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Maternal age- and gestation-specific risk for trisomy 21

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ABSTRACT

Objective *To provide estimates of maternal age- and gestational age-related risks for trisomy 21.*

Methods *The prevalence of trisomy 21 was examined in 57 614 women who had fetal karyotyping at 9–16 weeks of gestation for the sole indication of maternal age of 35 years or more. On the basis of the maternal age distribution and the reported maternal age-related risk for trisomy 21 at birth, the expected number of trisomy 21 cases was calculated for each gestational age subgroup (9–10 weeks, 11–14 weeks and 15–16 weeks). The ratio of the observed to expected number of cases of trisomy 21 was then calculated and regression analysis was applied to derive a smoothened curve. The formula for maternal age- and gestational age-related risk was then applied to a population of 96 127 pregnancies that were examined at 10–14 weeks to calculate the expected number of trisomy 21 pregnancies, and this number was compared to the observed number of 326.*

Results *In the 57 614 pregnancies there were 538 cases of trisomy 21. The relative prevalences of trisomy 21, compared to a prevalence of 1.0 at 40 weeks, was* $10\ exp(0.2718 \times log_{10}(gestation)^2 - 1.023 \times log_{10}(gestation) + 0.9425)$*. On the basis of the estimated maternal age- and gestational age-related risks, the expected number of trisomy 21 cases at 10–14 weeks of gestation in the 96 127 pregnancies was 329 (95% confidence interval 291–361), which was not significantly different from the observed number of 326 cases (*$\chi^2 = 0.02$*).*

Conclusion *The risk for trisomy 21 increases with maternal age and decreases with gestation. The prevalence of trisomy 21 at 12 and 16 weeks of gestation is higher than the prevalence at 40 weeks by 30% and 21%, respectively.*

INTRODUCTION

Estimates of the maternal age-related risk for trisomy 21 at birth are based on two surveys with almost complete ascertainment; in a survey in South Belgium, every neonate was examined for features of trisomy 21, and, in a survey in Sweden, information was verified using several sources such as hospital notes, cytogenetic laboratories, genetic clinics and schools for the mentally handicapped[1–3].

During the past decade, with the introduction of maternal serum biochemistry and ultrasound screening for chromosomal defects at different stages of pregnancy, it has become necessary to establish maternal age- and gestational age-specific risks for chromosomal defects. Previous studies derived such estimates by comparing the birth prevalence of trisomy 21[1] to the prevalence reported in two multicenter studies on amniocentesis at 16–20 weeks of gestation[4,5] and the prevalence in small series on chorionic villus sampling at 9–14 weeks of gestation[6,7]. In this study, we revised our previous estimates by examining 57 614 pregnancies that were karyotyped at 9–16 weeks of gestation. Furthermore, we examined the accuracy of these estimates in a group of 96 127 singleton pregnancies with complete follow-up that were recruited at 10–14 weeks of gestation[8].

SUBJECTS AND METHODS

Estimate of risk

To calculate estimates of risk for trisomy 21 at different gestations, we used data from 57 614 women who had fetal karyotyping at 9–16 weeks of gestation for the sole indication of maternal age of 35 years or more. On the basis of the maternal age distribution and maternal age-related risk for trisomy 21 at birth[1], the expected

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number of trisomy 21 cases was calculated for each gestational age subgroup (9–10 weeks, 11–14 weeks and 15–16 weeks) and for each maternal age. In these calculations, the appropriate corrections were made for those women whose age in years would increase between the time of antenatal assessment at 9–16 weeks and the time of delivery. Gestational age was available in completed weeks. Pearson correlation analysis was applied to examine whether the ratio changed significantly with maternal age and/or gestation. Regression analysis was applied to ratios at 9–10 weeks, 11–14 weeks, 15–16 weeks and 40 weeks (where the ratio was set at one) to derive a smoothened curve for the decrease in ratio with gestational age.

