

Functional linear discriminant analysis: a new longitudinal approach to the assessment of embryonic growth

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BACKGROUND: Functional linear discriminant analysis (FLDA) is a new growth assessment technique using serial measurements to discriminate between normal and abnormal fetal growth. We used FLDA to assess and compare growth in live pregnancies destined to miscarry with those remaining viable.

METHODS: This was a prospective cohort study of women with ultrasound scans on at least two separate occasions showing live pregnancies. Serial crown-rump length (CRL), mean gestational sac diameter and mean yolk sac diameter measurements were recorded. The ability of FLDA to predict subsequent miscarriage was compared with that of a single CRL measurement.

RESULTS: Of 521 included pregnancies, 493 (94.6%) remained viable at 14 weeks and 28 (5.4%) miscarried. The CRL growth rate was significantly lower in those that miscarried (one-sample *t*-test, $P = 2.638E-22$). The sensitivity of FLDA in predicting miscarriage from serial CRL measurements was 60.7% and specificity was 93.1% [positive predictive value (PPV) 33.3%, negative predictive value (NPV) 97.7%]. This was significantly better for predicting miscarriage than a single CRL observation of more than 2SD below that expected (sensitivity 53.6%, specificity 72.2%, PPV 9.9%, NPV 96.5%).

CONCLUSIONS: FLDA discriminates between normal and abnormal growth to predict miscarriage with high specificity. FLDA predicts miscarriage better than a single observation of a small CRL.

Key words: FLDA / crown-rump length / embryonic growth / miscarriage / viable pregnancy

Introduction

In the second and third trimesters of pregnancy, the growth of a fetus is normally evaluated according to the relationship between fetal biometry measurements and reference range centile charts (Snijders and Nicolaides, 1994; Altman and Chitty, 1997). Fetal growth in the first trimester has only been studied using single 'one-off'

measurements of crown-rump length (CRL) or gestational sac (GS) size (Mantoni and Pedersen, 1982; Falco *et al.*, 1996; Reljic, 2001; Choong *et al.*, 2003). These studies, of women with a pregnancy following *in vitro* fertilization (IVF) or threatened miscarriage, have shown that the observed CRL in pregnancies destined to miscarry is smaller than that expected for gestational age. In one study, there was an increased likelihood of miscarriage with increasing discrepancy

between observed and expected CRL; 13.7% of fetuses with a CRL more than 2SD below that expected for gestational age miscarried compared with an 8.3% miscarriage rate in those with less than 2SD difference (Reljic, 2001). Single measurements of small GS size and a small difference between mean gestation sac diameter (MSD) and CRL have also been associated with an increased likelihood of miscarriage (Bromley *et al.*, 1991; Dickey *et al.*, 1992, 1994; Makrydimas *et al.*, 2003). These studies have used one-off (cross-sectional) assessments of CRL or GS size in selected populations. The specificity is low because many pregnancies with normal outcome are also found to have a CRL or GS size that is less than expected. This is in part due to the fact that when using cross-sectional data to assess fetal size, gestational age assessment relies on accurate recall of the last menstrual period (LMP, Mukri *et al.*, 2008). It is known that reporting of LMP is susceptible to bias with a general tendency for women to overestimate their gestational age (Savitz *et al.*, 2002) and thus be found to have a discrepancy between observed and expected fetal size measurements. Furthermore, cycle length may be variable and may be altered by contraceptive hormone use. These limitations in assessing cross-sectional data mean that it has been difficult to discriminate between normal and abnormal early pregnancy growth by ultrasound and thus predict women in the general early pregnancy population who are likely to undergo miscarriage.

The first objective of this study was to evaluate whether functional linear discriminant analysis (FLDA), using serial early pregnancy biometry measurements (CRL, MSD, mean yolk sac diameter (MYD) or their combinations) for individual patients could be used to differentiate between normal and abnormal growth and thus discriminate ongoing live pregnancies from those destined to miscarry. The second objective was to compare the performance of FLDA with the cross-sectional approach of predicting miscarriage from a single observation of CRL of more than 2SD below the expected mean for gestation.

