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Abstract

Background: In recent years, the superior accuracy of maternal plasma cell-free DNA-based prenatal screening has resulted in > 50% national decline in amniocenteses and chorionic villus sampling (CVS), creating new implications for specialist training.

Objective: To compare the annual figures on amniocenteses and CVS in a tertiary hospital with national population-based trends between 2012-2015.

Methods: Retrospective study examining the amniocentesis and CVS procedures performed in a tertiary hospital between 2012 and 2015. Numbers of procedures,

indications for testing, type of test, and diagnostic results were analysed. Trends in the annual numbers of procedures were compared to national population-based data from Medicare Benefits Schedule database.

Results: The annual numbers of diagnostic procedures in our tertiary centre fell from 267 to 215 over the study period, representing a 19.5% decline. This was a significantly smaller than the corresponding national decline of 53.7% for the same period ($p< 0.0001$). In 2015, ultrasound abnormality (including nuchal translucency $\geq$ 3.5mm) surpassed high risk screening result as the most common indication for invasive testing. Thirty percent of procedures performed for an ultrasound abnormality occurred prior to 18 weeks gestation.

Conclusion: Our tertiary centre experienced a relatively smaller decline in prenatal diagnostic procedures compared with national figures, largely due to an increase in testing for ultrasound abnormalities. Our results demonstrate the increasing contribution of first trimester ultrasound in the detection of fetal abnormalities in the cfDNA era and the continued viability of specialist training in invasive procedures.

Background

The superior accuracy of maternal plasma cell-free (cf) DNA- based prenatal screening, also known as noninvasive prenatal testing (NIPT), has led to dramatic declines in invasive procedures locally[1] and globally[2]. Recently this journal reported a national reduction in amniocentesis and chorionic villus sampling (CVS) procedures of more than 50% over the past 5 years.[1] The greatest reduction within the 20-year study period was observed in the first year of cfDNA availability in 2013.[1] Similarly, in Victorian population-based data, 2013 marked the lowest rate of diagnostic procedures in 25 years.[3] These changes pose challenges for tertiary centres to maintain the procedural volume required for maintenance of skills and subspecialist training,[4] with a recent survey of Australian obstetric sonologists suggested that one in four are now performing less than 25 procedures a year.[5] Although the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) does not specify a minimum annual number of invasive procedures for subspecialists, it does set targets for maternal fetal medicine (MFM) and obstetrical and

gynaecological ultrasound (COGU) subspecialty trainees (100 amniocenteses and 50 CVS for MFM, and 100 each for COGU fellows over three years of accredited training).[6]

Due to the impact of cfDNA screening on training opportunities for subspecialists, we conducted a study of amniocenteses and CVS at one of three accredited subspecialty training sites in Victoria. We hypothesized that the unique nature of the referral population to a tertiary centre would mean a consistent case load of high risk referrals that would ensure continued access to procedural training. The aim of this study was to analyse the numbers, indications and results of diagnostic testing and to compare the single centre data with national figures for the four year period spanning the introduction of cfDNA based screening in Australia.

Materials and Methods

This study was a retrospective audit of amniocentesis and CVS procedures performed for genetic testing at the Mercy Hospital for Women (MHW), Heidelberg Victoria from January 2012 to December 2015 inclusive. Ethical approval for this study was granted by the Mercy Health Human Research Ethics Committee (R16/09).

Combined first trimester screening (CFTS) with nuchal translucency (NT) measurement and serum markers is the most common form of aneuploidy screening in Victoria and attracts government funding.[3] In contrast, cfDNA based screening is only available on a patient-funded basis. Public hospitals do not routinely fund cfDNA as a second tier test for women referred with high risk CFTS results.

Data on all amniocenteses and CVS were extracted from the procedural logbooks at the MHW for the study period. If the logbook records were incomplete, data was manually obtained from the electronic ultrasound reporting database (Viewpoint™), and/or review of the patient medical records. Demographic and clinical information were collected and recorded in a purpose-built secure online research database (RedCap™). We also collected information on the number of fetuses, type of diagnostic tests and final karyotype results.

Women with multiple pregnancies within the study period were considered as individual cases. Test results were considered abnormal if there was at least one fetal chromosome abnormality detected. Only results of fetal chromosome analysis are reported here.

The primary outcomes were annual figures on: (i) number of diagnostic procedures, (ii) indications for testing, and (iii) proportion of tests with a major chromosome abnormality (trisomy, triploidy, pathogenic copy number variation (CNV), mosaic trisomy, monosomy).

