

MAIN RESEARCH ARTICLE

Gradual implementation of first trimester screening in a population with a prior screening strategy: population based cohort study

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Abstract

Objective. To evaluate the implementation of first trimester screening in the Czech Republic during 1996–2007 on the number of infants born with numerical chromosomal anomalies, the gestational age at diagnosis and the number of invasive procedures. **Design.** A population based cohort study. **Setting.** National Registry of Congenital Anomalies, 53 Czech Republic Genetic Departments. **Population.** About 100,000 pregnancies per year. **Main outcome measures.** Primary outcomes were the rates of fetuses and newborns with diagnosed numerical chromosomal anomalies and the gestational age at diagnosis. Secondary outcomes were the rates of chorion villus sampling (CVS) and amniocenteses and the contribution of age groups on the detection rate of trisomy 21. **Results.** The number of newborns with Down's syndrome decreased from 5.42/10,000 in 1996 to 3.66/10,000 newborns in the 2007. The total incidence of Down's syndrome increased from 13.42 to 20.66/10,000. The detection rate in women <35 years increased from 35.59 in 1996 to 45.08 in 2007; in women >35 years from 23.73 to 38.52. The number of amniocenteses/detected case of Down's syndrome was 124 in 1996 and 123 in 2007. The corresponding number of CVS decreased dramatically from 83 in 1996 to 10 in 2007. **Conclusions.** Despite the increase of maternal age and the corresponding increase of Down's syndrome, the number of newborns with Down's syndrome decreased. Implementation of the first trimester combined screening leads to a shift towards earlier diagnosis of all major chromosomal abnormalities.

Key words: First trimester screening, Down's syndrome, prenatal, CVS, amniocentesis

Introduction

Screening for chromosomal abnormalities started in the early 1990's in the Czech Republic (1,2), when second trimester biochemical screening (the triple test) became standard in prenatal care of the whole population and covered by health insurance. Other strategies, like sequential and integrated tests, were introduced in some centers. This led not only to an 80% increase in the prenatal detection of Down's syndrome (DS) and other numerical chromosomal aberrations, but also a steep increase in the number of invasive procedures (3). Since 2003, combined first trimester screening gained more dominance in the population screening (4). The aim of this study was

to evaluate the impact of a gradual implementation of first trimester screening strategy in the Czech Republic during 1996–2007 on the number of infants born with major chromosomal abnormalities, the gestational age at diagnosis, and the number of invasive procedures.

Material and methods

The Czech Republic has a population of 10 million, primarily Caucasians, and about 100,000 live born infants per year (5,6). At birth or with immigration, everyone is assigned a unique personal registration number, which is used for identification in the Czech social and healthcare system. This centralized

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registration system enables good follow-up of individuals' health. The Czech registry of fetal malformations collects data from every genetics department on all malformations detected in the early neonatal period, the results of antenatal and postnatal chromosomal examinations, and the medical indications for pregnancy terminations. The number and kind of invasive procedures (amniocenteses and chorion villi sampling – CVS) were registered in the genetic labs and were centrally reported. The numbers of CVS before the year 2002 were not registered.

All newborn infants are examined by a pediatrician. The results of postnatal chromosome analysis, including the personal registration numbers of the mother and infant, are sent to the Czech central cytogenetic registry. The registry provided information on the number of infants with DS born during 1996–2007 as well as all fetuses antenatally diagnosed with DS during 1996–2007.

Nuchal translucency ultrasonography is carried out by certified doctors and midwives in accordance with the guidelines of the Fetal Medicine Foundation in London (www.fetalmedicine.com). Certified biochemical laboratories were involved in the first trimester testing of free beta human chorionic gonadotropin and pregnancy-associated plasma protein A using Brahms Kryptor (Brahms, Immunodiagnostic Systems, UK) for biochemical analyses. The second trimester screening is widely based on alpha-fetoprotein, free estriol, and human chorionic gonadotropin estimation. Different kinds of assays from a variety of providers were used. The data were

obtained from the registries anonymously. The collection of data in the registries is in accordance to the Czech law and with the Ethical Codex of the National Institute of Health Information and Statistics. Statistical analyses were performed using Pearson's chi-squared test.