Validation of the model

In a multicenter study of screening for trisomy 21 by combination of maternal age and fetal nuchal translucency thickness at 10–14 weeks of gestation, we obtained details on the outcome of 96 127 pregnancies[8]. This group included 326 pregnancies with trisomy 21. The new formula for maternal age- and gestational age-related risk was applied to this population, to calculate the expected number of trisomy 21 pregnancies, and this number was compared to the observed number of 326.

RESULTS

The maternal age and gestational age distributions of the 57 614 pregnancies are shown in Table 1. Trisomy 21 was diagnosed in 538 cases (Table 2). The relative prevalence of trisomy 21 (observed to expected ratio), compared to a prevalence of 1.0 at 40 weeks, was not significantly associated with maternal age ($r = 0.178$; $p = 0.31$) but decreased with gestational age ($r = 0.812$; $p < 0.01$). Data were grouped to derive the relative prevalence at different gestations (Table 3) and regression analysis was applied to derive a smoothened curve

Table 1 Maternal age and gestational age distribution of the 57 614 women who had fetal karyotyping

Maternal age (years)	*Gestational age* (weeks)								
	9	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*Total*
35	916	1832	823	233	192	1139	3 676	5 252	14 063
36	891	1736	805	258	185	971	3 101	4 484	12 431
37	744	1486	774	241	120	779	2 363	3 388	9 895
38	661	1139	629	170	109	567	1 789	2 614	7 678
39	413	905	479	164	104	364	1 211	1 740	5 380
40	278	597	339	115	60	274	749	1 147	3 559
41	168	408	231	85	48	172	459	689	2 260
42	97	219	128	59	29	96	283	357	1 268
43	45	108	84	32	13	46	135	184	647
44	23	75	29	18	1	30	64	86	326
45	4	17	16	2	8	9	24	27	107
Total	4240	8522	4337	1377	869	4447	13 854	19 968	57 614

Table 2 Maternal age and gestational age distribution of the 538 pregnancies with trisomy 21

Maternal age (years)	*Gestational age* (weeks)								
	9	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*Total*
35	5	9	5	1	0	4	14	18	56
36	6	9	4	2	1	5	16	31	74
37	7	10	7	2	0	5	15	18	64
38	8	11	5	2	1	5	14	25	71
39	7	16	8	1	1	5	14	23	75
40	3	14	8	2	1	4	14	10	56
41	4	11	4	2	1	3	10	16	51
42	4	8	3	2	1	2	7	12	39
43	2	5	4	1	1	2	5	7	27
44	1	5	1	0	0	1	3	5	16
45	0	2	2	0	1	1	1	2	9
Total	47	100	51	15	8	37	113	167	538

Table 3 Observed number of cases with trisomy 21 compared to the number expected in live births in relation to gestational age

Gestational age (weeks)	*n*	*Observed*	*Expected*	*Ratio*	*95% confidence interval*	*Regressed ratio*
9 + 0–10 + 6	12 762	147	93.6	1.57	1.32–1.82	1.55
11 + 0–14 + 6	11 030	111	82.4	1.35	1.10–1.60	1.38
15 + 0–16 + 6	33 822	280	217.8	1.29	1.14–1.44	1.27

[$\log_{10}$(relative prevalence) = $0.2718 \times \log_{10}(\text{gestation})^2 - 1.023 \times \log_{10}(\text{gestation}) + 0.9425$]. The estimated maternal age- and gestational age-related risks for trisomy 21 are given in Table 4. The estimated rates of spontaneous fetal death between different gestations and delivery at 40 weeks were derived on the basis of the relative prevalences between these gestations and 40 weeks (Table 5).

Validation of the model

The accuracy of the model was examined on the basis of findings in 96 127 pregnancies examined at 10–14 weeks of gestation. The expected number of cases with trisomy 21 was estimated to be 329 (95% confidence interval 291–361). This number is not significantly different from the observed number of 326 cases ($\chi^2 = 0.02$). There was no significant difference between the observed and expected numbers for different gestational age and maternal age subgroups (Table 6).

