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Title: Population-based trends in ultrasound-indicated prenatal diagnosis from 1994 to 2016: two decades of change

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Short Title: Ultrasound-indicated prenatal diagnosis

Abstract

Objectives:

To assess trends in ultrasound-indicated prenatal diagnostic testing over the past two decades, in the context of rapidly-changing practices in aneuploidy screening and chromosome analysis.

Methods:

Retrospective analysis of ultrasound-indicated amniocenteses and chorionic villus sampling from the Australian state of Victoria from 1994-2016. Ultrasound-indicated prenatal diagnostic testing included those performed for: fetal structural abnormality, fetal death, fetal growth restriction, abnormal amniotic fluid volume, genetic "soft marker", or unspecified ultrasound abnormality. Maternal age, indication for testing, type of diagnostic procedure, gestational age, type of chromosome analysis (G-banded karyotype or chromosomal microarray, CMA), and test results were obtained. Diagnostic yield (percent of tests yielding a major abnormality) was

analysed by year, maternal age, and gestational age. Statistical analysis was performed using the χ^2 tests for trend or difference in proportions as appropriate.

Results:

During the 23-year study period there were 1,533,317 births and 16,152 diagnostic procedures performed for the primary indication of ultrasound abnormality. In recent years, ultrasound abnormality became the most common indication for prenatal diagnosis (29.4% of tests in 2013-2016) due to steeper declines in testing for combined first trimester screening or maternal age alone. In 2016, > 95% of ultrasound-indicated procedures were performed with CMA; among these, pathogenic copy number variant (CNV) was the most common abnormality (3.5%), followed by trisomy 21 (2.8%). The diagnostic yield for ultrasound-indicated tests < 16w was significantly higher than > 20w (31.5% vs 9.0%).

Conclusions:

Ultrasound-indicated procedures are contributing to prenatal diagnosis in new ways in the genomic era. A pathogenic CNV is now the most likely diagnosis after ultrasound-indicated testing, rather than trisomy 21 or other whole chromosome aneuploidy. Despite steady improvements in first trimester screening for aneuploidy, the diagnostic yield of ultrasound-indicated tests > 20 weeks has remained stable due to increased utilization of CMAs.

Procedures performed for structural abnormalities < 16w continue to have the highest diagnostic yield, supporting the benefits of early fetal structural assessment at 11-13 weeks.

Introduction

After more than 60 years since its application to obstetrics, ultrasound has become a cornerstone of modern prenatal care, allowing assessment of gestation age, fetal viability, multiple pregnancy, placental location, fetal morphology and growth[1]. The detection of fetal anomalies, present in 2-3% of all pregnancies, provides timely opportunities for specialist assessment, genetic testing, counselling and perinatal management[2]. The midtrimester morphology scan, performed at 18-22 weeks, is a routine examination offered to all pregnant women in well-resourced countries[3]. Fetal chromosome analysis is usually offered in the presence of structural anomalies or "soft markers" due to their association with trisomy 21 and other chromosome abnormalities.

An 11-13 week ultrasound for aneuploidy screening is commonly performed in addition to the midtrimester morphology scan. The fetal nuchal translucency (NT) measurement at 11+0 to 13+6 weeks is integrated with serum pregnancy-associated plasma protein A and beta human chorionic gonadotrophin levels to form the combined first trimester screening test (CFTS) for trisomies 21, 13 and 18.[5,6] The 11-13 week NT scan has now assumed additional importance as a comprehensive early fetal anatomy survey, capable of detecting up to 50% of major fetal abnormalities.[7]

Parallel advances in genomics have also improved our screening and diagnostic capacity. Maternal plasma cell-free DNA-based (cfDNA) screening has unprecedented accuracy as a trisomy 21 screening test[8], and has been responsible for large reductions in diagnostic procedures due to its low false positive rate.[9] Furthermore, prenatal diagnosis with chromosomal microarrays (CMA) are now recommended for all structurally abnormal fetuses as 2.8% will have a pathogenic copy number variant (CNV) not detectable on G-banded karyotype.[10,11]

These combined advances have caused our field to re-examine the contribution of ultrasound to the diagnosis of fetal chromosome abnormalities.[12-16] Our specific objectives were to determine trends in (i) population-based rates of ultrasound-indicated diagnostic testing; (ii) the diagnostic yield of ultrasound-indicated testing by gestational age and maternal age; and (iii) the uptake of CMA analysis for ultrasound-indicated testing and its impact on diagnostic yield.

