A New Model for Early Prediction of Persistent Low-Lying Placenta

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Research Article

Keywords: low lying placenta, retrospective, anatomy, transvaginal ultrasound

Posted Date: April 30th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-432651/v1

Abstract

Objective

Finding a predictive model for persistent low lying placenta (LLP) based on early clinical and laboratory parameters.

Methods

This retrospective cohort study included patients with LLP detected during early anatomy scan. Additional transvaginal ultrasound exams assessed for resolution at 22–24 weeks and 36–39 weeks. Patients were categorized as: Group 1–LLP resolved by the second trimester scan, Group 2- LLP resolved by the third, and Group 3–LLP persisted to delivery. Clinical and laboratory parameters were compared between groups. A linear support vector machine classification was used to define a prediction model for persistence.

Results

Among 236 pregnancies with LLP, 80% resolved by 22–24 weeks, 10.5% resolved by 36–39 weeks and 9.5% persisted until delivery. Second trimester hCG levels were higher the longer the LLP persisted (0.8MoM + 0.7 vs. 1.13MoM + 0.4 vs. 1.7MoM + 1.5, P = 0.03, respectively) and Cervical length was shorter (P = 0.008, P = 0.02, respectively). A linear SVM classification model was calculated based on these parameters. The predictive accuracy of this model was 90.3%.

Conclusion

LLP persistence can be predicted with an accuracy of 90.3%, as early as the beginning of the second trimester. Persistence vs. resolution of LLP may represent different entities and not a spectrum of the same condition over time.

Introduction

The location of the placenta relative to the internal cervical os: previa, low-lying, or distant from the cervical canal, may be determined as early as the beginning of the second trimester, usually during the early anomaly scan. Low-lying placenta (LLP) is diagnosed when the inferior placental edge is within 2 cm of the internal cervical os but does not overlie it.[1–3] The management of pregnancies with LLP is based on data published regarding placenta previa. Information regarding the natural course, clinical and laboratory parameters and outcomes of isolated, LLP has not been published. LLP and placenta previa may be associated with antepartum hemorrhage and are indications for cesarean delivery if persistent

into the third trimester. However, these complications are also based on extrapolation from studies that investigated placenta previa and LLP as a single group.[1–5]

Moreover, data regarding differences between LLP that resolved early versus those that resolved later or persisted until delivery are lacking. In this study, we aimed to create a clinical model that would predict persistent LLP, based on clinical and laboratory parameters among pregnant women with LLP diagnosed at 13–16 weeks of gestation. We also aimed to assess whether resolution versus persistence of LLP is a spectrum of one clinical condition over time or two different entities with different clinical characteristics, complications and outcomes.

Material And Methods

This retrospective cohort study included all patients with a diagnosis of LLP detected during routine early ultrasound anatomy scan, performed at 13–16 weeks of gestation, at a tertiary academic institution, from 2010 through 2019. Patients were excluded if the pregnancy was terminated or ended in delivery or fetal loss before 24 weeks of gestation. Multiple pregnancies, pregnancies with placenta accrete or other placental anomalies and patients with prior uterine surgeries such as myomectomy or cesarean delivery were excluded, as well.

Placental location was evaluated using transvaginal ultrasound (TVS). After bladder emptying, a TVS probe (9 MHz GE Voluson E10, Milwaukee, WI) was inserted into the anterior vaginal fornix while the patient was lying in the dorsal lithotomy position. All measurements were performed by the same certified sonographer. The cervix was visualized in the sagittal plane. The distance between the placental edge and the internal os was measured. According to the American Institute of Ultrasound in Medicine (AIUM) standardized criteria[6] LLP was defined when this distance was 0 to 20 mm. Measurements collected before the AIUM classification was published, were categorized retrospectively according to these criteria.

Resolution of LLP was defined as > 20 mm in subsequent examinations. Follow-up TVS were performed to assess for resolution during second trimester anatomy scan at 21–24 weeks of gestation and before delivery at 36–39 weeks of gestation.

Patients were divided into three groups. Group 1 included those with resolution of LLP by the second trimester anatomy scan. Group 2 included patients with persistent LLP in the second trimester, but resolved in the third trimester and Group 3 were women with persistent LLP at delivery.

Data regarding demographics, obstetrical history, clinical and laboratory parameters during pregnancy, mode of delivery and perinatal complications were abstracted from electronic medical records.

