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Implementation of combined ultrasound and biochemistry for risk evaluation of chromosomal abnormalities during the first trimester in Sweden

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Abstract

Objective. To investigate how the first trimester risk evaluation for Down syndrome is offered and performed. *Setting.* Sweden. *Sample.* All 52 known units working with obstetric ultrasound. *Methods.* Study specific questionnaire. Descriptive statistical analyses.

Main outcome measures. Routines for offering CUB, questions about information, questions about tests and analysis used for diagnosis. *Results.* CUB was performed in 28 600 (26%) of the expected 110 000 pregnancies in Sweden during 2011. Of all pregnant women, 15% were living in a county not offering CUB (only invasive prenatal diagnosis); 44% regardless of age; 15% to women ≥ 33 years; 24% to women ≥ 35 years; and 2% to women ≥ 38 years old.

Amniocentesis was the most common method offered when the risk was estimated as high. Of the 47 units that answered, 29 (61.7%) offered only amniocentesis (AC). On the questions about information, 40 (95.2%) stated that they gave verbal information. In addition to the verbal information, 17 (40.5%) gave written information. Forty-one of the units (71.9%) stated that the CUB is offered to non-Swedish speaking women. *Conclusion:* Without consistent national guidelines, the prenatal diagnostic method of CUB is offered in an inequitable manner to pregnant women in Sweden. More than half of all pregnant women live in a county where CUB is not offered or only offered based on age. The results of the present study demonstrate the importance of national consistency before the introduction of new prenatal tests, to enhance equal care for all pregnant women.

Introduction

Pregnant women at the age of 35 or older have in Sweden traditionally been offered an invasive test, either amniocentesis (AC) or chorionic villus sampling (CVS), due to the increased risk of having a baby with chromosomal abnormalities with advanced maternal age (1, 2, 3). The disadvantage with invasive tests is the associated risk of miscarriage (4). Another known, but rare consequence of amniocentesis is talipes equinovarus. Further, the detection rate when chromosomal tests are based on maternal age is low, 20-30 per cent (5).

Another strategy, the first trimester scan for risk evaluation of having a baby with Down syndrome, was introduced in Sweden at the beginning of 2000 for high-risk patients. This risk assessment was performed by measuring nuchal translucency (NT), a method evaluated by a large randomized controlled multi-centre study (6). The detection rate of chromosomal aneuploidies was improved by a combination of ultrasound and a maternal blood sample (CUB) (7, 8). In the procedure of offering the CUB, the strategies of providing information are crucial to reassure and to enable the woman to make an informed choice (9). It is essential to have access to correct, balanced and non-directive information to be able to make decisions (10, 11). Due to Swedish legislation all pregnant women should be offered information regarding prenatal diagnostic possibilities (12) and The Swedish Council on Health Technology Assessment (SBU) concluded in 2006 (13) that CUB was the best test to achieve the optimum balance between the percentage of detected cases and false positive results. However, the 21 counties in Sweden provide health care differently and despite the SBU assessment, CUB-test has not been introduced in Sweden as suggested. In contrast to another Scandinavian country, Denmark, who made a national united implementation, the birth rate of children with Down syndrome remains unchanged in Sweden (14). The aim of the study was to investigate how the first trimester risk evaluation for Down syndrome is offered and performed in Sweden.

Material and methods

A questionnaire was sent to all known (52) units working with obstetric ultrasound, comprising 99% of all routine obstetric ultrasound in Sweden, in October 2011. The questionnaire was sent out by e-mail or regular mail, depending on contact information. The contact person was allowed to forward the enquiry to relevant persons and the questionnaire was answered and sent back by 56 professionals. The questionnaire responses were merged

and consolidated by ultrasound unit. The responses correspond to 47 units (9 private clinics, 31 county hospitals and all seven university hospitals).

CUB was performed in 28 600 of the expected 110 000 pregnancies in Sweden during 2011. Sixteen of the 21 counties offered CUB, but with different designs (table 1). Six counties offered CUB regardless of the pregnant women's age and without charging a fee. When CUB was offered it was offered free of charge except in one county who offered CUB to all women, but women below 35 years of age had to pay the full cost for the test, while women $\geq$ 35 years of age paid a small fee.