Materials and Methods:

Study Population:

This study analyzed data on prenatal diagnosis from the Australian state of Victoria for the years 1994-2016. During this period, there were approximately 66,000 births per year, and the fertility rate ranged from 1.7 to 2.0. Between 2004 and 2016, the median maternal age ranged from 31-33 years (Australian Bureau of Statistics http://stat.data.abs.gov.au).

Voluntary prenatal screening for chromosome abnormalities has been a longstanding component of routine pregnancy care in Australia. We divided our 23-year study period into three eras to reflect changing practices in aneuploidy screening and prenatal diagnosis.

i) Era 1 (1994-1999) "AMA". Advanced maternal age (AMA) was the most common indication for testing in this period and was fully Government-funded for women aged 37 years or older. Second trimester serum screening (STSS) for aneuploidy and neural tube defects using the quadruple test at 14–20 weeks gestation was offered to women of all ages from 1996 and is also Government-funded. A STSS result was considered positive if the risk of trisomy 21 was $\geq$ 1 in 250, the risk of trisomy 18 $\geq$ 1 in 200 or if the risk of neural tube defected was increased due to alpha-fetoprotein level > 2.5MoM. STSS was performed in 9.2% of all births during this era (Supplementary table 1, Figure S1).

ii) Era 2 (2000-2012) "CFTS". Combined first trimester screening (CFTS) for trisomies 21 and 18 was introduced as a government subsidized test in Victoria in 2000. Fetal nasal bone assessment

was included as an optional component of CFTS from 2011. There is an out-of-pocket expense for CFTS, but typically < 200AUD depending on the ultrasound and laboratory provider. A CFTS result was considered positive for trisomy 21 if the risk was $\geq$ 1 in 300. Population-uptake of CFTS and STSS were 50% and 12% respectively during this era (Supplementary table 1, Figure S1)

iii) Era 3. (2013-16) "cfDNA/CMA era" This period spans the introduction of cfDNA and CMA into prenatal testing. During this era, population-based uptake of CFTS remained high at 74%, while STSS declined to 5% of births (Figure S1). CfDNA screening became commercially available through overseas laboratories in early 2013 on a patient-funded basis at an average cost of AUD500. The utilization of cfDNA is not regulated or subsided by the government, but has been rapidly adopted within the private health sector and is typically performed at 10-11 weeks gestation. Data collection on total cfDNA testing numbers in our state is not performed, but based on the numbers diagnostic tests performed for high risk cfDNA results, it appears that approximately 19% of pregnant women utilized cfDNA screening in 2015 at an average cost of AUD500.[9] Despite the growing utilization of cfDNA as a primary screening test, the numbers of 11-13 week ultrasounds have continued to increase in Victoria, presumable due to its utility as an early morphology survey.[9]

A second trimester morphology scan between 18-22 weeks gestation is offered to all women as a standard Government-funded component of prenatal care. It is free when provided by a public hospital, and involves a variable out-of-pocket cost to the patient when performed in a private ultrasound practice. Uptake of the second trimester morphology ultrasound is anecdotally very high (>90%), but complete population data was not available for inclusion in this study.

Standard components of prenatal diagnostic testing (amniocentesis and CVS, and associated chromosome analysis) are fully government funded if performed for approved indications in a public hospital and partially funded if performed in a private ultrasound practice. There have been no significant changes to the funding structure for prenatal diagnosis during the study period.

Ethics approvals for this study were provided by the Human Research Ethics Committees of the Royal Children's Hospital (ref no. 3115A) and Monash Health (ref. no. 12063B).

Data Sources

Victorian Prenatal Diagnosis Database

Prenatal diagnosis data from 1994-2016 were obtained from the Victorian Prenatal Diagnosis Database. This database has been described elsewhere[17] and encompasses all prenatal diagnostic testing (amniocentesis and chorionic villus sampling (CVS) in the Australian state of Victoria, collected from the four cytogenetic laboratories (see Acknowledgements).

All amniocenteses and CVS performed in women with a Victorian residential postcode for a primary indication of ultrasound abnormality were included. Tests performed on fetal blood, urine or ascites were rare (<1% of the total data set) and excluded. Tests that had a dual indication of high risk CFTS or STSS were excluded; however, ultrasound-indicated tests that were performed in women for "enlarged nuchal translucency measurement" alone were included. Women with dual indications of "enlarged nuchal translucency" and advanced maternal age or positive family/personal history of chromosome abnormality were also included.

