NEW ASPECTS AND THE INTEGRATION OF THE FIRST AND EARLY SECOND TRIMESTER SCREENING TO THE FETO-MATERNAL MEDICINE

Ph.D. thesis

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Aims and objectives of the dissertation

1. To provide a comprehensive literate review in the main scopes of fetal medicine including prevention; ethology of prenatal conditions and diseases; ultrasonography, biochemical and non-invasive prenatal screening and of course diagnostics.

2. To summarize the clinically important and published findings in the field from the prevention up to the diagnostics.

3. To find and collect the most sensitive screening methods and markers of the trisomies.

4. To create and publish the population specific normograms of ultrasonography markers of the Hungarian population

5. To find and describe the best ultrasonography screening methodology for autosomal trisomies.

6. To develop more sensitive screening methods or techniques with the combination of new and old screening markers.

7. To confirm or deny the first and only publication in our knowledge about combination of nuchal translucency and ductus venosus pulsatility index in the first trimester.

8. To observer the possible efficacy of the second trimester facial markers in the first trimester screening.

9. To observe the combination of the first and second trimester nasal bone length normogram.

Introduction

Fetal Medicine is a multidisciplinary branch of medicine that trades with the growth, development, prevent, care, and treatment of the fetus and with environmental components that may harm the fetus. The major area of fetal medicine is the major physical anomalies. Which could be observed cc. They are seen in approximately 3-6% of newborns. The "major physical anomaly" means a physical anomaly that has cosmetic or functional significance, another 1-3% will have malformations (including internal, genetic - Biochemic, structural, mental, or perceptive condition) detected later in childhood or life. These congenital malformations account for about 20% of deaths in the perinatal period.

Scope of the fetal medicine: Fetal medicine has many interrelated studies such as maternal medicine, obstetrics, public health, midwifery, gynecology, birth rate, medical genetics and genomics, epigenetics, Neonatology, Perinatology, pediatrics, radiology...etc. Prenatal diagnostics and screening is the parts of fetal medicine.

Aim of the fetal medicine

The aim of the fetal medicine to observe, define, prevent, evaluate factors of fetal development and find solution or prevention strategy to fetal diseases.

Many countries has been ’separated’ from another branch of medicine and using as a unique field with or without maternal medicine (fetal medicine or feto-maternal medicine).

Thither was a substantial demographic change in the maternal age in the Hungarian population. A drastic decline can be observed in the proportion of women under 25, while a significant increasing tendency in the proportion of women over 30 or more. The rate of 35 year old or older pregnant increased 15.6% till 2009 with more than 7% from 2001.

Department of Hungarian *Congenital Abnormality Registry* (HCAR or VRONY) is a good monitor of fetal defects in Hungary. Approximately 5-6% of fetuses have congenital abnormalities at birth in Hungary (HCAR National Report of Birth Defects, 2011).

The incidence of fetal anomalies has been increased during the last decades, however many studies suggesting that's could be the issue of the modern lifestyle or the improved health and more developed technologies.

Not only the increasing maternal age, but there are many teratogen agents which are threatening and effecting fetal conditions.

Fortunately, there are many new promising results which could decrease the incidence of a numerous feto-maternal abnormalities.

Prenatal screening

Prenatal screening for fetal malformations means to detect embryos or fetuses with normal or abnormal features during their intrauterine life.

Ultrasound screening

The ultrasound screening is the one of the oldest way to follow-up the pregnancy. In the last few decades, the technical development and science were reached the new era prenatal screening. These innovations help us to observe the fetus on high-definition live images or volumes. Ultrasound screening is able to detect developmental, chromosomal and structural abnormalities.

The ultrasound screening needs normal ranges, these called reference ranges, normograms, or normograms in the literature. These reference intervals are necessary to calculate the real gestational age and follow the fetal development.

To create normal ranges an advanced statistical knowledge is necessary. The complexity and requirements of the normogram creation was published by our group in Hungarian

Medical Journal (Orvosi Hetilap). Another publication of our research group proved usefulness of combined normograms was published.

