Original Research

Observed Rate of Down Syndrome in Twin Pregnancies

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OBJECTIVE: To evaluate the observed incidence of Down syndrome in twins compared with that expected based on maternal age–matched singletons, which is the current clinical approach.

METHODS: This was a retrospective review of California Prenatal Screening Program participants with expected delivery dates between July 1995 and December 2012. Cases confirmed prenatally or postnatally with a genetic imbalance leading to phenotypic Down syndrome (trisomy 21, mosaic trisomy 21, or translocations) were included. Pregnancies conceived with ovum donation and women older than 45 years were excluded. We compared the observed Down syndrome incidence per pregnancy for twins with expected incidence by extrapolating from singleton data and expected zygosity as is the current clinical approach. This extrapolation assumes that monozygotic pregnancies have equivalent Down syndrome risk per pregnancy relative to maternal age–matched singletons and dizygotic pregnancies have twice the risk of at least one affected fetus. Zygosity for affected cases was presumed to be monozygotic with Down syndrome concordance and dizygotic with Down syndrome discordance. Counts were compared using cumulative Poisson distributions.

RESULTS: Of 77,279 twin pregnancies, 182 (0.2%) had at least one fetus with Down syndrome confirmed by karyotype. The ratio of observed-to-expected Down syndrome incidence per pregnancy was 33.6%, 75.2%, and 70.0% for monozygotic, dizygotic, and all twins, respectively ($P<.001$ for all comparisons). Considering maternal age subgroups and twin zygosity, a significantly lower-than-expected Down syndrome incidence was seen for women aged 25 to 45 years with monozygotic pregnancies and overall for women aged 25 to 45 years with dizygotic pregnancies.

CONCLUSION: The observed incidence of Down syndrome in twin pregnancies is lower than expected, most notably for monozygotic pregnancies and with increasing maternal age. Risk-based counseling can strongly affect women's choices regarding testing and management during pregnancy, so an understanding of the true Down syndrome risk in twin gestations is crucial.

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Down syndrome is the most common chromosomal disorder affecting liveborn neonates,[1,2] yet its risk in twin pregnancies is not well established. Monozygotic twins have been assumed to have equivalent Down syndrome risk per pregnancy relative to maternal age–matched singletons and dizygotic twins to have twice the risk of at least one affected fetus.[3] The American College of Obstetricians and Gynecologists advises that risk in monozygotic pregnancies is equivalent to the maternal age-adjusted risk and that each dizygotic fetus carries independent age-adjusted risk.[4] The National Institute for Health and Care Excellence guidelines reference a higher Down syndrome risk in twin pregnancies, although they do not quantify the extent.[5]

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Some evidence, however, suggests that the risk among twin pregnancies may actually be lower. Studies based on actual Down syndrome cases rather than extrapolated numbers, although limited, have found a lower-than-expected risk among twin pregnancies.[1,6–9] Understanding the true risk of Down syndrome in twin pregnancies is important, because risk calculations for aneuploidy screening and women's decisions about invasive testing rely on accurate knowledge of a priori risk.[10,11]

We designed a large retrospective cohort study using California Prenatal Screening Program data to compare the observed incidence of Down syndrome in women with twins with that expected based on zygosity and maternal age–matched singletons. We hypothesized that women with monozygotic and dizygotic twins would have a lower-than-anticipated incidence of Down syndrome per pregnancy relative to women with singletons at a similar maternal age.

MATERIALS AND METHODS

This retrospective cohort study utilized data from the California Prenatal Screening Program administered by the Genetic Disease Screening Program within the California Department of Public Health. Inclusion criteria were women 16 years of age or older with singleton or twin pregnancies who were participants in the Prenatal Screening Program and had expected dates of delivery between July 1995 and December 2012. Women known to have conceived using ovum donation were excluded because aneuploidy risk may differ when ovum age relative to maternal age is considered. Because the California Prenatal Screening Program does not have access to data on various types of fertility treatments, women older than 45 years of age were also excluded, because they were more likely to have used assisted reproductive technology, which would lead to a larger proportion of dizygotic pregnancies than expected based on maternal age. As a result of the deidentified nature of the data, this study was determined to be exempt from institutional review board approval by the California Committee for the Protection of Human Subjects.

