PRENATAL DIAGNOSIS, VOL. 14: 543–552 (1994)

MATERNAL AGE-SPECIFIC RISKS FOR TRISOMIES AT 9–14 WEEKS' GESTATION

R. J. M. SNIJDERS*, W. HOLZGREVE†, H. CUCKLE‡ AND K. H. NICOLAIDES*

The Harris Birthright Centre for Fetal Medicine, King's College Hospital Medical School, London, U.K.; †Zentrum für Frauenheilkunde, Westfalen Wilhelms-Universität, Münster, Germany; ‡Institute of Epidemiology and Health Services Research, University of Leeds, Leeds, U.K.

Received 22 July 1993
Revised 18 October 1993
Accepted 31 December 1993

SUMMARY

This study provides data on the incidence of fetal trisomies 21, 18, and 13 at 9–14 weeks' gestation in women aged 35–45 years and estimates of maternal age-specific risks in women aged 20–45 years. Our data from 5814 singleton pregnancies undergoing first-trimester karyotyping for the sole indication of maternal age ⩾35 years were combined with those from two previous reports and the incidence of the trisomies was calculated from a total of 15 793 pregnancies. Comparison of incidences at 9–14 weeks' gestation with published data at 15–20 weeks' gestation and in livebirths demonstrated that at birth the maternal age-specific incidence of trisomy 21 is 33 per cent lower than at 15–20 weeks' gestation and 54 per cent lower than at 9–14 weeks' gestation. Furthermore, the relative frequency of trisomies 18 and 13 decreases from 30 per cent at 9–14 weeks to 22 per cent at 15–20 weeks and 14 per cent at birth.

KEY WORDS—First trimester of pregnancy, fetal trisomies, maternal age.

INTRODUCTION

The risk of fetal chromosomal abnormalities increases with advancing maternal age and the incidence is higher at mid-pregnancy that at birth (Hook, 1978; Hook *et al.*, 1984; Ferguson-Smith and Yates, 1984). Furthermore, at mid-pregnancy the proportion of trisomies 13 and 18 is higher (Hook, 1978; Hook *et al.*, 1984; Ferguson-Smith and Yates, 1984). Since both screening and diagnosis of chromosomal abnormalities are increasingly being performed in the first trimester of pregnancy, it is necessary to establish maternal age-specific incidences for the various chromosomal abnormalities at 9–14 weeks' gestation. In this study, our data from 5814 pregnancies undergoing first-trimester fetal karyotyping are combined with those of Hook *et al.* (1988) and Kratzer *et al.* (1992) to calculate the incidence of fetal trisomies at 9–14 weeks' gestation in women aged 35–45 years and to establish estimates of maternal age-specific risks for women aged 20–45 years.

PATIENTS AND METHODS

Fetal karyotyping for the sole indication maternal age ⩾35 years was performed in 5814 singleton pregnancies at the Zentrum für Frauenheilkunde ($n=3618$) or the Harris Birthright Research Centre for Fetal Medicine ($n=2196$). Gestational age was 9–14 completed weeks, as determined from the maternal menstrual history and confirmed by measurement of the fetal crown–rump length. In all cases of either amniocentesis ($n=602$) or chorionic villus sampling (CVS) ($n=5212$), cytogenetic analysis was performed after culture.

The incidences of trisomies 21, 18, and 13 were calculated for each year of maternal age. In addition, the observed number of cases was compared with the number of cases predicted on the basis of incidences in the combined data of Hook *et al.*

Addressee for correspondence: Kypros Nicolaides, MD, The Harris Birthright Centre for Fetal Medicine, King's College Hospital Medical School, London, U.K.

CCC 0197–3851/94/070543–10

Table I—Maternal age and gestational age distributions in 5814 pregnancies that underwent CVS or amniocentesis for fetal karyotyping

Gestation (weeks+days)	*n*	Maternal age (years)										
		35	36	37	38	39	40	41	42	43	44	45
9+0 to 9+6	1020	189	203	188	175	106	72	32	32	11	9	3
10+0 to 10+6	2263	939	406	412	308	298	198	125	81	37	20	11
11+0 to 11+6	1318	169	186	243	195	178	128	85	62	38	16	18
12+0 to 12+6	461	42	63	93	67	63	52	32	27	11	7	4
13+0 to 13+6	215	30	37	33	35	25	18	17	8	7	2	3
14+0 to 14+6	537	142	116	86	70	47	30	24	12	5	5	—
Total	5814	939	1011	1055	850	717	498	315	222	109	59	39

(1988) and Kratzer *et al.* (1992). Since there was no significant difference (see Results), further analysis was performed using our series combined with those of Hook *et al.* (1988) and Kratzer *et al.* (1992).

