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Introduction.

Since the setting up of EUROCAT in 1980 there has been a continuous increase in the proportion of congenital malformations that are diagnosed prenatally. EUROCAT studies have shown significant regional differences in prenatal detection rates in Europe.

Different policies have been developed in different countries and in different areas within countries. The availability of different resources, termination of pregnancy laws and social and cultural factors are important issues which vary in different countries. With the advances in prenatal screening methods and with improved resolution and expertise at ultrasound scanning the questions of which screening test to use and when to offer ultrasound scans in pregnancy are difficult ones to answer.

In this report we will describe the policies of prenatal diagnosis in the European countries. One EUROCAT representative from each country has written a chapter describing their national policy for prenatal screening under the four headings:

Screening for Down syndrome
Indications for prenatal cytogenetic diagnosis
Screening for Structural Anomalies by Ultrasound Screening
Terminations of Pregnancy for Fetal Anomaly

After the country chapters a list of all EUROCAT publications in the area of prenatal diagnosis are given.
CROATIA

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1 Screening for Down Syndrome

In screening for Down syndrome, nuchal translucency measurement by ultrasound can be performed at 10-14 weeks of gestation (nuchal translucency measurement alone, or combined with the maternal serum biochemistry (double test) - pregnancy associated plasma protein A and free β-hCG). Triple test (AFP, hCG, uE₃), also sensitive for trisomy 18, Turner syndrome, neural tube defects, steroid sulfatase deficiency and Smith-Lemli-Opitz syndrome, is available between 15 and 18 weeks. Most gynaecologists perform the ultrasound screening for fetal malformations on three occasions: between 10 and 14 weeks, 18 and 23 weeks and between 29 and 33 weeks of gestation. Beside nuchal translucency, short femur and humerus, impaired fetal growth, ventriculomegaly, heart defects, duodenal atresia and hydronephrosis are used as markers for Down syndrome detection. If indicated, invasive diagnostic tests are performed: chorionic villus sampling (at 10-13 weeks of gestation) and amniocentesis (at 16-20 weeks of gestation).

2 Indications for Prenatal Cytogenetic Diagnosis

Prenatal cytogenetic diagnosis is indicated at maternal age of 35 and above. The maternal serum screening risk cut ratio is 1:250. Amniocentesis is recommended in all pregnancies with a higher risk. Family history of chromosomal anomaly, chromosomal abnormalities in parents or sibs and scan markers (soft signs) or major malformations
discovered by prenatal ultrasound are other indications for invasive techniques.

3 Screening for Structural Anomalies by Ultrasound Scanning

The prenatal ultrasound examinations are usually performed between 10 and 14 weeks, 18 and 23 weeks and 29 and 33 weeks of gestation. The recommendation of the Croatian Society for Perinatal Medicine is to perform the prenatal ultrasound screening in every pregnant woman at least once at about 20 weeks of gestation. If indicated, the ultrasound examination is performed more often.

4 Termination of Pregnancy for Fetal Anomaly

Termination of pregnancy is regulated by the Croatian law of 1978: after the first 10 weeks of pregnancy, the performance of the termination of pregnancy for fetal anomaly must be approved by a commission of experts, composed of two physicians, one of whom is a gynecologist, and a social worker or a registered nurse. The commission may give consent to an abortion when it is medically established that it is probable that the child would be born with a serious congenital physical or mental defect.
DENMARK

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Just recently (September 2004) a new national policy on prenatal diagnosis and screening has been formulated in Denmark. This policy replaces the national policy from 1994, and currently the field is therefore in a time of change.

