Single Embryo Transfer

Best chance for a healthy baby!!

April 16, 2010

OptumHealth℠

Optimizing Health and Well-Being℠

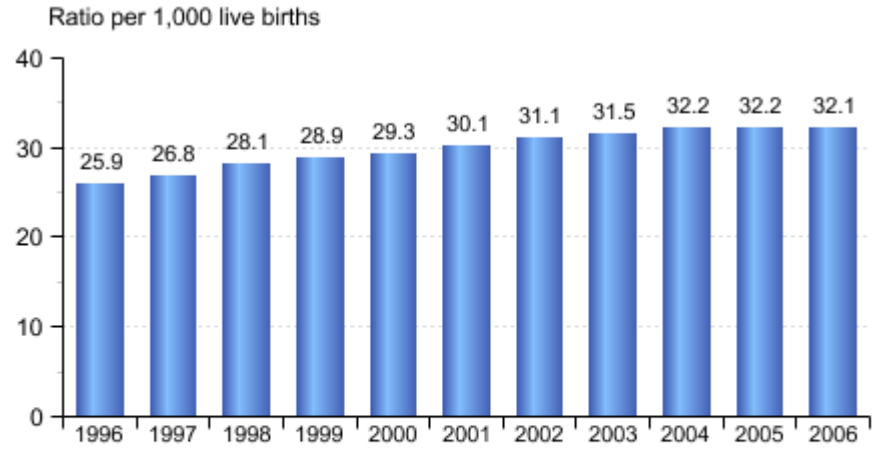
Assisted Reproductive Technology has greatly increased MULTIPLE BIRTHS

- 1960: 4.3 million births in the U.S.
  1198 triplet births 46 quadruplet births
- 2006: 4.27 million births in the U.S.
  6118 triplet births 355 quadruplet births
  67 quintuplet births
- In 2006, 96.6% of all births were singletons, 3.4% were multiple births and >80% of those were due to ART
- **More than 30% of ART pregnancies are twins or higher-order multiple gestations (triplets or greater)**.
- SART 2008: of all ART live births, 33.3% are twins, 1.9% are triplets or higher order multiples

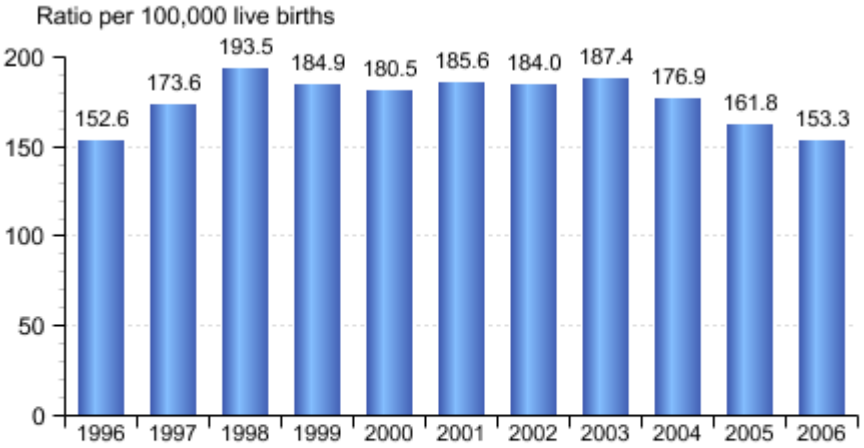
Infertility, assisted reproductive technology, and adverse pregnancy outcomes: executive summary of a National Institute of Child Health and Human Development workshop. Reddy UM; Wapner RJ; Rebar RW; Tasca RJ Obstet Gynecol. 2007 Apr;109(4):967-77.