Methods

This study aimed to evaluate a new technique by which serial growth measurements might be used to identify abnormal fetal growth. FLDA is an extension of classical linear discriminant analysis (LDA) to longitudinal data (James and Hastie, 2001). LDA aims to predict membership of two or more mutually exclusive groups from a set of predictor variables. It is used to determine which variables discriminate between these naturally occurring groups, with maximum separability aimed for between the two groups. FLDA uses curves (instead of one-dimensional variables) as predictor variables, distinguishing between classes by maximizing the ratio of the between-class variation to the within-class variation. FLDA is particularly useful where only fragments of the curves are observed. Individuals, parameterized with a five-dimensional coefficient vector, are used to estimate the mean coefficient vector of each class. Applying this to early pregnancy data, the 'curves' are the growth curves of the CRL, MSD or MYD, measured multiple times during the first trimester. Only portions are observed for each individual pregnancy such as from 6 to 10 weeks or 7 to 11 weeks.

Using our early pregnancy data, we aimed to classify patients with ultrasound measurements of a live fetus on at least two separate occasions into one class (ongoing viable pregnancy) or another (subsequent miscarriage) by determining the class with the closest mean coefficient vector.

The study was part of a prospective longitudinal study of consecutive unselected women attending an early pregnancy unit (EPU) within a London teaching hospital from January to October 2006. The overall study aim was to identify factors that predict first trimester outcome. This specific analysis was carried out retrospectively using the whole study database and anonymous patient data were included in the analysis if the woman had a known LMP date, a spontaneous singleton intrauterine pregnancy, at least two ultrasound examinations demonstrating a live fetus (heart pulsation seen) on separate occasions and known first trimester outcome. Women were included regardless of indication for assessment. Women were excluded if they subsequently underwent a termination of pregnancy (TOP), as it could not be known whether such fetuses would have remained viable to the end of the first trimester had the pregnancies been allowed to continue.

A detailed history was taken to determine the certainty of menstrual dates. 'Certain dates' was defined as being sure of the date of the start of the LMP, a regular cycle length of 26–30 days and no pregnancy or hormonal contraception in the 3 months preceding the pregnancy. All women had at least two scans and in all cases the initial scan was a transvaginal scan (TVS) in the EPU. Subsequent scans were transvaginal where there were indications for repeat EPU assessment (such as bleeding, pain or maternal anxiety), or were performed transabdominally at the routine 11–14 week dating and nuchal translucency assessment. All TVS assessments were performed using a 5 MHz transducer for B mode imaging (Aloka SSD 900, 2000, 4000 or GE Voluson 730) and measurements of CRL and three orthogonal measurements of GS and yolk sac diameter were obtained. Measurement of GS diameter was not, however, a part of the 11–14 week transabdominal scan assessment, where only CRL was measured. Measurements of CRL were taken from gestational age 35 to 98 days (the upper limit of CRL measurement at the 11–14 week assessment) and measurements of MSD were from 35 to 84 days (the upper limit of MSD assessment in EPU).

In the EPU, women were managed according to standard departmental protocols dependent on the outcome of the assessment. All pregnancies were followed up until the scheduled time of the routine 11–14 week assessment, by searching the EPU and Fetal Medicine Unit databases, or by telephone where outcomes were not otherwise available. The study outcomes were defined as ongoing viable pregnancy at 14 weeks gestation or miscarriage prior to 14 weeks. Miscarriage was defined as the finding of an intrauterine GS containing a fetal pole with no cardiac activity, the presence of heterogeneous, hyperechoic irregular tissues within the uterine cavity, or an empty uterus. Women were classified into two groups for analysis. Both groups had ultrasound measurements on at least two separate occasions showing live pregnancies. Group 1 was those where the pregnancy remained viable, while those in Group 2 had a subsequent miscarriage.

Statistical analysis

The CRL growth rate was calculated for each patient and the mean for all patients in each of the considered groups was then taken. Women with certain and uncertain dates were initially analysed separately and then compared, to determine the relevance of certain dates for the main FLDA.

FLDA was used to analyse the rate of change in CRL, MSD, the difference between MSD and CRL, the ratio of MSD to CRL and the rate of change of MYD (all as a function of gestational age), for their ability to predict miscarriage. Serial observations from each individual were modelled with a spline function (a curved line formed by two or more vertices), parameterized with a basis function multiplied by a five-dimensional coefficient vector. A training set was used to estimate the mean coefficient vector for each group. New patients were then classified by determining the group with the closest mean coefficient vector. The reader is referred

to the original FLDA description by James and Hastie (2001) for more detailed methodology.

