

REPORT ON
PRENATAL DIAGNOSTIC TESTING
IN VICTORIA 2004

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**The Consultative Council
on Obstetric and Paediatric
Mortality and Morbidity**

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1. KEY FINDINGS

- 1** The total number of prenatal diagnostic tests done in 2004 was 4372, approximately 500 (10%) less than in 2003. The total number of prenatal diagnostic tests reached a peak in 1998, with 5310 tests done. However, since then, there has been a substantial decline in the number of all CVS and AMN done in Victoria. **Pages 8 & 9**
- 2** Reasons for testing were similar in 2004 to those in 2003 with 41% of all prenatal diagnostic tests done for advanced maternal age as the only indication for testing and 44% because of an abnormal screening test **Pages 12 & 14**
- 3** The proportion of older pregnant women who have a prenatal diagnostic test has declined from almost 80% in 1996 to 51% in 2004 (40 years and over) and from 60% in 1996 to 26% in 2004 (37-39 years). **Page 11**
- 4** There were approximately 200 fewer tests done because of an abnormal ultrasound in 2004 (n = 626) compared to 2003 (n = 833), either suspected fetal anomaly on routine ultrasound or increased nuchal thickening (when not as part of first trimester combined screening). This represents 14.3% of all tests in 2004. 73% of these women were under 37 years of age. **Pages 14 & 15**
- 5** Over 40% of CVS, and 14% of AMN following an abnormal ultrasound were found to have a major chromosomal abnormality. This is a higher detection rate than in 2003, indicating that women who are referred in for a diagnostic test are at greater risk than in previous years. **Pages 24-26**
- 6** 1310 women had prenatal diagnosis for an increased risk maternal serum screen compared (MSS) with just over 500 in 1999 and 1366 in 2003. For the first time it was recorded that there were more diagnostic tests prompted by first trimester combined MSS (686 or 15.7%) than by second trimester MSS (624 or 14.3%) **Pages 16 & 17**
- 7** The majority of women having prenatal diagnosis following second trimester MSS were under 37 years of age (73.4%) whereas women having prenatal diagnosis following a first trimester combined MSS test were equally distributed across both age groups. **Pages 16 & 17**

- 8** Using information from Genetic Health Services Victoria, we estimate that there were 36,964 women who had MSS (either first trimester combined or second trimester serum) in 2004. The number tested for an increased risk MSS result corresponds to a diagnostic follow-up rate of 3.5%. **Page 16**
- 9** A fetal chromosome abnormality was detected in 5.0% of pregnancies tested for an increased risk second trimester MSS, and in 12.8% of tests for increased risk first trimester combined MSS. Trisomies accounted for 71.0% and 77.3% of these abnormalities in the respective tests. **Pages 27 & 28**
- 10** The number of tests done for indications outside the HGSA/RANZCOG recommendations continues to decline having more than halved since 1996, with 380 tests done in 2004. Indications outside HGSA/RANZCOG decreased mainly in women aged 35-36 years. This decline is explained by the increased utilisation of screening tests in women under 37 years of age. **Page 21**
- 11** Of all Victorian women who had CVS or AMN in 2004, 91.2% had a fetus with a normal karyotype and 7.0% of tested pregnancies were found to have a major fetal karyotype abnormality (11.1% of CVS and 4.7% of AMN). There has been a steady annual increase in the detection rate of abnormalities by both diagnostic tests (4.4% in 1999, 5.5% in 2002, 6% in 2003 and now 7% in 2004). **Page 22**
- 12** When routine ultrasound (including nuchal translucency screening without a combined serum test) was abnormal, 22.5% of the follow up diagnostic tests revealed an abnormal karyotype. This compares with 5% of diagnostic tests after increased risk second trimester MSS and 13% after first trimester. When maternal age alone was the indication, 2.7% had an abnormal karyotype **Pages 23-28**
- 13** Trisomy 21 accounted for just under half of all abnormal fetal karyotypes (46%), with 142 diagnosed prenatally in 2004, ten more than last year. For the majority of tests with a diagnosis of Trisomy 21, the major indication was an increased risk screening test result (80.3%). First trimester combined MSS accounted for 30.3%, second trimester MSS for 16.2%, second trimester routine ultrasound for 12.7%, while increased nuchal thickening alone and maternal age alone were associated with 19.0% and 19.7% respectively. **Pages 32-34**

2. INTRODUCTION

Chorionic villus sampling (CVS) and amniocentesis (AMN) are diagnostic procedures to detect fetal chromosomal abnormalities and are offered in Victoria as an option to pregnant women who are 37 years of age and over. In addition, testing is made available if the indication is other than age but falls within the Prenatal Diagnosis Policy (revised, March, 2004) of the Human Genetics Society of Australasia (HGSA) and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) (available at www.hgsa.com.au). For example, an abnormal ultrasound or increased risk maternal serum screen would be such an indication.

There are four Victorian cytogenetics laboratories analysing prenatal diagnostic samples. These are located at the Monash Medical Centre, Genetic Health Services Victoria and at the private laboratories of Melbourne Pathology and Cytogenetic Services.

This report provides information on the uptake and trends of prenatal testing according to the HGSA/RANZCOG recommendations and the numbers and types of chromosomal abnormalities diagnosed.

Prenatal Diagnostic Testing in Victoria is a report compiled annually in collaboration with Public Health Genetics at the Murdoch Childrens Research Institute and the Victorian Perinatal Data Collection Unit, the Department of Human Services. The primary purpose of this document is to report on the utilisation of these tests. The report presents descriptive statistics on the number of tests performed, the indications for testing and the fetal karyotype outcome of tests. Furthermore, by comparing data from the last 15 years, we are able to monitor changes in numbers of tests, reasons given for testing, especially that related to the age of women tested and abnormal fetal karyotype outcomes.

Information on pregnancy outcome for this data set is not routinely collected and would require record linkage to the Victorian Perinatal Data Collection Unit and the Birth Defects Register. This is done for specific projects with appropriate ethics approvals obtained.

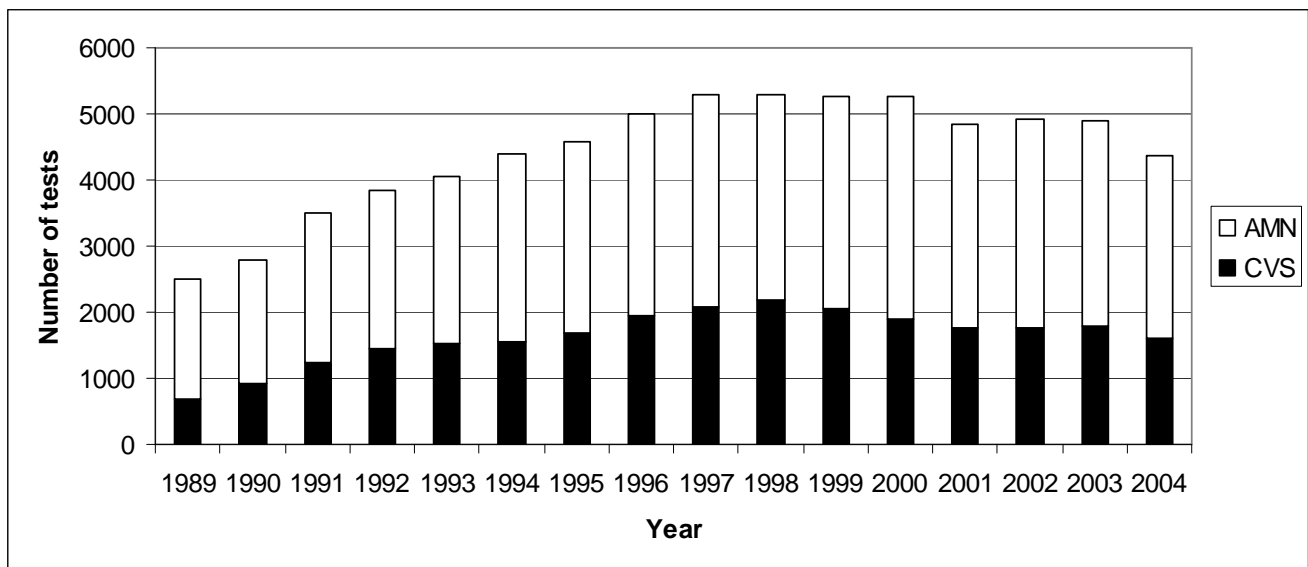
3. UTILISATION OF PRENATAL DIAGNOSTIC TESTS

3.1 NUMBER OF TESTS

The number of prenatal diagnostic tests analysed by Victorian laboratories in 2004 was 4682. This overall number includes some multiple procedures eg same day AMN and CVS samples, twin or triplet pregnancies – which have been condensed into one record – as well as 242 samples from women living interstate, 35 repeat samples and 34 late gestation tests.

