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Trisomy 21 – incidence, diagnostics and pregnancy terminations 1999–2018

ORIGINAL ARTICLE

HEGE MERETE AASEN

National Center for Fetal Medicine
St Olav's Hospital, Trondheim University Hospital
and
Centre for Women, Family and Children's Health
Campus Vestfold
University of South-Eastern Norway
She has contributed to the planning of the study, data collection, statistical analyses and drafting of the manuscript.
Hege Merete Aasen, ultrasound midwife.
The author has completed the ICMJE form and declares no conflicts of interest.

BERGE SOLBERG

Department of Public Health and Nursing
NTNU
He has provided input on the ethical implications of fetal medicine and contributed to the drafting of the manuscript.
Berge Solberg, professor in medical ethics.
The author has completed the ICMJE form and declares no conflicts of interest.

KRISTINE MARIE STANGENES

Medical Birth Registry of Norway
Norwegian Institute of Public Health, Bergen
She has interpreted national data and contributed to the drafting of the manuscript.
Kristine Marie Stangenes, PhD and senior consultant.
The author has completed the ICMJE form and declares no conflicts of interest.

ELLEN AAGAARD NØHR

Centre for Women, Family and Children's Health
Campus Vestfold
University of South-Eastern Norway
and
The Research Unit of Gynaecology and Obstetrics
University of Southern Denmark, Odense, Denmark
She has contributed to the planning of the study, supervision of the master's thesis and drafting of the manuscript.
Ellen Aagaard Nøhr, professor.
The author has completed the ICMJE form and declares no conflicts of interest.

TORBJØRN MOE EGGEBØ

tme@lyse.net
National Center for Fetal Medicine
St Olav's Hospital, Trondheim University Hospital
and
Department of Clinical and Molecular Medicine
NTNU
and
Department of Obstetrics and Gynaecology
Stavanger University Hospital
He has had overall responsibility for the planning of the study, and contributed to the data collection, statistical analyses and drafting of the manuscript.
Torbjørn Moe Eggebø, senior consultant and professor emeritus.
The author has completed the ICMJE form and declares no conflicts of interest.

BACKGROUND

We hypothesised that the examinations offered to pregnant women at fetal medicine centres differ from those offered to other pregnant women in Norway. We therefore wanted to investigate the incidence, prenatal diagnostics and pregnancy terminations in cases of trisomy 21. We also wanted to compare the figures from the National Center for Fetal Medicine, St Olav's Hospital, Trondheim University Hospital, with national figures for Norway.

MATERIAL AND METHOD

We analysed figures for the period 1999–2018 retrospectively. National data were compared with an unselected population whose local hospital is St Olav's Hospital. National figures were retrieved from the Medical Birth Registry of

Norway and local figures were from the quality registry at the National Center for Fetal Medicine.

RESULTS

The national incidence of trisomy 21 was 0.20 %, varying from 0.14 % to 0.23 %, and showed a significant increase over time ($p < 0.01$). The increasing incidence showed an association with increasing age in the women ($p < 0.01$). The incidence of live births was stable, even though the proportion of pregnancy terminations increased. In the local population, the incidence of trisomy 21 was 0.19 %. A total of 68.2 % of the local population were diagnosed prenatally, and 87.7 % of these pregnant women terminated the pregnancy. There was a significantly higher proportion of pregnancy terminations in the local population than in the remainder of the national population ($p < 0.01$).

INTERPRETATION

The difference in the proportion of pregnancy terminations may be associated with variation in access to prenatal diagnostics.

Main findings

National data for 1999–2018 showed a significant increase in the incidence of trisomy 21, which could be related to increasing age in pregnant women.

The incidence of live births with trisomy 21 was stable, despite the increase in the proportion of pregnancy terminations.

The proportion of pregnancy terminations in trisomy 21 cases was higher among the local population in Trondheim than elsewhere in Norway.

Since 1986, maternity care in the Norwegian public health service has included an offer of one ultrasound examination in gestational week 17–19, in accordance with international recommendations (1). Most routine ultrasound examinations are performed by midwives with one year of training in ultrasound diagnostics, while some examinations are performed by doctors. Most severe fetal malformations are nowadays detected before birth (2–4).

