Reducing Fetal Deaths in Multiple Births: Optimal Birthweights and Gestational Ages for Infants of Twin and Triplet Births[*]

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Abstract. The objective of this study was to determine the birthweight and gestational age associated with the lowest fetal mortality for twins and triplets. The study design was a population-based analysis of all live births and fetal deaths in the US between 1983-88. Fetal mortality was compared by categories of birthweight and gestational age, for twins and triplets versus singletons, and within each plurality by the lowest rate compared to all other rates as relative risks ± 95% Cls. The overall versus lowest fetal death rate per 1,000 conceptions for singletons was 4.3 versus 0.9 at 3700-4000 g and 40-41 weeks; for twins, 15.5 versus 3.3 at 2500-2800 g and 36-37 weeks; and for triplets, 21.0 versus 5.2 at 1900-2200 g at 34-35 weeks. Beyond these plurality-specific lowest ranges, the risk of fetal death increased, more for twins than singletons, and most for triplets. To conclude, fetal death rates can be reduced by 75-80% with attainment of birthweight and gestational age within a plurality-specific ideal range.

Key words: Fetal death, IUGR, Twins, Triplets

INTRODUCTION

An estimated 5.3 million women in the United States, or 9.1% of all women of reproductive age, have impaired fecundity [28]. Most infertility treatments carry a substantial risk of resulting in a multiple birth, ranging from 20-30% depending on the method [22, 23]. In a national survey of families with triplet births, 50% had resulted from ovulation stimulating drugs and 9% from in vitro fertilization and gamete intrafallopian transfer [5]. Data from the annual survey of US programs offering assisted repro-

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ductive technology procedures indicates that, of the resulting pregnancies, the propor-
tion of multiple births ranged from 25% twins, 4.8% triplets, and 0.2% higher order
multiples from in vitro fertilization; 27% twins, 6.6% triplets, and 0.3% higher order
multiples from gamete intrafallopian transfer; 28.6% twins, and 4.4% triplets from
zygote intrafallopian transfer; and 31.4% twins, and 5.7% triplets from donor oocytes
[22].

   There has also been a trend in the United States of postponing childbearing, with
multiple births occurring more frequently among older mothers. Between 1970 and
1994, among women aged 30 and older, the proportion of first births increased from 5%
to 21%, and the proportion of all births increased from 16% to 34% [24, 26]. As the
result of these two factors, infertility treatments and a trend towards delaying childbear-
ing, the incidence of multiple births has risen dramatically in the United States since the
mid-1970s [14]. In 1994, the most current year for which statistics are available, there
were 101,658 live infants in multiple births in the United States, the highest number ever
recorded in the history of the vital statistics system [26]. As a result, the frequency of
twins has increased from 1:48 births in 1985 to 1:40 births in 1994, and the frequency of
triplet and higher order births has increased from 1:1912 in 1985 to 1:838 births in 1994
[25, 26]. Multiple births are at high risk for antenatal complications [7, 9], including
fetal death of one or more siblings [2]. The purpose of this investigation is to estimate
the birthweight and gestational age associated with the lowest fetal death rate for infants
of multiple births.

MATERIAL AND METHODS

The data used was the computerized certificates of all live births and all fetal deaths in
the United States between 1983 and 1988, obtained from the National Center for Health
Statistics. Live births and fetal deaths were categorized as singleton, twin, or triplet and
higher order (triplets). Weeks' gestation was calculated from the last menstrual period
and categorized into two-week intervals, limited to births occurring between 24-44
weeks. Birthweight was categorized into 300-gram intervals, and limited to infants with
birthweights between 500-6,000 grame.

   The data was cleaned to eliminate live births and fetal deaths with biologically
implausible birthweight-gestational age combinations using a generally accepted tech-
nique for vital statistics data [4, 27, 30]. It is well known that a substantial portion of
births before 37 weeks' gestation have reported gestational ages that are in error by 4-20
weeks [4, 27, 30]. When plotted at each week of gestation below 37 weeks, the birth-
weight distribution is generally bimodal. The consensus of researchers is that the first
mode (at the lower birthweight) represents the "true" mode, or births with accurately
reported gestational ages. Since the birthweight distribution at each gestational week is
symmetrical [4, 27], a smoothed curve eliminating the second mode more accurately rep-
resents biologically plausible birthweights for gestational age. For each plurality type
this was done by eliminating all live births and fetal deaths beyond two standard devia-
tions from the mean of live births within each two-week gestational age period. This
resulted in less than a 2% reduction in fetal deaths and live births from the original study
population. The final study sample included for singletons: 19,468,170 live births and

83,263 fetal deaths; for twins: 352,629 live births and 5,467 fetal deaths; and for triplets: 9,523 live births and 204 fetal deaths.