1 Screening for Down Syndrome

From 1994-2004 the national policy was to offer women aged 35 or older a CVS or an AC. Women younger than 35 were offered a CVS or an AC only if they were considered of being at high risk of having a fetus with Down syndrome (e.g. close family member with Down Syndrome, previous child or fetus with Down Syndrome or if they had been exposed to potential teratogenic agents). In this period there were some regional variations in the policy (one county offered second trimester serum screening (triple test) to women younger than 35 years of age, some counties started offering Nuchal Translucency scan and first trimester serum screening during the latter part of the period). In the EUROCAT register area (Funen) the policy was very close to the national policy. In September 2004 a new national policy was formulated. Pregnant women of all ages will now be offered a first trimester serum test (GA 8+0 to 13+6) and an ultrasound scan for Nuchal Translucency (GA 11+0 to 13+6). This policy is now being implemented, but it is expected to take a while until the ultrasound scan capacity is increased to the necessary level in all regions. The new policy will be implemented in Funen County from May 2005.
2 Indications for Prenatal Cytogenetic Diagnosis
From 1994-2004 the indications were: Maternal age 35 years or older, second trimester serum screening test risk 1:400 or higher, family history of chromosome anomaly, translocation carrier, some ultrasound diagnosed major malformation, more than one ultrasound scan marker. All these indications were free of charge. From 2004 the indications are: First trimester serum test and Nuchal Translucency risk 1:250 or higher, first and second trimester serum test risk 1:250 or higher, integrated test risk 1:250 or higher, family history of chromosome anomaly (after genetic counseling), translocation carrier (after genetic counseling), some ultrasound diagnosed malformations. All these indications are free of charge.

3 Screening for Structural Anomalies by Ultrasound Scanning
From 1994-2004 the indications for screening for structural anomalies by second trimester ultrasound scanning (usually week 18) were: three or more miscarriages, family history of structural anomaly, history of stillbirth without a known cause, exposure to teratogenic agents. There have been regional variations, and some counties have been offering routine dating scans or malformation scans to all women. The registry area (Funen) has however followed the national policy. All above scans were free of charge. From 2004 all women will be offered a routine scan for structural anomalies around week 18, free of charge.

4 Termination of Pregnancy for Fetal Anomaly
The national policy (by law) is that up till 12 weeks of gestational age every woman may opt for a termination of pregnancy without special
permission. After week 12 termination of pregnancy for fetal anomaly can be performed after permission from a regional committee (two doctors and one employee at the Social Centre). The upper gestation limit for fetal anomaly is usually week 24 unless it is a serious or lethal anomaly. The upper gestation limit for termination of pregnancy for maternal medical reasons is usually week 24. There should be no regional variations.
FRANCE

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1 Screening for Down Syndrome

The current policy for prenatal screening of Down’s syndrome in France includes:
- nuchal translucency measurement as a matter of routine between 11 and 13 weeks of gestation
- Maternal serum screening between 14 and 16 weeks, which should be systematically proposed to all women as stated by a law implemented in January 1997.

Costs of antenatal screening are reimbursed, and in the case of an abnormal result in any of the screening tests, amniocentesis is proposed and its costs are reimbursed.

2 Indications for Prenatal Cytogenetic Diagnosis

In recent years, prenatal diagnosis of Down’s syndrome has expanded considerably from a system based on offering amniocentesis (or chorionic villus sampling) to women 38 years of age or older and those with a significant family history (paternal or maternal translocation, previous sibling with Down’s syndrome) to a regulated system of universal access to screening.

In 1988, the indications for prenatal cytogenetic diagnosis were extended to include ultrasound abnormalities suggestive of a chromosomal anomaly.
The indications for a cytogenetic diagnosis have been further extended to include "scan markers", including nuchal thickness greater than 3mm.

The policy of maternal serum screening implemented in 1997 includes offer of amniocentesis when the calculated risk is greater than 1/250.

For all of the indications noted above, the costs of amniocentesis (or CVS) are fully reimbursed.

In addition to access to modalities of prenatal screening as described above, mothers 38 years of age or older have the option of direct access to reimbursed amniocentesis (i.e. without prenatal screening tests).

3 Screening for Structural Anomalies by Ultrasound Screening
Three routine scans for detecting structural abnormalities are performed during pregnancy. These examinations are performed at around 12 weeks, 22 weeks (morphological scan with cardiac examination) and 32 weeks of gestational age.

