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The prevalence of live birth Down syndrome in the region of Primorsko-goranska County in Croatia, 1996-2005: the impact of screening and amniocentesis

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Abstract

Objectives To investigate the prevalence of live birth Down syndrome (DS) in the region of Primorsko-goranska County (PGC) in Croatia from 1996 to 2005 and to evaluate the impact of second-trimester maternal serum screening (MSS) and amniocentesis on live birth DS prevalence.

Methods Study was based on databases from the Department of Gynecology and Obstetrics, University Hospital Centre Rijeka, the Department of Biology and Medical Genetics, School of Medicine, University of Rijeka, and the Crotian National Institute of Public Health. The regional policy of prenatal diagnosis for DS includes amniocentesis for pregnant women aged 35 or over and MSS for younger women. We estimated live birth and total prevalence of DS and measured the proportion of pregnant women using MSS and amniocentesis. Trends of live birth and total prevalence of DS were tested by linear regression analysis.

Results The live birth prevalence of DS was 1.4/1000 in the period 1996-2005. A decreasing, but nonsignificant, trend of prevalence was observed over time (p=0.577). Women aged 35 or over represented 11.6% of all pregnant women included in the study. The proportion of women who had MSS was 33.9%. The proportion who underwent amniocentesis was 6.1%.

Conclusions No marked decrease in prevalence of live birth DS was observed in the region of PGC during the last ten years. The usage of MSS and amniocentesis was too low to have any significant impact on live birth DS prevalence. Women′s, as well as physician′s, knowledge and attitudes towards prenatal diagnosis of DS should be evaluated.

Key Words Down Syndrome; live birth prevalence; maternal serum screening; amniocentesis

Introduction

Trisomy 21, Down syndrome (DS), is the most prevalent autosomal trisomy encountered at birth (1). It is also the main cause of mental retardation and a major public health concern (2). Prevalence of DS at birth depends on the maternal age distribution in a population and on the availability and use of prenatal diagnosis and pregnancy termination (3,4-6). The modern concept of prenatal prevention of DS is based on non-invasive tests (biochemical and ultrasound screening) and invasive diagnostic methods, such as chorion villi sampling or amniocentesis.

In Croatia, maternal serum screening (MSS) has been avaliable since 1996, first in Rijeka and Zagreb (7,8), and later in Split and Osijek. A national policy of prenatal care was not established. Therefore, the pregnancy-care system in Croatia was established by individual regions. The current policy of the prenatal program in the region of Primorsko-goranska County (PGC) in Croatia includes amniocentesis for pregnant women aged 35 or over, and MSS for younger women.

The aim of the present study was to estimate the prevalence of live birth DS for the past ten years in the region of PGC. In addition, we evaluated the impact of MSS and amniocentesis on the prevalence of live birth DS.

Methods

Data collection

The present study was based on a database from the Department of Gynecology and Obstetrics at the University Hospital Centre Rijeka. This is the only birth center in the region of PGC with approximately 500,000 inhabitants, and about 2900 total births per year. About 20% of child-bearing women come from cunties other than PGC, and were excluded from the present study. This database provided data on the number of live born children with DS, the maternal age of their mothers,

and the number of total births. All data about maternal age of screened women, number of women who have increased risk for DS, number of diagnostic tests performed, indications for amniocentesis, and kariotype of fetuses affected with DS were obtained from databases of the Department of Biology and Medical Genetics, School of Medicine, University of Rijeka. In the region of study, this is the only Centre that performes cytogenetics diagnosis and biochemical screening for DS. The Croatian National Institute of Public Health provided data on maternal age for the general population of mothers with live born children in Croatia. All data were collected for the period from 1996 to 2005.

The regional policy of prenatal diagnostic program for DS

The policy of prenatal care in PGC has been that MSS is offered to women younger than 35 years. For those who had a positive result for DS, amniocentesis has been recommended. Because of the age-related risk of DS, women aged 35 or older are informed of the recommended diagnostic tests (amniocentesis) for DS. During counseling women can choose whether to have the diagnostic tests performed. Amniocentesis, regardless of indication, is covered by national health insurance but MSS is not. Termination of pregnancy for chromosome anomalies is reimbursed and legal in the studied region as it as in all of Croatia.