Women in the cohort underwent aneuploidy screening, which included first or second-trimester, or both, serum analysis as well as measurement of nuchal translucency after April 2009 if first-trimester screening was performed when fetal crown rump length was 45–84 mm.[12] California state regulations require that health care providers offer prenatal screening to all women seen for obstetric care before 20 weeks of gestation. Women who screen positive are provided follow-up services, including genetic counseling, ultrasonography, diagnostic procedures (chorionic villus sampling or amniocentesis), and karyotype through state-approved prenatal diagnostic centers.[10]

Cases of fetal and neonatal Down syndrome were diagnosed by karyotype, and patients with a genetic imbalance leading to phenotypic Down syndrome (trisomy 21, mosaic trisomy 21, or translocations) were included in this study.[13–15] State regulations require physicians, cytogenetic laboratories, hospitals, and prenatal diagnostic centers to report all chromosome abnormalities in a fetus or infant younger than 1 year of age to the Genetic Disease Screening Program. The California Registry of Cytogenetic Abnormalities collects information about chromosome abnormalities detected prenatally or postnatally in California as well as pregnancy outcomes for these births[10,16]; thus, chromosomally confirmed cases of Down syndrome diagnosed either before or after birth were captured. The California Prenatal Screening Program Coordinator staff was responsible for verifying details of each twin pregnancy and ensuring the quality of the data collected.

Chorionicity was not known for the majority of pregnancies in the study, because these data were available only by ultrasonography from the time that nuchal translucency examination was introduced in 2009. Furthermore, because zygosity provides more useful information regarding genetic risk than chorionicity, zygosity was estimated for affected twin pregnancies by presuming monozygosity in the setting of Down syndrome concordance and dizygosity with Down syndrome discordance. For unaffected twin pregnancies, zygosity was estimated by applying basic probabilities for fetal sex with sex confirmed by linking pregnancy records to birth records. Refer to further details in Appendix 1, available online at http://links.lww.com/AOG/A876, regarding these calculations.

For all analyses, the incidence of Down syndrome was considered as the incidence per pregnancy (in one or both twins) rather than for each twin independently. The observed incidence of Down syndrome among twin pregnancies was compared with that expected for each maternal age at birth with observed incidence calculated based on actual twin pregnancies in our cohort. Expected incidence of Down syndrome in twin pregnancies was calculated by extrapolating from singleton rates as is the current clinical approach,[3] and contemporaneous data from the California Prenatal Screening Program were applied for the incidence of Down syndrome in singleton pregnancies.[17] Calculation of expected incidence for twin pregnancies assumes that monozygotic pregnancies have equivalent risk per pregnancy to maternal age–matched singletons given the single embryologic origin of the fetuses and

that dizygotic pregnancies have twice the risk per pregnancy of at least one fetus being affected if each cotwin has an independent risk of this outcome.[3] We reported the observed and expected incidence of Down syndrome per twin pregnancy by maternal age subgroups in 5-year increments as well as the ratio of observed-to-expected Down syndrome incidence for each subgroup (observed incidence divided by expected incidence).

Analyses were based on data that was collected by the Genetic Disease Screening Program as of June 30, 2014. A one-sided test based on the cumulative Poisson distribution compared the observed number of Down syndrome cases with those expected. Population characteristics were compared using χ^2 tests. Analyses were performed with SAS 9.3, and a *P* value of <.05 was considered statistically significant.

RESULTS

The study population included 77,279 twin pregnancies. Some differences were observed in cohort characteristics, comparing women with singletons with those with twin pregnancies (Table 1). Notably, a greater proportion of white women had twin pregnancies compared with singleton pregnancies; although Latina women comprised the largest proportion of both singleton and twin pregnancies, relatively fewer Latina women had twin pregnancies. Additionally, a significantly increased rate of type 1 diabetes was seen in twin gestations compared with singletons, although the absolute difference was small.

Of the total cohort, an estimated 28.8% (22,282/77,279) of twin pregnancies were monozygotic and 71.2% (54,997/77,279) were dizygotic. The ratio of monozygotic and dizygotic twin pregnancies at each maternal age is also displayed with an overall greater proportion of dizygotic relative to monozygotic pregnancies with increasing maternal age (Table 2). The total number of twin pregnancies also increased with maternal age at expected date of delivery until 35 years, after which a decline was observed (Appendix 1, http://links.lww.com/AOG/A876).

