

REPORT ON
PRENATAL DIAGNOSTIC TESTING
IN VICTORIA 2003

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1. KEY FINDINGS

- 1** The total number of prenatal diagnostic tests done in 2003 was 4898. Historically, the total number of prenatal diagnostic tests steadily increased since 1992, reaching a peak with 5310 tests in 1998. However, there was a substantial decline in the number of all CVS and AMN in 2001 (n=4854) and utilisation of prenatal diagnosis has not significantly varied since then. **Pages 8 & 9**
- 2** In 2003, less than half (41.7%) of all prenatal diagnostic tests were done for advanced maternal age as the only indication for testing. 43% of diagnostic tests were done because of an abnormal screening test result whereas in 1996, before screening became widely available, only 14% were in this indication group. **Pages 12 & 14**
- 3** 833 women had prenatal diagnosis following an abnormal ultrasound, either suspected fetal anomaly on routine ultrasound or increased nuchal thickening (when not as part of first trimester combined screening). This represents 17.0% of all tests. 74% of these women were under 37 years of age. **Pages 14 & 15**
- 4** 29.5% of CVS following an abnormal ultrasound were found to have a major chromosomal abnormality, and 9.7% of AMN. 55% of abnormal karyotypes detected in this group were associated with increased nuchal thickening. **Pages 23-25**
- 5** 1366 women had prenatal diagnosis for an increased risk maternal serum screen from just over 500 in 1999 to 934 in 2002. This year, the report distinguishes between first trimester combined screening (FTC) and second trimester maternal serum screen (MSS) with 603 or 12.3% of tests prompted by FTC and 763 or 15.6% of tests following an increased risk MSS. **Pages 16 & 17**
- 6** The majority of women having prenatal diagnosis following MSS were under 37 years of age (74.7%) whereas women having a test following FTC were equally distributed across both age groups. **Pages 16 & 17**
- 7** Using information from Genetic Health Services Victoria, we estimate that there were 32836 women who had maternal serum screening (either first **Page 16**

trimester combined or second trimester serum) in 2003. This corresponds to a diagnostic follow-up rate of 4.2%.

- 8** A fetal chromosome abnormality was detected in 3.2% of pregnancies tested for an increased risk MSS, and in 12.9% of tests for increased risk FTC. Trisomies accounted for 75.0% of these abnormalities after MSS and 74.4% after FTC. **Pages 26 & 27**
- 9** The number of tests done for indications outside the HGSA/RANZCOG recommendations has more than halved since 1996, with 409 tests done in 2003. Indications outside HGSA/RANZCOG decreased mainly in women aged 35-36 years. This decline may be explained by the increased utilisation of FTC or MSS in women under 37 years of age. **Page 21**
- 10** Of all Victorian women who had chorionic villus sampling (CVS) or amniocentesis (AMN) in 2003, 93% had a fetus with a normal karyotype and 6.0% of tested pregnancies were found to have a major fetal karyotype abnormality. 9.5% of all CVS detected a chromosomal abnormality, compared with 3.9% of AMN. **Page 22**
- 11** Trisomy 21 accounted for just under half of all abnormal fetal karyotypes, with 132 diagnosed prenatally in 2003. For the majority of tests with a diagnosis of Trisomy 21, the major indication was an increased risk screening test result (82.6%). FTC accounted for 35.6%, MSS for 12.2%, second trimester routine ultrasound for 8.3% and increased nuchal thickening was associated with 26.5%. **Pages 31-33**

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, July, 2001) 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 currently 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.

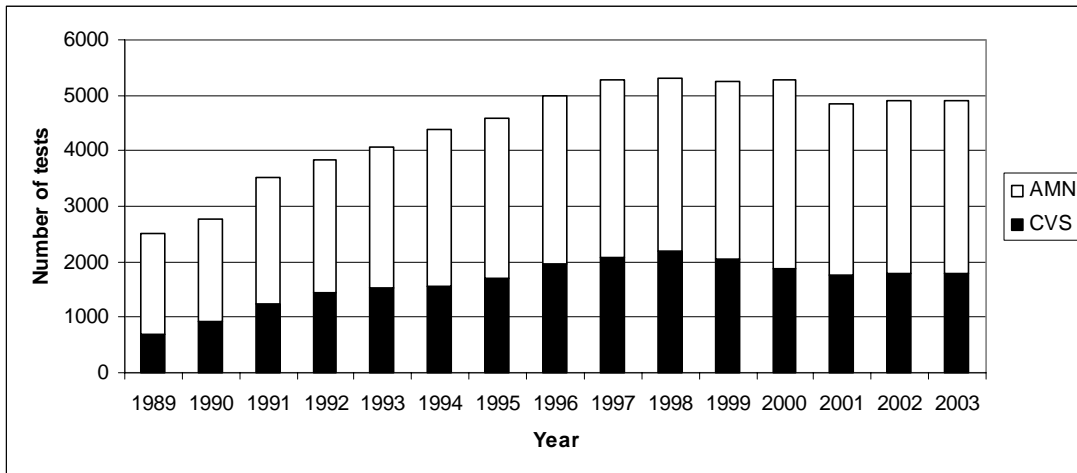
3. UTILISATION OF PRENATAL DIAGNOSTIC TESTS

3.1 NUMBER OF TESTS

The number of prenatal diagnostic tests analysed by Victorian laboratories in 2003 was 5219. 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 228 samples from women living interstate, 30 repeat samples, 59 late gestation tests, four fetal blood, urine or ascites analyses.