The data obtained for each case included: maternal age, indication(s) for testing, type of test done (amniocentesis or CVS), gestation at time of testing, test date, test result, and singleton or multiple pregnancy. A single record was created for twin pregnancies or women who had a repeat test during the same pregnancy. Annual rates of missing gestational age data ranged from 5-8%; approximately one third of these were CVS and two thirds were amniocenteses. If

GA data were missing, CVS were assumed to be < 16 weeks gestation, and amniocenteses at least 16 weeks gestation in keeping with common local clinical practice.

Clinical indications for testing were based on the information provided by the referring clinician. Ultrasound indications included fetal structural abnormalities, fetal death, fetal growth restriction, placental or amniotic fluid abnormalities, "soft markers" for aneuploidy, and unspecified ultrasound abnormalities. The markers of increased nuchal translucency/ nuchal fold or hypoplastic nasal bone were included if they were nominated by the clinicians as an isolated indication, without concurrent high risk serum screening result.

The types of chromosome analysis performed included G-banded karyotype and chromosomal microarray (CMA). Fluorescent in situ hybridization results and results from single gene testing were not considered in this analysis. The chromosomal microarray most commonly routinely used for testing was the Affymetrix CytoScan 750K, which has a genomic resolution of approximately 0.2 Mb.

Results of chromosome analyses were categorized as normal or abnormal. The abnormal results were then further categorized into 'major' and 'minor' abnormalities. Major abnormalities included all cases of autosomal and sex chromosome aneuploidy, polyploidy,

unbalanced translocations/rearrangements, level III mosaics, and pathogenic copy number variations (CNVs that encompass a region implicated in a well-described abnormal phenotype). Minor chromosomal abnormalities included confined placental mosaicism, balanced translocations/rearrangements, and CNVs of uncertain or variants of unknown or uncertain significance (VUS).

Australian Bureau of Statistics

Statistics on Victorian births were obtained from the Australian Bureau of Statistics (http://stat.data.abs.gov.au). These data do not incorporate stillbirths or terminations of pregnancy, and therefore are expected to underestimate total confinements by <1%.[17] *Population testing rate* was the number of ultrasound-indicated diagnostic procedures as a percentage of total births. *Diagnostic yield* was defined as the number of major chromosome abnormalities as a percentage of ultrasound-indicated diagnostic procedures.

Statistical analysis

Data analysis was performed in STATA 14 (College Station, TX: StataCorp LP) and PRISM 6 Version 6.0h (San Diego, CA, USA). Two-tailed χ^2 tests for comparison of two proportions, or for trends were performed as appropriate, with a p value of <0.05 being considered significant.

Results:

Overall trends in ultrasound-indicated prenatal diagnosis

During the 23-year study period there were 1,533,317 total births and 16,152 total diagnostic procedures performed for the primary indication of ultrasound abnormality. The annual number of ultrasound-indicated tests ranged from 392 to 1,086. The peak rate of diagnostic testing for ultrasound abnormalities occurred in the year 1999, when nuchal translucency ultrasounds were introduced (Fig 1). Since then, there has been an overall decline in the annual population rate of ultrasound-indicated testing from the peak of > 1000 to approximately 600.

As a percentage of all births, there was a significant reduction in the population rate of ultrasound-indicated testing across entire study period (χ^2 trend = 160.4, $p < 0.0001$). The decline was also observed in the 3 years before and after the introduction of cfDNA in 2013, from 1.0% in 2010 to 0.69% in 2016 (χ^2 trend = 60.34, $p < 0.001$). Apart from the period 1997 to 2005 when testing for isolated increased NT was common, the majority (51.6%) of ultrasound-indicated tests were performed after 18 completed weeks gestation (Fig 2). When analysed by gestational age group, there was no significant trend observed for the population-testing rate after 18 weeks gestation over the study period (χ^2 trend = 1.430, $p = 0.23$) but a highly significant declining trend for tests performed before 18 weeks gestation (χ^2 trend = 287.7, $p < 0.001$).

Ultrasound abnormality made up an increasing proportion of indications for testing over the study period, rising from 13.2% of tests in era 1, to 29.4% in era 3 (χ^2 trend = 1075, $p < 0.001$) (Table 1). Since 2015, ultrasound abnormalities have been the most common indication for prenatal diagnosis due to steep declines in other indications for testing such as CFTS and AMA (Fig 3).

