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Bedside estimation of Down syndrome risk during first-trimester ultrasound screening

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ABSTRACT

Objective *To construct tables for 'bedside' estimation of Down syndrome risk based on maternal age and nuchal translucency measurements.*

Methods *Likelihood ratios were calculated using the log multiple of median Gaussian model. The parameters for the model (mean and standard deviation) were derived from 5560 normal and 51 Down syndrome-affected pregnancies scanned during the first trimester in three different centers. Equations for calculating maternal background risk and median values were obtained from previous reports. The results were compared to two modalities using the log Gaussian model and software that uses the delta-value model.*

Results *The distribution fitted the data well, and the parameters obtained in the study group for the log multiple of median model were a mean of 0 and a standard deviation of 0.12356 among normal pregnancies and a mean of 0.305312 and a standard deviation of 0.240337 among Down syndrome-affected ones. The likelihood ratios obtained for the various combinations of fetal crown–rump lengths and nuchal translucency measurements were comparable to other modalities reported earlier.*

Conclusions *The results of the current study provide useful tables for simple and accurate 'bedside' estimation of Down syndrome risk without the need for computerized software or complicated calculations.*

INTRODUCTION

The possibility of identifying fetuses at risk for chromosomal defects during first-trimester nuchal translucency (NT) screening has enhanced the role for prenatal sonographers as integral members of the professional team dealing with this issue[1]. While the original protocol relied on a cut-off NT value ranging between 2.5 and 4 mm[1–3] for indicating increased risk for Down syndrome, the updated policy requires an accurate estimate of the risk that also incorporates maternal age (background risk) and fetal crown–rump length (CRL)[4,5]. This development has curtailed the capabilities of some sonographers involved in outreach pregnancy care programs. It established a need for either software that uses the delta-value approach, which is supplied by The Fetal Medicine Foundation (FMF) to their trainees who are subjected to on-going audit[6], a commercial software program that uses the log multiple of median (MoM) Gaussian model, or local enterprises that use either one of these models[7]. Applying the log MoM Gaussian model, Cuckle and Sehmi[8] recently reported on how to calculate the MoM values and, subsequently, the likelihood ratios out of NT thickness and fetal CRL measurements. The data provided in their publication were based on parameters obtained from a large number of cases, and may therefore be considered something of a 'gold standard'. However, because the method they presented[8] is rather cumbersome and not straightforward, it is not necessarily a convenient yardstick for the average practicing sonographer.

The aim of the present study was to construct tables for bedside estimation of a Down syndrome risk derived from NT measurements. The study design was based on our own findings during first-trimester ultrasound screening and prospective follow-up during pregnancy and after delivery.

METHODS

Maternal age-derived background risks of Down syndrome at term were calculated by using Hecht and Hook's[9] equation of a five-parameter model (Appendix 1).

The data for determining the parameters used for the calculations of the likelihood ratios (LR) were obtained from three fetal medicine centers located in Israel, Switzerland and Turkey. Overall, the study included 5560 completed normal singleton pregnancies and 51 cases of Down syndrome. The

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examinations were performed by sonographers qualified by The Fetal Medicine Foundation, and their audit report noted that their distribution of measurement values corresponded well with the distribution in UK centers. The examinations were performed with the fetuses in the midsagittal plane, and all NT measurements were conducted solely according to the on-to-on caliper placement methodology. Those women with an increased risk for Down syndrome were followed prospectively, and all other women were asked to report any abnormality that had been identified during pregnancy or after birth.

Calculations of the LRs were performed using the log MoM Gaussian model. The calculation of the MoM value of each examination was carried out by using the equation for median NT values as described by Nicolaides *et al.*[10] (Appendix 2).

Similar to previous reports[5,10], the distribution fitted the model well in unaffected pregnancies, while the fit was reasonable over a wide range in Down syndrome-affected pregnancies. The parameters of the MoM values among normal pregnancies had a mean value close to 1 with a standard deviation (SD) of 0.35307, and their $\log_{10}$ transformation was a mean of 0 with an SD of 0.12356. Among the Down syndrome-affected pregnancies, the MoM values had a mean of 2.612097 and an SD of 1.3405. After correction for viable subset bias, using the same factor reported previously[10], their $\log_{10}$ transformation resulted in a mean value of 0.305312 and an SD of 0.240337.