For maternal age-specific incidences of trisomies 21, 18, and 13 at 15–20 weeks, data on a total of 109 040 pregnancies published in two large surveys were used (Ferguson-Smith and Yates, 1984; Hook *et al.*, 1984). For incidences of trisomy 21 in livebirths, calculations by Cuckle *et al.* (1987) on a total of 3 289 114 pregnancies published in eight large surveys were used and for the relative incidence of trisomies 18 and 13 among livebirths, findings reported by Hook and Hamerton (1977) were used.

Trend analysis was applied to examine the significance of associations with maternal age, and analysis of variance (ANOVA) was used to determine if there was a significant difference between observed and expected incidences.

RESULTS

The maternal age and gestational age distributions of our 5814 cases are shown in Table I. The fetal karyotype was abnormal in 162 (2·8 per cent) cases, and in 109 (67 per cent) the chromosomal abnormality was trisomy 21, 18, or 13. Cytogenetic findings are summarized in Table II and details of all chromosomal abnormalities are given in Table III.

The maternal age-specific incidences for trisomies 21, 18, and 13 in the present study (Table IV) were not significantly different from the findings of Hook *et al.* (1988) and Kratzer *et al.* (1992); the ratio of the observed to the predicted number of cases for trisomy 21 was 0·998 [90 per cent confidence interval (CI) 0·800–1·200] and the ratio for all three trisomies was 1·007 (90 per cent CI 0·838–1·176). For comparison of the incidences at 9–14 weeks with findings in the second trimester and at birth, data from the present study were combined with those from Hook *et al.* (1988) and Kratzer *et al.* (1992) (Table IV).

In women aged 35–45 years, the incidences of trisomy 21 at 9–14 and 15–20 weeks increased exponentially (Table VI) and the slopes of regression lines were not significantly different (Fig. 1, $P=0·141$). The observed incidence of trisomy 21 at 9–14 weeks was 2·196 times higher than expected on the basis of crude incidences in livebirths (Cuckle *et al.*, 1987) and the ratio of the observed to the expected number of cases was not significantly associated with maternal age (Table V, $z=-1·92$). Similarly, the observed incidence of trisomy 21 at 15–20 weeks (Ferguson-Smith and Yates, 1984; Hook *et al.*, 1984) was higher (1·491 times) than expected on the basis of incidences in livebirths, and the ratio of the observed to the expected number of cases was not significantly associated with maternal age (Table V, $z=-1·53$). Estimates of the incidences for trisomy 21 at 9–14 and 15–20 weeks' gestation in women aged 20–45 years were derived by multiplying smoothened values for incidences of trisomy 21 in livebirths (Cuckle *et al.*, 1987) by 2·1956 and 1·4911, respectively (Table VII).

The incidences of trisomy 18 at 9–14 and 15–20 weeks increased exponentially (Table VI) and the slopes of regression lines were not significantly different for women aged 35–44 years (Fig. 2, $P=0·298$). The overall relative frequencies of trisomy 18 compared with trisomy 21 were 0·318 at 9–14 weeks' gestation, 0·224 at 15–20 weeks' gestation and 0·0973 in livebirths (Hook and Hamerton, 1977). Estimates for the incidences of

Table II—Cytogenetic abnormalities in cultured cells from 5814 chorionic villus or amniotic fluid samples taken at 9–14 weeks' gestation

Karyotype	*n*	%
47,XX,+21	33	20·4
47,XY+21	46	28·4
47,XX+18	12	7·4
47,XY+18	10	6·2
47,XX+13	4	2·5
47,XY+13	4	2·5
47,XXX	7	4·3
47,XXY	8	4·9
47,XYY	1	0·6
45,XO	9	5·6
69,XXX	1	0·6
69,XXY	2	1·2
69,XYY	1	0·6
Mosaic*	10	6·2
Other†	14	8·6
Total	162	100·0

*47,XX,+21; 47,XX,+13; 47,XX,+8; 47,XXY ($n=2$); 45,X ($n=3$); 46,XX,t(13;21); 92,XXYY.

