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ORIGINAL ARTICLE

Impact of prenatal screening and diagnostic testing on trends in Down syndrome births and terminations in Western Australia 1980 to 2013

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ABSTRACT

Objective To assess how prenatal screening and diagnostic testing have impacted the diagnosis, termination and birth prevalence of Down syndrome in Western Australia (1980–2013).

Method We analysed trends in termination rates and birth prevalence of Down syndrome using aggregated data (1980–2013). We modelled the expected live-birth rate and prevalence of Down syndrome and compared different eras of screening and diagnosis with respect to the impact on live-birth rate and prevalence of Down syndrome.

Results Between 1980 and 2013, the rate of Down syndrome pregnancies increased, corresponding to a greater proportion of babies born to older women. Following the introduction of screening in 1994, the rate of live-born infants with Down syndrome reduced significantly ($p = 0.001$). The rate of terminations of pregnancy for Down syndrome remained stable over this period. In the absence of termination, the Down syndrome live-birth rate would have risen from 1.1 per 1000 to 2.17 per 1000 between 1980 and 2013.

Conclusion Prenatal testing in Western Australia has reduced the birth prevalence of Down syndrome despite an increased rate of Down syndrome pregnancies. Most women for whom a prenatal diagnosis of fetal Down syndrome is made, chose to terminate the pregnancy (93%), and this proportion has not changed over the study period. © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION

Invasive diagnostic tests for fetal chromosomal abnormalities [such as Down syndrome (DS)] have been available since the 1970s.[1] These tests can detect the presence of a chromosomal abnormality via the karyotyping of fetal DNA within a sample of amniotic fluid (amniocentesis) or the placenta (chorionic villus sampling). As these tests carry a small but significant risk of miscarriage (0.6%–1.0%), their use has been generally recommended only among women with pregnancies considered to be at high risk for chromosomal abnormality.[2,3]

As the risk of chromosomal abnormality increases with advancing maternal age, invasive diagnostic tests were initially recommended only for women at high risk based on advanced maternal age (over 35 years of age), a threshold risk of 1 : 300, which was considered to balance the procedure related miscarriage risk with that of having a live-born infant with DS.[2] In the late 1980s, a screening test, based on the measurements of three maternal serum analytes at 15 to 18 weeks of pregnancy [maternal serum screening (MSS)], became available.[4] This offered a more refined risk assessment for fetal DS as well as Edwards and Patau syndromes. First-trimester combined screening (FTS) using two serum markers in combination with an ultrasound measurement of the nuchal fold in the fetal neck provided a yet more accurate test in the late 1990s and was available at an earlier stage of pregnancy (9–13 weeks). Until recently, this was the best option for the assessment of risk for fetal Down syndrome, with a detection rate of 86% at a false positive rate of 5%.[5] However, since 2012, a screening test has become available with a performance that approaches that of invasive testing, identifying pregnancies at high risk of fetal DS with a sensitivity and specificity of 98% to 99%.[6,7] In Australia, prenatal screening for fetal anomalies is offered to pregnant women through general practitioners and obstetric specialists, supported by a universal health insurance scheme for diagnostic

Table 1 **Data sources**

Data by year (1980–2013)	Source
Live-births, stillbirths and terminations of Down syndrome	WARDA [unpublished data]
Maternal age distribution among pregnancies with fetal Down syndrome	WARDA [unpublished data]
All births	WARDA[12]
Maternal age in all births (% over 35 years)	Western Australian Midwives Notification System,[13] Australian Bureau of Statistics[14]
Down syndrome fetal loss rate	Literature[27]
The number of benefits paid (and cost) by the AIHC for prenatal screening and diagnosis (1994–2013)	Australian Health Insurance Commission[18]
MSS (MBS Item 66321, 66740, 66751)	—
FTS bloods (MBS Item 66750)	—
FTS ultrasound (MBS Item 55707)	—
Amniocentesis (MBS Item 16600)	—
Chorionic Villus Sampling (MBS Item 16603)	—

WARDA, Western Australian Register of Developmental Anomalies; MSS, maternal serum screening; FTS, first trimester test; MBS, Medicare Benefits Schedule.

and therapeutic services. Government health services provide health professionals and individuals a range of genetic paediatric, obstetric and general genetic services, including counselling services for prenatal diagnosis, carrier detection, predictive testing and newborns. Regardless of their choice regarding screening or diagnostic testing, families can access free or subsidised health and support services for children with disabilities.

