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Research Article

Can Transvaginal Sonography Promote Management of Pregnancy of Unknown Location (PUL) and Reduce Number of βHCG Test?

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Received: October 07, 2021; **Published:** November 20, 2021

Abstract

Introduction: The management of women with pregnancy of unknown location (PUL) can vary significantly and often lack a clear evidence base. This study aims to improve the diagnosis and management of PUL by evaluating ultrasound images using specific criteria describing the gestation sac.

Method: Retrospective study. Data collected from the medical records of pregnant patients at initial visit to EPU. Data underwent specific ultrasound image criteria in reporting empty gestational sac (GS) and describing deciduae signs.

Result: A total of 69 cases were reviewed and 68 showed empty GS in the initial visit. There were three reports that described GS with double decidual (DD) signs sufficiently. After the image review process, GS DD signs were noted in 25 (69%) cases, one DD sign in 12 (85%), whilst 4 (44%) cases did not demonstrate any DD signs. Moreover, the sensitivity rate of the presence of DD signs and viability as the final outcome was 87.5%.

Conclusion: A well written ultrasound report considering specific criteria in describing intrauterine sac would help in decreasing numbers of PUL from initial visits and subsequently reduce the number of un-necessary laparoscopy and βHCG tests.

Keywords: *Pregnancy of Unknown Location; Transvaginal Ultrasound; Early Pregnancy; Sac-Like Structure; Intrauterine Gestation; Decidual Sac*

Abbreviations

PUL: Pregnancy of Unknown Location; βHCG: Beta Subunit of Human Chorionic Gonadotropin; IUP: Intrauterine Pregnancy; EPU: Early Pregnancy Unit; GS: Gestational Sac; RPOC: Retained Products of Conception; TVS: Transvaginal Ultrasonography; DD: Double Decidual Reaction; IDs: Intra-Decidual Sign; DDs: Double Decidual/Sac Sign; MSD: Mean Sac Diameter; CRL: Crown-Rump-Length; PACS: Picture Archiving and Communication System; NICE: The National Institute for Health and Care Excellence; RCOG: Royal College of Obstetrics and Gynaecology

Introduction

Pregnancy of Unknown Location (PUL) is defined when a pregnancy test is positive but there is no sign of intra or extra uterine pregnancy or retained products of conception (RPOC) visualized by transvaginal ultrasonography (TVS). PUL occurs in up to 30% of initial early pregnancy scans [1,2]. Many women classified as having PUL are usually presented with lower abdominal discomfort, pain and/or vaginal bleeding. Although these symptoms are not useful determinants of PUL, still show high risk of complication. Therefore, a combination of patient history and TVS scan it can lead to predicting one of the three possible diagnoses: likelihood of miscarriage; too early in the

pregnancy; or possible ectopic pregnancy. When PUL is likely to result in miscarriage, this would be indicated by a good history of heavy bleeding with clots and crampy pains [3]. While PUL possibility of being an early intrauterine pregnancy (IUP) with uncertain dates, there is minimal bleeding and homogenous echogenic thickening of endometrium expected to be visualized in TVS. Moreover, PUL as a possible sign of ectopic pregnancy is expected when minimal bleeding, unilateral pain, thin endometrium with intact midline or some free fluids present at the time of scan.

TVS is able to keep the rate of PUL under 15% and a gestational sac (GS) can be first visualized by TVS as early as 4.5 - 5.0 weeks of gestational age and appears as a 2 - 3 mm rounded intrauterine fluid collection or sac-like structure [4]. The mean sac diameter (MSD) growth rate is 1.13 mm per a day; however, it is often variable [5,6]. Prior visualization of the yolk sac and/or embryo, demonstration of fluid collection can be called a true GS with two signs of decidual reactions: double decidual sign (DDs) and intra-decidual sign (IDs). The gestational decidual signs were first described in the 1980s using a transabdominal scan [7,8]; with improved resolution of TVS sonography, decidual sac sensitivity and specificity of predicting IUP have been improved by 81.8% and 97.3% respectively [9].