The same parameters were used for calculating the LRs by using the equation derived from the normal distribution model published in 1987 by Cuckle *et al.*[11] (Appendix 3). Thus, a specific LR was assigned for each combination of CRL between 38 and 84 mm[6] and an NT thickness. The truncation limits were 0.8 MoM and 2.5 MoM and measurements outside these limits were assigned values equal to those limits.

Finally, our results were compared to three other modalities that present LRs based on fetal CRLs and NT thicknesses. They included the modalities of Wald and Hackshaw[5,12] (W&H) and Cuckle and Sehmi[8] (C&S), which use the log MoM Gaussian model, and the software provided by the FMF that uses the delta-value model. The comparison was arbitrarily standardized for a fetal CRL of 60 mm and included: (i) an evaluation of the LRs for various NT thicknesses; (ii) an assessment of NT values associated with an LR of 1.0; and (iii) a comparison of the MoM values of various NT thicknesses based on the equations of either Nicolaides *et al.*[10] or Schuchter *et al.*[13], according to the modality used.

RESULTS

Table 1 presents the maternal background risk of Down syndrome in live births: its application requires a simple adjustment of maternal age to 40 weeks' gestation. Risks are presented (1: number in the table) in completed months. For example, for a mother who was born on 12 February 1975 whose last menstrual period was 25 August 2001 and who is expected to deliver on 31 May 2002 when she will be 27 years and 3 months old, it is shown that her background risk of a Down syndrome live birth is 1 : 1195.

Table 2 presents the LRs obtained from the combination of various CRL measurements and NT thicknesses using

Table 1 Maternal background risk (1: number given in the table) of a Down syndrome birth*: adjustment of maternal age to 40 weeks' gestation

	Months											
Age (years)	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*
20	1514	1512	1511	1509	1508	1506	1505	1503	1502	1500	1498	1496
21	1495	1493	1491	1489	1487	1485	1483	1481	1479	1477	1474	1472
22	1470	1467	1465	1462	1460	1457	1455	1452	1449	1446	1444	1441
23	1437	1435	1432	1429	1425	1422	1419	1416	1412	1409	1405	1401
24	1398	1394	1390	1386	1382	1378	1374	1370	1366	1361	1357	1353
25	1348	1343	1339	1334	1329	1324	1319	1314	1309	1304	1298	1293
26	1287	1282	1276	1270	1264	1259	1253	1246	1240	1234	1228	1221
27	1215	1208	1201	1195	1188	1181	1174	1167	1159	1152	1145	1137
28	1130	1122	1114	1107	1099	1091	1083	1075	1066	1058	1050	1041
29	1033	1024	1016	1007	998	989	981	972	963	954	944	935
30	926	917	908	898	889	879	870	861	851	842	832	822
31	813	803	794	784	774	764	755	745	736	726	717	707
32	697	688	678	669	659	650	641	631	622	613	604	594
33	585	576	567	558	549	540	532	523	514	506	497	489
34	480	472	464	456	448	440	432	424	416	409	401	394
35	387	379	372	365	358	351	344	338	331	325	318	312
36	306	300	294	288	282	276	271	265	260	254	249	244
37	239	234	229	224	219	215	210	206	201	197	193	188
38	184	180	176	173	169	165	162	158	155	151	148	145
39	141	138	135	132	128	126	124	121	118	116	113	111
40	108	106	103	101	99	97	94	92	90	88	86	84
41	83	81	79	77	75	74	72	71	69	67	66	65
42	63	62	60	59	58	56	55	54	53	52	51	50
43	48	47	46	45	44	43	43	42	41	40	39	38
44	37	37	36	35	34	34	33	32	32	31	30	30
45	29	29	28	28	27	26	26	25	25	24	24	23

*Reproduced from Hecht and Hook's[9] equation of a five-parameter model.