In 2004, 4372 pregnant Victorian women had a CVS (1593) or an AMN (2779) before 25 weeks gestation (Figure 1 and Table 1). The body of this report discusses the utilisation, indications and outcomes of these tests.

Figure 1. Total number of prenatal tests on Victorian women under 25 weeks gestation



After an initial decline in the total number of Victorian women having prenatal diagnosis by CVS or AMN in 2001, numbers have been relatively steady for the last three years. However, in 2004 we observed the largest decrease so far in the number of tests with a drop of 526 samples from the previous year. Table 1 shows that the decline in numbers was due to a fall in both CVS and AMN.

Table 1. Number and proportion of Victorian CVS and amniocenteses under 25 weeks gestation

Year	Total	CVS	% total	AMN	% total
1989	2500	694	28%	1806	72%
1990	2777	916	33%	1861	67%
1991	3505	1239	35%	2266	65%
1992	3831	1449	38%	2383	62%
1993	4061	1537	38%	2524	62%
1994	4382	1559	36%	2823	64%
1995	4592	1689	37%	2903	63%
1996	4993	1957	39%	3036	61%
1997	5283	2072	39%	3211	61%
1998	5300	2179	41%	3121	59%
1999	5263	2043	39%	3220	61%
2000	5276	1887	36%	3389	64%
2001	4854	1753	36%	3101	64%
2002	4914	1776	36%	3138	64%
2003	4898	1793	37%	3105	63%
2004	4372	1593	36%	2779	64%

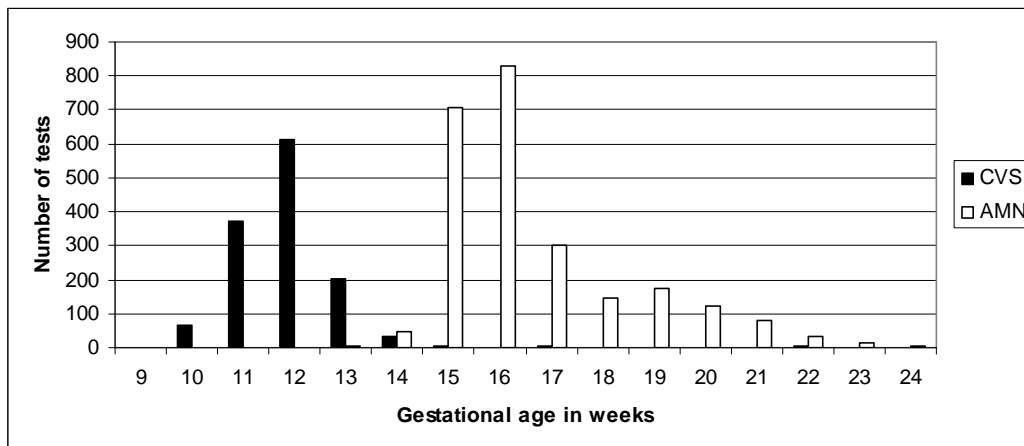
3.2 GESTATIONAL AGE

Figure 2 shows the distribution of recorded gestational ages for CVS and AMN for Victorian women under 25 weeks of gestation.

The recorded gestational ages used in Figure 2 were defined as that recorded at the time of the procedure, which was usually estimated by ultrasound. For the 2004 data, there were 600 missing gestations (14%).

For CVS the recorded gestational ages ranged from 8-24 weeks with a median of 12 weeks when 47% of these tests were performed. For AMN, the reported gestational ages ranged from 10-24 weeks with a median of 16 weeks when 34% of these tests were performed.

Figure 2. CVS and AMN by recorded gestation in weeks for Victorian women under 25 weeks of gestation



We have included the 600 records with missing gestational ages in the main body of the report, assuming the diagnostic test was done before 25 weeks of gestation.

3.3 ANNUAL UPTAKE RATES BY MATERNAL AGE

At the time of writing the report, the final 2004 birth file for Victoria from the Perinatal Data Collection Unit (PDCU), the Department of Human Services, was not available. We present annual uptake rates of prenatal diagnostic testing by maternal age group using an **interim** file of Victorian 2004 confinements (Table 2).

Seven percent of pregnant Victorian women had a prenatal test in 2004. The overall proportion of women having a test has dropped by one percent since 1998, and a further one percent since 2002.

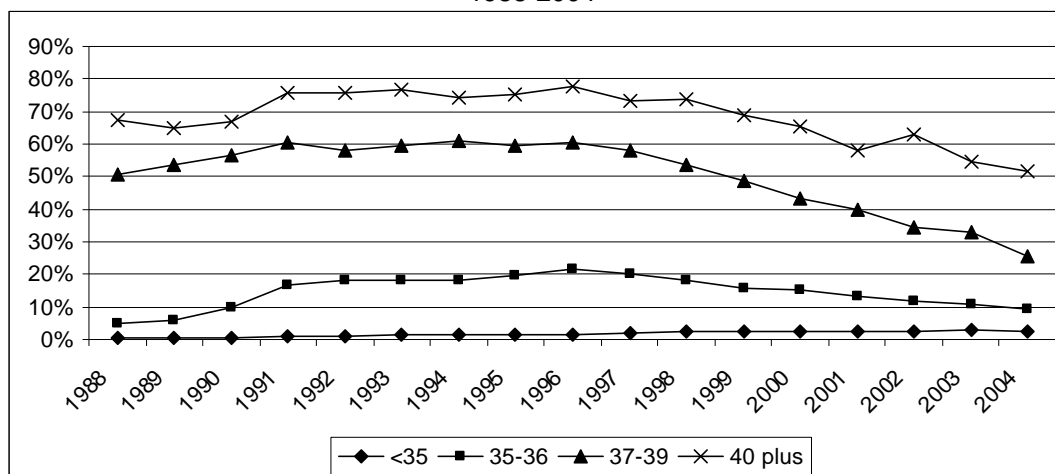
Uptake of prenatal diagnosis by women 35 years and older has declined over the last six years. It fell from 78% in 1996 to 63% in 2002 and to 51% in 2004 in the oldest age group, from 60% to 34% and 26% in the 37-39 year olds and from 21% to 12% and 10% in women aged 35-36. The overall proportion of tests in women under 35 years has increased from 1.5% in 1996 to 2.6% in 2004 (Figure 3).

Table 2. Age of Victorian women having a prenatal test under 25 weeks of gestation

	Confinements*	CVS		AMN		Total	
Age group (years)	Interim 2004 data	2004	Uptake	2004	Uptake	2004	Uptake
<35	48544	347	0.7%	900	1.9%	1247	2.6%
35-36	6463	225	3.5%	391	6.0%	616	9.5%
37-39	5255	494	9.4%	851	16.2%	1345	25.6%
≥40	2263	527	23.3%	637	28.1%	1164	51.4%
Total	62525	1593		2779		4372	7.0%

* data from PDCU

Figure 3. Annual uptake rates of prenatal diagnostic testing in Victoria, 1988-2004



4. INDICATIONS FOR PRENATAL DIAGNOSIS

4.1 OVERVIEW

The indications for testing used in this report are taken from prenatal chromosome and DNA test request slips sent to the cytogenetics laboratories with the sample. The accuracy and completeness of this information has not been confirmed with the referring doctor and the data must be interpreted within this limitation.

A number of women had more than one indication for testing and a summary of all indications given as reasons for prenatal diagnosis is presented in Figure 4.