Biochemical screening or maternal serum screening

Biochemical screening is introduced with AFP and HCG measurement in the middle of 80es, its overall screening performance was not higher than 40% sensitivity at 20-40% false positive rate. In the last decade multiple markers (such as PAPP-A, eostradiol, PlGF) were presented in the fetal medicine.

Combined Screening

The combination of the ultrasound and biochemical markers has improved the efficacy of the screening. The ultrasound dating by using CRL is successfully solved the vulnerabilities of the biochemical screening. The correct dating is allowed to use them as MoMs values (Multiple of Medians) which are age, habitual and gestational age specific values. These values are really useful in biochemical screening but not as much as during the ultrasound screening.

Non-invasive prenatal testing

Non-invasive prenatal testing (NIPT) is based-on fetal cell free DNA in maternal plasma. This method is could be easily used in the clinical practice, but actually basically big companies earn a huge profit. Olive Kagan and et al. has been published (in press in UOG) a QUALY based study comparing the new and old methods for screening for trisomies, this publication was suggested that NIPT is more expensive and not wide specturumed as combined or ultrasound screening.

This method is brand new. Till this time, there is no restrictions, no ethical observation or no further control of the samples is exits. This will be a very big and serious deal, because two (mother and fetus) plus a half (father) patients genetic data could be observed without a warning or acceptance. Private life and health insurance companies could use these data in future to find risk gene of complex disease (such as cancer, cardiovascular diseases...etc). The parents and fetus does not known about this risk.

Another possible field of usage is the Y detection to determine the sex of the fetus, which could be easily lead to demographic problems such as it happened before in the Far East regions (like China) during the introduction of CVS in 1980s.

Prenatal diagnostics

Prenatal diagnostics means to detect genetic diseases in the fetus using invasive procedures and genetic techniques.

Invasive procedure

The aim of the invasive procedure is to get a sample from a fetal cell culture for a genetic test. Because of the needle puncture for sampling the *invasive prenatal method* is the other term used. Ultrasound controlled sampling could be performed in the first trimester (Chorionic Villus Sampling - CVS), or in the second trimester (Amniocentesis - AC) or later in the pregnancy (cordocentersis - CC). The major problem of the sampling procedures is the risk of abortion, while the advantage is the certainty of the result which is above 99.8 per cent.

Reviewing the literature, from end of 80s up today, a huge decrease of the invasive procedure associated risk could be observed. Commonly known, AC and CVS risk were about 1-2%, however the education, trainings, and experience proves that there is no significant difference if the procedure technique was appropriate and the protocols were followed. The latest publication in this field suggesting that the procedure of miscarriage

The decision has been made by the parents, which based-on the estimated risk of aneuploidies in contrast to the risk of miscarriage associated with invasive procedures. Recent Guideline of the Hungarian College of Clinical Geneticist and of Obstetrics and Gynaecology (2010) recommends that all pregnant women of 37 years of age or over should be offered invasive testing to obtain a definitive diagnosis of fetal karyotype. However, from an ethical point of view the couples are left to have an autonomous decision if they want to have an invasive test or not. At genetic counselling the patient

is advised to the possibility that they can skip the expensive screening and can go straight for invasive testing.

A huge series of studies were presented on the risk of post procedure miscarriage. The significant discordance between the numbers should be observed and should be implicated to the genetic counselling.

The importance of the fetal biometry reference normograms during the screening for trisomy is well-known and some preliminary studies have been highlighted the importance of local normal curves and charts. To our knowledge, there was not any study to establish the Central European normograms.

Appropriate methodology has been published fetal biometry charts and equations for various populations using the correct methodology are now available in the international literature. Although there were many previous publications of the measurement and normal ranges of the human fetal biometric parameters, none of all had specific data on the Central European Region.

The first trimester fetal biometric characteristics have been observed, analyzed and published many times by the Fetal Medicine Foundation (FMF) London and its co-operators, but many papers highlighted the racial growth chart differences. Our study was established based on these findings.

