

**UNIVERSITY OF MEDICINE AND
PHARMACY OF CRAIOVA**

PhD THESIS
- SUMMARY -

**PRENATAL DIAGNOSIS OF MAJOR
STRUCTURAL ANOMALIES OF THE
CENTRAL NERVOUS SYSTEM**

**SCIENTIFIC COORDINATOR:
PROFESOR DOCTOR CERNEA NICOLAE**

**CANDIDATE:
ZORILĂ GEORGE LUCIAN**

Introduction

Ultrasonography (US) noted an remarkable progress in medicine over the past decades and in Obstetrics as well, where it has made it possible to monitor the evolution of pregnancy from an early stage, and represents a practical approach to decipher the fetal-maternal physio-pathological mechanisms to an important extent.

The stage of knowledge significantly developed in the past two decades, where early prenatal diagnosis became an important challenge, as early as the first trimester of pregnancy, and where it is still not accurately possible, prognostic factors are sought during this period of pregnancy. Fetal ultrasound descriptions and maternal serum biochemical parameters have been effectively used as predictors of most aneuploidies, abortion and fetal death, premature birth, preeclampsia, gestational diabetes, intrauterine growth restriction, macrosomia and lately, many of the structural defects were assessed in the first trimester, with encouraging results.

Although standard, basic and extensive protocols for ultrasound assessment have been described by professional international institutions such as ACOG (The American College of Obstetricians and Gynaecologists), AIUM (American Institute of Ultrasound in Medicine), ISUOG (International Society of Ultrasound in Obstetrics and Gynaecology), or national - Romanian Society of Ultrasound in Obstetrics and Gynaecology, there are still many areas where they have not been yet implemented.

Manny national health care systems offer a second-trimester ultrasound scan as in the standard care of the pregnant women, but obstetric practice varies significantly from one country to another; the factors that influence these disparities are the presence of qualified staff in ultrasound fetal assessment, the availability of dedicated imagistic equipment, legal issues, or the involvement of insurance companies in screening programs.

Confirmation with clear, tangible evidence, of major diagnosed structural anomalies, such as the anatomic and pathological (AP) analysis of the affected fetuses is extremely useful and addresses forensic and legal issues. Understanding the correlation between AP and US images brings useful data for the progress of prenatal diagnosis and helps the pregnancy and preconceptual counselling of couples regarding the rate of recurrence of anomalies to subsequent pregnancies which is one of the most important targets when such fetal conditions are suspected and diagnosed.

There are situations when the couple, after counselling, refuses to interrupt the course of pregnancy or the malformations diagnosed or suspected are not severe, although they are known to carry a more or less affected prognosis. In such cases, AP confirmation is unavailable. The postpartum follow-up of these children, sometimes on long-term, is extremely useful in assessing the prognosis of each anomaly.

Termination of pregnancy for therapeutic purposes should be provided in the case of anomalies with unfavourable prognosis, taking into account the territorial legislation, but this dramatic decision should be supported with accurate knowledge, judicious investigation and clear evidence of diagnosis.

The Central Nervous System (CNS) is the most complex system of the human body. Minor structural defects can cause major malfunctions, and some structural defects considered as major prenatally, may not greatly affect functionality. CNS is also a common site of structural abnormalities in genetic disorders cases. Therefore, the evidence of a malformation, sometimes even minor, can lead, through complementary investigations, to a much more significant genetic diagnosis.

The Importance of Prenatal Diagnosis - Identification of Structural and Genetic Anomalies

Genetic, infectious, mechanical or teratogenic factors can influence physiological development, inducing malformations that lead to a neuro-psycho deficit. Investigating CNS development and the detection of morphological anomalies have shown an upward trend, especially through neurosonography and, additionally, by fetal MRI investigations during pregnancy.

