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The Annual Report on Postnatal Diagnostic Testing in Victoria, 2020

Reproductive Epidemiology group

Genetics theme

Murdoch Children's Research institute

Contents

This report is produced by the **Reproductive Epidemiology group** in the Genetics theme at the MCRI. For more information about us, go to our page at *https://www.mcri.edu.au/reproductiveepidemiology*

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Background

The most common cause of spontaneous miscarriage is aneuploidy. When women experience a pregnancy loss, postnatal chromosome analysis may be offered, particularly in the setting of recurrent miscarriage. Molecular karyotyping with chromosomal microarrays (CMA) is preferred over G-banded karyotype for postnatal samples as there is no requirement for cell culture, and hence failure rates are low. This report is in addition to the Victorian Prenatal Diagnosis Report, 2020, providing results of postnatal chromosome testing in 2020 for women resident in Victoria, Australia. This report includes placental, fetal cord samples, and "products of conception" (POC) but no paediatric samples.

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Definitions

Major chromosome conditions: autosomal trisomies, autosomal monosomies, polyploidy, sex chromosome aneuploidies, pathogenic copy number variants (CNVs), unbalanced rearrangements, gestational trophoblastic disease, and high-level mosaicism.

Minor chromosome conditions: genomic CNVs of uncertain or unknown significance, long continuous stretches of homozygosity (LCSH), uniparental disomy (UPD), confined placental mosaicism (CPM), and balanced rearrangements.

Diagnostic yield: the percentage of women with a major fetal chromosome condition confirmed on diagnostic testing as a proportion of total tests.

Positive non-invasive prenatal testing (NIPT) result: 'increased chance', 'high risk', 'aneuploidy detected' or other result indicating an increased probability of a chromosome condition in the pregnancy.

Classification of genomic copy number variants (CNVs): CNVs were classified as *pathogenic, likely pathogenic, uncertain, or unknown significance, likely benign, or benign* according to the clinical laboratory interpretation, which is guided by the American College of Medical Genetics standards and guidelines for interpretation and reporting of copy number variants.[1, 2]

Variant of uncertain or unknown significance (VUS): CNV with uncertain, or unknown clinical significance as classified by the reporting laboratory

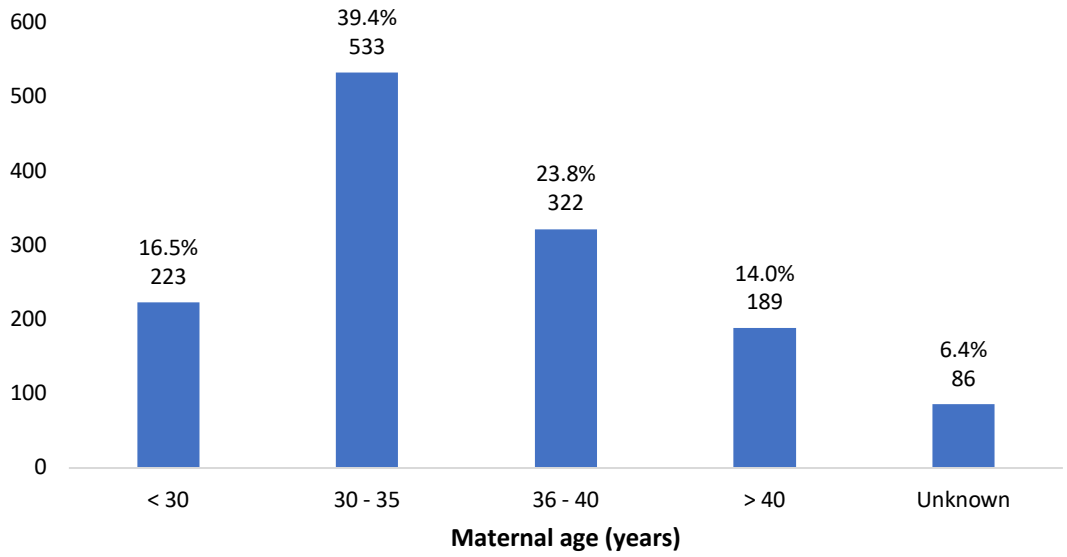
Summary statistics

In 2020, 1494 postnatal samples were referred for diagnostic testing. After excluding 141 samples (9.4%) that could not be processed or did not yield a result, there were **1353** samples with validated reports. Of these, 3.6% (49/1353) were found through record linkage to also have had a prenatal diagnostic test in the same pregnancy. Most samples (92.6%) were evaluated by CMA.

