The role of 3D ultrasound in the management of pregnancies of unknown location

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Introduction
In the first trimester, the location of the pregnancy should be established using ultrasound, as ectopic pregnancy (EP) is still one of the most common life threatening complications of early pregnancy. Some pregnancies cannot be visualized as either intra- or extra-uterine pregnancies at the time of the initial transvaginal scan (TVS). These pregnancies are classified as pregnancies of unknown location or “PULs”. Some women are classified with a PUL at the primary TVS because they are scanned too early in pregnancy’s development and the trophoblast, whether located intra- or extra-uterine, is too small to be visualized. Some women’s pregnancies have failed spontaneously by the time the scan is performed and therefore will never be seen on TVS. These are made up of early complete miscarriages and self-limiting forms of ectopic pregnancy (EP). The possible outcomes of PULs are: a failed PUL, intra-uterine pregnancy (IUP), EP and persistent PUL. The authors propose the use of 3D TVS to aid in the prediction of PUL outcome, which potentially can result in reduced follow up without compromising care.

Methods
All women in the first trimester of pregnancy presenting to the Early Pregnancy Unit (EPU) at Nepean Hospital underwent a TVS. If the woman was classified as having a PUL, 2 dimensional (D) images and 3D volumetric acquisitions were obtained of the endometrial cavity and adnexal regions using a 4-9 MHz transducer and the Accuvix V20 Prestige ultrasound machine (Samsung Medison Co., Ltd.). Virtual organ computer-aided analysis (VOCAL) was used for off-line analysis of these 3D volumes. The following volumetric indices were evaluated: symmetry of the endometrial cavity, endometrial volume (EV), mean gray-scale index (MGSI), volume of the ovary containing the corpus luteum (if present), as well as 3D Power Doppler vascular indices for the corpus luteum including flow index (FI), vascular index (VI), vascular-flow index (VFI) for early pregnancies classified as PULs.

The concept of measuring uterine and ovarian structures with 3D TVS to confirm early IUP originates from the knowledge of physiological changes that occur during menstruation and implantation of the blastocyst. The combined reaction to oestrogen and progesterone activity in the second half of the menstrual cycle leads to the secretory changes within the endometrium. The total endometrial height is fixed at roughly its pre-ovulatory extent of 5 - 6 mm, but the glands and the vessels continue to grow. This results in progressive tortuosity of the glands...
and intensified coiling of the spiral vessels within the endometrium. Within the glandular cells, vacuoles are formed. Initially they are located under the nucleus and subsequently migrate towards the glands' lumen to be secreted in the endometrial cavity. Thereafter, in the late secretory phase, the stroma cells become large and polyhedral producing a compact sturdy stroma. The subepithelial capillaries and spiral vessels become more and more engorged and by day 21 - 22 of the cycle oedema of the endometrial stroma due to increased capillary permeability, becomes the predominant morphologic feature.

Implantation of the blastocyst is usually accompanied by proliferation of the maternal decidua surrounding the blastocyst. Antero-posterior thickening of the decidua in the region of implantation has already been described by transabdominal scanning in intra-uterine gestations as early as 3½ weeks. Implantation of the blastocyst in the decidua is usually asymmetrical with regard to the transverse direction. We hypothesized that the decidual reaction may be present in very early IUPs even when the gestational sac itself is not visible on TVS. According to this concept it was hypothesized that this asymmetrical decidual reaction is lacking in PULs which subsequently develop into an EP.

The introduction of 3D imaging has allowed for major advancement in the use of TVS to assess fetal structures, as well as the uterus and ovaries. By using 3D imaging, the clinician is able to view the images interactively in three dimensions. In addition to improved visualisation of these structures, 3D TVS is also considered to have the advantages of improved accuracy, reproducibility and patient acceptability. When examining the coronal or C-plane using 3D TVS, the outline of the uterus and endometrial cavity can be assessed simultaneously using the section reconstruction method of a 3D volume. This is a major advantage over traditional TVS or trans-abdominal ultrasound, as the C-plane is difficult to obtain by the 2D method. When the uterus is analysed in three perpendicular planes using the 3D function, the result is a higher sensitivity and specificity when compared to 2D analysis. One of the weaknesses of the 3D imaging has been the lack of clarity of 3D images when compared to 2D. The new technology of High Definition Volume Imaging (HDVI™) has overcome this weakness, by improving the contrast and resolution of 3D images in the C-plane.