The analysis was conducted in several steps. First, the cumulative percent distribution of live births and fetal deaths was described by plurality, birthweight, and gestational age, and the 50% distribution determined for each. Second, within each plurality category, fetal death rates were calculated as fetal deaths per 1,000 conceptions (fetal deaths/[fetal deaths + live births] x 1,000) overall and for each category of birthweight, gestational age, and birthweight and gestational age. For each plurality type, the lowest fetal death rate was identified within the categories of birthweight, gestational age, and birthweight and gestational age. Third, within each category, the lowest fetal death rate was assigned a relative risk (RR) of 1.0 and all other rates within each category compared to this lowest rate, as RRs ± 95% confidence intervals (CIs). Exact two-sided probabilities were calculated using Fisher's Exact Test for this and subsequent analyses because of the small numbers within some cells for triplets. Fourth, RRs ± 95% CIs were calculated by comparing birthweight-, gestational age-, and birthweight and gestational age-specific rates for twins versus singletons, and for triplets versus singletons. Fifth, the overall and lowest fetal death rates by categories of birthweight ("ideal birthweight"), gestational age ("ideal gestational age"), and birthweight and gestational age ("ideal birthweight and gestational age") were compared for twins versus singletons, and for triplets versus singletons as RRs ± 95% CIs.

RESULTS

Based on the cumulative percent distribution by plurality, birthweight, and gestation, 50% of live births among singletons were less than 3100-3400 g and 38-39 weeks, compared to twins at 2200-2500 g and 35-36 weeks, and triplets at 1600-1900 g and 32-33 weeks. Fifty percent of fetal deaths among singletons were less than 1900-2200 g and 34-35 weeks, compared to twins at 1300-1600 g and 33-34 weeks, and triplets at 1000-1300 g and 31-32 weeks. The distribution of fetal deaths suggests a common factor of growth retardation for all pluralities, and a narrower range of birthweights (1000-2200 g) and gestational ages (31-35 weeks) than for live births (1600-3400 g and 32-39 weeks). Among live births, the distributions of birthweights and gestational ages of twins showed a downwards shift after 35 weeks' gestation, suggesting a slowing of growth. For triplets, this deviation occurred earlier, at about 30-32 weeks.

The lowest fetal death rate per 1,000 conceptions for singletons was 4.3 overall, 1.0 by birthweight alone (3700-4000 g), 1.6 by gestational age alone (40-41 weeks), and 0.9 by birthweight and gestational age (3700-4000 g at 40-41 weeks) (Table 1). Among twins, the lowest fetal death rate per 1,000 conceptions was 15.5 overall, 4.7 by birthweight alone (2500-2800 g), 8.1 by gestational age alone (36-37 weeks), and 3.3 by birthweight and gestational age (2500-2800 g at 36-37 weeks) (Table 2). Among triplets, the lowest fetal death rate per 1,000 conceptions was 21.0 overall, 9.3 by birthweight alone (1900-2200 g), 11.4 by gestational age alone (34-35 weeks), and 5.2 by birthweight and gestational age (1900-2200 at 34-35 weeks) (Table 3).

Assigning the lowest fetal death rate by birthweight alone, gestational age alone, and birthweight and gestational age a relative risk (RR) of 1.0, all other categories of birth-

Singleton Fetal Death Rates (per 1,000 conceptions)

- Overall fetal death rate: 4.3
- Lowest fetal death rate
  by birthweight alone: 1.0
  by gestational age alone: 1.6
  by birthweight and gestational age: 0.9

BIRTH WEIGHT (grams)	WEEKS GESTATION										
	24 - 5	26 - 7	28 - 9	30 - 1	32 - 3	34 - 5	36 -7	38 - 9	40 - 1	≥ 42	
≥ 4900											
4600 < 4900								3.6	1.9	2.1	2.3
4300 < 4600								1.7	1.2	1.6	1.4
4000 < 4300							3.0	1.1	1.0	1.3	1.1
3700 < 4000							2.2	0.9	0.9	1.4	1.0
3400 < 3700							2.2	1.0	1.1	1.5	1.2
3100 < 3400						2.9	2.6	1.3	1.4	1.8	1.5
2800 < 3100					6.4	5.0	3.5	2.0	2.2	2.6	2.5
2500 < 2800					12.1	8.8	6.5	4.1	4.5	4.8	5.3
2200 < 2500				21.4	19.4	14.2	13.9	10.3	11.2	12.0	12.9
1900 < 2200			49.2	37.1	29.6	27.8	31.1	26.2	24.4		29.1
1600 < 1900		68.9	72.1	43.7	49.8	61.8	72.3				57.0
1300 < 1600	150.2	99.2	66.2	68.4	103.2	127.3					89.4
1000 < 1300	193.2	93.5	95.1	142.9	212.5	.					128.6
700 < 1000	173.7	151.5	221.7	287.9	353.4						200.7
500 < 700	318.1	355.2	447.0	509.7							361.2
	231.3	157.3	126.7	86.8	45.2	15.1	5.9	1.9	1.6	1.9	4.3

Table 1 - Singleton fetal death rates (per 1,000 conceptions)

Twin Fetal Death Rates (per 1,000 conceptions)

- Overall fetal death rate: 15.5
- Lowest fetal death rate
  by birthweight alone: 4.7
  by gestational age alone: 8.1
  by birthweight and gestational age: 3.3

