

LOW AND VERY LOW BIRTH WEIGHT IN INFANTS CONCEIVED WITH USE OF ASSISTED REPRODUCTIVE TECHNOLOGY

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ABSTRACT

Background The increased risk of low birth weight associated with the use of assisted reproductive technology has been attributed largely to the higher rate of multiple gestations associated with such technology. It is uncertain, however, whether singleton infants conceived with the use of assisted reproductive technology may also have a higher risk of low birth weight than those who are conceived spontaneously.

Methods We used population-based data to compare the rates of low birth weight (≤ 2500 g) and very low birth weight (< 1500 g) among infants conceived with assisted reproductive technology with the rates in the general population.

Results We studied 42,463 infants who were born in 1996 and 1997 and conceived with assisted reproductive technology and used as a comparison group 3,389,098 infants born in the United States in 1997. Among singleton infants born at 37 weeks of gestation or later, those conceived with assisted reproductive technology had a risk of low birth weight that was 2.6 times that in the general population (95 percent confidence interval, 2.4 to 2.7). The use of assisted reproductive technology was associated with an increased rate of multiple gestations; however, its use was not associated with a further increase in the risk of low birth weight in multiple births. Among twins, the ratio of the rate of low birth weight after the use of assisted reproductive technology to the rate in the general population was 1.0 (95 percent confidence interval, 1.0 to 1.1). Infants conceived with assisted reproductive technology accounted for 0.6 percent of all infants born to mothers who were 20 years of age or older in 1997, but for 3.5 percent of low-birth-weight and 4.3 percent of very-low-birth-weight infants.

Conclusions The use of assisted reproductive technology accounts for a disproportionate number of low-birth-weight and very-low-birth-weight infants in the United States, in part because of absolute increases in multiple gestations and in part because of higher rates of low birth weight among singleton infants conceived with this technology. (N Engl J Med 2002;346:731-7.)

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INFANTS who have low birth weight, either because of early delivery or because of fetal growth restriction, are at increased risk for short- and long-term disabilities and death.^{1,2} The use of assisted reproductive technology is an important contributor to the rate of low birth weight in the United States because it is associated with a higher rate of multiple birth,^{3,4} which, in turn, is associated with low birth weight.⁵ By 1997, the use of assisted reproductive technology accounted for more than 40 percent of triplets born in the United States.⁴ In addition, studies have suggested that there is a higher rate of low birth weight among singleton infants conceived with assisted reproductive technology than among naturally conceived singleton infants⁶⁻⁸ or among all infants in the general population.⁹⁻¹³ However, these studies had methodologic limitations. In particular, they did not address the issue of whether infants born as singletons were conceived as part of a multiple gestation that was later reduced either medically or spontaneously to a singleton pregnancy.

In addition, it remains unclear whether the risk of low birth weight among singleton infants conceived with assisted reproductive technology is a direct effect of the procedure involving such technology^{14,15} or reflects some other factor related to the underlying infertility of the couples who conceive using these procedures.¹⁶⁻¹⁸ Studies have been limited by small sample sizes and lack of data regarding such potentially confounding variables as the factors causing infertility and their severity.

We used population-based data from records of procedures performed with assisted reproductive technology in the United States to compare the risk of low birth weight among infants conceived with assisted reproductive technology with that found in the general population. The large sample and detailed data on the procedures and resulting pregnancies provided an opportunity to analyze outcomes according to several important factors, including the number of infants born, the number of fetuses early in the pregnancy, cause of infertility, and factors involved in treatment.

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METHODS

Study Population

Clinics and medical practices in the United States are required to report data on every procedure involving assisted reproductive technology to the Centers for Disease Control and Prevention (CDC).¹⁹ Each year, the Society for Assisted Reproductive Technology collects data on such procedures performed in clinics in the United States and provides these data to the CDC. Procedures involving assisted reproductive technology are defined as procedures for the treatment of infertility in which both oocytes and sperm are handled outside the body; these include in vitro fertilization with transcervical embryo transfer, gamete and zygote intrafallopian transfer (in which gametes or zygotes are transferred into the fallopian tube rather than the uterus), frozen-embryo transfer, and donor-embryo transfer. Data abstracted from patients' records and submitted to the CDC include each patient's demographic characteristics and medical history, as well as clinical information on the procedures performed and resultant pregnancies and births. In 1996, 300 clinics reported more than 60,000 procedures; in 1997, 335 clinics reported more than 70,000 procedures. Five to 7 percent of clinics that were in operation during these years did not report data, despite the federal requirement; because most of these were known to be small practices, we estimate that the data reported represent more than 95 percent of all procedures performed with the use of assisted reproductive technology.