†47,XY,+8; 47,XX,+16 ($n=2$); 47,XX,+22; 47,XY,+22; 47,XY,+marker ($n=3$); 46,XX,+15q; 46,XY,+5q; 46,XY,unb(13;14); 46,XY,4q−; 46,XY,18p−; 46,XX,18p−.

Table III—Details of cytogenetic abnormalities

Age (years)	Karyotype	Age (years)	Karyotype
35	47,XY,+21	40	47,XY,+21 (*n*=6)
35	47,XX,+21 (*n*=3)	40	47,XX.+21 (*n*=4)
35	47,XY,+13	40	47,XX,+21/48,XX,+20,+21
35	47,XX,+13	40	47,XY,+18
35	47,XY,+mar	40	47,XY,+13
35	46,XY,del(4q)	40	47,XXY
35	45,X (*n*=5)	40	47,XXX
35	69,XXY	40	m 92,XXYY/46,XY
36	47,XX,+21 (*n*=4)	40	69,XYY
36	47,XY,+21	41	47,XY,+21 (*n*=4)
36	47,XY,+18 (*n*=2)	41	47,XX,+21 (*n*=3)
36	47,XX,+18	41	47,XX,+18
36	47,XY,+22	41	47,XX,+16
36	47,XX,+16	41	46,XY,del(18p)
36	47,XXY	41	47,XY,+mar
36	47,XYY	41	47,XXX
36	45,X (*n*=2)	41	69,XXY
36	47,XX,+15q	41	m 47,XX,+21/46,XX
36	45,XY, − 13, − 14,+t(13q;14q)	42	47,XY,+21 (*n*=5)
36	69,XXX	42	47,XX,+21 (*n*=2)
36	m 45,X/46,XX	42	47,XX,+18
36	m 47,XX,+8/46,XX	42	47,XY,+18
36	m 47,XXY/46,XY	42	47,XX,+13
37	47,XY,+21 (*n*=4)	42	47,XX,+22
37	47,XX,+21 (*n*=3)	42	45,X/46,X,+mar
37	47,XX,+18	42	m 47,XX,+13/46,XX
37	47,XY,+18	42	m 45,X/46,XX
37	47,XY,+8	43	47,XY,+21 (*n*=6)
37	46,XX,del(18p)	43	47,XX,+21 (*n*=2)
37	m 46,XX,t(13;21)/46,XX	43	47,XY,+18 (*n*=2)
38	47,XY,+21 (*n*=7)	43	47,XX,+18
38	47,XX,+21 (*n*=3)	43	47,XX,+13
38	47,XY,+18 (*n*=2)	43	47,XXY (*n*=2)
38	47,XX,+18	44	47,XX,+21 (*n*=2)
38	47,XY,+13	44	47,XY,+21
38	47,XXY	44	47,XX,+18 (*n*=2)
38	47,XXX	44	47,XY,+13
38	47,XY,+mar	44	47,XX,+5q
38	m 47,XXY/46,XY	44	47,XXY
39	47,XX,+21 (*n*=6)	45	47,XY,+21 (*n*=2)
39	47,XY,+21 (*n*=8)	45	47,XX,+18 (*n*=2)
39	47,XY,+21,t(1;20)	45	47,XXX
39	47,XX,+18 (*n*=2)	45	m 45,X/46,XX
39	47,XY,+18		
39	47,XX,+13		
39	47,XXY		

trisomy 18 were derived by multiplying the incidences of trisomy 21 by the appropriate relative frequency of trisomy 18 (Table VII).

