



Uterine junctional zone at three-dimensional transvaginal ultrasonography in patients with recurrent miscarriage: a new diagnostic tool?



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ABSTRACT

Objective: To evaluate the characteristics of the uterine junctional zone (JZ) by three-dimensional (3D) transvaginal sonography (TVS) in women with recurrent miscarriage (RM) as compared to normal fertile controls.

Study design: The thickness and the morphology of the JZ were evaluated in 75 women with a history of RM due to different causes and in 20 fertile women without a history of miscarriages or pelvic disease. All patients included in the study were selected among those who attended the outpatient clinic of "Tor Vergata" University. The JZ characteristics were evaluated in the midluteal phase of the cycle on the uterine coronal section obtained by 3D TVS.

Results: Patients with RM showed a JZ maximum thickness significantly increased when compared to that observed in control group (5.8 ± 0.7 vs. 5.0 ± 1.1 mm). When grouped according to the different causes of RM, all groups of patients with RM showed an increased JZ thickness when compared to fertile women, with the exception of those with anti-phospholipid antibody syndrome, probably due to the small number of cases with this pathology.

Conclusions: A thickened JZ could be an independent indicator of the risk of miscarriage and may represent an important contributing factor to some causes of RM. These observations may offer new perspectives for the screening and treatment of patients with RM. Although further studies are needed to ascertain if the reduction of the JZ thickness can determine a better pregnancy outcome, 3D TVS evaluation of the JZ could provide the opportunity to identify women in which appropriate therapeutic protocols can improve the possibility of successful pregnancy.

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1. Introduction

It is clear that a wide spectrum of obstetrical complications, including recurrent miscarriage (RM), are associated with defective placentation [1–3]. An impaired placentation process is characterised by a lack of endovascular trophoblast invasion and remodelling of the spiral arteries embedded within the inner myometrium [4,5]. From this point of view, it could be possible that the uterine junctional zone (JZ), which is the highly specialised inner third of the myometrium, can play a major role in this process. A normal placentation process is characterised by a full

conversion of the spiral arteries into large utero-placental vessels at the level of the JZ [1,3]. Defective placentation is characterised by an absent or incomplete remodelling of these arteries. Therefore, it may be hypothesised that the primary site of the vascular abnormalities responsible for defective placentation lies in the JZ.

It is not clear, however, if the appearance of the JZ before pregnancy could predict the risk of an abnormal placentation. Evidence suggests that conception cycles with successful implantation are characterised by a reduction in contrast signal intensity on magnetic resonance images (MRI) at the level of the JZ [6]. A reduced JZ thickness is associated with an increased likelihood of conception in patients undergoing in vitro fertilisation treatments (IVF) [7–10]. The mechanism through which an increased JZ thickness can reduce the possibility of a successful implantation is still unclear. Surprisingly, however, the JZ remains poorly studied in infertile patients.

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To our knowledge, no studies focused on the characteristics of JZ in patients having a history of RM have been published. This lack of information is probably due to the difficulties in the visualisation of the JZ. MRI was the first imaging technique used to examine the JZ and remains a useful tool in its evaluation. This technique has the advantage of low operator-dependent variability with reproducible images, but the high costs and the limited availability make the MRI an unfeasible tool for the evaluation of large groups of patients.

Transvaginal sonography (TVS) represents a largely available tool for the evaluation of the JZ characteristics. Nevertheless, it is difficult to visualise the JZ in all the orthogonal planes by 2D TVS and the high degree of operator dependence limits its usefulness. An accurate evaluation of the JZ can be achieved on the coronal section of the uterus obtained by 3D TVS [11,12]. It has been demonstrated that, through this technique, it is possible to assess minor changes in the lateral and the fundal part of the JZ, which are impossible to delineate using 2D ultrasound. In addition, processing modalities, such as volume contrast imaging, further enhance the visualisation of the JZ in comparison to that obtained using 2D imaging [13]. Moreover, a recent study has shown that 3D ultrasound assessment of the JZ has both good inter- and intra-observer variability [14].

Based on these observations, the aim of our study was the evaluation of the characteristics of the uterine JZ by 3D-TV S in women with a history of RM as compared to fertile women.