The new sonography era of the screening for Down Syndrome (DS) has been started by Szabó and Gellén with their breakthrough publication about nuchal translucency thickness in 1990. Following their paper many studies have been proved its clinical importance of their hypothesis and results.

From the beginning of the 20th Century, facial markers introduced to the trisomy screening. In the last decade, the importance of facial marker in the first and second trimester was published several year ago and our good preliminary results also proved the high efficacy of the fetal profile ratios in the second trimester. These results were suggested that to introduce them and to create normograms to observer these markers and ratios in the first trimester, too.

The aim of the study was to establish the local fetal growth charts and normograms of fetal biparietal diameter, femur and humeral length, nuchal translucency, prenasal thickness, nasal bone length, ductus venosus PI, and PT-to-NBL and NBL-to-PT ratio from about 10weeks and fetal heart rate and CRL from the 37 days of gestation to the midtrimester.

The secondary aim was to improve efficacy of screening for chromosomal abnormalities at the first trimester ultrasound screening.

Material and Methods

Materials:

This prospective observational study has been designed to measure, and describe the normal biometric parameters. All included 4321 cases scans have been performed from January, 2008 to February, 2014 in the MEDISONO Fetal and Maternal Health Research Centre and the Department of Medical Genetics, University of Szeged, Szeged, Hungary.

This study contains for (both low- and high) mixed-risk obstetric populations, and ethnically over 99.8% of pregnancies were a Caucasian population of Hungary. The study protocol was approved by the Regional Ethics Committee of the University of Szeged and all procedures were in full accordance with the Helsinki Declarations.

Measurements

All measurements were performed by one experienced sonographer using transabdominal ultrasound (GE Voluson E8 Expert, GE Healthcare Cipf, Austria). This sonographer was a holder of The Fetal Medicine Foundation's (FMF) Certificate of Competence for first-trimester scanning. All measurements were repeated for 3 times and the best one were selected.

Measurements of fetal biometry such as CRL were followed the INTERGROWTH-21st measurement of fetal crown rump length and standardization of ultra-sonographers (2010). CRL was measured in the mid-sagittal section, a neutral horizontal position,

using the optimal magnification with the correct calliper position. The intersection of the callipers were placed on the outer borders of the skin over the head and rump.

NT and DVPI measurements were fully followed the FMF criteria. DVPI-to-NT and NT-to-DVPI were established by the division NT and DVPI. Measurements of BPD were obtained from a transverse axial plane of the fetal head showing a central midline echo broken in the anterior third by the cavum septi pellucidi, if already present. BPD was measured from the outer border of the skull.

The femur length (FL) was measured from the greater trochanter to the lateral condyle if it was exits and shown, as if on the two ossification border of the bone.

To measure the FHR, M-Mode was used in acquiring volume with automatic calculation.

Facial profile (NBL and PT)

On the basis of technical descriptions of NBL measurements and our experience, both measurements could be obtained in the same image if the face of the transducer was positioned parallel to the nasal bone. The insonation angle should be close to 45 degrees. The following image settings were used: low gain, medium dynamic contrast, and maximum magnification so that the fetal head occupied the entire screen. Images were adjusted to ensure the correct midsagittal plane and sharp margins of the skin and the nasal bone. The diencephalon, nasal bone, lips, maxilla, and mandible were used as reference points for the correct measurements of NBL in the midsagittal plane. The following image settings were used: low gain, medium dynamic contrast, and maximum magnification so that the fetal head occupied the entire screen. Images were adjusted to ensure the correct midsagittal plane. Briefly, PT was measured as the shortest distance from the lower margin of the frontal bone to the outer surface of the overlying skin. The margins of the nasal bone are the proximal and the distal ends of the white ossification line. The NBL and PT were measured using the same view. If it was possible NT, NBL and PT were measured on the same image. PT-to-NBL and NBL-to-PT were established by the division of NBL and PT.

Additionally, between April 2008 and December 2013, 2549 women were included into another study and followed-up in the first and second trimester to improve the second trimester screening efficacy. First and second trimester measurements were combined in a normogram and compared to second trimester Down syndrome cases.