We included in the present analysis infants conceived through procedures performed in 1996 and 1997 in which the mother was between 20 and 60 years of age. Of 136,972 procedures, 23 percent (31,767) resulted in the delivery of one or more liveborn infants. Because some of these were multiple-birth deliveries, the total number of infants was 45,886. Although a delivery could include both liveborn and stillborn infants, we excluded from our analysis the 182 stillborn infants. A total of 3241 infants with missing data on birth weight were also excluded. Our final sample included 42,463 infants conceived with assisted reproductive technology.

Internal Comparisons

We classified infants according to the number at birth (singleton, twin, triplet, or quadruplet or higher-order birth). Although only liveborn infants were included in this study, the assignment of the number born was based on the total number of liveborn and stillborn infants delivered. Within each birth-number group we examined the risk of low and very low birth weight. Birth weight was recorded as a categorical variable in 500-g strata. We defined low birth weight as 2500 g or less and very low birth weight as less than 1500 g.

We assessed variations in risk according to maternal and treatment-related factors, using stratification and multivariable logistic regression. The factors we evaluated included the number of fetal hearts observed on early ultrasonography (i.e., the number of fetuses in the pregnancy), maternal age, parity, primary cause of infertility, previous procedures involving assisted reproductive technology, and the type of procedure that resulted in the current conception. Procedures were classified according to whether the embryos had been fertilized during the current procedure (i.e., were fresh) or had been previously fertilized and frozen until the current procedure and whether the source of the oocytes was the mother herself (nondonor) or another woman serving as an oocyte or embryo donor. In addition, procedures in which a woman other than the mother served as a gestational carrier or surrogate were classified separately. Thus, the procedure was categorized as involving fresh embryos and nondonor oocytes, frozen embryos and nondonor oocytes, fresh embryos and donor oocytes, frozen embryos and donor oocytes, or a gestational carrier. We considered separately whether intracytoplasmic sperm injection (a procedure in which a single sperm is injected directly into the oocyte) was

used in procedures involving fresh embryos and nondonor oocytes and those involving fresh embryos and donor oocytes.

External Comparison

We compared the observed numbers of low-birth-weight and very-low-birth-weight infants conceived with assisted reproductive technology with expected numbers. Expected numbers were calculated with the use of the public-use computer file containing the 1997 birth-certificate data for the United States (on 3,389,098 infants born to women who were 20 years of age or older)²⁰ and were adjusted to match the age and parity distributions for women who conceived with assisted reproductive technology. We computed standardized ratios for low birth weight and very low birth weight by dividing the observed numbers by the expected numbers and calculated 95 percent confidence intervals for each estimate.²¹

To rule out the possibility that the reduction of gestations that had initially involved multiple fetuses might explain a higher rate of low birth weight in singletons, we performed secondary analyses that included only those births in which the number of fetal hearts noted on ultrasonography did not exceed the number of infants who were born. (Data were not available to permit the differentiation of spontaneous reductions from medically induced reductions.) To separate the effects of treatment from underlying characteristics of the patients or embryos, we performed several additional analyses in this subsample. In one analysis, we restricted the sample to infants conceived with the use of donor oocytes among couples without a diagnosis of male-factor infertility, since these infants were considered most likely to have been conceived with healthy gametes. In a second analysis, we restricted the sample to infants born to couples with a diagnosis of male-factor infertility, since women in this subgroup were considered unlikely to have uterine or other infertility-related disease. And in a third analysis, we restricted the sample to infants who had been carried by a gestational surrogate, since these surrogates were presumably healthy women.

Analyses were conducted separately for singletons and twins. In addition, we subdivided low-birth-weight infants into term and preterm infants. Preterm delivery was defined as delivery at less than 37 completed weeks of gestation. We calculated gestational age as the interval from the date of oocyte retrieval and fertilization to the date of birth. For procedures performed with the use of frozen embryos and for other procedures for which the date of oocyte retrieval was missing, the gestational age was calculated as the interval from the date of embryo transfer to the date of birth. To make the estimates comparable with those in the general population, we computed the estimated postmenstrual age (the age according to the last menstrual period) as the gestational age in days plus 14. Term low birth weight was defined as a weight of 2500 g or less with delivery at term; preterm low birth weight was defined as a weight of 2500 g or less with preterm delivery.

