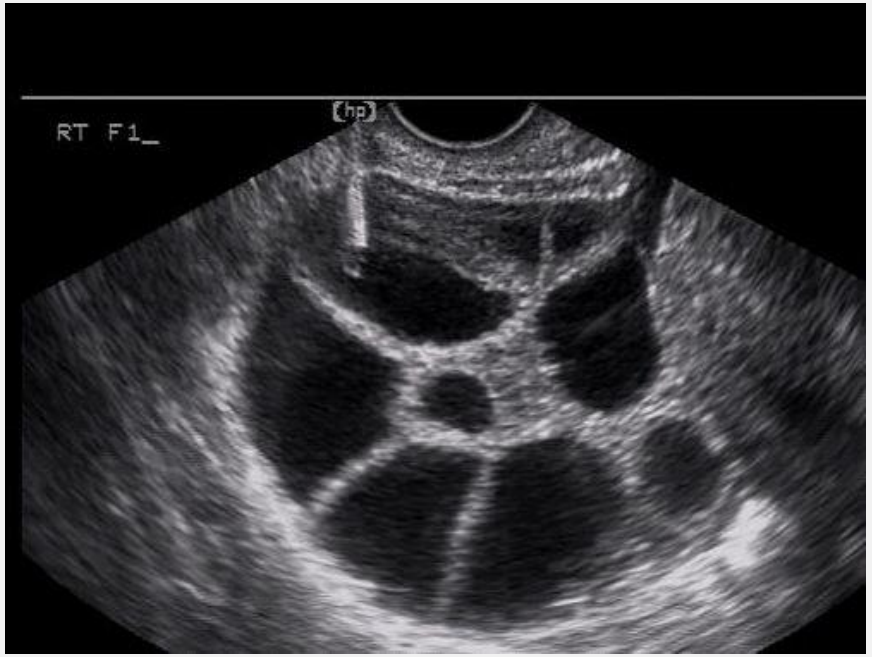
THE MONITORING

- Ultrasound and lab monitoring
  - Follicle measurements
  - Estradiol, Progesterone

~ 10 days



THE RETRIEVAL



- Moderate sedation
- Transvaginal ultrasound probe with needle guide

EMORY
REPRODUCTIVE CENTER

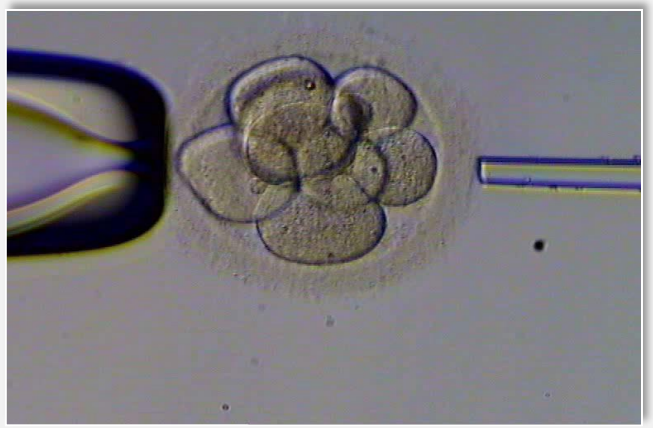
A percentage of retrieved oocytes are mature and capable of fertilization

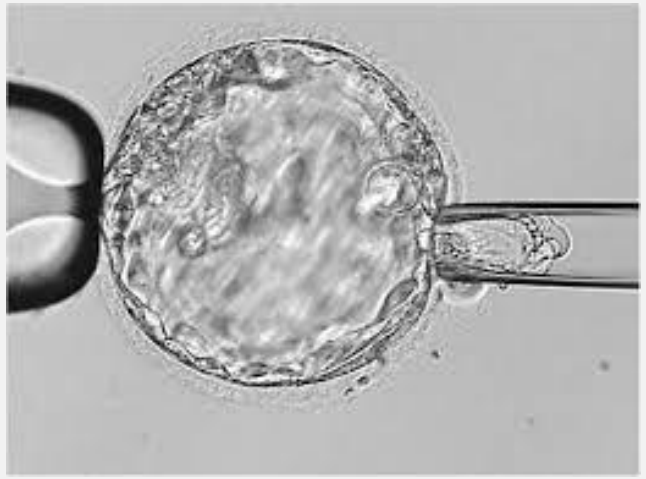
Fertilization

Cleavage Embryo

Blastocyst Embryo

PREIMPLANTATION GENETIC TESTING (PGT)

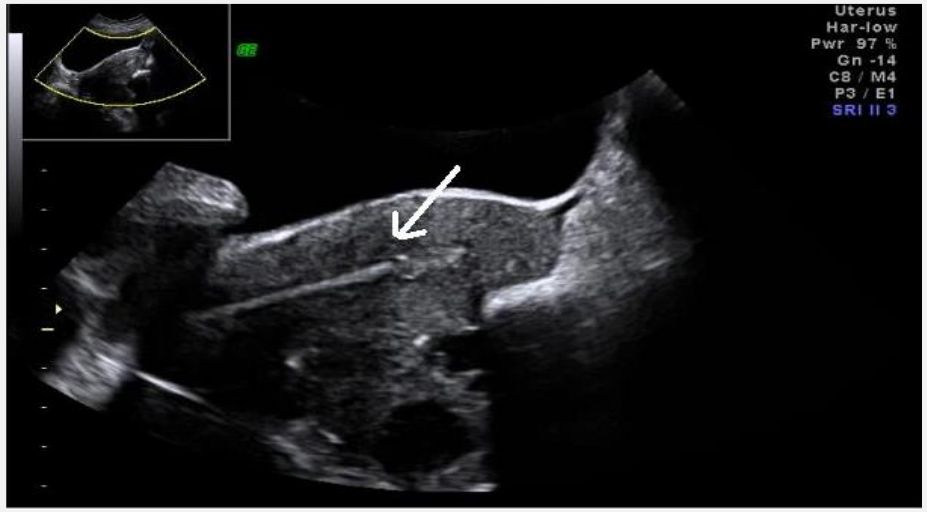




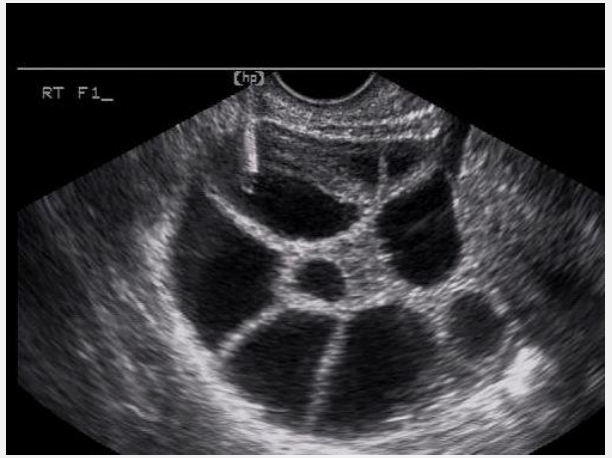
- Embryo biopsy - 5-7 cells from an ~100 cell blastocyst embryo
- Genetic testing of those cells to detect specific mutations (M) or aneuploidy (A)

EMORY
REPRODUCTIVE CENTER

EMBRYO TRANSFER



MATERNAL RISKS: IVF



Stimulation

- Ovarian hyperstimulation
- Medication reaction

Retrieval

- Anesthetic complication
- Infection
- Hemorrhage requiring transfusion
- Hospitalization

EMORY REPRODUCTIVE CENTER

MATERNAL RISKS, IVF

Surveillance study: All IVF procedures performed in the US: 2000 -2011[1]

- More than 1 million non-donor cycles, most commonly reported patient complication

Ovarian hyperstimulation syndrome

- Peak: 153.5 per 10,000 autologous cycles, 95% CI 146.0– 161.3, **1.5%**[1]
- 2014: <1% of all cycles[2]

RESEARCH LETTER

Safety of Assisted Reproductive Technology in the United States, 2000-2011

JAMA. 2015;313(1):88-90. doi:10.1001/jama.2014.14488

Jennifer F. Kawwass, MD[1]; Dmitry M. Kissin, MD, MPH[2]; Aniket D. Kulkarni, MBBS, MPH[2]; et al

1. Kawwass JAMA 2015
2. Schirmer F&S 2020

EMORY REPRODUCTIVE CENTER

MATERNAL RISKS, IVF

Hospitalizations

- Peak: 34.8 per 10,000 autologous cycles, 95% CI 30.9–39.3, **0.34%**[1]

Infection, medication adverse event, anesthetic complication, hemorrhage requiring transfusion

- All less than 0.1%[1]

Deaths within 12 weeks of stimulation start, zero reported[1]

RESEARCH LETTER

Safety of Assisted Reproductive Technology in the United States, 2000-2011

JAMA. 2015;313(1):88-90. doi:10.1001/jama.2014.14488

Jennifer F. Kawwass, MD[1]; Dmitry M. Kissin, MD, MPH[2]; Aniket D. Kulkarni, MBBS, MPH[2]; et al

1. Kawwass JAMA 2015
2. Schirmer F&S 2020

EMORY REPRODUCTIVE CENTER

IUI & IVF COSTS

- IUI
  - ~$1,000 per attempt
- IVF
  - Monitoring, Retrieval, Embryology: ~$15-20,000
  - Medications ($4-10,000)
  - Embryo Transfer (~$5,000)
- Biopsy and PGT: ~$5,000
  - $2,500 for the biopsy itself and ~$2,500 for the genetic testing
- Embryo storage: ~$600/ yr ($100-$1,500)

Fertility—a human right worthy of mandated insurance coverage: the evolution, limitations, and future of access to care

Jennifer F. Kawwass, M.D.,[a] Alan S. Penzias, M.D.,[b,c,d] and Eli Y. Adashi, M.D., M.S.[e]

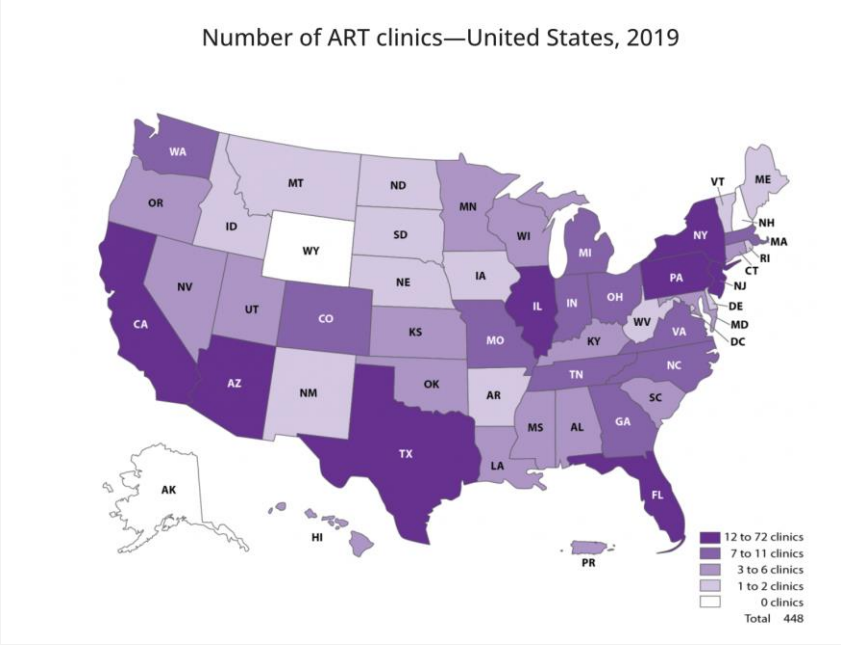
[a] Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia; [b] Boston IVF, Waltham, Massachusetts; [c] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; [d] Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School, Boston, Massachusetts; and [e] Department of Medical Science, Warren Alpert Medical School, Brown University, Providence, Rhode Island

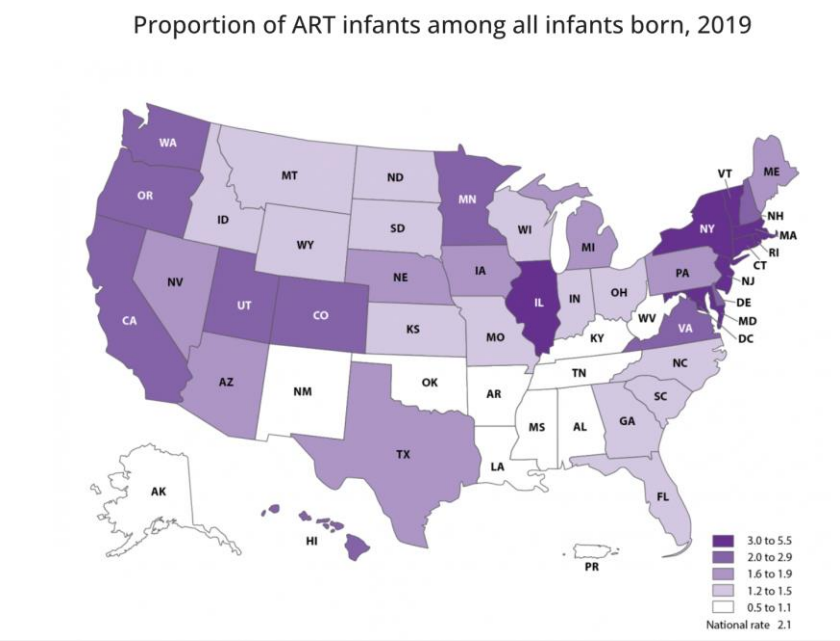
EMORY
REPRODUCTIVE CENTER

NATIONAL IVF TRENDS

NATIONAL IVF TRENDS

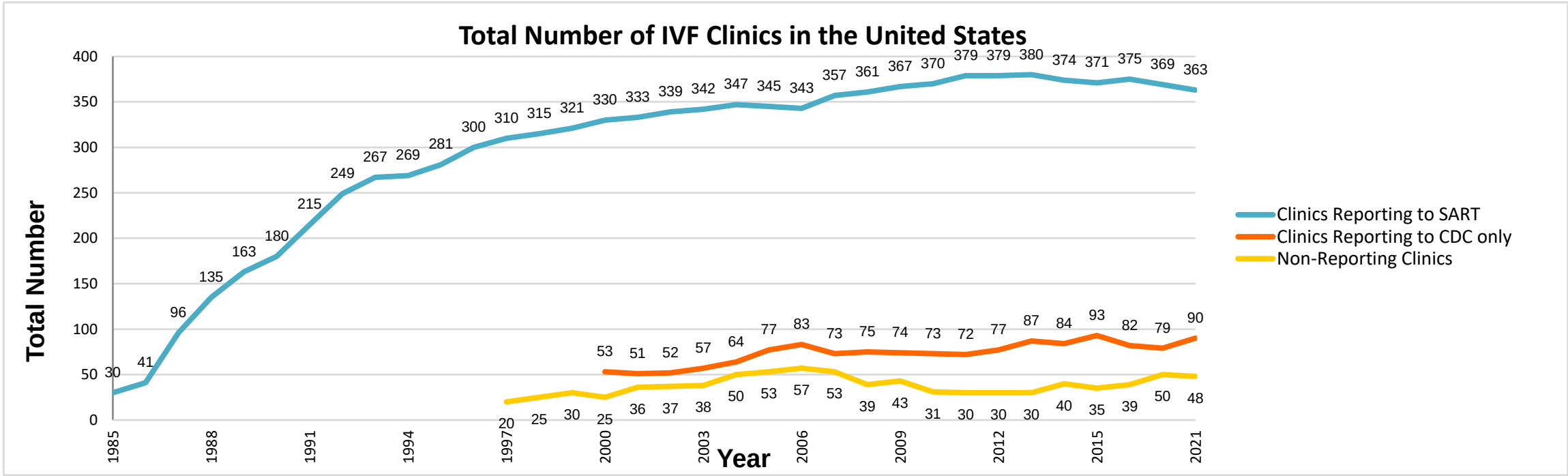
- 2019: IVF infants comprised 2.1% of total US live births
- 2022: 457 clinics reporting 91% of all cycles performed in the United States to the CDC