To obtain accuracy, sensitivity and specificity on the performance of each growth variable in distinguishing Group 1 from Group 2 pregnancies, a leave-one-out (LOO) cross-validation strategy was applied. As the goal was to predict miscarriages, women with ultimately non-viable pregnancies (Group 2) were considered as the positive cases, while the ongoing viable pregnancies (Group 1) constituted the negative group. In each LOO iteration, one sample was removed; an FLDA model was built from the remaining $n - 1$ samples and tested on the left out sample. This was repeated n times with n equal to the number of samples in the data set.

The performance of FLDA was then compared with the performance of using cross-sectional data points alone for prediction of miscarriage. For this analysis, a CRL measurement of more than 2SD (Reljic, 2001) below expected from standardized growth curves (Robinson, 1973), at the time of first TVS confirming a live pregnancy, was classified as predictive of miscarriage and compared with the best performing FLDA variable.

Results

During the study period, the number of women with a singleton fetus and fetal heart beat on ultrasound examination, who did not undergo subsequent TOP, was 1281. Of these, 1078 underwent at least two scans. Of the 1078 women, 557 (51.7%) were excluded. Reasons for exclusion were diagnosis of miscarriage at the time of the second scan (47% of excluded women), unknown LMP (36%), gestational age outside the considered range (10%) or missing values for CRL (7%). Of the 521 included pregnancies, the most common indications for scan assessment were bleeding (36%), pain (34%), follow-up for an inconclusive scan (18%), previous miscarriage (14%) and confirmation of dates (13%), with some women reporting more than one indication. Mean gestational age at first assessment of CRL was 54.5 (range 35–86) days. CRL was measured on at least two occasions in all 521 pregnancies; MSD was measured on at least two occasions in 198; both CRL and MSD were measured in 172; and MYD was measured on two occasions in 74. For all the considered growth variables, the frequency of scans and the number of available measurements are set out in Table I. In Group 1, 336 of 493 (68.2%) women had certain dates, 149 of 493 (30.2%) had uncertain dates and 8 of 493 (1.6%) were IVF pregnancies. In Group 2, 24 of

28 (85.7%) had certain dates and 4 of 28 (14.3%) had uncertain dates. In total, 1240 cross-sectional measurements were available for the analysis, of which 1163 were from Group 1 and 77 from Group 2 pregnancies.

The mean number of scans per patient was 2.4 (range 2–9). For Group 1, there was no statistically significant difference in growth rate between patients with certain and uncertain dates (one-sample t -test, $P = 0.803$). The growth rate in Group 2 pregnancies with uncertain dates was lower compared with those with certain dates, but no conclusions can be made because there were only four non-viable pregnancies with uncertain dates. Based on these results, Group 1 pregnancies with certain and uncertain dates were grouped together, whereas only Group 2 pregnancies with certain dates were included for the analysis of the CRL growth rate.

CRL growth rate

The actual growth (change in CRL with increase in gestational age) for each individual Group 1 and Group 2 pregnancy is shown in Figs 1 and 2, respectively. For Group 1 (493 women), the mean was only considered reliable when there were at least 10 patients with a known slope for gestational age. For Group 2 pregnancies, the mean was considered when there was data for at least five patients, because this group contained only 28 women. The growth rate was significantly lower for Group 2 than Group 1 (one-sample t -test, $P = 2.638E-22$). This is illustrated in Fig. 3, showing the increase in CRL when the corresponding gestational age increases by 1 day for patients in each group.

Functional linear discriminant analysis

The results of the FLDA technique are too detailed for this report, but an example of the results for CRL data is shown in Fig. 4. When observing the CRL data from Group 1 and Group 2 (Figs 1 and 2), there is no obvious separation between the groups. However plotting the transformed curves after using FLDA to remove the 'random component' from each curve (Fig. 4a) shows a clear separation between the groups (Fig. 4b). Thus for each of the considered variables, a discriminatory boundary was found to predict the group to which a new curve (pregnancy) belonged.