To compare results from our single centre experience with population-based data, we accessed publically-available information from the Medicare Benefits Schedule (MBS) database (accessible at http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp) for item numbers 16600 (diagnostic amniocentesis) and 16603 (chorionic villus sampling by any route) for the period 2012 to 2015 inclusive. The results to 2014 have been previously reported.[1] We updated these data to include the full calendar year of 2015 and compared the proportional decline from 2012 to 2015 with our tertiary centre experience.
Statistical analysis was performed with the 2 sample z-test for difference in proportions, or the chi-squared test for trend where appropriate, with $p < 0.05$ being considered significant.

Results

Annual numbers of procedures

A total of 915 diagnostic procedures were performed at MHW between January 2012 and December 2015. Of those procedures, 664 were amniocenteses, 237 were CVS and 14 were classified as "other", most commonly therapeutic amnioreduction. The vast majority of the procedures were performed on singleton pregnancies (n=877), with the remaining procedures performed on 36 twin and 2 triplet pregnancies.

The annual number of diagnostic procedures in our hospital decreased from 267 to 215 during the study period, equating to a 19.5% decline (Figure 1). Over the same time period, the annual national total of amniocenteses and CVS declined from 9834 to 4558, a decline

of 53.7%. The proportional decline in procedures from 2012 to 2015 was significantly less in our tertiary centre than the national population based figures ($p< 0.0001$).

There was an increase in the use of chromosomal microarray (CMA) instead of the traditional G-banded karyotype for prenatal samples, rising steadily from 20.5% to 95.6% of all testing during the study period (Figure 2). Chromosomal microarrays are able to detect small gains or losses of DNA (copy number variations, CNVs) that are not detectable by traditional karyotyping and increase the yield of testing, particularly in the presence of a structural fetal abnormality.[7]

The most common major chromosomal abnormalities detected during the study period were trisomy 21 (n=60), pathogenic CNVs (n=22, including 3 cases of 22q11.2 deletion syndrome), trisomy 18 (n=12), triploidy (n=8), monosomy X (n=7), other sex chromosome aneuploidies (n=4), and trisomy 13 (n=3).

Indications for testing

Over the four-year study period, the most common indication for diagnostic testing was a high risk screening result (50.3% of all procedures), followed by ultrasound abnormality (32.0%), risk of single gene disorder (5.8%), advanced maternal age alone (3.1%), obstetric history of previous chromosome abnormality (3.0%) and other indications (5.8%).

Figure 3 shows the annual number of procedures by indication. From 2012 to 2015 the volume of procedures performed for high risk screening results declined significantly from 147 to 94, representing an overall significant reduction in the proportion of all tests performed for this indication from 54% to 43% (chi-squared statistic for linear trend = 4.92, $p = 0.03$). Testing for high risk cfDNA testing increased from zero in 2012 to 11 in 2015. Two procedures were performed due to failed or inconclusive cfDNA results.

There was a significant increase in the number and the proportion of procedures performed for ultrasound abnormalities from 57/198 (28.8%) in 2014 to 88/218 (40.4%) in 2015 (p =

0.01). In 2015, the number of procedures performed for an ultrasound abnormality approached that performed for a high risk screening result (n= 88 and 94 respectively). If women who had diagnostic testing for a high risk CFTS in the presence of a nuchal translucency $\geq$ 3.5mm or cystic hygroma were included under the indication of ultrasound abnormalities, then ultrasound abnormality would have become the most common indication for testing in 2015 (n = 98).

Over the entire study period, 322 women had a diagnostic procedure performed in the presence of an ultrasound abnormality: 293 had testing for ultrasound abnormality as primary indication and 29 had testing for high risk CFTS with a NT $\geq$ 3.5mm. Of these women, 97 (30.1%) were less than 18 weeks gestation at testing, representing the contribution of early ultrasound for detection of fetal abnormalities in our population.

Prenatal diagnosis for advanced maternal age alone is increasingly rare in accordance with changing prenatal screening practices, with only four women undergoing testing for this indication in 2015. Other indications for testing remained constant over the study period.

Diagnostic yield

We defined diagnostic yield as the percentage of procedures that resulted in the diagnosis of a major chromosome abnormality, excluding benign CNVs, balanced translocations, confined placental mosaicism, and CNVs of uncertain or unknown significance. The overall diagnostic yield was 123/915 (13.4%). When grouped by indication for testing, high risk cfDNA result demonstrated the highest diagnostic yield of 12/17 (70.6%). When high risk cfDNA results for sex chromosomes aneuploidy were excluded, the diagnostic yield of NIPT was 11/12 (91.7%). Ultrasound abnormality yielded the next best diagnostic yield (17.7%), followed by high risk CFTS (14.9%). Three women had failed test results (failed culture or sampling).

