Screening for Aneuploidy in Twin Pregnancies: Maternal Age- and Race-specific Risk Assessment Between 9–14 Weeks

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The aim of this study was to calculate the risk for aneuploidy in twin pregnancies between 9–14 weeks utilizing maternal age, race and dizygotic twinning rates. Using previously published risks for aneuploidy in singletons and twins at the time of amniocentesis and at term, we calculated new risk estimates for twins at 9–14 weeks gestation or at the time of chorionic villus sampling. Using these tables, the risk for trisomy 21 in at least one fetus of a twin gestation in a 32-year-old at 9–14 weeks is 1/285 for Whites and for African-Americans. This is equivalent to the risk for trisomy 21 (1/265) in a 35-year-old woman with a singleton at the same gestational age. The risks for trisomies 18 and 13 also follow similar trends. In counseling women with twin pregnancies at the time of first trimester nuchal translucency screening or chorionic villus sampling, it should be noted that the maternal age-related risk for aneuploidy for a 32-year-old is equivalent to that of a 35-year-old woman with a singleton gestation.

The incidence of twin pregnancies has been rising partly due to the increasing use of ovulation induction and assisted reproductive technologies (ART). Prenatal screening and diagnosis for aneuploidy in twin pregnancies is limited by significant clinical, technical and ethical issues (Spencer, 2000). Although the use of "pseudo-risks" for twin pregnancies based on applying a correction factor to second trimester biochemical markers currently used for singleton pregnancies has been proposed (Neveux et al., 1996; Spencer et al., 1994; Wald et al., 1991), the validity of such an approach has been challenged (O'Brien et al., 1997). Consequently many obstetrical practices and prenatal diagnostic centers in the United States do not offer biochemical trisomy 21 screening for twin gestations, or rely only on maternal age for risk assessment, often with adjunctive ultrasound features.

In dizygotic twin gestations, the risk for trisomy 21 in one offspring is additive. Hence the age-related risk for a woman with a twin pregnancy is higher than for a woman at the same age with a singleton pregnancy. Maternal age-related risks for aneuploidy have been calculated for twin gestations at the time of amniocentesis (15–20 weeks) and at term (Meyers et al., 1997; Rodis et al., 1990). To our knowledge such calculations for twin gestations are not available for screening in the first trimester or at the time of chorionic villus sampling (CVS). First trimester screening for trisomy 21 using only nuchal translucency (NT) or combined with biochemical markers (Snijders et al., 1998; Spencer et al., 1999) has been established in several countries and preliminary studies in twin gestations have reported detection rates for trisomy 21 between 75–88% (Sebire et al., 1996; Spencer et al., 2000). Our aim is to calculate the risk of aneuploidy in twin pregnancies between 9–14 weeks gestation, taking into account the maternal age, gestational age and the influence of race on dizygotic twinning rate. We believe that it is important to have the most accurate numerical risks available to include in the counseling of women considering NT screening or prenatal diagnosis using CVS.

Materials and Methods

To calculate the risk for aneuploidy we used the following formulas devised by Rodis et al. (1990): a) risk of one dizygotic twin being affected = (2)(1/x)(y)([x–1]/x); b) risk of both dizygotic twins affected = (y)(1/x)(1/x); c) risk of both monozygotic twins affected = (1–y)(1/x); d) all twins, risk of both being affected = (b + c); and e) all twins, risk of one or both affected = (a + b + c), where 1/x is the age-related risk for chromosomal abnormality in a singleton, y is the proportion of twins that are dizygotic (0.8), 1–y is the proportion that are monozygotic (0.2), and x–1/x is the chance that the second twin is chromosomally normal. The assumption was that in a dizygotic gestation, each twin has an independent risk of aneuploidy. We used the same data source as Meyer et al. (1997) to calculate the twinning rates for our population (National Center for Health Statistics, 1994). No data for twins were reported for African-Americans after the age of 46 years.

The risk for trisomy 21 for singletons at 9–14 weeks was calculated using a relative prevalence of 30% more than at term. This relative prevalence for trisomy 21 at 9–14 weeks has previously been used and validated by Snijder et al. (1999) from a cohort of 57, 614 pregnancies. The prevalence for trisomies 18 and 13 were derived using

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the relative frequency of trisomy 18 compared with trisomy 21 of 0.318; and 0.114 for trisomy 13 compared with trisomy 21, at 9–14 weeks (Hook & Hammerton, 1977). These relative frequencies were similarly used and validated by Snijders et al. (1994; 1999). The prevalence of sex chromosomes was derived from data from Hook (1981) and modified assuming a 4.5% loss rate for XXY and XYY; and 70% loss rate for Turners syndrome detected in the first trimester (Hook et al., 1988).