There was an increase of the incidence of trisomy 13 in women aged 35–42 years (Table VI), but in older women the incidences were relatively

Table IV—Number of cases (percentage) with trisomies 21, 18, and 13 in association with maternal age for our data and those combined with Hock *et al.*, 1988 (n=3840) and Kratzer *et al.*, 1992 (n=6139)

	Our data				Combined data			
Age (years)	*n*	Trisomy 21	Trisomy 18	Trisomy 13	*n*	Trisomy 21	Trisomy 18	Trisomy 13
35	939	4 (0·43)	0 (0·00)	2 (0·21)	2716	16 (5·89)	2 (0·74)	4 (1·47)
36	1011	5 (0·49)	3 (0·30)	0 (0·00)	2723	14 (5·14)	7 (2·57)	1 (0·37)
37	1055	7 (0·66)	2 (0·19)	0 (0·00)	2736	21 (7·68)	6 (2·19)	1 (0·37)
38	850	10 (1·18)	3 (0·35)	1 (0·12)	2330	27 (11·59)	8 (3·43)	3 (1·29)
39	717	15 (2·09)	3 (0·42)	1 (0·14)	1989	38 (19·11)	12 (6·03)	2 (1·01)
40	498	11 (2·21)	1 (0·20)	1 (0·20)	1342	25 (18·63)	9 (6·71)	2 (1·49)
41	315	7 (2·22)	1 (0·32)	0 (0·00)	875	24 (27·43)	5 (5·71)	4 (4·57)
42	222	7 (3·15)	2 (0·90)	1 (0·45)	569	15 (26·36)	6 (10·54)	3 (5·27)
43	109	8 (7·34)	3 (2·75)	1 (0·92)	299	16 (53·51)	7 (23·41)	2 (6·69)
44	59	3 (5·09)	2 (3·39)	1 (1·70)	133	10 (75·19)	3 (22·56)	2 (15·04)
45	39	2 (5·13)	2 (5·13)	0 (0·00)	81	5 (61·73)	2 (24·69)	0 (0·00)
Total	5814	79 (1·36)	22 (0·38)	8 (0·14)	15 793	211 (1·34)	67 (0·42)	24 (0·15)

low and in the total group associations with age did not reach statistical significance (Fig. 3). Nevertheless, the overall relative frequencies of trisomy 13 compared with trisomy 21 were calculated and estimates for the incidences of trisomy 13 were derived by multiplying the incidences of trisomy 21 by the appropriate relative frequency (Table VII; 0·114 at 9–14 weeks' gestation, 0·066 at 15–20 weeks' gestation, and 0·042 in livebirths) (Hook and Hamerton, 1977).

Observed incidences and incidences predicted on the basis of estimated risks are shown in Table VI. At 9–14 weeks, the mean ratio for the observed to the expected incidence of trisomy 21 was 1·002 (90 per cent CI 0·89–1·11); for the incidence of trisomy 18 it was 1·014 (90 per cent CI 0·83–1·19) and for trisomy 13 it was 1·071 (90 per cent CI 0·66–1·48). At 15–20 weeks, the mean values were 0·975 (95 per cent CI 0·91–1·05) for trisomy 21, 0·950 (95 per cent CI 0·76–1·14) for trisomy 18, and 0·877 (95 per cent CI 0·54–1·22) for trisomy 13.

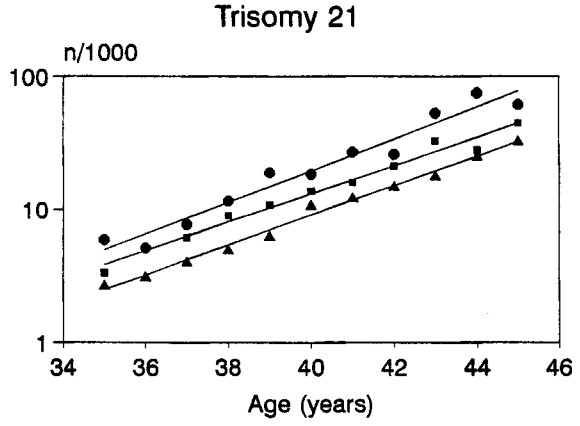

Fig. 1—Individual values and regression lines for the maternal age-related incidence of trisomy 21 per 1000 cases at 9–14 weeks' (●), 15–20 weeks' gestation (■), and in livebirths (▲)

DISCUSSION

This study provides data on the incidence of fetal trisomies 21, 18, and 13 at 9–14 weeks' gestation in women aged 35–45 years and estimates of maternal age-specific risks for women aged 20–45 years at 9–14 and 15–20 weeks' gestation. Analyses were confined to trisomies 21, 18, and 13, since they account for 67 per cent of all chromosomal abnormalities and on the basis of currently available data, they are the only ones for which estimates can be calculated. For the women aged 35–45 years, our findings were similar to those of Hook *et al.* (1988) and Kratzer *et al.* (1992), and by combining the data from the three series, the number of cases for each year of maternal age was sufficiently large to provide accurate predictions.