Twin deliveries predicted to continue to rise through 2009

Twin deliveries 1996-2006

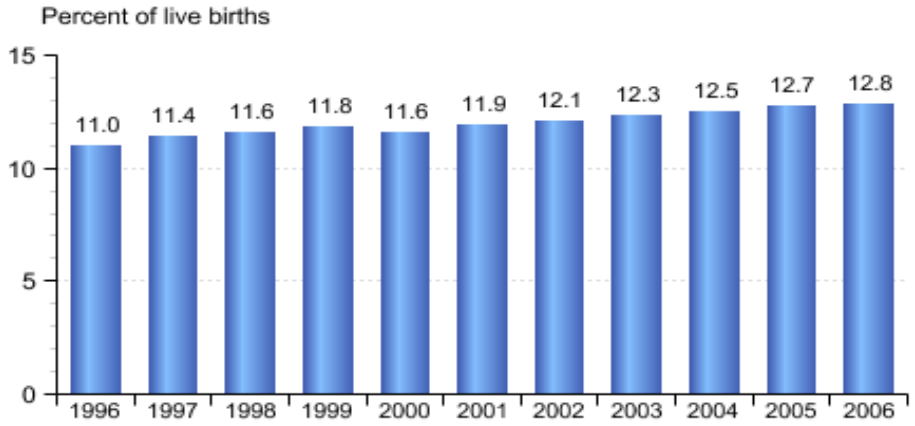


Triplet and higher order Multiple deliveries 1996-2006



ART multiple births are born PREMATURELY

- More than 30% of ART pregnancies result in premature births
- Compared with singleton births (one baby), multiple births in the United States were about 6 times as likely to be preterm in 2006 (March of Dimes)
- **ART created singleton births born are about twice as likely to be premature and 2.6 times more likely to be low birth weight.**
- In 2006, 1 in 8 babies (12.8%) of live births was born preterm 542,893 babies – most due to ART.



Increased risk of preterm birth in singleton pregnancies resulting from in vitro fertilization-embryo transfer or gamete intrafallopian transfer: a meta-analysis. AUMcGovern PG; Llorens AJ; Skurnick JH; Weiss G; Goldsmith LT SOFertil Steril 2004 Dec;82(6):1514-20.

Low and very low birth weight in infants conceived with use of assisted reproductive technology.
Schieve LA; Meikle SF; Ferre C; Peterson HB; Jeng G; Wilcox LS
N Engl J Med 2002 Mar 7;346(10):731-7.

Maternal issues occurring more often with multiple gestations

- Pregnancy loss – early or late
- Preeclampsia
- Gestational diabetes
- Hydramnios
- Anemia
- Antepartum bleeding
- Prolonged hospitalization
- Cesarean delivery
- Postpartum bleeding
- Psychological stress
- Financial stress

Fetal or neonatal issues occurring more often with multiple gestations

- Fetal demise or neonatal death
- Congenital abnormalities
- Preterm Delivery
  --cerebral palsy
  --sepsis
  --chronic lung disease
  --hyperbilirubinemia
  --hypoglycemia
  --prolonged hospitalization
  --retinopathy
  --intraventricular bleeds
  --necrotizing enterocolitis
  --patent ductus
  --hypocalcemia
- Longterm disability

Medical Costs of Premature Births

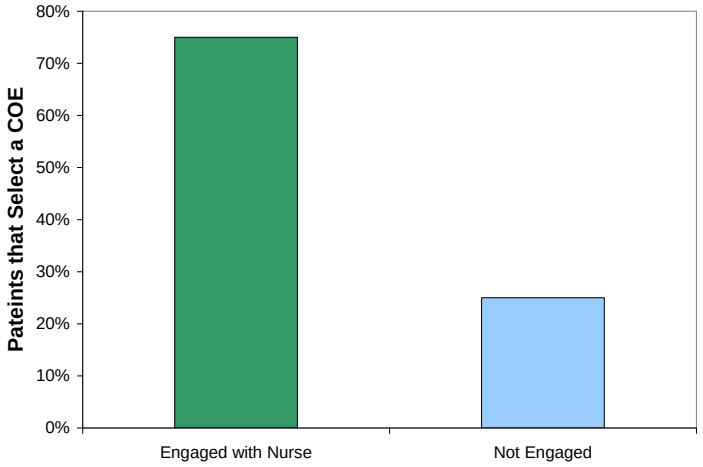
- The cost of premature births is considerable
  - In 2007, the average medical costs for a preterm baby were more than 10 times as high than for a healthy full-term baby
    - The costs for a healthy baby from birth to their first birthday were $4,551; for a preterm baby the costs were $49,033
    - The medical costs for both the mother and the baby were four times as high as they were when a mom had a healthy full-term infant
    - For the full-term infant, the costs were $15,047; for the preemie, the costs were $64,713 (outpatient visits, in-hospital care and prescriptions)

- Preterm babies spend more time in the hospital than healthy babies do:
  - Average length of hospital stays for a term infant for the first year of life in 2005: 2.3 days
  - Average length of stay of hospital stays for a preterm infant in 2005: 14.2 days
- Preemies also need more outpatient visits and prescriptions