Results

The maternal age related risks for trisomy 21 in twins at 9–14 weeks, showing the influence of race are shown in Table 1. Despite the differences in rates for Whites and African-Americans between the ages of 25–35, for all practical intents, this was not significant. After 35 years of age, the rates were similar. The risk for a 32-year-old with twins having at least one twin affected by trisomy 21 (1/291 for whites and 1/285 for African-Americans) was similar to that of a 35-year-old with singleton (1/265). Tables 2 and 3 show the rates for trisomies 18 and 13 respectively and again illustrate the differences between singletons and twins. Table 4 depicts the rates for XXY and demonstrates a relative insensitivity to age until after 35 years. Turner's syndrome and XYY are insensitive to maternal age as shown in Table 5.

For genetic counseling at the time of CVS, assuming a procedure-related fetal loss rate of 1%, the risk for a 35-year-old with twin gestation having at least one twin affected by trisomy 21 (1/140) is equivalent to the fetal loss rate.

Discussion

The current twin gestation tables for age related risks for aneuploidy were published by Rodis et al. (1990) and further modified by Meyer et al. (1997) taking racial differences into account. These tables were modified from data for singleton pregnancies published by Hook et al. (1978; 1983). We used the same source for our modified singleton data. As expected, our tables confirm that at 9–14 weeks gestation, the age related risks for aneuploidy are higher than at the time of amniocentesis. Furthermore, compared with the tables published by Snijders et al. (1999) for singleton pregnancies at 9–14 weeks, the present twin tables show higher rates for aneuploidy in at least one twin between 9–14 weeks. The data for singletons at 9–14 weeks in our tables are similar to those of Snijders et al. (1999). The rates for Turners syndrome confirm the high prevalence in the first trimester.

Table 1

Maternal Age and Race Specific Risks for Trisomy 21 at 9–14 Weeks

		White twins		African-American twins	
Maternal Age (years)	Singleton	One or Both	Both Affected	One or Both	Both Affected
25	1/875	1/473	1/5469	1/464	1/8228
26	1/823	1/444	1/5144	1/436	1/7739
27	1/778	1/420	1/4824	1/413	1/7316
28	1/737	1/398	1/4606	1/391	1/6931
29	1/700	1/378	1/4375	1/371	1/6583
30	1/666	1/360	1/4163	1/353	1/6263
31	1/636	1/343	1/3975	1/337	1/5981
32	1/538	1/291	1/3362	1/285	1/5059
33	1/421	1/227	1/2631	1/223	1/3959
34	1/339	1/183	1/2119	1/180	1/3188
35	1/265	1/143	1/1656	1/140	1/2492
36	1/202	1/109	1/1262	1/107	1/1899
37	1/157	1/85	1/981	1/83	1/1476
38	1/121	1/65	1/756	1/64	1/1138
39	1/95	1/51	1/594	1/50	1/893
40	1/74	1/40	1/462	1/39	1/696
41	1/57	1/31	1/356	1/30	1/536
42	1/44	1/24	1/275	1/23	1/414
43	1/34	1/19	1/212	1/18	1/320
44	1/27	1/14	1/169	1/13	1/254
45	1/21	1/11	1/131	1/10	1/197
46	1/16	1/9	1/100	1/8	1/150
47	1/13	1/7	1/81		
48	1/10	1/5	1/62		
49	1/8	1/4	1/50		

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Table 2

Maternal Age and Race Specific Risks for Trisomy 18 at 9–14 Weeks

		White twins		African-American twins	
Maternal Age (years)	Singleton	One or Both	Both Affected	One or Both	Both Affected
25	1/2752	1/1487	1/17,198	1/1459	1/25,875
26	1/2588	1/1396	1/16,176	1/1371	1/24,336
27	1/2446	1/1321	1/15,170	1/1299	1/23,006
28	1/2318	1/1251	1/14,484	1/1230	1/21,796
29	1/2201	1/1189	1/13,758	1/1167	1/20,701
30	1/2094	1/1132	1/13,091	1/1110	1/19,695
31	1/2000	1/1079	1/12,500	1/1060	1/18,808
32	1/1692	1/915	1/10,572	1/896	1/15,909
33	1/1324	1/714	1/8274	1/701	1/12,450
34	1/1066	1/575	1/6663	1/566	1/10,025
35	1/833	1/450	1/5207	1/440	1/7836
36	1/635	1/343	1/3968	1/336	1/5972
37	1/494	1/267	1/3085	1/261	1/4641
38	1/380	1/204	1/2377	1/201	1/3579
39	1/299	1/160	1/1868	1/157	1/2808
40	1/233	1/126	1/1453	1/123	1/2189
41	1/179	1/97	1/1119	1/94	1/1685
42	1/138	1/75	1/865	1/72	1/1302
43	1/107	1/60	1/667	1/57	1/1006
44	1/85	1/44	1/531	1/41	1/799
45	1/66	1/35	1/412	1/31	1/619
46	1/50	1/28	1/314	1/25	1/472
47	1/41	1/22	1/255		
48	1/31	1/16	1/195		
49	1/25	1/13	1/157		