4 Terminations of Pregnancy for Fetal Anomaly
In the event of a prenatal diagnosis of Down's syndrome, or in general any "serious illness, recognized as incurable at the time of diagnosis", termination of pregnancy is allowed regardless of gestational age. Decisions for pregnancy terminations are reviewed by multidisciplinary committees for prenatal diagnosis.
1 Screening for Down Syndrome

In the German "Mutterschutz-Richtlinien" (guidelines for the safety of the mother and the infant, http://www.mds-ev.org/download/RL_Mutterschaft.pdf) it is advised that all pregnant women ≥ 35 years of age undergo amniocentesis for cytogenetic diagnostics (not mandatory and free of charge). The voluntary Triple test (charged) is based on three specific serum markers (alpha-Fetoprotein (AFP), free Estriol (E3), and beta-Choriongonadotropin (beta-HCG) estimating the risk of having a child with Down syndrome. Within the last years the sonographical measurement of the nuchal translucency (ca. 10th week of gestation) is performed in most gynecological practices and increasingly becomes a part of the routine ultrasound examination.

2 Indications for Prenatal Cytogenetic Diagnosis

- Pregnant women ≥ 35
- Genetic disorders in parents and relatives
- Previous child with genetic disorder or metabolic defect
- Signs of developmental disorder in previous ultrasound examination
- Serological suspicion or sign of malformation
- Blood group incompatibility between mother and child
### 3 Screening for Structural Anomalies by Ultrasound Scanning

During pregnancy three routine ultrasound screening examinations are recommended by the "Mutterschutz-Richtlinien".

<table>
<thead>
<tr>
<th>Screening</th>
<th>Weeks of Gestation</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>9th to 12th</td>
<td>intrauterine pregnancy, number of Fetuses, biometric measurements</td>
</tr>
<tr>
<td>Second</td>
<td>19th to 22nd</td>
<td>vitality of embryo, biometric measurements, signs for developmental disorders, eg. malformations</td>
</tr>
<tr>
<td>Third</td>
<td>29th to 32nd</td>
<td>vitality of embryo, biometric measurements, timely development, signs for developmental disorders, placental location and structure</td>
</tr>
</tbody>
</table>

The ultrasound screening examinations are performed by gynecologists in private practice and/or specialized prenatal care centers.

### 4 Termination of Pregnancy for Fetal Anomaly

An embryopathic indication for the induction of an abortion after the 12th week of gestation does not exist. The indication for the termination of the pregnancy of a malformed fetus (medical indication) is based on severe physical and mental distress to maternal health.

In these cases there is no time limit for induced abortions. Terminations are regulated by law: §218a StGB [www.dejure.org/gesetze/StGB/218](http://www.dejure.org/gesetze/StGB/218)
1 Screening for Down Syndrome
There is no policy for screening of Down Syndrome. Nuchal translucency measurement is not routinely offered, it is available if requested on an individual basis.

2 Indications for Prenatal Cytogenetic Diagnosis
Pre-natal cytogenic diagnosis (amniocentesis or chorionic villus sampling) is not routinely offered, it is available if requested on an individual basis.

3 Screening for Structural Anomalies by Ultrasound Screening
A gestational age scan at approximately 18 weeks generally includes screening for structural anomalies.

4 Termination of Pregnancy for Fetal Anomaly
Termination of pregnancy is not legal for fetal anomaly.
1 Screening for Down Syndrome

The current policy for screening in The Netherlands includes:
- nuchal translucency between 11 and 13 weeks of gestation
- triple test at about 15 weeks of gestation

Cost of these test are reimbursed only in cases were the woman is 36 years and older in the 18th week of pregnancy, in cases of an earlier child with chromosomal anomalies, genetic diseases in the family, or an increased risk on a neural tube defect. Since recently women with no increased risk have to be informed that these tests are available but have to pay for it by themselves (60-80 Euros)