PUL is still a challenge to study because of confounding factors and one of these factors is wide heterogeneity and inconsistent classification of ultrasound findings. Therefore, the demonstration of GS DD signs in PUL for predicting IUP prior to the visualization of the embryonic contents using TVS is still crucial. What is known so far is that ultrasound of early gestation sac is variable and the two signs of double decidual reactions; double decidua (DD) and intra-decidua (IDs), are highly suggestive of an early IUP, while they are absent in at least 35% of gestational sacs [4,10,11]. Nevertheless, the absence of these two signs don't exclude IUP [12].

Expectant management of PUL has been shown to be safe and has reduced the need for unnecessary surgical intervention and is not associated with serious adverse outcomes. However, multiple visits to the early pregnancy unit (EPU) may be necessary before a diagnosis is made.

Aim of the Study

The aim of the study is to improve the diagnosis and management of PUL at EPU by evaluating and reviewing ultrasound images using specific criteria and correlating the data with urine/blood tests in order to:

1. Reduce the number of follow-ups in the low-risk group
2. Reduce number of scans and βHCG tests taken
3. Develop a scan template with specific detailed information of GS to minimize medical management confusion.

Objective of the Study

The objectives of this study:

1. Evaluate correlation between the presence of GS decidual reactions at first scan with IUP as an outcome.
2. Conversely, the lack of presence of GS DD signs would reveal invalid intrauterine progress, failed or ectopic pregnancy.
3. Test the significance between presence of GS DD signs in image review and the IUP as an outcome.

Materials and Methods

Study design: Retrospective study.

Data collection: Data collected from the medical records and the PACS system for patients presented with positive pregnancy test and other early pregnancy complications, who referred from general practice (GP) to the EPU at Queen Medical Centre (QMC) in Nottingham University Hospital (NUH) from September to December 2018. Data were collected from a number of visits to EPU, TVS scans obtained, and urine/blood tests, considering the national guidelines standards (1) NICE guidelines [13], and (2) NUH guidelines in management of PUL. Data were collected from:

1. Patient's initial visit to EPU. The initial scan images reviewed with consideration of inclusion and exclusion criteria for eligibility of the case.
2. Follow-up/repeat scans in second and third visits; this included the documentation of case progression and categorizes that into three groups according to the second visit result: viable IUP, too early gestation or persistent PUL.

Inclusion and exclusion criteria for collecting the data were considered according to the ultrasound image review of the initial ultrasound scan.

Data inclusion criteria:

1. All cases that show intrauterine sac-like structure with no presence of yolk sac or fetal pole.
2. Nonspecific, empty, rounded intrauterine fluid collection.
3. Absence of fluid collection or evidence of ectopic mass, pelvic free fluid at initial scan, associated with increased βHCG level and documented in the report as 'PUL' or 'ectopic pregnancy cannot be excluded' and a repeat scan is advised as per NICE and PUL protocol.

Data exclusion criteria:

1. Presence of ectopic mass at initial scans e.g. ovarian/adnexal mass.
2. Empty GS located in cervical cavity.
3. Presence of yolk sac and/ or fetal pole within GS
4. Evidence of RPOC or inner vascularity demonstrated within the endometrial cavity.

Ultrasound image review methodology

Follow specific ultrasound image review criteria in describing the sac-like structure GS and DD signs; double decidua (DD) and intra-decidua (IDs). This method helps to characterize the GS from the intrauterine sac-like or fluid collection in the very early stages of pregnancy by:

1. Presence or absence of GS double decidua signs; DDs and IDs
2. Location of GS or fluid collection within the uterine cavity.
3. Images being reviewed by two reviewers: the expert sonographer and obs/gyn consultant.

GS DD signs as described by Richardson., *et al.* 2015, Histed., *et al.* 2016: The intra-decidual sign (IDs) is defined as an eccentrically located gestational sac within the echogenic decidua with relatively undisturbed collapsed uterine cavity visualized as a thin echogenic line which is highly suggestive of an IUP (Figure 1). The double sac sign (DDs) is comprised of two concentric echogenic rings surrounding the fluid collection and separated by thin crescent of endometrial fluid which is a sign of definitive IUP. The outer echogenic ring represents the decidua parietalis, and the inner ring represents the decidua capsularis and chorion (Figure 1). The IDs is visible before the DDs as, the GS in IDs is not large enough to deform the contour of the uterine cavity. While in DDs, the GS is growing large enough to protrude into the endometrial cavity.