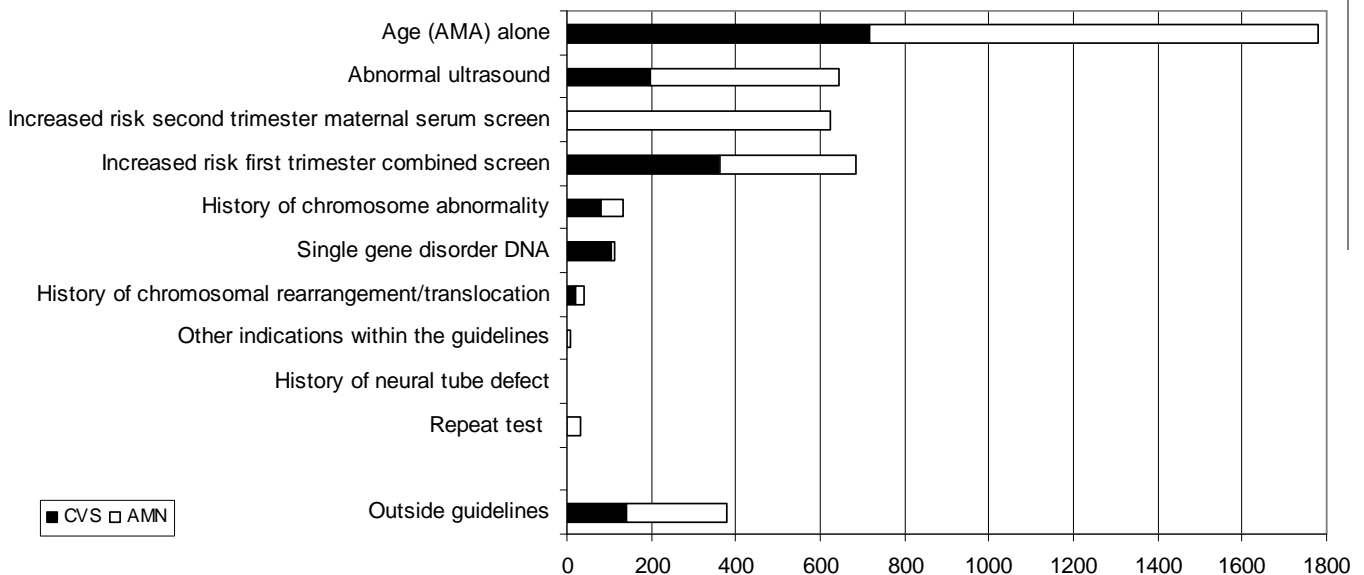
The five most common indications for prenatal diagnostic testing for Victorian women under 25 weeks gestation were maternal age, abnormal ultrasound, increased risk first trimester combined and second trimester maternal serum screen and indications outside the recommendations of the HGSA/RANZCOG Prenatal Diagnosis Policy. Other indications included previous chromosomal abnormality (132), tests for single gene disorders (112), history of chromosomal rearrangement (39), history of neural tube defects (2) and other within HGSA guidelines (8).

1. 1781 (40.7% of tests) women had maternal age as their only indication for testing. By definition these women were aged 37 and over (*see 4.2, maternal age*).
2. 626 (14.3% of tests) prenatal diagnostic tests followed an abnormal ultrasound, either raised nuchal translucency screen (excluding those done as part of first trimester combined screening) or a fetal anomaly scan (*see 4.3, abnormal ultrasound*).
3. 624 (14.3% of tests) tests were done because of a finding of increased risk second trimester maternal serum screening (*see 4.4, second trimester maternal serum screening*).
4. 686 (15.7% of tests) tests were done because of a finding of increased risk first trimester combined screening (*see 4.4.2, first trimester combined screening*).

5. 380 (8.7% of tests) indications were outside the HGSA/RANZCOG recommendations. These women were under the recommended age of 37 years but requested the service as part of their private health care (see 4.9, *outside recommendations*).

In order to estimate the approximate number of diagnostic tests prompted by prenatal screening we deducted the number of tests with an indication other than screening (n=2454) from the total (n=4372). Given that a number of tests had more than one indication for testing, in particular when prior screening was specified, this returned a more conservative estimate of the proportion of tests that were done because the woman had prenatal screening. Using this method, approximately 44% of all prenatal diagnostic tests were done following an increased risk screening test result (ie. nuchal translucency, first trimester combined screening, second trimester maternal serum screening and/or second trimester routine ultrasound).

Figure 4. Indications for prenatal diagnosis for Victorian women under 25 weeks gestation



4.2 MATERNAL AGE

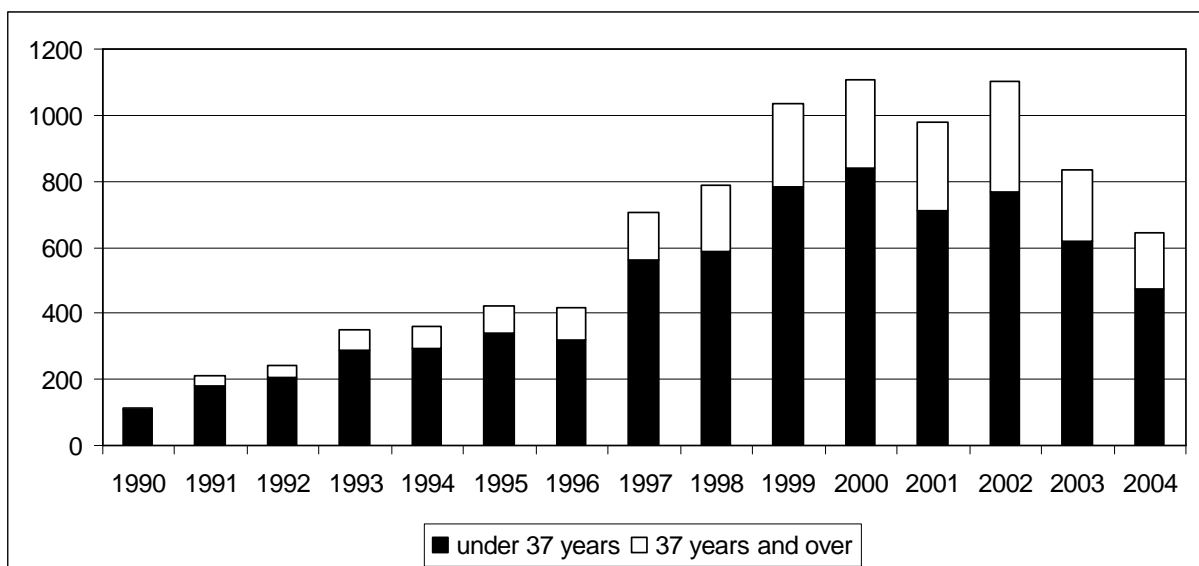
As shown on page 11 (3.3, *Utilisation*), 2509 (57.4%) of women having a prenatal diagnostic test were aged 37 years or over. 71.0% of these women had maternal age as their only indication (ie 40.7% of all women).

4.3 ABNORMAL ULTRASOUND

The number of women undergoing prenatal diagnosis following an abnormal ultrasound was 645 or 14.8% of all tests. 73% of these women were under 37 years of age.

Abnormal ultrasound was defined as suspected fetal or other pregnancy anomaly on routine ultrasound, or increased nuchal thickening (nuchal translucency screen). 19 tests had a double indication of fetal abnormality and increased nuchal translucency, making the total number of tests prompted by any ultrasound abnormality 629.. **Nuchal translucency screens done as part of first trimester combined screening are no longer included here, which accounts for an apparent drop in the number of tests following abnormal ultrasound since 2002.**

Figure 5. Number of Victorian women under 25 weeks gestation having prenatal diagnosis following abnormal ultrasound by age group



34% of the tests done for abnormal ultrasound were reported as nuchal translucency screens (when not as part of 1st trimester combined screening). Over half of abnormal nuchal translucency screens were followed by a CVS (55%). This compares with 17% of women having a CVS following a suspected fetal abnormality on routine ultrasound (Table 3). The median gestational ages for a CVS or AMN in these categories were 12 weeks and 19 weeks respectively.

Table 3. Abnormal ultrasound as indication for Victorian women under 25 weeks gestation, by maternal age and procedure

	CVS	AMN	Total	% Total
Abnormal nuchal translucency screen (includes 19 pregnancies which also had a suspected fetal abnormality on routine ultrasound)				
Maternal age				
<35 yrs	51	54	105	
35-36 yrs	21	14	35	
37 – 39 yrs	20	17	37	
≥40 yrs	26	10	36	
<i>Sub-total</i>	118	95	213	(33.9%)
	(55.4%)	(44.6%)	(100%)	
Other suspected fetal or pregnancy abnormality on routine ultrasound				
Maternal age				
<35 yrs	36	254	290	
35-36 yrs	10	34	44	
37 – 39 yrs	16	40	56	
≥40 yrs	9	14	23	
<i>Sub-total</i>	71	342	413	(66.1%)
	(17.2%)	(82.8%)	(100%)	
Total	189	437	626	
	(30.2%)	(69.8%)		(100%)

4.4 MATERNAL SERUM SCREENING

Increased risk maternal serum screen continues to be a frequent indication for testing since the introduction of second trimester maternal serum screen (2TMSS) in 1996 and first trimester combined screening (1TCS) in 2000.