Table I Number of scan measurements available for each patient in Group 1 (ongoing viable pregnancy) and Group 2 (subsequent miscarriage)

| | No. of scans | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Total |
|---|--------------|-----|-----|----|----|---|---|---|---|-------|
| Crown-rump length | Viable | 362 | 97 | 22 | 12 | 0 | 0 | 0 | 0 | 493 |
| | Non-viable | 17 | 7 | 2 | 1 | 0 | 0 | 0 | 1 | 28 |
| | Total | 379 | 104 | 24 | 13 | 0 | 0 | 0 | 1 | 521 |
| Mean gestation sac diameter | Viable | 115 | 33 | 11 | 2 | 0 | 0 | | | 161 |
| | Non-viable | 27 | 5 | 2 | 2 | 0 | 1 | | | 37 |
| | Total | 142 | 38 | 13 | 4 | 0 | 1 | | | 198 |
| Crown-rump length and mean gestation sac diameter | Viable | 104 | 29 | 11 | 1 | 0 | 0 | | | 145 |
| | Non-viable | 23 | 0 | 2 | 1 | 0 | 1 | | | 27 |
| | Total | 127 | 29 | 13 | 2 | 0 | 1 | | | 172 |
| Mean yolk sac diameter | Viable | 58 | 7 | 1 | | | | | | 66 |
| | Non-viable | 7 | 1 | 0 | | | | | | 8 |
| | Total | 65 | 8 | 1 | | | | | | 74 |

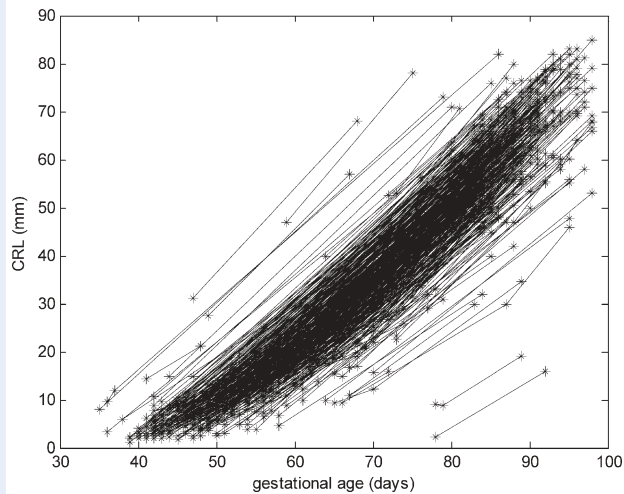


Figure 1 CRL growth curves for Group 1 (ongoing viable pregnancies). Each data point (*) represents a single CRL measurement (mm) at an estimated gestational age by LMP (days), with lines joining consecutive measurements for individual patients.

The number of true positives, false positives, true negatives, false negatives, the leave-one-out accuracy, sensitivity, specificity, positive predictive value and negative predictive value using FLDA for each variable or group of variables is shown in Table II.

The comparison between FLDA, using the best performing variable (rate of change in CRL), and a deviation of CRL of more than 2SD from expected based on the first scan only is also shown in Table II. The sensitivity of FLDA was 60.7% and the specificity was 93.1%, compared with a sensitivity of 53.6% and a specificity of 72.2% for the cross-sectional approach using the first scan only.

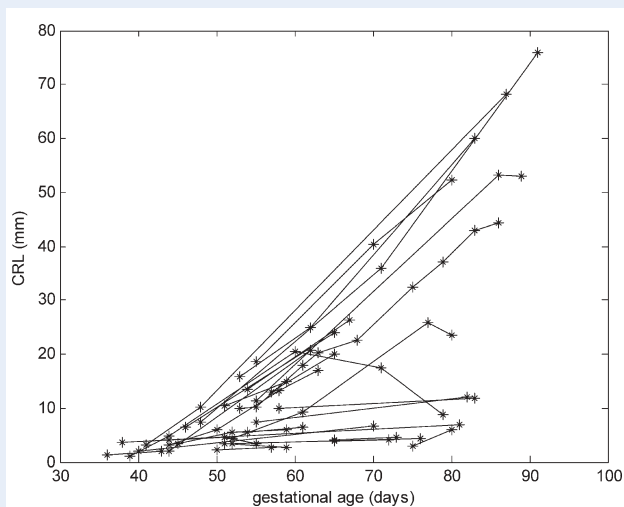


Figure 2 CRL growth curves for Group 2 (subsequent miscarriage). Each data point (*) represents a single CRL measurement (mm) at an estimated gestational age by LMP (days), with lines joining consecutive measurements for individual patients.