In the calculation of estimated risks, it was assumed that the ratios for the incidence of trisomy 21 at 9–14 weeks' gestation and at 15–20 weeks' gestation to the incidence at birth are independent of maternal age. Although for the ⩾35-year-old group there were no significant

Table V—Observed incidence of trisomy 21 at 9–14 and 15–20 weeks' gestation. The expected incidences were calculated from data in livebirths (Cuckle *et al.*, 1987)

	9–14 weeks' gestation				15–20 weeks'gestation			
Age (years)	*n*	Observed	Expected	Ratio	*n*	Observed	Expected	Ratio
35	2716	16	7·1	2·25	18 934	63	49·2	1·28
36	2723	14	8·8	1·59	17 797	90	57·3	1·56
37	2736	21	11·3	1·86	16 406	101	67·6	1·49
38	2330	27	12·3	2·20	14 988	134	79·0	1·69
39	1989	38	13·6	2·79	12 980	141	88·4	1·60
40	1342	25	11·9	2·10	11 057	153	98·0	1·56
41	875	24	10·1	2·38	7086	114	82·1	1·39
42	569	15	8·7	1·72	4560	98	69·4	1·41
43	299	16	6·0	2·67	2644	88	53·0	1·66
44	133	10	3·5	2·86	1448	41	38·3	1·07
45	81	5	2·8	1·79	699	30	23·4	1·28
Total	15 793	211	96·1	2·20	108 569	1053	706·2	1·49

Table VI—Observed and predicted numbers of cases with trisomy 21, 18, or 13 at 9–14 and 15–20 weeks' gestation

Age (years)	9–14 weeks' gestation							15–20 weeks'gestation						
		Trisomy 21		Trisomy 18		Trisomy 13			Trisomy 21		Trisomy 18		Trisomy 13	
	n	Observed	Predicted	Observed	Predicted	Observed	Predicted	*n*	Observed	Predicted	Observed	Predicted	Observed	Predicted
35	2716	16	15·5	2	4·9	4	1·8	18 934	63	73·3	15	16·4	8	4·8
36	2723	14	19·4	7	6·2	1	2·2	17 797	90	86·2	21	19·3	5	5·6
37	2736	21	24·7	6	7·9	1	2·8	16 406	101	100·7	21	22·6	9	6·6
38	2330	27	27·0	8	8·6	3	3·1	14 988	134	117·9	26	26·4	5	7·7
39	1989	38	29·8	12	9·4	2	3·4	12 980	141	131·9	30	29·5	9	8·6
40	1342	25	26·1	9	8·3	2	3·0	11 057	153	146·1	33	32·7	14	9·6
41	875	24	22·3	5	7·1	4	2·5	7086	114	122·4	23	27·4	10	8·0
42	569	15	19·0	6	6·0	3	2·2	4560	98	103·5	29	23·2	9	6·8
43	299	16	13·2	7	4·2	2	1·5	2644	88	79·0	28	17·7	0	5·2
44	133	10	7·7	3	2·5	2	0·9	1448	41	57·2	9	12·8	0	3·7
45	81	5	6·2	2	2·0	0	0·7	668	30	34·9	1	7·8	0	2·3
Total	15 793	211	210·9	67	67·1	24	24·1	108 569	1053	1053·1	236	235·8	69	68·9

Table VII—Estimates of age-specific risks for trisomies 21, 18, and 13 at 9–14 and 15–20 weeks' gestation and in livebirths