Many women seek to terminate their pregnancy in the event of severe fetal malformations, but there is no consensus on what constitutes a severe abnormality. Down syndrome is usually caused by the presence of an extra copy of chromosome 21, hence the name trisomy 21 (5). Translocation occurs in some cases, which involves part of the long arm of chromosome 21 becoming attached to another chromosome, but placental mosaicisms can also occur. Some fetuses with trisomy 21 have structural malformations that cannot be detected by ultrasound, which makes it difficult to screen for trisomy 21 during the routine examination in the second trimester (3).

All infants born with trisomy 21 have some intellectual disability, and some have other abnormalities such as heart defects or intestinal obstruction (3, 5). Access to first trimester screening for trisomy 21 is the subject of great debate

among healthcare personnel, politicians and the public in Norway (6–8); however, there is a general desire for the access to be standardised throughout the country (9).

Until 2020, first trimester screening was only available for women aged 38 years or older on their estimated due date, and women who had other specific indications. These indications are defined in the guidelines for the Biotechnology Act (10–12). Since 2005, a combined ultrasound and blood (CUB) test in gestational week 11 + 0 to 13 + 6 has been widely used as a predictive test for trisomy 13, 18 and 21 (13). Sensitivity and specificity for diagnosing trisomy 21 are highest during this period, and the test can detect more than 90 % of fetuses with trisomy 21 (14). In non-invasive prenatal testing (NIPT), a maternal blood sample is obtained to analyse cell-free DNA from the placenta. This test has a high accuracy for detecting trisomy 21 (15). NIPT was introduced in Norway in 2017 for women with > 1/250 risk of trisomy following CUB testing (10). In May 2020, the Norwegian parliament decided that NIPT should be offered to all pregnant women who have the right to prenatal diagnostics, and that the age threshold for prenatal diagnostics should be 35 years (16). Parliament also decided that all pregnant women, regardless of age, should be offered NIPT. This legislative change may have implications for diagnostics and care in relation to trisomy 21.

The main aim of the study was to investigate changes in incidence, prenatal diagnostics and pregnancy terminations in cases of trisomy 21. We hypothesised that the examinations offered to pregnant women at fetal medicine centres differ from those offered to other pregnant women in Norway. We therefore also wanted to compare the results among pregnant women examined at the National Center for Fetal Medicine in Trondheim with the results among pregnant women examined elsewhere in Norway.

Material and method

The study was retrospective. Anonymised national data from 1999–2018 were obtained from the Medical Birth Registry of Norway's statistics bank (17). This registry is a national, regulated health registry containing information about mothers' health, pregnancy and birth process, and the health of neonates. It also contains data on neonatal health problems, congenital diseases and anomalies, as well as any deaths in the first year of life. All pregnancies of more than 12 weeks are included in the registry. The Medical Birth Registry of Norway began registering pregnancy terminations in 1999, and this is therefore the first year for our study.

St Olav's Hospital is the local hospital for pregnant women in Trondheim and eight surrounding municipalities. Almost all pregnant women in the region attend this hospital for the ultrasound examination in the second trimester and give birth there. The women in the region therefore represent an almost unselected population of pregnant women and represent the local study population. The National Center for Fetal Medicine in Trondheim has a national function as well as a local one, with pregnant women being referred

here from other municipalities in Norway, but these women are not included in the local figures. The National Center's local quality registry therefore only contains data from the local population. A secretary is responsible for the quality registry, and all data are quality assured by a doctor prior to registration. We extracted data from this registry for the period 1999–2018.

The project was approved by the Regional Committee for Medical and Health Research Ethics on 23 June 2020 (REK-Midt 134730). The data protection officer at St Olav's Hospital assessed the study on 14 August 2020, and the project was approved by the Research Department at St Olav's Hospital on 18 August 2020.

Statistical methods

Incidence was calculated as new cases of trisomy 21 among all pregnant women. Descriptive statistics were produced showing numbers, incidences and percentages from the national population as a whole and from the local population. Local figures were deducted from national figures to compare pregnancy terminations in the two populations. Cross-tabulation was used to compare data. Two categorical variables were compared using chi-squared testing, and changes in the incidence of trisomy 21 during the study period were analysed in a linear-by-linear association test (chi-squared test for trend). A Kolmogorov-Smirnov test and normality plots were used to investigate normal distribution. The association between the incidence of trisomy 21 and maternal age in the national population was examined in a linear regression analysis. All analyses were performed using the statistical program SPSS version 25.0, and a p-value of < 0.05 was considered to be statistically significant.