To assess the contribution of the use of assisted reproductive technology to low birth weight in the United States, we examined 20,369 infants from our study population who were born in 1997; some had been conceived with assisted reproductive technology in 1996 and some in 1997. For singleton infants, twins, and infants from higher-order multiple births, we divided the number of low-birth-weight and very-low-birth-weight infants conceived with assisted reproductive technology by the total number of low-birth-weight and very-low-birth-weight infants born to women 20 years of age or older in the United States in 1997.

This study was approved by the institutional review board of the CDC; in accordance with federal regulations, the requirement to obtain informed consent was waived for this retrospective analysis.

RESULTS

The study population was similar to the total population of women treated with assisted reproductive

technology in terms of the characteristics of the women and the infertility treatment they received (Table 1). However, some factors associated with higher success rates for assisted reproductive technology — an age of less than 35 years, previous deliveries, no previous procedures involving assisted reproductive technology, and the use of fresh embryos (particularly fresh donor embryos) — were slightly more common among the study population.

A total of 43 percent of the infants in the study population were singletons, 43 percent were twins, 12 percent were triplets, and 1 percent were quadruplets or higher-order multiples. The percentage of infants with low birth weight varied from 13.2 percent among singletons to almost 100 percent among quadruplets or higher-order multiples. The percentage of infants with low birth weight varied with maternal characteristics and treatment-related factors (Table 2). Singletons were more likely to have low birth weight if there had been more than one fetal heart on early ultrasonography, and twins were more likely to have low birth weight if there had been more than two fetal hearts.

The rate of low birth weight was also higher among singletons and twins born to nulliparous women and women who had no previous procedures involving assisted reproductive technology (Table 2). Low birth weight was less common in infants conceived by couples with male-factor infertility, conceived with intracytoplasmic sperm injection, or carried by a gestational surrogate. Among triplets, 90 percent or more of the infants had low birth weight, regardless of maternal characteristics or treatment-related factors. The percentages of quadruplets and higher-order multiples with low birth weight are not shown in Table 2 but were nearly 100 percent in all groups. The results for singletons and twins were materially unchanged after multivariable adjustment for the maternal characteristics and treatment factors listed in Table 2.

The rate of very low birth weight ranged from 2.6 percent for singletons to 66.9 percent for quadruplets or higher-order multiples. The rate of very low birth weight also varied with maternal and treatment-related factors, but to a lesser degree than the rate of low birth weight did (data not shown).

As compared with all singleton infants born in the United States to women 20 years of age or older in 1997, singletons conceived with assisted reproductive technology in 1996 or 1997 were at increased risk for low and very low birth weight (Table 3). When the analysis was restricted to infants who were carried by a gestational surrogate the risk was no longer significantly increased, but there were relatively few infants in this group.

We stratified low-birth-weight infants according to whether they were born at term or were preterm

TABLE 1. MATERNAL CHARACTERISTICS AND CHARACTERISTICS OF ASSISTED REPRODUCTIVE TECHNOLOGY USED.*

CHARACTERISTIC	PERCENTAGE OF ALL PROCEDURES INVOLVING ART (N=136,972)	PERCENTAGE OF PROCEDURES THAT RESULTED IN A LIVE BIRTH (N=31,767)	PERCENTAGE OF INFANTS INCLUDED IN FINAL SAMPLE (N=42,463)
Age of mother			
20–29 yr	10.5	13.1	14.0
30–34 yr	31.2	37.2	38.4
35–39 yr	35.8	34.3	33.4
40–44 yr	19.2	12.3	11.2
≥45 yr	3.3	3.2	3.1
Parity			
0	76.9	75.6	75.3
1	17.0	18.2	18.5
≥2	6.2	6.1	6.2
Primary cause of infertility			
Female factor	69.4	68.0	68.1
Male factor	23.0	24.2	24.1
Idiopathic	7.7	7.8	7.8
Previous procedures involving ART			
0	49.8	55.2	55.8
1	24.7	23.1	22.7
2	12.1	10.8	10.7
≥3	13.4	11.0	10.8
Type of procedure†			
Fresh embryo, nondonor oocyte	76.3	76.9	78.0
Frozen embryo, nondonor oocyte	14.2	9.9	8.9
Fresh embryo, donor oocyte	6.6	10.3	10.5
Frozen embryo, donor oocyte	2.0	1.7	1.6
Gestational carrier	0.9	1.2	1.1
Use of intracytoplasmic sperm injection‡			
No	61.3	62.1	62.9
Yes	38.7	37.9	37.1

*Data on age, parity, primary cause of infertility, and type of procedure were missing for less than 1 percent of infants; data on previous procedures were missing for 3 percent of infants; and data on the use or nonuse of intracytoplasmic sperm injection were missing for 6 percent of infants. The final sample included all live-born infants with data on birth weight. ART denotes assisted reproductive technology.