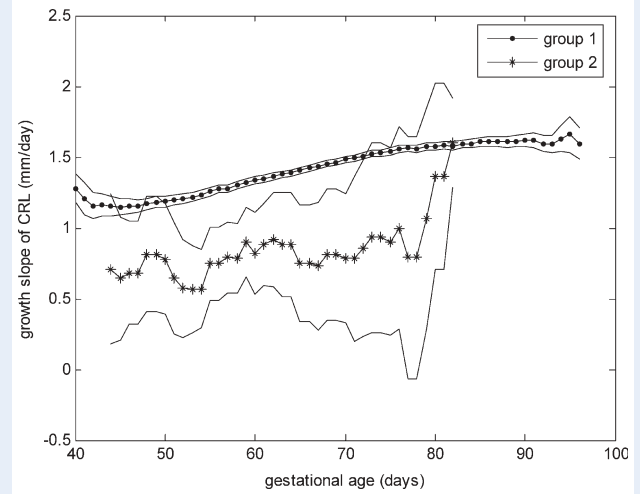


Figure 3 Rate of growth of CRL (mm per day) in all Group 1 (ongoing viable) pregnancies and in Group 2 (subsequent miscarriage) pregnancies with certain dates, with 95% confidence intervals.

Discussion

This study confirms that the first trimester growth rate of pregnancies destined to miscarry is significantly lower than in those that remain viable. It also shows that FLDA, using the rate of change of CRL with gestation, has the ability to differentiate normal from abnormal growth rates. In early pregnancy, this predicts over half of miscarriages in initially viable pregnancies, with high specificity. FLDA is also able to predict miscarriage with high specificity using the rate of change in MSD or MSD/CRL ratio. The rate of change of MSD – CRL difference and rate of change of MYD predict miscarriage very poorly.

The specificity of FLDA is considerably better than when using a single assessment of CRL (93.1% versus 72.2%). The sensitivity, though better than that for a single CRL assessment, is however still relatively poor. Inspection of Fig. 2 suggests that the low sensitivity may be because the pregnancies that are destined to miscarry fall broadly into two groups, one that is associated with antecedent growth restriction and another which is not. Thus, approximately half of the Group 2 pregnancies seem to have normal growth prior to miscarriage, limiting the sensitivity of the test.

With such a small number of Group 2 cases, it is not possible to define a specific cut-off growth rate beyond which a pregnancy can always be predicted to fail. If we assume linear growth, then the lowest growth rate at which a fetus remained viable was 0.36 mm/day. However, the measurements for this fetus were taken at 57 and 68 days (15 and 19 mm) and the possibility of observer error in measurement should always be considered. There is a lack of published evidence regarding inter-observer and intra-observer variability in early pregnancy measurement of fetal size, and therefore, it cannot be determined whether the results may have been influenced by such error. In addition, fetal growth is not in fact linear. Therefore, we do not feel that it is appropriate