Results

During the study period, a total of 1 195 872 fetuses and children were registered in the Medical Birth Registry of Norway. Of these, 2 370 (0.20 %, standard deviation 0.03) were registered with trisomy 21 (17). The annual national incidence varied from 0.14 % to 0.23 % and showed a significant increase over time ($p < 0.01$) (Figure 1). The mean age of birthing women increased from 29.5 years to 31.0 years during the study period. A significant association was found between women's age and the incidence of trisomy 21 ($r = 0.83$; $r^2 = 0.69$), with the incidence increasing by 0.057 % (95 % CI 0.038 to 0.076) for a one-year increase in women's age. In the local population, there were 56 483 births and 107 fetuses or children with trisomy 21 (0.19 %; standard deviation 0.08 and variation 0.04–0.39 %).

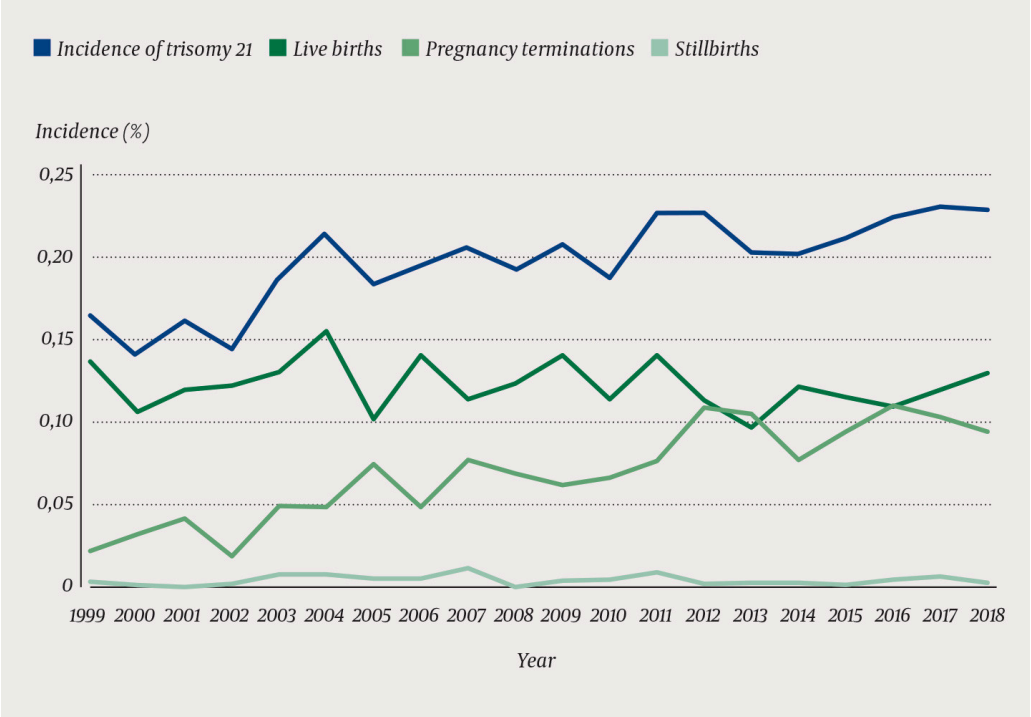

Figure 1 Variation in incidence, live births, pregnancy terminations and stillbirths among all trisomy 21 cases in Norway in the period 1999–2018.

The number of neonates born alive with trisomy 21 per year in Norway varied from 59 to 91 (mean 74, standard deviation 9). Table 1 shows the number, incidence and percentage of live births, stillbirths and pregnancy terminations in the two populations. Figure 1 shows the variation in incidence in the national population during the study period. There was no significant change in the incidence of neonates born alive with trisomy 21 ($p = 0.34$) or stillbirths ($p = 0.66$), but the incidence of pregnancy terminations increased ($p < 0.01$). Figure 2 shows the proportion of live births, stillbirths and pregnancy terminations among all trisomy 21 cases in the national population. A significant reduction in the proportion of live births ($p < 0.01$) and a significant increase in the proportion of pregnancy terminations were seen over time ($p < 0.01$).

Table 1

Descriptive data on trisomy 21 from the Medical Birth Registry of Norway and from the National Center for Fetal Medicine in Trondheim in the period 1999–2018. A total of 1 195 872 fetuses and children were registered in the Medical Birth Registry of Norway, and the corresponding figure for the National Center for Fetal Medicine in Trondheim was 56 483.