The primary aim of the study was to determine early clinical predictive criteria for the persistence of LLP among all LLP diagnosed during the early anatomy scan. Secondary aims were to define the natural course of pregnancy among women with LLP and to compare demographics, mode of delivery, obstetrical history, and maternal and fetal outcomes among the three groups.

Data were analyzed using SPSS-25 (IBM Corp., Armonk, NY). Statistical significance between two groups was calculated using the Chi-square test or Fisher's exact test for differences in quantitative variables and t-test or Mann-Whitney for continuous variables, each when appropriate. $P < 0.05$ was set as the level of statistical difference.

For our predictive model, we used a linear support vector machine (SVM) classification. 5-fold Cross-Validation was used. MATLAB software was used.

The study was approved by the Meir medical center institutional ethics committee. "consent waiver" was obtained from the ethics committee. All the experiment protocol for involving humans was in accordance to guidelines of the institutional Helsinki committee.

Results

A total of 236 pregnancies with LLP detected at 13 to 16 weeks of gestation were included in this study. On subsequent sonographic examinations, 189 (80%) had resolved by 21–24 weeks of gestation, 25 (10.5%) by 36–39 weeks, and 22 (9.5%) cases persisted until delivery.

Women with persistent LLP (Group 3) were older than women in Group 2 and were older than women in Group 1 (34.9 ± 4.5 vs. 31 ± 3.9 vs. 30 ± 4.9 years, $P = 0.001$; Table 1). There were no significant differences in gravidity, parity or BMI among the groups. Second trimester hCG levels, taken as part of second trimester prenatal genetic screening, were higher the longer the LLP persisted (0.8 ± 0.7 vs. 1.13 ± 0.4 vs. 1.7 ± 1.5 MoM, $P = 0.03$). Other second trimester markers were within normal range, without significant differences between groups.

Table 1
Maternal characteristics

Characteristic	Low lying placenta			P-value
	1st trimester N = 189	2nd trimester N = 25	At delivery N = 22	
Age, years (mean ± SD)	30 ± 4.9	31 ± 3.9	34.9 ± 4.5	0.001
Gravidity (mean ± SD)	2.7 ± 1.6	2.9 ± 1.9	2.9 ± 1.6	0.6
Parity (mean ± SD)	2.1 ± 1.2	2.4 ± 1.6	2.5 ± 1.1	0.3
BMI (mean ± SD)	24.7 ± 5	20 ± 1.25	24 ± 5	0.052
Smoking	0	0	0	NA
2nd trimester hCG, MoM (mean ± SD)	0.8 ± 0.7	1.13 ± 0.4	1.7 ± 1.5	0.03
Gestational age at delivery, weeks (mean ± SD)	39 ± 1.3	38.5 ± 1.5	37.7 ± 1.8	0.001
Cervical length 1st anatomical screening, cm (mean ± SD)	4.3 ± 0.7	4.1 ± 0.5	3.6 ± 1	0.008
Cervical length 2nd anatomical screening, cm (mean ± SD)	4.4 ± 0.1	4.1 ± 1.2	3.8 ± 0.8	0.02
Cesarean section (%)	0	16%	37.5%	0.001
Blood loss, ml (mean ± SD)	274 ± 190	283 ± 132	356 ± 195	0.005
3rd stage duration, minutes (mean ± SD)	10.2 ± 5.7	9.5 ± 2.7	10 ± 6.8	0.7
Hemoglobin before labor, g/dl (mean ± SD)	11.7 ± 1.5	11.3 ± 3.3	10.5 ± 3.1	0.06
Hgb < 10 after delivery (%)	6.7%	9.7%	20%	0.04
Hospitalization, days (mean ± SD)	3.7 ± 1.1	3.9 ± 1	4.2 ± 2.5	0.2

Gestation was shorter the longer the LLP persisted (39 ± 1.3 vs. 38.5 ± 1.5 vs. 37.7 ± 1.8 weeks, P = 0.001).

Cervical lengths measured during both anomaly scans were shorter in Group 3 compared to Group 2 (4.3 ± 0.7 vs. 4.1 ± 0.5 mm, P = 0.008), and in Group 2 compared with Group 1 (4.1 ± 0.5 vs. 3.6 ± 1 mm, P = 0.02). Intrapartum maternal bleeding was significantly higher in the persistent LLP group, who delivered vaginally, as compared to Groups 1 and 2; Table 1).