Diagnostic yield

The overall diagnostic yield of ultrasound-indicated tests did not change significantly over the three eras, remaining steady around 18% (χ^2 trend =0.11, p=0.74) (Fig 4). The diagnostic yield of US-indicated tests was inversely related to the gestational age at the time of testing. The average diagnostic yields were 31.5%, 14.4% and 9.0 % for tests performed at < 16 weeks, 16-19 weeks (inclusive) and ≥ 20 weeks gestation, respectively.

The mean maternal age during the study period was 32.2 years (range 15-50 years). The diagnostic yield of ultrasound-indicated testing was positively associated with advanced maternal age, (χ^2 trend = 631, $p < 0.001$) (Table 2). Major chromosome abnormalities were more than twice as common in those aged 40 years or more compared with women under 35 years (39.9% vs 14.2%).

Chromosomal microarrays

Utilization of CMAs for ultrasound-indicated tests rose steeply from 0.1% (1/567) of ultrasound indicated tests in 2009 to > 95% in 2016 (543/569). Conventional karyotypes had a significantly higher diagnostic yield (53.2% (175/325) than CMA (12.5%, 272/2169) in era 3.

Detection of major chromosome abnormalities

Fetal structural abnormalities have declined in their relative contribution to the annual detection of trisomy 21, dropping from 51 cases per annum in era 2, to 31 p.a. in era 3 (Table 3). Despite this decline in the ascertainment of trisomy 21 by ultrasound abnormality, the overall detection of total major chromosomal abnormalities remained consistent due to the increasing detection of pathogenic CNVs and atypical abnormalities (ie chromosome abnormalities other than trisomies 21, 13 and 18). Pathogenic CNVs (including 22q11.2 microdeletions) are now the most common major abnormalities detected via ultrasound, more frequently than trisomy 21 and trisomy 18 (Fig 5).

Of the 569 women who underwent ultrasound-indicated prenatal diagnosis in 2016, pathogenic CNVs were found in 3.5% (n=20), trisomy 21 in 2.8% (n=16), trisomy 18 in 2.6% (n=15),

monosomy X in 2.5% (n=14) and trisomy 13 in 2.3% (n=13). The percentage of results with variants of unknown or uncertain significance were 3.3% and 3.8% respectively.

The population prevalence of ultrasound-detected pathogenic CNVs has increased from 0.14/10,000 (1 in 71,428) in 2009 to 2.41/ 10,000 (1 in 4149) in 2016. (Fig 5). The majority of pathogenic CNVs were detected in second trimester. In era 3 (2013-16), 22.6%, 17.3% and 60.0% of pathogenic CNVs were detected at < 16 weeks, 16-19 weeks, and ≥20 weeks respectively.

The composition of the major abnormalities detected varied by maternal age. Trisomy 21 made up 13%, 26% and 34% of major abnormalities in the women aged < 35 years, 35-39 years and 40 years respectively, which would be expected given the association of maternal age with trisomy 21 risk. Conversely, pathogenic CNVs made up a greater proportion of major abnormalities in younger women, comprising 14%, 9% and 7% of major abnormalities in women aged < 35 years, 35-39 years and 40 years respectively.

Discussion

Ultrasound-indicated prenatal diagnosis has evolved significantly over the past two decades. Our historic overview demonstrates a gradual decline in the rate of procedures for this

indication group since its peak in 1999. Despite this overall decline, ultrasound abnormality has become the most common indication for diagnostic testing, responsible for 29.4% of tests in era 3 (2013-16). This is due to the steeper decline in other indications such as AMA and CFTS. Significantly, trisomy 21 is no longer the most common chromosome abnormality ascertained via an ultrasound abnormality - pathogenic CNVs and atypical abnormalities are now the most common abnormalities. This reflects the combined impact of cfDNA screening - which has assumed a major role in the detection of trisomy 21 since 2015[9] - and the high utilization of CMA observed in this study (> 95% of all ultrasound-indicated tests in era 3).