Sunderam MMWR 2020

CDC National Summary Report 2019



TOTAL NUMBER OF IVF CLINICS IN THE UNITED STATES STRATIFIED BY REPORTING STATUS, 1985 - 2021

IVF IN THE US 2022

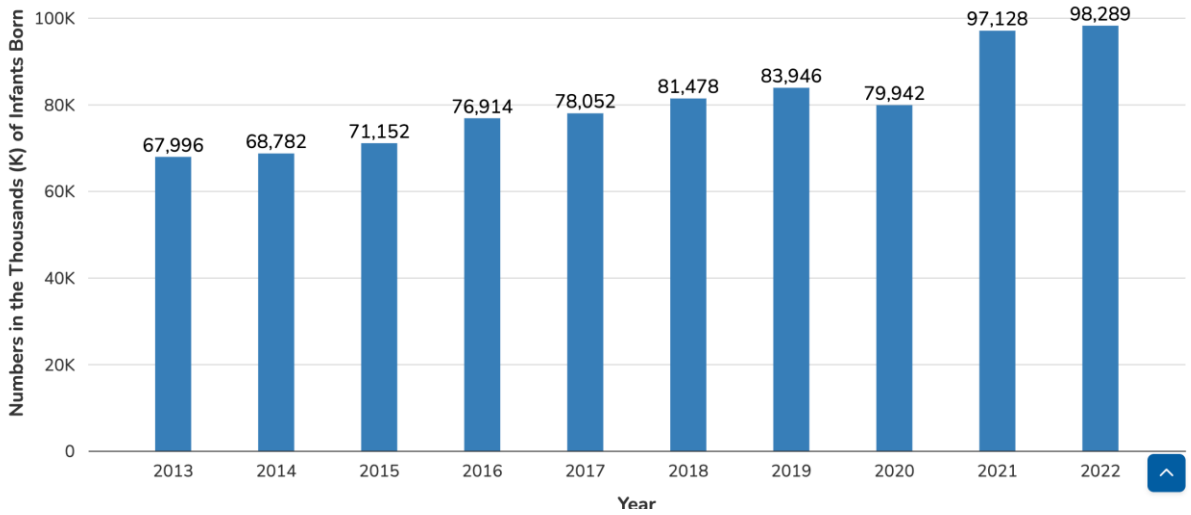
At a Glance, 2022

36.3 years — Average age of patients using ART.

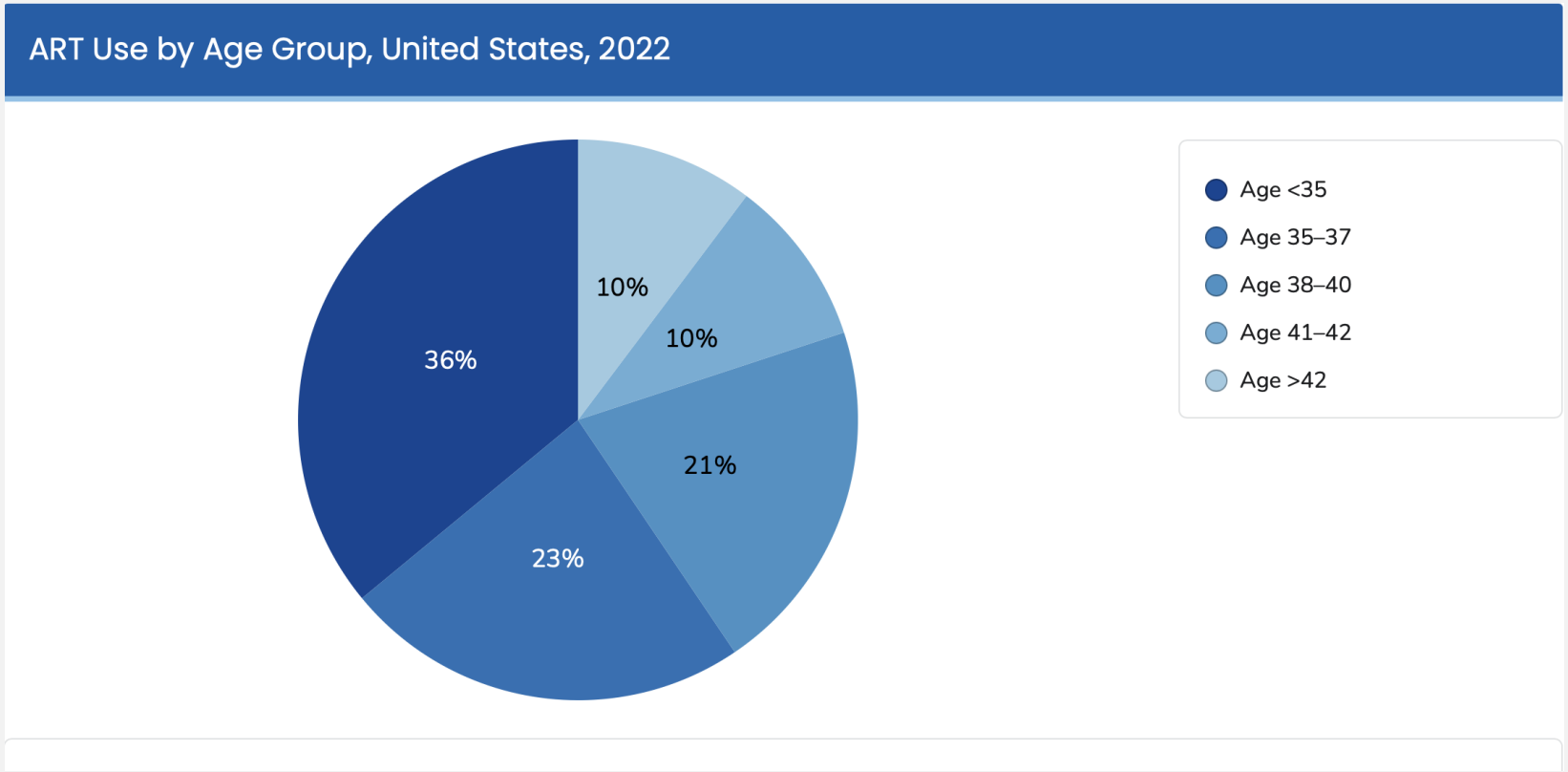
37.5% — Percentage of ART cycles that resulted in live-birth delivery.

85.9% — Percentage of embryo transfers that are single embryo transfers.

Number of Infants Born Who Were Conceived Through ART, 2013–2022

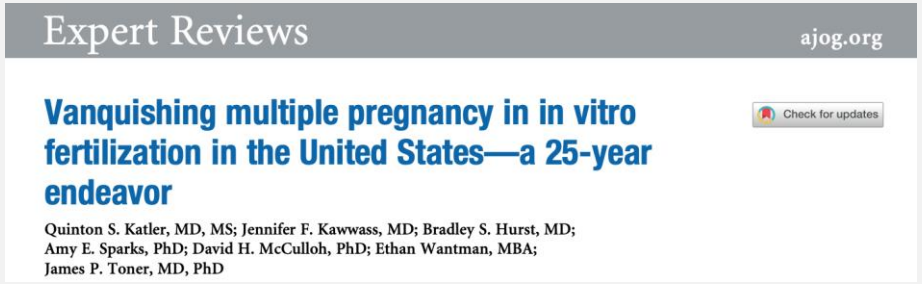


NATIONAL ART USE BY AGE GROUP



NATIONAL IVF TRENDS

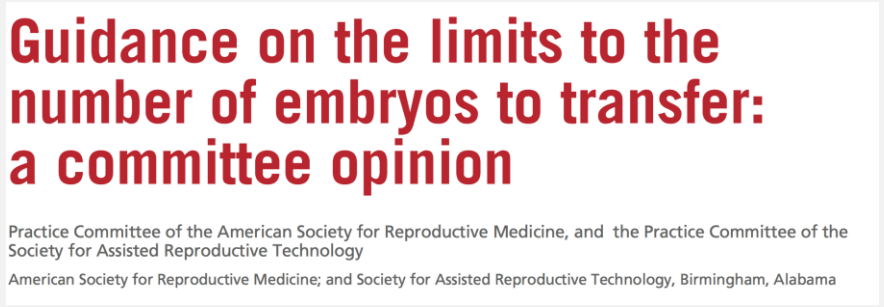
- Singleton Pregnancies are now the norm


Expert Reviews ajog.org

Vanquishing multiple pregnancy in in vitro fertilization in the United States—a 25-year endeavor

Check for updates

Quinton S. Katler, MD, MS; Jennifer F. Kawwass, MD; Bradley S. Hurst, MD; Amy E. Sparks, PhD; David H. McCulloh, PhD; Ethan Wantman, MBA; James P. Toner, MD, PhD

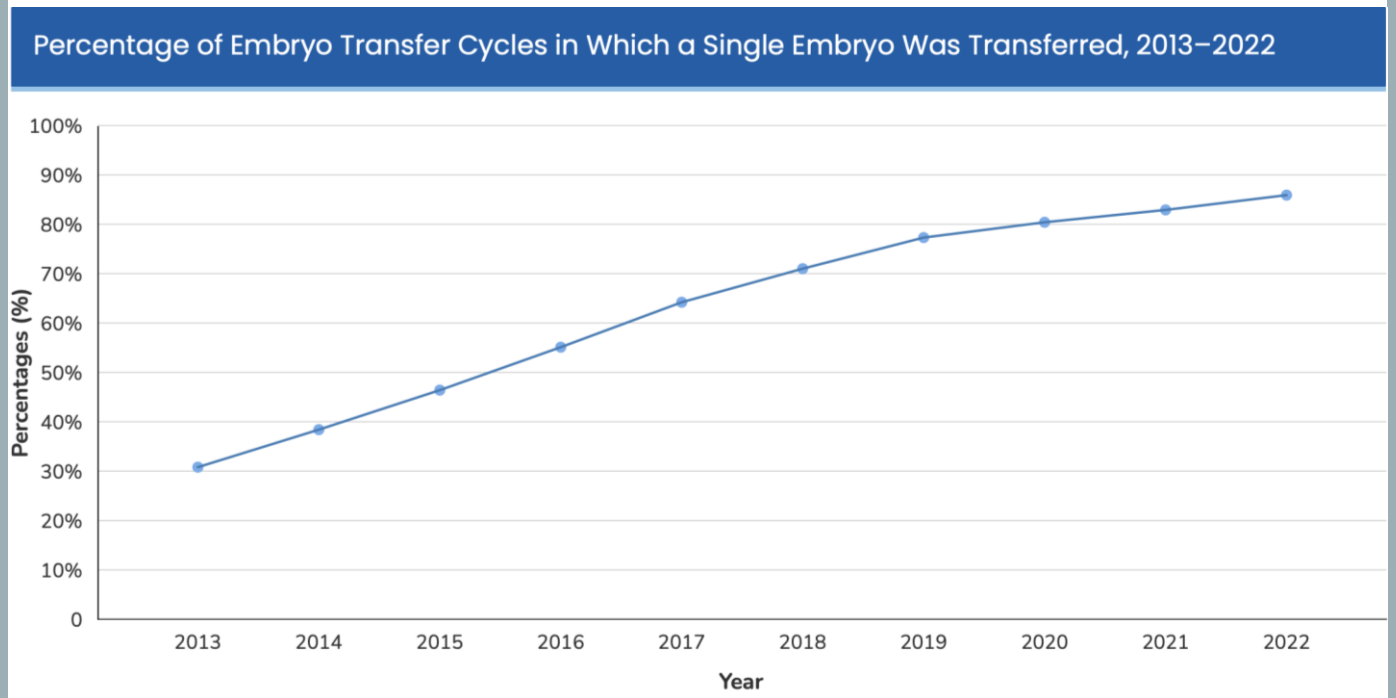

Guidance on the limits to the number of embryos to transfer: a committee opinion

Practice Committee of the American Society for Reproductive Medicine, and the Practice Committee of the Society for Assisted Reproductive Technology

American Society for Reproductive Medicine; and Society for Assisted Reproductive Technology, Birmingham, Alabama

EMORY REPRODUCTIVE CENTER

CDC National Summary Report 2019



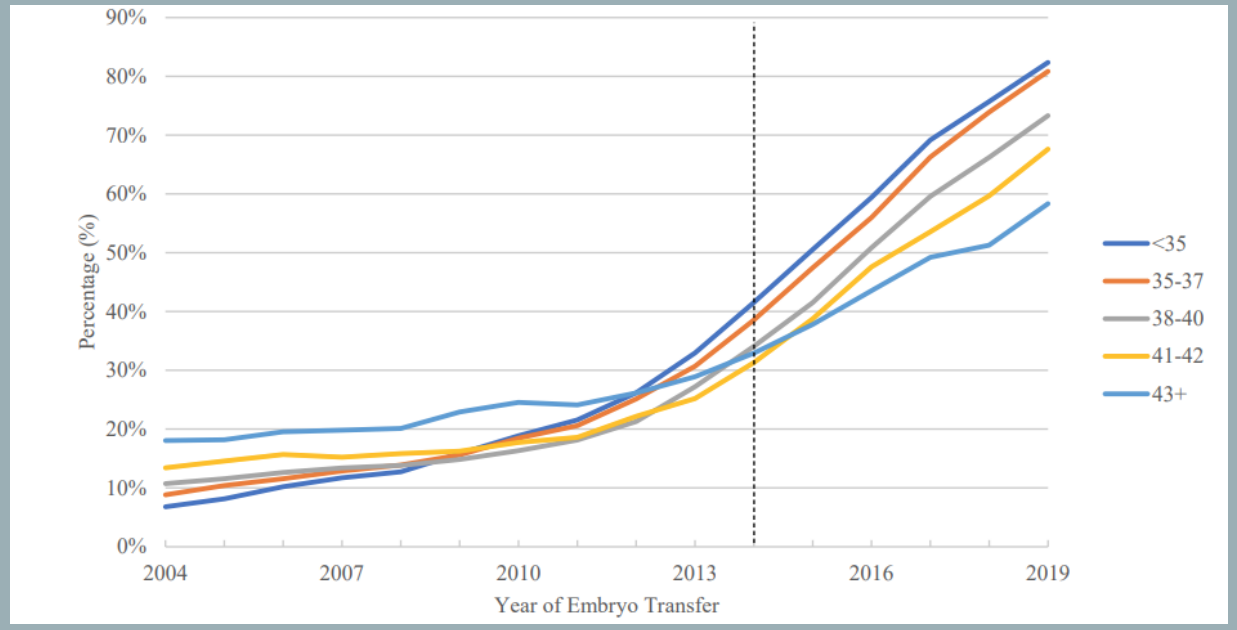
Fresh and frozen eggs or embryos from patients and donors are included. Banking cycles are excluded.