Results

The number of deliveries increased from 90,446 in 1996 to 114,632 in 2007. The percentage of mothers >35 years increased from 4.78% in 1996 to 10.46% in 2007 (Figure 1). The total incidence of DS increased from 13.42 to 20.66/10,000. The number of DS newborns decreased from 5.42/10,000 in 1996 to 3.66/10,000 in 2007 ($p < 0.001$). The number of antenatally diagnosed cases of DS fetuses increased from 8.6 in 1996 to 17.1/10,000 newborns in 2007 ($p < 0.001$) (Figure 2). The detection rate in women <35 years increased from 35.59 in 1996 to 45.08 in 2007; in women >35 years from 23.73 to 38.52.

The number of invasive procedures (amniocenteses and CVS) increased from 1,031/10,000 in 1996 to 1,673/10,000 newborns in 2007. The absolute number of CVS increased from 52 in 2002 to 497 in 2007; 122 prenatal invasive procedures (amniocentesis and CVS) were necessary for detection of one case of DS in the year 2003. In the year 2007 this number decreased to 91. The number of amniocenteses per one DS case remains unchanged, whereas the number of CVS per one detected DS decreased dramatically from 83 in 1996 to 10 in 2007 ($p < 0.001$).

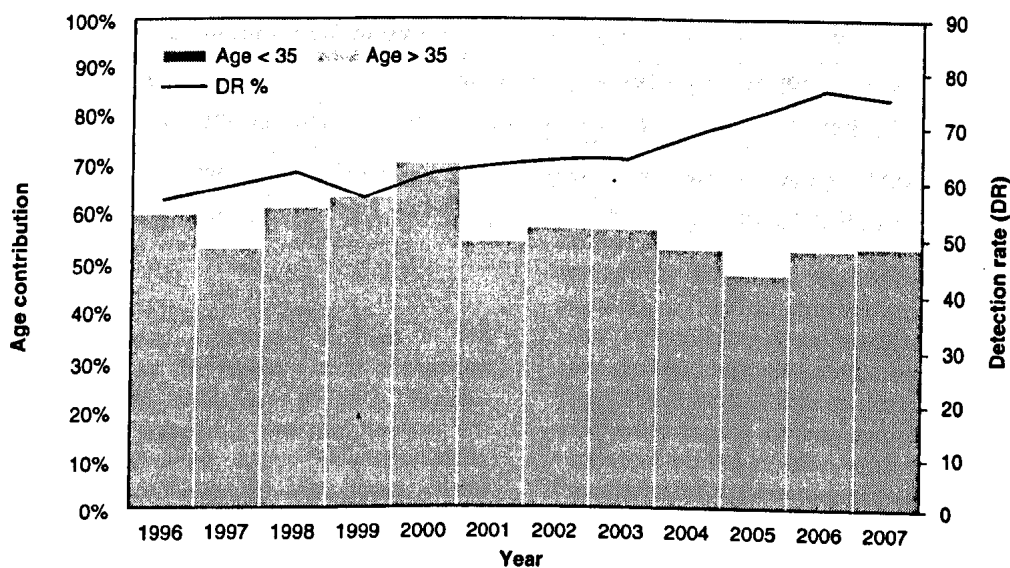


Figure 1. Detection rate of Down's syndrome in the Czech population and percentage of contribution of mothers younger and older than 35 years.