Maternal age

Maternal age at the time of diagnostic testing was calculated. The most common maternal age group was 30-35 years (**Figure 1**).

Figure 1. Maternal age at diagnostic test date



Specimen types

Postnatal specimens included 687 "POC" samples (not otherwise specified), 348 placental samples, and 258 fetal tissue samples (**Table 1**). Pregnancy outcome was inconsistently recorded in the clinical referrals for testing: a livebirth was presumed in 83 (6.1%) of postnatal samples based on the clinical indication for testing, e.g., where testing was performed to investigate fetoplacental mosaicism, such as when a positive NIPT result is followed by a 'normal' karyotype result on amniocentesis (n=20; 24.0%).

Table 1. Specimen types

Specimen types	n (%)
'POC' (unspecified)	701 (51.8)
Placenta (biopsy, cyst, villus)	348 (25.7)
Fetal (fetal tissue, rib/cartilage, skin, spleen)	258 (19.1)
Umbilical cord or cord blood	46 (3.4)
Total	**1353 (100.0)**

Gestational age

Gestational age (GA) was available for 717 (53.0%) of specimens. Approximately one in four tests were performed between 14 and 23 weeks' gestation. (**Table 2**).

Table 2. Gestational age

Gestational age (weeks)	n (%)
<14	274 (20.3)
14 - 23	341 (25.2)
≥ 24	102 (7.5)
Missing data	636 (47.0)
Total	**1353 (100.0)**

Clinical indications for testing

Testing indications were recorded according to the written clinical referral. Independent verification of the indications for testing was not performed. More than one indication could be recorded for each sample. Consequently, there were 1936 indications recorded for 1353 postnatal samples.

The most common reason for diagnostic testing was a pregnancy loss ('miscarriage', 'missed abortion', 'fetal demise' etc) at an unspecified gestation (37.8%). The second most common indication was a miscarriage at < 20wks gestation (28.5%); followed by a fetal abnormality on ultrasound (22.3%), which included structural abnormalities, increased nuchal translucency measurement, and absent nasal bone (**Table 3**).

Table 3. Indications for diagnostic testing

Indication	n (%)
Pregnancy loss, gestation unspecified	509 (37.8)
Miscarriage at < 20 weeks' gestation[1]	386 (28.5)
Fetal abnormality on antenatal ultrasound[2]	300 (22.3)
Previous or 'recurrent' miscarriage[3]	252 (13.0)
Stillbirth, fetal death in utero, or preterm prelabour rupture of membranes ≥ 20 weeks	153 (11.4)
Termination of pregnancy **(see Table 4.)**	158 (8.2)
Positive NIPT result	85 (4.4)
Other[4]	42 (2.2)
Clarification of previous diagnostic test	20 (1.0)
Prior pregnancy with a chromosomal condition	17 (0.9)
Postnatal indication[5]	11 (0.6)
No clinical notes	3 (0.2)
Total	**1936 (100.0)**

[1]Indications for miscarriages < 20 weeks included: "miscarriage, "missed abortion", and preterm prelabour rupture of membranes <20 weeks'

[2]Fetal abnormality on antenatal ultrasound included a structural abnormality (n=285), isolated increased nuchal translucency (n=11), and isolated absent nasal bone (n=4)

[3]'Recurrent' miscarriages included all miscarriages described as 'recurrent' by the clinical referrer

[4]Other testing indication included teratogenic exposure, twin-twin transfusion syndrome, and previous child with a structural abnormality, failed or inconclusive NIPT result, first trimester combined screening result, second trimester serum screening result, 'high risk' screening result (not otherwise specified), first trimester combined screening and single gene test.