Table 3

Maternal Age and Race Specific Risks for Trisomy 13 at 9–14 Weeks.

		White twins		African-American twins	
Maternal Age (years)	Singleton	One or Both	Both Affected	One or Both	Both Affected
25	1/7675	1/4149	1/47,974	1/4070	1/72,175
26	1/7219	1/3895	1/45,123	1/3825	1/67,886
27	1/6825	1/3684	1/42,315	1/3623	1/64,175
28	1/6465	1/3491	1/40,403	1/3430	1/60,798
29	1/6140	1/3316	1/38,377	1/3254	1/57,746
30	1/5842	1/3158	1/36,517	1/3096	1/54,939
31	1/5579	1/3009	1/34,868	1/2956	1/52,465
32	1/4719	1/2553	1/29,491	1/2500	1/44,377
33	1/3693	1/1991	1/23,079	1/1956	1/34,729
34	1/2974	1/1605	1/18,588	1/1579	1/27,965
35	1/2325	1/1254	1/14,526	1/1228	1/21,860
36	1/1772	1/956	1/11,070	1/939	1/16,658
37	1/1377	1/746	1/8605	1/728	1/12,947
38	1/1061	1/570	1/6632	1/561	1/9982
39	1/833	1/447	1/5210	1/439	1/7833
40	1/649	1/351	1/4053	1/342	1/6105
41	1/500	1/272	1/3123	1/263	1/4702

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Table 3 continued

Maternal Age and Race Specific Risks for Trisomy 13 at 9–14 Weeks

		White twins		African-American twins	
Maternal Age (years)	Singleton	One or Both	Both Affected	One or Both	Both Affected
42	1/386	1/210	1/2412	1/202	1/3632
43	1/298	1/167	1/1860	1/158	1/2807
44	1/237	1/123	1/1482	1/114	1/2228
45	1/184	1/96	1/1149	1/88	1/1728
46	1/140	1/79	1/877	1/70	1/1316
47	1/114	1/61	1/710		
48	1/88	1/44	1/544		
49	1/70	1/35	1/439		

Table 4

Maternal Age and Race Specific Risks for Klinefelters (47, XXY) at 9–14 Weeks

		White twins		African-American twins	
Maternal Age (years)	Singleton	One or Both	Both Affected	One or Both	Both Affected
25	1/2387	1/1289	1/14799	1/1241	1/22438
26	1/2387	1/1289	1/14799	1/1241	1/22438
27	1/2387	1/1289	1/14799	1/1241	1/22438
28	1/2387	1/1289	1/14799	1/1241	1/22438
29	1/1910	1/1031	1/11842	1/993	1/17954
30	1/1910	1/1031	1/11842	1/993	1/17954
31	1/1910	1/1031	1/11842	1/993	1/17954
32	1/1592	1/860	1/9870	1/828	1/14965
33	1/1364	1/736	1/8457	1/709	1/12822
34	1/1364	1/736	1/8457	1/709	1/12822
35	1/1061	1/573	1/6578	1/552	1/9973
36	1/955	1/516	1/5921	1/497	1/8977
37	1/868	1/469	1/5382	1/451	1/8159
38	1/734	1/396	1/4551	1/382	1/6899
39	1/637	1/344	1/3949	1/331	1/5988
40	1/530	1/286	1/3286	1/276	1/4982
41	1/434	1/234	1/2691	1/226	1/4080
42	1/353	1/191	1/2189	1/184	1/3318
43	1/289	1/156	1/1792	1/150	1/2717
44	1/233	1/126	1/1445	1/121	1/2190
45	1/187	1/101	1/1159	1/97	1/1758
46	1/149	1/80	1/924	1/77	1/1401
47	1/116	1/63	1/719		
48	1/90	1/48	1/558		
49	1/69	1/37	1/429		

Table 5

Maternal Age and Race Specific Risk for 47, XYY and Turners Syndrome at 9–14 Weeks