Down syndrome was diagnosed in one or both fetuses in 0.2% (182/77,279) of twin pregnancies in our cohort. Six percent (11/182) of these Down syndrome cases occurred in monozygotic pregnancies with the remaining 94% (171/182) in dizygotic pregnancies. In contrast, the expected incidence of Down syndrome among all twin pregnancies was 0.3% (260.1/77,279) with 12.6% (32.8/260.1) of these predicted to occur in monozygotic pregnancies and 87.4% (227.4/260.1) in dizygotic pregnancies. The corresponding *P* values for these comparisons were <.001.

Table 3 displays the number of observed and expected twin pregnancies with at least one fetus affected by Down syndrome as well as the ratio of observed-to-expected Down syndrome incidence.

Table 1. Demographic Characteristics of the Cohort

Demographic Characteristic	Singleton Pregnancies	Twin Pregnancies	*P*
Race–ethnicity			
White	26.2	37.1	
Latina	51.7	37.7	
Asian	9.4	8.7	<.001
Black	5.6	8.1	
Other	5.0	5.7	
Multiple	2.3	2.8	
Type 1 diabetes	0.6	0.7	<.001
Tobacco use	1.2	1.1	.054

Data are % unless otherwise specified.

Table 2. Estimated Percentages of Monozygotic and Dizygotic Twins by Maternal Age Based on California Birth Data

Maternal Age (y)	Monozygotic	Dizygotic
16	52.0	48.0
17	52.7	47.3
18	51.5	48.5
19	43.0	57.0
20	48.1	51.9
21	47.9	52.1
22	37.1	62.9
23	40.1	59.9
24	40.1	59.9
25	30.4	69.6
26	37.9	62.1
27	32.0	68.0
28	27.4	72.6
29	29.1	70.9
30	27.1	72.9
31	22.4	77.6
32	19.3	80.7
33	21.1	78.9
34	24.3	75.7
35	25.4	74.6
36	21.9	78.1
37	19.2	80.8
38	19.7	80.3
39	22.2	77.8
40	27.0	73.0
41	25.0	75.0
42	21.6	78.4
43	19.5	80.5
44	13.6	86.4
45	6.6	93.4

Data are % unless otherwise specified.

For all twin pregnancies, the ratio of observed-to-expected Down syndrome incidence was 70.0%. Considering monozygotic and dizygotic pregnancies specifically, the ratio of observed-to-expected Down syndrome incidence was 33.6% and 75.2%, respectively. These comparisons were statistically significant for monozygotic, dizygotic, and all twin pregnancies in the overall cohort ($P<.001$ for all comparisons).

Considering maternal age subgroups, significant differences between observed and expected incidence of Down syndrome were in general seen among all twin pregnancies at maternal ages of 25 to 45 years (Table 3), except for the 35- to 39-year subgroup. For monozygotic pregnancies, the observed Down syndrome incidence was significantly lower than expected at maternal ages of 25 to 45 years with the ratio of observed-to-expected Down syndrome incidence ranging from 20.4% to 38.4%. For dizygotic pregnancies, the observed Down syndrome incidence was also lower than expected, although not as low as seen with monozygotic pregnancies. The observed Down syndrome incidence for dizygotic pregnancies was significantly lower than expected at maternal ages of 25 to 45 years, except for the 35- to 39-year subgroup with the ratio of observed-to-expected incidence ranging from 41.6% to 62.3%. Figure 1 further illustrates the differences between observed and expected Down syndrome incidence per 10,000 twin pregnancies, considering both zygosity and maternal age.

Table 3. Observed Compared With Expected Incidence of Down Syndrome Per Pregnancy by Maternal Age and Twin Zygosity