Table 2 Likelihood ratios for calculating trisomy 21 risk for various fetal crown–rump lengths and nuchal translucency (NT) thicknesses

	Crown–rump length (mm)															
NT (mm)	*38*	*39*	*40*	*41*	*42*	*43*	*44*	*45*	*46*	*47*	*48*	*49*	*50*	*51*	*52*	*53*
Median*	1.09	1.11	1.14	1.16	1.18	1.20	1.22	1.24	1.26	1.28	1.31	1.33	1.35	1.37	1.39	1.41
1.0	0.19	0.19	0.18	0.18	0.18	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.1	0.23	0.22	0.21	0.21	0.20	0.18	0.19	0.18	0.18	0.18	0.18	0.18	0.17	0.17	0.17	0.17
1.2	0.30	0.28	0.27	0.25	0.24	0.23	0.22	0.21	0.21	0.20	0.20	0.19	0.18	0.18	0.18	0.18
1.3	0.39	0.37	0.34	0.32	0.30	0.28	0.27	0.26	0.25	0.23	0.23	0.22	0.21	0.21	0.20	0.20
1.4	0.53	0.50	0.45	0.42	0.39	0.37	0.35	0.33	0.31	0.29	0.27	0.26	0.25	0.24	0.23	0.22
1.5	0.74	0.69	0.62	0.57	0.51	0.48	0.45	0.42	0.39	0.37	0.35	0.33	0.30	0.29	0.28	0.27
1.6	1.05	0.97	0.86	0.77	0.71	0.64	0.59	0.55	0.51	0.48	0.43	0.41	0.39	0.37	0.35	0.33
1.7	1.50	1.38	1.23	1.09	0.97	0.90	0.80	0.74	0.69	0.62	0.57	0.53	0.50	0.46	0.43	0.41
1.8	2.26	1.92	1.70	1.56	1.39	1.23	1.09	1.01	0.90	0.83	0.77	0.71	0.64	0.59	0.55	0.51
1.9	3.30	2.79	2.46	2.17	1.92	1.70	1.56	1.39	1.23	1.13	1.01	0.93	0.86	0.80	0.71	0.66
2.0	4.83	4.07	3.59	3.16	2.79	2.46	2.17	1.92	1.70	1.56	1.39	1.28	1.13	1.05	0.97	0.86
2.1	7.1	6.0	5.3	4.63	3.91	3.44	3.03	2.67	2.36	2.08	1.92	1.70	1.56	1.39	1.28	1.18
2.2	10	8.8	7.7	6.5	5.7	4.83	4.25	3.74	3.30	2.91	2.56	2.36	2.08	1.92	1.70	1.56
2.3	15	13	11	9.6	8.1	7.1	6.0	5.3	4.63	4.07	3.59	3.16	2.79	2.56	2.26	2.08
2.4	23	20	16	14	12	10	8.8	7.4	6.5	5.7	5.0	4.44	3.91	3.44	3.03	2.79
2.5	35	28	24	20	17	14	12	10	9.2	8.1	6.8	6.0	5.3	4.63	4.25	3.74
2.6	51	61	35	29	25	21	17	15	13	11	9.6	8.4	7.4	6.5	5.7	5.0
2.7	75	85	51	41	35	29	25	21	18	15	14	11	10	8.8	7.7	6.8
2.8	85	85	75	61	51	41	35	29	26	22	18	16	14	12	10	9.2
2.9	85	85	85	85	72	61	51	41	36	31	26	22	19	17	14	12
3.0	85	85	85	85	85	85	72	61	49	41	36	31	26	23	20	17
3.1	85	85	85	85	85	85	85	85	69	58	49	41	36	31	27	23
3.2	85	85	85	85	85	85	85	85	85	82	69	58	49	41	36	31
3.3	85	85	85	85	85	85	85	85	85	85	85	82	69	58	49	41
3.4	85	85	85	85	85	85	85	85	85	85	85	85	85	78	66	58
3.5	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	78
3.6	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
3.7	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
3.8	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
3.9	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.0	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.1	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.2	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.3	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.4	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.5	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.6	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.7	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.8	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.9	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
5.0	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85