Out of all pregnant women, 15% lived in a county not offering CUB (only invasive prenatal diagnostic); 44% regardless of age; 15% to women $\geq$ 33 years; 24% to women $\geq$ 35 years; and 2% to women $\geq$ 38 years old. Age dependent design was in 84% based on economic reasons. In counties offering free CUB to all pregnant women, there was a 65-95% uptake of CUB, and for the age dependent design, the uptake was 15-30%.

The questionnaire was developed specifically for this study and consisted of 42 questions. The questionnaire was tested and approved by the working- and reference group of obstetric ultrasound within the Swedish Society of Obstetrics and Gynaecology. The answers from the units were based on the routines of offering tests for risk estimation of fetal chromosomal abnormalities in early pregnancy and the information provision in the region of the unit.

Descriptive statistics were used. All analyses were conducted using IBM SPSS Statistics 21 Software (SPSS Inc., Chicago, Illinois, USA).

According to recommendation of the board of ethics of research in Uppsala, this study did not need ethically examination. The data was only collected and analyzed on a group level and no personal identification was possible.

Results

Forty-two (73.7%) units answered the question about the most common method of information. Forty (95.2%) stated that they gave verbal information. In addition to the verbal information, 17 (40.5%) gave written information, four (9.5%) added information from the

Internet and six (14.3%) units informed verbally, in writing and from the Internet. One (2.4%) unit stated that they only gave written information.

On the question *who* gave the information, 41/43 (95.4%) units answered that there was a midwife involved in giving the information. Only two (4.6%) units stated that information prior to CUB was provided entirely by a doctor. Five (12.2%) stated that the midwife who gave information was specially trained and in two of those units a doctor was present during the provision of information. Further, two (4.9%) stated that the most common situation was that the midwives at the antenatal unit provided the information, but with the possibility to call in expert midwives. The majority of the units 32/36 (88.9%) stated that they considered women's knowledge about CUB as sufficient. The strategies for giving information varied as presented in table 2. The vast majority of units, 39 (92.9%) gave the information individually. On average provision of information for the CUB lasted for 19.6 minutes, range 5-30 minutes ($\pm 9.3SD$), and on 72.7% ($\pm 18.6SD$) of the occasions the partner was present.

Forty-one of the units (71.9%) stated that the CUB was offered to non-Swedish speaking women. The information about the test in these cases, was given by an interpreter in 27 of the 41 units (65.8%). Two of the units (4.9%) stated that they only used written information whereas two units used both an interpreter and written information. The units identified some deficiencies concerning in the information of the CUB (prior to the CUB); cultural aspects, women's previous knowledge, language; understanding the risk assessment, lack of time, nuanced information about consequences of Down syndrome, difficulties to give equal, neutral information.

Most of the units, 23 (54.8%) used the concept 'probability' when communicating risk information. The concept 'risk' was used by 16 units (38.1%). A few units, two (4.8%) used both concepts. Regarding the question about how the result of the CUB is given, the majority of the units, 37 (88.1%) answered that it is communicated by the midwife or the doctor who performed the ultrasound examination (first trimester nuchal scan). In three (7.0%) units the results of the CUB could be given by a doctor or midwife who did not perform the nuchal scan and one unit sent the results by letter.-The most common way to communicate the probability for chromosomal abnormalities was both as a number (e.g. 1/2020) and whether the woman was at high or low risk, 22 (52.4%). Thirteen units (31%) stated that they only

communicated the figure. One unit restricted the information to trisomy 21 and not trisomy 13 or 18 although they were included in the risk estimation software.