In 2003, 4898 pregnant Victorian women had a CVS (1793) or an AMN (3105) 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



The last three years have seen a decline in the number of Victorian women having prenatal diagnosis by CVS or AMN of approximately 10% when compared to previous years. Table 1 shows that this decline in numbers was mainly due to a fall in the number of CVS beginning in 1999 until 2001, when there was also a drop of nearly 300 in the number of 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%

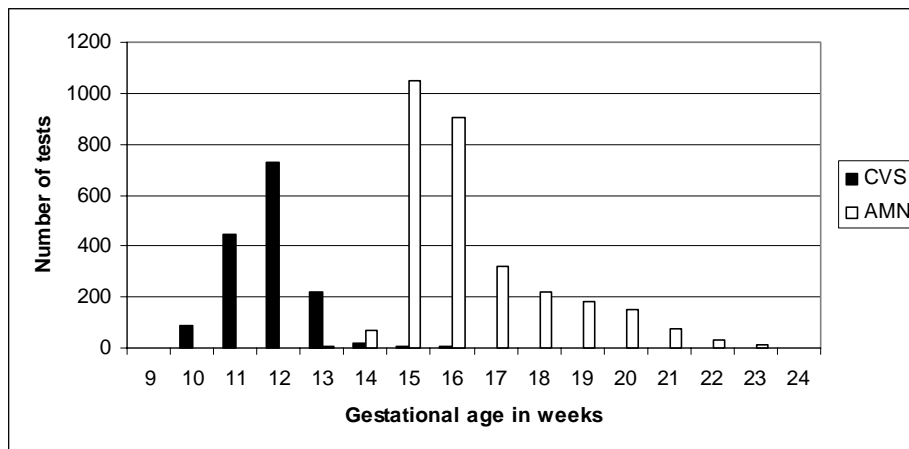
3.2 GESTATIONAL AGE

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 2003 data, there were 338 missing gestations (7%).

For CVS the recorded gestational ages ranged from 8-22 weeks with a median of 12 weeks when 48% of these tests were performed. For AMN, the reported gestational ages ranged from 12-24 weeks with a median of 16 weeks when 30% 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 338 records with missing gestational ages in the main body of the report, assuming the diagnostic test was done before 25 weeks of gestation.

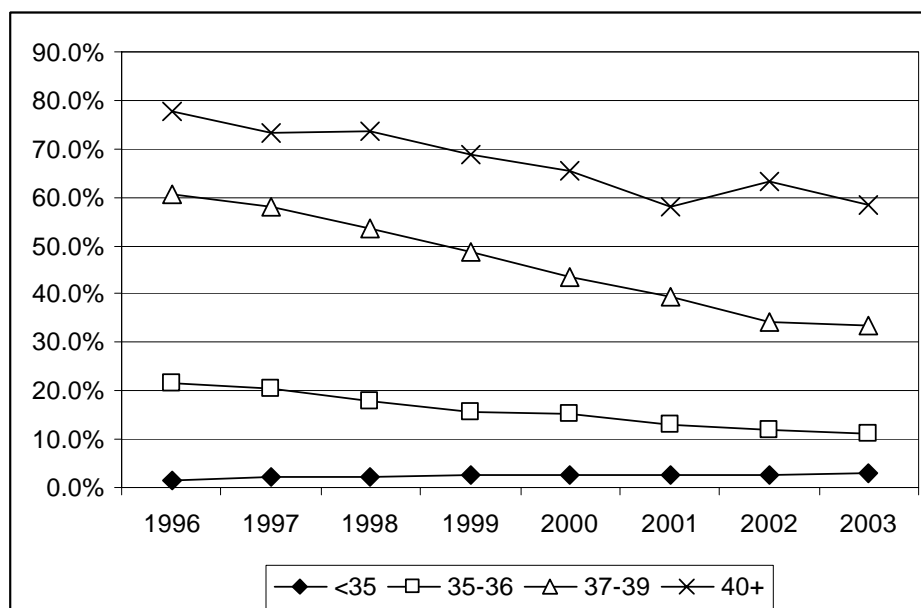
3.3 UTILISATION

At the time of writing the report, the 2003 birth file for Victoria from the Perinatal Data Collection Unit, the Department of Human Services, was not available. The total number of confinements in Victoria has remained relatively stable over the last ten years. Therefore, we present here comparison data for 2002 and 2003 which demonstrates little change between the two years (Table 2). Assuming there has been no decline in the number of older women having babies, utilisation remains on the decline in this group and on the increase in women under the age of 35 (Figure 3).

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

	Confinements	CVS		AMN		Total	
Age group (years)	2002 data	2002	2003	2002	2003	2002	2003
<35	49234	389	423	886	1006	1275	1429
35-36	5810	237	237	452	417	689	654
37-39	4902	622	633	1056	1006	1678	1639
≥40	2013	528	500	744	676	1272	1176
Total	61959	1776	1793	3138	3105	4914	4898

Figure 3. Utilisation of prenatal diagnostic testing in Victoria



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.

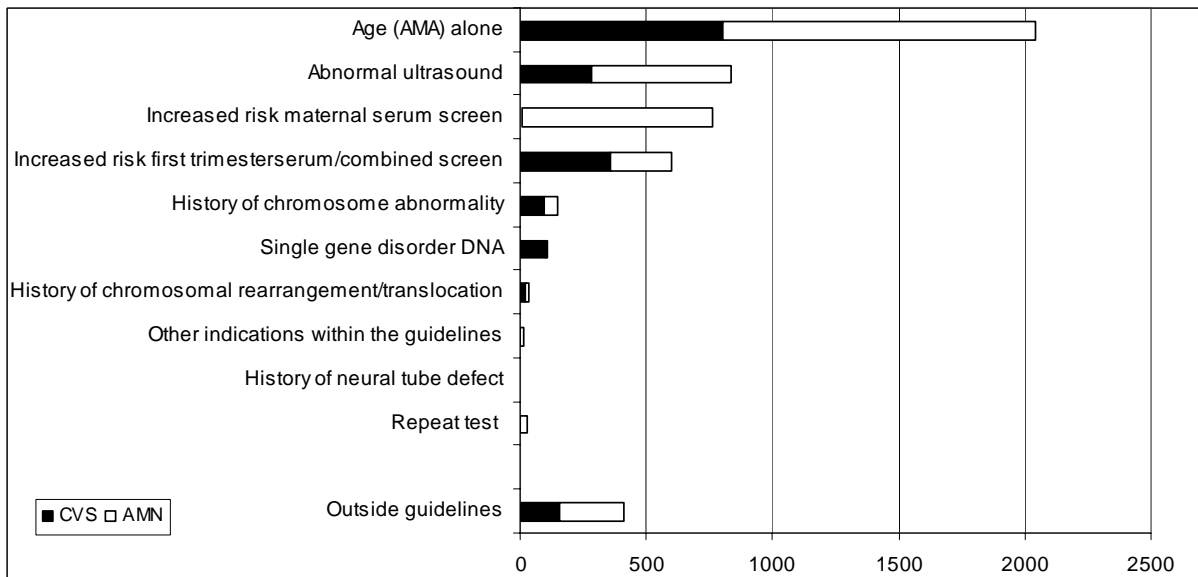
The five most common indications for prenatal diagnostic testing for Victorian women under 25 weeks gestation were maternal age, abnormal ultrasound, increased risk first trimester combined and second trimester maternal serum screen and indications outside the recommendations of the HGSA/RANZCOG Prenatal Diagnosis Policy. Other indications included previous chromosomal abnormality (145), tests for single gene disorders (108), history of chromosomal rearrangement (33), history of neural tube defects (5) and other within HGSA guidelines (15).