Table 2 *Continued*

	Crown–rump length (mm)															
NT (mm)	*54*	*55*	*56*	*57*	*58*	*59*	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*	*68*	*69*
Median*	1.43	1.46	1.48	1.50	1.52	1.54	1.56	1.58	1.60	1.62	1.64	1.66	1.68	1.70	1.72	1.74
1.0	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.1	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.2	0.18	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.3	0.19	0.19	0.18	0.18	0.18	0.18	0.18	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.4	0.22	0.21	0.21	0.20	0.20	0.19	0.19	0.19	0.19	0.18	0.18	0.18	0.18	0.17	0.17	0.17
1.5	0.26	0.25	0.24	0.23	0.22	0.21	0.21	0.21	0.20	0.20	0.19	0.19	0.19	0.18	0.18	0.18
1.6	0.32	0.30	0.28	0.27	0.26	0.25	0.25	0.23	0.23	0.22	0.21	0.21	0.21	0.20	0.20	0.20
1.7	0.38	0.37	0.35	0.33	0.32	0.30	0.29	0.28	0.27	0.26	0.25	0.24	0.23	0.23	0.22	0.22
1.8	0.48	0.46	0.43	0.41	0.38	0.37	0.35	0.34	0.32	0.31	0.30	0.28	0.27	0.27	0.26	0.25
1.9	0.62	0.57	0.55	0.51	0.48	0.45	0.43	0.41	0.39	0.37	0.36	0.34	0.33	0.32	0.30	0.29
2.0	0.80	0.74	0.69	0.64	0.62	0.57	0.53	0.50	0.48	0.45	0.43	0.41	0.39	0.38	0.36	0.35
2.1	1.05	0.97	0.90	0.83	0.77	0.71	0.69	0.64	0.59	0.55	0.53	0.50	0.48	0.45	0.43	0.42
2.2	1.39	1.28	1.18	1.09	1.01	0.93	0.86	0.80	0.74	0.71	0.66	0.62	0.59	0.55	0.53	0.51
2.3	1.84	1.70	1.56	1.44	1.28	1.18	1.09	1.01	0.97	0.90	0.83	0.77	0.74	0.69	0.66	0.62
2.4	2.46	2.26	2.00	1.84	1.70	1.56	1.44	1.33	1.23	1.13	1.05	0.97	0.93	0.86	0.83	0.77
2.5	3.30	3.03	2.67	2.46	2.26	2.00	1.84	1.70	1.56	1.44	1.33	1.23	1.18	1.09	1.01	0.97
2.6	4.44	4.07	3.59	3.30	2.91	2.67	2.46	2.17	2.00	1.84	1.70	1.56	1.50	1.39	1.28	1.23
2.7	6.0	5.3	4.83	4.25	3.91	3.44	3.16	2.91	2.67	2.36	2.17	2.00	1.92	1.77	1.63	1.50
2.8	8.1	7.1	6.5	5.7	5.0	4.63	4.07	3.74	3.44	3.16	2.91	2.67	2.46	2.26	2.08	1.92
2.9	11	9.6	8.4	7.7	6.8	6.0	5.5	4.83	4.44	4.07	3.74	3.44	3.03	2.91	2.67	2.46
3.0	15	13	11	10	8.8	8.1	7.1	6.5	5.7	5.3	4.83	4.44	3.91	3.59	3.30	3.16
3.1	20	17	15	14	12	10	9.6	8.4	7.7	6.8	6.5	5.7	5.0	4.63	4.25	3.91
3.2	27	24	21	18	16	14	12	11	10	8.8	8.1	7.4	6.5	6.0	5.5	5.0
3.3	36	32	27	24	21	18	16	15	13	11	10	9.6	8.4	7.7	7.1	6.5
3.4	49	43	36	32	28	25	22	19	17	15	14	12	11	10	9.2	8.4
3.5	66	56	49	43	36	32	28	25	23	20	17	16	14	13	11	10
3.6	85	75	66	56	49	43	38	33	29	26	23	21	18	17	15	14
3.7	85	85	85	75	66	56	49	43	38	33	29	27	24	22	19	17
3.8	85	85	85	85	85	85	63	56	49	43	38	35	31	27	25	23
3.9	85	85	85	85	85	85	85	75	66	56	51	45	40	35	32	28
4.0	85	85	85	85	85	85	85	85	85	75	66	58	51	45	41	36
4.1	85	85	85	85	85	85	85	85	85	85	85	75	66	58	51	47
4.2	85	85	85	85	85	85	85	85	85	85	85	85	85	75	66	61
4.3	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.4	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.5	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.6	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.7	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.8	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
4.9	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85
5.0	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85

