

ANTENATAL DOWN'S SYNDROME SCREENING PARAMETERS

Down's syndrome screening parameters are available in various publications. For convenience we here summarise published parameters and factors used in screening together with the relevant references.

Table 1. General Information

Marker Name	Type	Trimester	Predictor for medians	Median equation type
MS-AFP	Serum	Second	GA	$A*B**GA(\text{days})$
uE3	Serum	Second	GA	$A*B**GA(\text{days})$
total hCG	Serum	Second	GA	$A+B*e**(-0.08268*(GA(\text{days})-100))$
Free beta hCG	Serum	Second	GA	$A+B*e**(-0.054975*(GA(\text{days})-100))^1$
Inhibin-A	Serum	Second	GA	$A*1.000429**((GA(\text{days})-120)**2)^2$
NT	Ultrasound	First	CRL	$A*B**GA(\text{days})$
PAPP-A	Serum	First	GA	$A*B**GA(\text{days})$
total hCG	Serum	First	GA	$A*B**GA(\text{days})$
Free beta hCG	Serum	First	GA	$A*B**GA(\text{days})*C**(GA*GA)$

Table 2. Mean screening marker levels (log₁₀ MoM) in Down's syndrome pregnancies according to gestational age

Gestational age		Mean †						
Week	Day	NT ¹⁵	PAPP-A ⁸	Free β-hCG ⁸	Total hCG ⁸	AFP ⁸	uE ₃ ⁸	Inhibin-A ⁸
10	0	0.4027	-0.4689	0.2105	-0.0171	n/a	n/a	n/a
	1	0.3962	-0.4593	0.2182	-0.0050			
	2	0.3897	-0.4496	0.2259	0.0072			
	3	0.3833	-0.4400	0.2335	0.0193			
	4	0.3768	-0.4303	0.2412	0.0314			
	5	0.3703	-0.4207	0.2489	0.0436			
	6	0.3639	-0.4110	0.2566	0.0557			
11	0	0.3574	-0.4014	0.2643	0.0678	n/a	n/a	n/a
	1	0.3509	-0.3917	0.2719	0.0799			
	2	0.3444	-0.3821	0.2796	0.0921			
	3	0.3380	-0.3724	0.2873	0.1042			
	4	0.3315	-0.3628	0.2950	0.1163			
	5	0.3250	-0.3531	0.3027	0.1285			
	6	0.3186	-0.3435	0.3103	0.1406			
12	0	0.3121	-0.3338	0.3180	0.1527	n/a	n/a	n/a
	1	0.3056	-0.3242	0.3257	0.1649			
	2	0.2992	-0.3145	0.3334	0.1770			
	3	0.2927	-0.3049	0.3411	0.1891			
	4	0.2862	-0.2952	0.3487	0.2012			
	5	0.2798	-0.2856	0.3564	0.2134			
	6	0.2733	-0.2759	0.3641	0.2255			
13	0	0.2668	-0.2663	0.3718	0.2376	n/a	n/a	n/a
	1	0.2604	-0.2566	0.3795	0.2498			
	2	0.2539	-0.2470	0.3871	0.2619			
	3	0.2474	-0.2373	0.3948	0.2740			
	4	0.2410	-0.2277	0.4025	0.2862			
	5	0.2345	-0.2180	0.4102	0.2983			
	6	0.2280	-0.2084	0.4179	0.3104			
14-22	n/a	n/a	n/a	0.4249	0.3118	-0.1308	-0.1549	0.3384

† Unaffected means set to 0

n/a Not applicable

Regression equations used to estimate the biochemical marker median in affected pregnancies in the first trimester are⁸:

$$\text{median total hCG} = 10^{-0.8662 + 0.01213 \times \text{gestational age in days}}$$

$$\text{median free } \beta\text{-hCG} = 10^{-0.3271 + 0.00768 \times \text{gestational age in days}}$$

$$\text{median PAPP-A} = 10^{-1.1444 + 0.00965 \times \text{gestational age in days}}$$

Regression equation used to estimate the NT median in affected pregnancies is¹⁵:

$$\text{median NT (mm)} = .8554679 - .0064686 \times \text{gestational age in days}$$

Table 3. Standard deviations of the screening markers (log₁₀ MoM) in each trimester of pregnancy⁸