Non-invasive prenatal testing (NIPT) uses cell-free fetal DNA circulating within maternal blood to assess the risk of fetal DS and several other chromosomal abnormalities. Throughout this period of development in prenatal testing, there have been significant changes in maternal age distribution, with a growing percentage of babies born to women over the age of 35 years.[8] With this shift has come an increased prevalence of fetal chromosomal abnormality.[8]

Non-invasive prenatal testing is not yet in routine clinical use, with no public or health care funding for the test in Australia at this time. With recent discussion around the role of NIPT within the screening pathway and the potential impact of the introduction of this yet more accurate screening test,[9–11] it is timely to review the history of prenatal screening and diagnostic testing and births and terminations of Down syndrome in Western Australia over the last 30 years. This will allow us to assess the impact that these tests may have had on diagnosis and termination rates and the birth prevalence of DS in the Western Australian community.

METHODS

We used aggregated unpublished data from the Western Australian Register of Developmental Anomalies (WARDA)[12] and reports from the Western Australian Midwives Notification System[13] and Australian Bureau of Statistics[14] to analyse trends in termination rates and the birth prevalence of DS between 1980 and 2013. We provide data and analysis on three different eras of prenatal testing defined by when advances in prenatal testing occurred, specifically when the wide-spread use of maternal serum screening (from 1994 in Western Australia),[4] and first trimester screening (from 2004 in Western Australia). We also compare the pre and post screening periods (1980–1994 and 1995–2013). NIPT became available in Western Australia in late 2012 on a user-pays basis; however, its use is not expected to have yet been widespread enough to be able to report on the impact of this technology. WARDA data relate to all notified cases of Down syndrome (ICD9-BPA codes 75800–75809) born and terminated in Western Australia over this time. The Registry has been shown to have a high level of case ascertainment.[15] Of note, is that prenatally diagnosed DS that resulted in spontaneous miscarriage prior to 20 weeks are not recorded on the registry.

Using these data and assuming all terminations occurred following a confirmed diagnosis, we modelled the expected live-birth rate and live-birth prevalence of Down syndrome in the absence of prenatal diagnosis over this time, accounting for the expected miscarriage rate in fetal DS. Savva *et al.* showed that the loss rate for fetal DS between chorionic villus sampling (considered to be <16 weeks) and amniocentesis (considered to be >16 weeks) and full term pregnancy varied by maternal age, with older women having higher rates of loss.[16] To account for this variation, we calculated the expected fetal loss among terminations for each year based on the proportion terminated before and after 16 weeks and the median maternal age for these terminations using the fetal-loss rates reported by Savva *et al.*[16] The upper and lower confidence interval limits were also used to provide less and more conservative estimates of fetal loss, shown as error bars in figures. Data on the distribution of maternal age among pregnancies and among those pregnancies with fetal DS are also presented. We used piecewise linear (segmented) regression[17] to compare the live-born rates of DS and the percentage of DS terminated over the different eras of prenatal diagnosis (1980–1993, 1994–2003, 2004+) allowing possibly different line segment slopes and intercepts within each of these three periods. Analysis was done in Excel (Microsoft Corporation, Redmond, WA, USA) and TIBCO Spotfire S+ version 8.2 (TIBCO Spotfire, Boston, MA, USA).