Logistic regression of these two parameters was statistically significant (Table 2). Odds ratio (OR) for cervical length 0.14, 95%CI 0.052–0.38, P < 0.001 and hCG level OR 2.9, 95%CI 1.3–5.3, P < 0.001,). Receiver operating characteristics curve (Fig. 1) for the interaction of these two parameters was statistically significant (area under the curve of 0.681, P = 0.006).

Table 2
Logistic regression analysis

Variable	OR	95% CI	P-value
2nd trimester cervical length, mm	0.14	0.052–0.38	< 0.001
2nd trimester beta hCG, MOM	2.94	1.63–5.317	< 0.001

The rate of marked postpartum anemia, defined as postpartum Hb < 10 mg/dl, was significantly higher in Group 3 than in Groups 1 and 2 (20% vs. 9.7% vs. 6.7%, respectively, P = 0.04).

Neonatal complications are shown in Table 3. No significant differences were found between the groups regarding weight, Apgar scores or cord blood pH. No woman reported cigarette smoking while pregnant.

Table 3
Neonatal characteristics

Characteristic	Low lying placenta (N = 236)			P-value
	1st trimester n = 189	2nd trimester n = 25	At delivery n = 22	
Birth weight, g (mean ± SD)	3237 ± 462	3312 ± 412	3238 ± 454	0.7
1-min Apgar score ≤ 7 (%)	2.1%	0	4.8%	0.5
5-min Apgar score ≤ 7 (%)	0.5%	0	0	0.8
Umbilical cord pH ≤ 7 (%)	8.3%	0	0	0.7

Women with < 10 mm between the placental edge and the internal os (30% of Group 3) were delivered by elective cesarean section. The rate of cesarean section was 37.5% in the rest of Group 3—women with 10–20 mm between the placental edge and the internal os. The cesarean section rate was 16% in Group 2 and 37.5% in Group 3 (P = 0.001). The chance of having a cesarean section if LLP was diagnosed at 13–16 weeks of gestation was 9.3%. However, if it persisted to the second anatomy scan at 22–24 weeks, the chance of having a cesarean section was 46%.

After evaluating these results, we produced a model for predicting persistent LLP, detected at 13–16 weeks of gestation, based on cervical length at first anatomy scan and second trimester screening hCG level.

The data used for the model included 121 Group 1 and Group 2 patients and 23 Group 3 patients (we used data regarding only patients with both parameters). Each patient was represented by a point that was characterized by both cervical length at the first anatomy scan (x-axis) and the second trimester screening hCG (y-axis). The information is depicted in Fig. 2. A clear separation between Groups 1 and 2 to Group 3 is observed in this model.

Using this data classification, models can be produced by different classifiers. By using a linear support vector machine (SVM) classification, the prediction accuracy in our model was 90.3% (5-fold Cross-Validation was used). The classification surfaces of this model are visualized in Fig. 3.

Discussion

The current study describes the natural course of LLP diagnosed early in pregnancy and suggests a new model for predicting persistent cases. To the best of our knowledge, this is the first report regarding a cohort that includes only women with LLP. The executive summary of the joint Fetal Imaging Workshop recommended ultrasound evaluation at 16 weeks of gestation to rule out placenta previa. In cases of LLP, a follow-up ultrasound is recommended at 32 weeks of gestation [7]. The routine practice of fetal anomaly surveys in Israel includes early anomaly scan at 13–16 weeks of gestation and second trimester anomaly scan at 21–24 weeks. This provides a window of opportunity to investigate the clinical behavior and natural course of different types of placentation over a range of gestational ages, as described in this study.

According to our results, we can define phases of resolution that divide pregnancies with LLP into three categories, with different clinical characteristics. The small group of persistent LLP had unique characteristics compared to the other two groups. These included significantly older maternal age, earlier gestational age at delivery, higher second trimester hCG levels, shorter cervical lengths measured during first and second trimester anatomy scans and higher rate of peripartum complications. The combination of these findings defines persistent LLP pregnancies as high-risk pregnancies in contrast to cases of LLP that resolve during pregnancy.