There was an increase in the proportion of tests that detected minor chromosome abnormalities or CNVs of uncertain or unknown significance, from 1.8% to 8.7% of all tests in association with the increase in CMA use (Figure 4).

Discussion

This study confirms that our Victorian tertiary centre experienced a decline in invasive diagnostic procedures in line with global trends, but that this decline was not as steep as reported in national population-based statistics.[1,3] Furthermore, there was no actual decline in numbers between 2014 and 2015, suggesting that our centre has reached a steady state of approximately 200 procedures p.a., a volume adequate to maintain existing subspecialty training activity.[6]

The less than expected decline in procedures was due to the increasing case load of high risk pregnancies with structural abnormalities, no doubt reflecting the particular characteristics of our tertiary referral population. Advances in first trimester ultrasound are also a likely contributor to the increased number of structural anomalies detected in 2015. It is recommended that women at increased risk of aneuploidy due to an ultrasound abnormality (including NT $\geq$ 3.5mm) undergo diagnostic testing with chromosomal microarray, rather than consider secondary screening with NIPT, due to the increased risk of a pathogenic CNV.[8,9] Our hospital has increasingly adopted CMA as the standard method of chromosome analysis for all patients, with > 95% of prenatal samples in 2015 being sent for CMA rather than G-banded karyotype.

Another reason for the continued numbers of invasive prenatal procedures in our public hospital are the considerable financial barriers to cfDNA screening for public patients. Australian women accessing cfDNA screening are predominantly in private obstetric care, creating significant equity issues for practice.[10,11] In some health care systems, cfDNA is publicly-funded for high risk patients (eg. California Prenatal Screening Program http://www.cdph.ca.gov/programs/pns/Pages/default.aspx), but Australia has yet to adopt a government-funded model for cfDNA testing.

Thirty percent of our diagnostic procedures performed for an ultrasound abnormality (including NT $\geq$ 3.5mm) were performed prior to 18 weeks gestation. The high proportion of our sample that had ultrasound abnormalities detected prior to the routine 18-22 week scan has important implications for the role of first trimester ultrasound independent of CFTS. The retention of the 11-14 week ultrasound for women choosing cfDNA screening as a primary screening test has been advocated because early diagnosis is possible for approximately 50% of fetal abnormalities.[12] Furthermore, up to 16% of women choosing cfDNA screening will have an early ultrasound finding that would alter counselling on their prenatal screening strategy, such as correction of dates, detection of fetal anomaly, multiple gestation or nonviable pregnancy.[13]

The detection of fetal anomalies in late first trimester requires highly trained sonographers and high quality ultrasound equipment. Future analysis of our referral sources is planned to determine the level of obstetric ultrasound expertise associated with these early diagnoses of structural abnormalities.

As a tertiary referral centre, MHW experienced an overall diagnostic yield of 13.4% consistent with recent state-wide figures of 15.8%.[3] This reflects both the improved specificity of current screening methods and the high number of women referred with structural abnormalities. It has important implications for future planning of genetic counselling services and clinical pathways for women following the diagnosis of a major chromosome abnormality.

One of the limitations of this study is the use of MBS data to estimate national numbers of procedures. MBS billing statistics do not capture all procedures performed, and underestimate the number of procedures performed on public hospital patients. However, as we were only calculating the proportional decline over the study period, we believe that the MBS database provided an accurate quantification of national trends in prenatal diagnosis to compare with our hospital data. Another limitation of our study is the lack of national

data on indications for prenatal testing and the results of chromosome testing, highlighting current deficiencies in population-based data collection in this field.

The International Society for Ultrasound in Obstetrics and Gynecology has acknowledged the difficulty in defining the minimum number of procedures necessary for training a new specialist and has suggested that 100 procedures is an appropriate target.[14] Our centre currently has 2.0 full-time equivalent subspecialist trainees (1.6 FTE maternal fetal medicine and 0.4 FTE obstetrical and gynaecological ultrasound) who require this procedural training to be completed by the end of a three year fellowship program. Multiple consultants provide the supervision to these trainees, the majority of which have sessions in private ultrasound practices where they perform diagnostic procedures as primary operators. Our results support the ongoing viability of our tertiary centre for maintaining adequate diagnostic procedural volume for training, though we should continue to maximize existing training opportunities and explore novel training methods, such as simulation models in the future.