2003 was the first year this report distinguished between first trimester combined screening and second trimester maternal serum screening. However, the accuracy and completeness of this information has not been confirmed with the referring doctor and the data must be interpreted within this limitation.

Using information from Genetic Health Services Victoria, we estimate that there were 36,964 women who had maternal serum screening (either first trimester combined or second trimester serum) in 2004. The number having prenatal diagnosis for an increased risk screening result corresponds to a diagnostic follow-up rate of 3.5% (and compares to 4.2% in 2003).

4.4.1 Second trimester maternal serum screening (2TMSS)

624 or almost 15% of all prenatal diagnostic tests are done following an increased risk 2TMSS. By necessity, due to the gestation at which this screening is done, most of the tests are AMN (623, or 99.8%), rather than CVS (1, or 0.2%). Approximately half (57.1%) of tests prompted by increased risk 2TMSS were in women under the age of 35 (Table 4).

Table 4. Increased risk 2TMSS as indication for Victorian women under 25 weeks gestation, by maternal age and procedure

Age group (years)	CVS	% total	AMN	% total	Total	% Total
<35			356		356	57.1%
35-36			102		102	16.3%
37-39			106		106	17.0%
≥40	1		59		60	9.6%
Total	1	0.2%	623	99.2%	624	100.0%

4.4.2 First trimester combined screening (1TCS)

Increased risk 1TCS as an indication for prenatal diagnostic testing included 2 tests where the recorded indication was “increased risk first trimester *serum* screening” and 24 tests done before 14 weeks gestation because of “increased risk MSS”.

After inclusion of these data, 686 or 16% of prenatal diagnostic tests were prompted by an increased risk first trimester combined test. Of these, 364 (53.1%) were CVS and 322 (46.9%) were AMN (Table 5).

82.6% of all AMN following an increased risk 1TCS were done at 15-16 weeks and 72.0% of all CVS at 11-12 weeks gestation (data not shown).

Table 5. Increased risk 1TCS as indication for Victorian women under 25 weeks gestation, by maternal age and procedure

Age group (years)	CVS	% total	AMN	% total	Total	% Total
<35	117		113		230	33.5%
35-36	76		64		140	20.4%
37-39	92		76		168	24.5%
≥40	79		69		148	21.6%
Total	364	53.1%	322	46.9%	686	100.0%

4.5 HISTORY OF CHROMOSOME ABNORMALITY

Overall, 171 women were tested because of a history of chromosome abnormality, including 39 prenatal tests done because of a history of chromosome translocation or rearrangement (eg deletions or inversions) (Table 6).

132 of these tests were performed because of a previous pregnancy with a chromosomal abnormality but information on the type of abnormality was not available for 53% of these indications.

Table 6. History of chromosome abnormality as indication for testing in Victorian women under 25 weeks gestation

Previous abnormality	CVS	AMN	Total	%
Unspecified	30	40	70	53.0%
Trisomy 21	31	7	38	28.8%
Trisomy 18	8	3	11	8.2%
Trisomy 13	3	1	4	3.0%
Sex chromosome aneuploidy	5	0	5	3.0%
Other major chromosome	2	2	4	3.0%
Total	79	53	132	100%
Translocation	13	19	32	82.1%
Rearrangements	6	1	7	17.9%
Total	19	20	39	100%

4.6 SINGLE GENE TESTS

110 prenatal diagnostic tests were done because a DNA or biochemical test for a single gene disorder was requested, two procedures requiring two gene tests, giving a total of 112 prenatal single gene tests for 2004. This number is comparable to the previous four years. The majority of tests for single gene disorders were done following CVS (95%)

A list of the main conditions tested for in 2004 relative to the previous three years is provided in Table 7. Table 8 expands the category *other* where only one of each test was performed in 2002 (n=15).

Table 7. Single gene tests in Victorian women under 25 weeks gestation

Single gene test	2004	% 2004		2003	2002	2001	2000
Thalassaemia	25	22		25	38	23	30
Cystic fibrosis	15	13		17	11	15	12
Fragile X	9	8		13	8	10	13
Duchenne muscular dystrophy	7	6		9	6	5	10
Spinal muscular atrophy	6	5		4	6	7	8
Myotonic dystrophy	4	4		3	1	0	1
Haemophilia	3	3		5	5	5	3
X-linked Hydrocephalus	3	3		2	3	1	0
Epidermolysis Bullosa	3	3					
Neurofibromatosis	3	3					
Congenital adrenal hypoplasia	2	2		2	3	2	2
Mucopolysaccharidosis I	2	2		0	2	0	1
Sialidosis	2	2					
X-linked Lissencephaly/Double Cortin	2	2					
Adrenoleukodystrophy	1	1		4	4	0	1
Huntington disease	1	1		1	5	1	2
Connexin 26	0	0		3	1	0	0
Ornithine transcarbamylase deficiency	0	0		2	1	1	0
Prader Willi syndrome	0	0		2	0	0	1
BRCA 1	0	0		1	2	0	0
Other	24	21		16	19	24	24
Total	112	100.0		108	112	93	107

Table 8. 'Other' single gene tests in Victorian women under 25 weeks gestation

Alkaline phosphatase deficiency	Metabolic disease not spec.
Barth syndrome	Mucopolysaccharidosis Type IIIB
Carbohydrase deficient glycoprotein Type IA	Polycystic kidney disease
Carnithine acylcarnitine translocase deficiency	Retinoblastoma
Cavernous angiomas	Rett syndrome
Fanconi's anaemia	Ryanodine receptor Type I
Fascioscapulohumeral muscular dystrophy	Schwachman Diamond syndrome
Fibroblast growth factor receptor disorder	Tay Sachs
Hereditary sensory neuropathy	Tuberous sclerosis
Hypophosphatasia	Wolman's disease
Leigh syndrome	X-linked hypopituitarism
Marfan syndrome	Zellweger's

4.7 HISTORY OF NEURAL TUBE DEFECT

Two women had a prenatal diagnostic test by AMN because of a history of neural tube defects.

One of these tests was performed because of a previous fetus with spinal abnormalities and one test was done following previous non-specified neural tube defects.

The number of tests done for a history of neural tube defects has been low, with five tests done for that reason in 2003 and 2002 and four in 2001.

4.8 OTHER WITHIN HGSA/RANZCOG RECOMMENDATIONS

Eight prenatal diagnostic tests were performed for other indications within the HGSA/RANZCOG recommendations.

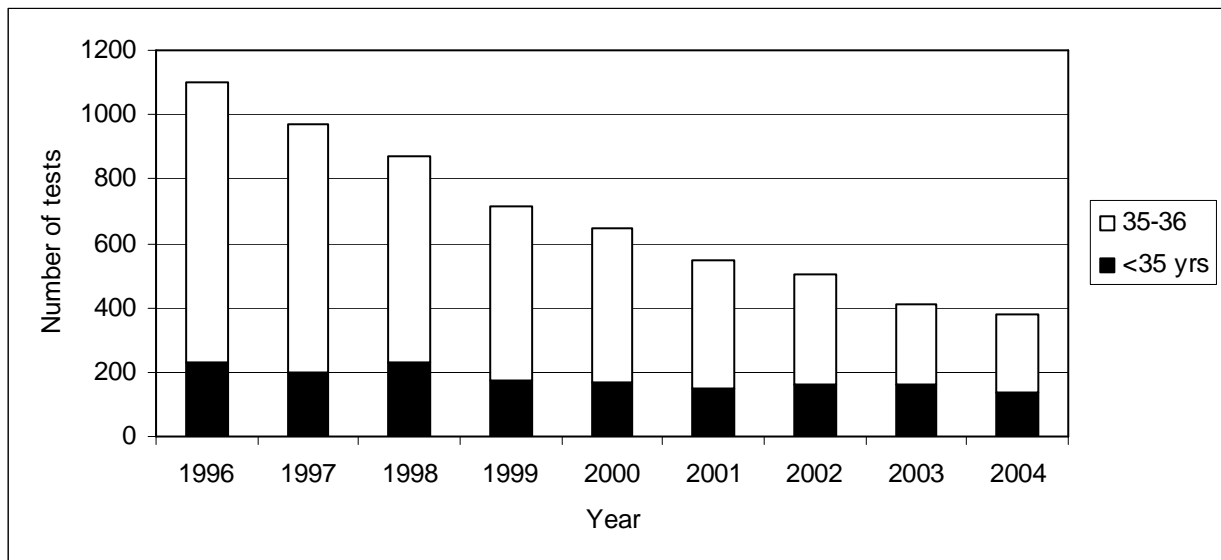
These included positive maternal serology for Cytomegalovirus or Toxoplasmosis, exposure to a teratogen and anti-Kell antibodies.