BIRTH WEIGHT (grams)	WEEKS GESTATION										
	24 - 5	26 - 7	28 - 9	30 - 1	32 -3	34 - 5	36 - 7	38 - 9	40 - 1	≥ 42	
≥ 4900											
4600 < 4900											
4300 < 4600											
4000 < 4300											
3700 < 4000											
3400 < 3700						8.9	7.7	6.2	7.6	13.6	7.3
3100 < 3400						6.2	4.5	5.8	5.7	11.6	5.9
2800 < 3100					11.1	4.3	3.6	4.8	4.8	9.7	4.8
2500 < 2800				22.0	9.5	5.2	3.3	4.1	7.7	11.4	4.7
2200 < 2500			29.9	19.8	9.4	9.1	5.9	9.1	12.2	17.5	7.8
1900 < 2200			22.5	17.5	9.3	17.3	12.4	19.4	22.2	30.1	13.4
1600 < 1900		55.8	24.0	26.0	14.2	60.0	33.1	42.4	58.3	76.2	23.8
1300 < 1600		57.4	41.5	58.0	35.7	126.2	90.7	105.5	73.8		44.6
1000 < 1300	142.9	68.5	106.7	180.8	97.2						65.1
700 < 1000	86.4	187.6	214.7	191.7	185.4						99.6
500 < 700	157.1										176.2
	123.4	85.5	57.0	41.0	21.5	11.7	8.1	8.2	10.1	16.7	15.5

Table 2 - Twin fetal death rates (per 1,000 conceptions)

Triplet Fetal Death Rates (per 1,000 conceptions)

- Overall fetal death rate: 21.0
- Lowest fetal death rate
  - by birthweight alone: 9.3
  - by gestational age alone: 11.4
  - by birthweight and gestational age: 5.2

BIRTH WEIGHT (grams)	WEEKS GESTATION										Total
	24 - 5	26 - 7	28 - 9	30 - 1	32 - 3	34 - 5	36 - 7	38 - 9	40 - 1	≥ 42	
≥ 4900											
4600 < 4900											
4300 < 4600											
4000 < 4300											
3700 < 4000											
3400 < 3700											
3100 < 3400											
2800 < 3100						27.8	22.2	39.0	117.6		34.0
2500 < 2800					41.7	14.3	9.5	32.0	78.9	200.0	23.0
2200 < 2500					15.2	6.8	9.0	18.8	59.7	130.4	13.8
1900 < 2200				16.7	7.0	5.2	8.1	15.5	40.8	100.0	9.3
1600 < 1900			22.7	11.0	7.0	7.2	21.8	46.2	76.9	125.0	13.4
1300 < 1600		29.4	15.7	11.4	12.0	24.6	54.3	60.6	93.8	272.7	21.5
1000 < 1300		37.4	15.9	24.2	34.7	54.8	80.0	133.3			29.1
700 < 1000	31.3	30.4	32.6	25.0	153.8	214.3					41.0
500 < 700	73.8	105.3	172.4								94.5
	54.2	43.8	25.5	15.5	14.2	11.4	15.0	31.5	69.9	147.7	21.0

Table 3 - Triplet fetal death rates (per 1,000 conceptions)

weight, gestational age, and birthweight and gestational age were then compared to these lowest rates, as RRs ± 95% confidence intervals (Cls). Among singletons, the lowest fetal death rate occurred at 3700-4000 g and 40-41 weeks, although the risk of fetal death was not significantly different at 3700-4000 g and 38-39 weeks, nor at 4000-4300 g and 40-41 weeks (Table 4). Beyond these three birthweight and gestational age categories, the risk of fetal death increased significantly, generally increasing by 20% (RR 1.2) two weeks above and two weeks below the 40-41 week ideal. By birthweight, the risk of fetal death increased 40-50% (RR 1.4-1.5) 600 g above and below the ideal of 3700-4000 g. Beyond these ranges, the risk of fetal death steadily increased with each lower category of birthweight, gestational age, or both. Before 35 weeks' gestation, within birthweight and gestational age categories, the highest risks for fetal death were among the lowest birthweight categories, suggesting a strong association between intrauterine growth retardation and fetal demise. Before 35 weeks' gestation, the lowest birthweights still had the highest risks of fetal death, but the risks at all categories of birthweight were significantly elevated due to the added effects of immaturity. Generally, intrauterine growth retardation was a greater factor for fetal death than immaturity, with a larger increase in risk across birthweights at a given gestational age than across gestational ages at a given birthweight. For example, for infants with birthweights of 2200-2500 g, the risk of fetal death increased 1.6-fold from 32-33 weeks to ≥42 weeks, whereas at 34-35 weeks' gestation, the risk of fetal death increased 25.2-fold across birthweights of 1300-1600 g to 2800-3100 g.

