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3 dimensional measurement of gestational and yolk sac volumes as  
predictors of pregnancy outcome in the first trimester

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Summary of Ph.D. Thesis

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### Study background

Understanding the normal development of early pregnancy and observing this process ultrasonographically has allowed us to effectively monitor first trimester pregnancy, and recognize early signs of abnormal outcome. Crown-rump length has been found the most accurate method to determine gestational age in the first trimester and in some cases to predict abnormal outcome as In addition, the size (diameter) of embryonic structures such as gestational sac and yolk sac was also found to have a good prognostic value for adverse outcome. The introduction of more advanced sonographic equipment (probes with higher frequency, higher resolution, new computer techniques, etc.) raised demand for the reevaluation of data to improve accuracy in predicting GA and pregnancy outcome. In addition, some authors suggested the creation of nomograms based on the time of the ovulation instead of the last menstrual period to avoid discrepancies in cases in which ovulation did not occur on day 14.

During the past decade the evaluation of the potentials of applying 3D ultrasonography in the first trimester has begun. The results are quite promising in terms of defining the advantages 3D ultrasound versus the 2D technique in the observation of delicate embryonic details. Nevertheless, the only study, which executed 3D volumetric measurements of the embryonic gestational sac to evaluate its predictive role for pregnancy outcome was the work of Steiner and colleagues in 1994. They hypothesized, that since the amniotic fluid in the first trimester (which is the major component of GS volume) is an ultrafiltrate of the maternal plasma, its amount would reflect the function of the early uteroplacental unit. The other studies that involved the examination of first-trimester pregnancies with 3D sonography concentrated only on general aspects and observations of embryonic development.

In the measurement of the embryonic structures, since both the patient anatomy and the interrogating ultrasound beam are three dimensional, it seems logical to perform all

measurements using the 3D technology. Applying 3D scans, gestational and yolk sac volumes can be measured directly rather than using a mathematical formula to calculate volume from linear (2D) dimensions.

### Study objectives

#### *Study on singleton pregnancies*

- I. It was proposed that by calculating the volumes of GS and YS in the first trimester in singleton pregnancies using 3D transvaginal sonography, the nomograms of their normal developments could be created (together with CRL).
- II. This study aimed as well to determine the type of correlation between the measured variables and GA.
- III. The study's further goal was to investigate whether these growth curves can be used as the basis of predicting adverse reproductive outcome and to find the best predictor for adverse outcome that can be used in routine diagnostics.

#### *Study on multiple pregnancies*

- I. The first aim of this study was to determine whether the GS and YS (and CRL) volumetric graphs established in normal singleton pregnancies could be applied to twins and triplets as well.
- II. It was also the study's aim to evaluate the predictive values of these measurements for first trimester abortion in case of twin and triplet pregnancies.

## Materials and Methods

### *Patients*

94 examinations were performed in this prospective study in case of singleton pregnancies with normal and 14 with abnormal outcome (first trimester abortion, blighted ovum). 44 GS and 36 YS volumetric measurements (obtained from 18 pregnancies) were performed in twins with normal outcome, and 16 and 11 with abnormal outcome (obtained from 7 pregnancies) respectively. 18 measurements could be carried out in normal triplets (obtained from 5 pregnancies), while no abnormal cases were found so far in this group. All patients were treated for infertility and had known dates of ovulation.

### *3D scanning and applied methods of volumetry*

3D scans were performed with a Voluson 530D (Medison, USA) ultrasound machine using a Voluson Endocavity transducer S-VDW 5-8 (Kretztechnik AG, Austria). The transvaginal sonographic examination in each case began with the evaluation of the pelvis and the pregnancy in 2D mode. After switching into 3D volume-mode, the region of interest was defined with the movable sector on the screen and the volume was acquired. Seconds after the acquisition, the scanned region was displayed on the screen in three orthogonal planes (frontal, sagittal, horizontal), and it was checked if the volume contains the whole pregnancy. The information was stored on 540 MB removable hard disc for subsequent analysis and calculation.