An important issue is represented by the territorial legislation on **abortion upon request**. In our country, this is allowed up to gestational age of 13 weeks and 6 days of pregnancy, a timing that marks the limit between the first two trimesters of pregnancy. Therapeutic abortion up to 24 weeks of gestational age (amenorrhea) can be provided to pregnant women with fetal malformations proven to be major, invalidating, with poor prognosis. For malformations detected later, the family may benefit from prenatal diagnosis, genetic and infectious investigation, but the psychosocial and economic impact is important in the short, medium and long term. The option to migrate to a state with permissive legislation for late termination of the pregnancy may be considered by the couple advised.

Central Nervous System (CNS) structural abnormalities are considered to have the highest incidence in the population - 10 cases per 1,000 new-borns, compared with 8 to 1,000

cardio-vascular abnormalities, 4 per 1000 reno-urinary abnormalities and 1 per 1000 limb abnormalities.

The social integration of disabled individuals is an important issue of the society, which involves special efforts by competent authorities, such as the development of medical recovery and care centres, special education and re-education programs, dedicated jobs, where those with medium and light deficiencies can activate. All these aspects, besides the particular involvement of specific institutions, have significant and wide economic implications, additional financial efforts, and targets not only individuals with various degrees of disability, but also other persons involved in the accompanying or caring processes (family members, social workers, etc.).

Ethical principles involved in prenatal diagnosis

There are data on the ethics of prenatal diagnosis and termination of pregnancy regarding the malformed fetuses, that the World Health Organization (WHO) has described. General guidelines were developed, which also highlight the importance of these medical investigations and procedures. Prenatal diagnosis is a personal decision of the patient or couple that cannot be imposed but should be offered as an option and applied only after obtaining informed consent. The decision to interrupt the course of a pathological pregnancy should not be influenced by the medical staff and should be strictly adopted by the couple (autonomy). Still, the physician should provide complete information to the couple regarding the data obtained during the investigation, and counselling regarding the manifestations of the conditions being discussed upon, to help the patient or the couple make a decision on the course of pregnancy.

Ultrasound evaluation of the fetal CNS

The second trimester morphological evaluation remains the standard in fetal structural assessment. The introduction of first trimester screening for the detection of aneuploidies has increased the interest for early morphological analysis.

The effectiveness of first trimester screening has been proven in many studies, and the rate of detection of structural anomalies has grown with the development of scanning techniques and evolving imagistic devices with increasingly advanced resolutions. Detection rates are reported on an average of 40%, but with wide limits between studies (12.5-83.7%) have been shown, and the most recent and extended protocols report much higher anomaly detection rates.

In the first trimester of pregnancy, some major CNS abnormalities may be detected in a large proportion (acrania / anencephaly, encephalocele, spina bifida aperta, hemivertebra, sacro-coccygian teratoma), and others have a low detection rate due to still early development of the neuro-cerebral system (microcephaly, craniosynostosis, corpus callosum agenesis, ventriculomegaly, cerebellar hypoplasia, vermis agenesis).

The most common CNS abnormalities are neural tube defects (NTD) such as spina bifida, cephalocele, and acrania / anencephaly. The association with folic acid deficiency has been described since 1976, when following the implementation of folic acid supplementation programs, a significant reduction in the incidence of these defects was subsequently reported.

The fetus may be affected by the transplacental passage of the various infectious agents. Infection can affect the fetal CNS in varying proportions and may be associated with systemic damage. The most common infectious etiological agents are Cytomegalovirus and *Toxoplasma gondii*. Identification of these pathogens in amniotic fluid or postpartum confirms the diagnosis.

Magnetic Resonance Imaging (MRI) and Prenatal Diagnosis of CNS Anomalies

The ultra-fast sequence acquisition techniques have made it possible to use MRI in the detection of prenatal CNS abnormalities, and many studies have compared the two methods of structural assessment of CNS, with controversies regarding their contribution to prenatal diagnosis, even today.

The development of MRI techniques has been enthusiastically presented in numerous studies, and the complementary data that is shown could not be obtained initially by ultrasound. Over time, developing techniques and knowledge of CNS development has led to comparable results between MRI and ultrasound.

Particularities of anatomopathological diagnosis in major CNS malformations

Fetal and perinatal autopsies are essential in the management of families with an abnormal pregnancy where the diagnosis was established prenatally.