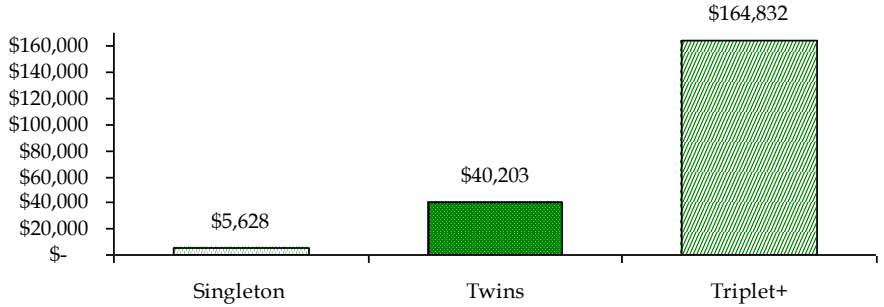
March of Dimes. The Cost to Business. Available at: http://www.marchofdimes.com/prematurity/index_about_15349.asp

OptumHealth infertility management delivers savings through best outcomes for members

- Higher order multiples are reduced through patient education and guidance, by nurse consultants, to the right provider
  - Members engaged with nurse consultants chose care at a Center of Excellence over 75% of the time, compared to 20-30% without intervention[1]
  - Nationally, patients treated at infertility Centers of Excellence are 45% less likely to have a triplet or higher order multiple gestation
  - Through patient education, clinical nurse consultants are able to reduce the desire for multiple births by 70% [2,3]



First Year Costs of Care



(1) Reproductive Resource Services study
(2) Gleicher et al. 1995
(3) Child, Henderson and Tan.. 2004

Decreasing Multiple Births

- **Decrease competition among infertility clinics** so that they can practice "best medicine"

  -- 1 study showed: *embryo transfer practices are not statistically significantly associated with the number of competitors*

  (Fert Steril 18 April 2008, Henne, et al., The effects of competition on assisted reproductive technology outcomes)

- **Multifetal pregnancy reduction**

  --there is good evidence that fetal reduction improves pregnancy outcome for survivors when there are 3 or more fetuses

  --fetal reduction can also be considered for a twin pregnancy, although this is controversial in the absence of a medical or obstetrical indication

  --in some states, patients may need to provide written consent for an abortion, which may require a specific waiting period

  --fetal reduction is usually performed between 10-13 weeks gestation

  --must know about placental attachments and whether or not there are MZG twins

  --overall unintended loss of the entire pregnancy is 10% or less

- **Single embryo transfer**

Improvement in outcomes of multifetal pregnancy reduction with increased Experience. Evans, et al. Am J Obstet Gynecol 2001 Jan;184(2):97-103

Ethical recommendations on multiple pregnancy and multifetal reduction, FIGO Committee For the Ethical Aspects of Human Reproduction and Women's Health. Int J Gyn Obstet 2006; 92:331.

Restricting the number of embryos transferred

Strategy	Country	Rate of delivery per embryo transfer	Rate of high order multiples per delivery
Laws to limit the number of embryos cultured	Germany	18.6	1.1
Laws to limit the number of embryos transferred	United Kingdom	25.8	0.3
	Norway	24.2	0.3
	Sweden	24.9	0.0
Guidelines for number of embryos to transfer	United States	34.0	2.1

Anderson, AN, et al. Human Reproduction 2008; 23:756.

American Society of Reproductive Medicine Guidelines for number of embryos to transfer (2009)

Characteristics	Number of cleavage stage embryos to transfer	Number of blastocysts to transfer
< 35 years old, most favorable prognosis	1-2 (1 recommended)	1
< 35 years old, other women	≤ 2	≤ 2
35-37 years old, more favorable prognosis	≤ 2	≤ 2
35-37, other women	≤ 3	≤ 3
38-40 years old, more favorable prognosis	≤ 3	≤ 2
38-40 years old, other women	≤ 4	≤ 3
41-42 years old, favorable prognosis plus all others	≤ 5	≤ 3