2. Materials and methods

2.1. Patients

Among patients attending the RM outpatient clinic of “Tor Vergata” University of Rome in the past two years, those meeting our inclusion criteria were selected for the study. Among the eligible women, 75 agreed to participate in the study. All patients had a history of two or more consecutive, first trimester miscarriages. Patients with two miscarriages were included in the study since equal frequencies of abnormal test results have been demonstrated among patients with two miscarriages or more [15]. Accordingly, the American College of Obstetrics and Gynaecologists states that the evaluation of couples with two consecutive miscarriages should be initiated [16].

All women underwent an extensive examination in order to evaluate all known RM etiologic factors, in agreement with the previously described diagnostic flow chart [17].

Patients were then grouped according to the different RM etiologic factors. Five groups were obtained: inherited thrombophilia (18 patients), thyroid abnormalities (15 patients), impaired uterine vascularisation (15 patients), antiphospholipid antibody (aPL) syndrome (9 patients), and women in which none of the investigated factors were found were classified as unexplained RM (18 patients).

Patients showing clinical and subclinical hypothyroidism were included in the thyroid abnormalities group [18,19]. Inherited thrombophilia was considered as the presence of one or more

major heritable anomalies [20]. We found factor V gene polymorphisms in 6 cases, prothrombin gene polymorphisms in 2 cases, homozygosity for methylenetetrahydrofolate reductase in 9 cases and the association of factor V and factor II polymorphism in one case.

Impaired uterine vascularisation was considered as the presence of increased resistance to uterine blood flow assessed by TV Doppler sonography [17]. The latest classification criteria were used for aPL syndrome diagnosis [21]. Patients with multiple etiological factors were excluded from the study. During the study period, only two patients showed genetic abnormalities and two patients showed autoimmune disorders. Due to the small number of cases these two groups of patients were excluded from the study. Patients with uterine malformations were excluded from the study to avoid the possible influence of these abnormalities on JZ characteristics.

Twenty healthy fertile women who attended the outpatient clinic of “Tor Vergata” University for a routine scan were recruited for the control group. Inclusion criteria required the absence of previous miscarriages and the presence of at least one previous uncomplicated pregnancy. Women with a history of pelvic disease or with abnormal findings during the ultrasound examination were excluded from the study.

In both groups, all women had a history of normal cycles prior to this study and subjects with chronic diseases were excluded from the study. None of the patients had received hormonal treatment during the last 3 months prior to the study.

Clinical findings of the different groups of patients are shown in Table 1.

2.2. Transvaginal sonography

The thickness and the morphology of the JZ were evaluated on the uterine coronal view obtained by 3D TVS (Fig. 1). The sonographic evaluation was performed in the midluteal phase of the cycle (18th to 22nd cycle day), to avoid possible hormonal influences, using an E8 (GE Healthcare, Zipf, Austria) ultrasound machine equipped with a multifrequency 3D volume endovaginal probe (2.8–10 MHz). The examination included a 2D-TV S evaluation of the pelvic organs to exclude any abnormalities. Transvaginal Doppler flow measurement of the impedance to uterine artery blood flow was performed.

In order to evaluate the JZ the coronal view of the uterus was obtained using 3D-TV S. Two to four static grey-scale volumes of the uterus were obtained from the sagittal plane and from the transverse plane. The volume acquisition technique was performed in a standardised fashion according to previously described criteria [11–13]. Recent studies indicate that the use of these criteria allow to an assessment of the JZ reproducible enough to be used in clinical practice [14]. In particular: frequency, 6–9 MHz; magnification of the uterus up to half of the screen; sweep angle, 120°; sweep velocity adjusted from medium to maximum quality; 3D volume box exceeding the uterus by 1 cm on each side. The coronal view reconstruction technique involved placing a straight or curved line (OmniView or rendering mode) along the

Table 1

Clinical features of patients. The mean age of patients with thyroid abnormalities was significantly higher with respect to that observed in all the other groups of patients.

	Mean age (yrs)	Mean miscarriage number	Mean week of miscarriage	BMI
Thyroid anomalies (n=15)	39 ± 3*	2.2 ± 0.4	7.5 ± 1.4	22.7
Impaired vascularisation (n=15)	37 ± 4	3.1 ± 1.1	7.8 ± 2.1	23.6
Inherited thrombophilia (n=18)	36 ± 2	2.7 ± 0.8	7.0 ± 1.9	22.6
Unknown (n=18)	37 ± 7	2.7 ± 0.9	7.0 ± 1.9	22.7
aPL syndrome (n=9)	36 ± 3	2.8 ± 0.8	6.7 ± 1.2	24.4
Controls (n=20)	35 ± 4	–	–	23.2

* p < 0.05.

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