MSS is performed in the second trimester of pregnancy. The screen positive result for DS was defined as a term risk $\geq$ 1/250. The ″double test″ (AFP and free β-hCG) was used from 1996 to the end of 1999. After 1999 the ″triple test″ (AFP, free β-hCG and uE) was established. DS detection rate was not changed during the study period or according to the methods applied. Prenatal diagnosis of DS was performed on amniotic fluid obtained from second trimester amniocentesis.

Definitions

The prevalence of live birth DS was defined as the number of live born DS cases per 1000 live births in the studied region. The total prevalence of DS was the total number of DS cases (live born and terminated) per 1000 births (live births, stillbirths, and terminated pregnancies affected by trisomy 21). Not one case of DS in stillbirths was recorded during the study period. The total prevalence of DS was corrected for the 25% DS fetal loss rate between the time of amniocentesis and term (9,10). *Because of the small number of DS recorded every year, the total DS prevalence was corrected for the overall ten years period.* The uptake of MSS and amniocentesis was defined as the number of tests performed per total number of births.

Statistical analysis

Statistical analysis was performed using Statistica v. 7.1 (StatSoft. Inc., Tulsa, OK, USA). Variations in live birth prevalence of DS, total birth prevalence of DS, and uptake of MSS and amniocentesis during the past 10 year were tested by linear regression analysis. Statistical values were considered significant at $p<0.05$.

Results

During the study period of 1996-2005 a total of 23,447 live births were recorded in the PGC. Mean maternal age over the ten year period was 28.42 years. Maternal age steadily increased from 1996 to 2005 ($p=0.006$). Women aged 35 or over represented 11.6% of all pregnant women included in the study.

There were a total of 33 DS live births throughout the study period. The prevalence of live born DS was 1.4/1000 births (Table 1). A nonsignificant decreasing trend in the prevalence of live born DS was observed over time ($p=0.577$). The mean

age of mothers who delivered children affected with DS was 32.7±5.8 years. Thirteen out of 33 DS children (39.4%) were born to women aged 35 years or more.

A total of 21 cases of DS were prenatally detected (Table 1). In 15 cases (71%) the indication for amniocentesis was advanced maternal age, in 4 cases (19%) it was a positive biochemical DS screening result, and in 2 cases (10%) it was abnormal ultrasound findings. The mean maternal age in these 21 cases was 37.4±3.8. All affected pregnancies were terminated after counseling. For prenatally and postnatally confirmed DS, in 52% (28/54) of cases the mother was 35 or more years old. Total prevalence of DS, corrected for the 25% DS fetal loss rate between the time of amniocentesis and term, was 2.0/1000, and did not change over time ($p=0.912$).

As shown in Table 1, the proportion of screened women, although fluctuated during the study period, did not significantly change ($p=0.829$). The number of amniocenteses significantly increased over the entire study period ($p<0.001$).

Discussion

The present study shows that the prevalence of live born DS in the PGC (1.4/1000) was not markedly changed from that observed in the period from 1986-1993 (1.7/1000) when prenatal care policy was age-related only, and MSS was not yet available in Croatia (11). However, 18% decrease in prevalence of live born DS following the introduction of MSS since 1996 was observed. The percentage of women aged 35 or over who gave birth to children with DS rose from 17.2% in the period 1986-1993 to 39.4% in the period 1996-2005. This was probably due to the increasing maternal age reported for the general population of mothers with live born children in Croatia (12). The percentage of mothers that were older than 35 increased

from 6% in 1996 to 11.8 % in 2005 (12). In the region of PGC, the proportion of mothers who were older than 35 was 10.7% since 1996, and steadily increased to 2005. According to the current policy of the prenatal program in the PGC, the percentage of older mothers with DS affected live born children (39.4%) was greater than it should be. We could partly explain this by low uptake of amniocentesis in the group of older women. During the study period the percentage of women aged 35 or more was 11.6%, and the overall uptake of amniocentesis was 6.1%. This is almost two times lower than the theoretical level of uptake for amniocentesis should be. Moreover, the observed amniocentesis rate included women with DS-positive MSS result as well. So, the uptake of amniocentesis in the group of older woman was even smaller then 6.1%. There are many factors that influence decision-making regarding uptake of amniocentesis, including physician′s and woman′s attitudes towards prenatal diagnosis and abortion, socioeconomic factors, and ethnicity (13). Although studies of these factors have not been done in Croatia, we would rule out an effect of economic factors and ethnicity because amniocentesis is covered by the national health insurance and Croatians are all of the same ethnicity. An evaluation of women′s, as well as physician′s, knowledge and attitudes towards prenatal diagnosis would be of great interest. The high proportion (52%) of women over 35 who carried fetuses affected by trisomy 21 (live born or prenatally detected) observed in this study requires greater attention from physicians otherwise the prenatal diagnostic program for DS could become meaningless. Other than maternal age, currently no other risk factors for DS are known.