To provide a picture of trends in the uptake and costs of prenatal screening, we also sourced data from the Australian Health Insurance Commission (AHIC), available from 1994 onwards. These data include the absolute number of, and

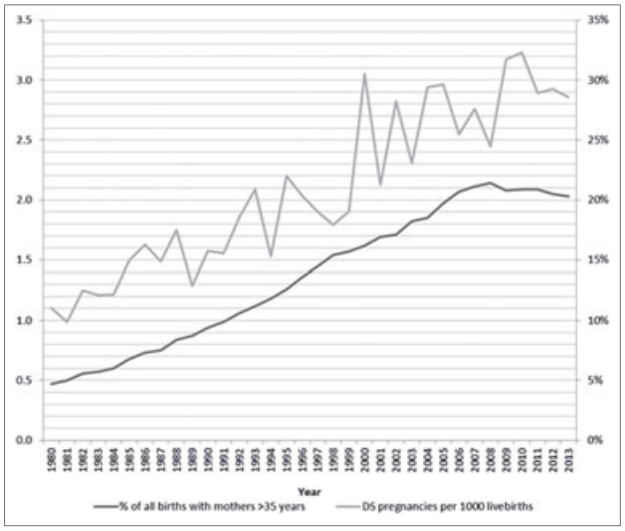


Figure 1 Down syndrome pregnancies per 1000 live births and % of babies born to women over the age of 35 years

* one case of fetal DS that was terminated following the prenatal diagnosis of other anomalies but diagnosed with fetal DS post mortem has been removed from this chart to prevent possible identification of the case.

Figure 2 Down syndrome pregnancies diagnosed prenatally and percent of Down syndrome pregnancies terminated

benefits paid by the AHIC via Medicare for first trimester and maternal serum screening between 1994 and 2013.[18] All women qualify for a rebate for MSS and FTS blood tests; however, some centres do not consider all women to qualify for the FTS ultrasound because of differences in the interpretation of the Medicare item number. We therefore used the number of FTS blood tests to quantify the number of FTS combined screens. We also report the number of invasive prenatal tests (amniocentesis and chorionic villus sampling); however, the data are not specific to the use of these tests for the diagnosis of Down syndrome. Item numbers used are shown in Table 1. Additional data used to develop the models are provided in Appendix 1.

RESULTS

Between 1980 and 2013, there were 1918 cases of fetal DS (including those terminated, stillborn and live-born) in Western Australia and 892908 births (2.1 cases of fetal DS per 1000 births). Fifty six percent of fetal DS (1082/1918) were diagnosed prenatally, and 52% of all cases (1006/1918) were terminated. Of the 48% of cases which were not terminated, 868 were live-born, and 44 were stillborn. There was no significant difference ($p=0.69$) between the percentage of pregnancies terminated following prenatal diagnosis of DS in the period 1980 to 1994 (94.9%) compared with the period 1994 to 2013 (92.6%).

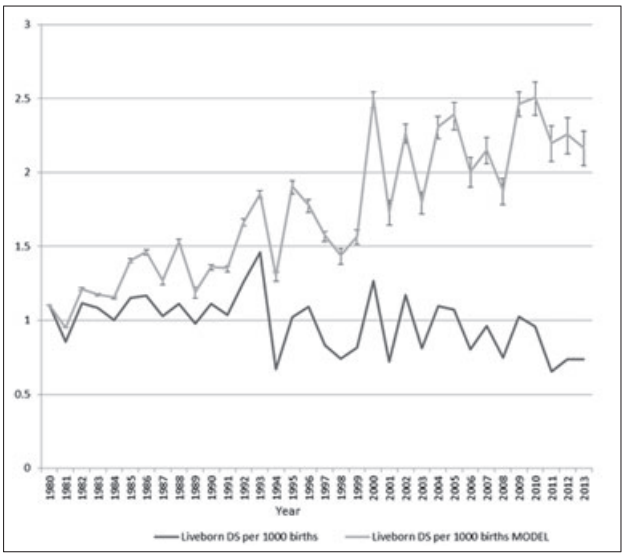
The rate of Down syndrome pregnancies (including terminations) per 1000 births increased from 1.1 in 1980 to 2.9 in 2013 (Figure 1), consistent with the steady increase in the percentage of babies born to women of advanced maternal age (>35 years; Figure 1). Over the same time period, the percentage of DS diagnosed prenatally and termination rates for fetal DS also increased (Figure 2).