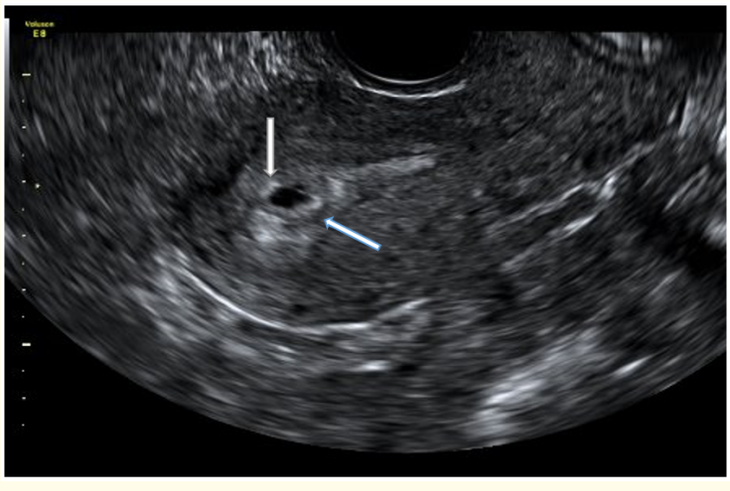

Figure 1: *TVS ultrasound image shows GS in sagittal view with presence of two decidual signs; decidual sign (green arrow) and intra-decidual sign (blue arrow).*

Data statistical analysis

Microsoft Excel and IBM SPSS 20 statistics were used for data collection and analysis. Data normality was tested by Kolmogorov-Smirnov, p-value was considered significant at 0.01. Data were described using diagrams and charts. The correlation between the presence of GS DDs in the ultrasound image and IUP as the final outcome was tested by Pearson correlation, p-value significant at 0.01. In addition, sensitivity and specificity values between the presence of GS DDs and viability were considered.

Ethical consideration

This study is a part of clinical audit/quality improvement project in Nottingham University Hospitals Trust (Project Reference Number 18-455C).

Results

A total of 69 cases were retrospectively collected and analyzed using Microsoft Excel and IBM SPSS 20 statistics. Data is normally distributed and statistically significant with p-value = 0.01. The indications of 69 scans performed for patients classified as 26 (38%) PUL and/or ectopic, 8 (12%) unsure/uncertain of date, 12 (17%) had PV bleeding, while 9 (13%) had a previous miscarriage and/or ectopic pregnancy, and 14 (20%) attended EPU with abdominal pain (Table 1). After initial TVS, the ultrasound reported 10 (14%) as PUL, 46 (67%) as too early gestation, whilst 13 (19%) as ectopic pregnancy can't be excluded and a re-scan is recommended as per protocol (Table 2). The medical records of those patients revealed that there were 43 cases had offered unnecessarily βHCG tests, in addition to 17 extra repeated scans were performed during that period of time.

Ultrasound scan indications	
PUL/ectopic	26 (38%)
Unsure/uncertain of date	8 (12%)
PV bleeding	12 (17%)
Previous miscarriage/ectopic	9 (13%)
Abdominal pain	14 (20%)

Table 1: *Indications of ultrasound scan for 69 patients at initial visit to EPU.*
EPU=Early Pregnancy Unit, PUL=Pregnancy of Unknown Location.

Ultrasound report indicates	
PUL can't be excluded- required a rescan	10 (14%)
Ectopic pregnancy can't be excluded - required a rescan	13 (19%)
Too early gestation - correlate with bloods	46 (67%)

Table 2: *Ultrasound report result of 69 patients had initial visit to EPU.*
EPU=Early Pregnancy Unit, PUL=Pregnancy of Unknown Location.

During the image review process, all ultrasonic images of 69 cases were reviewed and the GS characterized and precisely assessed according to the specific criteria of the sac-like structure appearance and presence of double decidua reaction DDs and IDs. The mean GS diameter was 5.76 mm (Figure 2). Total of 40 (58%) cases showed images with both deciduae signs, while 16 (23%) showed one decidua sign only, and 12 (17%) had no evidence of any decidua reaction sign (Table 3). There was only one case that showed no evidence of intrauterine fluid collection; however, it appeared as thickened endometrium and classified as PUL in the report of the initial scan (Figure 3).

