



Contribution of Assisted Reproduction Technology and Ovulation-Inducing Drugs to Triplet and Higher-Order Multiple Births—United States, 1980-1997

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2 tables omitted

IN THE UNITED STATES, PREGNANCIES associated with assisted reproductive technology (ART) or ovulation-inducing drugs are more likely to result in multiple births than spontaneously conceived pregnancies.¹ In addition, triplet and higher-order multiple births are at greater risk than singleton births to be preterm (≤ 37 completed weeks' gestation), low birthweight (LBW) (i.e., ≤ 2500 g), or very low birthweight (i.e., < 1500 g), resulting in higher infant morbidity and mortality.² Because preterm and LBW infants often require costly neonatal care and long-term developmental follow-up, the continuing increase in triplet and higher-order multiple births causes concern among health-care providers and policymakers.³ This report provides estimates of the contribution of ART and ovulation-inducing drugs to these birth outcomes for 1996 and 1997, and summarizes trends during 1980-1997, which indicate that the ratio of triplet and higher-order multiple births has more than quadrupled and that a large proportion of this increase can be attributed to ART or the use of ovulation-inducing drugs.

CDC's National Center for Health Statistics (NCHS) provided data on live-born infants of triplet and higher-order multiple deliveries,⁴ and the Society for

Assisted Reproductive Technology (SART) reporting system for ART clinics provided the clinical outcomes of ART-associated pregnancies. The 1992 Fertility Clinic Success Rate and Certification Act requires that every U.S. medical center that performs ART report to CDC data for every ART cycle* initiated annually to calculate clinic-specific pregnancy success rates.⁵ This report uses data from 1996, the first full year CDC collected ART data, and 1997, the latest year of completed data collection. In NCHS and SART, multiple births are counted as individual births rather than sets of triplet and higher-order multiple births.

Triplets constituted most triplet and higher-order multiple births: 5298 (89.2%) of 5939 in 1996 and 6148 (91.2%) of 6737 in 1997.⁴ ART-related triplet and higher-order multiple births for 1996 and 1997 were expressed as a ratio (i.e., the proportion of ART-related triplet and higher-order multiple births to all live-born infants). The impact of ovulation-inducing drugs not associated with an ART procedure was estimated by subtracting both ART-related births (from the SART reporting system) and spontaneously occurring triplet and higher-order multiple births⁶ from the total number of these births. To account for the upward shift in maternal age distribution since 1971 and the increase in spontaneously occurring triplets and higher-order multiple births in women of reproductive age, the ratios for spontaneously occurring outcomes were adjusted for the maternal age distribution of 1997 using the relevant ratios for 1971.² This adjustment resulted in a 10% increase in spontaneously occurring triplet and higher-order multiple births from 29 per 100,000 live-born infants in 1971 to 32 per 100,000 live-born infants in 1997.

The ratio of triplet and higher-order multiple births for all age groups increased from 29 in 1971 to 37 in

1980; this trend began after the Food and Drug Administration approved two ovulation-inducing drugs, one in 1967 and another in 1970. Following the introduction of ART approximately in 1980, the ratio more than quadrupled to 174 in 1997. Among mothers aged < 20 years, the ratio increased from 15 to 21; among mothers aged 35-39 years, the ratio increased from 48 to 403.

The contribution of ART to the overall triplet and higher-order multiple birth ratio was estimated to be 38.7% in 1996 and 43.3% in 1997, a substantial increase from the estimated 22% for 1990 and 1991. For both years, approximately 20% were attributable to spontaneously occurring triplets and higher-order multiple births and approximately 40% were attributable to ovulation-inducing drugs without ART.

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CDC Editorial Note: Despite small variations in fertility rates throughout the 1930s-1960s, the ratio for triplet and higher-order multiple births remained stable at approximately 30 per 100,000 live-born infants.⁶ The reported increase in the ratio of triplet and higher-order multiple births in subsequent decades illustrates the impact of ART and other infertility treatments.

The findings in this study are subject to at least three limitations. First, reliable information could not be obtained on the availability and use of ovulation-inducing drugs in the United States. Such information might have been useful in determining the contribution of these drugs to the reported increased ratios and to the increase in triplet and higher-order multiple births affecting all age groups. Second, because ART data were available for only 2 full years (1996 and 1997), trend analysis was not possible. Third, bias



might have been introduced using 1971 triplet and higher-order multiple birth ratios for direct age adjustment, which were based on a 50% sample of birth certificate data compared with 100% of data for 1985-1997.

Because of the risk factors associated with multifetal births, continued surveillance of pregnancies associated with infertility treatments is important. Although the impact of ART on overall triplet and higher-order multiple births can be estimated using SART data, no reporting system has information on the use of ovulation-inducing drugs not associated with ART. Modifying birth certificate registration to include the type of infertility treatment used to achieve pregnancy would provide such information. Massachusetts has implemented this modification.

Given the increased morbidity and mortality associated with multifetal pregnancies, efforts are needed to monitor patients receiving ovulation-inducing drugs and to limit the number of embryos transferred for patients receiving ART.⁷ These approaches should be preceded by evaluation and specific diagnosis of the infertility status of each patient, and should follow guidelines issued by organizations such as the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists.^{8,9} Strategies to reduce the risk for multifetal gestation have important public health implications that must be integrated with patient needs and concerns, provider practices, and rapidly changing technology.