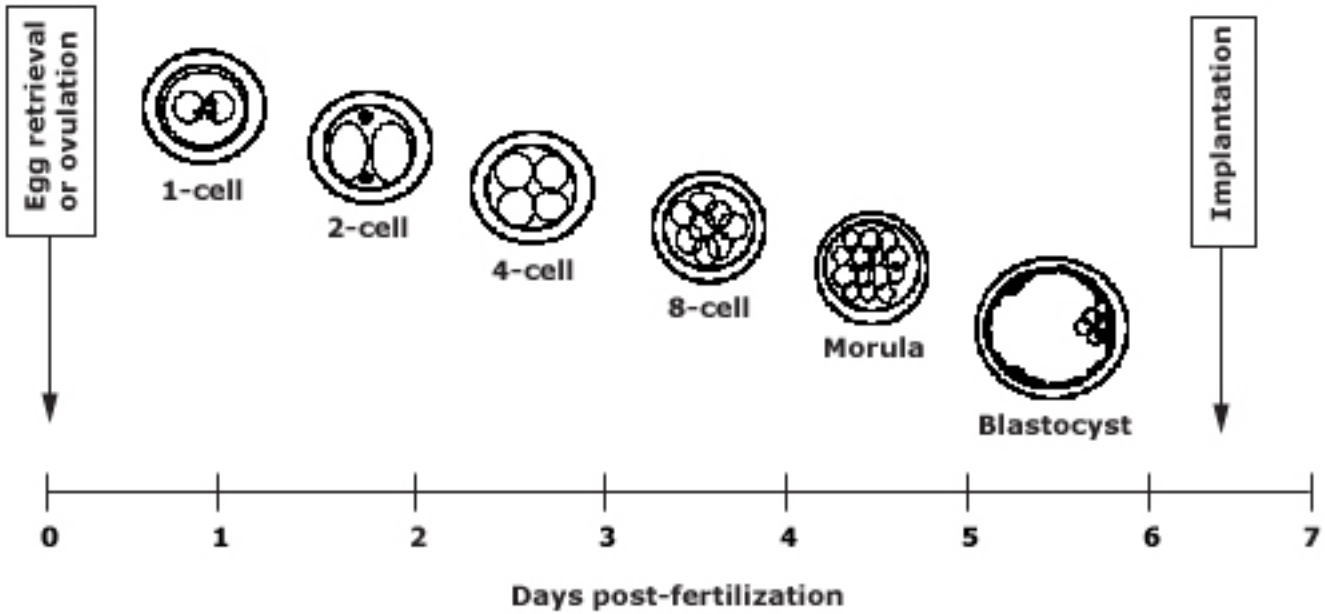
ASRM Practice Committee. Guidelines on number of embryos transferred. Fertil Steril 2009; 92:1518.

Effect of mother's age and # of embryos transferred on birth outcome

Maternal Age, years	3 embryos transferred, live birth rate	3 embryos transferred, triplet or higher	2 embryos transferred, live birth rate	2 embryos transferred, triplet or higher
< 35	41.6%	5.6%	48.6%	0.4%
35 to 37	39.4%	3.7%	39.7%	0.4%
38 to 40	29.0%	1.4%	27.3%	0.3%
41 to 42	15.7%	0.4%	12.0%	n/a

Sunderam, S, Chang, J, Flowers, L et al. MMWR Surveillance Summary 2009; 58:1

Preimplantation developmental time-line in humans



The blastocyst consists of an inner cell mass (which becomes the embryo) and an outer cell mass (cytotrophoblastic shell, which will become the placenta).

Courtesy of Catherine Racowsky, PhD.