[5]Postnatal indications included neonatal death (death within 28 days of birth at >20 weeks' gestation) and unexpected congenital anomaly at birth.

Table 4. Indications for testing among termination of pregnancy samples (n=158)

Indication	n (%)
Fetal abnormality on antenatal ultrasound	118 (74.6)
No other indication listed ('TOP' only)	18 (11.4)
Positive NIPT (no known prenatal diagnosis or another indication)	10 (6.3)
Fetal abnormality on ultrasound with a positive NIPT result	5 (3.2)
Other	7 (4.4)
Total	**158 (100.0)**

NIPT; non-invasive prenatal testing, TOP; termination of pregnancy

Chromosome results

Of the 1353 total postnatal tests, 608 detected a major chromosome condition, yielding a diagnostic yield of 44.9%.

The most common autosomal trisomies were Trisomy 16 (5.1%), Trisomy 21 (4.7%), Trisomy 22 (3.6%), Trisomy 15 (3.0%), Trisomy 13 (2.4%), and Trisomy 18 (2.0%).

Turner's syndrome (45, X) was the most frequent sex chromosomal aneuploidy (4.4%).

Rare autosomal aneuploidies (autosomal aneuploidies other than Trisomy 21, 13 or 18) were the most common group of chromosome conditions detected (16.6%) (**Table 5**).

Table 5. Diagnostic results

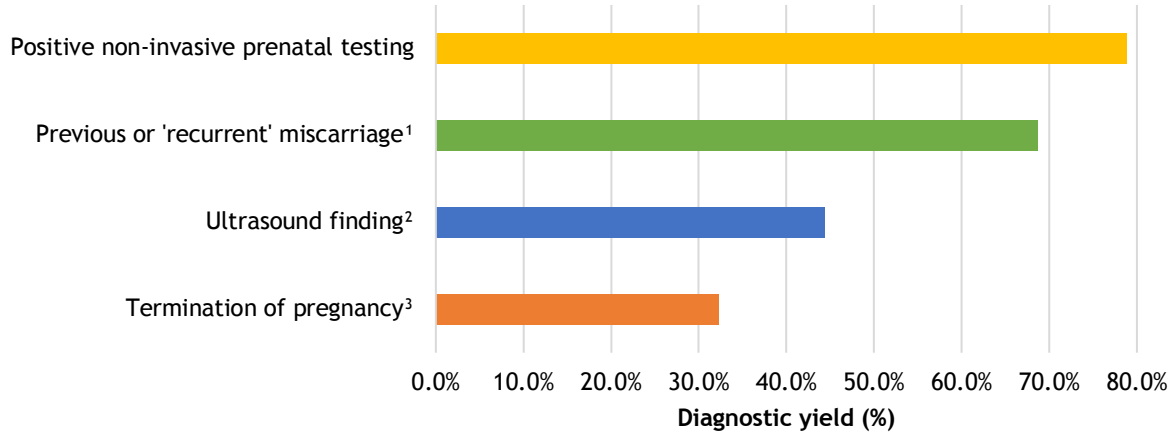
Result	n (%)
Normal/benign CNV	694 (51.3)
Rare autosomal aneuploidies	**224 (16.6)**
Trisomy 16	69 (5.1)
Trisomy 22	49 (3.6)
Trisomy 15	41 (3.0)
Other rare autosomal aneuploidy	65 (4.8)
Common autosomal aneuploidies	**122 (9.0)**
Trisomy 21	62 (4.6)
Trisomy 13	33 (2.4)
Trisomy 18	27 (2.0)
Sex chromosomal aneuploidies	**62 (4.6)**
Turner syndrome (45,X)	59 (4.4)
Klinefelter syndrome (47,XXY)	3 (0.2)
Triploidy	**68 (5.0)**
Multiple autosomal or sex chromosomal aneuploidies	55 (4.1)
Pathogenic CNV	28 (2.1)
CNV of uncertain or unknown clinical significance	31 (2.3)
Gestational trophoblastic disease	12 (0.9)
Confined placental mosaicism	2 (0.1)
Other major chromosome condition	17 (1.3)
Other minor chromosome condition	38 (2.8)
Total	**1353 (100.0)**

CNV; copy number variant

Diagnostic yield

Diagnostic yield was highest for women undergoing testing for a positive NIPT result (78.8%), followed by a previous or 'recurrent' miscarriage (69.4%), ultrasound finding (44.4%), and following termination of pregnancy (32.3%) (**Figure 2, Table 5**).