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*A cycle begins when a woman starts taking ovulation-inducing drugs or starts ovarian monitoring with the intent of having oocytes harvested for in vitro fertilization or other assisted reproductive technique. In most fresh, nondonor cycles, usually one of the following procedures is used: in vitro fertilization involves retrieving a woman's oocytes, fertilizing them in the laboratory, and transferring the resulting embryo(s) into the uterus through the cervix; gamete intra fallopian transfer involves placing unfertilized oocytes and sperm laparoscopically into the woman's fallopian tubes through a small abdominal incision; and zygote intra fallopian transfer involves fertilizing the woman's oocytes in the laboratory and then transferring the resulting zygotes into her fallopian tubes.

Suspected Brucellosis Case Prompts Investigation of Possible Bioterrorism-Related Activity—New Hampshire and Massachusetts, 1999

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BRUCELLA SPECIES, PARTICULARLY *B. melitensis* and *B. suis*, are potential agents of biological terrorism.^{1,2} This report describes the public health and law enforcement assessment of a suspected case of brucellosis in a woman, in which the atypical clinical presentation and suspicious circumstances surrounding the case raised the possibility of biological terrorism. Although the investigation did not identify evidence of biological terrorism, the safe resolution of the case illustrates the value of integrated clinical,

public health, and law enforcement biological terrorism preparedness and response.

On March 25, 1999, a 38-year-old woman who resided in New Hampshire was admitted to hospital A in New Hampshire with fever, myalgia, and weakness, which progressed over 3 days to respiratory failure requiring mechanical ventilation. On day 22, after 3 weeks of intensive care, the patient was transferred to hospital B in Boston, Massachusetts. Paired serum specimens obtained on day 4 and day 22 showed a 16-fold rise in titer (from 1:20 to 1:320) for *Brucella* antibodies by slide agglutination testing at hospital B. Cultures of blood were negative for *Brucella* species.

Hospital personnel interviewed family members who reported no history of traditional risk factors for *Brucella* exposure (e.g., relevant food, infected animal contact, or travel history). Although the rapid respiratory decompensation was not typical for brucellosis infection, the serologic findings met the surveillance case definition for brucellosis.³ As a result, hospital B made a routine case report of brucellosis to the Boston Public Health Commission (BPHC) on day 23.

On day 24, the patient's family reported to hospital personnel that the patient's illness might have been caused by exposure to "laboratory flasks" and "cultures" kept in her apartment by her boyfriend. He was described as a foreign national studying marine biology who was formerly affiliated with a local university but recently had returned to his country of citizenship. On day 25, the patient's family brought laboratory flasks, petri dishes, and culture media to hospital B from the patient's apartment. Several contained an unidentified clear liquid, and some were marked with dates from the 1980s. Infection-control staff at hospital B were notified of the laboratory-like materials on day 27. The positive *Brucella* antibody serology in association with the unusual laboratory-like equipment in the patient's residence and the acknowledged potential for *Brucella* species to



be used as a bioterrorist agents raised concerns among the infection-control staff that this case might be associated with a bioterrorist event or unintentional exposure to contaminated materials in the patient's home. Hospital B contacted local law enforcement in New Hampshire and BPHC. After discussion with BPHC, the hospital B laboratory retested the patient's paired serum specimens for both *Brucella* and *Francisella tularensis* antibodies. The specimens tested negative for tularemia but remained positive for *Brucella* antibodies. BPHC then notified the Massachusetts Department of Public Health (MDPH) and the Federal Bureau of Investigation about the unusual circumstances surrounding the case.

On day 28, CDC and the New Hampshire Department of Health and Human Services (NHDHHS) were notified. NHDHHS had received no reports of brucellosis through its passive surveillance system. In response to the case report, NHDHHS contacted hospital infection-control nurses, but identified no other cases of unusual febrile illness or brucellosis in southern New Hampshire during the preceding few weeks. In Massachusetts, public health authorities identified two additional cases of brucellosis during the previous 3 months, compared with an average state incidence of one to two cases per year. However, review of the cases revealed that both persons had consumed unpasteurized goat's milk or cheese during international travel.

On day 30, under the authority of state communicable disease statutes and in cooperation with the local police department, fire department, and hazardous materials unit, NHDHHS personnel entered the New Hampshire patient's apartment to assess any possibility of an ongoing public health hazard. No laboratory materials or biological hazards were found. Further epidemiologic investigation by federal and state public health authorities identified no common exposures among the three cases. The laboratory materials originally brought to hospital B by the family were cultured at MDPH and then

sent to the Armed Forces Institute of Pathology for further testing, where they tested negative when screened for several potential bioterrorism agents, including *Brucella* species.