The important goals of fetal autopsy are: to document the fetal growth and development, to detect congenital anomalies, to confirm imaging diagnosis and associated conditions and to determine the cause of death. It can also be useful when clinical data do not justify intrauterine death, especially when structural abnormalities have been previously described. The presence of one (or more) malformations described prenatally, is a clear indication to

perform fetal autopsy. In approximately 30% of cases, additional data can be obtained during autopsy, which can change the diagnosis and provide important data to the family during counselling. It is imperative to inform the couple as accurately as possible, so that the autopsy decision to be correctly adopted.

Anatomopathological confirmation of the ultrasound diagnosis for CNS malformations

Confirmation of prenatal findings is important for the audit and progress of the imaging diagnosis and for the couples counselling. The autopsy describes the structural anomalies and brings important feedback for the ultrasound scan, which can be retrospectively reviewed based on the stored data of each examination.

In case of CNS structural abnormalities, studies focusing on the definitive confirmation of prenatal diagnosis report an average correlation of over 80% between ultrasound diagnosis and anatomopathological diagnosis.

The anatomopathological examination of the brain is perhaps the most difficult of all organs due to autolysis and early degradation, because of the high vulnerability to hypoxic injury. In the case of abortions or stillbirths, the CNS assessment is extremely difficult, and the rate of satisfactory examination of this system is about 20%; in about 80% of cases there is an advanced maceration of this type of tissue. MRI exploration of these fetuses may be offered as an alternative, if autopsy is not acceptable, but the family should be advised on the limit of the method, especially that tissue fragments cannot be obtained, and important data may be lost. However, MRI can also be used in selected cases complementary to autopsy assessment. That is because the MRI assessment of fetal CNS malformations has been proved with a good correlation of approximately 60% with conventional autopsy.

The main objectives of the study were:

- the assessment of prenatal US diagnosis accuracy, using autopsy or postnatal assessment results as controls in the case of major CNS anomalies,
- to study the efficiency of an early prenatal ultrasound diagnosis, regarding CNS anomalies, using a baseline assessment protocol and follow-up.

Method

The study has been conducted at the Antenatal Diagnostic Unit (UDA) of the Department of Obstetrics and Gynecology, Emergency County Clinical Hospital of Craiova,

in collaboration with the Anatomical Pathology Laboratory (LAP), Regional Genetic Centre Craiova, the Centre for Radiology and Medical Imaging, the Neonatology, Paediatrics and Paediatric Surgery Clinics, located within the same hospital, from 01.10.2014 until 30.09.2017. Collaborations with the Anatomy and Histopathology Laboratory of the University of Medicine and Pharmacy Craiova have been initiated.

The fetuses diagnosed with major CNS malformations during screening ultrasound assessments were included to study, and extended neurosonography was performed in the respective cases. There have been added cases referred to our unit by primary and secondary screening centres, which targeted major CNS abnormalities. Patients lost for follow-up during the study and those who refused to participate in this study were excluded.

During the study there were two patterns of investigation, according the ultrasound diagnosis:

Type 1. When major CNS malformations were detected in the first or second trimester of pregnancy, patients were counselled and given the possibility of abortion if the diagnosis was established up to 24 weeks of pregnancy (according to the legislation in force). Fetuses with CNS malformations resulted from therapeutic abortions, and those spontaneously aborted, stillbirths or postnatal demise cases were subjected to subsequent autopsy and some selected cases to complementary imaging examination (CT, MRI, X-ray), to confirm the ultrasound suspected anomalies and their extent.

The autopsy was performed in all these cases. In selected cases, it was necessary to isolate the fetal brain to evaluate this type of tissue in the best possible conditions. The results were classified into the following categories:

- Complete correlation between ultrasound and autopsy (CC)
- The autopsy revealed abnormalities that were not described by ultrasound (A +)
- Ultrasound abnormalities were not confirmed by the autopsy (E +)

Type 2. The fetuses diagnosed late in pregnancy, after 24 weeks, and those where abortion was declined, have been monitored prenatally until birth and investigated postnatally through a psychological and neurological sequential assessment protocol. CT or MRI imaging investigations were performed as appropriate.