Table 2 *Continued*

NT (mm)	Crown–rump length (mm) 70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
Median*	1.76	1.78	1.79	1.81	1.83	1.85	1.86	1.88	1.90	1.91	1.93	1.94	1.96	1.97	1.98
1.0	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.1	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.2	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.3	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.4	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.5	0.18	0.18	0.18	0.18	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
1.6	0.19	0.19	0.19	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.17	0.17	0.17	0.17
1.7	0.21	0.21	0.21	0.20	0.20	0.20	0.19	0.19	0.19	0.19	0.18	0.18	0.18	0.18	0.18
1.8	0.24	0.23	0.23	0.22	0.22	0.21	0.21	0.21	0.21	0.20	0.20	0.20	0.20	0.19	0.19
1.9	0.28	0.27	0.27	0.26	0.25	0.25	0.24	0.23	0.23	0.22	0.22	0.22	0.21	0.21	0.21
2.0	0.34	0.33	0.31	0.30	0.29	0.28	0.27	0.27	0.26	0.26	0.25	0.25	0.24	0.23	0.23
2.1	0.39	0.38	0.37	0.36	0.35	0.34	0.33	0.32	0.31	0.30	0.29	0.28	0.27	0.27	0.27
2.2	0.48	0.46	0.45	0.42	0.41	0.39	0.38	0.37	0.36	0.35	0.34	0.33	0.32	0.32	0.31
2.3	0.59	0.57	0.53	0.51	0.50	0.48	0.45	0.43	0.42	0.41	0.39	0.38	0.38	0.37	0.36
2.4	0.74	0.69	0.66	0.62	0.59	0.57	0.55	0.53	0.51	0.50	0.48	0.46	0.45	0.43	0.42
2.5	0.90	0.86	0.80	0.77	0.74	0.69	0.66	0.64	0.62	0.59	0.57	0.55	0.53	0.51	0.50
2.6	1.13	1.05	1.01	0.97	0.90	0.86	0.83	0.77	0.74	0.71	0.69	0.66	0.64	0.62	0.59
2.7	1.44	1.33	1.23	1.18	1.13	1.05	1.01	0.97	0.90	0.86	0.83	0.80	0.77	0.74	0.71
2.8	1.77	1.70	1.56	1.50	1.39	1.33	1.23	1.18	1.13	1.05	1.01	0.97	0.93	0.90	0.86
2.9	2.26	2.08	2.00	1.84	1.77	1.63	1.56	1.44	1.39	1.33	1.23	1.18	1.13	1.09	1.05
3.0	2.91	2.69	2.46	2.36	2.17	2.00	1.92	1.84	1.70	1.63	1.56	1.44	1.39	1.33	1.28
3.1	3.59	3.44	3.16	2.91	2.67	2.56	2.36	2.26	2.17	2.00	1.92	1.84	1.70	1.63	1.56
3.2	4.63	4.25	3.91	3.74	3.44	3.16	3.03	2.79	2.67	2.46	2.36	2.26	2.17	2.00	1.92
3.3	6.0	5.5	5.0	4.63	4.25	4.07	3.74	3.59	3.30	3.03	2.91	2.79	2.67	2.46	2.36
3.4	7.4	6.8	6.5	6.0	5.5	5.0	4.63	4.44	4.07	4.25	3.59	3.44	3.30	3.16	2.91
3.5	9.6	8.8	8.1	7.4	6.5	6.5	6.0	5.5	5.3	4.83	4.63	4.25	4.07	3.91	3.59
3.6	12	11	10	9.6	8.8	8.1	7.4	7.1	6.5	6.0	5.7	5.3	5.0	4.83	4.44
3.7	16	14	13	12	11	10	9.6	8.8	8.1	7.7	7.1	6.8	6.2	6.0	5.5
3.8	20	18	17	15	14	13	12	11	10	9.6	8.8	8.4	7.7	7.4	6.8
3.9	26	24	21	19	17	16	15	14	13	12	11	10	9.6	9.2	8.8
4.0	33	29	27	25	23	21	19	17	16	15	14	13	12	11	11
4.1	41	38	35	31	28	26	24	22	20	18	17	16	15	14	13
4.2	53	47	43	40	36	32	29	27	26	24	22	20	19	18	17
4.3	69	61	56	49	45	41	38	35	32	29	27	25	24	22	21
4.4	85	78	69	63	58	51	47	43	40	36	33	32	29	27	26
4.5	85	85	85	78	72	66	61	53	49	45	43	40	36	33	32
4.6	85	85	85	85	85	82	75	69	63	58	53	49	45	41	40
4.7	85	85	85	85	85	85	85	85	78	72	66	61	56	51	49
4.8	85	85	85	85	85	85	85	85	85	85	82	75	69	66	61
4.9	85	85	85	85	85	85	85	85	85	85	85	85	85	82	72
5.0	85	85	85	85	85	85	85	85	85	85	85	85	85	85	85