To calculate GS volumes the "contour" method was used. Starting from the inner margin of the GS the contour was outlined in the measurement plane using a roller-ball calibrator. The contours were serially selected by viewing the cursor in another fixed plane moving from pole to pole in the GS. 7-15 contours were selected depending on the size of the sac. The volume was calculated from these data by the in-built computer immediately.

Volumetry of the YS was performed using the “3 diameter” method measuring the 3 diameters of the YS in the 3 displayed orthogonal planes. Each calculation of the GS and the YS volume was repeated 3 times changing the displayed planes on the monitor between calculations in order to reduce errors, and the mean of the 3 measurements was calculated and used afterwards. CRL was also measured 3 times in different planes when it could be visualized and the calculated mean value was taken into consideration. The examiner (A. Bábinszki), who performed all calculations, was blinded to obstetrical outcome.

### *Data analysis*

GS and YS volumes (and CRL measurements) were plotted against gestational age (25-65 days post ovulation) to create nomograms for normal outcome. To investigate whether the growth-curves created for singletons can be applied in multiple gestation GS and YS volumes of the twin pregnancies were fitted in the graphs of their singleton counterparts. Measurements of the pregnancies with abnormal outcome were compared with the values of the normal curves in singleton and multiple pregnancies as well.

### Results

#### *Study on singleton pregnancies*

A total of 94 values of GS volume were obtained in singleton pregnancies with normal outcome between the 16-65<sup>th</sup> days post ovulation. Because of practical reasons only the data from day 25 were used for the regression analysis leaving 73 values to apply. The mean and “2SD” limits derived from these GS volume measurements by means of a non-linear regression analysis were designed to obtain the best fitting curve. This analysis revealed a power-correlation between GS volumes and GA. GS volume with abnormal outcome were fitted in this graph and 8 of 12 fell beneath the intervals of the curve. The prognostic value of

GS volumetry for abnormal outcome was found to be statistically significant ( $p < 0.05$ ) and Odds ratio was 4.3 using 95% confidence interval (95% CI: 1.18-15.91).

Non-linear regression analysis (using 73 measurements) revealed a logarithmic correlation between YS volumes and GA in cases with normal outcome. 8 measurements of YS volumes with abnormal outcome could be obtained. Of the 8 values only 4 fell out of the normal range. The prognostic value of this method was statistically not significant ( $p = 0.07$ ).

A curve for normal CRL growth was also established, using 66 values, to facilitate comparison between the different methods. A logarithmic correlation was found with GA, and predictive value for adverse pregnancy outcome was calculated. 8 cases with first trimester abortion were applied and statistically significant predictive value was found for CRL ( $p < 0.05$ ). Odds ratio was 5.4 (95% CI: 1.16-25.19). Non-linear regression analysis showed a good diagnostic correlation between GS volumes and CRL.

Using another method to evaluate and compare the prognostic value of GS, YS volumetry and CRL measurement, the data with abnormal outcome were paired with the normal values on the basis of gestational age and the means of these values in each group were calculated and compared. Naturally, only those values could be used in this comparison, which had their matching pairs in terms of the GA. GS volumes and CRL were found to have statistically significant prognostic value for first trimester abortion by this method.

Similar specificity, sensitivity, positive and negative predictive values of GS volumetry and CRL measurements were found regarding pregnancy outcome. However, when the results of the two methods correlated with each other, specificity and positive predictive value could be improved. Mean YS/GS ratios were also calculated in both the normal and the abnormal groups to facilitate comparison. The mean YS/GS ratio ( $0.017 \text{ mm}^3/11.432 \text{ mm}^3$ ) was 0.0015 in case of normal and 0.0042 in case of abnormal outcome ( $0.012 \text{ mm}^3/2.855 \text{ mm}^3$ ) and the difference was statistically significant ( $p < 0.05$ ).