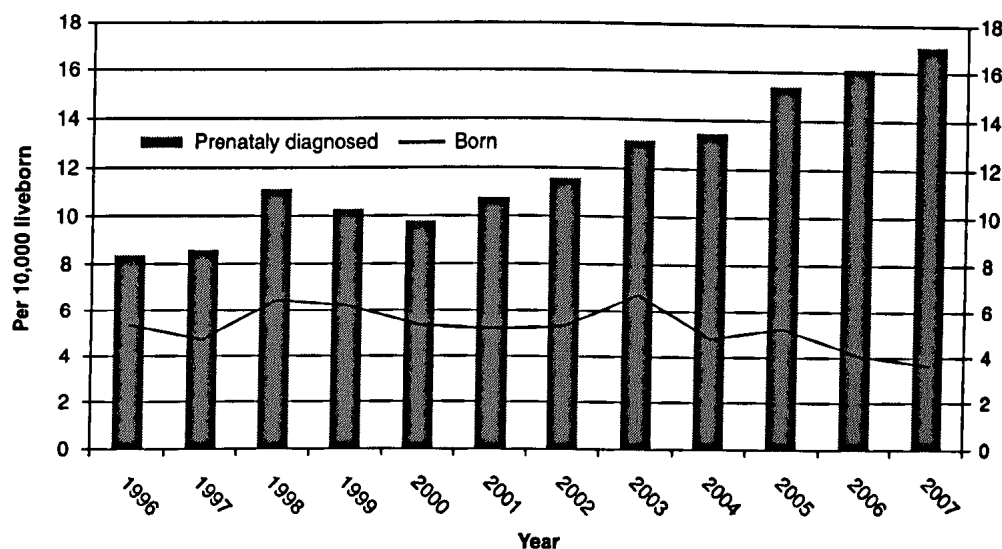


Figure 2. The number of prenatally and postnatally diagnosed Down's syndrome fetuses per 10,000 newborns in years 1993–2007 in Czech Republic.

We were able to prove the impact of first trimester screening in our population since the year 2005: there were 0.11 DS fetuses/10,000 newborns diagnosed up to 14 weeks of pregnancy. This number increased to 0.21/10,000 newborns in the year 2007 ($p < 0.001$) (Figure 3). With increasing abundance of combined first trimester screening, the detection rates of DS reached 79.53% in the year 2007 in the whole population.

The frequency of combined first trimester screening in the Czech Republic is not known. It could be estimated that about 10% of the pregnant population underwent first trimester combined testing in 2007. This corresponds with our observations, that in the same year 0.21/10,000 DS fetuses were detected already in the first trimester.

The trends in detection rates and numbers of newborns in Edward's, Patau's and Turner's syndrome pregnancies were similar (Tables 1 and 2).

Discussion

We have documented significant changes in DS screening practices in the whole Czech population during the years 1996–2007. Prior to 2002, the main test used for DS screening was the second trimester biochemical test, using alpha-fetoprotein, human chorionic gonadotropin and estriol in the 16–20th weeks. Using this strategy, the detection rates of DS in Czech Republic reached 67.1% in the year 2002. We can speculate that this was the maximum we could achieve in a population with predominance of second trimester biochemical

screening. Since 2003, first trimester combined test has been introduced in several centers with increased numbers of pregnancies examined.

Despite the continuing increase of maternal age and corresponding incidence of DS in the population, the number of born fetuses with trisomy 21 is decreasing. The incidence of DS is increasing not only due to the higher proportion of older mothers, but also as a result of introduction of first trimester testing. Fetuses with DS are detected in the first trimester, which would end with miscarriage prior to the second trimester. These two factors, higher maternal age and increased detection in the first trimester, contributed to the increasing incidences after the year 2003 (Figure 2).

It has been well documented, that the combined first trimester screening, has major advantages over the second trimester biochemical screening (6). Unfortunately, there is no national body, which would be able to mandate or promote a national policy for aneuploidy screening applied to the whole Czech population. This situation is similar to other countries. By contrast, as an example, Denmark did not have well established population strategy before the year 2004, but was able to introduce the new, more efficient screening system, in the whole country in a very short period of time, with excellent results (7). Paradoxically, the existing population screening strategy in Czech Republic is not advantageous in a situation where a new technique of screening should be introduced.