During the study period the overall uptake of MSS was 33.9%. The observed utilization rate of MSS is one of the lowest reported in comparison with other countries (6,14-17). Moreover, a declining trend in the uptake was presented in the

first five studied years, and then again, an increase was seen till 2005. It is impossible to give some rational explanation for that, since no changes in regional prenatal care policy have been done. In the present study only four cases (19%) of prenatally confirmed trisomies 21 were detected after positive MSS results. We know that the second trimester MSS detection rate of DS is lower in younger women, and that in younger mothers DS is more frequently detected during ultrasound anomaly scans than through MSS. Consequently women much younger than 35 should be participating in non-invasive prenatal programs (7,10,18). It should be stressed that the cost of MSS is not reimbursed. Therefore the financial concerns could have been an important factor influencing MSS uptake in the PGC. Both the financial issues and utilization problems with MSS should be resolved if the national consensus about prenatal diagnostic programs for DS are to be made available in Croatia.

In conclusion, in spite of a great effort to introduce MSS into routine prenatal care practice in PGC, only a small decrease in prevalence of live birth DS has been observed in the last ten years in contrast to the period from 1986-1993. It is clear that the current low rate of MSS and amniocentesis uptake could not have any significant impact on DS live birth prevalence. Further studies should be done to find out the reasons for low uptake of MSS and amniocentesis in Primorsko-goranska County. Any improvement or implementation of first trimester screening for DS would be useless until answers to these questions are available.

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Table

Table 1 - The prevalence of live birth DS, total prevalence of DS, the uptake of maternal serum screening (MSS) and amniocentesis (AC) in the region of Primorsko-goranska County in Croatia, 1996 to 2005

Year	Total births	Live births	DS live births	DS live birth prevalence /1000	DS prenatally detected	DS total prevalence /1000	Uptake of MSS** (%)	Uptake of AC** (%)	Mean maternal age (year)	No. of women ≥35 (%)
1996	2685	2566	3	1.2	2	1.7	23.4	2.5	28.02	10.74
1997	2578	2509	7	2.8	0	2.7	42.3	4.8	28.48	12.11
1998	2512	2432	0	-	2	0.8	37.3	4.2	28.35	11.50
1999	2360	2289	5	2.2	4	3.8	38.8	5.5	28.08	11.35
2000	2349	2286	3	1.3	2	2.1	36.9	5.9	28.40	10.75
2001	2295	2232	3	1.3	1	1.7	21.6	5.8	28.42	11.65
2002	2279	2216	3	1.4	3	2.6	30.4	7.3	28.54	11.46
2003	2333	2270	6	2.6	2	3.4	33.9	8.5	28.46	11.52
2004	2363	2308	2	0.9	2	1.7	33.9	9.2	28.66	12.01
2005	2409	2339	1	0.4	3	1.7	40.1	8.4	28.83	12.58
total	24163	23447	33	1.4	21	2.0*	33.9	6.1	28.42	11.6
statistics	r#			-0.202		0.041	0.091	0.955	0.797	0.552
	p			0.577		0.912	0.829	<0.001	0.006	0.098

*corrected for DS fetal loss (25%).
** uptake of MSS and AC were calculated according to the numer of total births
r# – coefficient correlation between year and examined variables

COMMENTS FOR THE AUTHOR:

Reviewer #1: Authors have used a very relevant and interesting area to research about, since it is very befitting the current prevailing need for preconceptional health in prevention of poor delivery outcomes.