†Procedures were classified according to whether the embryos had been fertilized during the current procedure (i.e., were fresh) or had been previously fertilized and frozen until the current procedure and whether the source of the oocytes was the mother herself (nondonor) or another woman serving as an oocyte or embryo donor; procedures in which a woman other than the mother served as a gestational carrier were classified separately.

‡Data are for procedures involving fresh embryos and nondonor oocytes and those involving fresh embryos and donor oocytes only.

(Table 4). Singleton infants conceived with assisted reproductive technology had a risk of term low birth weight that was more than twice that of singleton infants in the general population, and they had a smaller but still significant increase in the risk of preterm low birth weight. The risk of term low birth weight

TABLE 2. PERCENTAGE OF INFANTS WITH LOW BIRTH WEIGHT (≤ 2500 g) AMONG SINGLETONS, TWINS, AND TRIPLETS CONCEIVED WITH ASSISTED REPRODUCTIVE TECHNOLOGY IN 1996 AND 1997.*

VARIABLE	SINGLETONS (N=18,408)	TWINS (N=18,399)	TRIPLETS (N=5127)
% with low birth weight			
Total	13.2	55.2	92.4
No. of fetal hearts on early ultrasonography			
1	12.6		
2	17.6	53.2	
3	25.4	61.1	92.4
4	50.0	70.7	94.4
5	—	70.3	—
≥ 6	—	89.7	—
Age of mother			
20–29 yr	12.4	61.7	92.4
30–34 yr	13.4	55.3	92.7
35–39 yr	13.1	53.6	91.8
40–44 yr	13.5	51.3	91.0
≥ 45 yr	12.3	53.5	98.1
Parity			
0	13.7	57.3	93.1
1	11.3	48.4	90.0
≥ 2	12.4	49.8	90.6
Primary cause of infertility			
Female factor	13.6	56.1	92.4
Male factor	12.2	52.7	93.0
Idiopathic	12.5	54.7	90.4
Previous procedures involving ART			
0	14.3	56.6	93.3
1	11.5	54.0	91.5
2	12.7	53.3	93.2
≥ 3	11.9	51.1	89.6
Type of procedure†			
Fresh embryo, nondonor oocyte	13.6	56.0	92.1
Frozen embryo, nondonor oocyte	10.5	49.5	92.1
Fresh embryo, donor oocyte	14.0	53.6	94.5
Frozen embryo, donor oocyte	11.8	57.1	97.4
Gestational carrier	8.7	50.0	90.0
Use of intracytoplasmic sperm injection‡			
No	14.3	56.8	92.4
Yes	12.7	54.0	93.0

*Data on age, parity, primary cause of infertility, and type of procedure were missing for less than 1 percent of infants; data on previous procedures were missing for 3 percent of infants; and data on the use of intracytoplasmic sperm injection were missing for 6 percent of infants. The percentage of infants with low birth weight is not provided if there were fewer than 20 infants in the category. Global P values were calculated by the chi-square test and were adjusted for correlations between infants within each birth-number group. Global $P < 0.05$ for all variables except the age of the mother among singletons and all variables among twins. ART denotes assisted reproductive technology.

†Procedures were classified according to whether the embryos had been fertilized during the current procedure (i.e., were fresh) or had been previously fertilized and frozen until the current procedure and whether the source of the oocytes was the mother herself (nondonor) or another woman serving as an oocyte or embryo donor; procedures in which a woman other than the mother served as a gestational carrier were classified separately.

‡Data are for procedures involving fresh embryos and nondonor oocytes and those involving fresh embryos and donor oocytes only.

remained elevated in analyses restricted to subgroups of the study population conceived with presumably healthy gametes or carried by a presumably healthy woman. The risk of preterm low birth weight was no longer increased in analyses restricted to study infants who had been carried by presumably healthy women.

Singletons conceived with assisted reproductive technology and delivered at term tended to be born slightly earlier than singletons in the general population (mean gestational age, 39.1 vs. 39.5 weeks). We therefore further adjusted our analyses for the week of gestation at delivery (37 to 41 or more) in addition to maternal age and parity. This adjustment did not substantially change our findings (adjusted term-low-birth-weight ratio, 2.4; 95 percent confidence interval, 2.3 to 2.6).