A national computer programme for risk estimation (PreNatalQualityregister, PNQ) (15) was used for 72% and the Fetal Medicine Foundation (FMF) programme for the remaining 28% of all examinations. The risk estimate used was valid for the time of sampling and not for the time of birth. Cut-off for a positive test indicating the need for invasive testing varied between 1:200 and 1:400. The most common cut-off was 1:200 in 26 (60.5%) units (table 3). All units, except two, reported fewer invasive tests when introducing CUB (in Stockholm a 20% reduction was reported).

Amniocentesis (AC) was the most common method offered when the risk was estimated as high. Of the 47 units that answered, 29 (61.7%) offered only AC. Eighteen (38.3%) units offered both AC and CVS. The most common method for fetal karyotyping in the units surveyed was QF-PCR (29, 61.7%), and the second most common was FISH (15, 31.9%). Complete analysis was performed in three units (4.3%). However, complete fetal karyotyping was offered when the NT had passed 2.0 mm in one unit (2.8%), 3.0 mm in 15 units (41.7%), 3.5 mm in 19 units (52.8%) and 4.0 mm in one unit (2.8%). In almost all units (42/43, 97.7%) a specific ultrasound for examination of the fetal heart was offered when the NT was > 3.5 mm in 22 (52.4%) of the units, and > 3.0 mm in 17 (40.5%) of the units. A few units (3, 7.2%) used other NT limits. Rapid analysis was used routinely in 45 of 52 units (86.5%), 35 (77.8%) of the units included sex chromosomes in the analysis, whereas 10 (22.2%) of the units did not. Of those who included the gender in the analysis (35), 32 (91.4%) stated that the parents-to-be could be informed of the result.

Discussion

In 2011 in Sweden, there were no national guidelines or recommendations for prenatal diagnostics concerning the risk estimation of fetal chromosomal abnormalities in early pregnancy. This study reveals considerable differences in how the first trimester risk assessment was interpreted in different parts of Sweden, e.g. widely varying information given prior to and after the test; CUB was offered for free, for a small charge or for full payment; high risk cut offs varied between 1/200-1/400; 62% of all units offered only amniocentesis and not CVS. There was a pronounced inequity in the possibility for pregnant women to undergo a

first trimester risk assessment with the CUB. In some counties the test was not offered at all, while in other counties the test was offered either to some or to all pregnant women. This strategy is not in line with the Swedish legislation which advocates optimal health and equal conditions and care for all people, irrespective of whom you are or where you live (17). This conflicts with the principle of justice, one of the four fundamental ethical principles in Swedish health care (18). Up to date, no national guidelines or recommendations regarding CUB-test has been introduced in Sweden.

Good quality information about prenatal examinations is a prerequisite to facilitate for the woman to make an informed choice. There are several definitions of informed choice. Informed choice in the context of prenatal screening means to undergo prenatal examinations when the woman has relevant knowledge about the test, a positive attitude towards it and actually undergoes it (19, 20, 21, 22). Informed choice is thus questioned by this study as is illustrated by the wide variation (65 to 95%) in attendance for the CUB-test among the counties offering free CUB-test to all pregnant women. Two of these are university counties and the attendance of 65% in one county and 95% in the other is hardly explained by different populations alone. In a recent study from Denmark, where all pregnant women are offered risk assessment for Down syndrome, only 80% of the women made an informed choice about undergoing a CUB (23).

Prior to the CUB examination most of the units gave information verbally and individually. About two thirds of the units gave written information and of those, some units used the Internet as a complementary source of information. The National Board of Health and Welfare strongly recommends that written information is available, as well as care givers having the necessary qualifications (24). In Sweden today, midwives in antenatal care have the responsibility for providing information. In the UK, a study showed that midwives in antenatal care sometimes lack accurate knowledge about antenatal screening and the conditions which are screened for (25). The family situation as well as the women's expectations about living with a child with Down syndrome (26) and the knowledge about the condition should be taken into account (27). It is conceivable that there is a need for further education among Swedish midwives. Educating the midwives would facilitate accurate information provision.