	Medical Birth Registry of Norway		National Center for Fetal Medicine	
Condition	Number (proportion)	Incidence (%)	Number (proportion)	Incidence (%)
All trisomy 21 cases	2 370 (100)	0.20	107 (100)	0.19
Live births	1478 (62)	0.12	40 (37)	0.07
Stillbirths	52 (2.2)	0.004	3 (2.8)	0.005

	Medical Birth Registry of Norway		National Center for Fetal Medicine	
Condition	Number (proportion)	Incidence (%)	Number (proportion)	Incidence (%)
Pregnancy terminations	840 (35)	0.07	64 (60)	0.11

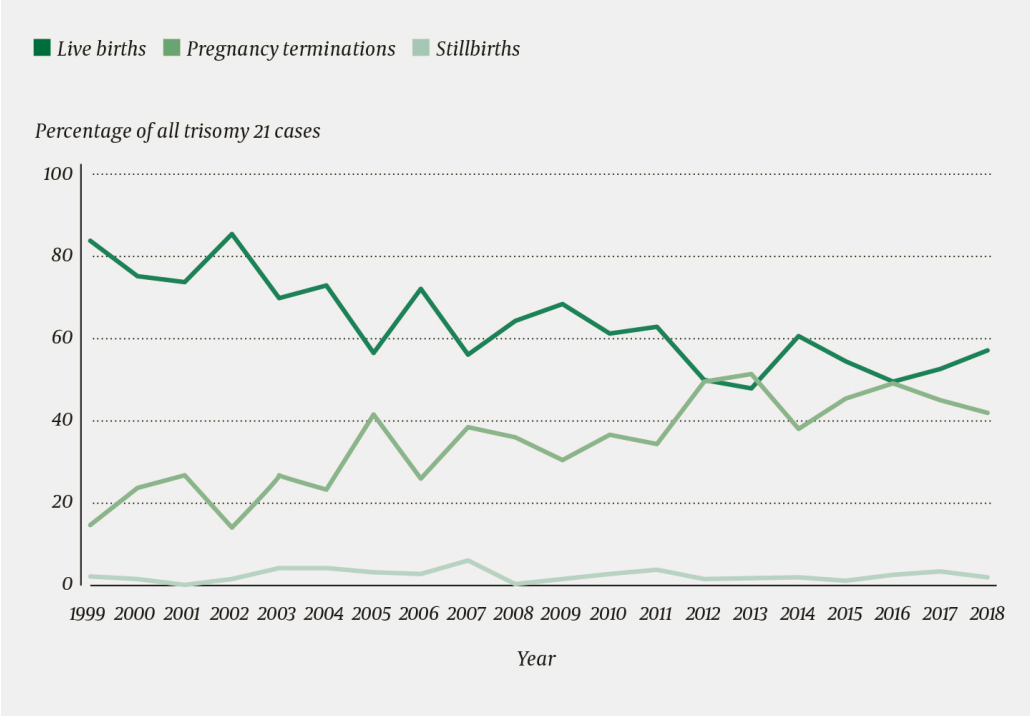

Figure 2 Proportion of live births, pregnancy terminations and stillbirths among all trisomy 21 cases in the national population (N = 2 370) in the period 1999–2018.

In the local population, 73/107 (68.2 %) cases were diagnosed prenatally and 34/107 (31.7 %) postnatally. A total of 64/73 (87.7 %) of the pregnant women who received a trisomy 21 diagnosis prenatally, terminated the pregnancy. The proportion of pregnancy terminations was significantly higher in the local population than in the rest of the national population: 64/107 (59.8 %) compared to 776/2 263 (34.3 %), ($p < 0.01$).

Discussion

Between 1999 and 2018, a significant increase was observed in the incidence of trisomy 21 in the national population, and the mean age of birthing women also increased. The incidence of live births and stillbirths was stable, but both the incidence and the proportion of pregnancy terminations increased. The proportion of pregnancy terminations due to trisomy 21 was significantly higher in the local population than in the rest of the national population.

One of the strengths of the study is that all births and pregnancy terminations after gestational week 12 are registered in the Medical Birth Registry of Norway. The local registry is also subject to a thorough quality assurance process. Most infants with trisomy 21 are diagnosed at birth or during the

neonatal period. Those who are diagnosed after being discharged from the maternity or neonatal ward are not always registered in the Medical Birth Registry of Norway (18). The incidence may therefore be somewhat higher than we have reported. One limitation is that the data entered in the Medical Birth Registry on prenatally diagnosed trisomy 21 are not quality assured and therefore not reliable enough to be published. The fact that we only have data from one of the five centres for fetal medicine is also a limitation.