Among twins conceived with assisted reproductive technology, the risks of both term and preterm low birth weight were similar to those in the general population of twins. The ratio of the rate of low birth weight at term among twins conceived with assisted reproductive technology to the rate among all twins born at term was 1.0 (95 percent confidence interval, 1.0 to 1.1).

The 20,369 infants conceived with assisted reproductive technology and born in 1997 represented 0.6 percent of the 3,389,098 infants born to women 20 years of age or older in the United States in that year. However, we estimate that the use of assisted reproductive technology accounted for 3.5 percent of the infants with low birth weight and 4.3 percent of the infants with very low birth weight born to women in this age group. The excesses were due in large part to the increased number of infants from multiple births who were conceived with assisted reproductive technology. However, the increased rates of low birth weight among singletons conceived with assisted reproductive technology also played a small part (0.6 percent of low-birth-weight singletons were conceived with assisted reproductive technology, as compared with the 0.2 percent that would have been expected).

DISCUSSION

Singleton infants conceived with assisted reproductive technology were at increased risk for low birth weight at term relative to singletons in the general population of the United States. This risk was not explained by known differences between the two populations in the distribution of maternal age, maternal parity, or gestational age at delivery. In addition, there was an increased risk even in analyses in which the sample was restricted to infants from pregnancies that had not originated as multiple gestations, infants conceived with gametes from apparently fer-

TABLE 3. OBSERVED AND EXPECTED CASES OF LOW BIRTH WEIGHT AND VERY LOW BIRTH WEIGHT AMONG SINGLETON INFANTS CONCEIVED WITH ASSISTED REPRODUCTIVE TECHNOLOGY IN 1996 AND 1997.*

VARIABLE	TOTAL NO.	NO. OF CASES OBSERVED	NO. OF CASES EXPECTED†	STANDARDIZED RISK RATIO (95% CI)
Low birth weight				
All infants	18,398	2423	1339.4	1.8 (1.7–1.9)
Pregnancies with one fetal heart	16,730	2104	1197.1	1.8 (1.7–1.8)
Use of donor oocytes, no diagnosis of male-factor infertility	1,397	190	119.3	1.6 (1.4–1.8)
Diagnosis of male-factor infertility	2,759	329	195.9	1.7 (1.5–1.9)
Use of gestational carrier	180	16	13.3	1.2 (0.6–1.8)
Very low birth weight				
All infants	18,398	480	263.4	1.8 (1.7–2.0)
Pregnancies with one fetal heart	16,730	408	239.2	1.7 (1.5–1.9)
Use of donor oocytes, no diagnosis of male-factor infertility	1,397	49	23.5	2.1 (1.5–2.7)
Diagnosis of male-factor infertility	2,759	78	38.5	2.0 (1.6–2.5)
Use of gestational carrier	180	0	2.6	—

*Ten infants with missing data on parity were not included in these analyses. CI denotes confidence interval.

†The number of expected cases was calculated by applying the rates of low birth weight from the 1997 U.S. birth-certificate data to the population of infants conceived with assisted reproductive technology. The values were adjusted to account for differences in the distributions of age (in the following categories: 20 to 29 years, 30 to 34 years, 35 to 39 years, 40 to 44 years, and ≥45 years) and parity (0, 1, or ≥2) between the two populations.

tile persons, and infants from pregnancies carried by women who were unlikely to have an underlying uterine or other infertility-related disease. Thus, this study suggests that the increased risk of low birth weight in singleton infants born at term who were conceived with assisted reproductive technology may be directly related to such treatments for infertility.

Singletons who were conceived with assisted reproductive technology also had a moderately elevated rate of preterm low birth weight. However, increased risks were not observed among all subgroups; in particular, the risk was not increased among infants delivered by a gestational carrier rather than the mother. These subgroup analyses involved greatly reduced samples and must therefore be interpreted cautiously. However, a possible explanation is that the risk of preterm low birth weight associated with assisted reproductive technology may be related to some underlying condition in the women who undergo procedures involving such technology rather than to the procedures themselves.