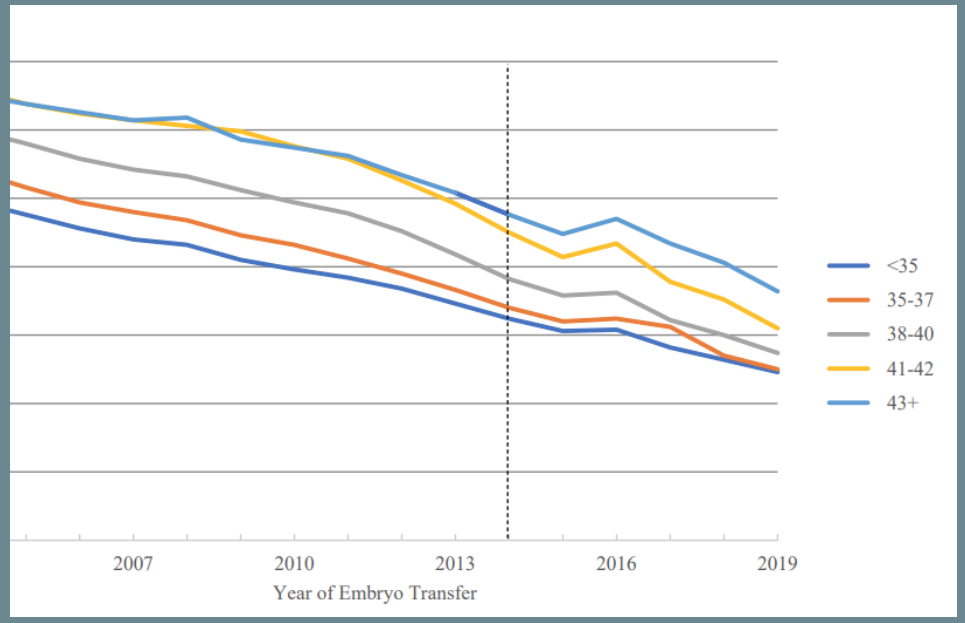
The percentage of single embryo transfer (SET) procedures is the percentage of all embryo transfer cycles in which only one embryo is transferred to the uterus, regardless of the number of embryos available. The use of SET is a strategy to avoid a multiple-fetus pregnancy and reduce the risk of poor health outcomes, such as prematurity and low birth weight, among infants.

IVF IN THE US 2022

SINGLE EMBRYO TRANSFER

NATIONAL IVF TRENDS
ELECTIVE SINGLE EMBRYO TRANSFER

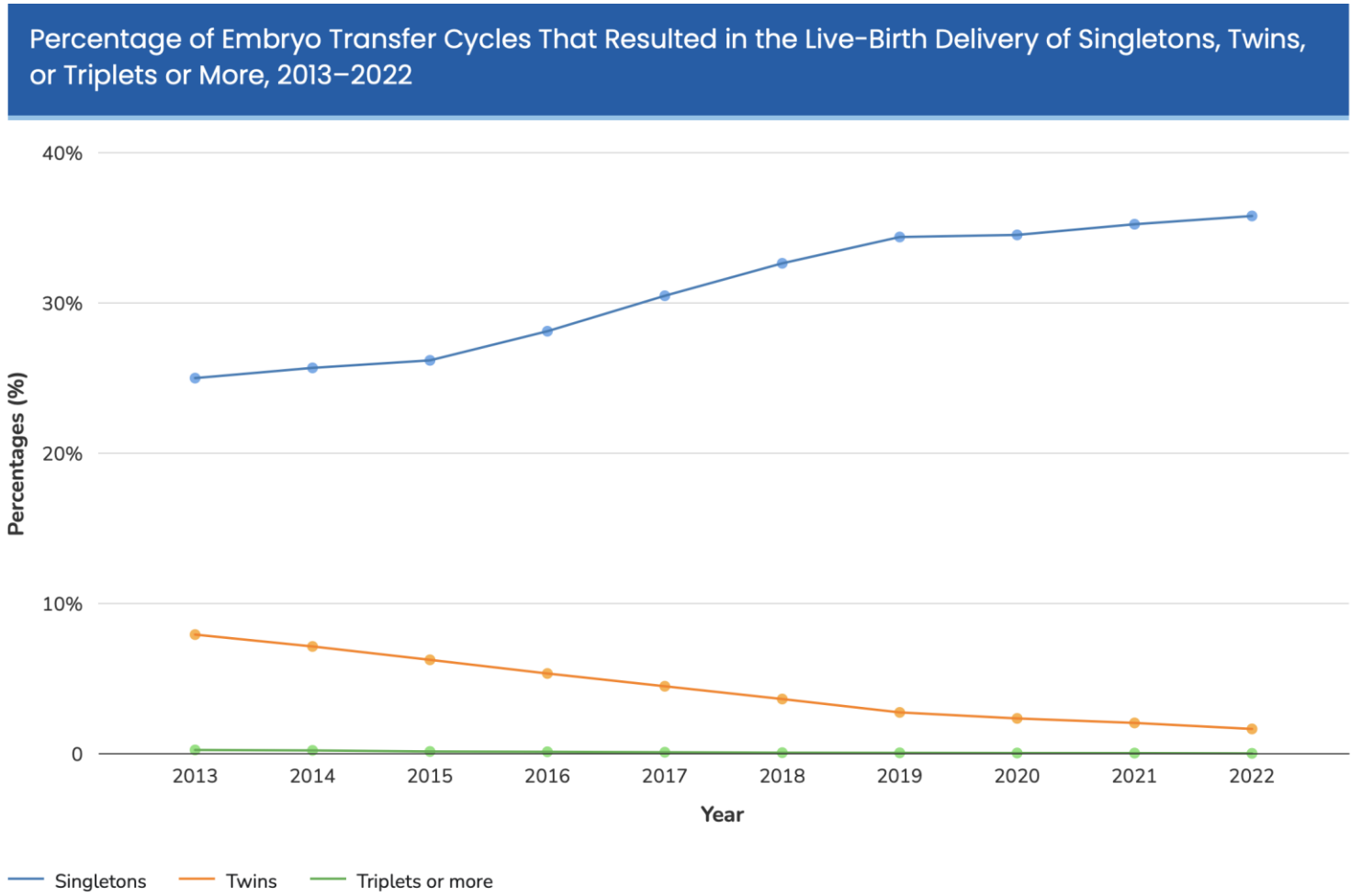




Katler et al AJOG 2022

IVF BIRTH OUTCOMES 2022

SINGLETON LIVE BIRTHS

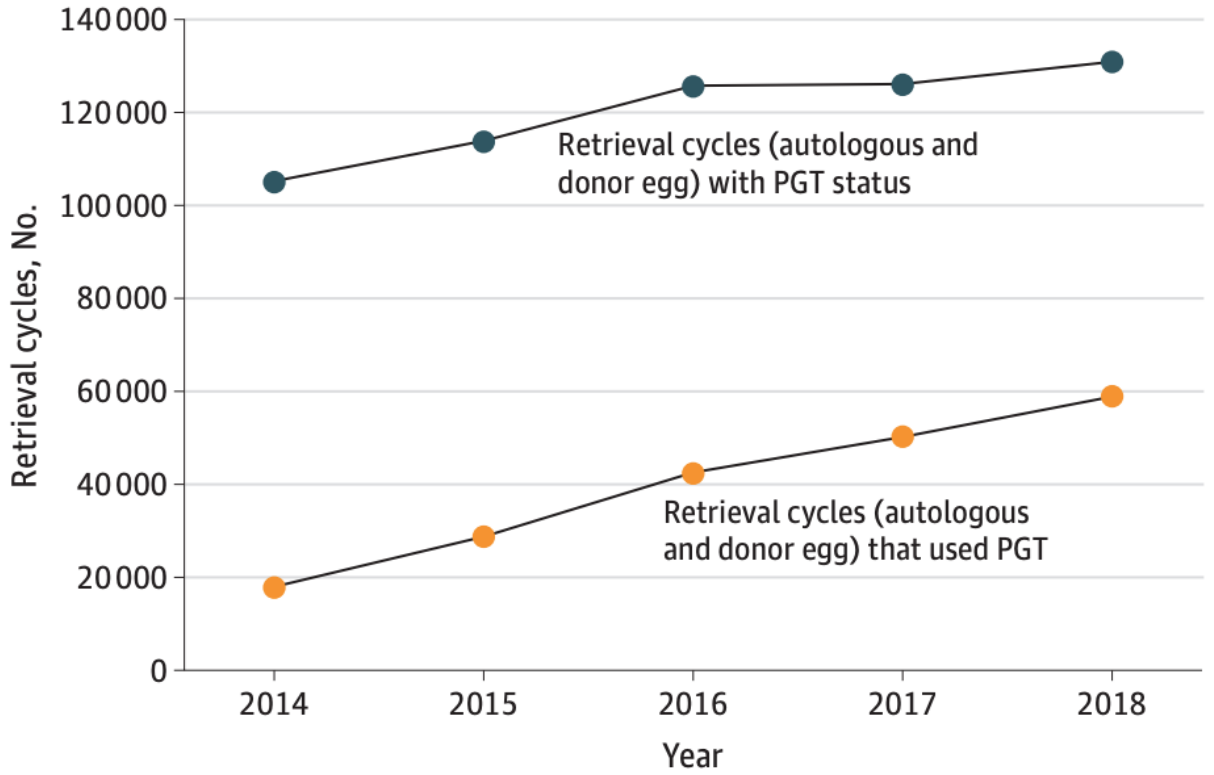


Fresh and frozen eggs or embryos from patients and donors are included. Banking cycles are excluded.

Singletons are defined as one infant born alive (no stillbirths). Twins are two infants born with at least one born alive, and triplets or more are at least three infants born with at least one born alive. The increased use of single embryo transfer (SET) in recent years has likely contributed to the trend shown of an increasing percentage of embryo transfer cycles that resulted in live-birth delivery of singletons. SET is used to avoid multiple-fetus pregnancies and reduce the risk of poor health outcomes, such as prematurity and low birth weight, among infants.

INCREASE IN PGT USE

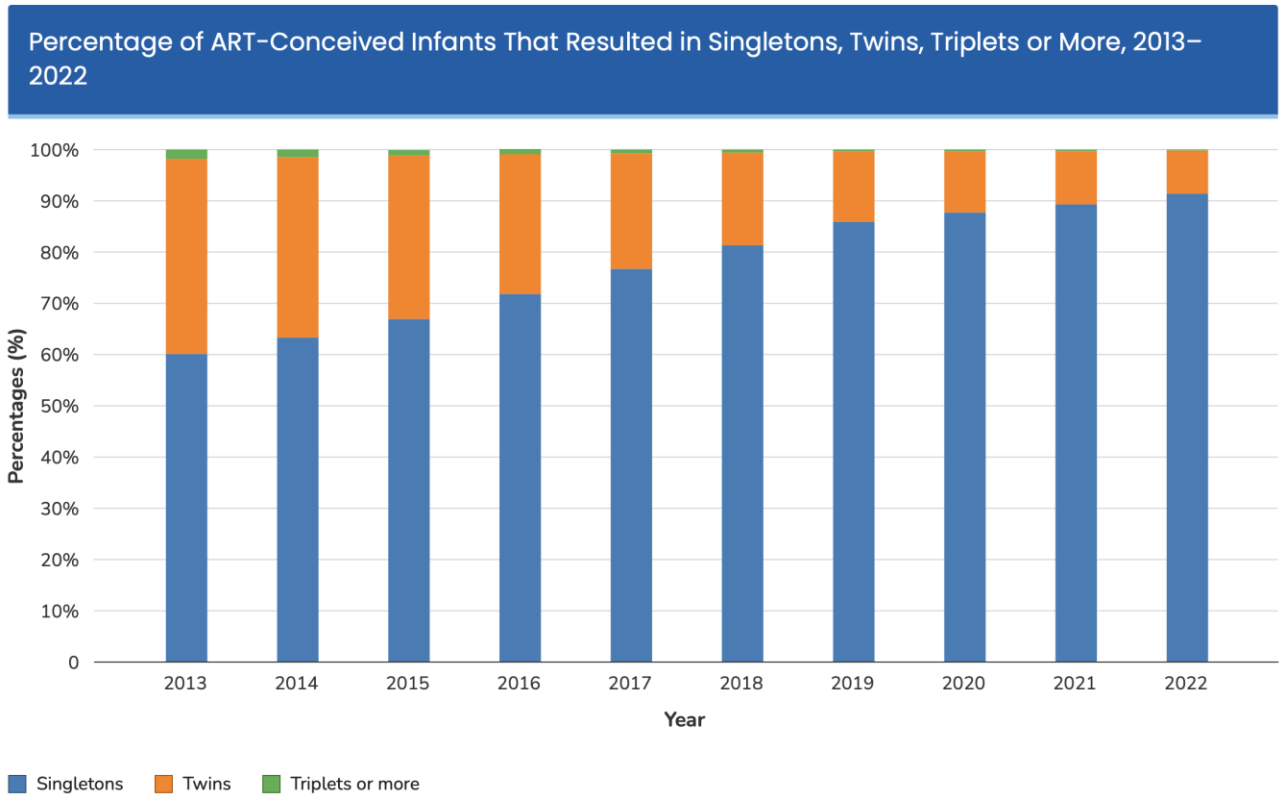
Figure 1. Trends in Absolute Number of In Vitro Fertilization Retrieval Cycles and Cycles Using Preimplantation Genetic Testing (PGT), 2014-2018