1. 2041 (41.7% 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. 833 (17.0% 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. 763 (15.6% of tests) tests were done because of a finding of increased risk second trimester maternal serum screening (MSS) (see 4.4, *maternal serum screening*).
4. 603 (12.3% of tests) tests were done because of a finding of increased risk first trimester combined screening (FTC) (see 4.4.2, *first trimester combined screening*).

- 5. 409 (8.3% 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=2789) from the total (n=4898). 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 43% 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

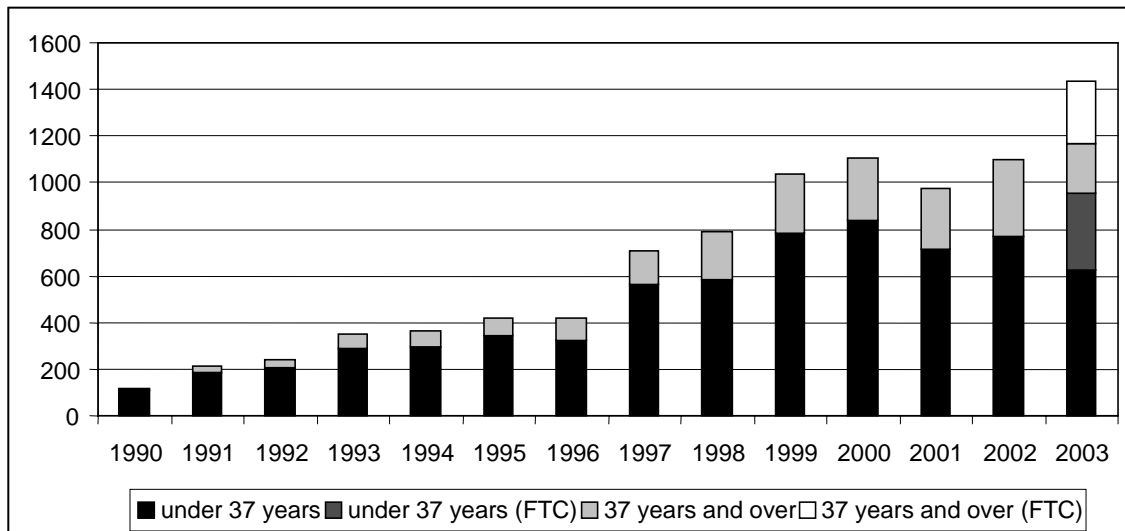
As shown on page 11 (3.3, *Utilisation*), 2815 (57%) of women having a prenatal diagnostic test were aged 37 years or over. 72.5% of these women had maternal age as their only indication (ie 41.7% of all women). However, 27.5% of women in this age group had a combination of two or more indications.

4.3 ABNORMAL ULTRASOUND

The number of women undergoing prenatal diagnosis following an abnormal ultrasound was 833 or 17.0% of all tests. 74% 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). 2003 is the first year first trimester combined screening has been listed as a distinct indication for prenatal diagnostic testing. **Nuchal translucency screens done as part of first trimester combined screening are no longer listed separately, which accounts for an apparent drop in the number of tests following abnormal ultrasound.** However, to present trend data for tests done for abnormal ultrasound, we included nuchal translucency screening done as part of first trimester combined screening (see 4.4.2, *first trimester combined screening (FTC)*) in Figure 5.

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



47% of the tests done for abnormal ultrasound were reported as nuchal translucency screens (when not as part of FTC). Over half of abnormal nuchal translucency screens were followed by a CVS (58%). This compares with 12% 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 37 pregnancies which also had a suspected fetal abnormality on routine ultrasound)				
Maternal age				
<35 yrs	114	95	209	
35-36 yrs	33	22	55	
37 – 39 yrs	38	24	62	
≥40 yrs	42	22	64	
<i>Sub-total</i>	227	163	390	(46.8%)
	(58.2%)	(41.8%)	(100%)	
Other suspected fetal or pregnancy abnormality on routine ultrasound				
Maternal age				
<35 yrs	36	252	288	
35-36 yrs	8	60	68	
37 – 39 yrs	3	53	56	
≥40 yrs	7	24	31	
<i>Sub-total</i>	54	389	443	(53.2%)
	(12.3%)	(87.6%)	(100%)	
Total	281	554	833	
	(33.7%)	(66.3%)		(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 (MSS) in 1996 and first trimester combined screening (FTC) in 2000.

2003 is the first year this report distinguishes 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 32836 women who had maternal serum screening (either first trimester combined or second trimester serum) in 2003. This corresponds to a diagnostic follow-up rate of 4.2%.

4.4.1 Second trimester maternal serum screening (MSS)

763 or almost 16% of all prenatal diagnostic tests are done following an increased risk second trimester MSS. By necessity due to the gestation at which this screening is done, most were done by AMN (759, or 99.5%), rather than by CVS (4, or 0.5%). More than half (56.6%) of tests prompted by increased risk MSS were in women under the age of 35 (Table 4).

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

Age group (years)	CVS	% total	AMN	% total	Total	% Total
<35	4		428		432	56.6%
35-36			138		138	18.1%
37-39			132		132	17.3%
≥40	0		61		61	8.0%
Total	4	0.5%	759	99.5%	759	100.0%

4.4.2 First trimester combined screening (FTC)

Increased risk FTC as an indication for prenatal diagnostic testing included 62 tests where the recorded indication was “increased risk first trimester *serum* screening” and 7 tests done at 12 weeks gestation because of “increased risk MSS”.