Therefore, the challenge of managing early diagnosis of LLP is to detect the cases that will persist until delivery, early. To meet this challenge, we present a novel predictive model for persistent LLP that uses two statistically significant clinical parameters—early second trimester cervical length and second trimester hCG. By utilizing this linear SVM classification, the predictive accuracy of the model was 90.3% (5-fold Cross-Validation was used. The parameters of cervical length and beta hCG measurements used in this model are easily detected as part of routine pregnancy follow-up.

The clinical implications of this novel model enable us to detect a high-risk population of women with persistent low-lying placenta as early as the first anatomy scan and the second trimester hCG level evaluation. Early detection will improve the follow-up and management of these women and will reduce stress and uncertainty among all women with LLP.

Regarding the natural course of LLP detected early in pregnancy, we found that most cases resolved by 21–24 weeks of gestation. About half of the persistent cases resolved in the third trimester and only 9.5% persisted until delivery.

Previous studies reported that placenta previa diagnosed in the mid-trimester resolved in 66–98% of cases and the resolution is more likely with LLP [4,8]. The process of resolution is termed migration. There are various hypotheses considering the etiology of migration. One of these is trophotropism, the process of atrophy of thin placental margins due to a poor vascular supply in the lower uterine segment [1,9]. Another theory is dynamic placentation, in which it is hypothesized that the anterior uterine wall expands more than the posterior wall. This can relate to possibly higher migration rate of anterior placentas because the lower uterine segment will lengthen due to elongation and hypertrophy during pregnancy, causing the uterus to enlarge on the anterior side[1]. The migration process might explain our results. In cases of migration failure, LLP will persist.

Earlier studies that tried to approach this subject were heterogenous and included cases of LLP and complete placenta previa in the same study group[1–4, 8,10]. Durst et al. reported 91.9% resolution of LLP or placenta previa among 1,663 pregnant women at the mid-trimester anatomy survey.[1] The median time to resolution was 10 weeks. The probability of resolution was inversely proportional to the distance from the internal os. However, this finding is limited because the distance of the placenta from the internal cervical os was known in only 51% of women. Our findings in the selected population with LLP are consistent with these results.

Alouini et al.[2] found that complete placenta previa and most placentas less than 1 cm from the internal cervical os did not migrate. Most cases with placentas located more than 1 cm away, migrated three to four weeks later. They used 1 cm from internal cervical os as a cutoff value.

The trend toward shorter cervix and earlier delivery in Group 3 may reflect negative effects of persistent LLP on the cervix. This might be explained by abnormal vascular changes due to the lower placentation.

Pathological placentation is a term used to describe an abnormal location of the placenta, abnormal invasion of the placenta into the uterine wall, or both[11]. Increased levels of biological markers, such as hCG in maternal serum are thought to result from early placental vascular damage and possibly be due to their greater absorption into maternal blood flow [11]. Berezowsky et al. found that second trimester hCG levels were significantly higher among cases of pathological placentation, such as those in the spectrum of placenta previa and placenta accreta[12]. Interestingly, we found higher levels of hCG the longer the LLP persisted. This can be due to abnormal placentation and is used as a marker in our suggested model.

Peripartum maternal bleeding is another well-known complication of low placentation. Our results revealed that persistent LLP is a risk-factor for heavier bleeding and lower postpartum hemoglobin levels. Therefore, labor involving persistent LLP should be managed carefully, blood products should be appropriately prepared and careful intra- and postpartum clinical surveillance should be performed.

The main limitation of the current study lies in its retrospective design. Nevertheless, it has several important strengths. First, all data were collected from a single center with uniform management protocols and all measurements were performed by the same sonographer. Moreover, the relatively large sample of patients with LLP without placenta previa is unique.

In conclusion, a new model for detecting persistent LLP is presented in this study. Most cases of LLP diagnosed at early anomaly scan resolve before delivery. Persistence versus resolution of LLP may represent two different clinical entities and not a resolution spectrum of the same clinical condition. The longer the persistence, the less likely it will resolve. Those who persisted until delivery were associated with unique clinical characteristics including shorter cervical length, high second trimester hCG level and maternal complications, which partially may be explained by a different pathophysiology of the placentation process. These characteristics can be recognized as soon as the low placentation is diagnosed and may serve as a predictive factor for non-resolution, with an accuracy of 90%, as seen in the predictive model. This can increase physician awareness regarding the need for closer surveillance. These findings are very important for obstetricians managing LLP during pregnancy and in the delivery room and while consulting with patients and making shared decisions throughout the pregnancy.