Kawwass Hipp JAMA 2022

NATIONAL DATA:

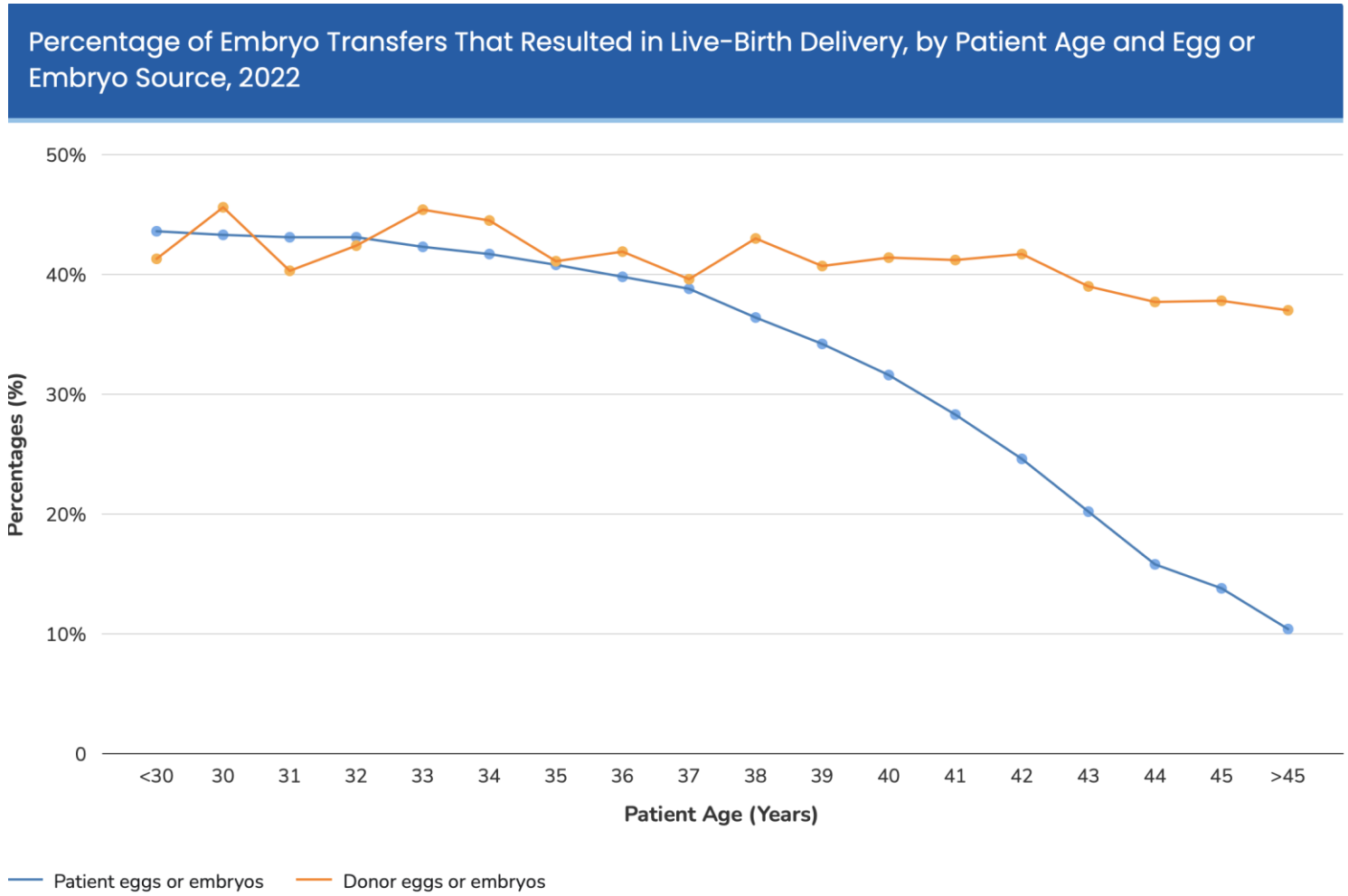
IMPROVING NEONATAL OUTCOMES



Fresh and frozen eggs or embryos from patients and donors are included. Banking cycles are excluded.

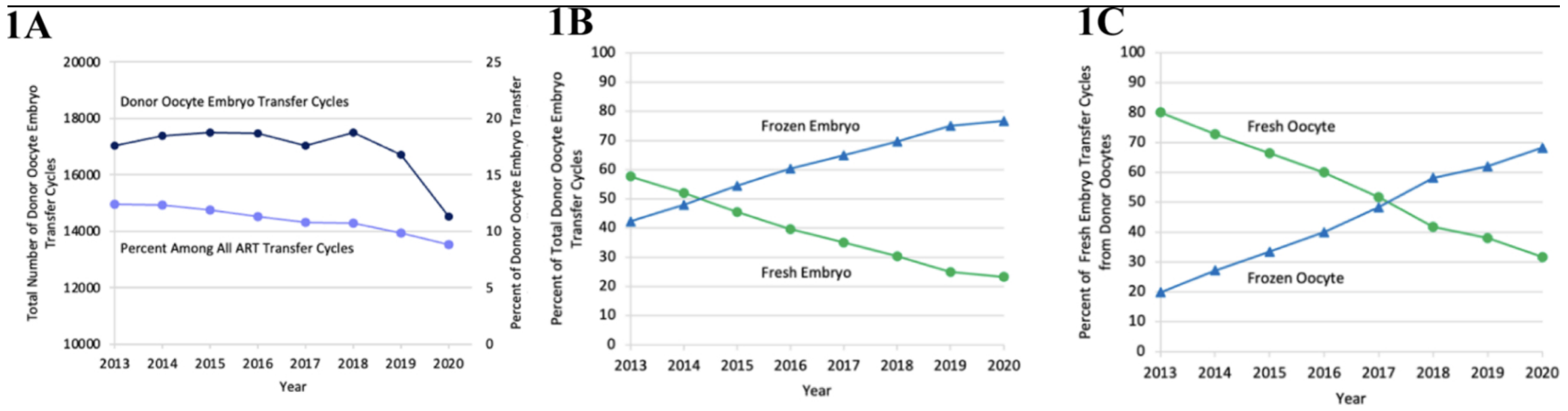
Singletons are defined as one infant born alive (no stillbirths). Twins are two infants born with at least one born alive, and triplets or more are at least three infants born with at least one born alive. Infants born from multiple gestations, including twins, are at higher risk of poor outcomes—including preterm birth, low birth weight, neurological impairments, or death—than infants born as singletons.

IVF UTILIZATION: AUTOLOGOUS V DONOR EGG



Fresh and frozen eggs or embryos from patients and donors are included. Banking cycles are excluded.

EMORY REPRODUCTIVE CENTER



IVF UTILIZATION TRENDS: DONOR EGG

EMORY REPRODUCTIVE CENTER

DONOR EGG CONCEPTION

Original Investigation

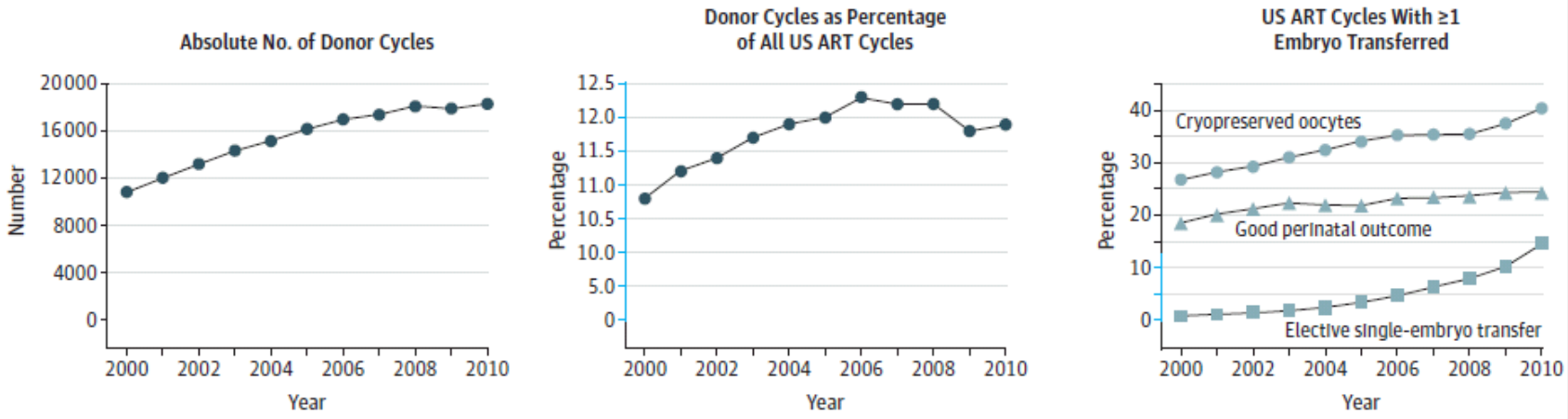
Trends and Outcomes for Donor Oocyte Cycles in the United States, 2000-2010

Jennifer F. Kawwass, MD; Michael Monsour, PhD; Sara Crawford, PhD; Dmitry M. Kissin, MD, MPH; Donna R. Session, MD; Aniket D. Kulkarni, MBBS, MPH; Denise J. Jamieson, MD, MPH; for the National ART Surveillance System (NASS) Group

Donor oocytes further extend reproductive window

- Increasingly common
- Increasingly associated with good perinatal outcome, trend toward eSET

Figure. Donor Oocyte Trends in the United States From 2000-2010



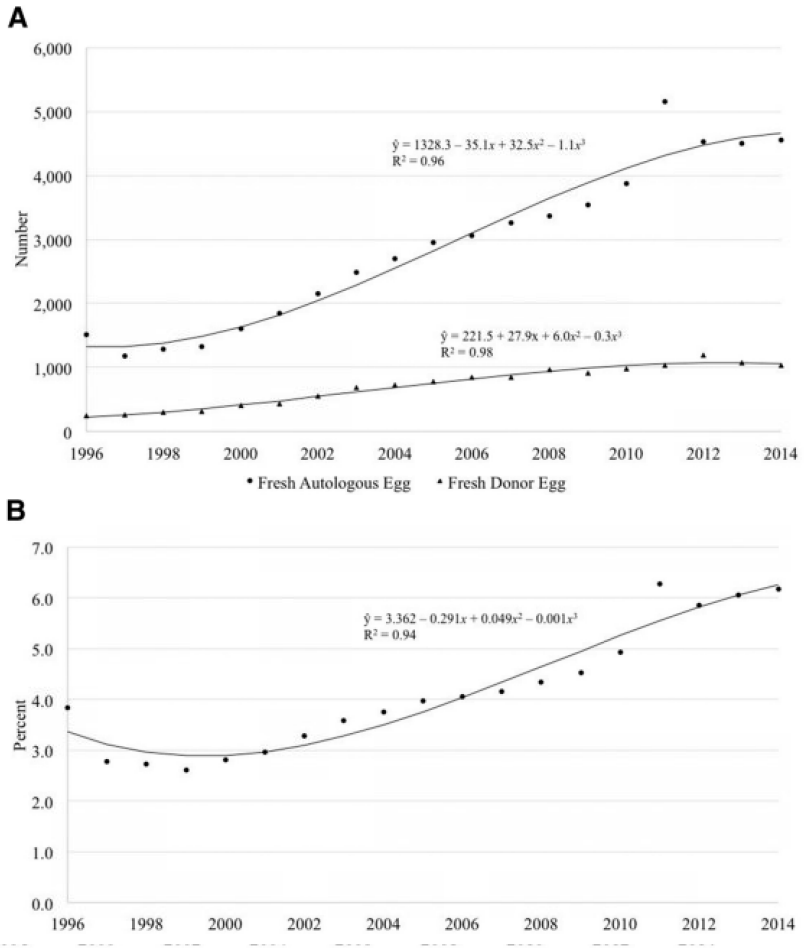
Good perinatal outcome defined as a singleton live birth at 37 weeks or later and birth weight of 2500 g or more. Y-axes shown in blue indicate the interval 0% to 12.5%. ART indicates assisted reproductive technology.

Kawwass et al. 2013 *JAMA*

EMORY REPRODUCTIVE CENTER

IVF UTILIZATION TRENDS: DONOR SPERM

FIGURE 1
Number of fresh cycles using donor sperm



A, Number of fresh autologous and donor oocyte ART cycles[a] using donor sperm, United States, 1996—2014. The number of fresh cycles using donor sperm with autologous oocytes has increased over time. The number of fresh cycles using donor oocytes followed a similar pattern except for a decline in recent years peaking in 2012. **B,** Percentage of all banking and fresh ART cycles[a] using donor sperm, United States, 1996—2014. Although there was a slight initial decline between 1996 and 1999, the percentage of cycles using donor sperm has since continued to increase over time, accounting for 4.9—6.2% of all ART cycles between 2010 and 2014.

ART, assisted reproductive technology.

[a] Cycles in which oocyte retrieval was performed.

Gerkowicz et al. ART with donor sperm: national trends and perinatal outcomes. Am J Obstet Gynecol 2018.