After inclusion of these data 603 or 12% of prenatal diagnostic tests were prompted by an increased risk first trimester combined test. Of these, 357 (59.2%) were done by CVS and 246 (40.8%) by AMN (Table 5).

79.7% of all AMN following an increased risk FTC were done at 15-16 weeks and 74.1% of all CVS at 11-12 weeks gestation (data not shown).

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

Age group (years)	CVS	% total	AMN	% total	Total	% Total
<35	127		86		213	35.3%
35-36	70		49		119	19.7%
37-39	109		65		174	28.9%
≥40	51		46		97	16.1%
Total	357	59.2%	246	40.8%	603	100.0%

4.5 HISTORY OF CHROMOSOME ABNORMALITY

Overall, 178 women were tested because of a history of chromosome abnormality, including rearrangements.

145 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 45% of these indications.

33 prenatal tests were done because of a history of chromosome translocation or rearrangement (eg deletions or inversions) (Table 6).

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

Previous abnormality	CVS	AMN	Total	%
Unspecified	33	32	65	44.8%
Trisomy 21	36	15	51	35.2%
Trisomy 18	8	2	10	6.9%
Trisomy 13	5	0	5	3.5%
Sex chromosome aneuploidy	5	2	7	4.8%
Other major chromosome	5	2	7	4.8%
Total	92	53	145	100%
Translocation	16	13	29	
Rearrangements	3	1	4	
Total	19	14	33	100%

4.6 SINGLE GENE TESTS

108 prenatal diagnostic tests were done because a DNA or biochemical test for a single gene disorder was requested. This number is comparable to the previous three years. The majority of tests for single gene disorders were done following CVS (96%)

A list of the main conditions tested for in 2003 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	2003	% 2003		2002	2001	2000
Thalassaemia	25	22.5		38	23	30
Cystic fibrosis	17	15.3		11	15	12
Fragile X	13	11.7		8	10	13
Duchenne muscular dystrophy	9	8.1		6	5	10
Haemophilia	5	4.5		5	5	3
Spinal muscular atrophy	4	3.6		6	7	8
Adrenoleukodystrophy	4	3.6		4	0	1
Myotonic dystrophy	3	2.7		1	0	1
Connexin 26	3	2.7		1	0	0
Congenital adrenal hypoplasia	2	1.8		3	2	2
X-linked Hydrocephalus	2	1.8		3	1	0
Ornithine transcarbamylase deficiency	2	1.8		1	1	0
Prader Willi syndrome	2	1.8		0	0	1
BRCA 1	1	0.9		2	0	0
Huntington disease	1	0.9		5	1	2
Mitochondrial disorder	0	0		2	0	1
Mucopolysaccharidosis I	0	0		2	0	1
Other	15	16.2		17	24	24
Total	108	100.0		112	93	107

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

Angelman's	Leigh syndrome
Diastrophic displasia	Menkes disease
Galactosialidosis	Mucopolysaccharidosis IV
Gangliosidosis	Neurofibromatosis
Glycogen storage disease	Norrie's disease
Hereditary sensory neuropathy	Rett syndrome
Hypogammaglobulinaemia	Smith-Lemli Opitz syndrome
Hypophosphatasia	

4.7 HISTORY OF NEURAL TUBE DEFECT

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

One of these tests was performed because spina bifida was seen on ultrasound, one because of a previous child with spina bifida, one because of a previous fetus with anencephaly and two tests were done following previous non-specified neural tube defects.

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

4.8 OTHER WITHIN HGSA/RANZCOG RECOMMENDATIONS

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

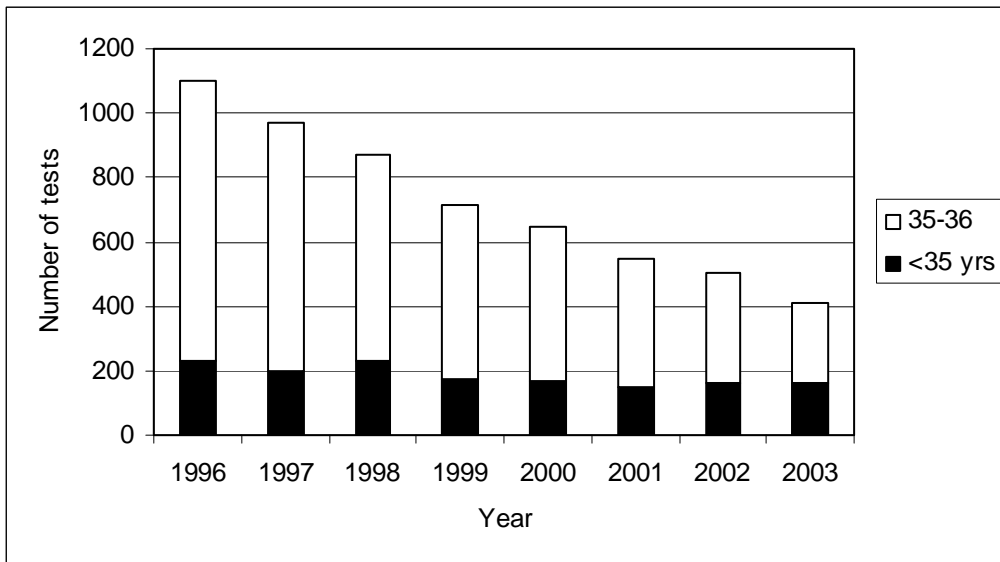
These included positive maternal serology for Cytomegalovirus, Toxoplasmosis or Varicella, exposure to radiation, elevated maternal serum alphafetoprotein and anti-Kell antibodies.

4.9 OUTSIDE HGSA/RANZCOG RECOMMENDATIONS

The majority of the 409 women with an indication outside the HGSA/RANZCOG recommendations were in the 35-36 year age group (59.9%). The indication given was *Age* or *Anxiety* for 91.0% of this group and for 83.5% of women under 35 years. The remaining indications related to 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 409 tests done in 2003. 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

4534 (92.6%) of CVS and AMN had a normal fetal karyotype. An additional 65 (1.3%) showed a minor non-clinically significant variation in fetal karyotype. This group of variations was not expected to result in an abnormal fetal outcome. Seven CVS or AMN were not karyotyped because a single gene test was the reason for testing or because of a failed sample. (Table 8).