Results and discussions

3,250 patients were evaluated. An important source of cases that met the inclusion criteria was represented by the population screened in the primary and secondary centres of our region and referred to our tertiary centre. 185 CNS abnormalities of varying degrees were detected during the ultrasound examinations and 60 of them were considered major, of which 11 were excluded. The type and associations of the studied major CNS abnormalities is presented in Table 1.

The rate of major CNS abnormalities was 1.84% of the total study group. If we only consider the anomalies detected during screening examinations (12 cases), then the **incidence of major anomalies** in the studied population would be calculated as 0.36%. Similar incidences of major CNS anomalies are reported in the literature, ranging from 0.31% to 0.9%. Associated major malformations in the CNS anomalies group were found in 32.4%. We encounter a high **rate of lost patients for follow-up** of 18.3% but justified by the population characteristics of our group.

Early diagnosis of anomalies, within the legal age for therapeutic abortion, was achieved in 75.5% of cases. Thus, a significant number of CNS anomalies did not benefit from timely diagnosis, although 75% of them could have been detected before 24 weeks.

Termination of pregnancy was offered and accepted in almost two thirds of cases (63%). Of these, in 10.2% surgical interruption / uterine curettage was preferred by the pregnant women, and fetal autopsy for anomaly confirmation became impossible to practice.

The cases of **fetal death**, were represented by 5 stillbirths, and 7 peripartum fetal demises, (12 cases - 25% of the group of major CNS abnormalities). These cases reflect the severity of these abnormalities and their impact on fetal development.

In 14% of cases, the **affected fetuses were delivered alive**. Their evolution was monitored and the correlation with the prenatal diagnosis was achieved by other methods. Complementary imaging support was recommended in all cases. No significant additional information was obtained and the presumed diagnosis was confirmed at variable time intervals from birth.

In more than one quarter of **genetically investigated** cases (28%), aneuploidy was diagnosed, and the most common genetic anomaly was trisomy 18. An interesting aspect is related to holoprosencephaly, which associated trisomy 18 in 3 out of 5 cases, while trisomy 13 was not found in any case.

Table 1. Distribution of major CNS anomalies in the study

Type of CNS anomaly	Nr	Associated with other CNS abnormalities	Associations with abnormalities, other than CNS	Genetic associations
Neural tube defects	19	1	3	1
Defects of the posterior cerebral fossa	10	7	5	2
Agenesis (or hypoplasia) of the corpus callosus	7	4	3	0
Hydrocephalus	5	3	1	0
Cerebral cyst	4	1	1	1
Microcephaly	2	2	1	0
Choroid plexus cysts	1	0	1	1
Holoprosencephaly	4	0	3	3
Syntelencephaly	1	0	0	0
Porencephaly	1	0	0	0
Schizencephaly	1	0	0	0
Sacroccygeal teratoma	1	0	0	0
Lissencephaly	1	1	1	0
Echogenic cavum septi pellucidi	1	0	0	0
Galen's vein aneurysm	1	0	0	0
Massive brain haemorrhage	1	0	0	0

In our study, the association of major CNS anomalies with anomalies of other systems was found in over one third of cases (34.6%). Given the multi-systemic structural damage principle, genetic investigation remains a mandatory exploration and its availability has a very important role in counselling.

The most common type of CNS structural anomalies was represented by the **neural tube defects (NTD)** - 39%, one fifth of which were cephalocele and the rest in equal proportions anencephaly / acrania and spina bifida aperta / rachiskisis. NTDs associate a significant phenotypic and ultrasound expression in most cases, which is easily recognizable. They also represented the majority of abnormalities diagnosed in the first trimester of pregnancy - three quarters of them (75%). The literature reports the NTDs as the most common anomalies in the population, with a prevalence between 0.5 and 10/1000 pregnancies, similarly to our study.

Abnormalities of the corpus callosum were described in one-seventh of the cases (14.2%): hypoplasia in one case, partial agenesis in one case, and 5 cases of total agenesis. The incidence in our study was 2.1 per 1000 cases, higher than reported in recent studies, around 1 to 4000 births, and the most pertinent explanation is that most major CNS anomalies from our group were included after primary population filtering in primary or secondary centres, therefore the incidence from our high- or medium risk study group is overestimated.