EMORY
REPRODUCTIVE CENTER

IVF UTILIZATION TRENDS: DONOR EMBRYO

Increasing Utilization and Live Birth Rates

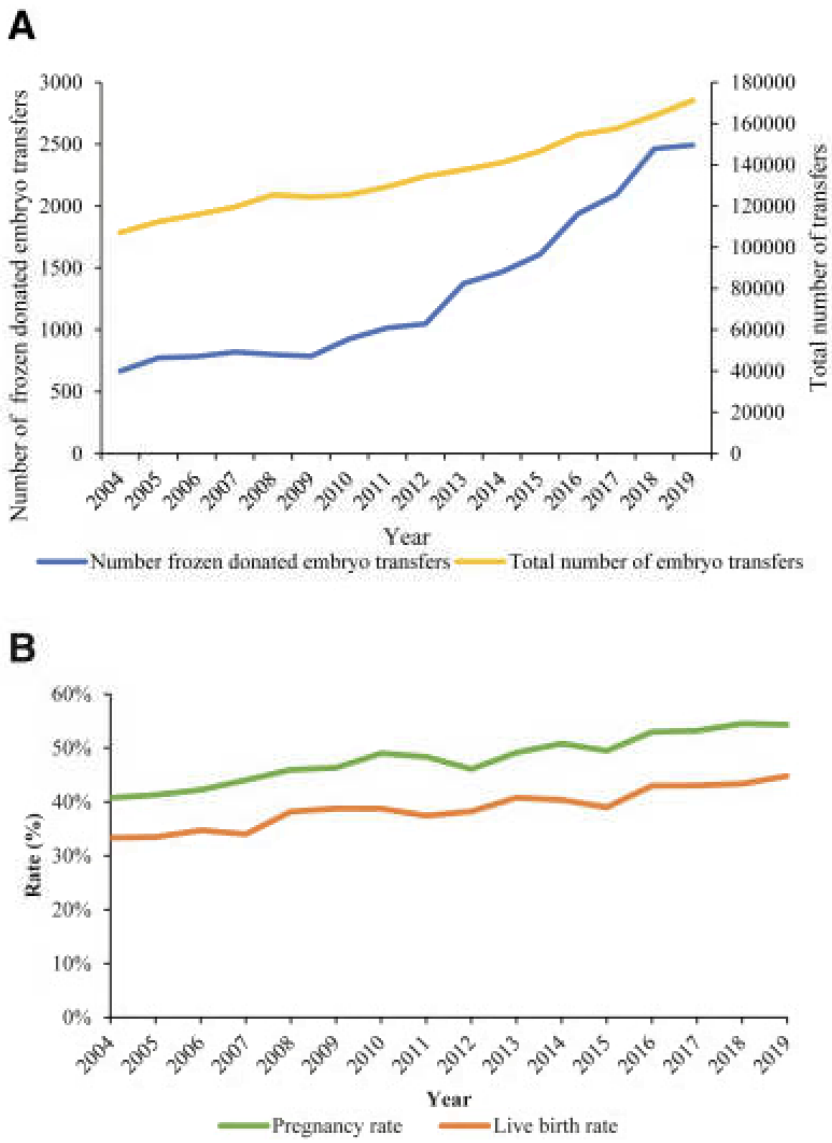
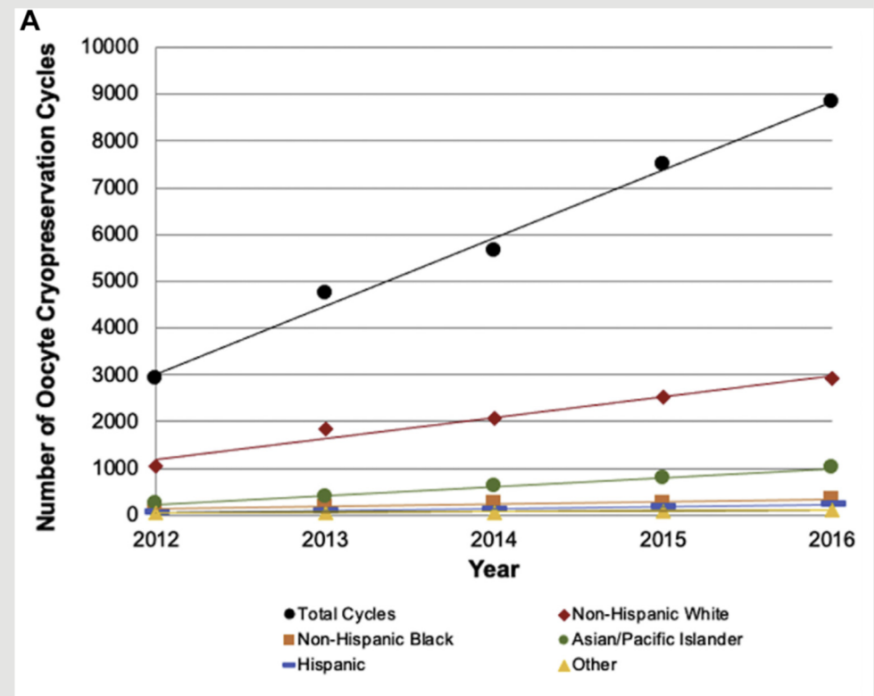
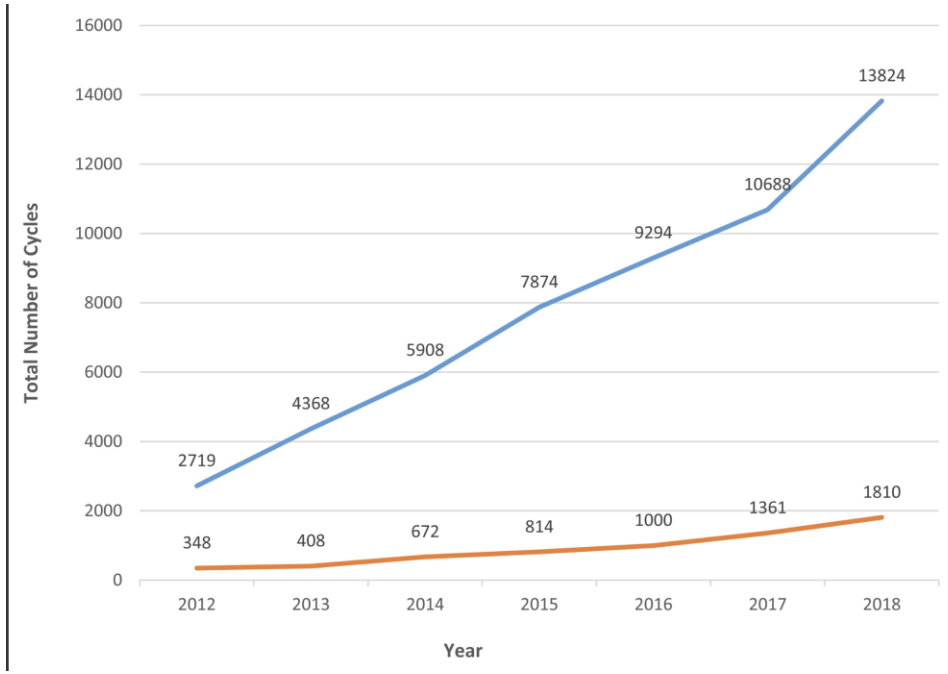


Figure Trends in frozen donated embryo transfers and outcomes, 2004–2019

EMORY REPRODUCTIVE CENTER

IVF UTILIZATION TRENDS: OOCYTE CRYOPRESERVATION



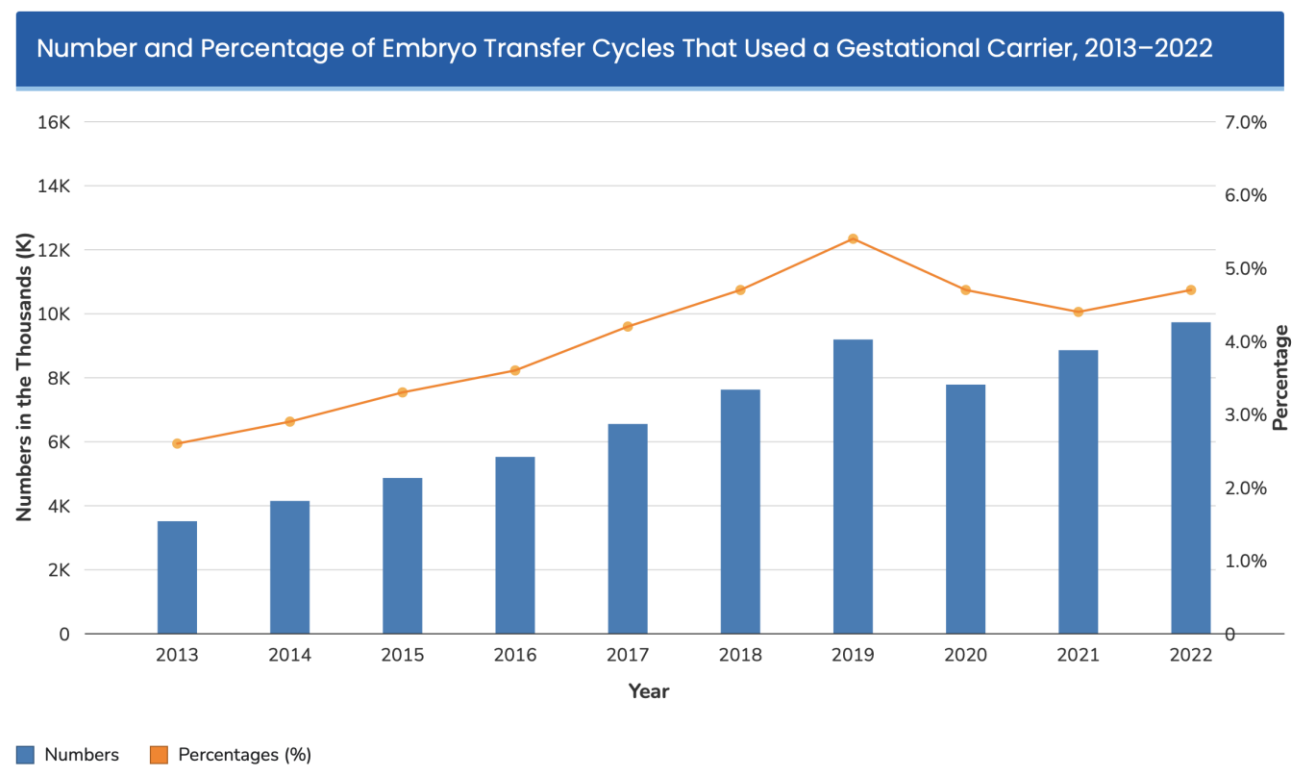


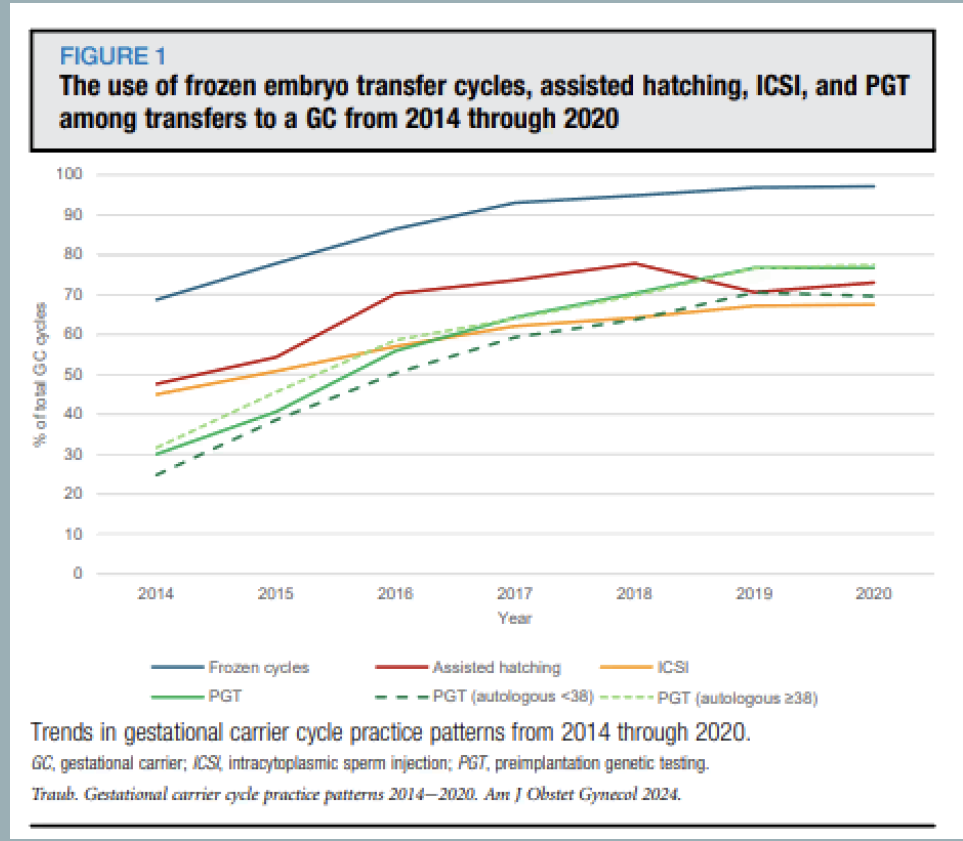
Oocyte Cryopreservation Cycles*

Oocyte Thaw Cycles**

EMORY REPRODUCTIVE CENTER

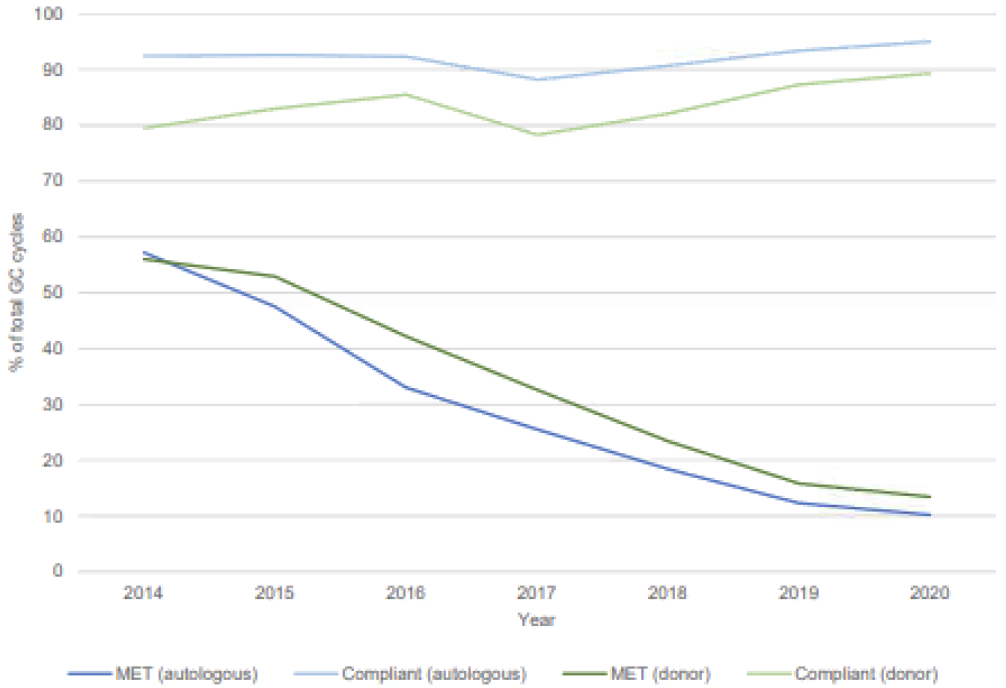
NATIONAL TRENDS: GESTATIONAL CARRIER





GESTATIONAL CARRIER – IMPROVEMENT IN ADHERENCE TO RECOMMENDATIONS

FIGURE 2
Use of MET and guideline compliance among autologous and donor transfers to a GC from 2014 through 2020



Trends in the transfer of multiple embryos to a GC and compliance with ASRM national guidelines (new guidelines in 2013 and 2017) from 2014 through 2020.