The birth prevalence rate of Down syndrome per 1000 live-born infants fluctuated from year to year with a gradual downward trend. In the absence of prenatal diagnosis and termination, taking into account the percentage of fetal DS that would have been lost by term based on the median maternal age among terminations (Table 2), the birth rate for DS would have risen steadily from 1.1 per 1000 in 1980 to 2.17 per 1000 in 2013 (Figure 3). Using a more conservative estimate of DS fetal loss, the birth rate would have been 2.27 per 1000 in 2013, while the less conservative estimate gave a birth rate of 2.05 per 1000.

Table 2 Births, Down syndrome and prenatal diagnosis and termination rates by prenatal testing era

	1980–1993	1994–2003	2004 onwards	Overall
Observed data	—	—	—	—
All births in women >35 years (%)	8	15	20	14
Fetal DS per 1000 births	1.48	2.16	2.87	2.15
Live-born DS per 1000 births	1.11	0.91	0.87	0.97
Fetal DS terminated (%)	22	55	68	52
DS diagnosed prenatally (%)	24	60	73	56
Modelled data	—	—	—	—
Reduction in live-born DS (%) (range)	18 (16,19)	49 (47,50)	59 (57,61)	45 (43,47)

DS, Down syndrome.



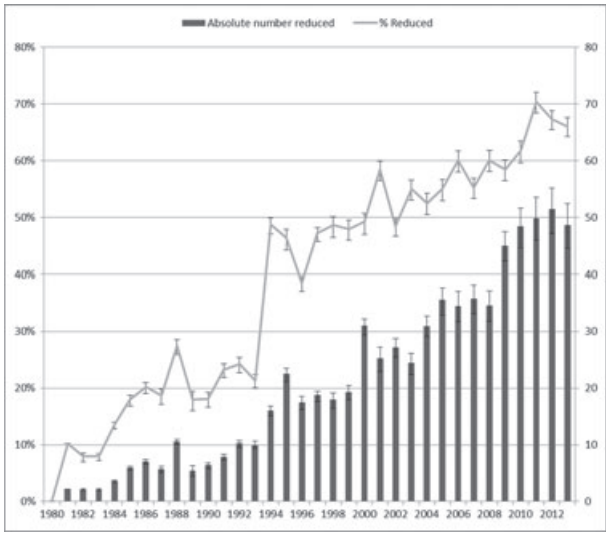
* Error bars denote the potential rate range with low and high estimates of fetal loss for pregnancies with Down syndrome for women aged 38.

Figure 3 Live-born Down syndrome per 1000 births and the modelled rate for live-born Down syndrome per 1000 births in the absence of prenatal diagnosis and termination

In absolute terms prenatal diagnosis and termination resulted in a reduction in the number of babies that would have been born with DS by 714 (657–762 with high and low fetal loss rates) or 45% (43%–47% with high and low fetal loss rates; Figure 4).

Results by era

The majority of Down syndrome cases identified and terminated (386) occurred from 2003 onwards, following the introduction of FTS, a period in which 73% of fetal Down syndrome were diagnosed prenatally, compared to 60% between 1994 and 2003 and 24% prior to 1994 when the use of MSS became widespread (Table 2). The rate of live-born DS per 1000 births was relatively steady in the pre screening period (1980–1993) and also in the post screening period to 2003 (Figure 3; Table 2), but the rate was lower by an estimated 0.19 from 1994 to 2003 ($p = 0.01$). From 2004 to 2013, the rate of live-born DS decreased significantly (−0.037/year, $p = 0.04$; Figure 3). There was no difference in the rate of increase in the percentage of DS terminations for DS pregnancies between 1980 and 1993 and the rate after 1994 (Figure 4; $p = 0.58$). However, there was a slight jump (0.16%) between 1993 and 1994 ($p < 0.00005$) corresponding to the introduction of MSS.



* Error bars denote the potential rate range with low and high estimates of fetal loss for pregnancies with Down syndrome for women aged 38.