Among twins, the lowest fetal death rate occurred at 2500-2800 g and 36-37 weeks, although the risk of fetal death was not significantly different at 2500-2800 g and either 34-35 weeks or 38-39 weeks, nor at 36-37 weeks at birthweights of 2800-3400 g (Table 5). Beyond these five birthweight-gestational age categories, the risk of fetal death increased significantly, by 30-50% (RR 1.3-1.5) two weeks above and two weeks below the ideal of 36-39 weeks, and by 60-70% (RR 1.6-1.7) 600 g above and 300 g below the ideal of 2500-3100 g. Beyond these ranges, the risk of fetal death increased with each category decrease in birthweight, gestational age, or both. The increase in risk with each category deviation from the ideal was greater for twins than singletons. For example, at 600 g below the plurality-specific ideal birthweight and gestational ages, the risk of fetal death was 1.5 (95% Cl, 1,4, 1.6) for singletons compared to 3.7 (2.8, 4.9) for twins; at 900 g below the respective ideals, the risk was 2.4 (2.2, 2.6) for singletons compared to 10.1 (7.7, 13.4) for twins. As seen in singletons, the highest rates of fetal death within each gestational age category were among the lowest birthweight categories. Also among twins, intrauterine growth retardation was a greater factor for fetal death than immaturity, with a larger increase in risk across birthweights for a given gestational age than across gestational ages for a given birthweight. Using the same ranges as discussed for singletons above, at birthweights of 2200-2500 g, the risk of fetal death increased 1.9-fold from 32-33 weeks to ≥42 weeks, compared to the 10.5-fold increased risk for infants born at 34-35 weeks with birthweights of 2800-3100 g to 1300-1600 g. By gestational age alone, the risk of fetal death for twins beyond 39 weeks' gestation increased significantly, with RRs of 1.3 (1.1, 1.4) at 40-41 weeks and 2.1 (1.8, 2.4) at ≥42 weeks. When this twin-specific range of maturity was combined with intrauterine growth retardation (i.e., birthweights below 2200 g after 37 weeks' gestation), there was a doubling and tripling of RRs with each category decrease in birthweight.

Singleton vs Lowest Singleton Fetal Death Rates

RRs ± 95% CI of fetal death for singletons compared to the lowest birthweight rate, gestational age rate, and birthweight-gestational age rate.

BIRTH WEIGHT (grams)	24-5	26-7	28-9	30-1	32-3	34-5	36-7	38-9	40-1	≥42	RR ± 95% CI
≥4900											
4600<4900								3.9 (3.3-4.7)	2.1 (1.8-2.5)	2.3 (1.8-2.9)	2.3 (2.0-2.5)
4300<4600								1.9 (1.6-2.1)	1.3 (1.1-1.4)	1.8 (1.5-2.1)	1.4 (1.3-1.5)
4000<4300							3.3 (2.7-3.9)	1.2 (1.1-1.3)	1.0 (0.9-1.1)	1.4 (1.2-1.6)	1.1 (1.0-1.1)
3700<4000							2.4 (2.1-2.8)	0.9 (0.8-1.0)	1.0	1.5 (1.4-1.7)	1.0
3400<3700							2.4 (2.2-2.6)	1.1 (1.0-1.1)	1.1 (1.1-1.2)	1.6 (1.5-1.8)	1.1 (1.1-1.2)
3100<3400						3.2 (2.8-3.6)	2.8 (2.6-3.1)	1.4 (1.3-1.5)	1.5 (1.4-1.6)	2.0 (1.8-2.2)	1.5 (1.4-1.6)
2800<3100					7.0 (6.0-8.1)	5.5 (5.0-6.0)	3.9 (3.6-4.1)	2.2 (2.0-2.3)	2.4 (2.2-2.6)	2.8 (2.6-3.1)	2.4 (2.3-2.5)
2500<2800					13.2 (11.7-14.9)	9.6 (8.8-10.4)	7.1 (6.6-7.6)	4.4 (4.1-4.7)	4.9 (4.6-5.3)	5.2 (4.7-5.8)	5.2 (5.0-5.4)
2200<2500				23.3 (20.2-26.9)	21.2 (19.3-23.1)	15.4 (14.4-16.6)	15.1 (14.1-16.2)	11.2 (10.5-12.1)	12.2 (11.2-13.2)	13.1 (11.7-14.6)	12.7 (12.2-13.2)
1900<2200			53.6 (46.2-62.1)	40.4 (36.4-44.9)	32.3 (29.9-34.9)	30.2 (28.1-32.5)	33.9 (31.5-36.4)	28.6 (26.4-30.9)	26.5 (24.0-29.4)		29.1 (27.9-30.4)
1600<1900		75.1 (64.3-87.6)	78.5 (70.6-87.4)	47.6 (43.9-51.6)	54.3 (50.6-58.2)	67.3 (62.7-72.2)	78.8 (73.2-84.8)				58.6 (56.1-61.2)
1300<1600	163.6 (143.6-186.3)	108.0 (97.1-120.2)	72.0 (66.4-78.2)	74.5 (69.3-80.0)	112.4 (104.9-120.4)	138.6 (129.1-148.9)					95.1 (91.0-99.3)
1000<1300	210.4 (191.0-231.7)	101.8 (94.1-110.3)	103.5 (96.5-111.1)	155.6 (145.3-166.7)	231.4 (216.1-247.9)						143.0 (136.8-149.4)
700<1000	189.1 (177.5-201.5)	165.0 (154.8-175.8)	241.4 (226.4-257.4)	313.6 (293.5-335.0)	384.9 (358.8-412.9)						243.3 (233.4-253.6)
500<700	346.4 (326.7-367.3)	386.9 (363.5-411.7)	486.8 (456.3-519.3)	555.1 (518.0-594.8)							548.0 (524.3-572.7)
RR ± 95% CI	192.9 (186.7-199.2)	119.7 (115.8-123.6)	93.0 (90.1-96.0)	60.9 (59.1-62.8)	29.0 (28.2-29.8)	9.8 (9.6-10.1)	3.8 (3.7-3.9)	1.2 (1.1-1.2)	1.0	1.2 (1.2-1.3)	4.6 (2.7-7.9)

Legend: blue = Significant and higher than 1.0   pink = Reference

Table 4 - Singleton vs lowest singleton fetal death rates

Twin vs Lowest Twin Fetal Death Rates

RRs ± 95% CI of fetal death for twins compared to the lowest birthweight rate, gestational age rate, and birthweight-gestational age rate.