Figure 2. Diagnostic yield according to indication for testing



[1]'Recurrent' miscarriage included all miscarriages described as 'recurrent' by the clinical referrer.

[2]Ultrasound finding included fetal anomaly on antenatal ultrasound, missed abortion, PPROM at <20 weeks', stillbirth, fetal death in utero, PPROM at ≥20 weeks', and fetal loss at an unspecified gestation

[3]Termination of pregnancy information was provided in the clinical referral.

Chromosome results by indication for testing

Chromosome results differed by indication for testing. The chromosome results for the four indications with the highest diagnostic yield are shown in **Table 6**.

Trisomy 21 was the most common chromosome result following testing for a positive NIPT result (27.1%) or following TOP (8.9%).

The most common indications for testing among the rare autosomal trisomies were previous or recurrent miscarriage (34.1%), or an ultrasound finding (including missed miscarriage) (7.4%).

Table 6. Chromosome results by indication for testing

Indication	Total tests	Total abnormal[#] n (%)	Normal/ benign n (%)	T21 n (%)	T18 n (%)	T13 n (%)	RAT n (%)	SCA n (%)	pCNV n (%)	Other* n (%)	Multiple AA/SCA n (%)	Polyploidy n (%)	GTD n (%)	CPM n (%)	VUS n (%)
Positive NIPT	85	67 (78.8)	14 (16.5)	23 (27.1)	5 (5.9)	6 (7.1)	5 (5.9)	16 (18.8)	2 (2.4)	8 (9.4)	2 (2.4)	1 (1.2)	0 (0.0)	2 (2.4)	1 (1.2)
Previous or recurrent miscarriage	252	173 (68.7)	72 (28.6)	10 (4.0)	2 (0.8)	10 (4.0)	86 (34.1)	14 (5.6)	3 (1.2)	15 (6.0)	19 (7.5)	17 (6.7)	0 (0.0)	0 (0.0)	4 (1.6)
Ultrasound finding[^]	1266	562 (44.4)	655 (51.7)	50 (3.9)	25 (2.0)	31 (2.4)	220 (17.4)	51 (4.0)	26 (2.1)	48 (3.8)	52 (4.1)	64 (5.1)	12 (0.9)	1 (0.1)	29 (2.3)
Termination of pregnancy	158	51 (32.3)	101 (64.0)	14 (8.9)	2 (1.3)	4 (2.5)	1 (0.6)	4 (2.5)	11 (7.0)	3 (1.9)	6 (3.8)	8 (5.1)	0 (0.0)	0 (0.0)	4 (2.5)

*Other results included mosaic autosomal or sex chromosomal aneuploidies, long continuous stretches of homozygosity and unbalanced translocations.

[#]'Total abnormal' includes all major chromosome abnormalities; the % is the percentage of total tests performed for that indication

[^]Ultrasound finding included fetal anomaly on antenatal ultrasound, miscarriage (including missed abortion, PPROM) at <20 weeks', birth (including stillbirth, fetal death in utero, PPROM) at ≥20 weeks', and fetal loss at an unspecified gestation.

AA, autosomal aneuploidy; CPM, confined placental mosaicism; GTD, gestational trophoblastic disease; pCNV, pathogenic copy number variant; NIPT, non-invasive prenatal testing, RAT, rare autosomal trisomies; SCA, sex chromosomal aneuploidy; T21, Trisomy 21; T18, Trisomy 18; T13, Trisomy 13; VUS, copy number variant of uncertain or unknown clinical significance.

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