The role of three-dimensional power Doppler ultrasound in diagnosis of abnormally invasive placenta

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Abstract: Background: The diagnosis of morbidly adherent placenta involves a number of different ultrasound variables, some qualitative and others that have been quantified. **Aim of the work:** to investigate whether ultrasound marker of largest area of confluent three-dimensional power Doppler signal (Acon) can accurately predict both the presence and severity of abnormally invasive placenta. **Patients and methods:** Fifty pregnant women were included (25 suspected of placental invasion (study group) and 25 not suspected of placental invasion (control group)). All patients included in the study were subjected to careful history taking, clinical and obstetrical examination and ultrasound examination (Gray-scale ultrasound, Three-dimensional power Doppler ultrasound). A series of 2D slices was used to establish the 3D volume. The presence and severity of abnormally invasive placentation were assessed at delivery according to clinical grading system. **Results:** There was statistically significant increase of loss of reteroplacental clear zone, intraplacental lacunae, disruption of uterine bladder serosal interface and small myometrial thickness in study when compared to control groups. Area of confluence (Acon), there was statistically significant increase in study when compared to control group (46.16±12.68 vs 29.72±8.94 respectively). There was positive correlation between Acon with age, parity and severity of placental invasion, and inverse correlation with Apgar score at first minute. Acon had a good predictive power (area under the curve was 0.995); and at cutoff value of 31.5; the sensitivity was 100.0% and specificity was 99.5%. **Conclusion:** The marker Acon provides a quantitative measure for diagnosis of abnormally invasive placenta and can be used in assessment of the condition severity. However, it is not recommended to use it as a sole diagnostic tool for placental invasion until it is validated in future large scale studies.

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1. Introduction

Placental development is a major cause of successful pregnancy, and in the presence of placental dysfunction, there is a higher risk of pregnancy complications **(Farina, 2014).** Women with invasive placentation including placenta increta (PI) and placenta percreta (PP) are at high risk of obstetric hemorrhage; however, the severity of hemorrhage and perioperative morbidity may differ according to the degree of placental invasion **(Brookfield et al., 2014).** Unfortunately, the rates of previa and accrete are increasing, probably as a result of increasing rates of cesarean delivery, maternal age, and assisted reproductive technology **(Silver, 2015).**

Antenatal diagnosis of placental invasion has the potential to improve maternal and fetal outcomes **(Warshak et al., 2010).** Predelivery knowledge of morbidly adherent placenta allows for multidisciplinary planning and delivery before the onset of labor and/or vaginal bleeding **(Rac et al., 2015).**

Sonography with gray-scale and color Doppler imaging is the recommended first line modality for diagnosing morbidly adherent placenta **(Society for Maternal-Fetal Medicine, 2010; American College of Obstetricians and Gynecologists, 2012).** In addition, more elaborate forms of imaging are promising in defining the topography of the placenta, such as 3-dimensional Doppler and volume contrast ultrasound. However, validation studies are lacking as well as generalized applicability of technique **(Cali et al., 2013).**

In fact, use of 3-D ultrasound in obstetrics has undergone dramatic development over the past 20 years. Since the first publications on this application in clinical practice, several 3-D ultrasound techniques and rendering modes have been proposed and applied. Furthermore, angiographic patterns of fetal organs and the placenta have been assessed using 3-D power Doppler ultrasound quantification **(Tonni et al., 2015).** Three-dimensional power Doppler ultrasonography provides a quantitative means for

diagnosing abnormally invasive placenta and assessing severity.

The present study was designed to investigate whether ultrasound marker of largest area of confluent three-dimensional power Doppler signal (Acon) can accurately predict both the presence and severity of abnormally invasive placenta.

2. Patients and methods

The present study is a case control study. It was conducted at Al-Azhar University Hospital (Dameitta) after obtaining informed consent from the studied women. It included a total of 50 pregnant women (25 pregnant women suspected of placental invasion (study group) and 25 pregnant women not suspected of placental invasion (control group)). They were selected according to the following criteria: pregnancy more than 20 weeks, high risk women for placental invasion (Placenta previa, Prior uterine scar of CS myomectomy, Grand multiparity). Cases with multiple gestations were excluded from the study.