4.9 OUTSIDE HGSA/RANZCOG RECOMMENDATIONS

The majority of the 380 women with an indication outside the HGSA/RANZCOG recommendations were in the 35-36 year age group (64.7%). The indication given was *Age* or *Anxiety* for 95% of this group and for 85% of women under 35 years. The remaining indications related to paternity testing, family history of Trisomy 21 or previous non-chromosomal abnormalities.

The number of tests done for indications outside the HGSA/RANZCOG recommendations has dropped steadily since 1996, with 1099 tests done for that reason in 1996 and 380 tests done in 2004. Figure 6 shows that indications outside HGSA/RANZCOG recommendations decreased mainly in women aged 35-36 years. This decline may be explained by the increased utilisation of prenatal screening in women under 37 years.

Figure 6. Indications outside HGSA/RANZCOG recommendations for Victorian women under 37 years and under 25 weeks gestation



5. FETAL KARYOTYPES

5.1 OVERVIEW

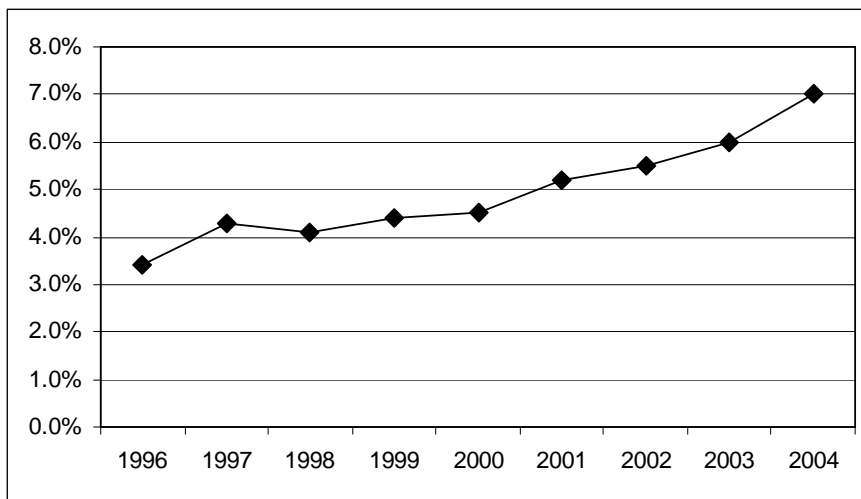
3989 (91.2%) of CVS and AMN had a normal fetal karyotype. An additional 69 (1.6%) showed a minor non-clinically significant variation in fetal karyotype. This group of variations was not expected to result in an abnormal fetal outcome. Five CVS or AMN were not karyotyped because a single gene test was the reason for testing or because FISH was the only test performed. (Table 9).

Table 9. Summary data on all fetal karyotypes for Victorian women tested at under 25 weeks gestation

Fetal karyotype	CVS	AMN	Total	%
Normal				
Normal	1379	2610	3989	91.2%
No growth/not done	4	2	5	0.1%
Minor abnormalities				
Confined placental mosaicism (CPM)	14		14	0.3%
Balanced rearrangement	9	25	34	0.8%
Balanced translocation	9	12	21	0.5%
<i>Total minor abnormalities</i>	69	37	69	1.6%
Major abnormalities				
Autosomal aneuploidy:				
Trisomy 21	78	64	142	3.2%
Trisomy 18	35	21	56	1.3%
Trisomy 13	8	7	15	0.3%
Other trisomy	1		1	0.02%
Polyploidy	11	4	15	0.3%
Sex chromosome aneuploidy:				
45,X	18	7	25	0.6%
47,XXX	2	2	4	0.1%
47,XXY	4	1	5	0.1%
47,XYY		1	1	0.02%
Fragile X	1		1	0.02%
Unbalanced rearrangement	5	7	12	0.3%
Microdeletion syndrome (22q)	1		1	0.02%
Level III Mosaicism	13	17	30	0.7%
<i>Total major abnormalities</i>	177	131	308	7.0%
<i>% abnormal of procedure</i>	11.1%	4.7%	7.0%	
Total	1593	2779	4372	100.0%

308 (7.0%) of pregnancies tested were found to have a major abnormality. This compares with 292 (6.0%) in 2003, 272 (5.5%) in 2002 and 254 (5.2%) in 2001. A greater proportion of all CVS were found to have a major abnormality (11.1%), compared with the proportion of all AMN (4.7%).

Figure 7. Proportion of diagnostic tests with a major karyotype abnormality.
1996-2004



Trisomy 21 accounted for 46% of these abnormalities, Trisomy 18 for 18% and Trisomy 13 for 5%. More detailed information on the detection of autosomal trisomies is available in section 6.0 of this report. Other abnormalities included 15 polyploidies, 36 sex chromosome abnormalities (including one fragile X), 30 Level III mosaicisms and 13 unbalanced rearrangements (including one 22q deletions).

5.2 ADVANCED MATERNAL AGE AS THE ONLY INDICATION

48 or 2.7% of 1781 diagnostic procedures following an indication of advanced maternal age only were found to have a chromosomal abnormality, 40.1% of which were done by CVS (Table 10).

Across all age groups, 30 of the abnormal karyotypes were trisomies (62.5%), the highest proportion of which was in women aged 40 and over.

Table 10. Maternal age as only indication and fetal karyotype outcome by maternal age group and procedure for Victorian women under 25 weeks gestation

	CVS	AMN	Total	% in age group
37-39 years	336	595	931	
Normal/minor abnormality	328	585	913	98.1%
Trisomy 21	3	4	7	} 0.95%
Trisomy 18	1	1	2	
Other Trisomy				
Other chromosomal	4	5	9	0.95%
<i>Sub-total major abnormal</i>	8	10	18	1.9%
40+ years	379	471	850	
Normal/minor abnormality	364	456	820	96.4%
Trisomy 21	7	12	19	} 2.5%
Trisomy 18	1		1	
Other Trisomy	1		1	
Other chromosomal	6	3	9	1.1%
<i>Sub-total major abnormal</i>	15	15	30	3.6%
Total major abnormal	23	25	48	
<i>% of all AGE only abnormalities</i>	47.9%	52.1%	100%	
<i>% abnormal of procedure</i>	3.2%	2.3%	2.7%	
Total	715	1066	1781	

5.3 AFTER ABNORMAL ULTRASOUND

The majority of the 626 pregnancies with an abnormal ultrasound indication had a normal fetal karyotype (76.2%) or a minor non-clinically significant fetal karyotype outcome (1.3%). 22.5% of the tests were found to have a major abnormality, compared to 16.4% in 2003. A greater proportion of abnormalities was detected by CVS (56.7%) (Table 11).