BIRTH WEIGHT (grams)	24-5	26-7	28-9	30-1	32-3	34-5	36-7	38-9	40-1	≥ 42	Total
≥ 4900											
4600 < 4900											
4300 < 4600											
4000 < 4300											
3700 < 4000											
3400 < 3700							2.3 (1.2-4.1)	1.8 (1.3-2.7)	2.3 (1.5-3.5)	4.1 (2.1-7.7)	1.6 (1.2-2.0)
3100 < 3400						2.7 (1.2-5.7)	1.3 (0.9-2.1)	1.7 (1.3-2.3)	1.7 (1.1-2.5)	3.5 (2.1-5.8)	1.3 (1.0-1.5)
2800 < 3100					3.3 (1.4-7.5)	1.8 (1.1-3.0)	1.1 (0.8-1.5)	1.4 (1.1-1.9)	1.7 (1.1-2.5)	2.9 (1.9-4.5)	1.0 (0.9-1.2)
2500 < 2800					2.8 (1.5-5.2)	1.3 (0.9-1.9)	1.0	1.2 (0.9-1.6)	2.3 (1.7-3.1)	3.4 (2.3-5.2)	1.0
2200 < 2500				6.7 (3.8-11.5)	2.8 (1.9-4.2)	1.5 (1.1-2.1)	1.8 (1.3-2.3)	2.7 (2.1-3.6)	3.7 (2.6-5.1)	5.3 (3.6-7.8)	1.7 (1.4-1.9)
1900 < 2200			9.1 (4.6-17.8)	6.0 (3.9-9.3)	2.8 (2.0-3.9)	2.7 (2.0-3.6)	3.7 (2.8-4.9)	5.9 (4.4-7.8)	6.7 (4.7-9.6)	9.2 (6.1-13.9)	2.9 (2.5-3.3)
1600 < 1900			6.8 (3.8-12.0)	5.3 (3.8-7.4)	4.3 (3.2-5.7)	5.2 (3.9-7.0)	10.1 (7.7-13.4)	13.1 (9.7-17.7)	18.4 (12.9-26.1)	24.5 (16.3-36.6)	5.2 (4.5-5.9)
1300 < 1600		17.5 (10.9-28.0)	7.3 (5.1-10.5)	7.9 (5.9-10.6)	11.0 (8.3-14.6)	18.9 (14.3-25.1)	29.6 (22.2-39.6)	35.0 (25.3-48.4)	23.6 (14.9-37.2)		9.9 (8.6-11.3)
1000 < 1300	49.4 (33.0-74.0)	18.1 (13.2-24.7)	12.8 (9.7-17.0)	18.3 (13.7-24.4)	31.9 (23.7-43.1)	42.8 (31.2-58.8)					14.7 (12.8-16.9)
700 < 1000	28.0 (21.3-36.9)	21.8 (16.7-28.5)	35.4 (26.9-46.6)	65.5 (49.2-87.2)	67.5 (48.2-94.6)						23.4 (20.5-26.7)
500 < 700	55.3 (43.0-71.2)	68.5 (52.2-90.0)	81.1 (59.4-110.8)	70.4 (49.9-99.3)							45.2 (39.4-51.9)
WEEKS GESTATION	17.3 (15.4-19.5)	11.5 (10.2-13.0)	7.4 (6.6-8.4)	5.4 (4.7-5.9)	2.7 (2.4-3.0)	1.5 (1.3-1.6)	1.0	1.0 (0.9-1.1)	1.3 (1.1-1.4)	2.1 (1.8-2.4)	4.5 (3.7-5.6)

= Reference

= Significant and higher than 1.0

Table 5 - Twin vs lowest twin fetal death rates

Among triplets, the lowest fetal death rate occurred at 1900-2200 g and 34-35 weeks. Because of the relatively small sample size of triplets (9,523 infants of live births and 204 fetal deaths), the relative risks in 35% of the birthweight and gestational age categories were not significant (Table 6). Despite this limitation, the magnitude of the relative risks across gestational ages, birthweights, and by both, show a pattern consistent with those of singletons and twins. Generally, the risk of fetal death for triplets was much greater than for twins or singletons at the same deviation from each plurality's ideal. Within a narrower range around the ideal (about 300 g above and below ideal birthweight, and two weeks above and below ideal gestational age), the risk of fetal death for triplets increased by 30-40%. Beyond these ranges, the risk doubled or tripled with each category of birthweight or gestational age, even more dramatically than for twins. Using the same example as above, at 600 g below each plurality's respective ideal birthweight and gestational age, the risk of fetal death was 4.7 (1.3, 17.4) for triplets, compared to 3.7 (2.6, 5.1) for twins, and 1.5 (1.4, 1.6) for singletons; at 900 g below the ideal, the risk was 10.5 (2.7, 41.0) for triplets, 10.1 (7.7, 13.4) for twins, and 2.4 (2.2, 2.6) for singletons. The effects of plurality-specific postmaturity, alone or in combination with intrauterine growth retardation, were even more pronounced with triplets than with twins. By gestational age alone, the RRs of fetal death increased to 1.3 (0.8, 2.3) at 36-37 weeks, 2.8 (1.5, 4.9) at 38-39 weeks, 6.1 (3.4, 11.2) at 40-41 weeks, and 13.0 (6.9, 24.3) at ≥42 weeks. Combined with intrauterine growth retardation (i.e., birthweights of 1900 g or less after 35 weeks' gestation), these gestational age-specific risks increased by three-to twelve-fold. Even at birthweights above the ideal, at gestational ages beyond the triplet-specific range of maturity (34-35 weeks), there was a threefold increased risk of fetal death.