Major posterior cerebral fossa defects were present in one-fifth (20.4%) of all major CNS anomalies included in the study, with an incidence of 3 in 1,000 cases in the studied population. The association of posterior fossa defects, especially the Dandy-Walker malformation, has been frequently communicated in association with corpus callosum formation anomalies. Also, in our study, this situation was found in 2 cases: one vermis hypoplasia and one Blake pouch cyst.

Amniotic Band Syndrome (ABS) can cause malformations from mild to severe, incompatible with life. The prevalence of this entity was reported at 0.89 per 10000 births. In our study there were 3 cases diagnosed with intrauterine ABS, all three cases involving important craniofacial defects. They were diagnosed before 24 weeks and the pregnancies were completed by therapeutic abortion. The incidence was 1 in 1,000 cases, well above the one described in the literature.

During the study we also found very challenging to counsel/manage some cases. For example, a case of **echogenic CSP** (which has not been widely described in the literature) has been extensively investigated with US and MRI for structural and functional cerebral integrity including normal relations of the corpus callosum, as the close development relationship of the two anatomical structures is well-known. Moreover, the evaluation of the

transverse axonal tracts, which connect the two cerebral hemispheres and form the corpus callosum, could be made possible by special techniques of the MRI, named tractography.

Another case that was difficult to manage implied the presence of a **sacroccocygeal teratoma** in a dichorionic twin pregnancy, first examined at 20 weeks of GA. The case involved this major malformation in one fetus that eventually died prenatally and a minor fetal malformation of the other fetus - bilateral varus equin. Genetic analysis of the pregnancy was declined by the couple. Continuing pregnancy was possible, while monitoring standard, inflammatory and infectious analyses. Asynchronous birth added a special feature to this case, as the intrauterine demised fetus was expelled at 29 weeks of GA, followed by umbilical cord stitching and prolongation of the pregnancy for another 11 days. Autopsy confirmed the major malformation of the stillbirth and the outcome of the second fetus was good and the anomaly resolved with orthopaedic treatment.

Efficiency of ultrasound detection of major CNS abnormalities during the first trimester of pregnancy

The detection rate for major CNS abnormalities was 81.25%, which is similar to literature results, where a detailed early morphological assessment was systematically performed. The comparative analysis of the first trimester and follow-up evaluations revealed comparable detection rates. In our view, this may be due to the fact that, on one hand, major CNS abnormalities with a high degree of severity and high prevalence, such as neural tube defects and holoprosencephaly, are easily detectable early in pregnancy and, on the other hand, abnormalities that cannot be diagnosed in the first trimester, because these structures are not sufficiently developed, such as corpus callosum anomalies or posterior fossa defects, are often missed at latter morphologic assessments in pregnancy.

In our study, another important aspect of the early diagnosis of CNS anomalies is the absence of false positive results, meaning that in all cases where the pathology evaluation could be performed, ultrasound suspected abnormalities were confirmed. This adds an important argument for couples counselling and early assessment of CNS, meaning that the risk of interrupting unaffected pregnancies and inducing unjustified anxiety for couples is negligible. Predictive positive value and specificity, recorded values of 100% and the predictive negative value was 99.81%, with a false negative rate of 18.75%.

Major CNS structural anomalies detected in the second trimester before 24 weeks GA

The second trimester provides the possibility of detecting structural anomalies that cannot be detected early, especially for CNS, that continues to develop rapidly throughout the pregnancy and shows significant morphological changes in the second trimester of pregnancy. Often the early suspicion of CNS abnormalities needs later confirmation. Within this group, we consider that in about one third of cases (30.7%), the type of structural abnormalities had an early ultrasound expression, and the diagnosis could have been established since the first trimester of pregnancy if the patients would have been examined earlier. Most of these abnormalities were NTDs, followed by lobar holoprosencephaly (potentially diagnosed in the first trimester of pregnancy).