All patients included in the study were subjected to: Careful history taking, thorough clinical and obstetrical examination (General examination including vital signs as pulse, temperature, blood pressure, pallor, cardiac examination with the presence of thrills or murmurs, limb clubbing, abdominal examination including ascites, and presence of scars of previous operation, and Local examination including inspection of external genitalia), and ultrasound examination (Gray-scale ultrasound, Three-dimensional power Doppler ultrasound: using Voluson 730 Pro V). All scans performed for all subjects in the supine position with sufficient bladder volume. Pregnancy and delivery data were collected from antenatal records, operative and delivery notes, and postpartum records. Three-D ultrasound: The transabdominal transducer was used. A series of 2D slices was used to establish the 3D volume. Ultrasound was done using the GE voluson 730 Pro V real-time machine with a 5–2-MHz transducer. All 3D ultrasound was performed with a S-VDW 5-8 B probe of the same machine which is an electronic sector transducer with frequency range of 5-8 MHZ. The presence and severity of abnormally invasive placentation were assessed according to scale of **Collins et al. (2015)** at delivery according to clinical grading system and from histopathology results in which hysterectomy was performed. Three dimensional Doppler studies was done as described by **Collins et al. (2015).**

Statistical analysis:

The collected data were statistically analyzed using statistical package for social sciences (SPSS Inc., USA) version 22. Quantitative data were expressed as mean and standard deviation, minimum and maximum; while categorical variables were presented as relative frequency (number) and percent distribution. For comparison between two means, student (t) test was used; while chi square (X^2) was used for comparison between categorical variables. Pearson's correlation coefficient (r) was calculated for correlation between two variables (it was mile if $r < 0.3$; powerful if $r > 0.7$; and moderate if r extended from 0.3 to 0.7). Receiver operation curve was constructed to determine sensitivity and specificity of Acon in diagnosis of placental invasion. P value < 0.05 was used as a measure of significance for interpretation of results.

3. Results

In the present work, female's age ranged from 23 to 33 years with a mean of 27.24±2.23 years; and there was no statistically significant difference between study and control groups (27.48±2.66 vs 27.00±1.73 respectively). Examination of female revealed that, 8 females (16.0%) were Primipara; 19 females (38.0%) were para 1; 14 females (28.0%) were para 2 and 9 females (18.0%) were Para 3 or more. There was statistically significant increase of females para 3 or more in study group when compared to control group (36.0% vs 0.0% respectively; i.e., there is increased parity in study when compared to control group). Previous cesarean delivery was reported in 88.0% of females in study group compared to 12% of females in the control group; with statistically significant increase of prior CS in study when compared to control group. Gestational age at delivery ranged from 32 to 38 weeks of gestation with the mean of 35.56±1.65 weeks; and there was statistically significant decrease of gestational age at delivery in study group when compared to control group (34.16±0.89 vs 36.96±0.84 weeks respectively). Anterior placentation was reported in 44% of study group compared to 12% of the control group with statistically significant increase of anterior placentation in study when compared to control group. Hysterectomy in the present work was done for 36% of females in study group, compared to 4% of the control group; with statistically significant increase of hysterectomy in study when compared to control group. For ICU admission, 2 females (8.0%) in study group were admitted to ICU; compared to one female (4.0%) in the control group; and there was no statistically significant difference between study and control groups (Table 1).