The majority of abnormalities detected following an abnormal ultrasound were in women 37 years and over (Table 12). Trisomies were diagnosed in 32.2% of women aged 37 years and over, compared to 25.3% for women aged 35-36 years and 6.3% in the youngest age group. This represents a substantial increase in detection rate from 2003 when 25% and 11% of tests diagnosed a trisomy in the two older age groups

Table 11. Abnormal ultrasound and fetal karyotype outcome by procedure for Victorian women under 25 weeks gestation

Fetal karyotype	CVS	AMN	Total	%
Normal/minor abnormality				
Normal	104	373	477	76.2%
Balanced rearrangement or translocation	3	23	6	1.0%
CPM	2		2	0.3%
Total normal or minor abnormal	109	396	505	77.5%
Major abnormalities				
Autosomal aneuploidy:				
Trisomy 21	26	14	49	7.8%
Trisomy 18	19	7	33	5.3%
Trisomy 13	5	3	12	1.9%
Polyploidy	9	3	12	1.9%
Sex chromosome aneuploidy:				
45,X	16	6	22	3.5%
47,XXX	1		1	0.2%
Unbalanced rearrangement or translocation	2	5	7	1.1%
Microdeletion syndrome (22q)	1		1	0.2
Mosaic Level III	1	3	4	0.6%
Total major abnormal	80	61	141	22.5%
% of all ultrasound abnormalities	56.7%	43.3%	100%	
% abnormal of procedure	42.3%	14.0%		
Total	189	437	626	100.0%

Table 12. Abnormal ultrasound and fetal karyotype outcome by maternal age group for Victorian women under 25 weeks gestation

	Increased nuchal thickness	Other abnormal ultrasound	Total	% in age group
≥37 years (AMA)	73	79	152	
Normal/minor abnormality	44	51	95	62.5%
Trisomy 21	16	7	23	} 32.2%
Trisomy 18	9	12	21	
Trisomy 13	1	4	5	
Other chromosomal	3	5	8	5.3%
<i>Sub-total major abnormal</i>	29	28	57	37.5%
35 – 36 years	35	44	79	
Normal/minor abnormality	25	28	53	67.1%
Trisomy 21	8	5	13	} 25.3%
Trisomy 18	1	4	5	
Trisomy 13		2	2	
Other chromosomal	1	5	6	7.6%
<i>Sub-total major abnormal</i>	10	16	26	32.9%
<35 years	105	290	395	
Normal/minor abnormality	95	242	337	85.3%
Not done/no growth				
Trisomy 21	3	10	13	} 6.3%
Trisomy 18		7	7	
Trisomy 13		5	5	
Other chromosomal	7	26	33	8.4%
<i>Sub-total major abnormal</i>	9	48	57	14.4%
Total major abnormal	48	92	140	
<i>% abnormal of ultrasound indication</i>	22.5%	22.3%	22.4%	
Total	213	413	626	

5.4 AFTER INCREASED RISK SECOND TRIMESTER MATERNAL SERUM SCREEN (2TMSS)

5.0% of the 624 procedures done following an increased risk 2TMSS were found to have a chromosomal abnormality, compared to 3.2 of 759 in 2003.

22 or 71% of the abnormalities found after an increased risk 2TMSS were trisomies. The highest proportion of trisomies was found in women aged 37 and over, with nine diagnoses (5.4%) in the 166 women tested.

Table 13. Increased risk second trimester maternal serum screen and karyotype outcome by maternal age and procedure for VIC women under 25 weeks gestation

	CVS	AMN	Total	% in age group
≥37 years	1	165	166	
Normal/minor abnormality	1	156	157	94.6%
Trisomy 21		8	8	} 5.4%
Trisomy 18		1	1	
Other Trisomy				
Other chromosomal				
<i>Sub-total major abnormal</i>		9	9	5.4%
35 – 36 years		102	102	
Normal/minor abnormality (incl. 1 not karyotyped)		98	98	96.1%
Trisomy 21		2	2	} 2.0%
Trisomy 18				
Other Trisomy				
Other chromosomal		2	2	2.0%
<i>Sub-total major abnormal</i>		4	4	4.0%
<35 years		356	356	
Normal/minor abnormality		338	338	94.9%
Trisomy 21		7	7	} 3.1%
Trisomy 18		4	4	
Other Trisomy				
Other chromosomal		7	7	2.0%
<i>Sub-total major abnormal</i>		18	18	5.1%
Total major abnormal		31	31	
<i>% of all MSS abnormalities</i>		100%	100%	
<i>% abnormal of procedure</i>		5.0%		
Total	1	623	624	

5.5 AFTER INCREASED RISK FIRST TRIMESTER COMBINED SCREEN (1TCS)

88 or 12.8% of 603 diagnostic procedures following an increased risk 1TCS were found to have a chromosomal abnormality, 85.2% of which were done by CVS (Table 14).

Across all age groups, 68 of the abnormal karyotypes were trisomies (77.3%), the highest proportion of which was in women aged 37 and over.

Table 14. Increased risk first trimester combined screen and fetal karyotype outcome by maternal age group and procedure for Victorian women under 25 weeks gestation

	CVS	AMN	Total	% in age group
≥37 years	171	145	316	
Normal/minor abnormality	130	140	270	85.4%
Trisomy 21	28	1	29	} 12.7%
Trisomy 18	9	1	10	
Trisomy 13	1		1	
Other chromosomal	3	3	6	1.9%
<i>Sub-total major abnormal</i>	41	5	46	14.6%
35 – 36 years	79	64	144	
Normal/minor abnormality	61	61	122	84.7%
Trisomy 21	5	3	8	} 7.6%
Trisomy 18	3		3	
Trisomy 13				
Other chromosomal	6		6	4.2%
<i>Sub-total major abnormal</i>	14	3	17	11.8%
<35 years	117	113	230	
Normal/minor abnormality	97	108	205	89.1%
Not done/no growth				
Trisomy 21	7	5	12	} 7.4%
Trisomy 18	3		3	
Trisomy 13	2		2	
Other chromosomal	8		8	3.5%
<i>Sub-total major abnormal</i>	20	5	25	10.9%
Total major abnormal	75	13	88	
<i>% of all FTC abnormalities</i>	85.2%	14.8%	100%	
<i>% abnormal of procedure</i>	20.6%	4.0%	12.8%	
Total	364	322	686	

5.6 AFTER HISTORY OF CHROMOSOMAL ABNORMALITY

5.6.1 History of chromosomal aneuploidy

Of the 132 women tested because of a known history of chromosome aneuploidy, two women who had a previous Trisomy 21 pregnancy and one woman with an unspecified previous chromosomal abnormality were found to have a fetus with Trisomy 21 (Table 15).

Detailed information on the previous chromosomal abnormality was not available for 53% in this category. Therefore we were unable to estimate a Trisomy 21 recurrence rate from this data set.

Table 15. Fetal karyotype outcome for Victorian women under 25 weeks gestation when there is a history of chromosome aneuploidy

Previous abnormality	Normal/minor abnormal		Abnormal outcome		Total	%
	CVS	AMN	CVS	AMN		
Unspecified	29	39, 1 BR	1 T21		70	53.1%
Trisomy 21	28, 1 CPM	7	2 T21		38	28.8%
Trisomy 18	8	3			11	8.3%
Trisomy 13	3	1			4	3.0%
Sex chromosome aneuploidy	4		1 LIII		5	3.8%
Other major chromosome	2	2			4	3.0%
Total	75	53	5		132	100%

CPM: Confined placental mosaicism
 BT: Balanced rearrangement
 LIII: Level III mosaicism
 T21: Trisomy 21

5.6.2 Previous chromosomal translocation or other rearrangement

39 women were tested because of a family history of chromosome translocation or rearrangement. 18 of these tests showed fetal karyotypes with balanced translocations or rearrangements (56.0%) and one (2.6%) with a major abnormality (ie 22q microdeletion syndrome) (Table 16).

Table 16. Fetal karyotype outcome for Victorian women under 25 weeks gestation when there was a previous chromosomal translocation or other rearrangement, and/or parents are carriers

Previous fetal karyotype or parental carrier	Normal/minor abnormal		Abnormal outcome		Total	%
	CVS	AMN	CVS	AMN		
Translocation	5N / 7BT / 1BR	9N / 6BT / 4BR				
<i>Sub-total</i>	13	19			32	82.1%
Rearrangements (deletions, inversions, etc)	4N / 1BT	1N	1 22Q			
<i>Sub-total</i>	5	1	1		7	17.9%
Total	18	20	1		39	100%

N: Normal
 BR: Balanced rearrangement
 BT: Balanced translocation
 22Q: 22q Microdeletion

5.7 AFTER HISTORY OF NEURAL TUBE DEFECT

Of the two women who had a prenatal diagnostic test by AMN because of a history of neural tube defects both had a normal fetal karyotype.

5.8 OTHER WITHIN HGSA/RANZCOG RECOMMENDATIONS

Of the eight prenatal diagnostic tests done for other indications within the HGSA/RANZCOG recommendations, all had a normal fetal karyotype.

5.9 OUTSIDE HGSA/RANZCOG RECOMMENDATIONS

There were four (1.6%) abnormal outcomes amongst the 246 women aged 35-36 years who were tested for reasons outside the HGSA/RANZCOG recommendations. In women under 35 years, three of 134 tested women had a fetal karyotype abnormality (2.2%) (Table 17).