On day 33, tube agglutination testing on the patient's paired serum specimens from day 4 and day 22 was negative for *Brucella* antibodies at CDC. On the same day at hospital B, the patient died from adult respiratory distress syndrome. An autopsy was requested by public health authorities; however, the possibility of a biological terrorist threat created concern on the part of the hospital pathology staff and the autopsy was postponed. Further testing of the patient's tissue samples was conducted through the CDC Unexplained Deaths and Critical Illness Surveillance Project, including immunohistochemistry for *Brucella*; although no diagnosis has been confirmed, CDC testing results and the patient's prolonged antecedent medical history of multiple febrile illnesses over the past decade suggest an unspecified autoimmune process.

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CDC Editorial Note: In this report, an initial serologic diagnosis of brucellosis was complicated by an unusual clinical presentation and other circumstances raising suspicion of a criminal act or possible biological terrorism.²⁻⁴ Although this case did not represent an actual biological crime or terrorism event, and brucellosis was ruled out as a cause of the patient's illness, this report highlights several key aspects of effective public health response to a possible biological terrorism crime or terrorism threat involving a biological agent or other unusual or unexplained illness. These aspects include (1) sensitive, specific, and rapid laboratory diagnosis of patients and

characterization of biological agents; (2) early detection through improved surveillance; (3) effective communication; and 4) coordinated local, state, and federal response in the investigation of unusual events or unexplained illnesses.

Early detection is essential to ensure a prompt response to a biological terrorist event. Local public health authorities must rely on clinicians to recognize and report suspicious or unusual presentations of disease. However, correlating suspicious cases originating from diverse locations or discerning an increase in common presentations above the normal baseline is difficult. As in this case, public health practitioners coordinating disease surveillance may be able to receive reports of rare diseases and to determine whether they are occurring at a higher than normal rate in a large surveillance area.

CDC, in collaboration with local, state, and territorial health departments, is enhancing existing disease surveillance systems for specific diseases that are normally rare in the United States but thought to have a high potential for public health impact if used as biological terrorism agents.^{5,6} This is being accomplished by improving training of clinical, laboratory, and public health personnel in recognizing suspicious disease presentations and by expanding of existing, disease-specific surveillance infrastructure. In addition, surveillance is being improved for disease presentations such as acute respiratory distress, hemorrhagic, or meningeal symptoms normally caused by common infectious agents but that could indicate an increase in illnesses caused by a biological agent used in terrorism. Surveillance mechanisms to rapidly assess changes in rates of disease include monitoring of calls to local emergency medical systems, regularly reviewing emergency department discharge diagnoses, and linking infection control practitioner networks.

This report illustrates the dilemmas inherent in laboratory detection of po-



tential agents of biological terrorism. Although the standard laboratory test for *Brucella* antibody is the tube agglutination test,⁷ the more rapid simple slide agglutination test is commonly used in commercial and hospital laboratories. The slide agglutination test is 97%-100% sensitive and may be as low as 88% specific.⁸ However, if used in a population with a low prevalence of disease, even a diagnostic test with 99% specificity will have a low positive predictive value. Because agents high on the list of possible biological terrorism have very low incidence of natural infection in the United States, the risk for a false-positive result is high. Therefore, diagnostic laboratory testing should be integrated with epidemiologic investigation when assessing potential covert biological terrorism events to rule out false-positive laboratory findings. To ensure that evaluation of materials from suspected biological terrorism events or threats is sensitive, specific, and rapid, CDC is working with its public health partners to improve laboratory diagnostic tests for many of the potential agents of biological terrorism and to transfer these diagnostic capabilities to state health department laboratories.⁶ CDC and other federal, state, and territorial public health laboratories are creating a multilevel Laboratory Response Network for Biological Terrorism that links state and local public health agencies to advanced capacity facilities that collectively maintain state-of-the-art capabilities for a wide range of biological agents.

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Injuries From Fireworks in the United States

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FIREWORKS TRADITIONALLY ARE USED IN the United States to celebrate Independence Day on July 4th. The U.S. Consumer Product Safety Commission (CPSC) estimates that 8500 persons in the United States are treated in emergency departments each year for fireworks-related injuries.¹ Of all fireworks-related injuries, 70%-75% occur during a 30-day period that surrounds the July 4th holiday (June 23-July 23).² Seven of every 100 persons injured by fireworks are hospitalized, approximately 40% of those injured are children aged less than or equal to 14 years, and males are injured three times more often than females.¹ The injury rate is highest among boys aged 10-14 years.³ Most commonly, injuries from fire-

works affect the hands (34%), face (12%), and eyes (17%).⁴ Injuries are more frequent and more severe among persons who are active participants than among bystanders.³

The estimated annual cost of fireworks-related injuries is \$100 million.⁴ In 1997, the U.S. National Fire Protection Association (NFPA) estimated that fireworks were responsible for direct property damage of \$22.7 million.⁵

Although some types of fireworks are legal in some states, CDC, NFPA, and CPSC recommend that fireworks be used only by professionals. All fireworks potentially are dangerous (e.g., sparklers burn at more than 1000 F [538 C]), especially to children. Because fireworks are unregulated, there is always a risk for injury with fireworks. Additional information about fireworks safety is available from CDC on the World-Wide Web, <http://www.cdc.gov/ncipc>, or CPSC, <http://www.cpsc.gov>.*

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