I studied the **efficiency and accuracy** of the ultrasound examination for this group, taking into account the cases detected during this pregnancy period, which were subsequently confirmed by autopsy and pre- or postnatal monitoring. Data showed that this type of examination performs better, when compared to the first trimester evaluation: the sensitivity of the method was 89.29%, with no false positives. Specificity and predictive-positive values were 100% at a 99.79% predictive-negative value. Overall, the accuracy of the technique was very good, 99.79%.

Analysis of major CNS structural anomalies detected in the second and third trimester, after 24 weeks GA

Most of the CNS abnormalities that were diagnosed late in pregnancy are cases that were first scanned in pregnancy at this unappropriated and late gestational age. The pattern of anomalies shows that an important part - one third of the abnormalities described, could have been diagnosed in the first trimester and almost half (41.66%) could have been diagnosed during the second trimester standard anomaly scan assessment, before 24 weeks.

It is acknowledged that during fetal evolution, aggression, the development of tumour formations or unpredictable acute incidents can occur at any GA. Thus, in this group of pregnancies studied, there were previously evaluated cases without detectable abnormal structural aspects, but later diagnosed with anomalies, such as massive intracranial haemorrhage or bilateral periventricular cerebral cysts.

Fetal autopsy

Many recent studies have deplored the low rate of fetal and ever-declining autopsies in Western society, especially due to the reduced acceptability of couples. This is not a problem in Romania due to legislation on autopsy indications. However, the autopsy rate was

only 77.5% of all cases due to other well-known factors that influence the availability of the conception product for autopsy.

For example, 41% of cases diagnosed in the first trimester with major CNS abnormalities required surgical termination of the pregnancy, resulting in a curettage product completely inappropriate for autopsy assessment. This is undesirable for several reasons. Obviously, the impossibility of performing autopsy in these cases prevents early morphological ultrasound assessment from being audited. Another reason is medical, being acknowledged that, as opposed to medical abortion, evacuation of the pregnancy by using brutal cervical dilatation and systematic curettage of the uterine cavity entails additional risks for subsequent fertility, such as ischemic-cervical insufficiency and residual uterine synechia.

Another important impediment was cerebral tissue autolysis (8.1% of total cases with CNS abnormalities), noted especially in cases of intrauterine or peripartum fetal death.

In our study, **total concordance** of the ultrasound and autopsy in cases with CNS anomalies was 84%. In cases where **the fetal brain has been isolated** and studied, there was a complete concordance in 90.9% of cases. In one case, the autopsy completed the malformation syndrome with diastematomyelia, in the case of a fetus with NTD, and an Arnold Chiari type III malformation. The clinical expression of this additional abnormality detected is significant, specific, variable, and frequently result in motor deficits or severe vegetative disorders and thus, it was considered valuable additional information for the complete fetal assessment. This also represents an argument for enlarged cerebromedullary preparation along the proximal spinal cord by careful tracing dissection margins, which may lead to significant additional diagnostics with an additional unfavourable prognosis.

In 5.2% of the cases, **autopsy added significant information to prenatal imaging diagnosis**. Conversely, in 10.5% of the cases, **ultrasound has provided additional information** to the autopsy. In most of these cases, marked autolysis of the cerebral tissue rendered autopsy impossible. We tried to overcome this impediment using specific techniques, as the vascular investigation in a case of Galen's vein aneurysm with significant arteriovenous shunt located by ultrasound scan between the middle cerebral artery and the median prosencephalic vein (Markowski). The Galen aneurism was evident, but autopsy failed in highlighting the arteriovenous shunt.

The confirmation of the main diagnosis of the major CNS abnormality was possible in 92.16%, which confirms recent reports that recognize the progress of imagistic and autopsy techniques.

Complementary investigations were recommended and performed in our study to confirm the ultrasound diagnosis. **Transfontanellar ultrasound** was used for the cases of structural CNS abnormalities continued until birth and confirmed the prenatally detected conditions. **Magnetic resonance imaging** (MRI) confirmed the ultrasounds findings and provided important additional data for counselling - as the description of morpho-functional development of the brain with echogenic CSP. **Computer tomography** its potential to represent a complementary alternative to diagnosis. In the indicated cases, it was used to confirm post-abortum abnormal aspects in cases where autopsy had technical difficulties - as in the case of early diagnosed rachischisis.