Results

Normograms were created for Fetal Heart Rate (FHR), Femur Length (FL), Biparietal Diameter (BPD), Nasal Bone Length (NBL), Prenasal Thickness (PT), NBL/PT ratio, PT/NBL ratio, Nucthal Translucency (NT), Ductus Venosus flow Pulsatility Index (DVPI), DVPI+NT, DVPI+NT+PT/NBL ratio, NT/DVPI-to-PT/NBL ratios and DVPI/NT-to-PT/NBL ratios. The specific sensitivity, specificity and likely-hood ratios were determined for trisomies to FHR, FL, BPD, NBL, PT, NBL:PT, PT:NBL, NT, DVPI and their combinations. DVPI/NT-to-PT/NBL ratios were reached best efficacy with100 % sensitivity and 99.47 % of specificity at 188.50 positive likelihood ratio.

Significant differences were observed between euploid and trisomy group from the aspect of nuchal translucency, fetal heart rate, nasal bone length, prenasal thickness, ductus venosus PI, prenasal thickness-to-nasal bone length and ductus venous-to-nuchal translucency to prenasal thickness-to-nasal bone length ratios. ($p > 0.001$)

Combined normogram of Nasal bone length

Forty-one cases of trisomy 21 were identified (cytogenetically) and all of them were detected between 14^{th} and 28^{th}weeks. In 33 cases the measured NBL values were lower than the 5^{th} percentile and 8 cases of trisomy 21 fetuses were higher than 5^{th} percentile, respectively. These results showed 80.49% sensitivity with 98.17% specificity. Positive and negative likelihood ratio for trisomy 21 fetuses were 43.98 and 0.2, respectively.There was significant difference between the nasal bone length of euploid and trisomy 21 fetuses ($P =< 0.001$).

Discussion

This study represented the high sensitivity ultrasound screening methods and reference charts of the fetal biometric parameters of the Caucasian population.

NT was the first and the most sensitive screening marker of Down syndrome. This study proved its strength in first trimester screening.

DVPI was found one of the most sensitive marker of trisomies during the first trimester. It has high sensitivity and a medium-high specificity on trisomies. This finding was also confirmed by our study.

The most sensitive marker was the combined DVPI and NT plot, but the best result was reached when NT and DVPI were combined with the facial markers.

Our preliminary results were proved the efficacy of PT, NBL and their ratios in the second trimester. Slightly, these markers were fitted to the first trimester scan. They could be measured easily on the same image with NT. The common measurement, possibility could decrease the necessary time of observation and extremely increase efficacy of screening. In contrast with previous result PT-to-NBL is overwhelming in the first trimester.

The FL, BPD and HL should act as an important screening marker of the early IUGR and not for the trisomies. These markers may help to identify the bi- and unilateral cranial and limb anomalies during the first trimester.

The clinical aspects of these findings were the introduction of the facial profile ratio to the first trimester screening, using DVPI-to-NT and PT-to-NBL ratios in the first trimester as new markers of trisomies.

The ductus venosus-to-nuchal translucency to prenasal thickness-to-nasal bone length ratio reached an impressive 100% detection rate of 0.6% false positive rate. The risk of chromosomal defects is very high and the first line of management of such pregnancies should be the offer of NIPT or chorionic villus sampling (CVS) for fetal karyotyping.

The latest screening strategy for first and second trimester was introduced by Nicolaides et al. in a congress. (Advances in Fetal Medicine Dec 2013 London). Their opinion was to focus on the neck on first and focus on the face (facial profile) in the second trimester. These was a summary of the long development and research of the screening for trisomy, booth direction were introduced and published from several groups in last two and the half decades.

CRL, BPD, FHR and FL were measured from the beginning of the obstetric ultrasound era. These markers were easily measured with the low-resolution devices, but provided much useful information about fetal development to the examiner. Our study had been set the normograms of these markers and tried to use them in the screening for trisomy. Excluding FHR, these markers have efficacy in the developmental and well-being scans, and they should not be used for trisomy screening. FHR proved a really high sensitivity and a fair specificity to detect fetal defects in the early pregnancy. Our previous observation also proved its importance during the early first trimester scans to find the pregnancy outcome or the early and late fetal loss from the 6 weeks.