Figure 4 The impact of termination on the number of live-born babies with Down syndrome (% reduction and absolute numbers)

The number of benefits paid by the AHIC via Medicare increased steadily between 1994 and 2013. While initially dominated by MSS the focus transitioned to first-trimester combined screening between 2002 and 2005 (Figure 5a). The total number of screening tests (MSS and FTS, as determined by the number of blood tests) increased by 135% over this time, while the number of live births (and therefore, we assume, pregnancies) increased by 33%. The total cost of screening and diagnostic tests including karyotyping to Medicare was $30.9 million (Figure 5b; $38.2 million when converted to 2013 Australian dollars).[19] However, the karyotype data are not specific to screening and diagnosis of Down syndrome and therefore must be interpreted with caution. The number of invasive prenatal diagnostic tests over this same-time period, as percentage of births, showed a steady downward trend, from 6.13% of all births in 1994 to 3.59% of all births in 2013 [data not shown].

DISCUSSION

Steadily increasing maternal age over the last 30 years, in the absence of prenatal testing and termination for fetal Down syndrome, would have resulted in an annual increase in the birth rate of Down syndrome, with a live-birth rate in 2013 estimated to be twice that of 1980. Rather, as a result of increasing prenatal diagnosis and subsequent termination, the live-birth rate decreased between the pre and post screening eras (<1993, >1993; $p = 0.001$). Overall prenatal diagnosis resulted in the births of around 45% fewer children with Down syndrome (701) than would have been expected over the 33-year period. However, because of the increase in births overall, the absolute number of children born with DS has remained relatively stable. In Australia, UK and Denmark, the uptake of Down syndrome screening is 56% to 84%, and the proportion of screen positive women who proceed to invasive diagnostic testing is >75%.[20–22] The rate of pregnancy termination following prenatal screening for Down syndrome in Canada, USA, The Netherlands, Scotland and Taiwan in the 1990s varied between 70% and 100%[23]; while in Europe, the overall rate of pregnancy termination for fetal anomalies was 83%.[24] The rates of screening, diagnostic testing and terminations of pregnancy in the current study are consistent with the data reported from other countries.

The increase in the percentage of fetal DS diagnosed prenatally is likely to be a result of improving prenatal screening tests as well as increasing uptake of testing among pregnant women. At the same time, invasive prenatal diagnostic tests as a percentage of live births declined. In the absence of MSS or FTS, this percentage –and the number of procedure related miscarriages– is likely to have increased because of advanced maternal age, with 20% of babies born to mothers over 35 years of age in 2013 compared with 12% in 1994 and 4.7% in 1980.[4]