ASRM, American Society of Reproductive Medicine; *GC*, gestational carrier; *MET*, multiple embryo transfers.

Traub. Gestational carrier cycle practice patterns 2014–2020. Am J Obstet Gynecol 2024.

EMORY REPRODUCTIVE CENTER

NATIONAL LEGAL LANDSCAPE

Current Commentary

Roe v Wade and the Threat to Fertility Care

Eve C. Feinberg, MD, Jennifer F. Kawwass, MD, and Marcelle I. Cedars, MD

- Defining "Personhood" at fertilization makes effective, evidence-based IVF treatment impossible
- Alabama court ruling in 2023 attributing personhood to embryos paused fertility treatment in the state
- Multiple states are considering such legislation
- Important to understand the downstream impact on fertility care of personhood legislation

- In Georgia:
  - Georgia Fertility Network
  - Passed 2 bills in 2025 in effort to protect fertility access in the state

(Obstet Gynecol 2022;140:557–9)
DOI: 10.1097/AOG.0000000000004928

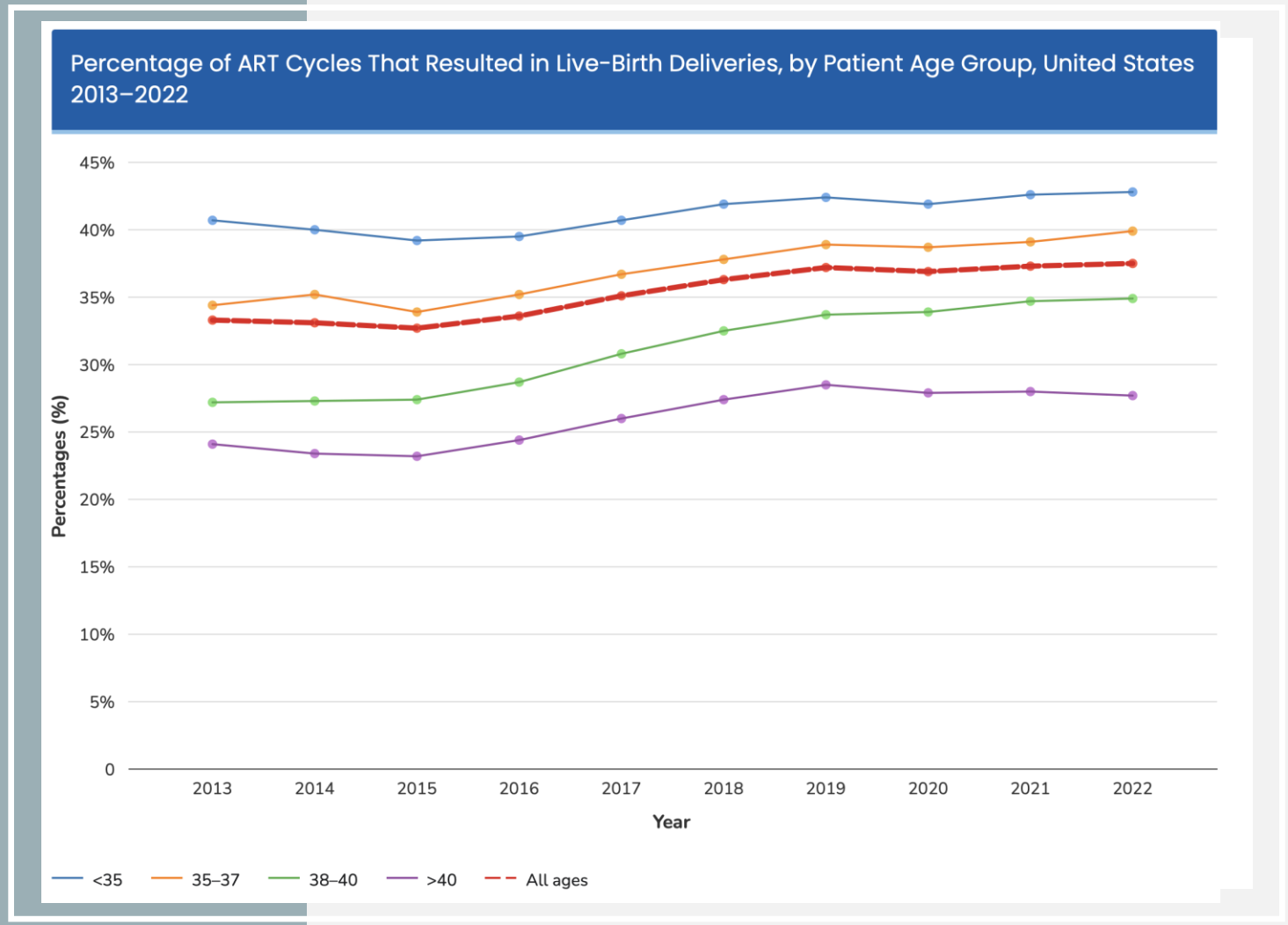
Georgia Fertility Network

IVF NEONATAL OUTCOMES

EMORY
REPRODUCTIVE CENTER

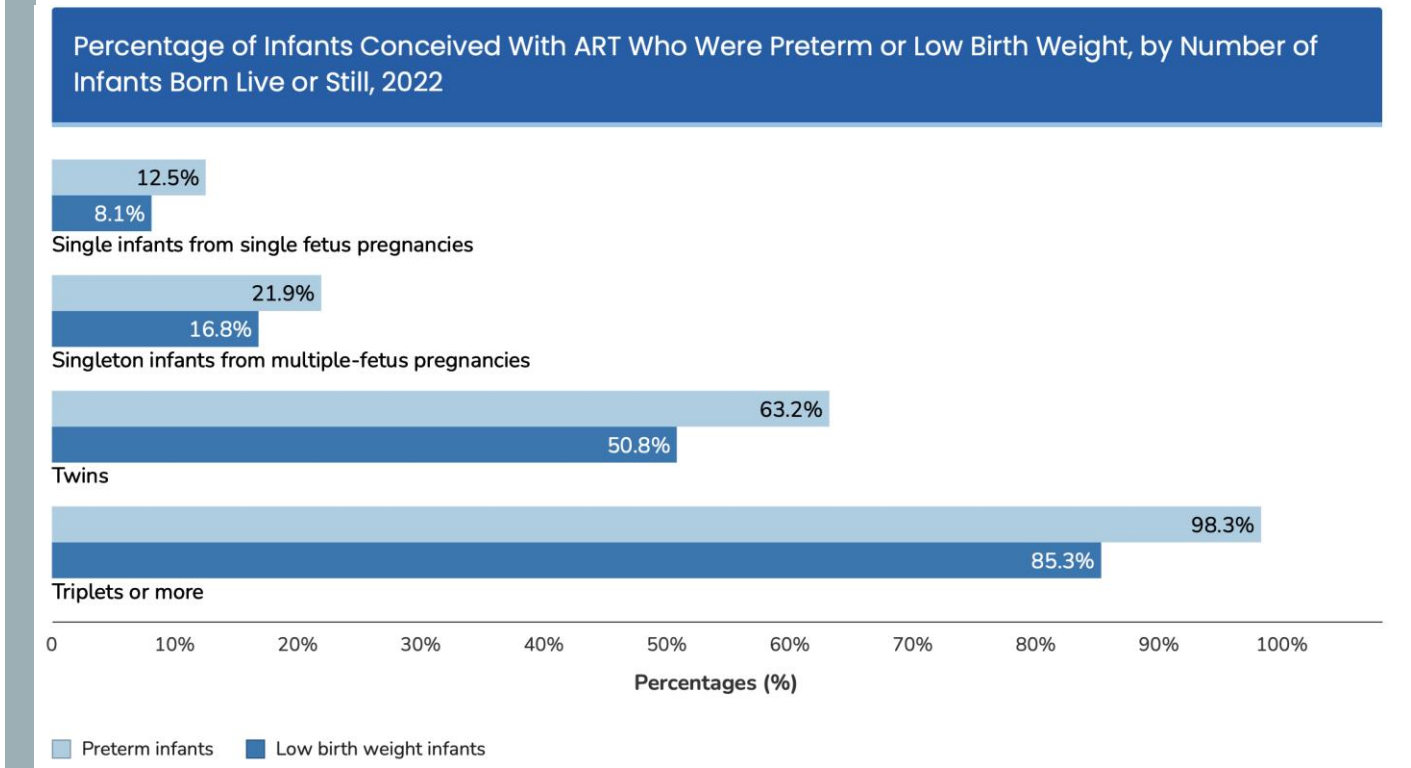
IVF: LIVE BIRTH PER CYCLE START

Stratified by Age



NATIONAL OUTCOMES BY PLURALITY

Preterm Birth and Low Birthweight Delivery much more common among multifetal pregnancies



INFERTILE POPULATION, COMPARISON GROUPS

Generally healthy population at baseline, undergoing medical intervention

- Minimize risk associated with procedure and outcome

Risk quantification

- Varies by comparison group
  - Consider whether underlying infertility itself versus IVF procedures
    - Spontaneous conception in a fertile couple
    - Non-IVF assisted conception in an infertile couple

Consideration of alternative

- Not undergoing IVF, not having a biological child

Relative versus absolute risk

- Consider absolute increase in risk

EMORY
REPRODUCTIVE CENTER

FETAL RISKS, SINGLETON GESTATION

IVF singleton pregnancies may be at higher risk of adverse perinatal outcomes including **preterm birth** and **low birth weight** compared with spontaneously conceived singletons, even after controlling for known risk factors such as age, weight, and tobacco use[1-4]

ACOG CO No 671 2016
Pandey HR Update 2012
Schieve MCHJ 2007
Qin AGO 2017

EMORY
REPRODUCTIVE CENTER

LIMITATIONS OF META-ANALYSES

- Although the associated relative risk is higher in the IVF group, absolute risk not clearly delineated
- Limited by heterogeneity, residual confounding, publication bias
- Association $\neq$ Causation
- Underlying mechanism by which IVF may be associated with increased risk remains uncertain
  - Ovarian stimulation?
  - Resultant effect on the uterine hormonal milieu?
  - Gamete manipulation?
  - Embryo exposure to culture media?
  - Couple's underlying infertility itself?

EMORY REPRODUCTIVE CENTER

FETAL RISKS, SINGLETON GESTATION UNDERLYING INFERTILITY

Underlying Infertility as the Etiology of Increased Adverse Perinatal Outcomes

- IVF versus non-IVF births.[1-5]
- Discordant sibling design
  - Attempt to evaluate inherent IVF risk compared with underlying maternal factors
  - Early relatively small studies using this model found conflicting results[6,7]
  - 2016 larger cohort discordant singleton 6,458 sibling pairs[8]
    - One conceived IVF, other conceived spontaneously
    - IVF use remained associated: increased LBW and PTB
    - Absolute risk:

	IVF	Non-IVF
PTB	9.7%	7.9%
LBW	6.8%	4.9%

1. Cooper F&S 2011
2. Declercq F&S 2015
3. Kondapalli F&S 2013
4. Stern F&S 2015
5. Luke JARG 2016
6. Romundstad Lancet 2008
7. Henningsen F&S 2011
8. Dhalwani F&S 2016

FETAL RISKS, SINGLETON GESTATION UNDERLYING INFERTILITY

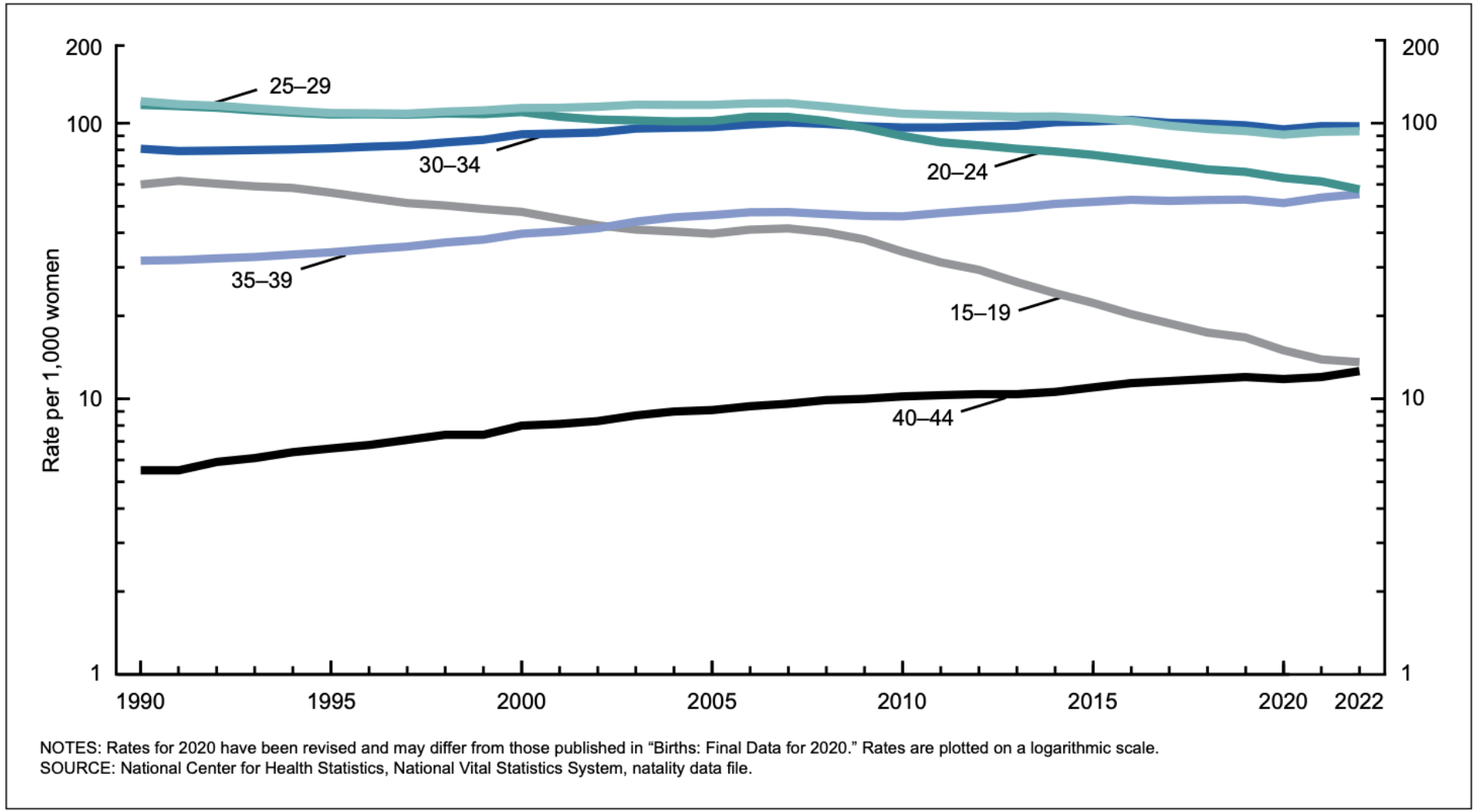
Underlying Infertility as the Etiology of Increased Adverse Perinatal Outcomes