Maternal weight correction	Gestational age based on				
	Dates		Scan		
	No	Yes	No	Yes	
Unaffected					
First trimester (10-13 weeks)					
NT	10 weeks	-	-	0.1732	0.1732
	11 weeks	-	-	0.1439	0.1439
	12-13 weeks	-	-	0.1329	0.1329
PAPP-A		0.2893	0.2670	0.2722	0.2495
Free β-hCG		0.2731	0.2718	0.2669	0.2651
Total hCG		0.2091	0.1994	0.2037	0.1950
Second trimester (14-22 weeks)					
AFP		0.1498	0.1417	0.1486	0.1399
uE ₃		0.1292	0.1284	0.1156	0.1142
Total hCG		0.2307	0.2279	0.2305	0.2276
Free β-hCG		0.2639	0.2612	0.2602	0.2577
Inhibin-A		0.2135	0.2078	0.2135	0.2078
Down's syndrome					
First trimester (10-13 weeks)					
NT		-	-	0.2313	0.2313
PAPP-A		0.3161	0.2959	0.3006	0.2802
Free β-hCG		0.2651	0.2637	0.2587	0.2569
Total hCG		0.2202	0.2111	0.2151	0.2069
Second trimester (14-22 weeks)					
AFP		0.1497	0.1416	0.1485	0.1398
uE ₃		0.1377	0.1370	0.1251	0.1238
Total hCG		0.2424	0.2397	0.2422	0.2395
Free β-hCG		0.3020	0.2996	0.2987	0.2965
Inhibin-A		0.2723	0.2679	0.2723	0.2679

Table 4. Truncation limits (MoM) for Down's syndrome screening markers⁸

Marker	Truncation limits [†]
First trimester (10-13 weeks)	
NT	0.65 ¹⁶ – 2.5
PAPP-A	0.2 – 3.0
Free β-hCG [‡]	0.3 – 5.0
Total hCG	0.3 – 3.0
Second trimester (14-22 weeks)	
AFP	0.4 – 3.0
uE ₃	0.4 – 2.0
Total hCG	0.4 – 5.0
Free β-hCG	0.3 – 5.0
Inhibin-A	0.3 – 5.0

[†] For MoM values outside the specified range, the risk is estimated for the corresponding limit

5 Correlation coefficients for the screening markers in unaffected pregnancies

Table 5.1 Correlation coefficients for the screening markers in unaffected pregnancies (gestational age based on dates, without adjustment for maternal weight)⁸

	First trimester			Second trimester			
	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester							
Free β -hCG	0.7023						
PAPP-A	0.2067	0.1315					
Second trimester							
AFP	0.1085	0.0571	0.2461				
uE ₃	0.0044	-0.0479	0.2820	0.2595			
Total hCG	0.7050	0.5667	0.0816	0.1781	-0.0825		
Free β -hCG	0.6968	0.7494	0.0692	0.1168	-0.0904	0.8607	
Inhibin-A	0.3295	0.3094	0.0652	0.2293	-0.0876	0.4412	0.4122

Table 5.2 Correlation coefficients for the screening markers in unaffected pregnancies (gestational age based on dates, with adjustment for maternal weight)⁸

	First trimester			Second trimester			
	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester							
Free β -hCG	0.6953						
PAPP-A	0.1490	0.0763					
Second trimester							
AFP	0.0481	0.0048	0.1728				
uE ₃	-0.0162	-0.0654	0.2776	0.2473			
Total hCG	0.7010	0.5401	0.0214	0.1336	-0.1008		
Free β -hCG	0.6967	0.7292	0.0127	0.0722	-0.1089	0.8475	
Inhibin-A	0.3095	0.2852	0.0030	0.1896	-0.1083	0.4225	0.3957

Table 5.3 Correlation coefficients for the screening markers in unaffected pregnancies (gestational age based on scan, without adjustment for maternal weight)⁸

	First trimester			Second trimester						
	NT (10 weeks)	NT (11 weeks)	NT (12-13 weeks)	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester										
Total hCG	-0.0626	-0.0753	-0.0815							
Free β -hCG	-0.0334	-0.0402	-0.0436	0.7281						
PAPP-A	-0.0417	-0.0503	-0.0544	0.2795	0.1961					
Second trimester										
AFP	-0.0097	-0.0116	-0.0126	0.1298	0.0736	0.2105				
uE ₃	0.0476	0.0573	0.0621	0.0572	-0.0023	0.1533	0.2219			
Total hCG	-0.0556	-0.0669	-0.0725	0.7225	0.5858	0.1217	0.1939	-0.0193		
Free β -hCG	-0.0507	-0.0610	-0.0660	0.7258	0.7781	0.1186	0.1417	-0.0357	0.8764	
Inhibin-A	-0.0414	-0.0499	-0.0540	0.3366	0.3179	0.0877	0.2411	-0.0627	0.4441	0.4242