2 Indications for Prenatal Cytogenetic Diagnosis

Cytogenetic diagnosis (with amniocentesis or chorion villus sampling) is offered to all women:
- 36 years and older in the 18th week of pregnancy
- with calculated risk higher than 1/250 on the basis of the above mentioned tests
- who have a previous child with chromosomal abnormality
- that have, or their partners have, a chromosomal abnormality (e.g. translocation)
- have DNA abnormality or metabolic disorder in their or their spouses family
- have a previous child with a congenital abnormality
- have ultrasound scan abnormalities suggestive of a chromosomal abnormality

In the above mentioned cases the costs are reimbursed

3 Screening for Structural Anomalies by Ultrasound Screening
In The Netherlands there is no policy for any routine ultrasound scan in pregnancy for all pregnant women. More and more pregnant women undergo one scan at the first visit to midwife or obstetrician to determine the duration of pregnancy, but this is not a general routine and is not aimed at discovering congenital defects.

Indications (and so reimbursement) for a screening on structural anomalies by ultrasound in the 18-20th week of pregnancy are:
- Presence of known risk factors for structural anomalies in the fetus: previous child with structural anomaly, Diabetes Mellitus in mother, use of anti-epileptics or other drugs that are known for teratogenic affects.
- indications for a structural anomaly in a routine ultrasound scan

4 Termination of Pregnancy for Fetal Anomaly
In The Netherlands termination of pregnancy for fetal anomaly is allowed until the 24th week of pregnancy, parents have to be informed about all the facts concerning their situation but have the sole power to decide whether to terminate the pregnancy in a controlled facility. After 24 weeks of pregnancy termination is only possible in the case of a fetus
with a disorder not compatible with life and a woman who has fierce mental problems with carrying out the pregnancy. The decision has to be reviewed by a multidisciplinary committee and has to be reported to the counsel for the prosecution.
1 **Screening for Down Syndrome**

Pregnant women 38 years + of age at term or with a previous Ds offspring are offered prenatal screening in terms of ultrasound examination and amniotic fluid analysis.

2 **Indications for Prenatal Cytogenetic Diagnosis**

Pregnant women 38 years + of age or a previous birth defect offspring.

3 **Screening for Structural Anomalies by Ultrasound Screening**

Pregnant women 38 years + of age or a previous birth defect offspring.

4 **Termination of Pregnancy for Fetal Anomaly**

Practice is regulated by law (1975/78) specifying that termination of pregnancy may be permitted by request to a regional commission on the indication of a diagnosed condition representing a threat to the mother, or representing a serious malfunction to the unborn infant. Other indications are if the birth represents an unreasonable burden on the woman’s physical or mental health, or on her general circumstances of life, if the pregnancy was caused by an act of crime, or if the woman is mentally ill or retarded. After 18 weeks of gestation, a pregnancy must not be terminated without particularly weighty reasons.
1 Screening for Down Syndrome

In July 1997 an important official text was published by the Ministry of Health concerning organization and procedures of prenatal diagnosis (PND) at national level. PND network is organized at three levels according to different degrees of complexity:

1 - Level one - at local level, family doctors and general practitioners must identify pregnancies at risk and send them to level 2.

2 - Level two - Hospital based Obstetric Departments may set up the so-called PND Centers. These Centers must be prepared to offer genetic counseling, ultrasound and invasive procedures, termination of pregnancy, when indicated, and fetal pathology examination.

3 - Level three - More specialized Centers must offer diagnosis to more complex cases and fetal therapy when possible, in addition to all level 2 activities.

Thirty eight of the fifty four existing Hospital based Obstetric Departments all over the country have set up level 2 PND Centers since then, but only thirteen have requested official recognition so far. None of them have requested to be recognized as level 3.
Biochemical screening for Down syndrome is optional and not yet officially recommended. However it is a widely extended procedure and private laboratories are the most important sources of biochemical screening.