- 2016 Cohort discordant singleton 6,458 sibling pairs[1]
  - IVF-conceived singletons versus spontaneously conceived singletons
    - 33 grams lighter (95% CI 18–49 grams)
    - Born ½ day (95% CI 0.14– 1.02 of a day) sooner
  - Adverse perinatal outcomes differed by underlying infertility cause
    - Female infertility: 35% increased risk of preterm birth
    - No significant increased risk with underlying male infertility
  - Discordant sibling design may not be applicable to all women
    - Many cannot conceive spontaneously

1. Dhalwani F&S 2016

EMORY REPRODUCTIVE CENTER

Figure 2. Birth rate, by selected age of mother: United States, 1990–2022



NOTES: Rates for 2020 have been revised and may differ from those published in "Births: Final Data for 2020." Rates are plotted on a logarithmic scale.
SOURCE: National Center for Health Statistics, National Vital Statistics System, natality data file.

EMORY
REPRODUCTIVE CENTER

FETAL RISKS, SINGLETON GESTATION ADVANCED MATERNAL AGE

- Advancing age remains the single most important factor associated with infertility
- Increasing purposeful delay of child-bearing
- Advanced maternal age (regardless of means of conception) increased risk of…
- Preterm birth
  - Low birth weight
  - Hypertensive disorders
  - Stillbirth
  - Cesarean delivery
- Increased risk may be compounded by use of IVF, although age appears to be primary predictor independent of IVF use

EMORY
REPRODUCTIVE CENTER

IVF, SINGLETON GESTATION: BIRTH DEFECTS

EMORY
REPRODUCTIVE CENTER

IVF, SINGLETON GESTATION: BIRTH DEFECTS


Birth defects in children conceived by in vitro fertilization and intracytoplasmic sperm injection: a meta-analysis

Juan Wen, B.S.,[a,b] Jie Jiang, B.S.,[a,b] Chenyue Ding, B.S.,[d] Juncheng Dai, M.D.,[b] Yao Liu, B.S.,[b] Yankai Xia, M.D., Ph.D.,[a,c] Jiayin Liu, M.D., Ph.D.,[a,d] and Zhibin Hu, M.D., Ph.D.[a,b]

[a] State Key Laboratory of Reproductive Medicine, [b] Department of Epidemiology and Biostatistics, [c] Department of Toxicology, Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, and [d] Center of Clinical Reproductive Medicine, the First Affiliated Hospital, Nanjing Medical University, Nanjing, People's Republic of China

IVF, Infertility, and Birth Defects

- Several heterogeneous cohort studies and meta-analyses
  - Increased risk pooled birth defects IVF neonates vs. spontaneously conceived[1-4]
  - 2012 meta-analysis, 46 studies[1]
    - Significantly increased risk of birth defects
    - Pooled risk 1.37 [95% CI 1.26– 1.48] conventional and ICSI v. spontaneous
    - No difference between conventional and ICSI
    - Contribution of parental infertility is unclear

1. Wen F&S 2012
2. Pandey HR Update 2012
3. Hansen HR Update 2013
4. Boulet JAMA Pediatr 2016

EMORY REPRODUCTIVE CENTER

Society for Maternal-Fetal Medicine
High-risk pregnancy experts

SMFM Consult Series

smfm.org

Society for Maternal-Fetal Medicine Consult Series #60: Management of pregnancies resulting from in vitro fertilization

Society for Maternal-Fetal Medicine (SMFM); Alessandro Ghidini, MD; Manisha Gandhi, MD; Jennifer McCoy, MD; Jeffrey A. Kuller, MD; Publications Committee

Check for updates

TABLE

Pooled estimates of rates (per 1000) for specific congenital anomalies in singleton pregnancies following in vitro fertilization, with or without intracytoplasmic sperm injection compared with naturally occurring pregnancies (95% confidence interval)

Organ system	IVF with or without ICSI pregnancies	Naturally occurring pregnancies
Cleft lip or palate	1.3 (0.9–1.7)	1.2 (1.0–1.6)
Eye, ear, face, neck	1.7 (0.8–3.6)	1.5 (0.8–2.8)
CNS	1.7 (1.2–2.4)	1.7 (1.2–2.6)
Respiratory system	0.8 (0.4–1.6)	0.8 (0.5–1.4)
GI	3.8 (2.4–6.0)	2.5 (1.4–4.5)
Musculoskeletal	11.0 (6.7–18.1)	8.1 (4.7–13.6)
Urogenital	10.9 (6.9–17.2)	6.4 (4.5–9.1)
Cardiovascular	5.7 (5.3–11.2)	5.2 (4.5–9.1)

Data from Chen et al.[54]

CI, confidence interval; *CNS*, central nervous system; *GI*, gastrointestinal; *ICSI*, intracytoplasmic sperm injection; *IVF*, in vitro fertilization.

Society for Maternal-Fetal Medicine. SMFM Consult Series #60: Management of pregnancies resulting from in vitro fertilization. Am J Obstet Gynecol 2022.

IVF, SINGLETON GESTATION: BIRTH DEFECTS

Original Investigation

Assisted Reproductive Technology and Birth Defects Among Liveborn Infants in Florida, Massachusetts, and Michigan, 2000-2010

Sheree L. Boulet, DrPH, MPH; Russell S. Kirby, PhD; Jennita Reefhuis, PhD; Yujia Zhang, PhD; Saswati Sunderam, PhD; Bruce Cohen, PhD; Dana Bernson, MPH; Glenn Copeland, MBA; Marie A. Bailey, MA, MSW; Denise J. Jamieson, MD, MPH; Dmitry M. Kissin, MD, MPH; for the States Monitoring Assisted Reproductive Technology (SMART) Collaborative

Table 2. Prevalence and Risk Ratios for Selected Birth Defects by Mode of Conception Among Liveborn Infants in Florida, Massachusetts, and Michigan, 2000-2010

	ART (n = 64 861)		Non-ART (n = 4 553 215)			
Birth Defect	No.	Prevalence per 10 000	No.	Prevalence per 10 000	aRR (95% CI)[a]	*P* Value[b]
≥1 Nonchromosomal defects[c]	389	59.97	22 036	48.40	1.28 (1.15-1.42)	<.001
Spina bifida with or without anencephaly	22	3.39	1640	3.60	1.47 (0.94-2.29)	.65
Transposition of great vessels	35	5.40	2068	4.54	1.20 (0.85-1.70)	>.99
Tetralogy of Fallot	45	6.94	2165	4.76	1.34 (0.99-1.82)	.51
Atrioventricular septal defect	41	6.32	2068	4.54	0.94 (0.68-1.30)	>.99
Cleft palate only	41	6.32	2577	5.66	1.11 (0.81-1.52)	>.99
Cleft lip and/or cleft palate	46	7.09	3702	8.13	0.97 (0.72-1.30)	>.99
Tracheoesophageal fistula/esophageal atresia	41	6.32	1093	2.40	1.93 (1.40-2.67)	.001
Rectal and large intestinal atresia/stenosis	52	8.02	1893	4.16	2.03 (1.51-2.74)	<.001
Reduction deformity, upper limbs	21	3.24	1049	2.30	1.41 (0.90-2.19)	.79
Reduction deformity, lower limbs	22	3.39	756	1.66	2.18 (1.39-3.43)	.007
≥1 Chromosomal defects, <35 y[d]	36	11.97	3715	9.62	1.27 (0.90-1.78)	.85
Down syndrome, maternal age <35 y	35	11.64	3136	8.12	1.39 (0.98-1.96)	.51
≥1 Chromosomal defects, ≥35 y	79	22.71	2936	42.56	0.61 (0.48-0.76)	<.001
Down syndrome, maternal age ≥35 y	74	21.27	2603	37.73	0.63 (0.49-0.80)	.001

1. Boulet JAMA Pediatr 2016

EMORY REPRODUCTIVE CENTER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Reproductive Technologies and the Risk of Birth Defects

Michael J. Davies, M.P.H., Ph.D., Vivienne M. Moore, M.P.H., Ph.D., Kristyn J. Willson, B.Sc., Phillipa Van Essen, M.P.H., Kevin Priest, B.Sc., Heather Scott, B.Mgmt., Eric A. Haan, M.B., B.S., and Annabelle Chan, M.B., B.S, D.P.H.

Table 3. Odds Ratio for Birth Defects According to Category of Defect and Multiplicity.*

Birth-Defect Category	Singleton Births			
	Assisted Conception (N=4333)	Spontaneous Conception (N=295,220)	Unadjusted Odds Ratio	Adjusted Odds Ratio†
	no. of births (%)			
Any defect	361 (8.3)	16,989 (5.8)	1.48 (1.32–1.65)	1.30 (1.16–1.45)
Multiple defects	95 (2.2)	4,690 (1.6)	1.38 (1.13–1.70)	1.24 (1.00–1.54)
Congenital abnormalities: ICD-9 codes 740–759	335 (7.7)	15,372 (5.2)	1.52 (1.35–1.70)	1.32 (1.17–1.48)
Cardiovascular abnormalities: BPA codes 74500–74799	78 (1.8)	3,472 (1.2)	1.54 (1.22–1.93)	1.36 (1.08–1.72)
Musculoskeletal abnormalities: BPA codes 75400–75699	130 (3.0)	4,776 (1.6)	1.87 (1.57–2.24)	1.50 (1.24–1.80)
Urogenital abnormalities: BPA codes 75200–75399	95 (2.2)	4,872 (1.7)	1.34 (1.09–1.65)	1.25 (1.01–1.55)
Gastrointestinal abnormalities: BPA codes 74900–75199	34 (0.8)	1,832 (0.6)	1.26 (0.89–1.78)	1.18 (0.83–1.68)
Central nervous system abnormalities: BPA codes 74000–74299	22 (0.5)	1,104 (0.4)	1.37 (0.89–2.09)	1.34 (0.86–2.07)
Respiratory abnormalities: BPA codes 74800–74899	3 (0.1)	455 (0.2)	0.41 (0.12–1.40)	0.36 (0.11–1.18)
Chromosomal abnormalities: BPA codes 75800–75899	23 (0.5)	1,088 (0.4)	1.43 (0.94–2.17)	0.87 (0.57–1.33)
Metabolic abnormalities: BPA codes 24390–27790	3 (0.1)	379 (0.1)	0.59 (0.19–1.79)	0.53 (0.16–1.74)
Hematologic abnormalities: BPA codes 28200–28699	5 (0.1)	225 (0.1)	1.38 (0.56–3.35)	1.61 (0.61–4.23)
Cerebral palsy	17 (0.4)	496 (0.2)	2.35 (1.45–3.81)	2.22 (1.35–3.63)

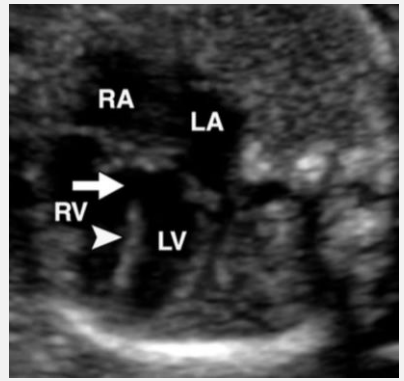
* All odds ratios are for assisted conception as compared with spontaneous conception, with adjustment for clustering of births within the mother. BPA denotes British Paediatric Association, and ICD-9 *International Classification of Diseases, 9th Revision.*

† Analyses were adjusted for maternal age, parity, fetal sex, year of birth, maternal race or ethnic group, maternal country of birth, maternal conditions in pregnancy, maternal smoking during pregnancy, socioeconomic status, and maternal and paternal occupation.