Conclusion

The 19.5% decline in prenatal diagnostic procedures observed in our tertiary centre since 2012 was significantly less that than the 53.7% decline reported in nationally, due to increasing referrals for fetal structural abnormalities, and possibly less access to cfDNA screening among public patients. Overall, one in seven invasive procedures in our population yielded a diagnosis of a major chromosome abnormality. Our results demonstrate the substantial contribution of the first trimester ultrasound for early detection of fetal abnormalities in the cfDNA era and the continued viability of specialist training in invasive prenatal procedures.

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Figure legends

Figure 1. Tertiary centre prenatal diagnostic procedures and major chromosome abnormalities detected by year

Major abnormalities excluded benign copy number variations (CNVs), balanced translocations, confined placental mosaicism, and CNVs of uncertain or unknown significance.

Figure 2. Tertiary centre G-banded karyotype and chromosomal microarray tests (CMA) by year.

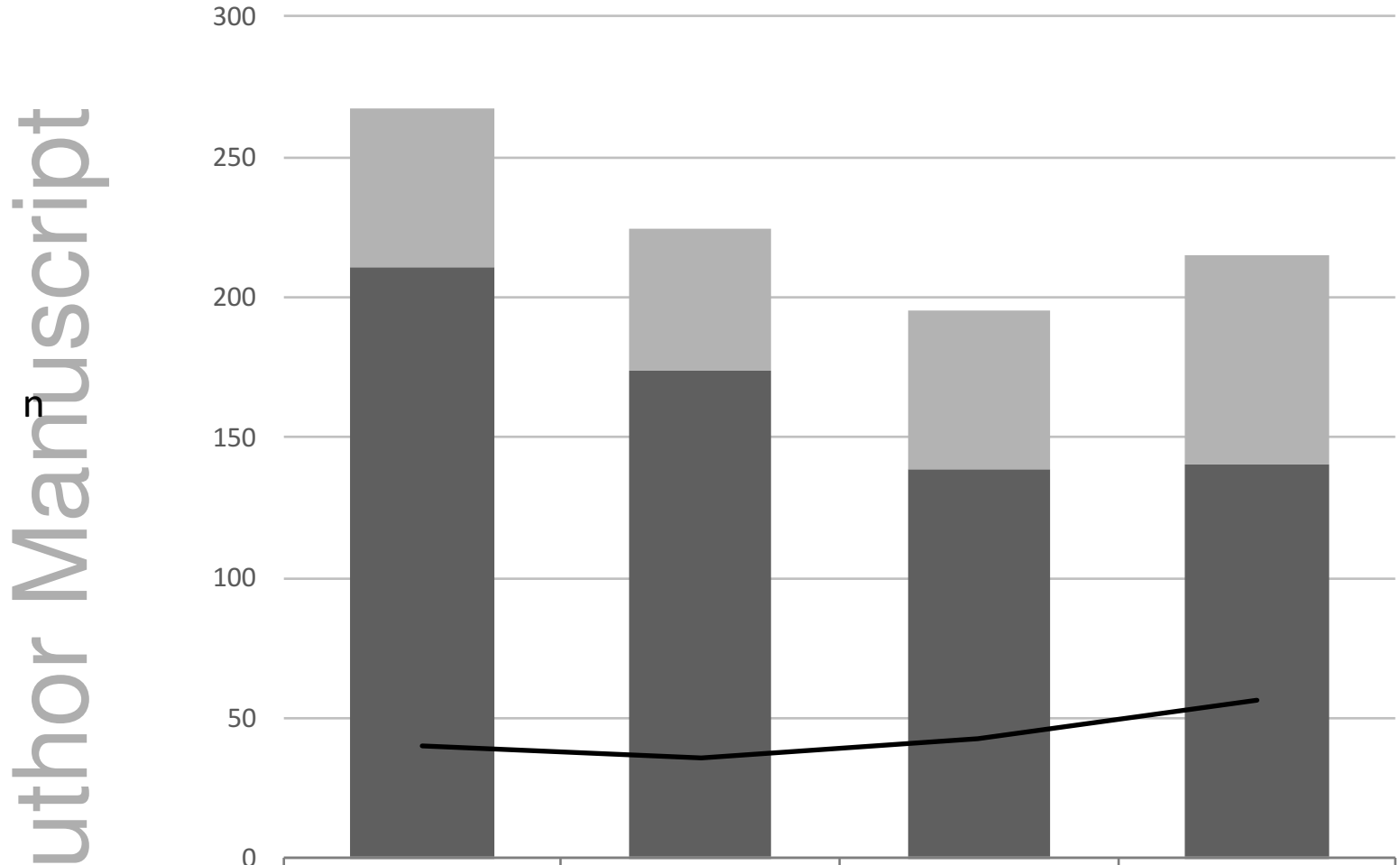
Figure 3. Annual tertiary centre procedures by indication for testing