I found some discrepancies in the impact evaluation part of the paper. In the abstract and in the Title the authors state that their objective is to evaluate the impact of second-trimester maternal serum screening (MSS) and amniocentesis on live birth DS prevalence but in the Introduction (pg2 line 36) they mention "….we evaluated the impact of regional policies of prenatal care, including MSS and amniocentesis…." To me as a reviewer this presents a very confusing scenario since evaluation of the impact of a screening test and the impact of a policy are two very different issues and need to be evaluated in a correct manner. If the main objective of the authors was to study the impact of a policy implementation the design of the research needs to be revised: When was the policy implemented? Why was it implemented? Was any evidence-based data used to drive the formulation of this policy? What was the impetus? How does this compare to an area where there is no national policy for the screening tests? In addition to this there is no mention of DS prevalence in Zagreb, Split and Osijek and then did their prevalence change after the availability of MSS in these areas? If the authors say that their objective was to evaluate the impact of regional policies and/ screening tests then I think they present an incomplete picture. My recommendation would be that the authors focus on evaluation of the implementation of screening tests in the region and if possible compare it with a region that does not have these tests implemented.

As a matter of fact, we wanted to evaluate the impact of second-trimester maternal serum screening (MSS) and amniocentesis on live birth DS prevalence. It is not possible to make a comparison with a region that does not have these tests implemented. That information is not available/reported.

Pg 2 line 51 The number 500.000 needs a comma instead of a period

Corrected

Pg 2 line 56 In the sentence "this database provided……..number of total births." Authors need to specify the # of total births in the hospital or in the region? Does total number of births in the University Hospital Center equal total # of live births in the region? A statement clarifying this would be helpful

The total number of births in the University Hospital Center is not equal to the total # of live births in the region, so we specified it.

Pg 4 line36 Result: the authors state that 13 out of 33 were born to women aged 35 years or more. It would be interesting to know about the rest of the women (n=20) aged less than 35 years, whether they were offered MSS? if they were why did they not take the test? Was it financial concerns only? Or other concerns? It may be worthwhile to find if 20 babies born with DS could have been prevented. This could help in directing policy towards payment of MSS through national insurance.

We put the following sentence in the text: Mothers of live born DS were not participated in MSS program.

Table 1 Uptake of MSS: from 1997-2001 there seems to be a declining trend in the uptake of MSS and then again an increase is seen till 2005. Is it possible for the authors to explore the reason behind this trend? Any change in hospital policy? Administrative changes?

We put the following sentence in the text (discussion): Moreover, a declining trend in the uptake was presented in the first five studied years, and then again, an increase was seen till 2005. It is impossible to give some rational explanation for that, since no changes in regional prenatal care policy have been done.

Reviewer #2: This paper addresses an important public health topic—down syndrome, public health policy, and prenatal care practices. The main weakness of the study is the small number of cases on which to base conclusions, and an analysis that is too ambitious for the limitations of the data. After addressing specific points below, I offer some suggestions for improving the paper.

Introduction

The paper seems to have an unstated assumption that public health policy should be to reduce DS births by detecting and terminating DS pregnancies. This assumption should be stated explicitly and discussed in more detail in the discussion.

Methods

What is the relation of the three different data sources to each other and to the study population? What proportion of the population in covered by each data set? How is the covered population of each data set different? In the discussion, address how these differences could have affected the study results.

The database from the Department of Gynecology and Obstetrics at the University Hospital Centre Rijeka and the database of the Department of Biology and Medical Genetics cover the same population, primarily the population of the region PGC. Both Departments belong to the School of Medicine, University of Rijeka. The Croatian National Institute of Public Health provided data on maternal age for the general population of mothers with live born children in Croatia. All Croatian Counties are obligated to deliver information about maternal age and others to the Croatian National Institute of Public Health.

"The regional policy of prenatal diagnostic program for DS" This section belongs in the introduction.
We put it in the introduction.

Is termination of pregnancy for chromosome anomalies covered by national health insurance?
Yes it is, we mentioned it in the section "The regional policy of prenatal diagnostic program for DS".

Is amniocentesis recommended to women with a positive MSS? Is amniocentesis following a positive MSS for women under 35 covered by national health insurance?
Yes, we mentioned it in the section "The regional policy of prenatal diagnostic program for DS".

If the answer to any of these is "no," then possible impact on study results needs to be addressed in the discussion. Give the units or explain the 1/250. Tell how the improved test introduced in 2000 affects DS detection, and in the discussion address how this change could have affected the results?
DS detection rate was not changed during the study period or according to the methods applied.

Define uptake of MSS and AC.
We defined it in the text, and in the legend of the table.