	9–14 weeks' gestation			15–20 weeks' gestation			Livebirths		
Age (years)	Trisomy 21	Trisomy 18	Trisomy 13	Trisomy 21	Trisomy 18	Trisomy 13	Trisomy 21	Trisomy 18	Trisomy 13
20	1/696	1/2193	1/6125	1/1025	1/4576	1/15656	1/1529	1/15507	1/36148
21	1/687	1/2164	1/6042	1/1012	1/4514	1/15444	1/1508	1/15298	1/35660
22	1/675	1/2126	1/5936	1/994	1/4435	1/15172	1/1482	1/15029	1/35031
23	1/659	1/2077	1/5800	1/971	1/4333	1/14824	1/1448	1/14684	1/34228
24	1/640	1/2015	1/5628	1/942	1/4204	1/14385	1/1405	1/14249	1/33214
25	1/616	1/1939	1/5414	1/906	1/4045	1/13839	1/1352	1/13708	1/31954
26	1/586	1/1846	1/1554	1/863	1/3850	1/13174	1/1287	1/13049	1/30417
27	1/551	1/1735	1/4844	1/811	1/3619	1/12382	1/1209	1/12265	1/28588
28	1/510	1/1606	1/4485	1/751	1/3351	1/11464	1/1120	1/11356	1/26469
29	1/464	1/1462	1/4082	1/683	1/3050	1/10434	1/1019	1/10336	1/24092
30	1/415	1/1306	1/3646	1/610	1/2724	1/9320	1/910	1/9232	1/12520
31	1/363	1/1143	1/3193	1/535	1/2385	1/8161	1/797	1/8083	1/18842
32	1/311	1/981	1/2739	1/459	1/2046	1/7001	1/684	1/6935	1/16165
33	1/262	1/825	1/2303	1/386	1/1721	1/5887	1/575	1/5832	1/13594
34	1/216	1/681	1/1901	1/318	1/1420	1/4859	1/475	1/4813	1/11218
35	1/175	1/552	1/1542	1/258	1/1152	1/3942	1/385	1/3905	1/9102
36	1/140	1/411	1/1233	1/206	1/921	1/3151	1/308	1/3121	1/7274
37	1/111	1/348	1/973	1/163	1/727	1/2486	1/243	1/2463	1/5740
38	1/86	1/272	1/760	1/127	1/567	1/1941	1/190	1/1923	1/4482
39	1/67	1/211	1/588	1/98	1/439	1/1503	1/147	1/1489	1/3470
40	1/51	1/162	1/452	1/76	1/338	1/1156	1/113	1/1145	1/2668
41	1/39	1/124	1/346	1/58	1/258	1/884	1/86	1/875	1/2040
42	1/30	1/94	1/263	1/44	1/197	1/673	1/66	1/667	1/1554
43	1/23	1/72	1/200	1/33	1/149	1/511	1/50	1/506	1/1179
44	1/17	1/54	1/151	1/25	1/113	1/387	1/38	1/383	1/893
45	1/13	1/41	1/114	1/19	1/85	1/292	1/29	1/289	1/675

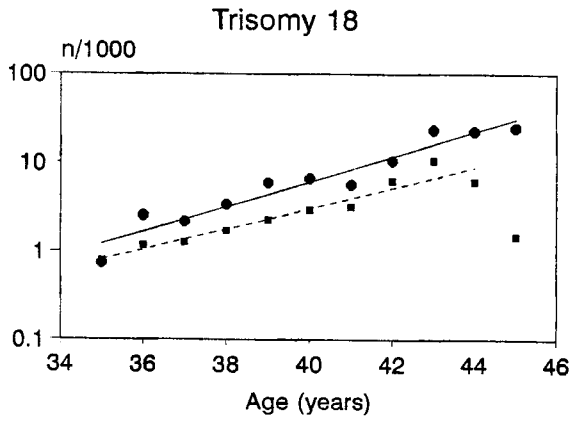

Fig. 2—Individual values and regression lines for the maternal age-related incidence of trisomy 18 per 1000 cases at 9–14 weeks' gestation (●) and 15–20 weeks' gestation (■)

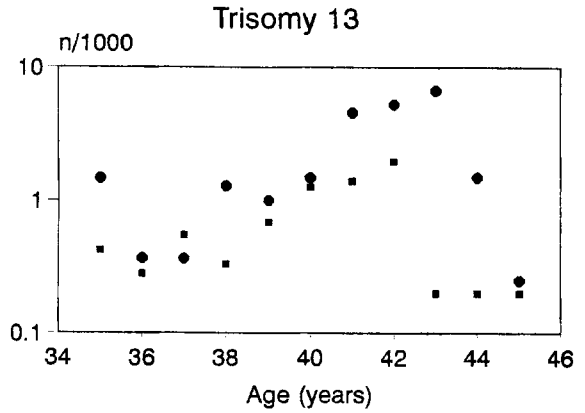

Fig. 3—Individual values for the maternal age-related incidence of trisomy 13 per 1000 cases at 9–14 weeks' gestation (●) and 15–20 weeks' gestation (■)