NT were the real first marker of autosomal trisomies but several study proved its usefulness in different conditions and diseases. Current paper used NT after the first trimester and proved a really good efficacy on trisomy.

Nasal bone length was proved high screening efficacy during the pregnancy. However, in the first trimester its repeatability is very low and there is no linear increase till 60mm of CRL, but the production lines were padded to the border of the plot and it was useful to screen out cases in the early pregnancy.

Prenasal thickness (PT) was published a several years later by Maymon et. al. PTwas improved the second trimester screening efficacy for trisomies. Current study as a preliminary studies before used the PT as a first trimester marker –successfully. Szabó et al. published facial profile based ratios and its inverse counterpart and proposed that they could be utilized as well in the first trimester. This study confirms the usefulness of these markers in the first trimester. However, during the second trimester NBL-to-

PT was better than the PT-to-NBL, although PT-to-NBL was better in the first trimester. The problem with this ratio is the zero division so if there is no nasal bone, it is unable to use for risk estimation.

In case of combined normograms, these data demonstrates that hypoplastic nasal bone between 14 and 28th gestational weeks was found in 1.83% of euploid and 80.49% of trisomy 21 fetuses, respectively. These findings are showed a better screening performance than to previous studies with 2D ultrasound. The nasal bone length was used as an isolated marker in our study. However, other studies used nasal bone length in combination bi-parietal diameter (BPD), femur length (FL) and moreover they used multiple of medians (MoMs) values instead of simple measurement value in millimetres. Our analysis showed that using MoMs in a statistical evaluation is misleading. Since the millimetre measurements day-by-day are more reliable and much easier to use in practice than a more complex summarized and corrigated values.

Conclusions

These local normograms and the most sensitive first ultrasound screening model for trisomy 21, and 18 were introduced. Using these ratios could be comparable with NIPT. These measurements and methods should be incorporated into first trimester screening for trisomy. Further investigation will be necessary to observe these findings on different population and also in the second and third trimester.

New findings and newly developed methods in the thesis

- We first described the national normograms of the fetal biometry parameters of the Hungarian population.
- We first described a new practical-based, easy-to-use and cost-effective two-dimensional measurement techniques of the NBL and PT in the first trimester.

- We first described a high risk pregnancy management protocol for low income countries
- We first described that the NIPT how to be placed into the screening system in Hungary.
- We first described that the combined the first and second trimester mammogram to enhance the efficacy of the second trimester screening of nasal bone length.
- We first described in the international literature who introduced NBL and PT with their ratios in the first trimester.
- We first described that the combination of different ratios could increase the screening efficiency in the first trimester.
- We first described that highest sensitivity and specificity could be reached for the bedside in the first trimester without any biochemical or DNA test.
- We first described that development of a statistical method to a practical method of the ultrasound screening, which has comparable screening performance to NIPT but much cheaper and could be widely used also in the low income countries.

New observations during my fellowship

1) In the major trisomy markers of euploid and trisomy fetuses a significant difference was observed.
2) We elaborated the method how the fetal nasal bone length (NBL) and prenasal thickness (PT) can be obtained and measured in a single volume acquisition (image) during the first trimester anatomy scan.
3) Validated normograms have been created for the Hungarian population for the first and second trimester.
4) We first demonstrated the combination of nasal bone length (NBL) and prenasal thickness (PT) as a ratio could be used in the first trimester as a screening marker of aneuploidies.