Conclusions

Carrying out the study in a regional prenatal diagnostic centre and in a tertiary hospital was the key point in recruiting a large number of CNS abnormalities and providing a wide range of malformation patterns. On the other hand, low adherence to screening programs and loss of patient follow-up are important factors in failing early detection of structural anomalies. An important cause of this reduced compliance is the poor implementation of national screening programs targeting this type of investigation.

CNS anomalies prophylaxis and reduction of their prevalence may be possible through national programs, by large-scale folic acid administration for the prevention of neural tube defects. A higher incidence of this defect is found in the rural group in our study, where health care, medical information and counselling are deficient.

Timing of fetal structural assessments is important, and screening becomes effective if at least one examination is provided. In the first trimester of pregnancy the morphological assessment has the advantage that it overlaps with the combined evaluation for genetic risk calculation and does not necessitates a separate visit. The second morphological assessment should be planned in the second trimester, between 18-22 weeks GA, when the detectable anomaly spectrum is significant larger than in the first trimester. However, in our study many of the major CNS abnormalities were detected late in pregnancy, after 24 weeks of GA, when according to our legislation, the option of abortion cannot be provided. The main cause of this late detection is represented by the delayed first presentation of pregnant women for structural assessment. Third trimester evaluation is important in detecting late-onset anomalies, but these have a low incidence, and international studies have not achieved a

favourable cost-effective ratio for routine screening structural assessment in the third trimester, overall or concerning only CNS.

The diagnosis of major CNS abnormalities in the first trimester of pregnancy is very important because it has the potential to detect the most severe and prevalent, thus termination of the pregnancy involves lower risks compared to the second trimester therapeutic abortion. Still, the first trimester evaluation does not substitute the second trimester anomaly scan, because of the insufficient structural development of the CNS, which continues until 20 weeks of GA.

Identifying CNS structural anomalies requires genetic counselling that becomes even more important when multiple defects are diagnosed, affecting CNS or other systems. The couple must be well informed before making a decision regarding the evolution of the pregnancy. Prenatal diagnosis, prognosis estimation and couple counselling usually involve the availability of several specialists in Obstetrics, Imagistics, Genetics, Neonatology, Paediatric Surgery, Neurology and Cardiology, Fetopathology etc.

CNS anomalies are a major public health issue involving many areas: medical, social and economic. Their detection and prognosis assessment are a key element in counselling the couple. The extensive, systemic structural assessment of the fetus and fetal adnexa may change prognosis or subsequent attitudes, therefore it should be routinely performed.

Confirmation by another method (autopsy, CT, MRI, genetic testing, etc.) of prenatal diagnosis rise professionals and patient's confidence and strengthens the role of ultrasound in prenatal diagnosis. Moreover, it can add significant information for the prognosis of the current pregnancy or may correct the rate of recurrence in subsequent pregnancies.

Fetal autopsy also plays an important audit role for the prenatal imagistic diagnosis, providing a thorough, palpable assessment and with minimal artefacts. Still, we should keep in mind the vulnerability of the cerebral tissue to hypoxia and its rapid degradation. The need for trained fetopathologists in regional centres is obvious, as the progression of prenatal diagnosis requires appropriate autopsy confirmation.

In CNS abnormal cases where the pregnancy termination is declined and pregnancy continues until birth, it is important to be monitor the postnatal development in the early years of life, but also later, to determine the degree of long term neuro-psyhic impairment.

The establishment of national databases of prenatal detected anomalies represents an important aspect for centralising and monitoring the abnormal conditions. It will also provide

demographic indicators for CNS abnormalities, that plays an essential role in establishing or modifying population health policies. Last but not least, the statistical data available on large population would serve for improved counselling of couples.

Keywords: *prenatal diagnosis, central nervous system, malformations, fetopathology, autopsy, genetics.*