Our results support the clinical utility of performing a first trimester ultrasound for structural abnormalities, in addition to the routine second trimester scan performed at 17-22 weeks. The diagnostic yield for ultrasound-indicated tests performed prior to 16 weeks gestation was 3 times higher than those performed after 20 weeks gestation (31.5% vs 9.0%), providing earlier diagnosis and maximising management options for these women. The International Society of Ultrasound in Obstetrics and Gynecology recommends that all women should be offered a first-trimester ultrasound regardless of their intention to undergo cfDNA screening.[15] This practice has not been assessed for cost-effectiveness in our population, but in 2015 appeared to be widespread.[9]

Importantly, we did not observe any changes in the diagnostic yield of ultrasound-indicated testing after 20 weeks gestation as a result of advances in first trimester aneuploidy detection. An effective first trimester aneuploidy screening program would be expected to result in a midtrimester pregnancy population with a low prevalence of the common aneuploidies. However, diagnostic testing performed after 20 weeks gestation maintained its diagnostic yield of around 9.0% in era 3 due to the detection of pathogenic CNVs by CMA. In fact, the majority (> 60%) of pathogenic CNVs were detected after 20 weeks, presumably as a result of abnormalities seen at the midtrimester morphology scan. This finding goes some way to allaying concerns regarding the impact of cfDNA screening on the detection of atypical abnormalities.[19]

One of the negative consequences of the high utilization of CMA is the genetic counselling load associated with managing VOUS, which were present in approximately 5% of results. The most common CMA used was a high resolution whole genome SNP-array, which may be partly responsible for the relatively high rate of VUS. There is evidence that a prenatal diagnosis of VUS may increase maternal anxiety and utilization of medical services both prenatally[20] and postnatally.[21] This highlights the increasing demand for health professionals with genetic counselling skills and the need for long term follow-up of children born with a VUS.

G-banded karyotypes only made up 5.9% (148/2494) of the total tests in era 3. Unexpectedly, we found the rate of major chromosome abnormalities to be higher for those samples analysed by conventional karyotype than by CMA. We speculate that the high rate of abnormality returned on these samples is because G-banded karyotypes may be selectively utilized in cases with very high clinical certainty of a common aneuploidy such as trisomy 21, or where a rapid aneuploidy test, such as fluorescent in situ hybridisation, has already returned an abnormal result. In these cases, structural information about the chromosomes may be useful for excluding inherited forms of aneuploidy and be more informative than a CMA.

The major strength of our study is the large state-wide dataset on prenatal diagnosis, including clinical indications, maternal age, gestational age and chromosome results. The population-based collection avoids the bias of tertiary centre studies and enables us to make confident conclusions about patterns of clinical practice in our state.

Our study had a number of limitations. The level of detail about the ultrasound abnormality was dependent on the clinical information provided by the referrer to the laboratory. We did not have access to ultrasound reports or the total number of ultrasounds scans performed over the study period. We were thereforeunable to confidently distinguish “low risk” cases with isolated soft markers from those at high risk due to structural abnormalities as many referrals

were ambiguous ("hydronephrosis" or "short long bones") or nonspecific ("ultrasound abnormality"). We also could not assess the rate of prenatal diagnostic testing after a diagnosis of a particular fetal abnormality (other than NT/nuchal fold/hypoplastic nasal bone), nor assess the total number of ultrasounds over the study period. Government billing statistics can provide estimates but underestimate total numbers as they do not include services provided by hospital doctors to public patients in public hospitals. However, our examination of publicly-available billing data for the period 2010-2016 suggests at least 70% of pregnancies in Victoria were scanned with either a 11-13 week NT scan or a 12-16 week ultrasound.[22]

Our study provides important data that may assist in future cost-benefit analyses of prenatal screening and diagnosis in our state. The government cost savings brought about by the decline in invasive prenatal diagnosis have been achieved through improved screening with CFTS and cfDNA. CfDNA screening still remains entirely patient-funded, yet contributes to > 50% of all prenatal diagnosis of trisomy 21.[9] These facts suggest that the cost to the public health system per diagnosis of trisomy 21 may have declined, since well-resourced women have assumed the cost of technological improvements in aneuploidy screening.[23]

Conclusion

Our population-based study shows that ultrasound-indicated prenatal diagnosis is contributing in new ways in the genomic era. Ultrasound abnormalities are now the most common indication for diagnostic testing and are more likely to reveal a pathogenic CNV than trisomy 21 or trisomy 18. While the diagnostic yield of ultrasound-indicated tests performed after 20 weeks gestation has remained stable, testing prior to 16 weeks gestation has the highest diagnostic yield, supporting the benefits of early fetal structural assessment in the cfDNA era.

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Disclosures of interests

None declared.