Table 17. Fetal karyotype outcome for Victorian women under 25 weeks gestation if indication outside HGSA/RANZCOG recommendations

Outside HGSA/RANZCOG recommendations	Normal/minor abnormal		Abnormal outcome		Total	%
	CVS	AMN	CVS	AMN		
35-36 years						
Age/anxiety	83N / 1CPM	144N / 2BT	1 SA 1 LIII	1 SA 1T21	234	
Family history of T21	2N	2N			4	
Other	2N	6N			8	
<i>Sub-total</i>	88	154	2	2	246	64.7%
<35 years						
Age/anxiety	37N	73N / 1BT	1T21 1T18	1LIII	114	
Family history of T21	2N	3N			5	
Other	8N	7N			15	
<i>Sub-total</i>	47	84	2	1	134	35.3%
Total	135	238	4	3	380	100%

N: Normal

BT: Balanced translocation

BR: Balanced rearrangement/translocation

CPM: Confined placental mosaicism

LIII:

SA:

T21:

T18:

Level III mosaicism

Sex chromosome aneuploidy

Trisomy 21

Trisomy 18

6. AUTOSOMAL TRISOMIES

In 2004, prenatal diagnostic tests before 25 weeks of gestation resulted in the diagnosis of 142 Trisomy 21, 56 Trisomy 18, 15 Trisomy 13 and one Trisomy 22. In addition, one Trisomy 21 was diagnosed at 37 weeks and one Trisomy 18 at 40 weeks (*see 8. Indication and fetal karyotype outcome for Victorian women over 24 weeks of gestation*).

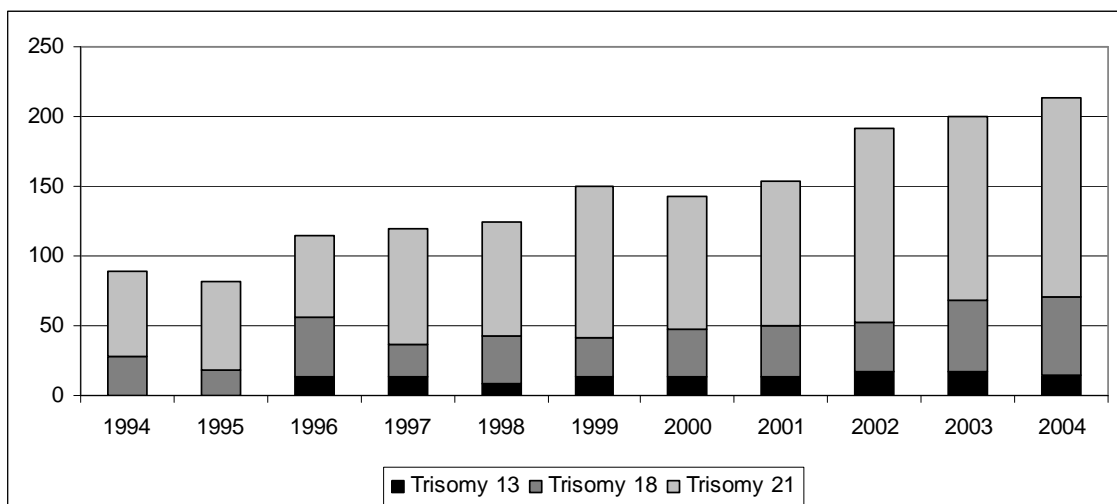
One of the karyotypes classified as Trisomy 21 also had a sex chromosome aneuploidy and a balanced translocation.

In this section we present detailed information on the more common Trisomies 21, 18 and 13, diagnosed before 25 weeks of gestation.

54.9% of Trisomies 21, 62.5% of Trisomies 18 and 53.3% of Trisomies 13 were diagnosed following CVS.

Figure 8 shows that the number of trisomies diagnosed prenatally has more than doubled since 1994 and continues to increase. This was mainly due to an increasing rate of Trisomy 21 diagnoses until 2003, when the contribution of Trisomy 18 findings started to rise.

Figure 8. Autosomal trisomies diagnosed in Victorian women under 25 weeks gestation



Tables 18, 19 and 20 present Trisomies 21, 18 and 13 respectively, by indication.

The majority of Trisomies were detected by prenatal diagnosis following an increased risk prenatal screening test result. Only 28 of the 142 Trisomies 21 diagnosed (19.7%) had no prior increased risk screening test result reported and three were recurrences in women 40 years or over (Table 18).

Similarly, in the diagnosis of Trisomy 18 and Trisomy 13, the most common indication was an increased risk screening test result (92.9% and 100% respectively), with fetal abnormality on ultrasound (other than increased nuchal thickening) accounting for 37.5% and 73.3% (Tables 19 and 20 respectively).

Table 18. Trisomy 21 detected by prenatal diagnosis in Victorian women under 25 weeks gestation, grouped by age and indication

Indication	Age	CVS				AMN				Total	%
		<35	35-36	37-39	≥40	<35	35-36	37-39	≥40		
Increased nuchal thickness		3	5	5	7		3	3	1	27	19.0%
First trimester combined screening		7	3	14	10	5	3		1	43	30.3%
Second trimester maternal serum screen			2		4	7	2	3	5	23	16.2%
Other ultrasound abnormality		1	2	1	0	8	3	2	1	18	12.7%
Previous chromosomal abnormality					3					3	2.1%
No screening test, prompted by anxiety or age alone		1		3	7		1	4	12	28	19.7%
Total		12	12	23	31	20	12	12	20	142	100%

Table 19. Trisomy 18 detected by prenatal diagnosis in Victorian women under 25 weeks gestation, grouped by age and indication

Indication	Age	CVS				AMN				Total	%
		<35	35-36	37-39	≥40	<35	35-36	37-39	≥40		
Increased nuchal thickness			1	3	6					10	17.9%
First trimester combined screening		3	3	1	7				1	15	26.8%
Second trimester maternal serum screen				1		4			1	6	10.7%
Other ultrasound abnormality				3	4	6	4	2	2	21	37.5%
No screening test, prompted by anxiety or age alone		1		1	1			1		4	7.1%
Total		4	4	9	18	10	4	3	4	56	100%

Table 20. Trisomy 13 detected by prenatal diagnosis in Victorian women under 25 weeks gestation, grouped by age and indication

Indication	Age	CVS				AMN				Total	%
		<35	35-36	37-39	≥40	<35	35-36	37-39	≥40		
Increased nuchal thickness				1						1	6.7%
First trimester combined screening		2	1							3	5.4%
Other ultrasound abnormality		2		1	1	3	2	1	1	11	73.3%
Total		4	1	2	1	3	2	1	1	15	100%

7. REPEAT TESTS AND FETAL KARYOTYPES

35 (0.8%) prenatal diagnostic tests were repeated.

20 of the repeat tests were AMN done to clarify a LIII mosaic found on CVS. For 14 of these, the mosaicism was confined to the placenta (CPM), including one which also had a confirmed balanced translocation. Five were confirmed as LIII mosaic and one was found to be a Trisomy 21.

One Trisomy of chromosome 16 and three polyploidies on CVS were found to be normal on repeat AMN. One Trisomy of chromosome 22 was identified as a Level III mosaicism on repeat and one XXX female karyotype was confirmed on repeat.