We know that the probability of trisomies increases with age, and data from the Medical Birth Registry of Norway showed that the incidence increased by 0.057 % when the women's mean age increased by one year (19). Age may also be a factor in other fetal abnormalities (20). Only women who were more than 38 years on their estimated day of delivery, or who had other risk factors for giving birth to a child with a disability had access to first trimester screening in the public health service during the study period (11). About 7.5 % of all pregnant women have undergone CUB testing in recent years: 4 075 in 2018 and 4 399 in 2019 (personal communication, Department of Medical Biochemistry, St Olav's Hospital).

The authorities want to standardise the access to health care throughout the country (9). The high proportion of pregnancy terminations in the local population may be due to the fact that the fetal examinations are more detailed at the fetal medicine centres than at other hospitals. Another factor may be that women living in large cities have more access to ultrasound examinations in the private health service. If a malformation is suspected in a private examination, this is an indication for prenatal examinations at a fetal medicine centre (10). In 2019, a study of 1 212 women in Oslo reported that 86 % of pregnant women had attended a first trimester ultrasound examination in the private health service (21). All the municipalities in the local population are geographically close to Trondheim, and pregnant women have good access to private ultrasound examinations. Differing attitudes can also play a role. It has been shown that attitudes to the use of ultrasound vary between healthcare personnel (22) and that doctors do not always adhere to the provisions of the Biotechnology Act (23). Attitudes can also vary between women in urban and rural areas.

Amendments were made to the Biotechnology Act in May 2020. All pregnant women will be offered an ultrasound examination in the first trimester, and women over the age of 35 on their estimated day of delivery will be offered NIPT to screen for trisomy (16). NIPT will be available for a fee for women below the age of 35 (16).

The modification of the law is likely to democratise access to prenatal examinations throughout Norway. Politicians in Norway have feared that greater use of prenatal examinations will lead to more pregnancy terminations. The term 'selection society' has been widely used in the Norwegian discourse, where it is implied that deliberate selection is being facilitated through genetic screening for trisomy 21. There is an ambivalence in society towards trisomy 21 as a diagnosis: on the one hand, many pregnant women fear having a child with Down syndrome, but on the other hand, many also fear a society without Down syndrome (6, 8). It is regarded as both a serious diagnosis and as a

'syndrome of possibilities' (24). The Biotechnology Act is aimed at 'a society for everyone' (12). However, pregnant women must also be guaranteed the right to information and autonomy. Prenatal diagnostics have been criticised for lacking a clearly defined purpose (6).

The proportion of pregnancy terminations increased steadily during the study period, but the number of children born with trisomy 21 remained stable. The explanation for this apparent paradox is the increase in women's age (19). Steadily more women will carry a fetus with trisomy 21, and a higher proportion of pregnancy terminations is thus consistent with a stable number of children born with trisomy 21.

In Denmark, prenatal diagnostics in the first trimester was introduced for pregnant women in 2004. Prior to that, about 60 children were born with trisomy 21 in Denmark annually, but this has subsequently dropped to 23–35 (25). In the local population in our study, 88 % of women with prenatally diagnosed trisomy 21 terminated their pregnancy. Following the legislative change, children with trisomy 21 will still be born in Norway, but the number is likely to be lower than today. Society must ensure good health care in order to support parents who have children with trisomy 21 (26).

The strongest ethical defence for prenatal diagnostics is based on pregnant women's right to information and the right to autonomy. In the Oslo study, 78.4 % of the pregnant women thought that prenatal diagnostics should be offered in the public health service to all pregnant women (21). In 2020, sixteen years after Denmark introduced prenatal diagnostics in the first trimester, with autonomy as the main reason, Norway decided to give all pregnant women greater freedom of choice. Time will tell whether Norwegian and Danish women make different choices. Society must have reliable information about how prenatal diagnostics are handled, and improvements must be made to the registration of prenatal diagnostic and genetic examinations in the Medical Birth Registry of Norway.

Conclusion

National data showed a significant increase in the incidence of trisomy 21 and an increase in pregnancy terminations, but a stable incidence of live births. This can be explained by the increasing age of pregnant women. The proportion of pregnancy terminations was higher in a local population in Trondheim than in the rest of the national population.

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The article has been peer-reviewed.

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