The category-specific comparisons of fetal death rates for twins versus singletons and triplets versus singletons are shown in Table 7 and 8, respectively. Generally, at birthweights under 2800 g and gestational ages below 35 weeks, twins had significantly lower category-specific risks for fetal death compared to singletons, and significantly higher risks at birthweights and gestational ages above these ranges. For triplets, a similar pattern was observed, although the cutoffs were at 2200 g and 33 weeks, and there was a wider birthweight and gestational age transitional range that was not significant, but with RRs in the same trend.

The final analysis included a comparison of fetal death rates for twins versus singletons and triplets versus singletons at overall fetal death rates, and at the plurality-specific lowest fetal death rates by birthweight ("ideal birthweight"), gestational age ("ideal gestational age"), and birthweight and gestational age ("ideal birthweight and gestational age") as RRs ± 95% CIs. Overall, the RR of fetal death was 3.6 (3.5, 3.6) for twins compared to singletons, and 4.9 (4.7, 5.1) for triplets compared to singletons. At the plurality-specific ideal birthweight, the RR of fetal death was 4.6 (4.1, 5.1) for twins compared to singletons and 9.1 (5.6, 14.6) for triplets compared to singletons. At the plurality-specific ideal gestational age, the RR of fetal death was 5.1 (4.8, 5.6) for twins compared to singletons and 7.3 (5.0, 10.6) for triplets compared to singletons. At the plurality-specific ideal birthweight and gestational age, the RR of fetal death was 3.7 (2.9, 4.6) for twins compared to singletons and 5.7 (2.1, 15.2) for triplets compared to singletons.

Triplet vs Lowest Triplet Fetal Death Rates

RRs ± 95% CI of fetal death for triplets compared to the lowest birthweight rate, gestational age rate, and birthweight-gestational age rate.

BIRTH WEIGHT (grams)	24-5	26-7	28-9	30-1	32-3	34-5	36-7	38-9	40-1	≥ 42	
≥ 4900											
4600 < 4900											
4300 < 4600											
4000 < 4300											
3700 < 4000											
3400 < 3700											
3100 < 3400											
2800 < 3100						5.3 / 0.6-46.3	4.2 / 1.0-18.8	7.4 / 1.7-32.6	22.5 / 4.4-114.4		3.6 / 1.6-8.1
2500 < 2800					8.0 / 0.9-68.5	2.7 / 0.5-14.8	1.8 / 0.4-8.1	6.1 / 1.5-24.1	15.1 / 3.5-65.0	38.2 / 7.9-185.2	2.5 / 1.2-4.9
2200 < 2500					2.9 / 0.5-15.6	1.3 / 0.3-5.2	1.7 / 0.5-6.4	3.6 / 0.8-15.8	11.4 / 2.9-44.6	24.9 / 5.9-105.0	1.5 / 0.8-2.8
1900 < 2200				3.2 / 0.4-28.0	1.3 / 0.3-6.0	1.0	1.5 / 0.3-6.8	3.0 / 0.5-16.0	7.8 / 1.5-41.5	19.1 / 3.7-98.3	1.0
1600 < 1900			4.3 / 0.5-38.0	2.1 / 0.5-9.3	1.3 / 0.4-4.9	1.4 / 0.3-5.5	4.2 / 1.1-15.4	8.8 / 2.0-38.5	14.7 / 2.8-76.6	23.9 / 5.7-100.8	1.4 / 0.8-2.6
1300 < 1600		5.6 / 0.6-48.9	3.0 / 0.7-13.3	2.2 / 0.6-7.7	2.3 / 0.6-8.5	4.7 / 1.3-17.4	10.4 / 2.8-38.0	11.6 / 2.2-61.0	17.9 / 4.2-76.7	52.1 / 13.2-205.7	2.3 / 1.3-4.1
1000 < 1300		5.8 / 1.8-19.1	3.0 / 0.7-10.7	4.6 / 1.4-15.7	6.6 / 1.8-24.4	10.5 / 2.7-41.0	15.3 / 2.9-79.6	25.5 / 5.0-128.5			3.1 / 1.7-5.6
700 < 1000	6.0 / 1.5-23.6	7.1 / 1.8-28.1	6.2 / 1.8-21.8	4.8 / 0.9-25.7	29.4 / 8.6-99.9	40.9 / 10.1-166.1					4.4 / 2.4-7.9
500 < 700	14.1 / 4.6-43.7	20.1 / 6.2-65.2	32.9 / 9.3-116.3								10.1 / 5.5-18.6
Triplet vs lowest triplet fetal death rates	4.8 / 2.6-8.8	3.8 / 2.2-6.7	2.2 / 1.3-3.9	1.4 / 0.8-2.4	1.3 / 0.7-2.1	1.0	1.3 / 0.8-2.3	2.8 / 1.5-4.9	6.1 / 3.4-11.2	13.0 / 6.9-243	4.0 / 1.5-10.7

= Significant and higher than 1.0   = Reference

Table 6 - Triplet vs lowest triplet fetal death rates

Twin vs Singleton Fetal Death Rates, RRs ± 95% CI

Compared to singletons, the RRs ± 95% CI for twins are generally significantly higher at birthweights > 2800g and gestational ages > 35 weeks, and significantly lower below these ranges.