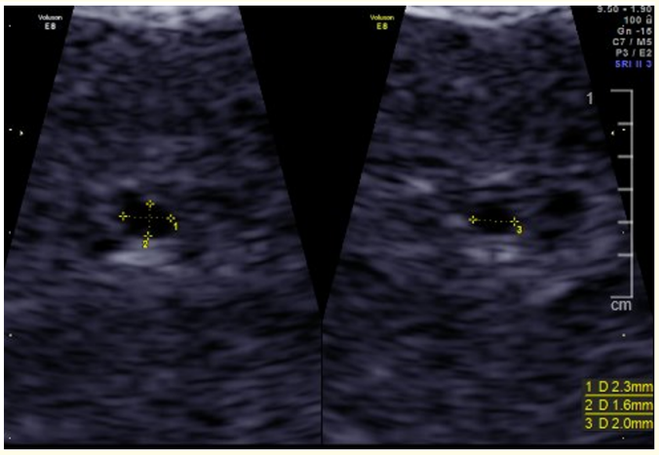

Figure 2: *TVS ultrasound image shows MSD measurements of GS in sagittal view demonstrated two diameters and in transverse view with one diameter.*

(1) Image review and demonstration of GS DD signs	
GS MSD	5.76 mm
No evidence of DD or ID signs	12 (17%)
GS DD sign only	16 (23%)
DD and ID signs	40 (58%)
Thickened endometrium (no GS visible. ET= 10mm	1
(2) Ultrasound report described a sac-like structure at initial visit as	
Endometrial cyst	1
Pseudo cyst or pseudo sac	6 (9%)
Sonolucent sac-like structure	1
Decidua reaction, suggestive of GS	2 (3%)
No GS description	59 (86%)

Table 3: *Determining of GS DD signs from perspective of (1) image review and (2) ultrasound report for 69 patients visited EPU. EPU=Early Pregnancy Unit, MSD=Mean Sac Diameter, DD=Double Decidua Sign, ID=Intra-Decidua Sign, ET=Endometrial Thickness.*

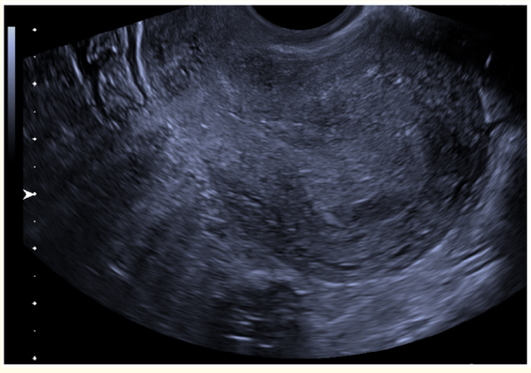

Figure 3: *TVS ultrasound image shows sagittal view of endometrium lining appears thickened heterogenous in echotexture, measuring = 10 mm, with no evidence of intrauterine endometrial fluid collection. This case reported after initial scan as PUL and became a viable IUP in the following repeat scan.*

In terms of describing the sac-like structure in the ultrasound report, the majority of the reports had a lack of GS DDs description. There were only four reports described GS in different ways. One of these reports described GS as an endometrial cyst whereas another report stated it was a pseudo cyst, and the remaining two reports documented GS as a sonolucent sac-like structure without describing GSDD signs (Table 4).

	Second USS result (n = 69)	**Third USS result (n = 19) (50 cases excluded from second scan as they were; viable IUP, miscarried, lost to follow up)**
Viable IUP	35 (51%)	6(9%)
Too early gestation	17 (25%)	X
Persistent PUL	2 (3%)	X
Miscarriage (GS MSD > 25 mm, FP > 7 mm, no FH)	7 (10%)	3 (4%)
Failed pregnancy (Irregular empty GS, GS MSD > 25 mm)	X	4 (6%)
RPOC	X	3 (4%)
Molar pregnancy	X	1
Lost to follow up	8 (12%)	2 (3%)

Table 4: *Result of follow-up and repeat TVS scan of 69 patients after their initial visit to EPU.*
IUP=Intrauterine Pregnancy, GS MSD=Gestational Sac Mean Diameter, FP=Fetal Pole, FH=Fetal Heartbeat.