Table 5.4 Correlation coefficients for the screening markers in unaffected pregnancies (gestational age based on scan, with adjustment for maternal weight)⁸

	First trimester			Second trimester						
	NT (10 weeks)	NT (11 weeks)	NT (12-13 weeks)	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester										
Total hCG	-0.0630	-0.0758	-0.0821							
Free β -hCG	-0.0325	-0.0391	-0.0423	0.7178						
PAPP-A	-0.0429	-0.0516	-0.0559	0.2198	0.1395					
Second trimester										
AFP	-0.0079	-0.0095	-0.0103	0.0675	0.0167	0.1160				
uE ₃	0.0495	0.0596	0.0645	0.0306	-0.0255	0.1213	0.1981			
Total hCG	-0.0549	-0.0661	-0.0716	0.7191	0.5606	0.0624	0.1535	-0.0416		
Free β -hCG	-0.0502	-0.0604	-0.0654	0.7236	0.7605	0.0627	0.0974	-0.0585	0.8651	
Inhibin-A	-0.0415	-0.0499	-0.0540	0.3167	0.2937	0.0237	0.2033	-0.0875	0.4293	0.4092

6 Correlation coefficients for the screening markers in Down's syndrome pregnancies

Table 6.1 Correlation coefficients for the screening markers in Down's syndrome pregnancies (gestational age based on dates, without adjustment for maternal weight)⁸

	First trimester			Second trimester			
	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester							
Free β -hCG	0.5115						
PAPP-A	0.1330	-0.0456					
Second trimester							
AFP	0.1416	0.1063	0.1945				
uE ₃	-0.1656	-0.3446	0.4586	-0.0017			
Total hCG	0.6809	0.4695	-0.1761	0.2121	-0.3796		
Free β -hCG	0.5605	0.7675	-0.2484	0.2060	-0.4172	0.8160	
Inhibin-A	0.2618	0.3031	-0.1282	0.1976	-0.2989	0.4296	0.4394

Table 6.2 Correlation coefficients for the screening markers in Down's syndrome pregnancies (gestational age based on dates, with adjustment for maternal weight)⁸

	First trimester			Second trimester			
	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester							
Free β -hCG	0.4929						
PAPP-A	0.0749	-0.1112					
Second trimester							
AFP	0.0879	0.0554	0.1211				
uE ₃	-0.1921	-0.3646	0.4671	-0.0288			
Total hCG	0.6758	0.4418	-0.2487	0.1725	-0.4008		
Free β -hCG	0.5551	0.7494	-0.3170	0.1738	-0.4366	0.8046	
Inhibin-A	0.2442	0.2824	-0.1879	0.1661	-0.3182	0.4148	0.4284

Table 6.3 Correlation coefficients for the screening markers in Down's syndrome pregnancies (gestational age based on scan, without adjustment for maternal weight)⁸

	First trimester				Second trimester			
	NT	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester								
Total hCG	-0.0804							
Free β -hCG	0.1063	0.5272						
PAPP-A	-0.1420	0.1894	0.0004					
Second trimester								
AFP	0.0744	0.1627	0.1250	0.1580				
uE ₃	0.0679	-0.1410	-0.3387	0.3788	-0.0670			
Total hCG	0.0451	0.6960	0.4869	-0.1552	0.2276	-0.3540		
Free β -hCG	0.1454	0.5803	0.7955	-0.2293	0.2294	-0.4106	0.8279	
Inhibin-A	0.1818	0.2668	0.3117	-0.1217	0.2069	-0.3035	0.4319	0.4485

Table 6.4 Correlation coefficients for the screening markers in Down's syndrome pregnancies (gestational age based on scan, with adjustment for maternal weight)⁸

	First trimester				Second trimester			
	NT	Total hCG	Free β -hCG	PAPP-A	AFP	uE ₃	Total hCG	Free β -hCG
First trimester								
Total hCG	-0.0819							
Free β -hCG	0.1080	0.5053						
PAPP-A	-0.1506	0.1284	-0.0692					
Second trimester								
AFP	0.0809	0.1075	0.0697	0.0660				
uE ₃	0.0695	-0.1741	-0.3666	0.3712	-0.1093			
Total hCG	0.0466	0.6912	0.4598	-0.2295	0.1920	-0.3808		
Free β -hCG	0.1471	0.5735	0.7797	-0.3004	0.1981	-0.4356 ¹⁰	0.8178	
Inhibin-A	0.1854	0.2493	0.2909	-0.1842	0.1770	-0.3276	0.4197	0.4384