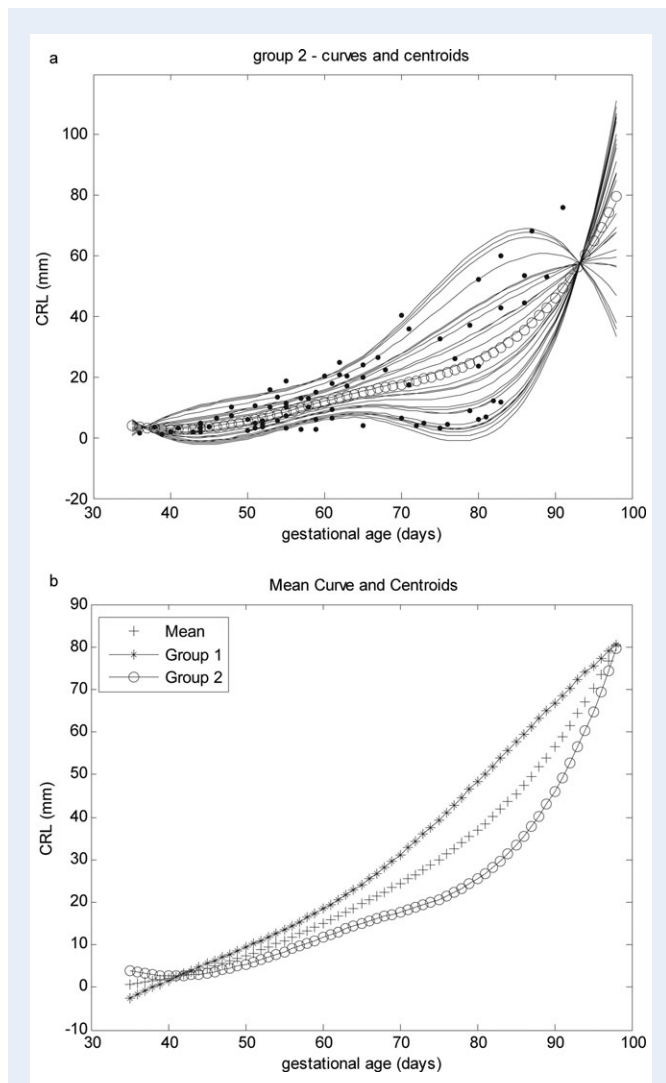


Figure 4 Illustrative examples of the FLDA technique.

Graphs of CRL measurements for 493 Group 1 and 28 Group 2 pregnancies after using the FLDA procedure to remove the random component from each curve. (a) Centroid and spline functions for Group 2 only. (b) Mean curve and centroids for Group 1 (*), and Group 2 (○), with discriminatory boundary (+).

to interpret this data to suggest an absolute growth rate at which a fetus will definitely not remain viable.

Although 70% of miscarriages are related to chromosomal abnormality (Fritz *et al.*, 2001), we cannot assume that the antecedent growth restriction shown in this study is only due to chromosomal abnormality because both chromosomally normal and abnormal pregnancies may exhibit slow growth (Bessho *et al.*, 1995). In our study, chromosomal analysis of the miscarried fetuses was not performed, due to the extensive use of expectant management of miscarriage in our unit and the reservation of cytogenetics for women with recurrent early pregnancy loss (Royal College of Obstetricians and Gynaecologists guideline, 2003). Maternal factors related to placental development are also likely to be relevant to early growth and this is supported by previous studies of placental histology at the time of miscarriage (Jauniaux and Burton, 2005).

This is the first study to report the application of FLDA to fetal growth and also the first study to report longitudinal growth analysis in early pregnancy. FLDA is better at identifying abnormal growth than conventional cross-sectional techniques. It does not rely on an accurate report of menstrual gestational age and is therefore appropriate for use in all women, including those with uncertain dates or irregular cycles. FLDA may have potential value in assessing growth in pregnancy in high-risk conditions such as recurrent miscarriage. It may also identify some pregnancies at risk of an adverse outcome in later pregnancy, in addition to those likely to miscarry. Such identification of poor growth as an early pregnancy marker of subsequent adverse outcome might potentially allow early interventions to women at risk.

Conclusion

FLDA is useful for the assessment of longitudinal fetal growth. It can be used to identify abnormal growth from the rate of change of measurements of CRL and MSD and can predict over half of the subsequent miscarriages before 14 weeks gestation with high specificity (up to 96.6%). FLDA predicts miscarriage better than using a single observation of CRL of more than 2SD below the expected mean.

Table II Performance of FLDA in predicting miscarriage using an leave-one-out (LOO) cross-validation method

| | True positives | False negatives | True negatives | False positives | Accuracy | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|-------------------|----------------|-----------------|----------------|-----------------|----------|-------------|-------------|---------------------------|---------------------------|
| CRL versus GA | 17 | 11 | 459 | 34 | 91.36 | 60.71 | 93.10 | 33.33 | 97.66 |
| MSD versus GA | 25 | 12 | 136 | 25 | 81.31 | 67.57 | 84.47 | 50.00 | 91.89 |
| MSD-CRL versus GA | 14 | 13 | 91 | 54 | 61.05 | 51.85 | 62.759 | 20.59 | 87.50 |
| MSD/CRL versus GA | 12 | 15 | 140 | 5 | 88.37 | 44.44 | 96.55 | 70.59 | 90.32 |
| MYD versus GA | 1 | 7 | 18 | 48 | 25.68 | 12.50 | 27.27 | 2.04 | 72.00 |
| First scan | 15 | 13 | 355 | 137 | 71.15 | 53.57 | 72.15 | 9.87 | 96.47 |

Variables tested are crown-rump length (CRL), mean gestation sac diameter (MSD), MSD – CRL difference, MSD/CRL ratio and mean yolk sac diameter (MYD), each as a function of gestational age. Comparison is made with the finding of greater than 2SD between observed CRL and expected CRL at first scan ('First scan'), to predict miscarriage.

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