According to the outcome of the second ultrasound scan, the majority of cases were viable IUP, 35 (51%), whereas 7 (10%) miscarried. The outcome for the remaining cases were not exclusive and persistent PUL and thus required repeat scans. After repeat scan, two were reported as persistent PUL and 17 (25%) as too early gestation (Table 5). With regard to the third scan (previously classified as too early gestation in second scan), two cases were lost to follow-up, while 4 (6%) were viable IUP, and 8 (12%) were divided into: one miscarriage, four failed pregnancies and three RPOC (Diagram 1). One persistent PUL at the third scan was found to be a viable IUP and another was a molar pregnancy. Moreover, the diagram shows a flowchart of cases with evidence of GS DD signs at the initial scan. From a total of 50 cases, there were 37 cases that became viable IUP, there were two GSDD signs demonstrated in 25 of cases, while remaining twelve cases showed only one decidual sign. With regard to the absence of GS DDs, from a total of nine, there were four that become viable IUP. However, the remaining five cases were failed pregnancy included being either miscarriage, RPOC or molar pregnancy.

	(N = 50)		**(N = 9)**	
	DD signs (n = 36)	**Only one DD sign (n = 14)**	**No evidence of DD signs (n = 9)**	**ET (n = 1)**
Lost to follow-up	3	3	2	X
Viable IUP	25	12	4	1
Miscarriage	2	1	2	X
Failed pregnancy	3	1		X
RPOC	2	X	2	X
Molar pregnancy	X	X	1	X

Table 5*: Evidence of GS DD signs and viable IUP as final outcome as shown in the flowchart of diagram 1.*
PUL=Pregnancy of Unknown Location, IUP=Intrauterine Pregnancy, GS=Gestational Sac, RPOC=Retained Products of Conception, DD=Double Decidual Reaction, IDs=Intra-Decidual Sign, DDs=Double Decidual/Sac Sign.