2 Indications for Prenatal Cytogenesis Diagnosis
- Maternal age: all women 35 years or more at time of delivery.
  However, PNC centers may decide otherwise if this cut-off cannot be met.
- Chromosomal abnormality in a previous child
- Parental chromosomal abnormality
- Ultrasound markers or malformations diagnosed at ultrasound
- Abnormal maternal serum marker

3 Screening for Structural Anomalies by Ultrasound Screening
Norms for routine scans were published in May 2001. In low risk pregnancies three ultrasound scans are officially recommended:
- in the first trimester between 11 and 13 weeks of gestational age
- in the second trimester between 20 and 22 weeks of gestational age
- in the third trimester between 28 and 32 weeks of gestational age
A standard report type for each of these procedures has been published.

4 Termination of Pregnancy for Fetal Anomaly
Termination of pregnancy for fetal anomaly is permitted by law up to 24 weeks of gestational age since 1997 (previously up to 22 weeks of gestational age). There is no upper limit for termination in lethal conditions.
Women may ask for termination after genetic counseling and a technical commission in each PND center (obstetrician, neonatology's and clinical geneticist if any) evaluates all cases to decide if it is legal. Official coordination of PND activities is the task of two Commissions at the General Directorate of Health: a national commission and a commission for each Health Region.
1 Screening for Down Syndrome
No policy for prenatal screening of Down syndrome exist in Sweden. Nuchal translucency measurement as a matter of routine between 11 and 13 weeks of gestation has been evaluated, but no general policy does yet exist.

2 Indications for Prenatal Cytogenetic Diagnosis
Prenatal diagnosis of Down syndrome is based on offering amniocentesis (or chorionic villus sampling) to women 35 years of age or older and those with a significant family history (paternal or maternal translocation, previous sibling with Down syndrome) to a regulated system of universal access to screening. Half of all pregnant women, who are offered prenatal diagnosis, will today use this offer. If the woman is younger than 35 years of age, but very worried of having a child with Down syndrome, she is offered prenatal diagnosis.

The costs of amniocentesis (or CVS) are fully reimbursed.

3 Screening for Structural Anomalies by Ultrasound Screening
One routine scan for detecting structural abnormalities is performed during pregnancy. These examinations are performed at around 16-17 weeks (morphological scan with cardiac examination)
Terminations of Pregnancy for Fetal Anomaly

In the event of a prenatal diagnosis of Down syndrome, or in general any "serious illness, recognized as incurable at the time of diagnosis", termination of pregnancy is allowed before the end of 18 weeks gestation. For pregnancies that are >18 weeks gestation decisions for pregnancy terminations are reviewed by multidisciplinary committee at the National Board of Health and Welfare. Very seldom termination of pregnancy is permitted after 22 weeks gestation.
1 Screening for Down Syndrome

Screening for Down Syndrome should be offered to every woman independently of maternal age. Gynecologists are encouraged to perform the first trimester maternal blood test rather the 2nd trimester because of its better accuracy. The 1st trimester screening is performed between the 10th and the 14th week of gestation. It is based on the measurement of the nuchal translucency by ultrasound combined with the maternal age and the levels of pregnancy associated plasma protein A (PAPP-A) and free subunit of beta human chorionic gonadotrophin (β-hCG). The 2nd trimester screening is performed between the 15th and the 19th week of gestation. It is based on the levels of alpha-fetoprotein (AFP), β-HCG and unconjugated estriol (uE3) of the maternal serum. In the cases where a 1st trimester screening is chosen, a 2nd semester assay of AFP is recommended to exclude open neural tube defects.

2 Indication for Prenatal Cytogenetic Diagnosis

Prenatal cytogenetic diagnosis is offered to every woman whose 1st trimester screening established a risk over 1/300 or 2nd trimester screening showed a risk over 1/380.

Prenatal cytogenetic diagnosis is also offered to women who are over 35 years old and to patients where an ultrasound scanning suggested an anomaly. It can also be offered when the couple wishes to undertake such
test. If the test is performed only for parental anxiety, it is billed to the couple.