BIRTH WEIGHT (grams)	24-5	26-7	28-9	30-1	32-3	34-5	36-7	38-9	40-1	≥ 42	Total
≥ 4900											
4600 < 4900											
4300 < 4600											
4000 < 4300											
3700 < 4000											
3400 < 3700							3.5 (2.0-6.1)	6.4 (4.6-8.8)	7.2 (4.9-10.5)	9.2 (5.0-16.8)	6.4 (5.2-7.8)
3100 < 3400						3.1 (1.4-6.4)	1.7 (1.2-2.6)	4.5 (3.6-5.6)	4.1 (2.9-5.6)	6.4 (4.0-10.2)	3.9 (3.3-4.5)
2800 < 3100					1.7 (0.7-3.8)	1.2 (0.8-1.9)	1.0 (0.8-1.3)	2.4 (2.0-2.9)	2.2 (1.6-2.9)	3.8 (2.6-5.6)	1.9 (1.7-2.2)
2500 < 2800				1.0 (0.6-1.7)	0.8 (0.4-1.4)	0.5 (0.3-0.7)	0.5 (0.4-0.6)	1.0 (0.8-1.2)	1.7 (1.3-2.2)	2.4 (1.7-3.4)	0.9 (0.8-0.9)
2200 < 2500			0.6 (0.3-1.1)	0.5 (0.4-0.8)	0.5 (0.3-0.7)	0.4 (0.3-0.5)	0.4 (0.4-0.5)	0.9 (0.7-1.1)	1.1 (0.8-1.4)	1.5 (1.1-2.0)	0.6 (0.5-0.7)
1900 < 2200			0.3 (0.2-0.5)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.3 (0.3-0.4)	0.4 (0.3-0.5)	0.7 (0.6-0.9)			0.5 (0.4-0.5)
1600 < 1900			0.3 (0.3-0.5)	0.4 (0.3-0.4)	0.3 (0.2-0.3)	0.3 (0.2-0.3)	0.4 (0.4-0.5)				0.4 (0.3-0.4)
1300 < 1600		0.5 (0.3-0.8)	0.4 (0.3-0.5)	0.4 (0.3-0.4)	0.3 (0.3-0.4)	0.4 (0.4-0.5)					0.5 (0.4-0.5)
1000 < 1300	0.7 (0.5-0.9)	0.6 (0.5-0.7)	0.4 (0.3-0.5)	0.5 (0.4-0.7)	0.4 (0.3-0.5)						0.5 (0.4-0.5)
700 < 1000	0.5 (0.4-0.5)	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.2 (0.2-0.3)	0.4 (0.3-0.5)						0.4 (0.4-0.5)
500 < 700	0.4 (0.3-0.5)	0.4 (0.3-0.5)	0.3 (0.3-0.4)								0.4 (0.3-0.4)
Total	0.5 (0.4-0.5)	0.5 (0.4-0.6)	0.4 (0.4-0.5)	0.5 (0.4-0.5)	0.5 (0.4-0.5)	0.8 (0.7-0.8)	1.4 (1.3-1.5)	4.4 (4.1-4.8)	6.5 (5.9-7.2)	8.7 (7.6-10.0)	3.6 (3.5-3.6)

WEEKS GESTATION

= Reference

= Significant and higher than 1.0

= Twin vs singleton fetal death rates

Table 7 - Twin vs singleton fetal death rates

Triplet vs Singleton Fetal Death Rates, RRs ± 95% CI

Compared to singletons, the RRs ± 95% CI for triplets are generally significantly higher at birthweights > 2500g and gestational ages > 35 weeks, and significantly lower below these ranges.