As regard to grade of placental invasion; it was grade 1 (absent) in 16 (32.0%); grade 2 (absent) in 6 (12.0%); grade 3 in 6 (12.0%); grade 4 in 9 (18.0%); grade 5 in 9 (18.0%) and grade 6 in 4 (8.0%); and there was statistically significant increase of higher grades of invasion in study when compared to control group. As regard to birth weight, it ranged from 2350

to 3210 g with a mean of 2818.70±229.80 g; and there was statistically significant decrease of birth weight in study when compared to control group (2647.20±164.70 vs 2990.20±139.33 g respectively). Apgar score at the first minute ranged from 5 to 9 with a mean of 7.90±1.07; and there was statistically significant decrease of Apgar score at first minute in study group when compared to control group (7.28±0.97 vs 8.52±0.77 respectively). In addition, there was statistically significant decrease of Apgar score at fifth minute in study group when compared to control group (8.56±0.58 vs 8.92±0.40 respectively) (table 3). As regard to ultrasound findings, there was statistically significant increase of loss of reteroplacental clear zone, intraplacental lacunae, disruption of uterine bladder serosal interface and small myometrial thickness in study when compared to control groups (table 3). As regard to area of confluence (Acon), it ranged from 22 to 64 with a mean of 37.94±13.67 cm2 and there was statistically significant increase in study when compared to control group (46.16±12.68 vs 29.72±8.94 respectively) (table 4). As regard to correlation, there was positive (proportional), moderate correlation between A con with age; and the correlation between Acon and parity was proportional, powerful and statistically significant. On the other hand, there was inverse (negative), mild and statistically significant correlation between Apgar score at first and Acon. Finally, there was powerful, proportional correlation between Acon and severity of placental invasion (table 5). Running Receiver operation curve for estimation of the predictive power of Acon in diagnosis of placental invasion regardless the degree of invasion, we found that the test had a good predictive power (area under the curve was 0.995); and at cutoff value of 31.5; the sensitivity was 100.0% and specificity was 99.5% (figure 1).

A representative cases study was illustrated in figures (2, 3). It was for 27years old from Om-Elreda-Damietta; P2+1 pregnant, previous 2 c.s with placenta previa centeralis with focal accretion; in surgical theatre gestational age 34 weeks with mild attack of antepartum hemorrhage; she had had general anesthesia -supine position opening abdominal wall in layers (skin-subcutaneous fat-rectus sheath-rectus muscle spliting-abdominal peritoneum - upper segment uterine incision). Then, delivery of the fetus, delivery of the placenta, transverse B-lynch suture; closure of abdominal wall in layers. Power Doppler examination revealed increased A_{con} with mild placental invasion (grade 3). Ultrasound examination revealed the following data: Placenta previa centralis; obliteration of retro placental clear space; appearance of placental lacunae; moth eaten appearance of the placenta; interruption of the posterior uterine serosa bladder interface; localized wall thickening of the adjacent urinary bladder wall with increased vascularity. By 3D power DOPPLER, there was disruption of retro placental sonolucent zone with abnormal placental lacunae; numerous vessels invading the uterine serosa bladder interface; and numerous vessels within the adjacent wall of the urinary bladder. Another case illuration was presented in figures (3,4). It was for A 33 years old from Elshoaraa-Damietta; P2+0 pregnant, previous 2 c.s with placenta previa marginalis with focal accretion; in surgical theatre gestational age 34 weeks with mild attack of antepartum hemorrhage; she had had general anesthesia -supine position opening abdominal wall in layers (skin-subcutaneous fat-rectus sheath - rectus muscle splitting-abdominal peritoneum - upper segment uterine incision); then, delivery of the fetus; caesarean hysterectomy. Finally, closure of abdominal wall was done in layers. Power Doppler examination showed Acon of 57cm^2; and histopathological examination confirmed the results. Ultrasound examination revealed oblitration of retro placental clear space; appearance of placental lacunae. By 3D power Doppler, there was disruption of retro placental sonolucent zone with abnormal placental lacunae.