The mechanisms underlying the association between the use of assisted reproductive technology and low birth weight among infants born at term remain unclear and warrant further research. The use of human menopausal gonadotropin as part of procedures

involving assisted reproductive technology has been associated with increases in insulin-like growth factor-binding protein 1; this protein has been linked to intrauterine growth restriction.²² During pregnancies initiated with assisted reproductive technology, altered levels of other endometrial proteins and increased rates of structural abnormalities of the placenta have also been found.^{23,24} These factors may also contribute to growth restriction. A less direct mechanism is also possible. The use of assisted reproductive technology has been linked to such maternal complications as pregnancy-induced hypertension.^{25–27}

Studies also suggest that women who have conceived with assisted reproductive technology are more likely to undergo elective cesarean section, resulting in deliveries that occur earlier than those following spontaneous pregnancies.^{6,7,25–27} We did not have data on complications of pregnancy or type of delivery, but we did find that singletons conceived with assisted reproductive technology and born at term were delivered slightly earlier than term singletons in the general population. Adjustment for the week of gestation at delivery did not substantially reduce the risk ratio for low birth weight at term. We observed an excess risk of low birth weight among the singletons conceived with assisted reproductive technology.

TABLE 4. OBSERVED AND EXPECTED CASES OF LOW BIRTH WEIGHT AMONG TERM AND PRETERM SINGLETON INFANTS CONCEIVED WITH ASSISTED REPRODUCTIVE TECHNOLOGY IN 1996 AND 1997.*

VARIABLE	TOTAL NO.	NO. OF CASES OBSERVED	NO. OF CASES EXPECTED†	STANDARDIZED RISK RATIO (95% CI)
Term low birth weight				
All infants	18,182	1180	455.2	2.6 (2.4–2.7)
Pregnancies with one fetal heart	16,530	1059	413.1	2.6 (2.4–2.8)
Use of donor oocytes, no diagnosis of male-factor infertility	1,390	80	42.4	1.9 (1.5–2.3)
Diagnosis of male-factor infertility	2,730	190	66.5	2.9 (2.5–3.3)
Use of gestational carrier	180	8	4.7	1.7 (0.5–2.9)
Preterm low birth weight				
All infants	18,182	1206	859.6	1.4 (1.3–1.5)
Pregnancies with one fetal heart	16,530	1011	780.3	1.3 (1.2–1.4)
Use of donor oocytes, no diagnosis of male-factor infertility	1,390	110	75.7	1.5 (1.2–1.7)
Diagnosis of male-factor infertility	2,730	131	126.1	1.0 (0.9–1.2)
Use of gestational carrier	180	8	8.5	0.9 (0.3–1.6)

*Term infants were defined as those born at or after 37 weeks of gestation, and preterm infants were defined as those born at less than 37 weeks of gestation. Ten infants with missing data on parity and 216 infants (1 percent) with missing data required to calculate gestational age were not included in these analyses; of the infants missing gestational-age data, 37 had low birth weight and 179 had normal birth weight. CI denotes confidence interval.

†The number of expected cases was calculated by applying the rates of low birth weight from the 1997 U.S. birth-certificate data to the population of infants conceived with assisted reproductive technology. Values were adjusted to account for differences in the distributions of age (in the following categories: 20 to 29 years, 30 to 34 years, 35 to 39 years, 40 to 44 years, and ≥45 years) and parity (0, 1, or ≥2) between the two populations.

gy who were born at every week of gestation between 37 and 41 weeks.

Twins conceived with assisted reproductive technology and born at term were not at higher risk of low birth weight than twins in the general population. It is possible that the additional risk associated with the use of assisted reproductive technology is negligible in twin pregnancies, which are already at high risk. Twins conceived with the use of medications for ovarian stimulation but without assisted reproductive technology may also be at increased risk for low birth weight and may have accounted for a sizable proportion of twins in the general population. We do not have data on the use of these medications among the mothers of the general birth cohort.

We did not compare the birth weights of triplets and higher-order multiples in our study population with those in the general population. More than 40 percent of the triplets and higher-order multiples in the general population were conceived with assisted reproductive technology, and the risk of low birth weight was greater than 90 percent among such infants in both groups.

We estimate that more than 3 percent of the low-birth-weight infants and more than 4 percent of the very-low-birth-weight infants born in 1997 were conceived with assisted reproductive technology — six times the proportions that would be expected on the basis of the frequency of these procedures. These higher-than-expected proportions are largely explained by the increased rate of multiple births. Although the use of assisted reproductive technology did not appear to increase the already high risk of low birth weight among infants from multiple gestations, the increased risk of low birth weight among singletons conceived with assisted reproductive technology and delivered at term indicates that infants from both singleton and multiple births must be considered in assessing the effect of assisted reproductive technology on the rate of low birth weight in the United States.

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