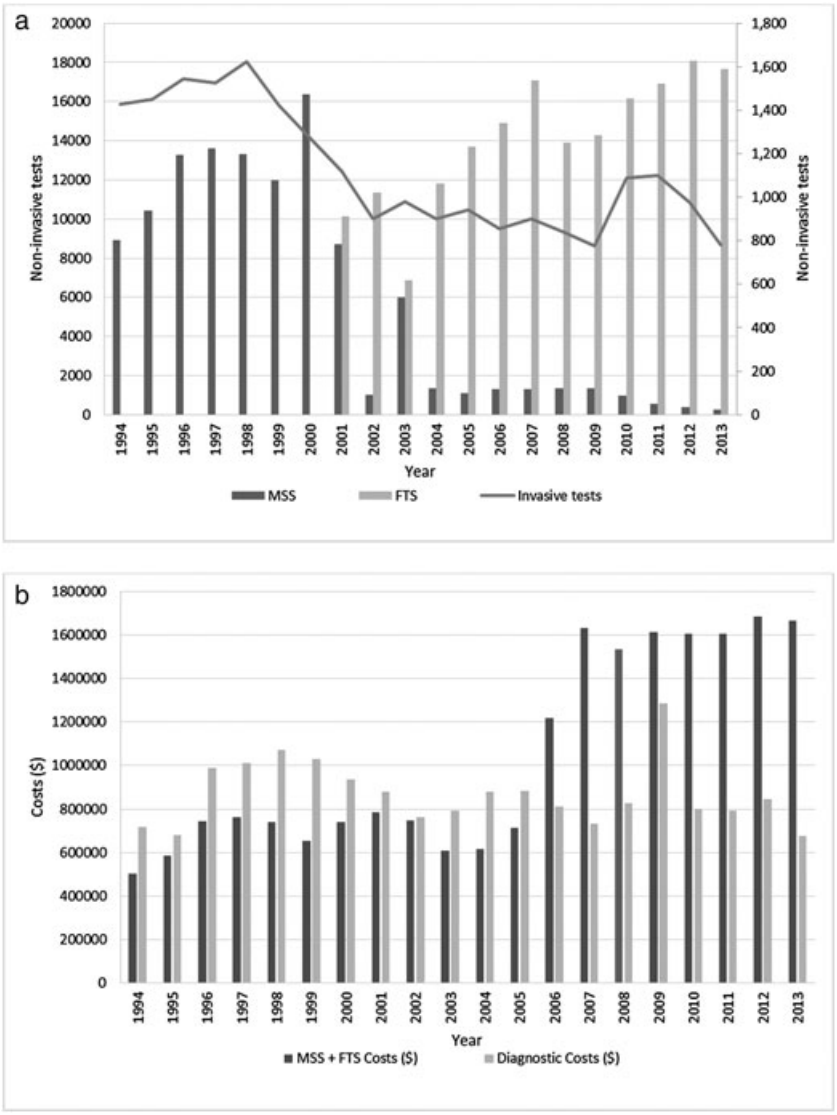


Figure 5 a) Numbers of non-invasive maternal serum screening and first trimester test and invasive tests performed (1994–2013); b) Medicare benefits paid (1994–2013) for screening and diagnostic tests including karyotyping (1994–2013)

The Medicare data demonstrate a clear pattern in the use of prenatal screening in Western Australia. MSS uptake rose steadily from 1994, with the introduction of this test having a significant impact on the percentage of terminated DS. MSS decreased from 2001, as FTS became more commonly used. Although available in Western Australia from around 2000, it was not until late 2004 that the ultrasound nuchal translucency measurement was officially funded by Medicare. We are unsure about the uptake of FTS during this transition time but expect that some women may have been self-funding the test and/or that other Medicare item numbers non-specific to FTS could have been used by providers during this time.

The commonly stated aim of prenatal screening is to provide information that will enable women and their partners to make autonomous reproductive choices. However, within the context of a public health prenatal screening programme, participants encounter two apparently contradictory messages: first, the screening programme's clinical effectiveness is determined by the proportion of affected cases detected, and secondly, the utility depends on the proportions of those who choose to continue or terminate an affected pregnancy. The recommendations of the European and American Societies of Human Genetics are especially pertinent in this context: Prenatal screening should inform the trade-offs between meaningful reproductive choices, the balance of benefits and burdens to the individuals, and the goals and values that are acceptable to society.[25]

Although we can quantify the impact of prenatal diagnosis and termination on rates of live-born Down syndrome, it is more difficult to analyse the impact of prenatal diagnosis on women and their families. The number of women who have been faced with a diagnosis of fetal DS and therefore a decision regarding the continuation of their pregnancy rose from 0 in 1980 to 75 in 2013. Overall, 1082 women were faced with this decision, and of these, 1006 chose to terminate. In two Dutch surveys of women who terminated their pregnancy following the diagnosis of a fetal anomaly, Korenromp *et al.* described the decision to terminate a wanted pregnancy as a 'profoundly difficult decision' and a 'major life event' with emotions

encompassing grief for the 'chosen' loss of a child, relief and doubt arising from guilt about ending a life, partner disagreement and uncertainty about how DS would have manifested in their child,[20] as well as sustained pathological morbidity.[21] Assuming diagnosis occurred before 20 weeks and the option of termination was available, 76 of these 1082 women made the decision to carry their baby to term. For these women, the value of having this information before birth may have been the opportunity to resolve their grief before the birth of their child with DS.[22]