### *Study on multiple pregnancies*

Statistical calculations were carried out to determine if there were any significant differences between the GS and YS volumes measured in singleton and multiple pregnancies. These analyses, using the Breslow-Day test to compare the homogeneity of Odds ratios in normal singletons and twins, showed no significant difference between the two groups ( $p=0.095$ ) in case of GS volumetry. On the basis of these results it was concluded that the nomogram of normal singletons' GS volumetry could be applied in twins as well. Similar comparison of singleton and twin pregnancies with normal outcome was carried out in case of YS volumetry. Statistical analysis revealed no significant difference between the groups ( $p=1.3$ ) suggesting that the graph of YS volumetry created for singletons can be used in case of twins.

Determination of the predictive value of GS volumetry in twins was carried out by fitting GS volumes of twins with abnormal outcome in the "basic" GS volume graph (singletons with normal outcome). 12 of the 16 values fell outside the range of the curve. Statistical analysis showed the prognostic value of GS volumetry for first trimester abortion statistically significant ( $p=0.005$ ). This kind of evaluation was performed in case of YS volumetry as well. Only 4 of the 11 YS volumes with abnormal outcome fell outside the range of the graph and no statistically significant prognostic value of this method was revealed ( $p=0.974$ ).

There were no cases with abnormal outcome in case of triplets, so statistical analysis could not be performed to evaluate whether the graphs of singletons in GS and YS volumetry could be used in this group. Nevertheless, in case of GS volumetry 12 of the 18 values fell outside the range of the graph (9 above, 3 below) suggesting a substantial difference between the normal GS volumes of singletons and triplets. Contrary to this, in case of YS volumetry

only 5 of the 17 values fell outside the curve (4 above, 1 below) suggesting no substantial difference between YS volumes of singletons and triplets.

### Discussion

#### *The "singleton study"*

In this present study it was proposed that by calculating the volumes of GS and YS in the first trimester in singleton pregnancies using 3D transvaginal sonography, the nomograms of their normal developments could be created (together with CRL). First trimester growth-curves of GS and YS volumes were determined in this prospective study by using 73 values. The predictive values of these variables for pregnancy outcome were compared with that of CRL as well.

Besides, this study aimed to determine the type of correlation between the measured variables and the gestational age. Power correlation was observed between GS volumes and GA (calculated from the time of ovulation), and logarithmic correlation when YS volumes were plotted against GA. The relationship between GS diameter and GA as well as CRL and GA was found to be linear by 2D ultrasound in the literature and curvilinear in case of YS diameter and GA. The graph of CRL and GA showed a logarithmic correlation in the present study.

The study's further aim was to investigate whether these growth-curves can be used as the basis of predicting adverse reproductive outcome and to find the best predictor for adverse outcome that can be applied in routine diagnostics. Using the created nomograms, GS volume and CRL proved to have good negative predictive values for first trimester abortion, while YS volumetry did not appear to be a reliable predictor in our study. In addition, when cases with abnormal outcome were paired with normals on the basis of GA and the mean values of aborters and non-aborters were compared in the 3 groups, similar results were observed. It is



difficult to determine, whether YS volume (in case of normal appearing YS) being a non-informative predictor is due to the small case-number with adverse outcome.

The diagnostic value of GS volumetry and CRL measurements were found to be similar when they were compared by non-linear regression analysis as well as by calculating sensitivity, specificity, positive and negative predictive values. It was observed that combinatory application of the two methods improves specificity and positive predictive value in case they predict similar outcome. In case GS volume and CRL measurements are contradictory, close follow up can be suggested to find out if the pregnancy is endangered. Nevertheless, positive and negative predictive values were found to be lower than in the study by Steiner et al. in 1994. When the mean YS/GS ratios were calculated in both groups, the prognostic value of this ratio was found to be a reliable variable since it was statistically significantly higher in the abnormal group.