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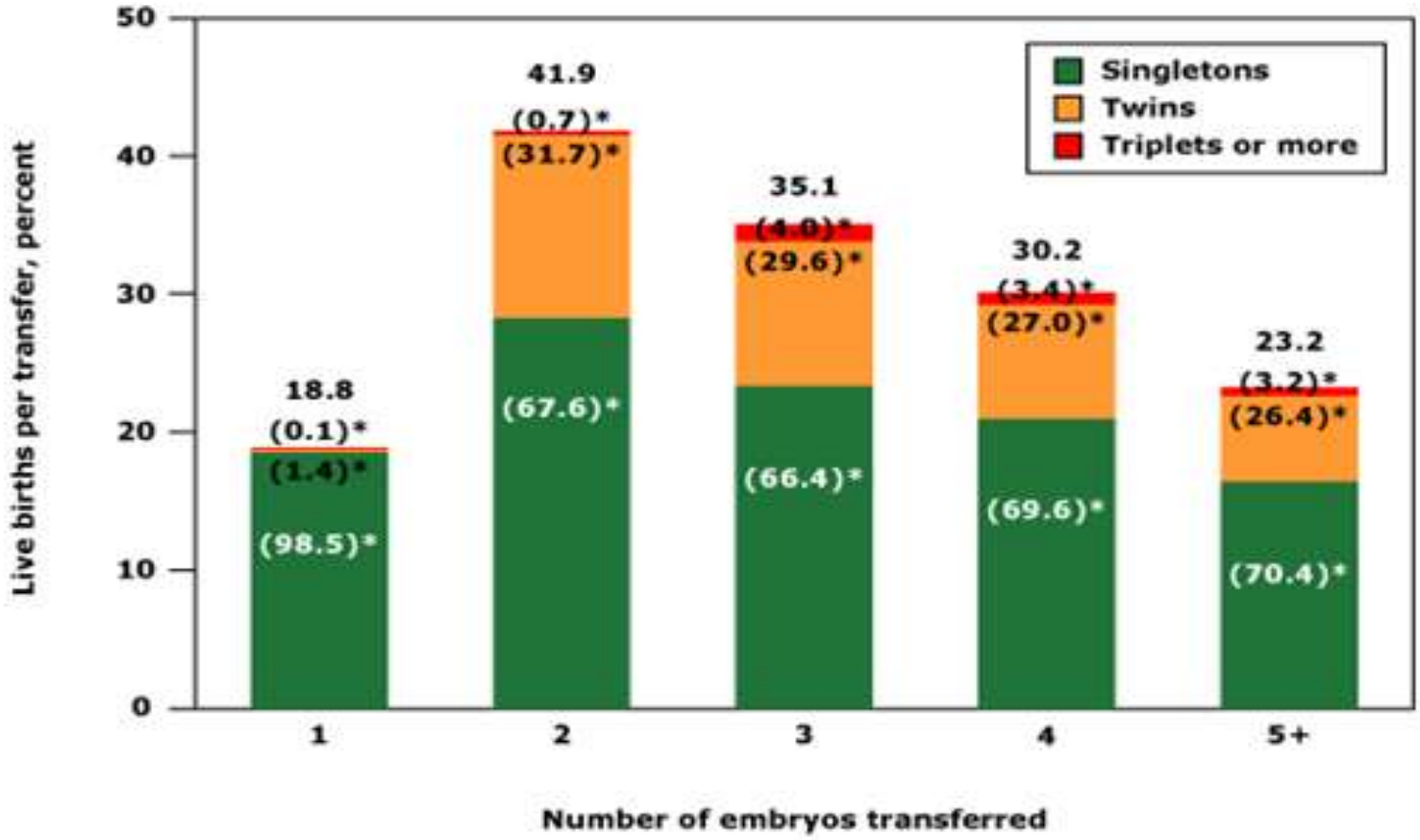
Percentages of transfers that resulted in live births and percentages of multiple-infant live births for ART cycles using fresh nondonor eggs or embryos, by number of embryos transferred, 2006

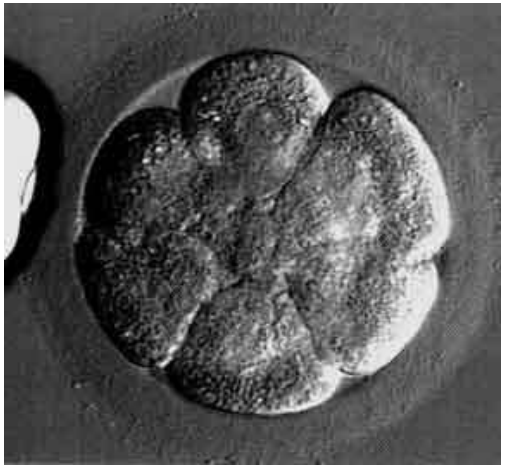


Embryo Selection

- ASRM: Number of embryos to transfer are based on quality and maternal age.
- Day of Transfer in the U.S. 63.5% day 3 (cleavage), 26.5% day 5 (blastocyst)

CLEAVAGE STAGE (generally day 3) – 8 cell

Perfect 8 cell cleavage stage embryo



BLASTOCYST STAGE (generally day 5)

Good looking blastocyst

Which day to transfer??