Women are referred by their gynecologists either directly to the ultrasound service where the amniocentesis or CVS is performed or to the genetic service where they have counseling beforehand. In the latter situation, a medical geneticist or a genetic counselor sees the patient half an hour before the amniocentesis or CVS. During the counseling session, the professionals gather information about the pregnancy, draw the pedigree, discuss the screening results, explain the technique, discuss its risks and other available options (screening for women who where referred for maternal age only). They also answer the patients' questions and listen to their anxieties.

3 Screening for Structural Anomalies by Ultrasound Scanning
The first ultrasound scanning is performed between the 10th and the 12th week of the pregnancy and the second between the 20th and the 23rd week. When risk factors are present, extra tests may be performed. The 1st ultrasound scan helps to determine the gestational age of the fetus and measures of the nuchal translucency. These data are used in the 1st and 2nd trimester maternal serum screening. The 2nd ultrasound scan assesses for fetal malformations, growth delay and amniotic fluid quantity.

4 Termination of Pregnancy for Fetal Anomaly
According to the Swiss penal code there is no legal limit for termination of a pregnancy according to gestation age. However in practice, it is performed until the 24th week of gestation.
1 Screening for Down Syndrome

England and Wales

The policy statement from Department of Health giving model of best practice for providing Down’s Syndrome screening states

Programme outcomes

- Detection rate of at least 60% with FPR of 5% or less (by 2004/5)
- Detection rate of >75% with FPR <3% (by April 2007)
- First trimester screening (nuchal translucency scan with biochemistry) or serum integrated tests must be offered by 1st April 2007.

Different tests are suggested which must give the above detection and FPR rates.

In practice by the end of 2004 approximately 96% of women in England and 100% of women in Wales were offered some form of screening test. By April 1st 2005 all hospitals in England and Wales should be offering screening. The type of test varies throughout UK with much of London offering nuchal scans and most other areas using triple or quadruple tests.

Scotland

The Scottish Executive policy is that all women should be offered screening for Down’s syndrome with a recommendation to follow the UK National Screening Committee (NSC) guidelines. In practice all centers
offer serum screening for Down's Syndrome using the estimation in the maternal blood of two hormones which act as two biochemical markers to assess their risk in the second trimester of pregnancy.

Policy for Down’s syndrome screening is currently being reviewed by the Scottish Executive in light of recommendations from the UK NSC.

Northern Ireland
No official policy and no screening except by private tests.

2 Indications for Prenatal Cytogenetic Diagnosis
Maternal age (usually over 35 years), high risk Down’s syndrome screening test result (usually > 1 in 250 at term), family history of chromosome anomaly, translocation carrier, ultrasound malformations and soft markers are all indications for prenatal cytogenetic diagnosis. With the move from maternal age screening to serum screening and nuchal translucency scanning the numbers based purely on maternal age are diminishing.

3 Screening for Structural Anomalies by Ultrasound Screening
The National Institute for Clinical Excellence and the Scottish Executive recommend that every pregnant woman should be offered a fetal anomaly scan at 18 - 20 weeks gestation. In practice 96% of centres in England, 100% in Wales and approximately 60% of centres in Scotland offer routine 20 week anomaly scans. Many but not all centres offer routine dating scans.
Termination of Pregnancy for Fetal Anomaly (TOPFA)

The law allows TOPFA if the pregnancy "has NOT exceeded its 24th week and the continuance of the pregnancy would involve risk, greater than if the pregnancy were terminated, or injury to the physical or mental health of the pregnant woman".

There is no gestation limit if "There is substantial risk that if the child were born it would suffer from such physical or mental abnormalities as to be seriously handicapped".

There is also no gestation limit if "the continuance of the pregnancy would involve risk to the life of the pregnant woman greater than if the pregnancy were terminated".

In practice there is regional variation in availability of late TOP.
EUROCAT Publications on Prenatal Diagnosis


Abramsky L and Chapple J (1997) "47,XXY (Klinefelter Syndrome) and 47,XYY: Estimated Rates of and Indication for Postnatal Diagnosis with Implications for Prenatal Counselling" Prenatal Diagnosis, Vol 17, No 4, pp 363-368.