The images in Figures 1 and 2 display the endometrial cavity evaluated in C-plane to assess symmetry. Three aspects of the C-plane were inspected to determine whether the endometrial cavity was symmetrical or asymmetrical. If all of the following were present, then the endometrial cavity was deemed to be symmetrical:

1. the endometrial areas near the left and right tubal corner mirrored each other,
2. the height of the tubal horns, i.e. their distance from the upper margin of the uterine fundus, was the same, and
3. the configuration of both sides of the total endometrium with respect to the median uterine long axis was the same.

If one or all of the above were absent, then the endometrial cavity was deemed to be asymmetrical.
Results

IUPs represent 35 - 38% of the PUL population, and these early pregnancies tend to demonstrate an asymmetrical endometrial cavity on 3D TVS. Figure 1 represents a 3D image in the C-plane of an asymmetrical endometrial cavity. The triangular shape of the endometrium is deformed in this image, and this endometrial asymmetry is present in the majority of early IUPs.

Published data suggest that, in experienced sonological hands, 8 - 14% of women with PUL at the initial TVS will be later diagnosed with an EP. Figure 2 represents a 3D image in the C-plane of the endometrial cavity in a PUL, which subsequently developed into an EP. The 3D Mirror View™ function can also be used to assess cavity shape, with the added ability to view sagittal and coronal planes simultaneously (Figure 3). In the case of early EPs, the endometrial cavity almost always displays a symmetrical shape on 3D TVS. The absence of a decidual reaction in EPs may explain why these pregnancies display a symmetrical shape compared to IUPs.

Failed PULs represent 50 - 53% of PULs, and these early pregnancies also demonstrate a symmetrical endometrial cavity on 3D TVS. Less than 2% of PULs will remain non-visible on serial 2D TVS, however the serum human chorionic gonadotrophin (hCG) levels plateau or continue to rise sub-optimally. These are known as persistent PULs and may also display a symmetrical endometrial cavity.

The EV, ovarian volume, and 3D power Doppler indices (FI, VI, VFI) in the ovary can also be analyzed using 3D TVS. The ability to manipulate these 3D images at any chosen section in the volume data set allows for thorough examination of the structure of interest. During 3D imaging, the structure’s volume can be measured regardless...
of its shape. The EV, ovarian volume and 3D Power Doppler indices of the ovary can be manually calculated with VOCAL analysis in the longitudinal plane, with 30 degrees rotational steps. Studies using 3D TVS with VOCAL analysis to measure endometrial and ovarian volumes have shown this method to be acceptable in terms of accuracy, reliability and intra- and inter-observer agreement, and are deemed better than that of 2D TVS.

The image in Figure 4 represents the EV and the corresponding histogram for MGSI in a persistent PUL. The inferior margin of the endometrial volume tracing performed during off-line VOCAL analysis is demarcated at the level of the internal cervical os. A reduction in EV is predictive of early pregnancy loss (prior to visualisation of the gestational sac) in women undergoing IVF. PULs, which develop into IUPs, tend to have a higher MGSI compared to PULs that are later identified as EP or failed PULs. The MGSI for PULs can be derived using the histogram facility during off-line VOCAL analysis.

3D TVS and VOCAL analysis has been used in previous studies to measure ovarian volume and ovarian Power Doppler indices, mainly in association with assisted reproduction. 3D Power Doppler allows for the quick and easy visualization of vessels, with regard to the overlapping of vessels and the association of surrounding vessels or structures. Substantial changes in ovarian volume and ovarian Power Doppler indices during the normal menstrual cycle have been confirmed using 3D TVS. Figure 5 displays an image of 3D Power Doppler indices for an ovary with a corpus luteum in early pregnancy. According to preliminary data, IUPs appear to have a significantly higher FI in the ovary containing the corpus luteum, than seen in EPs.

Discussion

By using 3D imaging and VOCAL off-line analysis to determine endometrial cavity symmetry, EV, MGSI, ovarian volume and ovarian Power Doppler vascular indices, there appears to be usefulness in the prediction of both location and viability of PULs. The novel use of 3D volumetric data and symmetrical analysis of the endometrium, in combination with biochemical data, may indeed have prognostic value in the management of PULs moving forward. Future research in women with PULs will aim to evaluate the use of 3D imaging
with the advanced technology of HDVI™. If proven to be valid, the use of 3D volumetric data and off-line VOCAL analysis of the endometrial cavity and ovary will localise those pregnancies classified to be PULs and in turn potentially reduce follow up.

References