*Median values obtained from the equation of Nicolaides *et al.*[10].

our above-mentioned parameters. If the fetus of the same theoretical mother described above has a CRL of 62 mm and an NT of 2.4 mm, it is shown that the corresponding LR is 1.23. The Down syndrome calculated risk at term is therefore 1 : 972. Table 2 also presents the median NT value for each CRL, and the measurement may also be presented in MoM units (in this case, the measurement would correspond to 1.5 MoM).

Table 3 presents results of the current study together with those of three other modalities for various NT thicknesses and a CRL of 60 mm. A comparison of the results obtained by ourselves and C&S shows that the figures were identical for a wide range of NT values and very close for the rest. An assessment of the NT values that correspond to an LR of 1.0 demonstrated similar results (i.e. between 2.25 and 2.35 mm for C&S, FMF and the current study), while the modality of W&H indicated an NT of 1.75 mm. This means that one modality increased the risk and three others reduced it, with a range as high as 0.5 mm. For example, for an NT of 2.0 mm, the LRs were 0.53, 0.37 and 0.53 according to C&S, the FMF and our group, respectively, whereas the LR was 1.59 according to W&H. Another feature presented in Table 3 is the comparison of MoM values. While the FMF, C&S and our group used the same equation for assessing the medians, thus assigning the same MoM values, W&H used a different equation. This equation was obtained from another study[13] and resulted in substantially higher MoM values for all NT measurements, as shown in Table 3.

DISCUSSION

Simultaneous presentation of detailed tables of maternal age-dependent Down syndrome risk and the LRs obtained from various combinations of fetal CRLs and NT thicknesses provides the sonographer with useful tools for an accurate 'bedside' estimation of the calculated risks. Thus, the performance of first-trimester ultrasound screening may be able to provide a comprehensive examination that includes both the technical part of an NT measurement and the connotation of the findings. The FMF has to be complemented for supplying their software free of charge to FMF-qualified sonographers who participate in their ongoing audit. The campaign they conducted established the need for standardized examinations to be carried out in a meticulous and reproducible manner. Now that this goal has been reached with laudable success, we contend that the time is propitious to enable those who did not participate in the FMF courses, or who do not operate computerized software, to benefit from the knowledge that has been gathered and to have the necessary yardsticks to operate their own screening programs independently. The parameters and the equations presented in the current paper will enable others to construct their own computerized programs based on widely available software, such as Microsoft Excel (Microsoft Corp., Redmond, WA, USA). Furthermore, users may independently incorporate other factors affecting Down syndrome risk, such as previous affected pregnancy or other ultrasonographic findings. Use of computer software programs may facilitate ongoing quality control, although an image scoring method[14] may also be used for this purpose.