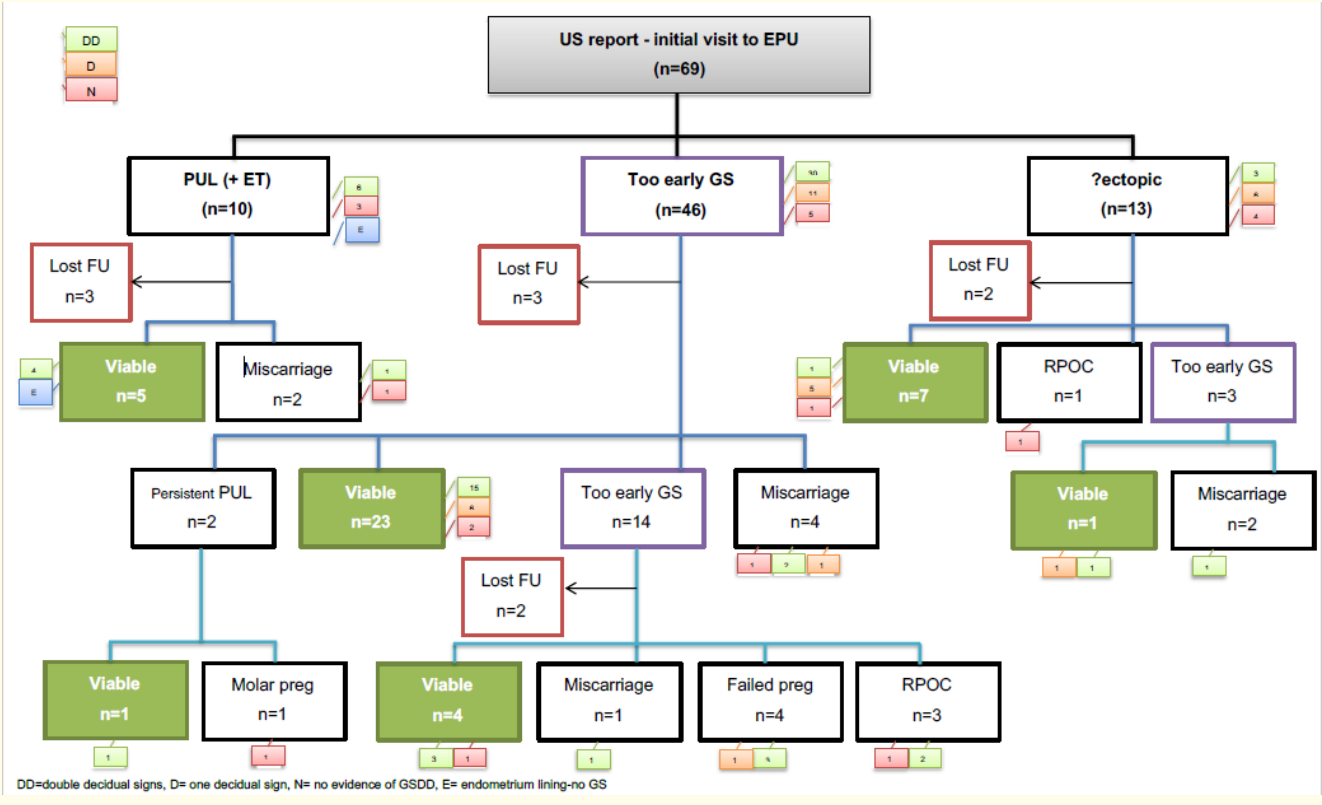

Diagram 1: *Flowchart of USS visit outcome indicating number of GS DD signs as determined after image review process.*

In terms of test correlation of demonstration of GS DD signs after the image review and viability as an outcome, including repeat scan results, the finding was not significant at p-value = 0.01 as tested by the Pearson correlation. Conversely, there was significant difference between GSDDs as seen in the image review to what was reported at the initial visit, p-value = 0.09 (Table 6). Moreover, the sensitivity of the demonstration of GS DD signs and IUP as the final outcome was 87.5%, whereas the specificity was 22.2% (Table 7).

Presence and absence of GS DD signs as shown in the image review and correlated with	**Pearson Correlations P-Value**
1) Initial ultrasound report	0.01*
2) IUP as a final outcome	0.09
*Correlation is significant at the 0.01 level	

Table 6: *Significance of difference of presence and absence of GS DD signs as a result from the image review and ultrasound report.*
IUP=Intrauterine Pregnancy, GS=Gestational Sac, DD=Double Decidual Reaction.

Sensitivity		**Specificity**
87.5%	Presence of GS DD vs viable IUP	22.2%

Table 7: *Sensitivity and specificity of presence of GS DD signs and viable IUP as final outcome.*
GS=Gestational Sac, DD=Double Decidual Reaction.

Discussion

The image review process in this study demonstrated the visualization of GS DD signs in 56 (81%) among 69 cases classified as PUL at the initial visit; while the majority of ultrasound reports (66 - 95%) inadequately described the GS DD signs at initial scan. The result found that there were 43 cases had offered unnecessarily βHCG tests, in addition to 17 extra repeated scans were performed during that period of time. This leads to the conclusion that a specific protocol for sonographers in reporting and describing GS DD in PUL cases can play role in reducing unnecessary repeated βHCG tests. Setting a protocol for reporting GS DD signs is needed to help in improving PUL outcome especially when using high resolution TV scanners. The sensitivity of GS DD signs for predicting IUP in our study was 87.5% which is slightly higher than a published estimated sensitivity in other studies (81.8%), while 22.2% specificity is low in our result [9]. Although the sensitivity and specificity of visualization of GS DD in ultrasound images and predicting of IUP as mentioned, it is important to highlight the wide variation in sensitivity and specificity in other published studies which ranged from 14% to 75% considering population heterogeneity.

In terms of improving ultrasound practice, it is known that GS can be first visualized by high resolution TVS as early as 4.5 - 5.0 weeks and appears as a 2 - 3 mm rounded intrauterine fluid collection or sac-like structure [4-14]. The visualization of GS DD signs is an identifiable appearance for a qualified sonographer, but the need for standardizing the documentation of GS DD signs for PUL cases has still not yet been addressed in early pregnancy guidelines, e.g. NICE, RCOG or ISUOG [13,19-21]. Although these guidelines are prepared to promote and facilitate standardization and consistency of practice using a multi-disciplinary approach, the standardization documentation in scanning has not been added. Merely current standardizing in these guidelines include: presence and absence of intrauterine GS, fetal pole (FP), yolk sac (YS). Also include the measurements of GS (MSD), and FP crown – rump- length (CRL), besides the presence or absence of fetal cardiac activity (FH); in addition to documentation of the presence of haematoma or any ovarian or adnexal mass or pelvic fluid collection. We believe adding standardizing the description of GS DD signs as part of routine practice would support and enhance PUL outcomes and early pregnancy clinical management [3-4,12,15].