The definition for total prevalence includes stillbirths in the denominator. Does it include DS stillbirths in the numerator?
Are there cases of undetected DS in stillbirths and non-DS terminations? In the discussion, address how this affects study results.
No one case of DS in stillbirths was recorded during the study period, and we had not non-DS terminations.

Results

Much of the use of statistical significance testing is inappropriate. If the numbers and rates are considered total population values, then there is no random variation and p-values are meaningless. If the numbers are a sample of the population, that is not clear. If the data are taken to represent a statistical superpopulation that generates random variation, that needs to be justified, given the very local nature of the study.

The numbers and rates were considered total population values and we wonted to test the changes over the 10 years period in the well-organised County of Croatia.

"if we look just at the period of the last five years, a statistically significant increase in the use of MSS was observed" The rationale for looking at the data this way is not clear. The trend in these five years is driven by an unusually high rate in the last year and an unusually low rate in the first year. Overall, the rates in the previous five years were as high or higher.

We put the following sentences in the text (discussion): Moreover, a declining trend in the uptake was presented in the first five studied years, and then again, an increase was seen till 2005. It is impossible to give some rational explanation for that, since no changes in regional prenatal care policy have been done.

"the last five years" state the years explicitly.
We omitted this statement.

"number" in the last paragraph of the results should be "proportion."
Corrected

Give the units for age.
We did it

Discussion

The second aim stated in the introduction needs to be addressed with more focus in the discussion. The first sentence of the discussion describes an 18% decrease in prevalence following the introduction of screening. Is this not an "impact of regional policies of prenatal care, including MSS and amniocentesis, on the prevalence of live birth DS"?

Yes it is, but the difference was not statistically significant ($\chi 2=0.41;p=0.524$). Still, we mentioned 18% decrease in prevalence of live born DS following the introduction of MSS since 1996.

"The percentage of women aged 35 or over who gave birth to children with DS rose from 17.2% in the period 1986-1993 to 39.4% in the period 1996-2005. This was probably due to the increasing maternal age reported for the general population of mothers with live born children in Croatia." How could a shift in the maternal age distribution affect the proportion of older women with DS births? The rate of termination of DS pregnancies must have decreased.

"The high proportion (52%) of women over 35 who carried fetuses affected by trisomy (live born or prenatally detected) observed in this study suggests that the maternal age profile has greatly changed during the last decade in PGC." How does this conclusion follow from the observation? Doesn't it rather suggest that DS termination rates among older women have dropped?

Author's answer to the both previous statements of reviewer:
The greater percentage of women over 35 would have been expected to lead to an increase in the prevalence of DS. A rise in the childbearing age of the populations as a whole causes an increase in the incidence of DS, since the risk of chromosomal nondysjunction rises exponentially with increasing age of the mothers. The reason why older women did not consume the amniocentesis was unknown at the moment, so we could not tell/conclude that the rate of termination of DS decreased.

"the number of DS cases detected in this study was too small to make conclusions regarding total prevalence of DS." Yet, you make conclusions about the prevalence of DS live births. Either the data are too sparse to draw any conclusions about DS prevalence, or the data are not being interpreted properly.

To calculate the total prevalence, the correction for fetal loss is needed. In the study the number of DS detected or born per every year was to small to make the correction and testing the change over the time.

"percentage of women aged 35 or more was 11.6%, and the overall uptake of amniocentesis was 6.1%." This comparison should be with the uptake for older women, not overall.

Data about the uptake of amniocentesis for older women are not available at the moment, so we explained it in the text.

"small decrease in prevalence of live birth DS has been observed in the last ten years." This conclusion is not supported by the data.

"greater than it should be." This is vague.

"the theoretical level of uptake for amniocentesis." This is vague.

Table 1 - what data does the single * refer to?

Because of the small number of DS recorded per every year, the total DS prevalence was corrected only for the overall ten years period.

Suggestions

Collapse the data into five year groups, 1996-2000 and 2001-2005. Stratify by age (<35 and 35+). Make comparisons between the two periods within age groups; in other words, compare younger women for 1996-2000 with younger women for 2001-2005, and older women for 1996-2000 with older women for 2001-2005. Make comparisons of DS prevalence; rates of MSS, AC following positive MSS, AC, and termination following positive AC. Take shifts in maternal age distribution and other changes into account.

We could not accept the suggestion for two main reasons. First, our intention was not to make comparison between two periods, and second, DS detection rate was not changed during the study period or according to the methods applied. Moreover, no changes in regional prenatal care policy have been done.