Table (1): Comparison between study and control groups as patient characteristic and examination

Variable		Study group	Control group	Total	Test	P value
Age (mean±SD)		27.48±2.66	27.0±1.73	27.24±2.23	0.76	0.45
Parity (n,%)	Primipara	3(12.0%)	5(20.0%)	8(16.0%)	11.10	0.011*
	P1	7(28.0%)	12(48.0%)	19(38.0%)		
	P2	6(24.0%)	8(32.0%)	14(28.0%)		
	P3 or more	9(36.0%)	0(0.0%)	9(18.0%)		
Previous CS		22(88.0%)	3(12.0%)	27(54.0%)	28.88	<0.001*
Gestational age at delivery		34.16±0.89	36.96±0.84	35.56±1.65	11.38	<0.001*
Anterior placentation		11(44.0%)	3(12.0%)	14(28.0%)	6.34	0.012*
Hysterectomy		9(36.0%)	1(4.0%)	10(20.0%)	8.0	0.005*
Need for ICU admission		2(8.0%)	1(4.0%)	3(6.0%)	0.35	0.55(ns)

Table (2): Comparison between study and control groups as regard to neonatal outcome

Variable	Study group	Control group	Total	Test	P value
Birth weight	2647.20±164.70	2990.20±139.33	2818.70±229.80	7.94	< 0.001*
Apgar first minute	7.28±0.97	8.52±0.77	7.90±1.07	4.97	<0.001*
Apgar fifth minute	8.56±0.58	8.92±0.40	8.74±0.52	2.55	0.014*

Table (3): Comparison between study and control groups as regard to ultrasound findings

		Study		Control		Total		Test	P value
		n.	%	n.	%	n.	%		
Loss of retro placental clear zone	Yes	12	48.0%	5	20.0%	17	34.0%	4.36	0.037*
	No	13	52.0%	20	80.0%	33	66.0%		
Intraplacental Lacunae	Yes	21	84.0%	9	36.0%	30	60.0%	12.0	0.001*
	No	4	16.0%	16	64.0%	20	40.0%		
Disruption of uterine- bladder serosal interface	Yes	21	84.0%	7	28.0%	28	56.0%	15.90	<0.001*
	No	4	16.0%	18	72.0%	22	44.0%		
Small myometrial Thickness	Yes	21	84.0%	8	32.0%	29	58.0%	13.87	<0.001*
	No	4	16.0%	17	68.0%	21	42.0%		

Table (4): Comparison between study and control groups as regard to Acon

		Mean	SD	Minimum	Maximum	t	p
Acon	Study	46.16	12.68	22.00	64.00	5.29	<0.001*
	Control	29.72	8.94	22.00	59.00		
	Total	37.94	13.67	22.00	64.00		

Table (5): Correlation between Acon and other variables in study group

	Acon	
	r	p
Age	0.509	0.009*
Parity	0.749	<0.001*
GA delivery	-0.032	0.88(ns)
Birth weight	0.099	0.63(ns)
Apgar first	-0.688	<0.001*
Apgar fifth	-0.418	0.038*
Severity of invasion	0.97	<0.001*

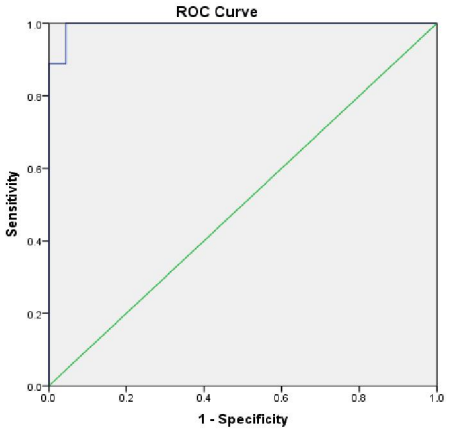

Figure (1): ROC for sensitivity and specificity of Acon in diagnosis of placental invasion regardless the degree of invasion

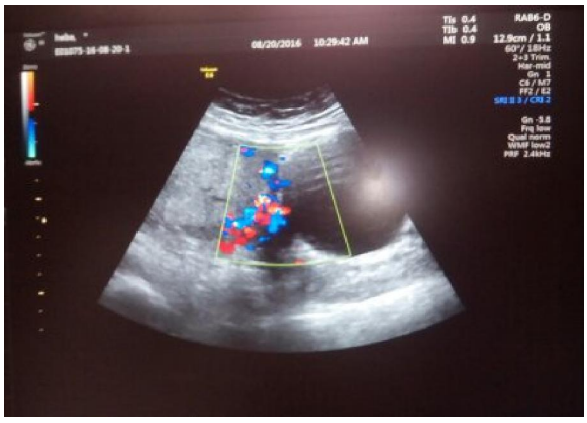

Figure (2): Numerous vessels invading the uterine serosa bladder interface

Figure (3): disruption of retro placental sonolucent zone with abnormal placental lacunae