The definition of risk communication is not evident, neither is how risk information should be provided, but the ultimate goal of risk communication is to facilitate informed decisions about medical treatment and management. This is clearly demonstrated in the present study as well as in previous studies (28, 29). The fact that there is no standardized counseling may lead to lack of knowledge and limited possibilities to make an informed choice about prenatal examinations (29). An American study highlighted the importance of guidelines for risk communication and also states how explaining risk can be performed “without losing the benefits that are traditionally associated with the art, rather than the science, of medicine” (28 s 827). Optimally, it is suggested that the risk information should be performed in two steps (28). This study also highlights the difficulties with risk communication, since the definition of high risk varied between 1/200 to 1/400 in different counties. One women’s clinic consisted of two hospitals where high-risk cut-off was defined as 1/200 and 1/300 although it was the same clinic. Under these circumstances it is difficult to assume that pregnant women feel confident with the prenatal risk estimation.

In several Swedish regions there are a high proportion of immigrants which leads to further demands regarding information. Even if the women regard the care and medical technique as impressive (30), attention has to be paid to ensure that non-Swedish-speaking parents-to-be receive sufficient information. Almost one third of the units stated that they do not offer non-Swedish speaking women the CUB. Among the units offering CUB to non-Swedish speaking women, information about the test is given (either written information or via an interpreter) in only three out of four units. This is also contrary to the principle of justice (18), which is even regulated in Swedish fundamental law in health and medical service (17).

Amniocentesis is still reported as the most common follow-up diagnostic test after high risk estimation from a CUB. Only 38% of all units offered CVS. Amniocentesis has to be performed after gestational week 15+0 to minimize the risk for miscarriage. If earlier diagnosis is required, transabdominal CVS is preferable (31). For both medical reasons (the earlier the abortion is performed the less complications there are (32) and for psychological reasons (to avoid a stressful waiting time (33, 34), it is desirable to have as early a diagnosis by prenatal examinations as possible.

The results from this study reveal the disadvantages of interpretation of a new prenatal risk assessment method for chromosomal abnormalities, without a national consistency of the

practical performance. In 2011, only 40% of all pregnant Swedish women were offered the CUB regardless of age and less than 30% underwent CUB. The CUB is thus introduced in a different manner from that suggested by the scientific evaluation of The Swedish Council on Health Technology Assessment (SBU) in 2006. The main reason for this, according to this study, is the economic issue (stated by 84% of the units). National economic health calculations do not include care costs for children born with Down syndrome due to Swedish ethical opinion. The implementation of CUB-test in Sweden has, as expected, achieved a decreased number of invasive tests but the birth rate of children with Down syndrome remains unchanged. This is completely different from our neighbouring country, Denmark, who introduced CUB in a nationally coordinated way and presently has about 95% attendance and also a lower birth rate of children with Down syndrome. The authors of this study did not aim to investigate other side effects of introducing a first trimester ultrasound scan. However, since less than 30% undergo a first trimester scan it is likely that many pregnant women in Sweden are denied the possibility of testing for chromosomal abnormalities and consequently the option of whether to carry on or to terminate a pregnancy if Down syndrome of the fetus is detected. Furthermore, they are to some extent also denied the possible benefits of a first trimester scan, such as early accurate gestational age determination, chorionicity of multiple pregnancy and detecting severe malformations in early pregnancy. Non invasive prenatal testing (NIPT) with maternal blood sample for cell-free fetal DNA is today in clinical use in many countries. The introduction of NIPT in Sweden will be a new challenge and the results of this study strongly suggest that national consistency should be achieved before introduction, according to scientific evaluation and following Swedish health care law for the provision of equal care for all pregnant women (Health and Medical Services Act, 1982).

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Conclusion

Despite the scientific evaluation of prenatal tests by The Swedish Council on Health Technology Assessment in 2006, there were still no consistent national guidelines in 2011 and CUB was offered in an inequitable manner. More than half of all pregnant women lived in a county where CUB was not offered or only offered based on age, which may explain the unchanged birth rate of children with Down syndrome in Sweden. The results of the present study demonstrate the importance of achieving national consistency before the introduction of new prenatal tests, e.g. NIPT, to enhance equal care for all pregnant women.

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