As graduates of the FMF, we operate first-trimester ultrasound screening programs strictly according to its scanning methodology[14]. This allows us to use the FMF equation[10] for assessing median NT values in calculating our parameters. The only, but not inconsequential, exception is that we used a log MoM Gaussian model rather than their delta-value

Table 3 Comparison between the current study's results and The Fetal Medicine Foundation, Wald and Hackshaw[5] and Cuckle and Sehmi[8] modalities of calculating Down syndrome likelihood ratio for a crown–rump length of 60 mm and various nuchal translucency thicknesses

NT thickness (mm)	*FMF** *LR (MoM)*	*W&H†* *LR (MoM)*	*C&S‡* *LR (MoM)*	*Current study§* *LR (MoM)*
Median	1.56 mm	1.19 mm	1.56 mm	1.56 mm
1.0	0.17 (0.64)	0.21 (0.84)	0.20 (0.64)	0.17 (0.64)
1.2	0.17 (0.77)	0.31 (1.00)	0.16 (0.77)	0.17 (0.77)
1.4	0.17 (0.90)	0.47 (1.18)	0.18 (0.90)	0.19 (0.90)
1.6	0.17 (1.03)	0.70 (1.34)	0.24 (1.03)	0.25 (1.03)
1.8	0.22 (1.15)	1.06 (1.51)	0.34 (1.15)	0.35 (1.15)
2.0	0.37 (1.28)	1.59 (1.68)	0.53 (1.28)	0.53 (1.28)
2.2	0.66 (1.41)	2.37 (1.85)	0.89 (1.41)	0.86 (1.41)
2.4	1.17 (1.54)	3.48 (2.02)	1.53 (1.54)	1.44 (1.54)
2.6	2.01 (1.67)	4.97 (2.18)	2.69 (1.67)	2.46 (1.67)
2.8	3.43 (1.79)	7.2 (2.35)	4.59 (1.79)	4.07 (1.79)
3.0	5.7 (1.92)	10 (2.52)	8.3 (1.92)	7.1 (1.92)
3.2	7.3 (2.05)	15 (2.69)	15 (2.05)	12 (2.05)
3.5	19 (2.24)	24 (2.94)	36 (2.24)	28 (2.24)
3.8	36 (2.44)	38 (3.19)	88 (2.44)	66 (2.44)
4.0	54 (2.56)	52 (3.36)	> 100 (2.56)	85 (2.56)
LR = 1.0	NT = 2.35 mm	NT = 1.75 mm	NT = 2.25 mm	NT = 2.25 mm

*Produced from the software provided by the FMF. †Based on the parameters of Wald and Hackshaw[5,12], medians in Schuchter *et al.*[13] and Gaussian equation in Cuckle *et al.*[11]. ‡Based on the parameters and medians in Cuckle and Sehmi[8] and Nicolaides *et al.*[10] and Gaussian equation in Cuckle *et al.*[11]. §Based on the parameters in current study, medians in Nicolaides *et al.*[10] and Gaussian equation in Cuckle *et al.*[11]. FMF, The Fetal Medicine Foundation; W&H, Wald and Hackshaw; C&S, Cuckle and Sehmi; NT, nuchal translucency; LR, likelihood ratio; MoM, multiple of median.

method in the current study. Although the latter model is proven to be accurate, considering the estimated risk and the observed prevalence[15], the log Gaussian model is a better-established method and normally distributed data appear to be more 'epidemiologically correct'[5,7,8]. This is especially true in light of the recent trend to combine NT results with first-trimester[5] and/or second-trimester[16,17] maternal serum tests, whose results are processed with the Gaussian model. In essence, our findings, which were based on a considerable number of normal and Down syndrome-affected pregnancies, were almost identical to those of Cuckle and Sehmi[8].