#### *The "multiple gestation study"*

The first goal of this study was to determine whether the GS and YS volumetric graphs established in normal singleton pregnancies could be applied to twins and triplets as well. Both GS and YS growth-diagrams of normal singleton pregnancies were found to be applicable in twin pregnancies. Although no statistical analysis could be performed in triplets because of the lack of cases with abnormal outcome in that group, on the basis of the ratios it seems that GS volumes of triplets are larger than that of singletons. This observation suggests that a specific graph should be determined and used to predict embryonic demise in triplets. Nevertheless, the nomogram of YS volumetry established in singletons seems to be applicable in triplet pregnancies.

It was also the study's aim to evaluate the predictive values of GS and YS volume measurements for first trimester abortion in multiple gestations using 3D transvaginal

sonography and to find an accurate method to determine embryonic status in these pregnancies. Based on the results of the statistical analysis, GS volumetry itself proved to be a statistically significant predictor for first trimester abortion however, YS volumetry did not have statistically significant predictive value just like it occurred in the study on singletons.

GSV was found to have around 70% sensitivity and specificity to predict abnormal pregnancy outcome in the first trimester in singletons and in twins as well. Positive predictive values of GS volumetry were better in twins, while negative predictive values of these measurements were found to be better in singletons.

### Conclusions

#### *The 3D technology*

During the execution of these studies several advantages of 3D ultrasound over the 2D technology were realized. Visualization of the desired image in three rather than two spatial planes allows greater flexibility in evaluating the region of interest because the examiner can move back and forth through different planes as well as rotate these planes with 360°. The third plane, which cannot be displayed by the conventional ultrasound, can also be demonstrated. These additional views provide more accurate information regarding normal anatomy and pathologic features. More precise, direct volumetric measurements can be done in three dimensions.

Since volumes can be acquired in seconds and stored either into the machine or on computer diskettes, the patient examination time is significantly reduced. The stored volumes and images can be entirely viewed, assessed and consulted at a later time. Time-consuming evaluations and measurements can be performed without the presence of the patient. 3D imaging also offers the patients an improved visual perspective on their pregnancy's condition. The clinician thus is better equipped to counsel the women about the findings and

is able to provide them with a better understanding of their problems. These features seemed to facilitate the doctor-patient relationship.

### *3D volumetry of the gestational and the yolk sac*

Growth curves of GS and YS volumes and that of CRL were determined in the first trimester using transvaginal 3D ultrasound in case of singleton pregnancies. These nomograms were found to be applicable for twin pregnancies but did not seem to be useful in case of triplets. It was concluded that GS volumetry is a good predictor for embryonic jeopardy and can be a good supplement to CRL measurements in the first trimester in case of singletons and possibly in twin pregnancies as well. These results suggest that 3 dimensional volumetric measurements enable us an early and accurate prediction of first trimester pregnancy loss.

### *Main findings of the studies:*

#### *Singleton pregnancies*

- I. First trimester growth-curves of GS and YS volumes were determined in this prospective study.
- II. Power correlation was observed between GS volumes and GA (calculated from the time of ovulation), and logarithmic correlation when YS volumes were plotted against GA. The graph of CRL and GA showed a logarithmic correlation in the present study.
- III. GS volume and CRL proved to have good negative predictive values for first trimester abortion, while YS volumetry did not appear to be a reliable predictor in our study.

#### *Multiple pregnancies*

- I. Both GS and YS growth-diagrams of normal singleton pregnancies were found to be applicable in twin pregnancies. A specific graph should be determined and used to predict

embryonic demise in triplets. The nomogram of YS volumetry established in singletons seems to be applicable in triplet pregnancies.

II. GS volumetry itself proved to be a statistically significant predictor for first trimester abortion however, YS volumetry did not have statistically significant predictive value just like it occurred in the study on singletons.

**List of abbreviations:**

2D – two dimensional

3D – three dimensional

GA – gestational age

GS – gestational sac

GSV – gestational sac volumetry

YS – yolk sac

YSV – yolk sac volumetry

CRL - crown-rump length

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