CLEAVAGE STAGE

- Scoring for “viability” and theoretically “implantability” involves cell number, fragmentation and embryo symmetry + other characteristics
- if not at 8 cell stage by 72 hours, don’t use it
- No great looking cleavage stage embryos on day 3 = transfer embryos on day 3
- Poor prognosis patients may benefit from transferring embryos on day 2-3
- Labs that do not have high implantation rates usually transfer on day 3
- Labs that cannot accommodate the needs of blastocysts usually transfer on day 3

BLASTOCYST STAGE

- Changing metabolic needs of the embryo require a very unique, controlled environment and changing culture media – sophisticated lab
- Embryos are lost between day 3 and day 5 (higher cycle cancellation rate than cleavage stage)
- Prolonging culture appears to select out the best embryos – the embryos most likely to implant successfully
- Success rates are high with 1 or 2 blastocysts; recent studies show little difference in singleton pregnancy rate, as long as lab is good
- There is a higher frequency of MZG twinning with blastocysts than cleavage stage embryos

Single Embryo Transfer (SET)

- In good prognosis patients, satsifactory, (but lower), delivery rates can be achieved with SET. Overall, delivery rate is 28% vs 42% with double embryo transfer. SET reduces twin pregnancies substantially (2% in SET vs 35% with double embryo transfer).
- Two cycles of SET is statistically equivalent to one cycle of double embryo transfer. Using “cumulative” cycles decreases multiple gestation from 33% to 0.8%
- SET appears to be superior to double embryo transfer when the number of deliveries with at least one live born child, incremental cost-effectiveness ratio, and maternal and pediatric complications are taken into account.
- If SET is performed, the pregnancy rate appears to be better with blastocysts
- When embryo quality is suboptimal at day 3, there should not be culturing to day 5

Nurse Considerations for SINGLE EMBRYO TRANSFER

- Age ≤ 35 (up to 37 in the right clinic)
- First or second IVF cycle (preferably frozen if 2nd cycle)

Before you recommend SET – do your homework!!

- Clinic implantation rate needs to be high (>35%, >50% preferred)
- Obtain the center's criteria – how many good embryos need to be available prior to considering SET, and at what stage?
- Blastocyst transfers are appropriate for those labs that have that capability
- Single cleavage stage transfers are appropriate for women who have other good quality embryos available for freezing
- Ask the clinic about "warranties" or "guarantees". More and more clinics are offering free frozen cycles if the first fresh SET cycle was not successful.

Educate the patient/spouse on the negatives associated with multiples

- Maternal complications, including the high likelihood of prolonged bed rest
- Baby complications, including the morbidity and mortality associated with multiple births – (twin pregnancies increase cerebral palsy risk 8 times, triplet pregnancies increase cerebral palsy risk 47 times).

Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s.
Petterson B; Nelson KB; Watson L; Stanley F
BMJ 1993 Nov 13;307(6914):1239-43.

Benefits of Having One Baby

- Decreased health risks to mother and baby
- Decreased risk of congenital abnormalities
- Decreased risk of cerebral palsy
- Decreased risk of pregnancy loss or infant death
- Decreased risk of parenteral depression and anxiety
- Decreased parenteral stress

- Improved parenting
- Improved financial well-being of the family
- Improved child and family quality of life

Potential adverse outcomes in singleton in vitro fertilization pregnancies

	Absolute risk ART pregnancies, percent	OR, 95% CI*
Perinatal risks		
Preterm birth	11.5	2.0 (1.7-2.2)
Low birthweight (less than 2500 g)	9.5	1.8 (1.4-2.2)
Very low birthweight (less than 1500 g)	2.5	2.7 (2.3-3.1)
Small for gestational age	14.6	1.6 (1.3-2.0)
NICU admissions	17.8	1.6 (1.3-2.0)
Stillbirth	1.2	2.6 (1.8-3.6)
Neonatal mortality	0.6	2.0 (1.2-3.4)
Cerebral palsy	0.4	2.8 (1.3-5.8)
Maternal risks		
Preeclampsia	10.3	1.6 (1.2-2.0)
Placenta previa	2.4	2.9 (1.5-5.4)
Placental abruption	2.2	2.4 (1.1-5.2)
Gestational diabetes	6.8	2.0 (1.4-3.0)
Cesarean delivery	26.7	2.1 (1.7-2.6)
Genetic risks		
Epigenetic or imprinting disorders•	0.03	17.8 (1.8-432.9)
Major birth defects	4.3	1.5 (1.3-1.8)
Chromosomal abnormalities (post-ICSI)		
De-novo sex chromosomal aneuploidy	0.6	3.0
Structural autosomal abnormalities	0.4	5.7

ART: assisted reproductive technology; OR: odds ratio; CI: confidence interval; NICU: neonatal intensive care unit; ICSI: intracytoplasmic sperm injection.
* Assisted reproductive technology singleton compared with spontaneously conceived singleton offspring.
• Absolute risk and odds ratio reported for Beckwith Wiedemann Syndrome.

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