5) These data have been supported previous observations which highlighted the importance of nuchal translucency and ductus venosus flow pulsatility index as the most effective screening co-maker of autosomal trisomy.
6) We first demonstrated the combination of nuchal translucency and ductus venosus flow pulsatility index as a ratio versus the combination of nasal bone length (NBL) and prenasal thickness (PT) as a ratio, could be used in the first trimester as a more sensitive ultrasonography screening marker of aneuploidies.
7) We first described *in the international literature* that the combination of first and second trimester NBL measurement on a mixed mammogram could increase the efficacy of screening in the second trimester.
8) We first described *in the international literature* that the PT: NBL and NBL: PT ratio in the first trimester.
9) We first published *in the international literature* that the ultrasound measurements of these new markers can successfully be incorporated into the first and second trimester fetal anatomy scan.
10) We first described *in the Hungarian literature* that how to create and validate obstetrical normograms.

As the main result and conclusion, we have to highlight the importance of the ultrasound scan during pregnancy. Wide scale of fetal and maternal condition could be offered by ultrasonographic scans and trisomy screening is only a small part of them. Our research found a cheap, easy and fast method for first trimester trisomy screening, which could reach the efficacy of NIPT. However, further studies will be required on a large population.

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List of publications related to the dissertation

I. **Response to "Comment to "Nasal bone length: prenasal thickness ratio: a strong 2D ultrasound marker for Down syndrome""**
Károly Szili, Andrea Szabó, János Szabó
Prenatal Diagnosis 2015, (in press) Impact Factor: 2.514

II. **Új módszerek a Down-szindróma második trimeszterbeli ultrahangszűrésére: az orrcsonthosszúság és a praenasalis lágyrész-vastagság mérésének statisztikai elemzése**
Szili Károly, Szabó Andrea, Vanya Melinda, Bártfai György, Szabó János
Orvosi Hetilap Orv.Hetil., 2014, *155*(47), 1876–1881 (precalc. Impact Factor. :0.390)

III. **Is it Possible to Improve 2nd Trimester Screening Efficacy with a Combined 1st and 2nd Trimester Nasal Bone Length Normogram?**
Szili K., Szabó A.Sz., Vanya M., Szabó J.
The Journal of Reproductive Medicine (In press, Accepted: Oct. 2014)
Impact Factor: 0.688

IV. **Nasal bone length:prenasal thickness ratio: a strong 2D ultrasound marker for Down syndrome**
Szabó Andrea, Szili Károly, Szabó János Tamás, Sikovanyecz János, Isaszegi Dóra, Horváth Emese, Szabó János
PRENATAL DIAGNOSIS Volume 34, Issue 12 (pages 1139–1145) Impact Factor: 2.514

V. **Az egészséges élettér—az otthoni mikrokörnyezet vizsgálati modellje**
Lipták-Váradi Julianna, Szili Károly, Vanya Melinda, Széll Márta, Szabó János, Szabo Andrea, Kató Lilla
ÉPÍTÉS ÉPÍTÉSZETTUDOMÁNY 41:(3) pp. 271-282. (2013) IF: 0

VI. **A prenazális lágyrész vastagodás a 21-es triszómia ultrahang jele a második trimeszterben**

Szabó Andrea, Szili Károly, Szabó János Tamás, Isaszegi Dóra, Horváth Emese, Sikovanyecz János, Szabó János

MAGYAR NŐORVOSOK LAPJA 76: pp. 24-27. (2013) Impact Factor: 0

VII. **Early embryonic heart rate and pregnancy outcome** *(citable abstract)*

Szili K, Ferencz E, Szabó A, Szabó J, Sikovanyecz J

ULTRASOUND IN OBSTETRICS & GYNECOLOGY 40:(S1) pp. 234-235. (2012) IF:3.14

VIII. **Diagnosis and counselling of women with single umbilical artery should be confined to first-trimester** *(citable abstract)*

Szabó J, Horváth E, Szili K, Sikovanyecz J

ULTRASOUND IN OBSTETRICS & GYNECOLOGY 36:(S1) p. 119. 1 p. (2010) IF:3.14

IX. **Effects of maternal epilepsy and antiepileptic therapy in women during pregnancy**

Melinda Vanya, Nóra Árva-Nagy, Károly Szili, Délia Szok,György Bártfai

Ideggyógyászati Szemle/Clinical Neuroscience Impact Factor:0.382