Reviewer #3: This paper requires major revision and clarification, primarily of statistical analyses. As is, the paper is simply descriptive in presenting changes in prenatal screening prevalence and DS prevalence over time. Only maternal age seems to emerge as a predictor of DS (which is not a new finding). Specific issues that should be addressed are:

Methods

Statistical analyses

1) It is unclear what hypotheses are actually being tested. The specific regression model (or models) need to be clarified. For example, what are the dependent variables (prevalence of DS?) and independent variables (prevalence of prenatal screening, maternal age, time period...). This section seems to suggest that DS prevalence and screening were dependent variables.

In all regression analysis time period was independent variable, and dependent variables were prevalence of DS, number of screening, number of amniocentesis, maternal age.

2) Was year of birth included as an independent variable? Since prenatal screening changed in 1999, including birth year as a category variable would seem more appropriate.

The year of birth was included as an independent variable. We did not consider birth year as a category variable since we did not tested the difference of DS live birth prevalence according to screening test. DS detection rate was not changed during the study period or

according to the methods applied. Moreover, no changes in regional prenatal care policy have been done.

3) Given the low DS prevalence (and possible effects on the variable's distribution), the suitability of linear regression should be addressed. Logistic regression may be used to predict rare events (with appropriate corrections).

4) Results of the regression analysis are not included in a table making it impossible to evaluate the results.

The results of the regression analysis were included in the table

5) Maternal age statistics (mean, percent over 35) should be included in a table.

Data were included in the table.

Introduction

The main premise of the study..."prevalence of DS depends on.... availability and use of prenatal diagnosis and pregnancy termination" is not sufficiently discussed or referenced.

The statement was referenced.

Other
Avoid use of first person throughout the manuscript.

Reviewer #4: The authors state the objectives of reporting the live birth prevalence of DS in a county of Croatia and of assessing the impact of 2nd trimester MSS and amniocentesis on this. However, to do so as the authors have done without discussion of the implications of the finding for public health policy in Croatia or of the applicability of the findings in any way results in a sterile report. The authors' submission reads like a counting of birth prevalence and prenatal testing that would be submitted to a Ministry of Health for an annual report.

The numbers in this paper do not add up. The authors report 33 live DS births out of 23,477 babies born in the study period. Their birth prevalence of 1.4 per 1,000 seems reasonable. However, they report that 21 pregnancies were terminated because of a diagnosis of DS. Assuming no termination, this would mean a birth prevalence of 2.3 per 1,000. To sustain that, you would need women aged 35 and over to represent 18-19 percent of all pregnant women in the population. Even halving the number of terminations would result in a birth prevalence of about 1.9 requiring that 15-16 percent of all pregnant women be of advanced maternal age to sustain that. Something is off. At the very least, the authors should have noted this and explored possible reasons for these findings.

Author's answer:

We calculated the live births prevalence of DS as the number of live born DS cases per 1000 live births in the studied region (33/23447=1.4/1000). The total prevalence of DS was the total number of DS cases (live born and terminated) per 1000 births (live births, stillbirths, and terminated pregnancies affected by trisomy 21) (54/24163=2.2/1000). But, the total prevalence of DS was corrected for the 25% DS fetal loss rate between the time of amniocentesis and term according to references No.9 and 10. Finally, the total prevalence of DS was 2.0/1000. If we had halved the number of terminations as you said, we should have had the total births prevalence of 1.8/1000 (33+11=44/2416 = 1.8/1000).
What could be said on that criticism. The situation was just like we described in the paper. Maybe the number of DS cases was too small for making any conclusion about the requiring percentage of pregnant women of advanced maternal age.

There are no conclusions of note. One can surmise that prenatal diagnosis in Primorsko-goranska County "works" but what is the take-home message? The suspect numbers aside, what lessons or best practices can be learned from this report? How does the article contribute to improved public health practice in Croatia or other similar settings?

The take-home messages are: 1. unreasonable number of DS born by mothers of advanced age, 2. low uptake of MSS. The reasons of both should be evaluated before any improvement in prenatal care was done.

The authors use a mixture of terms, some incorrectly. The article requires light editing and some rephrasing, for example, "The percentage of women aged 35 or over who gave birth to children with DS rose from 17.2% in the period 1986-1993 to 39.4%."