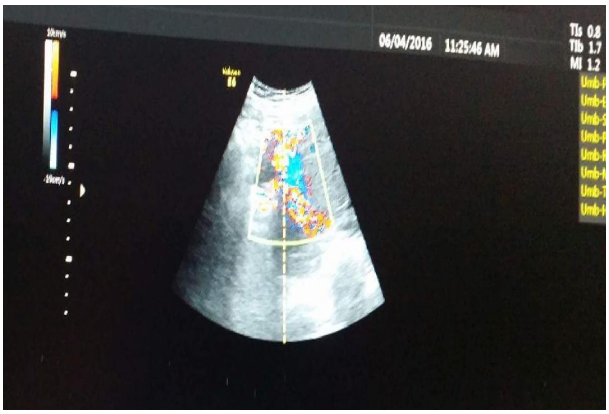

Figure (4): Numerous vessels invading the uterine serosa bladder interface

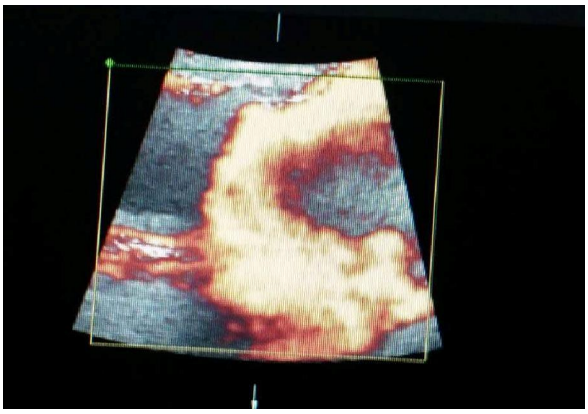

Figure (5): disruption of retro placental sonolucent zone with abnormal placental lacunae

4. Discussion

The present study was designed to investigate the ultrasound marker of largest area of confluent three-dimensional power Doppler signal (Acon) can accurately predict both the presence and severity of abnormally invasive placenta. It included 25 females with higher risk factors for placental invasion as a study group and another 25 females with low or no risk for placental invasion as a control group.

In the present work, female's age ranged from 23 to 33 years with a mean of 27.24±2.23 years; and there was no statistically significant difference between study and control groups (27.48±2.66 vs 27.00±1.73 respectively). These results are in agreement with **Rac et al. (2015)** who reported that, there were no differences in age between pregnancies with and without histologic evidence of placental invasion. On the other hand, these results are in contradiction to those reported by **Eshkoli et al. (2013)** who reported that, females with placenta accreta were significantly older than those without placenta accreta. This may be due to small sample size of the present work when compared to their work as they reviewed sheets of more than 34000 females.

As regard to previous cesarean delivery, it was reported in 88% of females in study group compared to 12% of females in the control group; with statistically significant increase of prior CS in study when compared to control group. These results are in agreement with previous studies reported that, the increase in placenta accreta in recent years is attributed to the increase in the prevalence of known risk factors, particularly the increased number of caesarean deliveries (CD) **(Orbach et al., 2011).** In addition, **Rac et al. (2015)** reported that, the number of prior cesarean deliveries was significantly associated with risk for placental invasion.

The most common and established risk factor for development of placenta accreta is a previous CD. This is emphasized even more so in cases of placenta previa after a prior CD **(Esh-Broder et al., 2011).** Increasing numbers of prior CD exponentially increase the risk of placenta accreta **(Silver et al., 2006).**

As regard to anterior placentation, it was reported in 44% of study group compared to 12% of the control group with statistically significant increase of anterior placentation in study when compared to control group. These results are comparable to those reported by **Rac et al. (2015)** who reported that, anterior placentation was significantly associated with placental invasion, $P < 0.05$.