Declarations

Ethics approval and consent to participate: The study was approved by the 'Meir medical center' affiliated to Tel-Aviv university institutional ethics committee. "Consent waiver" was also obtained from the ethics committee of Meir medical center affiliated to Tel-Aviv university.

Consent for publication: not applicable.

Availability of data and materials: The data that support the findings of this study are available on request from the corresponding author.

Authors' contributions: S.F.G, T.B.S, O.M- Conception or design of the work, Data analysis and interpretation, writing and editing; H.G, M.S.W, H.S, G.S.M, O.W- data collection. All authors approved the final version of the article.

Acknowledgements: not applicable.

Conflict of interest: None to declare

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Figures

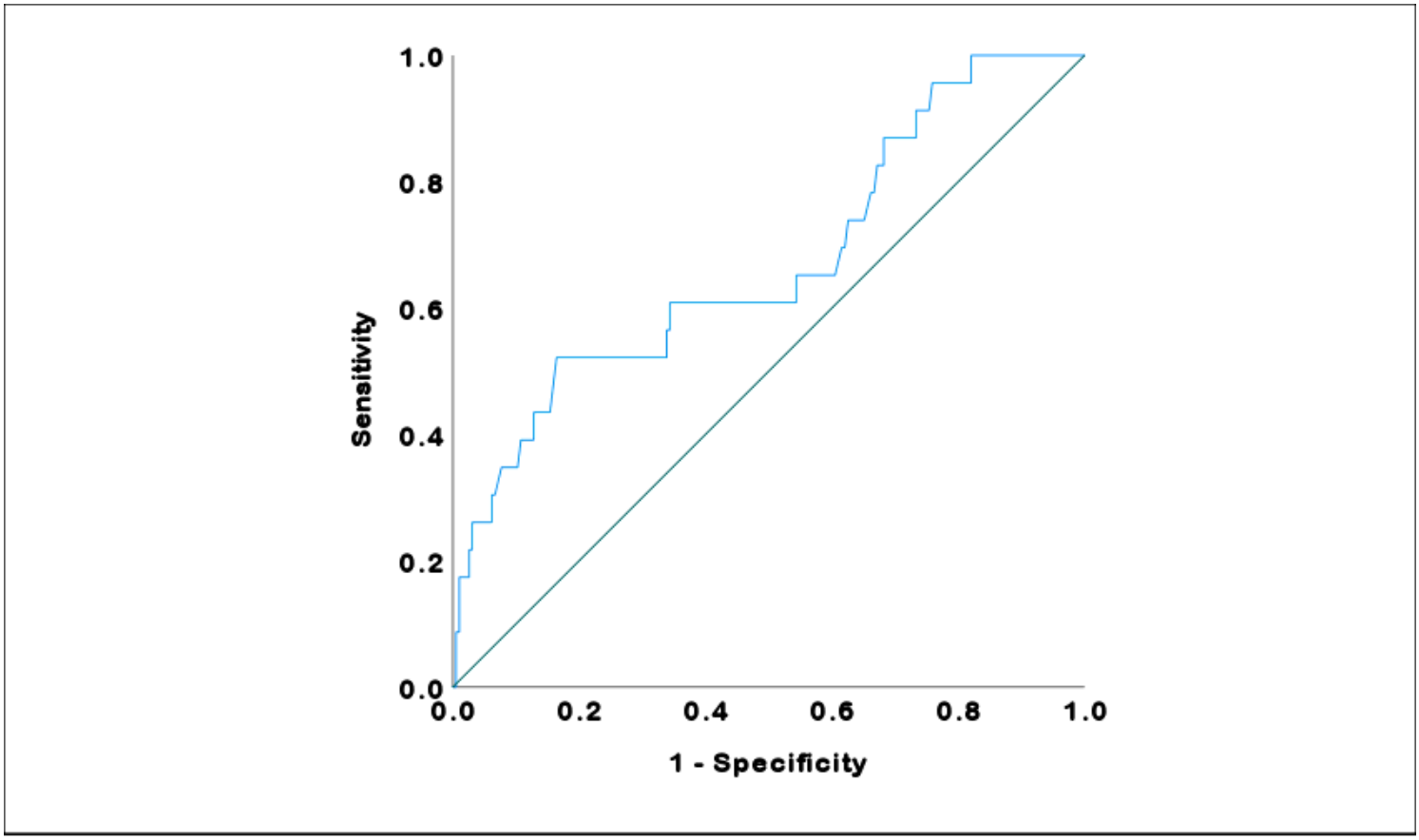

Figure 1

Receiver operating characteristics curve of the interaction between early second trimester cervical length and second trimester hCG level