BIRTH WEIGHT (grams)	24-5	26-7	28-9	30-1	32-3	34-5	36-7	38-9	40-1	≥ 42	Total
≥ 4900											
4600 < 4900											14.1 (6.8-28.1)
4300 < 4600											4.4 (2.5-7.5)
4000 < 4300											0.9 (0.7-1.7)
3700 < 4000											0.3 (0.2-0.5)
3400 < 3700											0.2 (0.1-0.3)
3100 < 3400											0.2 (0.1-0.3)
2800 < 3100						5.6 (1.0-38.3)	6.4 (2.4-207)	20.4 (9.1-67.0)	60.6 (27.5-276.1)	52.1 (21.9-263.9)	0.2 (0.1-0.3)
2500 < 2800					3.5 (0.5-247)	1.6 (0.4-67)	1.5 (0.5-47)	8.1 (2.6-22.8)	18.9 (8.1-64.0)	12.3 (4.8-43.9)	0.2 (0.1-0.3)
2200 < 2500					0.8 (0.2-3.2)	0.5 (0.2-1.3)	0.6 (0.2-1.6)	1.8 (0.6-6.9)	5.6 (1.7-16.0)		0.2 (0.1-0.3)
1900 < 2200				0.4 (0.06-29)	0.2 (0.08-0.7)	0.2 (0.06-0.5)	0.3 (0.09-0.8)	0.6 (0.1-2.4)	1.7 (0.4-7.2)		0.3 (0.2-0.5)
1600 < 1900			0.3 (0.05-20)	0.2 (0.09-0.8)	0.1 (0.05-0.3)	0.1 (0.03-0.3)	0.3 (0.1-0.7)				0.2 (0.1-0.3)
1300 < 1600		0.3 (0.04-1.9)	0.2 (0.08-0.7)	0.2 (0.06-0.4)	0.1 (0.04-0.3)	0.2 (0.06-0.4)					0.2 (0.1-0.3)
1000 < 1300		0.4 (0.1-1.1)	0.2 (0.06-0.4)	0.1 (0.06-0.3)	0.1 (0.05-0.3)						0.2 (0.1-0.3)
700 < 1000	0.2 (0.05-0.4)	0.2 (0.08-0.4)	0.1 (0.05-0.3)	.06 (0.02-0.3)	.02 (01-0.8)						0.2 (0.1-0.3)
500 < 700	0.2 (0.1-0.3)	0.2 (0.1-0.5)	0.3 (0.1-0.7)								0.2 (0.1-0.3)
Total	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.3 (0.2-0.5)	0.7 (0.5-1.1)	2.6 (1.7-3.9)	17.5 (10.7-28.1)	48.1 (279-817)	89.0 (47.1-165.0)	4.9 (4.7-5.1)

WEEKS GESTATION

= Reference = Significant and higher than 1.0 = Significant and lower

Table 8 - Triplet vs singleton fetal death rates Table

COMMENT

These findings indicate that infants of multiple births are at increased risk for fetal death, but with the attainment of birthweight and gestational age within a plurality-specific ideal range, these risks can be dramatically reduced. The fetal death rate at 3700-4000 g and 40-41 weeks for singletons, 2500-2800 g and 36-37 weeks for twins, and 1900-2200 g and 34-35 weeks for triplets is 75-80% less than the respective plurality-specific over-all rates. Even at immature gestational ages, adequate intrauterine growth is consistently associated with substantial reductions in the risk of fetal death, regardless of plurality. The similarity in all fetal deaths, with the 50% distribution occurring under 1900 g and before 34 weeks, suggests a common etiology of growth retardation across all pluralities. These findings confirm previous reports that intrauterine growth retardation is associated with an increased risk of fetal and neonatal death [4, 7, 8, 15, 20, 30], as well as higher rates of morbidity among survivors, regardless of plurality [12, 13, 18]. This analysis also confirms and extends the first phase of this study, which demonstrated that the lowest fetal mortality occurs at an earlier gestational age and lower birthweight for twins compared to singletons [15].

Infants of multiple gestations also achieve maturity at an earlier gestational age and lower birthweight compared to singletons. This analysis demonstrates that the singleton range of birthweight and gestational age maturity is actually postmature for twins and triplets, and if applied strictly to these pregnancies, results in a significantly higher incidence of fetal death among multiples. At the singleton ideal gestational age, 40-41 weeks, the risk of fetal death is 6.5-fold higher for twins and 48.1-fold higher for triplets. Conversely, at the twin ideal birthweight and gestational age, 2500-2800 g and 36-37 weeks, the fetal death rate for singletons is two-fold higher (6.5 vs 3.3), and at the triplet ideal birthweight and gestational age, 1900-2200 g and 34-35 weeks, the fetal death rate for singletons is 5.3-fold higher (27.8 vs 5.2). Other researchers have shown that fetal lung maturation occurs several weeks earlier for twins than singletons [10], and that even at very low birthweights and immature gestational ages (500-1499 g at 28-31 weeks) twins have a significantly lower incidence of bronchopulmonary dysplasia [29]. Although there is a need to supplement this current population-based analysis with clinical studies to determine the subsequent postnatal risk of prematurity-related morbidity among twins and triplets born at these "ideal" birthweight and gestational ages, current evidence suggests that this weight for age is associated with a good outcome.

In multiple births there are also a variety of unique factors known to increase the risk for fetal death that are not amenable to change, including placental vascular anastomoses, cord complications, and congenital anomalies, as well as a higher incidence of such complications as anemia, hemorrhage, and premature rupture of membranes. Current therapies to improve birthweight or prolong gestation in multiple births, including hospitalization [3, 21] and prophylactic tocolysis have not been consistently effective. Maternal weight gain, on the other hand, is strongly associated with enhanced birthweights for gestational ages in singletons [6] as well as twins [1, 11, 13, 16, 17, 19]. Preliminary studies in triplet gestations indicate that maternal weight gain may have an even greater positive effect on the birthweight of these high-risk infants [16].

There are several limitations of this study: this analysis did not consider the dependent nature of sibships among infants of multiple gestations, discordancy, infant race or

gender, or antenatal or intrapartum complications. These factors will be considered in the third and final component of this study. Despite these limitations, this study represents the first series of population-based clinical guidelines for the management of multiple gestations.

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