		Absolute Numbers (Down Syndrome Twin Pregnancies)		Down Syndrome Incidence (per 10,000 Twin Pregnancies)			
Maternal Age (y)	Pregnancies by Twin Zygosity	Observed Incidence	Expected Incidence	Observed Incidence	Expected Incidence	% of Expected	*P*
Younger than 20	Monozygotic (n=1,596)	0	1.1	0	6.6	0.0	.349
	Dizygotic (n=1,732)	1	2.3	5.8	13.2	43.7	.334
	All twin pregnancies (n=3,328)	1	3.3	3.0	10.0	29.9	.154
20–24	Monozygotic (n=5,045)	1	2.4	2.0	4.8	41.4	.305
	Dizygotic (n=6,941)	8	6.6	11.5	9.6	120.4	.774
	All twin pregnancies (n=11,986)	9	9.1	7.5	7.6	99.3	.580
25–29	Monozygotic (n=6,094)	1	4.9	1.6	8.0	20.4	**.044**
	Dizygotic (n=13,476)	9	21.6	6.7	16.1	41.6	**.002**
	All twin pregnancies (n=19,570)	10	26.5	5.1	13.6	37.7	**<.001**
30–34	Monozygotic (n=5,798)	3	7.8	5.2	13.5	38.4	**.048**
	Dizygotic (n=19,651)	33	53.0	16.8	27.0	62.3	**.002**
	All twin pregnancies (n=25,449)	36	60.8	14.1	23.9	59.2	**<.001**
35–39	Monozygotic (n=2,979)	4	11.1	13.4	37.2	36.1	**.014**
	Dizygotic (n=10,520)	70	78.2	66.5	74.3	89.5	.193
	All twin pregnancies (n=13,499)	74	89.3	54.6	66.1	82.9	.056
40–45	Monozygotic (n=769)	2	9.5	26.0	123.8	21.0	**.004**
	Dizygotic (n=2,678)	40	66.3	149.4	247.6	60.3	**<.001**
	All twin pregnancies (n=3,447)	42	75.8	121.8	220.0	55.4	**<.001**
All years	Monozygotic (n=22,282)	11	32.8	4.9	14.7	33.6	**<.001**
	Dizygotic (n=54,997)	171	227.4	22.1	29.4	75.2	**<.001**
	All twin pregnancies (n=77,279)	182	260.1	18.3	26.1	70.0	**<.001**

The observed incidence of Down syndrome per twin pregnancy was compared with that expected, with expected incidence calculated by extrapolating from maternal age–matched singleton rates as is the current clinical approach.
Bold incidates statistical significance.

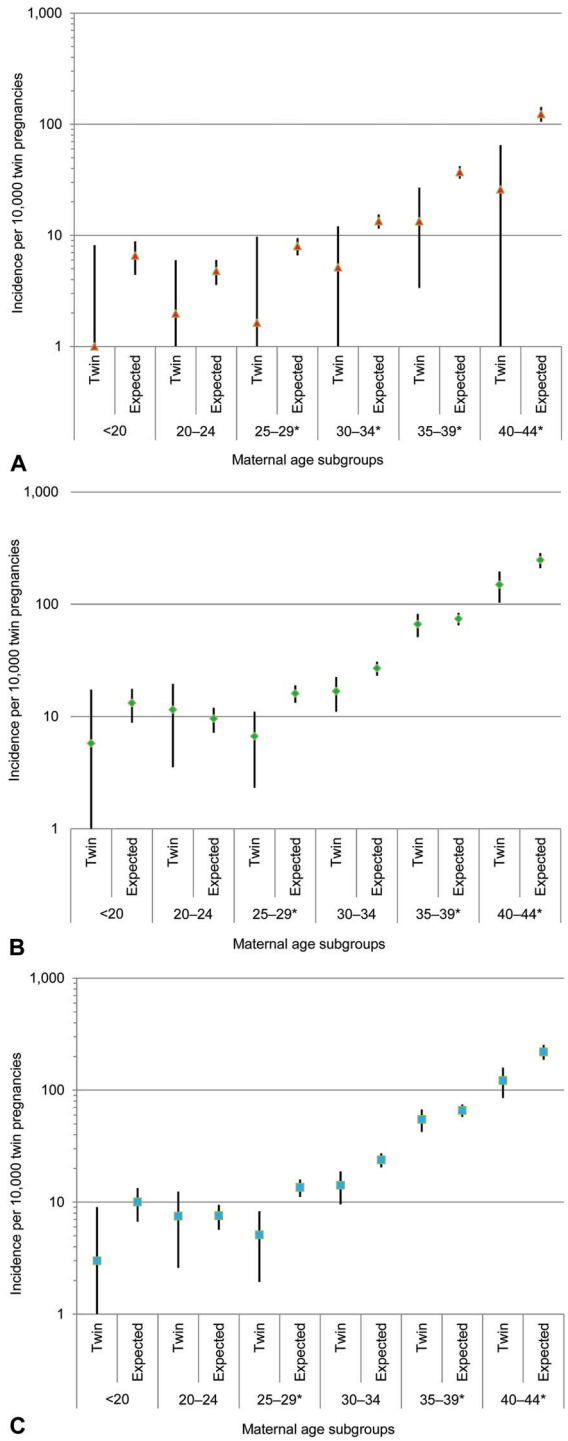

Fig. 1. Observed compared with expected incidence of Down syndrome per pregnancy for monozygotic (**A**), dizygotic (**B**), and all (**C**) twin pregnancies. The observed incidence of Down syndrome per twin pregnancy was compared with that expected, with expected incidence calculated by extrapolating from maternal age–matched singleton rates as is the current clinical approach. *Asterisks* indicate statistical significance.