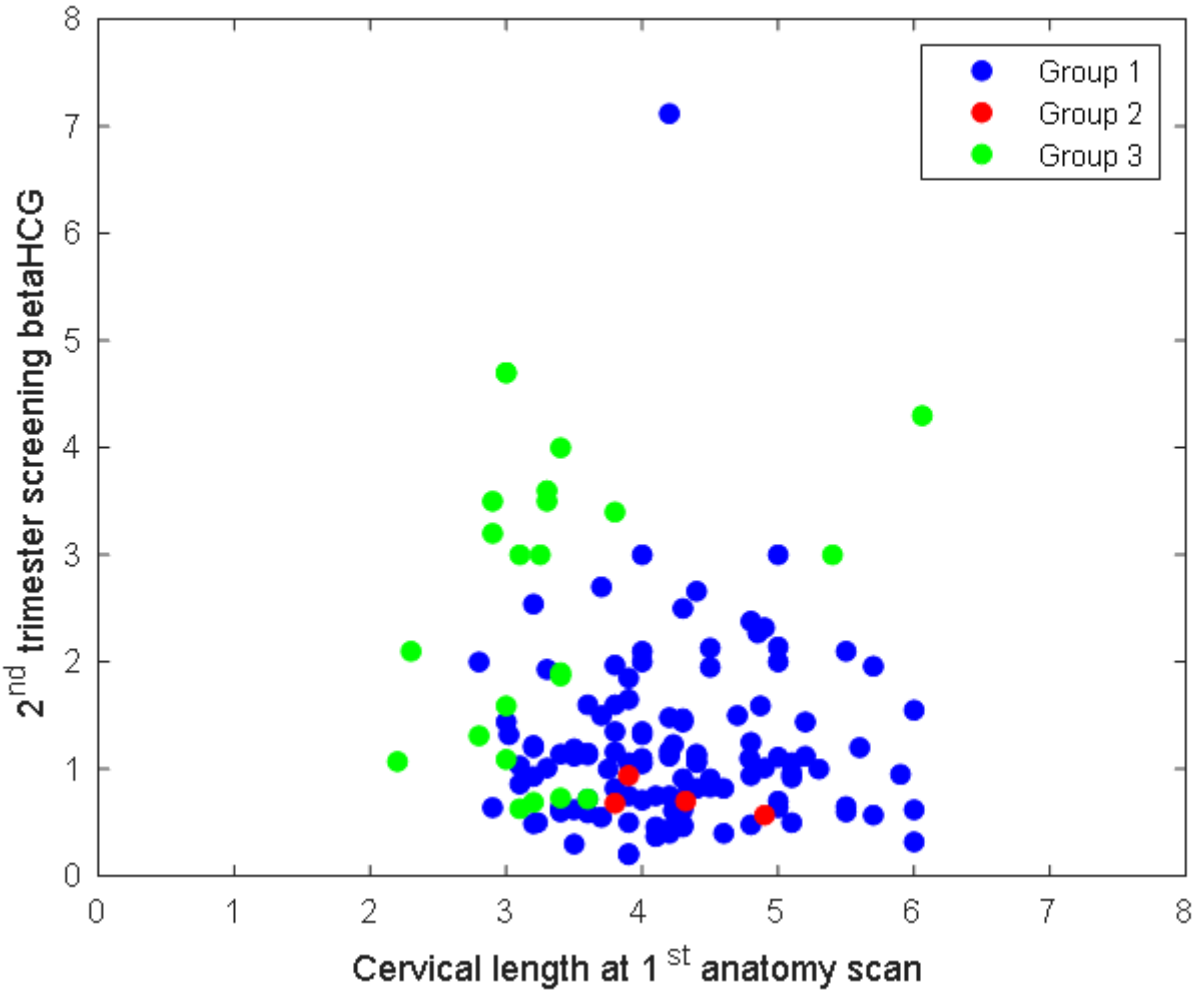

Figure 2

Visual representation of the data. Each point corresponds to a woman in Group 1, 2 or 3 and is characterized by the cervical length at the first anatomy scan and the second trimester screening hCG. Groups 1 and 2 are clearly delineated from Group 3.