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Figure Legends

Figure 1. Annual numbers of prenatal diagnostic tests performed in Victoria (1994-2016)

NT/NF: nuchal translucency/ nuchal fold

AMA, advanced maternal age

CFTS, combined first trimester screening

cfDNA/CMA, cell-free DNA/chromosomal microarray

Ultrasound abnormality includes: fetal structural abnormalities, fetal death, fetal growth restriction, placental or amniotic fluid abnormalities, "soft markers" for aneuploidy, and unspecified ultrasound abnormalities

Figure 2: Population testing rate of ultrasound indicated tests by gestational age (%)

AMA, advanced maternal age

CFTS, combined first trimester screening

cfDNA/CMA, cell-free DNA/chromosomal microarray

* NS

** $p < 0.0001$

Figure 3: Prenatal diagnostic tests by indication 1994-2016

AMA, advanced maternal age

CFTS, combined first trimester screening

US abn, ultrasound abnormality

STSS, second trimester serum screening

cfDNA, cell-free DNA screening

Other, includes obstetric or family history of chromosome abnormality, anxiety,

Testing for single gene disorders not shown (<10% of all tests annually)

Figure 4: Diagnostic yield of ultrasound-indicated tests by weeks of gestation

AMA, advanced maternal age

CFTS, combined first trimester screening

cfDNA/CMA, cell-free DNA/chromosomal microarray

Figure 5: Prenatal detection of major chromosome abnormalities per 10,000 births

AMA, advanced maternal age

CFTS, combined first trimester screening

cfDNA/CMA, cell-free DNA/chromosomal microarray

pCNVs, pathogenic CNVs

Other: includes sex chromosome aneuploidy, triploidy, rare autosomal trisomies/monosomy, level III mosaicism, unbalanced rearrangements

Table 1: Ultrasound-indicated prenatal diagnostic testing in Victoria (1994-2016)

Ultrasound-indicated prenatal tests	**Total study period (1994-2016)**	**Era 1 (AMA) (1994-1999)**	**Era 1 (CFTS) (2000-2012)**	**Era 3 (cfDNA/CMA) (2013-2016)**	**P value (chi sq trend)**
Rate per 100 births	1.05%	1.06% (3890/367807)	1.13% (9,768/860857)	0.82% (2494/304653)	< 0.001
Percent of total diagnostic tests	17.1%	13.0% (3890/29813)	17.4% (9,768/56033)	29.4% (2494/8477)	< 0.001
Diagnostic Yield	18.5%	17.9% (695/3,890)	18.9% (1845/9768)	17.9% (447/2,496)	0.7

Table 2: Diagnostic yield of ultrasound-indicated testing by maternal age and screening era

Maternal age (years)	Era 1 (AMA) (1994-1999)	Era 2 (CFTS) (2000-2012)	Era 3 (cfDNA/CMA) (2013-2016)	Overall
< 35	13.8% (386/2792)	14.2% (960/6761)	14.8% (269/1,813)	14.2% (1,615/11,366)
35 – 39	22.9% (170/742)	24.6% (506/2061)	22.1% (106/479)	23.8% (782/3,282)
≥ 40	41.6 % (133/320)	40.2 % (379/942)	35.6% (72/202)	39.9% (584/1,464)

Table 3:
Annual numbers of chromosome abnormalities detected via ultrasound-indicated testing by screening era

	Screening era		
	Era 1 (AMA) (1994-1999) n= 3890	**Era 2 (CFTS) (2000-2012) n= 9,768**	**Era 3 (cfDNA/CMA) (2013-2016) n = 2,494**
Average annual ultrasound-indicated tests (n)	648	751	623
Average annual births (n)	61,301	66,220	76,163
Average annual no. of major chromosome abnormalities detected via ultrasound indication	**99.66**	**121.54**	**85.25**
Trisomy 21	43.33	51.31	31.25
Trisomy 18	25.83	32.77	20.25
Trisomy 13	8.17	12.69	12
Turners (XO)	11.83	15.08	11.5
Other sex chromosome abnormality	2.5	2	4
Other autosomal aneuploidy	0.17	0.92	1
Polyploidy	7.83	6.77	5.25
Pathogenic Copy Number Variation	**0.17**	**3.84**	**18.75**
22q11.2 deletion	0	1.46	5
Other Pathogenic Copy Number Variation	0.17	2.38	13.75

Other major abnormalities	**16**	**16.54**	**7.75**
Minor Chromosome Abnormalities	4.34	8.69	48.5

Title: Population-based trends in ultrasound-indicated prenatal diagnosis from 1994 to 2016: two decades of change

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