In addition, it had been reported that, placenta previa and previous uterine surgery, such as caesarean section, represent the most commonly reported risk factors associated with invasive placentation. In particular, the finding that most of the invasive placentas are implanted on the area of the previous uterine scar poses particular relevance on the role of a previous uterine surgery in determining this condition in women with placenta previa **(D'Antonio and Bhide, 2014).** The risk of invasive placentation seems to be related also to the number of caesarean sections; in a meta-analysis assessing the role of multiple caesarean deliveries on maternal morbidity, **Marshall et al. (2011)** found that the likelihood of invasive placentation in women with placenta previa progressively increases as the number of previous caesarean section increases, with an odd ratio of 29.8 in women who have undergone caesarean delivery.

In the present work, gestational age at delivery was significantly younger in study when compared to control group (34.16±0.89 vs 36.96±0.84 weeks respectively). Hysterectomy was done for 36% of females in study group, compared to 4% of the control group; with statistically significant increase of hysterectomy in study group. Also, birth weight ranged from 2350 to 3210 g and there was statistically significant decrease of birth weight in study when compared to control group (2647.20±164.70 vs 2990.20±139.33 g respectively). Furthermore, Apgar score at the first minute ranged from 5 to 9 with a mean of 7.90±1.07; and there was statistically significant decrease of Apgar score at first minute in study group when compared to control group (7.28±0.97 vs 8.52±0.77 respectively). In addition, there was statistically significant decrease of Apgar score at fifth minute in study group when compared to control group (8.56±0.58 vs 8.92±0.40 respectively). These results reflected the unfavorable outcome in cases with placental invasion. These results are comparable to those reported by **Eshkoli et al. (2013)** who reported that, placenta accreta was significantly associated with several adverse pregnancy outcomes, such as second-trimester vaginal bleeding, peri-partum hysterectomy, uterine rupture, postpartum hemorrhage, maternal blood transfusion, fever morbidity, and wound infection, as well as intensive care unit admissions and total hospitalization days. They added, neonates born after a pregnancy complicated with placenta accreta had significantly lower birthweights. However, the low Apgar scores (<7) after 1 and 5 minutes did not differ between the groups. Results regarding Apgar score are inconsistent with that of the present study.

Results of the present work are consistent with previous studies showing that pregnancies complicated with placenta accreta are prone to adverse outcomes, such as massive blood loss at delivery and peripartum hysterectomy **(Garmi and Salim, 2012).**

In a retrospective multicenter study by **Sentilhes et al. (2010)** included women with a history of conservative management for placenta accreta. Of the 27 women who desired farther fertility, 24 (88.9%) women had had 34 pregnancies (21 third-trimester deliveries, 1 ectopic pregnancy, 2 elective abortions, and 10 miscarriages). All 21 deliveries had resulted in healthy neonates born >34 weeks of gestation. Placenta accreta recurred in 28.6% (6 of 21 cases) and was associated with placenta previa in 4 cases. Postpartum hemorrhage occurred in 4 cases (19.0%). This study agreed with our work as regard to favorable neonatal outcome.

In the present study, the most common ultrasound features in predicting placenta accreta were the presence of a smallest myometrial thickness less than 1 mm (sensitivity 96.3%), disruption of urinary bladder–uterine interface (96.3%) and the presence of multiple placental sonolucent area (100.0%). These results are in concordance with the study done by **Twickler et al. (2000)** that reported that the presence of SMT <1 mm or large intraplacental lucencies using color Doppler was present in all cases of myometrial invasion with 100% sensitivity, 72% specificity.

This agrees also with a study done by **Japaraj et al. (2007)** that reported the main ultrasound finding was the presence of multiple placental lakes which was seen in 6 out of 7 patients confirmed of having placenta accreta. However, myometrium thinning or focal disruption of uterine serosa was detected in only 4 out of 7 cases of placenta accreta.