A comprehensive comparison between the modalities used for presenting Down syndrome risk in an NT screening program, as was carried out for second-trimester serum screening[18], is beyond the scope of the current study. The only purpose for the comparison of different modalities presented in Table 3 was to validate our results and to point out major differences between our approach and those of others. The most pronounced difference between the FMF software, Cuckle and Sehmi[8] and our group vs. Wald and Hackshaw[5] was demonstrated by the NT values that assign a likelihood ratio of 1.0. This difference stems mainly from the substantially different equations for calculating median values that result in the different measurements' MoMs. Wald and Hackshaw[5] used the equation reported by Schuchter *et al.*[13] among 561 pregnancies without Down syndrome. Although this number is rather small compared to other studies, including ours, the main difference is derived from the use of a different method of measurement. Those authors[13] specified that the 'electronic calipers were placed directly on the border of echogenic to non-echogenic tissue (that is, inner to inner margins)'. As mentioned earlier, we use the on-to-on methodology described by Snijders *et al.*[6] which measures the maximum thickness of the subcutaneous translucency between the skin and the soft tissue overlying the cervical spine. Another explanation for this difference stems from the fact that Schuchter *et al.*[13] used the mean of six measurements, whereas the FMF recorded the maximum value. As a result, it is not surprising that the median values obtained by the equation of Schuchter *et al.*[13] are consistently smaller than those obtained by the equation of Nicolaides *et al.*[10]. For example, for CRLs of 40, 50, 60 and 70 mm, the corresponding median values are 0.93 vs. 1.14, 1.05 mm vs. 1.35 mm, 1.19 vs. 1.56 and 1.35 vs. 1.76 mm, respectively. While those differences are less pronounced following log MoM transformation for assessing the parameters used for LR calculations, they are most substantial for assigning an MoM result of an individual examination. Indeed, substituting the median NT of a 60-mm CRL from 1.19 mm to 1.56 mm and still using their[5,12] parameters leads to a remarkable change of the NT associated with an LR of 1.0, (i.e. from 1.75 mm to 2.35 mm, a value that is similar to the other three modalities). This emphasizes the importance for a test system to be homogeneous[19], and that operators who use the modality of W&H[5] should be alert to the subtleties of NT measurement and the utilization of an average value obtained from several measurements.

The issue of utilizing MoM values deserves further elaboration. Table 3 gives the median values for each CRL measurement, contending that the NT result should specify the NT measurement not only in mm, but also in MoM units. Souka *et al.*[20] recently reported the outcome of chromosomally normal fetuses with 'increased' NT ≥ 3.5 mm. That same center, which is arguing against the use of an arbitrary NT cut-off with regard to Down syndrome risk, is now objecting to another aspect of NT measurement. Given that an NT of 2.8 mm for a CRL of 45 mm (2.3 MoM) is clearly more 'increased' than an NT of 3.5 mm for a CRL of 75 mm (1.9 MoM), the only solution for this inconsistency would appear to be regular implementation of MoM units. Until more data are gathered on various abnormalities associated with an increased NT (expressed in MoM units), we advocate using a cut-off value of 2.0 MoM for the requirement of further work-up, as previously proposed by Souka and coworkers[20].

In summary, our results are in accordance with those derived from other modalities based on findings obtained among a large-scale population and using the same methodology of NT measurement. We have constructed tables that enable an easily calculated 'bedside' estimation of Down syndrome risk to be made based on maternal background risk and ultrasound findings.

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APPENDIX 1

Calculation of maternal background risk of Down syndrome live birth[9]:

$$0.0005907 + \exp(-5.182617 - 0.6321469\,\text{age} + 0.0252150\,\text{age}^2 - 0.0002285\,\text{age}^3)$$

APPENDIX 2

Median nuchal translucency (NT) thickness for various fetal crown–rump lengths (CRL)[10]:

$$\log_{10}\text{NT} = -0.3599 + 0.0127(\text{CRL}) - 0.000058(\text{CRL})^2$$

APPENDIX 3

Calculation of likelihood ratio of Down syndrome (DS) using log MoM Gaussian distribution[11]:

$$\text{Likelihood ratio} = (\text{SD}_{\text{unaffected}}/\text{SD}_{\text{DS}}) \times \exp[-0.5\,(Z^2_{\text{DS}} - Z^2_{\text{unaffected}})]$$

where Z = (measurement – mean)/SD.