Table 8. Summary data on all fetal karyotypes for Victorian women tested at under 25 weeks gestation

Fetal karyotype	CVS	AMN	Total	%
Normal				
Normal	1584	2950	4568	93.0%
No growth/not done	5	2	7	0.2%
Minor abnormalities				
Confined placental mosaicism (CPM)	16		16	0.3%
Balanced rearrangement	7	8	15	0.3%
Balanced translocation	11	23	34	0.7%
<i>Total minor abnormalities</i>	<i>34</i>	<i>31</i>	<i>65</i>	1.3%
Major abnormalities				
Autosomal aneuploidy:				
Trisomy 21	79	53	132	2.7%
Trisomy 18	30	21	51	1.0%
Trisomy 13	9	8	17	0.4%
Other trisomy	1		1	0.02%
Polyploidy	7	2	9	0.2%
Sex chromosome aneuploidy:				
45,X	18	1	19	0.4%
47,XXX	2	4	6	0.1%
47,XXY	1	3	4	0.08%
47,XYY	1		1	0.02%
Fragile X	4		4	0.08%
Other sex chromosome abnormality		1	1	0.02%
Unbalanced rearrangement	2	7	9	0.2%
Unbalanced translocation	1	3	4	0.08%
Microdeletion syndrome (22q)		3	3	0.06%
Level III Mosaicism	15	16	31	0.6%
<i>Total major abnormalities</i>	<i>170</i>	<i>122</i>	<i>292</i>	6.0%
<i>% abnormal of procedure</i>	<i>9.5%</i>	<i>3.9%</i>	<i>6.0%</i>	
Total	1793	3105	4898	100.0%

292 (6.0%) of pregnancies tested were found to have a major abnormality. This compares with 272 (5.5%) in 2002 and 254 (5.2%) in 2001. A greater proportion of all CVS were found to have a major abnormality (9.5%), compared with the proportion of all AMN (3.9%).

Trisomy 21 accounted for 45% of these abnormalities, Trisomy 18 for 17% and Trisomy 13 for 6%. More detailed information on the detection of autosomal trisomies is available in section 6.0 of this report. Other abnormalities included 9 polyploidies, 35 sex chromosome abnormalities, 31 Level III mosaicisms and 16 unbalanced rearrangements or translocations (including three 22q deletions).

5.2 AFTER ABNORMAL ULTRASOUND

Most of the 833 pregnancies with an abnormal ultrasound indication had a normal fetal karyotype (82.6%) or a minor non-clinically significant fetal karyotype outcome (1.0%). 16.4% of the tests were found to have a major abnormality. A greater proportion of abnormalities was detected by CVS (60.6%) (Table 9.).

The majority of abnormalities detected following an abnormal ultrasound were in women 37 years and over (Table 10). 28.2% of the women tested in this group were found to have an abnormal fetal karyotype, and trisomies accounted for 88.3% of these abnormalities. Trisomies were diagnosed in 24.9% of women aged 37 years and over, compared to 11.4% for women aged 35-36 years and 6.6% in the youngest age group.

Table 10 also shows that 76 of the 138 major abnormalities, detected following an abnormal ultrasound, were associated with an increased nuchal thickening (55.0%), but were only 47% of all ultrasound indications (Table 3, page 15).

Table 9. Abnormal ultrasound and fetal karyotype outcome by procedure for Victorian women under 25 weeks gestation

Fetal karyotype	CVS	AMN	Total	%
Normal/minor abnormality				
Normal	195	493	688	82.6%
Balanced rearrangement or translocation	2	5	7	0.9%
No growth/Not done	1		1	0.1%
Total normal or minor abnormal	198	500	698	83.6%
Major abnormalities				
Autosomal aneuploidy:				
Trisomy 21	32	19	51	6.1%
Trisomy 18	21	14	35	4.2%
Trisomy 13	7	7	14	1.7%
Polyploidy	5	2	7	0.8%
Sex chromosome aneuploidy:				
45,X	15	1	16	1.9%
47,XXX		1	1	0.1%
Unbalanced rearrangement or translocation	1	6	7	0.8%
Mosaic Level III	2	4	6	0.7%
Total major abnormal	83	54	137	16.4%
<i>% of all ultrasound abnormalities</i>	60.6%	39.4%	100%	
<i>% abnormal of procedure</i>	29.5%	9.7%		
Total	281	552	833	100.0%

Table 10. Abnormal ultrasound and fetal karyotype outcome by maternal age group for Victorian women under 25 weeks gestation

	Increased nuchal thickness	Other abnormal ultrasound	Total	% abn in age group
≥37 years (AMA)	126	87	213	
Normal/minor abnormality	84	69	153	71.8%
Trisomy 21	21	7	28	} 24.9%
Trisomy 18	15	6	21	
Other Trisomy	1	3	4	
Other chromosomal	5	2	7	3.3%
<i>Sub-total major abnormal</i>	42	18	60	28.2%
35 – 36 years	55	68	123	
Normal/minor abnormality	44	60	104	84.6%
Trisomy 21	5	4	9	} 11.4%
Trisomy 18		1	1	
Other Trisomy	4		4	
Other chromosomal	2	3	5	4.1%
<i>Sub-total major abnormal</i>	11	8	19	15.5%
<35 years	209	288	497	
Normal/minor abnormality	185	253	438	88.1%
Not done/no growth	1		1	
Trisomy 21	9	5	14	} 6.6%
Trisomy 18	5	8	13	
Other Trisomy	2	4	6	
Other chromosomal	7	19	26	5.2%
<i>Sub-total major abnormal</i>	23	36	59	11.9%
Total major abnormal	76	62	138	
<i>% of ultrasound indication</i>	19.5%	14.0%	16.6%	
Total	390	443	833	

5.3 AFTER INCREASED RISK SECOND TRIMESTER MATERNAL SERUM SCREEN (MSS)

3.2% of the 759 AMN done following an increased risk MSS were found to have a chromosomal abnormality. The four late CVS in this category (reported at 15, 17 or 18 weeks gestation) returned a normal karyotype (Table 11).