According to **Japaraj et al. (2007)** ultrasound examination had 85% and 100% sensitivity and specificity, respectively in the diagnosis of placenta accreta. This specificity is lower than that of the present work.

In addition, **Hamisa et al. (2015)** study revealed that, thinning of myometrium less than 1 mm or disruption of uterine serosa showed 100% sensitivity and specificity. In all cases in which the uterine serosa–bladder interface was abnormal or interrupted, and confirmed to be placenta accreta. This sensitivity and specificity are higher than that presented in our work, however, they included only 4 cases in their study and this may explain this higher percentage. However, **Comstock et al. (2004)** where interruption

of bladder uterine interface showed 93% sensitivity and 84% specificity. This is lower than the present work.

The most dominant color Doppler finding in the current study was the presence of intraplacental lacunar flow (with sensitivity of 100.0%). These results agree with **Lerner et al. (1995)** who reported that the presence of color flow within intraplacental lacunae alone showed sensitivity 100% in diagnosing placenta accreta and so he said that color Doppler results can be added to the intraplacental lacunae diagnosed by ultrasound to improve the accuracy of diagnosis.

Results of the present work suggested that a quantitative measure, designated here as largest Area of Confluence (Acon), can differentiate between the presence and absence of abnormally invasive placenta, and is associated with the histopathologic and clinical severity of abnormally invasive placenta. The test had a higher sensitivity for diagnosis of placental invasion with 16% false positive rate. These results suggested that this technique could allow reliable prenatal diagnosis. This would enable adequate preparation and intervention for cases of abnormally invasive placenta while minimizing the iatrogenic adverse events. But, results of the present study should be taken with care when interpreting this false positive rate, because the included females were taken from women who were already considered to be at risk of abnormally invasive placenta. It would be inappropriate for this test to be used as a screening tool on a low-risk population as a result of the risk of the false-positive paradox (the false-positive rate being greater than the true-positive rate as a result of the rarity of the condition) **(Vacher, 2003).**

Results of the present study are comparable to those reported by **Collins et al (2015)** who reported that, Acon values were greater for the group clinically diagnosed with abnormally invasive placenta than those without abnormally invasive placenta. They added, Acon rose with more severe histopathologic diagnosis focal accreta (32.2 cm2 [17.2–57.3]), accreta (59.6 cm2 [40.1–89.9]), and percreta (n522, 46.6 cm2 [37.5– 71.5], P<0.001, analysis of variance test for linear trend between means). Likewise, when Acon was plotted against the clinical grade assigned to each case, all grades had an elevated Acon relative to control (P,.001, analysis of variance test for linear trend between means).

Little is known of the process underlying the development of the area of confluence. One theory is that it represents enlarged arteriovenous anastomoses located in the subplacental myometrium, generating a large circulating pool, which can be detected as an abnormal area of power Doppler signal in abnormally invasive placentas **(Schaaps et al., 2005).** This agrees with the findings of **Tantbirojn et al. (2008),** who showed trophoblast-induced remodeling deep in the myometrium.

How Acon develops over time remains unclear, but serial data across gestation may reveal not only the natural history, but whether abnormally invasive placenta progresses, for example, from an accreta to percreta. This is not trivial; current American College of Obstetricians and Gynecologists' recommendations suggest delivery at 34 weeks of gestation **(ACOG, 2012).**

Results of the present study were supported by previous work, where **Shih et al. (2009)** concluded that 3DPD ultrasound may be useful as a complementary technique for the antenatal diagnosis or exclusion of placenta accreta.

In short, results of the present study revealed that, the marker Acon provides a quantitative measure for diagnosis of abnormally invasive placenta and can be used in assessment of the condition severity. However, as the study is a preliminary one, it should be further validated in future studies and thus it can be used subjectivity for the diagnosis of abnormally invasive placenta with subsequent decrease of both morbidity and mortality associated with the condition.

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