Our data have some limitations and aspects of these data must be interpreted with caution. The data clearly show an increase in the prevalence of fetal DS. While this, in the absence of other risk factors, can largely be attributed to the increase in maternal age, some of the rise is likely to be an artefact of prenatal diagnosis itself, as in the absence of prenatal diagnosis and termination cases of DS lost before 20 weeks would not have been identified. Another limitation is that the WARDA data do not include fetal DS cases diagnosed but spontaneously lost before 20 weeks. This may result in an underestimate of diagnosis and an over-estimate of the termination rate following prenatal diagnosis. It may also result in an over-estimate of the number of cases of fetal DS lost by term within our model of DS live-birth rates in the absence of prenatal testing, if most loss occurs by 20 weeks. Furthermore, while the Medicare data demonstrate the trend in prenatal testing, they only account for reimbursements for government-subsidised services and will not include services charged directly to women by private practitioners or the small proportion (<2%) of public inpatient services. We cannot be sure what percentage of screening and diagnosis occurs without Medicare rebate because the overall uptake of screening varies between 39% and 80% of pregnancies in different regions.[26] However, it is likely that data on 95% of pregnancies would have been captured.

CONCLUSION

Prenatal screening and diagnosis has reduced the birth prevalence of DS in the Western Australian community. Proportionately, fewer invasive diagnostic tests are being performed while a larger percentage of fetal DS is being diagnosed. Many women and their families have been faced with a diagnosis of fetal DS and decisions about the continuation of their pregnancy. With the introduction of another more accurate screening test, efforts to ensure informed choice for all women and information and support for women following a prenatal diagnosis of fetal DS must continue. The need for support and services for children with Down syndrome and their families remains.

ACKNOWLEDGEMENTS

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- There have been many advances in screening to assess the risk of fetal aneuploidy 39 over the last 30 years, with the most recent development being use of cell-free 40 DNA (non-invasive prenatal testing).

WHAT DOES THIS STUDY ADD?

- The availability of prenatal tests for fetal aneuploidy over the last 30 years has significantly reduced the live-birth prevalence of Down syndrome in Western Australia. This is despite of an increasing rate of fetal Down syndrome.
- Without prenatal diagnosis and termination, the rate of live-born infants with Down syndrome would have doubled between 1980 and 2013.

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APPENDIX 1

Table A1 **Median maternal age among terminations by year and gestation at time of termination**

Year	Age at TOP <16 weeks	Age at TOP >16 weeks
1980	NA	NA
1981	NA	39
1982	NA	39
1983	NA	39
1984	NA	39
1985	NA	37
1986	NA	40.5
1987	NA	39
1988	40	39
1989	38	40
1990	40	34.5
1991	38.5	38
1992	38	36
1993	36	39
1994	40	35
1995	NA	36
1996	NA	45
1997	40	37
1998	41	36
1999	38	38
2000	34.5	34
2001	34	36
2003	37.5	36
2004	35	37
2005	37	36
2006	37.5	36
2007	37	36
2008	36.5	36
2009	37	37
2010	37	36
2011	37	38
2012	37	36
2013	37	35

Table A2 **Fetal loss rates in pregnancies with fetal DS as reported by Savva *et al*[16]**

	Fetal loss rate (%)	
Maternal age at EDD (years)	CVS (<16 weeks) to term (95% CI)	Amniocentesis (>16 weeks) to term(95% CI)
25	23 (16–31)	19 (14–27)
26	24 (17–32)	20 (14–28)
27	24 (18–32)	20 (15–28)
28	25 (19–32)	21 (16–28)
29	26 (20–32)	21 (17–28)
30	27 (21–33)	22 (17–28)
31	28 (22–34)	23 (18–29)
32	29 (23–35)	23 (19–29)
33	30 (24–36)	24 (20–29)
34	31 (26–36)	24 (20–30)
35	32 (27–38)	25 (21–31)
36	33 (27–39)	26 (22–31)
37	34 (28–40)	26 (22–32)
38	35 (29–42)	27 (23–33)
39	36 (30–43)	28 (23–35)
40	38 (31–45)	29 (24–36)
41	39 (31–47)	30 (24–37)
42	40 (32–49)	30 (25–39)
43	41 (32–51)	31 (25–41)
44	43 (33–53)	32 (25–43)
45	44 (33–56)	33 (26–45)
Average	32 (27–38)	25 (21–30)

EDD, estimated due date; NA, not available.