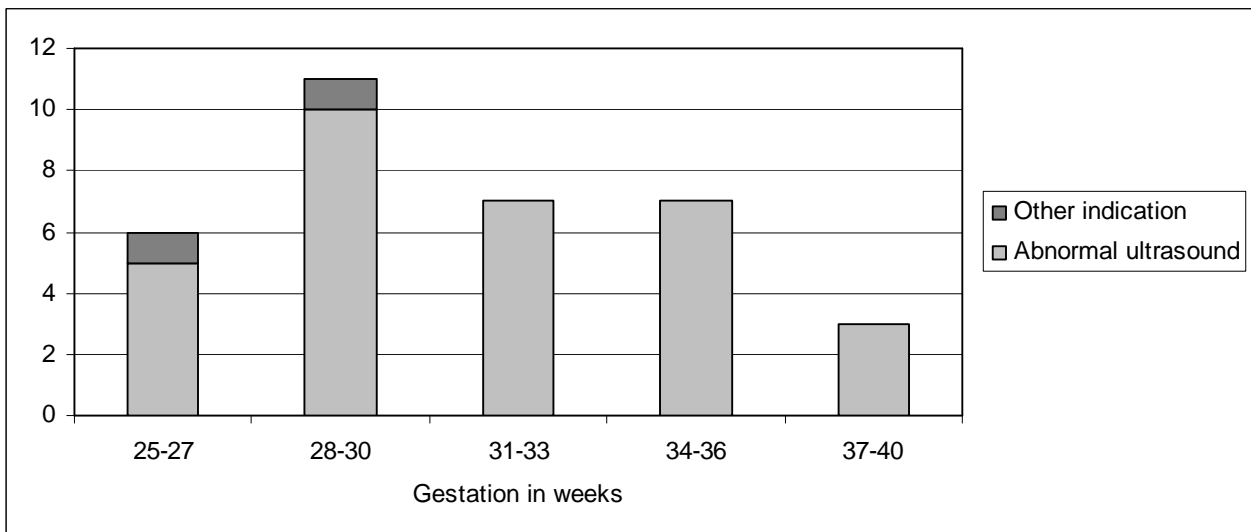
One ambiguous CVS was confirmed as a Trisomy 21 and one as Turner syndrome (45,X).

Six apparently normal karyotypes on CVS were confirmed as normal.

8. INDICATION AND FETAL KARYOTYPES FOR WOMEN OVER 24 WEEKS OF GESTATION

34 women had a late (over 24 weeks gestation) prenatal diagnosis, four of which were done by CVS at 26, 30, 33 and 35 weeks.

Figure 9. Prenatal diagnosis for Victorian women over 24 weeks gestation by gestational age and indication



32 (94.1%) of these tests were done because of an abnormal ultrasound and all but four were done in women under 37 years (Figure 9). Other indications included one test done for anxiety and paternity testing at 30 weeks and one test for iso-immunisation at 25 weeks gestation.

Four abnormal karyotypes were found in this category (11.8%), one Trisomy 21, one Trisomy 18 and two unbalanced rearrangements. All abnormal outcomes followed an abnormal ultrasound at 28, 33, 37 and at 40 weeks gestation (Table 21).

Table 21. Fetal karyotype outcome for Victorian women over 24 weeks gestation

Gestation (weeks)	Normal outcome	Abnormal outcome (All with indication of abnormal ultrasound)	Total
25 - 27	6		6
28 - 30	10	1 UBR	11
31 - 33	6	1 UBR	7
34 - 36	7		7
37 - 40	1	1 T18 / 1 T21	4
Total	30	4	34
% total	88.2%	11.8%	100%

T18: Trisomy 18

T21: Trisomy 21

UPR: Unbalanced rearrangement

9. FLUORESCENT IN SITU HYBRIDISATION (FISH) FOR ANEUPLOIDY

FISH analysis is a molecular test, which uses fluorescence-labelled DNA probes to detect the presence or absence of specific chromosomes or chromosome regions. Currently, FISH analysis is mainly performed to detect autosomal trisomies and sex chromosome aneuploidies. Although all samples are also karyotyped in the traditional manner, the advantage of this test is that a result is usually available within one or two days.

Since its introduction in 1999, there has been a marked increase in use of FISH for chromosome analysis from 427 FISH in 2000 to 2420 tests in the year 2003 and 2331 in 2004. This corresponds to approximately 50% of all CVS or AMN in the two most recent years.

The percentage of FISH done in each age group (Table 22) is similar to the overall distribution of diagnostic tests across all ages, with a slightly higher use of FISH for tests done on women under the age of 35 (35.5% FISH vs 28.5% of all tests).

Table 22. FISH for Victorian women under 25 weeks gestation, by maternal age and procedure

Age group (years)	CVS	% total	AMN	% total	Total	% Total FISH
<35	233		572		805	35.5%
35-36	148		216		364	15.6%
37-39	255		321		576	24.8%
≥40	317		269		586	24.1%
Total	953	40.9%	1378	59.1%	2331	100.0%

Of the 2331 FISH done, 28.4% followed an indication of advanced maternal age and 59.4% had a prior increased risk screening test as indication for testing. 7.6% of FISH were requested in women under the age of 37 years for reasons outside the HGSA/RANZCOG guidelines (Table 23).

Table 23. FISH for Victorian women under 25 weeks gestation, by indication for testing and procedure

Indication	CVS	AMN	Total	% Total
AMA	324	339	663	28.4%
Ultrasound	151	336	487	20.9%
MSS	1	364	365	15.7%
FTC	323	207	530	22.8%
Previous chromosomal abnormality	49	20	69	3.0%
History rearrangement/translocation	7	1	8	0.3%
Single gene test	27	2	29	1.2%
Other within guidelines		3	3	0.1%
Outside guidelines	71	106	177	7.6%
Total	953	1378	2331	100.0%

Results of FISH are not collected in our database, however Table 24 provides karyotype outcomes for all tests that included FISH. 10.6% of tests that included FISH were found to have an abnormal karyotype. This proportion is higher than the overall proportion of abnormal karyotypes in all tests done in 2003 (7.0%). This may be the result of the high proportion of FISH requested following an increased risk screening test result (59.4% vs 44.0% across all tests).

Table 24. FISH for Victorian women under 25 weeks gestation, by karyotype outcome and procedure

Indication	CVS	AMN	Total	% Total
Normal/minor abnormality	791	1292	2083	89.4%
Not done/no growth		1	1	
Trisomy 21	73	39	112	
Trisomy 18	35	18	53	
Other trisomy	9	6	15	
Polyploidy	11	6	17	
Sex chromosome abnormality	20	4	24	
Unbalanced rearrangement (incl.22q)	4	4	8	
Level III mosaic	10	8	18	
Total major abnormal	162	85	247	10.6%
<i>% abnormal of procedure</i>	17.0%	6.2%	10.6%	
Total	953	1378	2331	

10.0 INTERSTATE SAMPLES

Victorian cytogenetics laboratories analysed 243 CVS and AMN sent in from interstate or overseas in 2004. The majority of samples came from Tasmania (60.9%) and New South Wales (35.4%) (Table 25). The majority of NSW samples came from women residing on the Victorian border who may have given birth in Victoria.

Table 25. Interstate samples by state and maternal age group

Age group (years)	NSW	QLD	WA	TAS	NT	International	Total
<35	38	3	1	71	0		113
35-36	10	1		18			29
37-39	21	2		32	1	1	57
≥40	17	0		26			43
Unknown				1			1
Total	86	6	1	148	1		243
<i>%Total</i>	<i>35.4%</i>	<i>2.5%</i>	<i>0.4%</i>	<i>60.9%</i>	<i>0.4%</i>	<i>0.4%</i>	<i>100%</i>

Of the 243 interstate samples done, the majority were done for an increased risk screening test result (58.9%) and only 24.7% were for advanced maternal age alone. 7.0% of interstate samples were on women under the age of 37 years for reasons outside the HGSA/RANZCOG guidelines (Table 26).

Table 26. Interstate samples by state and indication for testing

Indication	NSW	QLD	WA	TAS	NT	International	Total	<i>% Total</i>
AMA	29	1		30			60	24.7%
Ultrasound	10			19			29	11.9%
MSS	20	1		27			48	19.8%
FTC	15	2		49			66	27.2%
Previous chromosomal abnormality	1			2	1		4	1.6%
Single gene test	2			11			13	5.3%
History translocation/rearrangement	2			2		1	5	2.1%
Outside guidelines	7	1	1	8			17	7.0%
Repeat		1					1	0.4%
Total	86	6	1	148	1	1	243	100.0%

7.0% of tests originating from interstate were found to have an abnormal karyotype. The tests included a further six Trisomy 21 diagnoses, two in samples from New South Wales, one from Queensland and three from Tasmania (Table 27).

Table 27. Interstate samples by state and karyotype outcome

Indication	NSW	QLD	WA	TAS	NT	International	Total
Normal/minor abnormality	82	5	1	136	1	1	226
Not done/no growth				1			1
Trisomy 21	2	1		3			6
Trisomy 18	1			1			2
Sex chromosome abnormality	1			2			3
Level III mosaic				5			5
Total major abnormal	4	1		12			17
<i>% abnormal</i>	4.7%	16.7%	0%	8.1%	0%	0%	7.0%
Total	86	6	1	148	1	1	243