In accordance with the aforementioned, it highlights the anticipation of improvement in the quality of images in the visualization of true gestation [3-4,12,15]. Our result found no statistical significance between the presence of GS DDs, either in one or both signs, DDs and IDs, and IUP as an outcome. A few ultrasound reports that described GS DDs properly were found to be IUP. Therefore, we believe a well-written descriptive ultrasound report of GS DD signs (demonstrating DDs and IDs) is not just helpful in minimizing clinical confusion of PUL, but also it is may influence practice for sonographers to enhance reporting style in visualization of the true sac. Although there were only three reports that demonstrated the GS DD signs, the conclusion of the initial scan for the majority of 46 (67%) of the reports was "too early gestation" and required a repeat scan. This leads to the conclusion that the majority of sonographers had an impression that the sac-like structure or intrauterine fluid collection would represent a true sac but they didn't not report correspondingly. One reason may be based on the lack of protocol in reporting early gestation and describing the visualization of GS DD signs. Another reason may rely on the sonographer's experience and confidence in reporting early gestation.

In our result, most of sac-like structure cases became IUP regardless being failed pregnancy at the end. There was one case demonstrated a thickened endometrium with no evidence of intrauterine fluid collection; it had been included in the study because it was classified as PUL in the initial scan report and became a viable IUP afterwards. The most common outcome in women with PUL is complete miscarriage. Our rate of miscarriage in women with PUL was 17 (27%). This rate is lower than other published studies quoting ranges of 50% to 70% and the reason may rely on the small sample size of our study [4]. Interestingly, the GS DD signs were present in 50 of the cases and 37 (74%) were viable IUP, while such signs were absent in nine cases and four (44%) of those were viable IUP. Similar results were found in one of the published studies when GS DDs found in 58 cases out of 61 were viable IUP, with absence of GS DDs in a total of four cases, two of which were viable IUP [9]. This is compatible with the fact that the absence of GS DDs signs in ultrasound doesn't exclude IUP [5,12]. Likewise, a nonspecific, empty, rounded intrauterine fluid collection which is seen in ectopic pregnancy can also represent IUP until proven otherwise.

Fortunately, no ectopic pregnancy case was recorded in our data; however, the majority of published studies assess the behavior of ectopic pregnancy in PUL with regard to the presence and absence of GS DD signs. In our study, the absence of ectopic pregnancy as an outcome is a coincidence and not considered a bias because all cases underwent specific inclusion/exclusion criteria. Furthermore, it has been highlighted that the presence of IDs was found to be reliably excluding ectopic pregnancy [4,7,16-18]. A recent study that assessed more than 600 intrauterine sac-like structures in pregnant women with an absence of ovarian/adnexal/pelvic mass, found all cases were IUP which led to the conclusion that, whether the sac-like structure showed an echogenic rim, DDs or IDs, these sonographic features are irrelevant [17]. The authors believe that the sac-like structure in a woman with a positive pregnancy test should be interpreted as a 'highly likely' or 'virtually certain' gestation sac [17].

Conclusion

To summarize, the suggestion is in increasing awareness among the sonographers or practitioners in EPU of the importance of describing GS DD signs in cases of PUL as well as linking this practice with sonographers' training and Continuing Professional Development (CPD). We believe standardizing the description of GS DD signs and an implementation strategy is important step in develop early pregnancy scanning guidelines to all interested parties, members of maternal units and educational training bodies.

Acknowledgements

We are thankful to the team in Ultrasound Department in Early Pregnancy Assessment Unit in QMC for their assistance. This study was presented in Association of Early Pregnancy Unit (AEPU) Annual Scientific Meeting 2019 in Glasgow, Scotland.

Conflict of Interest

The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Volume 10 Issue 12 December 2021