* chi-square test for trend, p = 0.03

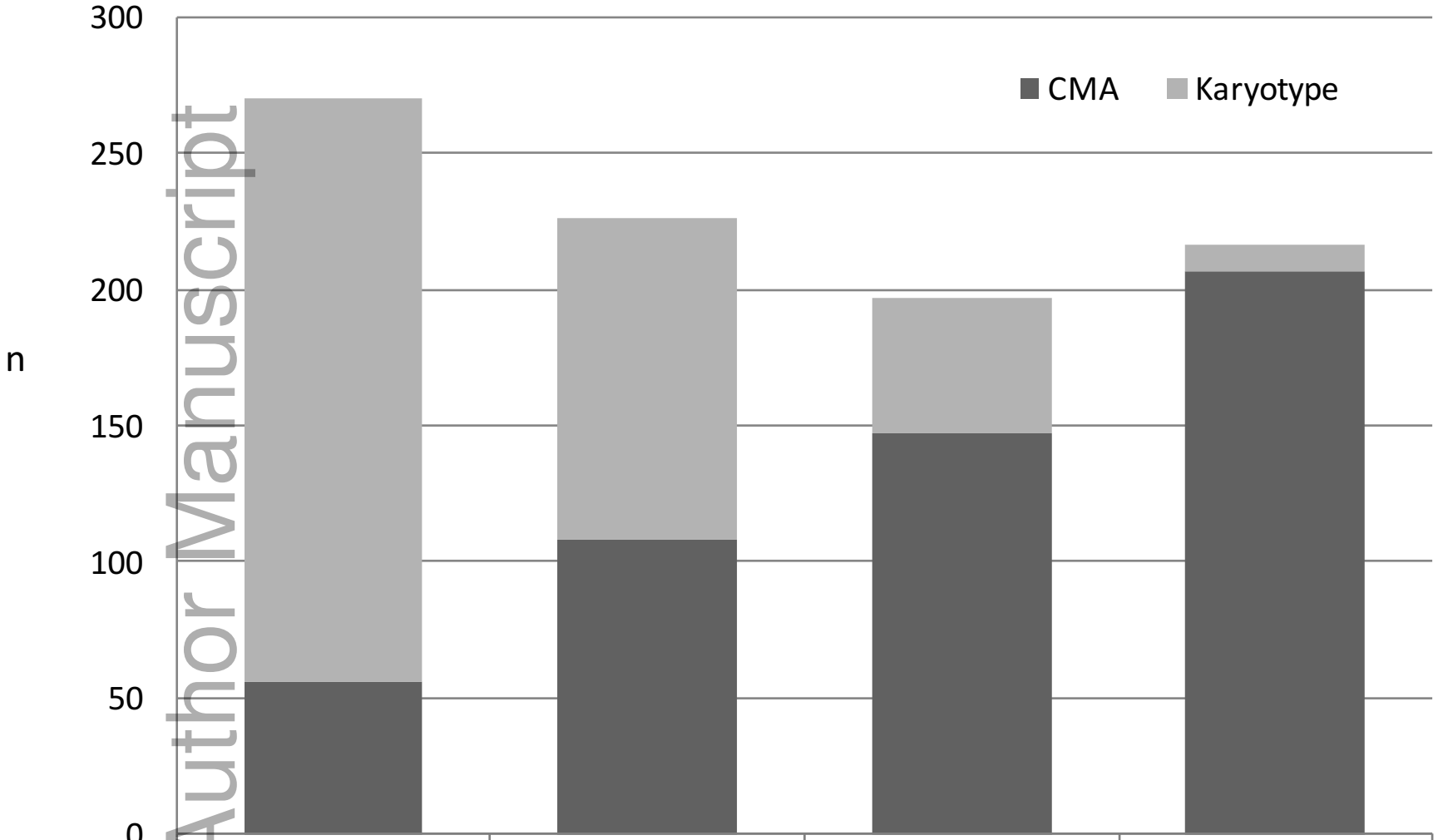
z-test for difference in proportions, p = 0.01

Figure 4. Tertiary hospital diagnostic yield of prenatal testing by year.

Major abnormalities excluded benign copy number variations (CNVs), balanced translocations, confined placental mosaicism, and CNVs of uncertain or unknown significance.



	2012	2013	2014	2015
CVS	56	50	56	75
Amniocentesis	211	174	139	140
Major abnormalities	40	36	43	56



	2012	2013	2014	2015
Karyotype	214	118	50	9
CMA	56	108	147	207