		White twins		African-American twins	
	Singleton	One or Both	Both Affected	One or Both	Both Affected
All ages 47, XYY	1/2387	1/1289	1/14799	1/1241	1/22438
All ages Turners syndrome	1/2000	1/1080	1/12400	1/1040	1/18800

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Most obstetrical and prenatal diagnostic units in the USA depend on maternal age risk assessment as the only method for counseling regarding the risk for aneuploidy for twin gestations. This is due to the impression that using "pseudo-risks" calculated for multiple marker screening may not be valid (O'Brien et al., 1997). Therefore, maternal age related risks and ultrasound findings are generally used for counseling women with twins of their risk for an aneuploid fetus. However, reliable data for age-related risks for twins during late first trimester are not available. When screening or diagnostic tests in the first trimester are being considered, the use of aneuploidy risks calculated for the mid-second trimester (Meyers et al., 1997; Rodis et al., 1990) would be inappropriate as these are lower compared with those at 9–14 weeks as shown in this report.

Prenatal screening and diagnosis for twin gestations in the first trimester is increasingly requested by couples. In addition, women with higher order multiple gestations may request reduction to twins or singletons and are requesting prenatal diagnosis prior to the procedure. That CVS in multiple gestations is not only feasible, but also safe has been demonstrated (Sebire et al., 1996; Wapner et al., 1993). Many women decide to have invasive prenatal diagnosis if the balance of their perceived risk for the condition is greater than or equal to the procedure related loss rate. Thus, the risks for aneuploidy compared to the fetal loss rate from CVS would be perceived to be lower for each age group using data derived from estimates at the time of amniocentesis. For example, using the data from our tables the chance that a patient at the age of 35 years would have at least one twin with trisomy 21 would be roughly the same as the loss rate from CVS (1%). For women between 32 and 35 years who also have increased risks for aneuploidy (but lower risks than the procedure-related loss rate from CVS), it may be reasonable to have an amniocentesis in the second trimester (Sebire et al., 1996; Sebire et al., 1996).

With the promising detection rates for aneuploidy in twin gestations using first trimester NT, either alone or perhaps combined with PAPP-A and hCG, it is now possible to calculate the risk for aneuploidy in twin pregnancies by combining the likelihood ratios from the NT and biochemical markers with maternal age (Sebire, 1996; Spencer 2000). In calculating the post-test risk for aneuploidy in at least one twin, data for maternal age related risks as derived from this report would be more appropriate than using those for singleton pregnancies at 9–14 weeks (Snijders et al., 1999; Snijders et al., 1994).

Some of the assumptions made in calculating the risks may need to be validated in clinical practice. For example, if the prevalence of heterokaryotypic monozygotic twins (each twin with a different karyotype) is not as rare as previously suggested, then the calculated risks may not be accurate (Rodis et al., 1990). Similarly, in populations where the prevalence of dizygotic twinning is higher than 80% used in our calculations and the prior twin data, these tables may not be applicable (Meyers et al., 1997; Rodis et al., 1990). We used the same assumption of 80% as used in these previous reports as we have no recent data to use. Although risks calculated using Rodis et al.'s formula have been criticized for over-estimating the risk of Down syndrome at term (Cuckle, 1998), the use of the data from National Center for Health Statistics is the only epidemiologically sound option available to us. We have therefore used this same data source, as was used by Meyers et al. (1997).

Furthermore, Wenstrom et al.(1993) have reported an increasing rate of monozygotic twinning with the use of ART. This may change the proportion of monozygotic to dizygotic twins in the future and may necessitate revising the model.

In addition, recent reports have suggested that with the use of first trimester ultrasound, chorionicity may be accurately determined and patients counseled regarding the probability that the assumptions of the model are accurate (Sepulveda et al., 1996). Future studies should explore the possibility of determining risks accurately based on sonographically assigned chorionicity. Until more centers become comfortable with the use of ultrasound only for determination of chorionicity, maternal age-based risk assessment for aneuploidy in twins will continue to be used. We also used a prevalence rate of trisomy 21 that is 30% higher at 9–14 weeks than at term. The same prevalence was used by Snijders et al. (1999) in their calculations for singleton pregnancies and since this model was validated by their large center's experience, we believe it may be more accurate compared with the assumption of Meyer's et al. (1997) who used the same prevalence for the time of amniocentesis.

With the tables published in this report, we can effectively counsel patients presenting with a twin gestation for first trimester screening for aneuploidy or CVS regarding their age-related risk. The influence of race has also been used. Large population based studies would however be required to validate the model.

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