18 or 75% of the abnormalities found after an increased risk MSS were trisomies. The highest proportion of trisomies was found in women aged 37 and over, with nine diagnoses in the 193 women tested.

Table 11. 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	% abn in age group
≥37 years		193	193	
Normal/minor abnormality		182	182	94.3%
Trisomy 21		8	8	} 4.7%
Trisomy 18		1	1	
Other Trisomy				
Other chromosomal		2	2	1.0%
<i>Sub-total major abnormal</i>		11	11	5.7%
35 – 36 years		138	138	
Normal/minor abnormality		137	137	99.3%
Trisomy 21				} 0.0%
Trisomy 18				
Other Trisomy				
Other chromosomal		1	1	0.7%
<i>Sub-total major abnormal</i>		1	1	0.7%
<35 years	4	428	432	
Normal/minor abnormality	4	416	420	97.0%
Trisomy 21		8	8	} 2.1%
Trisomy 18		1	1	
Other Trisomy				
Other chromosomal		3	3	0.9%
<i>Sub-total major abnormal</i>		12	12	3.0%
Total major abnormal		24	24	
<i>% of all MSS abnormalities</i>		100%	100%	
<i>% abnormal of procedure</i>		3.2%		
Total	4	759	763	

5.4 AFTER INCREASED RISK FIRST TRIMESTER COMBINED SCREEN (FTC)

78 or 12.9% of 603 diagnostic procedures following an increased risk FTC were found to have a chromosomal abnormality, 80.8% of which were done by CVS (Table 12).

Across all age groups, 58 of the abnormal karyotypes were trisomies (74.4%), the highest proportion of which was in women aged 37 and over.

Table 12. 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	% abn in age group
≥37 years	160	111	271	
Normal/minor abnormality	123	106	229	84.5%
Trisomy 21	29	2	31	} 13.3%
Trisomy 18	3	1	4	
Other Trisomy		1	1	
Other chromosomal	5	1	6	2.2%
<i>Sub-total major abnormal</i>	37	5	42	15.5%
35 – 36 years	70	49	119	
Normal/minor abnormality	60	45	105	88.2%
Trisomy 21	3	3	6	} 8.4%
Trisomy 18	2	1	3	
Other Trisomy	1		1	
Other chromosomal	4		4	3.4%
<i>Sub-total major abnormal</i>	10	4	14	11.8%
<35 years	127	86	213	
Normal/minor abnormality	111	79	190	89.7%
Not done/no growth		1	1	
Trisomy 21	6	3	9	} 5.6%
Trisomy 18	2		2	
Other Trisomy	1		1	
Other chromosomal	7	3	10	4.7%
<i>Sub-total major abnormal</i>	16	6	22	10.3%
Total major abnormal	63	15	78	
<i>% of all FTC abnormalities</i>	80.8%	19.2%	100%	
<i>% abnormal of procedure</i>	17.6%	6.1%	12.9%	
Total	357	246	603	

5.5 AFTER HISTORY OF CHROMOSOMAL ABNORMALITY

5.5.1 History of chromosomal aneuploidy

Of the 145 women tested because of a known history of chromosome aneuploidy, one woman who had a previous Trisomy 21 pregnancy and one who had a previous Trisomy 18 were found to have a fetus with Trisomy 21 (Table 13).

However, detailed information on the previous chromosomal abnormality was not available for 45% in this category. Therefore we were unable to estimate a Trisomy 21 recurrence rate from this data set.

Table 13. 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	30N / 1CPM	32N	1UBR / 1LIII		65	44.8%
Trisomy 21	35N	14N / 1BT	1 T21		51	35.2%
Trisomy 18	6N	2N	1LIII / 1T21		10	6.9%
Trisomy 13	5N				5	3.5%
Sex chromosome aneuploidy	5N	2N			7	4.8%
Other major chromosome	5N	2N			7	4.8%
Total	87	53	5		145	100%

N: Normal
 BT: Balanced translocation
 CPM: Confined placental mosaicism
 LIII: Level III mosaicism
 T21: Trisomy 21
 UBR: Unbalanced rearrangement

5.5.2 Previous chromosomal translocation or other rearrangement

33 women were tested because of a family history of chromosome translocation or rearrangement. 14 of these tests showed fetal karyotypes with balanced translocations or rearrangements (42.4%) and one (3.0%) with a major abnormality (ie Level III mosaicism) (Table 14).

Table 14. 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	12N / 3BT / 1BR	2N / 9BT / 1BR		1LIII		
<i>Sub-total</i>	16	12		1	29	87.9%
Rearrangements (deletions, inversions, etc)	3N / 1CPM					
<i>Sub-total</i>	4				4	12.1%
Total	20	12		1	33	100%

N: Normal

BR: Balanced rearrangement

BT: Balanced translocation

CPM: Confined placental mosaicism

LIII: Unbalanced Level III mosaicism

5.6 AFTER HISTORY OF NEURAL TUBE DEFECT

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

5.7 OTHER WITHIN HGSA/RANZCOG RECOMMENDATIONS

Of the 15 prenatal diagnostic tests done for other indications within the HGSA/RANZCOG recommendations, all were of normal fetal karyotype.

5.8 OUTSIDE HGSA/RANZCOG RECOMMENDATIONS

There were 11 (3.2%) abnormal outcomes amongst the 340 women aged 35-36 years who were tested for reasons outside the HGSA/RANZCOG recommendations. In women under 35 years, only one of 164 tested women had a fetal karyotype abnormality (Table 15).

Table 15. 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	95N / 2BT 1BR / 1CPM	134N / 1BT	1 LIII	1LIII / 2T21 1SA	239	
Family history of T21	1N				1	
Other	2N	2N		1UBR	5	
<i>Sub-total</i>	102	137	1	5	245	59.9%
<35 years						
Age/anxiety	35N / 1BR	99N / 1BT		1LIII	137	
Family history of T21	4N	3N			7	
Other	10N / 1BT	8N / 1BT			20	
<i>Sub-total</i>	51	112	0	1	164	40.1%
Total	153	249	1	6	409	100%

N: Normal

BT: Balanced translocation

BR: Balanced rearrangement/translocation

CPM: Confined placental mosaicism

LIII:

SA:

T21:

UBR:

Level III mosaicism

Sex chromosome aneuploidy

Trisomy 21

Unbalanced rearrangement

6. AUTOSOMAL TRISOMIES

In 2003, prenatal diagnostic tests before 25 weeks of gestation resulted in the diagnosis of 132 Trisomy 21, 51 Trisomy 18, 17 Trisomy 13 and one Trisomy 8. In addition, two Trisomies 21 were diagnosed at 27 and 32 weeks and two Trisomies 18 at 28 and 29 weeks (*see 8. Indication and fetal karyotype outcome for Victorian women over 24 weeks of gestation*).