The ominous number of invasive procedures must be seen as complication of extensive use of second

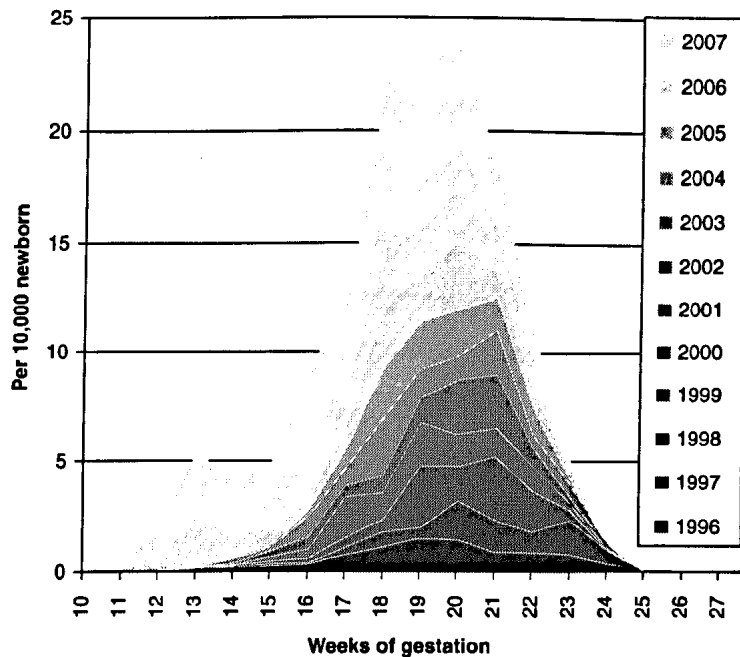


Figure 3. Trends in prenatal Down's syndrome detection in the years 1996-2007: number of DS fetuses per 10,000 newborns and gestational age at detection.

Table 1. Trends in postnatal prevalence and antenatal detection in Edward's, Patau's and Turner's syndromes between 1996 and 2007.

Year	Edward's syndrome/10,000		Patau's syndrome/10,000		Turner's syndrome/10,000	
	Newborns	Prenatally diagnosed	Newborns	Prenatally diagnosed	Newborns	Prenatally diagnosed
1996	1.11	2.65	0.33	0.11	0.33	2.21
2007	0.17	3.66	0	1.65	0.26	3.22
p-Value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table 2. Trends in antenatal detection before the 14th week of pregnancy in Edward's, Patau's and Turner's syndromes between 2003 and 2007.

Year	Edward's/10,000	Patau's/10,000	Turner's/10,000
2003	0.75	0.32	0.05
2007	1.22	0.52	0.12
p-Value	<0.001	<0.001	<0.001

trimester biochemical screening. CVS is mainly used for karyotyping in cases with positivity of first trimester scan. The low number of CVS per one detected case of DS in the year 2007 can be seen as consequence of very low false positivity rate of first trimester screening. There is a large potential in decreasing the number of procedures in the whole population to 3-5%, if the first trimester combined screening would become the main screening tool (8).

Recent studies that have examined the pregnancy loss rates after CVS and amniocentesis that was performed under continuous ultrasound guidance, have challenged the traditionally quoted fetal loss rate of 1.0% for CVS and 0.5% for amniocentesis (9,10).

The average fetal loss rate after a CVS or an amniocentesis could be lower than the traditionally quoted risk. The fetal loss rate that is quoted should be institution specific or based on the experience of the physician who performed the procedure (11). Further studies should clarify whether the fetal loss rates after a CVS or an amniocentesis are similar, because this may influence which procedure a screen-positive woman decides to undergo.

We were able to demonstrate on population-based data, that the existing DS screening strategies, despite all confusing discussions about the best screening protocol, led to significant decrease in the

number of newborns with DS. Since 2003, gradual increase of the contribution of first trimester combined screening leads to provable shift towards early diagnosis of all major chromosomal abnormalities near the end of the first trimester. Even gradual implementation of this strategy allowed reduction in the high number of prenatal invasive diagnoses carried out.

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