associations between the ratios and age, it remains to be established whether this is also true for younger mothers. The findings of the present study do not confirm a maternal age-related selective increase in the miscarriage rate of trisomy 21 pregnancies, as suggested by the smaller series of Kratzer *et al.* (1992). However, the incidence for trisomy 13 in women aged 43–45 years and that of trisomy 18 in women aged 45 years were lower than expected from the trend in younger women. This may indicate that younger women can sustain pregnancies with highly lethal abnormalities longer than older women.

At birth, the maternal age-specific incidence of trisomy 21 was 33 per cent lower than at 15–20 weeks and 53 per cent lower than at 9–14 weeks. Furthermore, the relative frequency of trisomies 18 and 13 decreased from 30 per cent at 9–14 weeks to 20 per cent at 15–20 weeks and 12 per cent at birth. These findings are compatible with previous estimates of the spontaneous loss rates of chromosomally abnormal fetuses, and demonstrate that there is a high intrauterine lethality for all three trisomies which is particularly high for trisomies 18 and 13 (Hook, 1978, 1983; Hook *et al.*, 1984, 1988; Ferguson-Smith and Yates, 1984).

Traditionally, counselling parents as to the risk of fetal chromosomal abnormalities has depended on the provision of livebirth incidences of mainly trisomy 21. The findings of the present study make it possible to give estimates for the three most common trisomies at 9–14 weeks' gestation, when screening and invasive testing for chromosomal abnormalities are performed. Furthermore, the data can be used to calculate the expected incidence of the three trisomies in any study group when new ultrasonographic or biochemical methods of first-trimester screening are being evaluated.

ACKNOWLEDGEMENTS

We thank Professor E. B. Hook of the University of California, U.S.A. for the advice on the preparation of this manuscript.

REFERENCES

Cuckle, H.S., Wald, N.J., Thompson, S.G. (1987). Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level, *Br. J. Obstet. Gynaecol.*, **94**, 387–402.

Ferguson-Smith, M.A., Yates, J.R.W. (1984). Maternal age specific rates for chromosomal aberrations and factors influencing them: report of a collaborative European study on 52,965 amniocenteses, *Prenat. Diagn.*, **4**, 5–44.

Hook, E.B. (1978). Differences between rates of trisomy 21 (Down syndrome) and other chromosomal abnormalities diagnosed in livebirths and in cells cultured after second trimester amniocentesis—suggested explanations and implications for genetic counseling and program planning. In: Bergsma, D., Summitt, R.L. (Eds). *Birth Defects: Original Articles Series*, Vol. 14, New York: Alan R. Liss, 249–267.

Hook, E.B. (1983). Chromosome abnormalities and spontaneous fetal death following amniocentesis: further data and associations with maternal age, *Am. J. Hum. Genet.*, **35**, 110–116.

Hook, E.B., Hamerton, J.H. (1977). The frequency of chromosome abnormalities detected in consecutive

newborn studies—differences between studies—results by sex and severity of involvement. In: Hook, E.B., Porter, I.H. (Eds). *Populations Cytogenetic Studies in Humans*, New York: Academic Press, 63–80.

Hook, E.B., Cross, P.K., Regal, R.R. (1984). The frequency of 47,+21, 47,+18, and 47,+13 at the uppermost extremes of maternal ages: results on 56,094 fetuses studied prenatally and comparisons with data on livebirths, *Hum. Genet.*, **68,** 211–220.

Hook, E.B., Cross, P.K., Jackson, L., Pergament, E. (1988). Maternal age specific rates of trisomy 21 and other cytogenetic abnormalities diagnosed in the first trimester of pregnancy in chorionic villus biopsy specimens: comparison with rates expected from observations at amniocentesis, *Am. J. Hum. Genet.*, **42,** 797–807.

Kratzer, P.G., Golbus, M.S., Schonberg, S.A., Heilbron, D.C., Taylor, R.N. (1992). Cytogenetic evidence for enhanced selective miscarriage of trisomy 21 pregnancies with advancing maternal age, *Am. J. Med. Genet.*, **44,** 657–663.