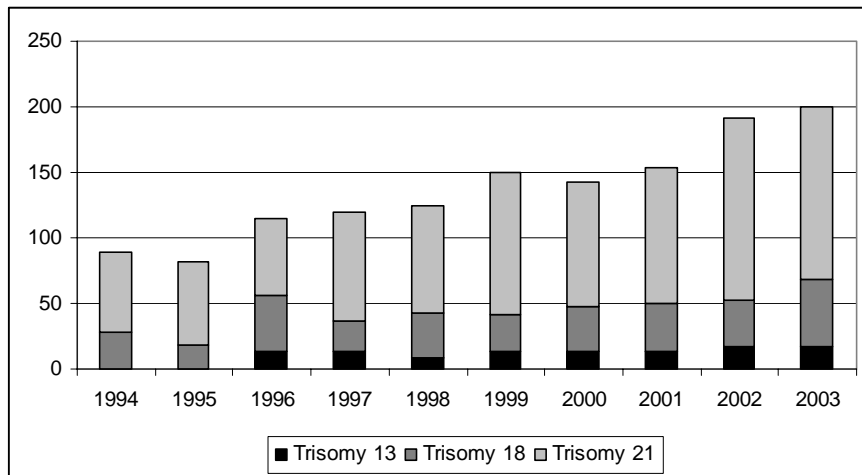
Diagnoses included two double aneuploidies: One of the karyotypes classified as Trisomy 21 also had a Trisomy of chromosome 18 and one Trisomy 18 also had a sex chromosome aneuploidy.

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

59.8% of Trisomies 21, 58.8% of Trisomies 18 and 52.9% of Trisomies 13 were diagnosed following CVS.

Figure 7 shows that the number of trisomies diagnosed prenatally has more than doubled since 1994. This rise is mainly due to an increase in Trisomy 21, whereas diagnosis of Trisomy 13 and Trisomy 18 has remained relatively stable. However in 2003, the rise in Trisomy diagnoses was due to an increased number of Trisomy 18.

Figure 7. Autosomal trisomies diagnosed in Victorian women under 25 weeks gestation



Tables 16, 17 and 18 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 23 of the 132 Trisomies 21 diagnosed (17.4%) had no prior increased risk screening test result reported (Table 16).

Similarly, in the diagnosis of Trisomy 18 and Trisomy 13, the most common indication was an increased risk screening test result (90.2% and 100% respectively), with increased nuchal thickening accounting for 39.2% and 41.2% and abnormal second trimester ultrasound for 29.4% and 41.2% (Tables 17 and 18 respectively).

Table 16. 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		7	4	5	12	2	1	3	1	35	26.5%
First trimester combined screening		6	3	16	13	3	3		3	47	35.6%
Second trimester maternal serum screen						8		7	1	16	12.1%
Other ultrasound abnormality				1	2	5	1	1	1	11	8.4%
No screening test, prompted by anxiety or age alone				3	7		1	6	6	23	17.4%
Total		13	7	25	34	18	6	17	12	132	100%

Table 17. 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		3		6	7	2			2	20	39.2%
First trimester combined screening		2	2	2	1		1	1		9	17.7%
Second trimester maternal serum screen						1			1	2	3.9%
Other ultrasound abnormality		3		1	1	5	1	2	2	15	29.4%
No screening test, prompted by anxiety or age alone				2				1	2	5	9.8%
Total		8	2	11	9	8	2	4	7	51	100%

Table 18. 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		2	3	1			1			7	41.2%
First trimester combined screening		1	1						1	3	17.6%
Other ultrasound abnormality					1	4		1	1	7	41.2%
Total		3	4	1	1	4	1	1	2	17	100%

7. REPEAT TESTS AND FETAL KARYOTYPES

30 (0.6%) prenatal diagnostic tests were repeated including two without a record of the first sample. One of these two tests was found to be of normal karyotype and one was an unbalanced rearrangement on repeat AMN.

Three repeats were performed due to failure of the first sample. One of these returned a normal karyotype and one test failed on repeat as well.

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). Six were confirmed as LIII mosaic.

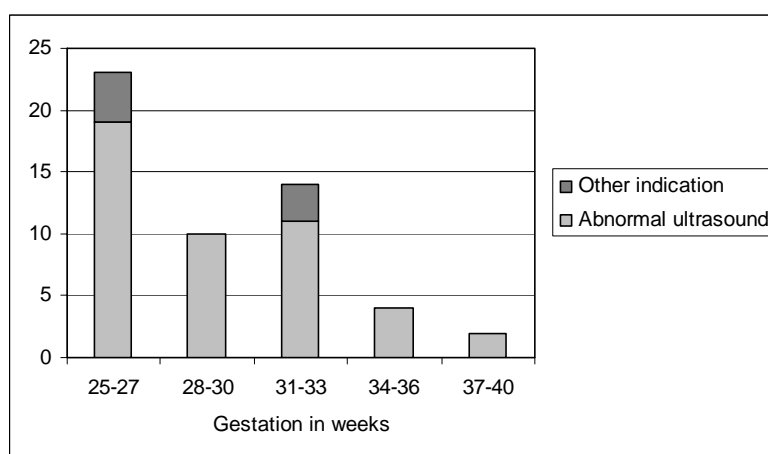
Three Trisomies of chromosome 2, 16 and 22 on CVS were found to be normal on repeat AMN.

Two normal CVS were repeated for unknown reasons and confirmed to be of normal fetal karyotype.

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

53 women had a late (over 24 weeks gestation) prenatal diagnosis, one of which was done by CVS at 27 weeks.