Table 4 Prevalence of trisomy 21 by maternal age and gestational age

Maternal age (years)	*Gestational age* (weeks)					
	10	*12*	*14*	*16*	*20*	*40*
20	1/983	1/1068	1/1140	1/1200	1/1295	1/1527
25	1/870	1/946	1/1009	1/1062	1/1147	1/1352
30	1/576	1/626	1/668	1/703	1/759	1/895
31	1/500	1/543	1/580	1/610	1/658	1/776
32	1/424	1/461	1/492	1/518	1/559	1/659
33	1/352	1/383	1/409	1/430	1/464	1/547
34	1/287	1/312	1/333	1/350	1/378	1/446
35	1/229	1/249	1/266	1/280	1/302	1/356
36	1/180	1/196	1/209	1/220	1/238	1/280
37	1/140	1/152	1/163	1/171	1/185	1/218
38	1/108	1/117	1/125	1/131	1/142	1/167
39	1/82	1/89	1/95	1/100	1/108	1/128
40	1/62	1/68	1/72	1/76	1/82	1/97
41	1/47	1/51	1/54	1/57	1/62	1/73
42	1/35	1/38	1/41	1/43	1/46	1/55
43	1/26	1/29	1/30	1/32	1/35	1/41
44	1/20	1/21	1/23	1/24	1/26	1/30
45	1/15	1/16	1/17	1/18	1/19	1/23

Table 5 Estimates for spontaneous loss rates for fetuses with trisomy 21 between various gestations and delivery at 40 weeks

Gestational age (weeks)	*Estimated loss rate* (%)
10	36
12	30
14	25
16	21

DISCUSSION

This study provides revised estimates of maternal age- and gestational age-related risk for trisomy 21. Compared to our previous report[7], in this study the number of cases with fetal karyotyping was much higher (57 614 compared to 15 793). Additionally, in this study the appropriate corrections were made for the increase in maternal age with advancing gestation.

The estimates for the rate of spontaneous fetal death for trisomy 21 are lower than in our previous report (30% compared to 41% for the loss rate between 12 and 40 weeks of gestation and 21% compared to 31% for the loss rate between 16 and 40 weeks)[7]. The main reason for this apparent discrepancy is that in the previous analysis there was no correction for the increase in maternal age with advancing gestation. This led to an underestimate for the expected number of trisomy 21 live births and thus to an overestimate of the loss rate. The new estimates of loss rates are similar to the 31% from 12 weeks and 18% from 16 weeks reported by Halliday and colleagues[9]; they compared the prevalence of trisomy 21 in 10 545 women having chorionic villus sampling or amniocentesis for the sole indication of maternal age of 36 years or more, to the prevalence in live births from 12 921 women of similar age who did not have fetal karyotyping[9].

Assessment of the model on the basis of findings in 96 127 pregnancies indicates that the estimated prevalences are accurate at least for the gestational range of 10–14 weeks; the estimates at 16 weeks and 20 weeks of gestation require validation with an independent data set.

The model makes it possible to counsel patients presenting at different stages of pregnancy concerning the risk that their fetus has trisomy 21 and the chances that the pregnancy will result in a live birth with this condition. Furthermore, the data can be used to calculate the expected

Table 6 Expected and observed number of pregnancies with trisomy 21 for different gestations and maternal age subgroups

	n	*Expected*	*Observed number*	*Observed 95% CI*	χ^2
Gestational age (weeks)					
10	4 889	15.8	11	5–18	0.86
11	34 046	119.1	137	114–160	1.26
12	42 884	146.2	141	118–164	0.09
13	14 308	48.0	37	25–49	1.43
Maternal age (years)					
< 30	39 834	46.2	36	24–48	1.03
30–34	32 489	73.9	67	51–83	0.25
35–39	20 263	128.2	125	103–147	0.02
≥ 40	3 541	80.8	98	79–117	1.51
Total	96 127	329.1	326	291–361	0.02

prevalence of trisomy 21 in any study group when new ultrasonographic or biochemical methods of screening are being evaluated.

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