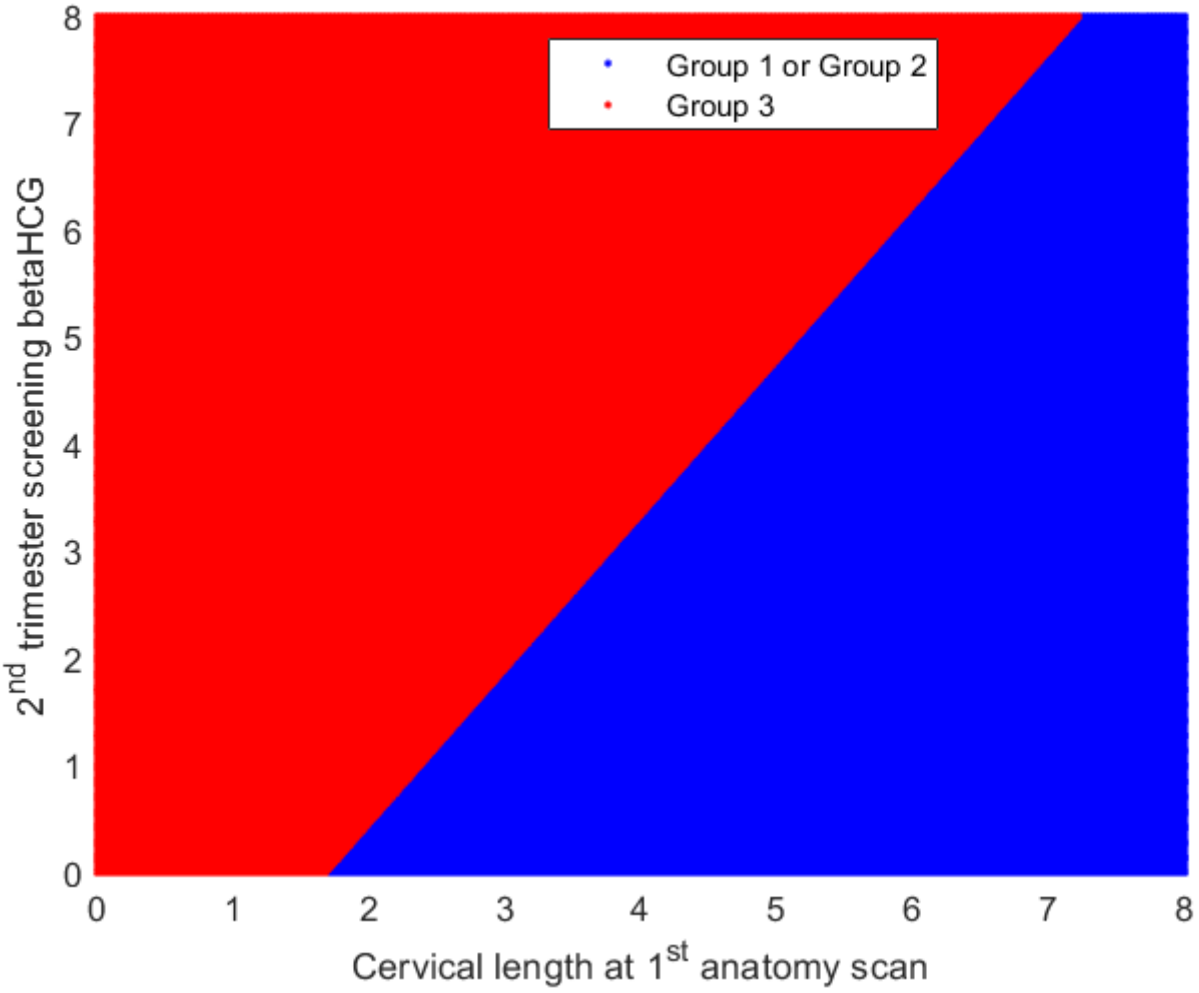

Figure 3

Visualization of classification surfaces obtained by a Linear SVM model