Sparks. Down Syndrome in Twin Pregnancies. Obstet Gynecol 2016.

DISCUSSION

In this 20-year statewide review, the observed incidence of Down syndrome was lower than expected for monozygotic, dizygotic, and all twin pregnancies, most notably among monozygotic pregnancies and with increasing maternal age. The ratio of observed-to-expected Down syndrome incidence per pregnancy was 33.6%, 75.2%, and 70.0% for monozygotic, dizygotic, and all twins, respectively. Furthermore, a significantly lower-than-expected Down syndrome incidence was seen for women 25 years or older to 45 years with monozygotic pregnancies and overall for women 25 years or older to 45 years with dizygotic pregnancies.

Few other studies have assessed actual Down syndrome rates in twin pregnancies using actual cases rather than extrapolated numbers, and most are based on older data.[1,6–9] However, these studies similarly found a lower-than-expected Down syndrome incidence in both monozygotic and dizygotic pregnancies, most notably for those that were monozygotic.[1,6] A more recent large cytogenetic registry study[1] reported risks of Down syndrome in monozygotic and dizygotic pregnancies that were 66% lower than expected based on current models. Reasons for these findings, however, as well as those in our study will require further research to elucidate.

Higher rates of fetal loss with Down syndrome have been well described, up to 43% from the first trimester to term.[15] Potential reasons include advancing maternal age and genetic risks associated with aneuploidy,[18–20] although the true mechanisms remain unknown. Furthermore, there is little certainty regarding how applicable these increased rates of loss are to twins and higher order multiples, which likely have a further risk inherent to multifetal gestations in addition to that imposed by aneuploidy. In our study, cases of Down syndrome were included if diagnosed by prenatal or postnatal karyotype, but it is likely that some cases were lost or terminated early in the pregnancy before diagnosis. Among twin pregnancies, some may have resulted in either early spontaneous reduction of a twin with Down syndrome or miscarriage of the entire twin pregnancy. Furthermore, monochorionic twin pregnancies carry a greater risk of early loss[21–23] and, in the setting of concordance for aneuploidy, an even higher risk of loss may have contributed to the lower Down syndrome incidence in monozygotic pregnancies.

One strength of our study is that it includes more than 77,000 twin pregnancies, enabling evaluation of the actual Down syndrome incidence in a statewide,

geographically and ethnically diverse population. Additionally, we considered both twin zygosity and maternal age subgroups and directly compared observed incidence with that which is currently used for prenatal counseling. Our study is generalizable to most women with twin pregnancies, although less so for those who conceived using ovum donation or who are older than 45 years of age.

A primary limitation of our study is the incomplete ascertainment of all Down syndrome cases. Our cohort was limited to women who participated in state aneuploidy screening (approximately 71% of pregnant women)[10] and whose fetuses and infants had chromosomal confirmation of Down syndrome. Prior work has shown an ascertainment rate of 79% for singletons in the California Registry of Cytogenetic Abnormalities,[10] but we anticipate a higher rate for our cohort as outcomes are collected for all twin pregnancies. Women could have been missed for inclusion in the absence of aneuploidy screening, lack of prenatal or postnatal karyotype, or either spontaneous early loss or pregnancy termination before diagnosis. It is possible that Down syndrome rates would be higher if such cases were included, although they could have been missed from euploid or Down syndrome pregnancies as well as from singleton or twin pregnancies. Twin zygosity was estimated for this study, but zygosity is generally unknown in the prenatal setting, prenatal counseling regarding risk of aneuploidy is usually based on presumed zygosity, and confirmation of zygosity for a cohort this large would be challenging. Finally, diagnostic testing for women in our cohort followed a screen-positive result through conventional first- or second-trimester screening rather than cell-free fetal DNA, and further research would be needed to understand whether use of cell-free fetal DNA instead affects follow-up rates of diagnostic confirmation with karyotype.

The observed incidence of Down syndrome is lower than expected for monozygotic, dizygotic, and all twin pregnancies, most notably among monozygotic pregnancies and with increasing maternal age. An accurate understanding of a priori risk is essential not only for counseling of women with twin pregnancies, but also for aneuploidy screening and decision-making about prenatal testing and pregnancy management.

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