Figure 8. Prenatal diagnosis for Victorian women over 24 weeks gestation by gestational age and indication



46 (86.8%) of these tests were done because of an abnormal ultrasound and all but two were done in women under 37 years (Figure 8 and Table 19). One of the abnormal ultrasounds that prompted a test at 32 weeks was stated as 'increased nuchal thickening'. Other indications included 4 tests done for advanced maternal age at 25 and 32 weeks, paternal translocation carrier at 31 weeks and iso-immunisation at 25 and 27 weeks gestation.

Table 19. Indications for Victorian women over 24 weeks gestation

Gestation (weeks)	Abnormal ultrasound (≥37 years)	Abnormal ultrasound (<37 years)	Other indication (All ages)	Total
25 - 27	2	17	4	23
28 - 30	0	10	0	10
31 - 33	0	11	3	14
34 - 36	0	4	0	4
37 - 40	0	2	0	2
Total	2	44	7	53
% total	3.8%	83.0%	13.2%	100%

Five abnormal karyotypes were found in this category (9.4%), two Trisomies 21, two Trisomies 18 and one unbalanced rearrangement. All abnormal outcomes followed an abnormal ultrasound with two at 27 weeks, two at 28-30 weeks and one at 32 weeks gestation (Table 20).

Table 20. 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	21	1 T21 / 1 UBR	23
28 - 30	8	2 T18	10
31 - 33	11 / 1 ND / 1 BT	1 T21	14
34 - 36	4		4
37 - 40	2		2
Total	48	5	53
% total	90.6%	9.4%	100%

ND: Not done/no growth

BT: Balanced translocation

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. This corresponds to approximately 50% of all CVS or AMN in that year.

The percentage of FISH done in each age group (Table 21) 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 (38.7% FISH vs 29.2% of all tests).

Table 21. FISH for Victorian women under 25 weeks gestation, by maternal age and procedure

Age group (years)	CVS	% total	AMN	% total	Total	% Total FISH
<35	299		637		936	38.7%
35-36	143		205		348	14.4%
37-39	303		362		665	27.5%
≥40	260		211		471	19.5%
Total	1005	41.5%	1415	58.5%	2420	100.0%

Of the 2420 FISH done, 26.2% followed an indication of advanced maternal age and 62.4% had a prior increased risk screening test as indication for testing. 6.9% of FISH were requested in women under the age of 37 years for reasons outside the HGSA/RANZCOG guidelines (Table 22).

Table 22. FISH for Victorian women under 25 weeks gestation, by indication for testing and procedure

Indication	CVS	AMN	Total	% Total
AMA	309	325	634	26.2%
Ultrasound	227	425	652	26.9%
MSS	2	414	416	17.2%
FTC	302	141	443	18.3%
Previous chromosomal abnormality	58	16	74	3.1%
Single gene test	33		33	1.3%
Other within guidelines		2	2	0.1%
Outside guidelines	74	92	166	6.9%
Total	1005	1415	2420	100.0%

Results of FISH are not collected in our database, however provided Table 23 provides karyotype outcomes for all tests that included FISH. 9.4% 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 (6.0%). This may be the result of the high proportion of FISH requested following an increased risk screening test result (62.4% vs 43.0% across all tests).

Table 23. FISH for Victorian women under 25 weeks gestation, by karyotype outcome and procedure

Indication	CVS	AMN	Total	% Total
Normal/minor abnormality	853	1335	2188	90.4%
Not done/no growth	2	2	4	0.2%
Trisomy 21	69	33	102	
Trisomy 18	28	16	44	
Trisomy 13	9	7	16	
Polyploidy	7	2	9	
Sex chromosome abnormality	22	4	26	
Unbalanced translocation/rearrangement	3	9	12	
Level III mosaic	12	7	19	
Total major abnormal	150	78	228	9.4%
<i>% abnormal of procedure</i>	14.9%	5.5%	9.4%	
Total	1005	1415	2420	

10.0 INTERSTATE SAMPLES

Victorian cytogenetics laboratories analysed 228 CVS and AMN sent in from interstate in 2003. The majority of these samples came from Tasmania (66.7%) and New South Wales (31.6%) (Table 24). The majority of NSW samples came from women residing on the Victorian border who may have given birth in Victoria.

Table 24. Interstate samples by state and maternal age group

Age group (years)	NSW	QLD	TAS	NT	Total
<35	30	0	66	1	97
35-36	9	1	21		31
37-39	21	0	37		58
≥40	12	2	28		42
Total	72	3	152	1	228
<i>%Total</i>	31.6%	1.3%	66.7%	0.4%	100%

Of the 228 interstate samples done, 26.8% followed an indication of advanced maternal age and 57.9% had a prior increased risk screening test as indication for testing. 7.4% of interstate samples were on women under the age of 37 years for reasons outside the HGSA/RANZCOG guidelines (Table 25).

Table 25. Interstate samples by state and indication for testing

Indication	NSW	QLD	TAS	NT	Total	<i>% Total</i>
AMA	21	1	39		61	26.8%
Ultrasound	17		29		46	20.2%
MSS	8		39		47	20.6%
FTC	10	1	28		39	17.1%
Previous chromosomal abnormality	4			1	5	2.2%
Single gene test	2		4		6	2.6%
History translocation/rearrangement	3		4		7	3.1%
Outside guidelines	7	1	9		17	7.4%
Total	72	3	152	1	228	100.0%

7.9% of tests originating from interstate were found to have an abnormal karyotype. This proportion is higher than the overall proportion of abnormal karyotypes in all tests done in 2003 (6.0%) and included a further 6 Trisomy 21 diagnoses, two in samples from New South Wales and four from Tasmania (Table 26).

Table 26. Interstate samples by state and karyotype outcome

Indication	NSW	QLD	TAS	NT	Total
Normal/minor abnormality	67	2	136	1	206
Not done/no growth			4		4
Trisomy 21	2		4		6
Trisomy 18	1	1	2		4
Sex chromosome abnormality			3		3
Unbalanced translocation/rearrangement	2		2		4
Level III mosaic			1		1
Total major abnormal	5	1	12		18
<i>% abnormal</i>	6.9%	3.3%	7.9%	0%	7.9%
Total	72	3	152	1	228