FACTORS USED IN ADJUSTING MOM VALUES

Serum marker levels may differ, on average, between twin and singleton pregnancies, between women with and without insulin-dependent diabetes mellitus, between smokers and non-smokers, and between women who undergo *in-vitro* fertilisation (IVF) and those who conceive naturally. This can lead to differences in the false-positive rate among the different groups screened. For example, the false-positive rate among IVF pregnancies screened with the Quadruple test is about twice that in naturally conceived pregnancies.¹² To avoid this adjustments can be made to the MoM values in twin, diabetic and IVF pregnancies, and in women who smoke, using the adjustment factors given in the table below. Since women with diabetes tend to be heavier than those without, two adjustment factors are given, one used when a diabetic woman's MoM values are weight adjusted, and the other when they are not.

Table 7 Median marker levels (MoM) in twin, diabetic and IVF pregnancies and in smokers, relative to singleton, non-diabetic, and non-IVF pregnancies and non-smokers

Serum marker	Twin pregnancies	Diabetic pregnancies		Smokers	IVF pregnancies ^{12‡}
		Not adjusted for weight	Adjusted for weight		
Second trimester (14-22 weeks)					
AFP	2.13 ⁴	0.77 ³	0.88 ¹¹	1.05 ⁷	n/a
uE ₃	1.67 ⁴	0.92 ⁵	0.95 ¹¹	0.96 ⁷	1.1
total hCG	1.84 ⁴	n/a	n/a	0.82 ¹⁷	0.9
free β-hCG	1.90 ¹³	n/a	n/a	0.80 ⁷	0.9
inhibin-A	1.99 ⁶	n/a	n/a	1.62 ⁷	n/a
First trimester (10-13 weeks)					
PAPP-A	1.86 ¹⁴	n/a	n/a	0.81 ¹⁸	n/a
free β-hCG	2.10 ¹⁴	n/a	n/a	0.94 ¹⁸	n/a

‡ Multiplication factors

ADJUSTMENT FOR RECURRENT FALSE POSITIVE SCREENING RESULTS

In prenatal screening for Down syndrome women who are screen- positive in one pregnancy have an increased chance of being screen-positive in a subsequent pregnancy.⁹

The recurrent high false-positive rate can be avoided if all MoM values of screening markers in all pregnancies are adjusted to take account the values of previous pregnancy. This can be done by dividing the observed MoM value for each marker in a current pregnancy by the expected MoM given the previous one. The expected MoM values are summarized in the table by taking the previous MoM value and raising it to the power of *b* so that for a current pregnancy:

The adjusted MoM = observed MoM / expected MoM

where the expected MoM in current pregnancy = Previous Pregnancy MoM^b.

Table 8 Adjustments for Recurrent False positives

First trimester	b
PAPP-A	0.42
Free β-hCG	0.49
Second trimester	
AFP	0.41
uE ₃	0.26
Free β-hCG	0.42
Inhibin-A	0.40

ALLOWED COMBINATIONS OF MARKERS

The table below shows the marker combinations that are allowed in Down's syndrome screening.

Table 9 Allowed combinations of markers

Marker Name		Second trimester					First trimester			
		MS-AFP	uE3	total hCG	Free beta hCG	Inhibin-A	NT	PAPP-A	total hCG	Free beta hCG
Second trimester	MS-AFP	-	Y	Y	Y	Y	Y	Y	Y	Y
	uE3	Y	-	Y	Y	Y	Y	Y	Y	Y
	total hCG	Y	Y	-	N	Y	Y	Y	N	N
	Free beta hCG	Y	Y	N	-	Y	Y	Y	N	N
	Inhibin-A	Y	Y	Y	Y	-	Y	Y	Y	Y
First trimester	NT	Y	Y	Y	Y	Y	-	Y	Y	Y
	PAPP-A	Y	Y	Y	Y	Y	Y	-	Y	Y
	total hCG	Y	Y	N	N	Y	Y	Y	-	N
	Free beta hCG	Y	Y	N	N	Y	Y	Y	N	-

Table 10 Other Information

Marker Name	Trimester	Expected change with GA	Expected change with maternal weight
MS-AFP	Second	Increases	Decreases
uE3	Second	Increases	Decreases
total hCG	Second	Decreases	Decreases
Free beta hCG	Second	Decreases	Decreases
Inhibin-A	Second	Not specified	Decreases
NT	First	Increases	No change
PAPP-A	First	Increases	Decreases
total hCG	First	Decreases	Decreases
Free beta hCG	First	Not specified	Decreases

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