EMORY REPRODUCTIVE CENTER

IVF
CARDIAC DEFECTS

Congenital Heart Defects



- American Institute of Ultrasound in Medicine (AIUM), American Heart Association (AHA), and the Society for Maternal Fetal Medicine (SMFM) recommend fetal echocardiogram in IVF-conceived pregnancies

- 2018 meta-analysis[1]
  - Absolute rates:

    Any cardiac defect (including minor defects such as ASD and VSD)
    - 0.68% in the spontaneously conceived group
    - 1.30% in the IVF–ICSI group

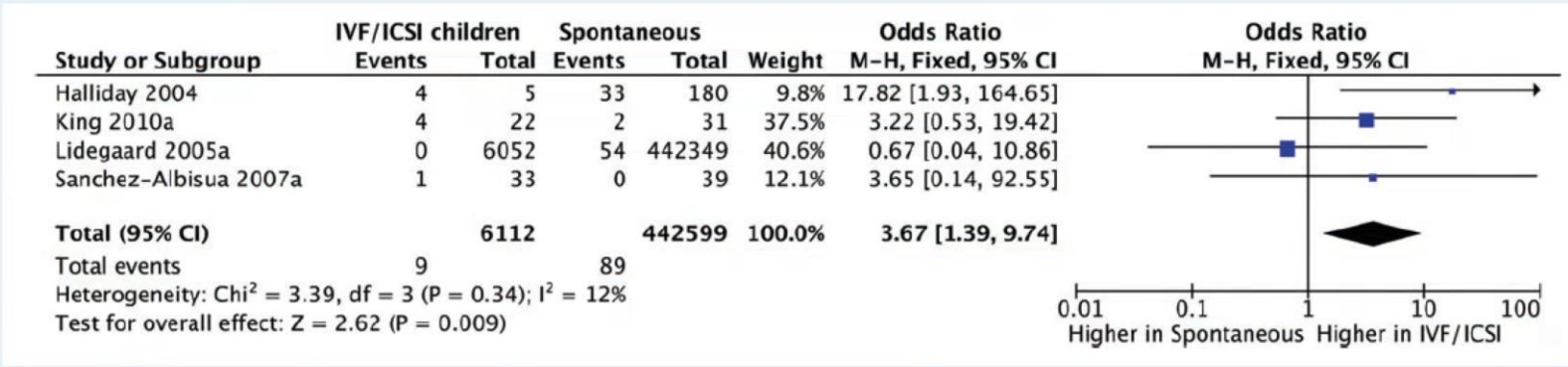
EMORY REPRODUCTIVE CENTER

1. Giorgioni Ultrasound Obstet Gynecol 2018

IVF
METHYLATION AND IMPRINTING DISORDERS

DNA methylation and imprinting disorders

- Increased association imprinting disorders but not overall DNA methylation patterns[1,2]
- Absolute risk remains low
  - 0.15% in IVF–ICSI conceptions
  - 0.02% in spontaneous conception



Study or Subgroup	IVF/ICSI children Events	Total	Spontaneous Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Halliday 2004	4	5	33	180	9.8%	17.82 [1.93, 164.65]
King 2010a	4	22	2	31	37.5%	3.22 [0.53, 19.42]
Lidegaard 2005a	0	6052	54	442349	40.6%	0.67 [0.04, 10.86]
Sanchez-Albisua 2007a	1	33	0	39	12.1%	3.65 [0.14, 92.55]
Total (95% CI)		**6112**		**442599**	**100.0%**	**3.67 [1.39, 9.74]**
Total events	9		89			

Heterogeneity: $Chi^2 = 3.39$, $df = 3$ ($P = 0.34$); $I^2 = 12\%$
Test for overall effect: $Z = 2.62$ ($P = 0.009$)

Figure 4 Forest plot analyses for risk of any imprinting disorder between IVF/ICSI versus spontaneously conceived children.

1. Lazaraviciute HR Update 2014
2. Lazaraviciute HR Update 2015

EMORY REPRODUCTIVE CENTER

IVF & BIRTH DEFECTS

Balance of Evidence

- Association with pooled birth defects

- Reasonable to inform patients of potential increased risk keeping in mind the low absolute risk and limited alternatives to conception

1. Lazaraviciute HR Update 2014
2. Lazaraviciute HR Update 2015

EMORY REPRODUCTIVE CENTER

IVF AND CHILDHOOD CANCER


JAMA Pediatrics

Original Investigation ONLINE FIRST

April 1, 2019

Association of In Vitro Fertilization With Childhood Cancer in the United States

Logan G. Spector, PhD[1]; Morton B. Brown, PhD[2]; Ethan Wantman, MBA[3]; et al

Author Affiliations

JAMA Pediatr. Published online April 1, 2019. doi:10.1001/jamapediatrics.2019.0392

Spector *JAMA Pediatrics 2019*

- 2004 – 2012
- IVF v no-IVF
- Linkage:

  SART CORS IVF live birth with birth and cancer registries in 14 states

- Outcome: 251.9 v 192.7 hazard ratio, 1.17; 95% CI, 1.00-1.36

  59 more cancers per 1 million person years

  Equivalent to: 0.0059 per 100 years

EMORY REPRODUCTIVE CENTER

IVF AND CHILDHOOD CANCER


JAMA Pediatrics

Original Investigation ONLINE FIRST

April 1, 2019

Association of In Vitro Fertilization With Childhood Cancer in the United States

Logan G. Spector, PhD[1]; Morton B. Brown, PhD[2]; Ethan Wantman, MBA[1]; et al

Author Affiliations

JAMA Pediatr. Published online April 1, 2019. doi:10.1001/jamapediatrics.2019.0392

Table 2. Data on the Rates of Cancer by Study Group for All Children (Singleton and Multiple Births Combined)[a]

	Cases, No.		Cancer Rate/1 000 000 Person-Years		HR (95% CI)[b]
Cancer	IVF	Non-IVF	IVF	Non-IVF	
Any cancer	321	2042	251.9	192.7	1.17 (1.00-1.36)
Leukemia	93	707	73.0	66.7	0.93 (0.70-1.22)
ALL	72	534	56.5	50.4	0.96 (0.71-1.32)
AML	13	108	10.2	10.2	0.74 (0.35-1.53)
Lymphoma	22	139	17.3	13.1	1.00 (0.56-1.80)
CNS cancer	59	383	46.3	36.1	1.26 (0.89-1.79)
Astrocytoma	34	197	26.7	18.6	1.50 (0.95-2.36)
Ependymoma	5	48	3.9	4.5	0.53 (0.16-1.72)
Intracranial embryonal tumors	13	83	10.2	7.8	1.41 (0.67-2.95)
Neuroblastoma	47	260	36.9	24.5	1.10 (0.74-1.65)
Retinoblastoma	14	127	11.0	12.0	1.11 (0.57-2.18)
Renal cancer	28	186	22.0	17.6	1.10 (0.66-1.84)
Hepatic cancer	23	60	18.1	5.7	2.46 (1.29-4.70)
Soft-tissue sarcoma	18	97	14.1	9.2	1.50 (0.81-2.84)
Germ cell tumors	11	43	8.6	4.1	2.13 (0.91-4.96)
Embryonal tumors[c]	131	746	102.8	70.4	1.28 (1.01-1.63)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS, central nervous system; HR, hazard ratio; IVF, in vitro fertilization.

[a] The final population included 275 686 children in the IVF group (1 274 070 person-years; 209 586 births) and 2 266 847 children in the non-IVF group (10 596 144 person-years; 2 230 378 births).

[b] Adjusted for state of birth, maternal race and ethnicity, maternal educational level (college graduate vs less than college graduate), maternal age, and child's sex; missing data for maternal race (4.3%) and educational level (2.2%) were replaced by a category labeled "missing" in each variable.

[c] Neuroblastoma, retinoblastoma, nephroblastoma, hepatoblastoma, embryonal rhabdomyosarcoma, pulmonary and pleuropulmonary blastoma, medulloblastoma, primitive neuroectodermal tumor, medulloepithelioma, and atypical teratoid and rhabdoid tumor.

EMORY REPRODUCTIVE CENTER

CONCLUSION

EMORY
REPRODUCTIVE CENTER

STEADY IMPROVEMENT

Over the past 40 years, the field of IVF has made tremendous strides forward

- **IVF increasingly effective**
  - Improvement in pregnancy rates
  - Decrease in risk of multiple gestation
  - Optimization of maternal and perinatal outcomes
- **Preimplantation genetic testing**
  - Allows single euploid embryo transfer in older women
- **Elective single-embryo transfer**
  - Rates in the United States are increasing in women of all ages
  - Room for further improvement
    - Continued research risks associated with multiple gestation
    - Scientific progress in embryo selection
    - Tailoring IVF practice norms
    - Improved financial support from insurance companies

EMORY
REPRODUCTIVE CENTER

IVF PERINATAL RISK – THE BIG PICTURE

- Although IVF-conceived pregnancies have been shown to be associated with **increased perinatal risk** of PTD and compared with spontaneously conceived pregnancies, the **absolute risk to an individual fetus remains low.**
- Given the **alternative** of not conceiving or having a child with an inheritable genetic disease, moving forward with IVF remains a logical next step for many couples with infertility or another medical diagnosis that warrants IVF.
- Risk of multiple gestation **lower with IVF** than with other fertility treatments
- Physicians can minimize risks associated with stimulation, retrieval, and subsequent pregnancies by following most current **ASRM guidelines**
- **Pre-conception MFM involvement** can help ensure adequate informed decision-making in women who desire to pursue conception despite underlying medical conditions or advanced maternal age.

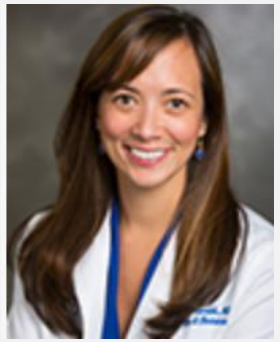
EMORY
REPRODUCTIVE CENTER

EMORY
REPRODUCTIVE CENTER

Heather S. Hipp, MD
Fellowship Director

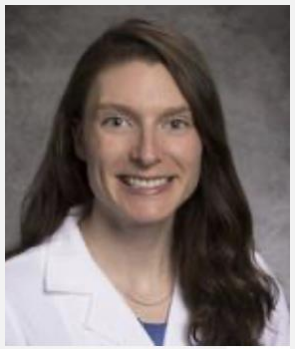
D. Austin Schirmer, MD
REI IT Lead
Assoc PD, Gyn/OB

Jim Toner, MD, PhD

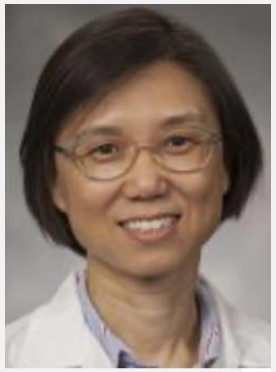


Audrey Marsidi, MD
Third Party Director

Jessica B. Spencer, MD, MSc

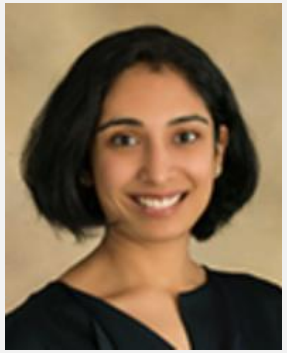


Jackie Lee, MD
Oncofertility Director



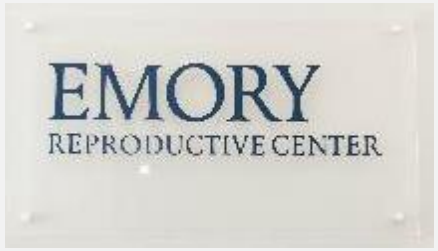
Weirong Shang, PhD, HCLD
Embryology Lab Director

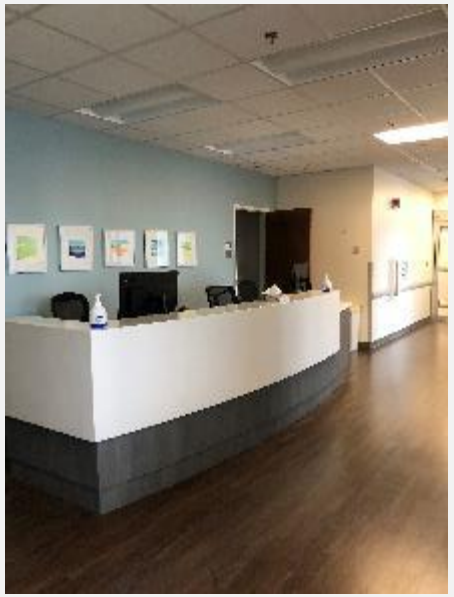
Jennifer F. Kawwass, MD
Division Director
Medical Director



Akanksha Mehta, MD
Reproductive Urologist

Heather Hoff, MD
LGBTQ+ Director


EMORY
REPRODUCTIVE CENTER



Thank you!

SUPPLEMENTAL SLIDES

EMORY
REPRODUCTIVE CENTER

SART VERSUS NASS

Table 18.1 The comparison of two assisted reproductive technology data collection systems in the US

Characteristics	US National ART Surveillance System (NASS, CDC)	Clinical Outcomes Reporting System (SART CORS, SART)
Reporting Requirements, Coverage and Data Validation		
Reporting requirements	All ART clinics	SART member clinics
Legal requirements	FCSRCA	SART by-laws
Reporting clinics	94% of all clinics	78% of all clinics
Reported cycles	~98% of all cycles	~90% of all cycles
Data validation	Random validation to assess discrepancy rates for key variables (approximately 35 clinics annually)	Targeted validation to detect systematic reporting errors (approximately 10 clinics annually)
Data cleaning	Basic data cleaning and reconciliation prior to publication	Publication as is with option to correct the data
Using ART Data for ART Reports and Clinical Practice		
Reporting clinic-specific data	ART Success Rates Report online at www.cdc.gov/ART	Clinic Tables online at www.sart.org
Reporting national data	National ART success rates data and ART National Summary Report	National ART success rates data
Reporting state-level data	State-specific ART Surveillance Summary	None
Using data for clinical guidelines / recommendations	Through peer-reviewed publications informing practice guidelines	Through peer-reviewed publications, practice guidelines, committee opinions
Primary research focus	Infant health outcomes (multiple births, preterm births, low birth weight, long-term outcomes), maternal health outcomes (pregnancy and birth complications, long-term outcomes), access to fertility treatments	ART effectiveness (laboratory quality, effectiveness of various ART methods), ART safety (multiple births, preterm births)
Using data to improve clinical care	Patient and provider education, prevention of multiple births (CDC/SART joint projects)	Patient and provider education, prevention of multiple births (CDC/SART joint projects), quality assurance activities
Using ART Data for Research and Data Linkages		
Data users	Any researcher with strong research proposal	SART member or individuals approved by the SART Executive Council
Data access	Onsite at the Division of Reproductive Health (CDC)	De-identified dataset provided to approved researcher
Confidentiality protection	Assurance of Confidentiality; public health surveillance does not require patient informed consent	Health Insurance Portability and Accountability Act of 1996 (HIPAA) requirement; patient informed consent may be required

Toner JP, Lanes A and Kissin DM. "ART Surveillance in North America" in Kissin DM et al. (Eds.), Assisted Reproductive Technology Surveillance, Cambridge, UK, Cambridge University Press; 2019.