Quantitative added information of 3T Magnetic Resonance Imaging in the evaluation of uterine scar after caesarean deliveries respect to routine transvaginal sonographic assessment.

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Purpose

In recent years there has been an increase of caesarean sections in developed countries, quantifiable in the last report of 2007 of 31.8% compared to 2006 (1). One reason that lead to this increase was that this practice was thought to be a safe clinical procedure both for mother and fetus. Nonetheless the World Health Organization Global Survey on Maternal and Perinatal Health recently concluded that caesarean sections were associated with an increased risk of severe maternal outcomes (2). Abnormalities in placentation, frequent complications of caesarean sections, are an important cause of maternal peripartum morbidity and mortality (3).

Transvaginal ultrasonography (TVU) has been considered for years the gold standard in lower uterine segment assessment in pregnant women with previous caesarean section to decide a possible vaginal delivery (4) but it is an operator dependent technique with several limitations regarding correct analysis of uterine scar morphology (especially thickness). Evidence based guidelines nowadays do not consider anymore TVU a reliable method and actually is not an obstetric regularly performed practice (5).

In some studies TVU has been used in non-pregnant patients with previous caesarean delivery to study expressly scar morphology in order to have a sort of prediction of the feasibility of eventual future deliveries (whether again caesarean or vaginal) (6).

Even if TVU remains first choice imaging technique in the initial diagnosis, due to low cost and large availability, Magnetic Resonance (MR) has gained an established role in studying female pelvis, especially high field (3T) with dedicated protocols and in recent years it emerged as an important, often essential tool, to obtain clinical relevant information in obstetric-gynecological field (7). However the study of caesarean section with MR is somewhat innovative especially with diffusion the presented tensor imaging approach. In particular, the aim of this study was to investigate the potential added value of 3T Magnetic Resonance (3T MR) in assessing uterine scars in women with previous caesarean section (pCS) in comparison to TVU. MR Diffusion Tensor Imaging (MR-DTI) is an non-invasive method to determine the amount of random diffusion (Brownian motion) of water molecules in tissues, providing physiological information about the mobility of water that aids tissue characterization (8). The technique assumes that water molecules more likely moves in the same direction as general fibre organisation (anisotropy). MR-DTI consists of multiple diffusion weighted acquisitions with directionally varying diffusion sensitzation gradients that lead to highlight preferential water movement orientation. Moreover fibre tractography post-processing is a novel software application that permits to obtain the direction of fibres in a 3D image, starting from water diffusion profile and estimated tensor value of each voxel. Tractography works by depicting inter-voxel connectivity based on anisotropic preferential diffusion movement of water molecules to give quantitative information on the dominant direction in a well-organized tissue.
MR-DTI with 3D fibre tractography approach has been successfully applied to the analysis of neuronal pathways in the brain in-vivo with almost no studies except for neuronal applications. In particular, there was only one study on ex-vivo uteri using MR-DTI where uterine muscle fibre direction or anisotropy has been estimated (9). In the case of uterus, water molecules diffuse more easily along the muscle fibres than across them, highlighting the extremely structured muscular tissue (inner circular and external longitudinal layers). If such a well organized structure is in anyway altered, for example by caesarean surgery, uterine muscular fibre architecture could show some degree of disarray.

Therefore our hypothesis is that 3T MR-DTI could provide morphological objective assessment of endometrial and myometrial thicknesses compared to TVU as well as additional qualitative and quantitative data on microstructural disarray of uterine fibre muscle altered by caesarean scar.
Methods and Materials

From April 2010 to August 2011, 18 women, 4 with two pCS - I group, 9 with one pCS - II group and 5 with vaginal delivery after pCS - III group (mean age respectively 37±5.65 years-old in I group, 34±2.97 years-old in II group and 38±3.11 years-old in III group) were subjected to TVU (Esaote Mylab 50 XVision) and 3T MR-DTI (Philips Achieva, The Best NL) in the same day to evaluate the agreement between these two methods in scar assessment. Women were investigated in follicular phase, 6 or 12 month after delivery. All patients gave written informed consent to the study, that was approved by local ethic committee.

One of these 18 volunteers was then subjected to hysterectomy due to an in-situ cervical carcinoma.

Two caesarean women of group II had subsequent deliveries at anamnestic follow-up, one with vaginal delivery and the other with caesarean section due to placental mal-insertion complication (placenta previa).

3T MR-DTI protocol consisted of morphologic sequence: axial T2 weighted Spin Echo (SE), sagittal T2 weighted SE on uterus long axis and para-sagittal T2 weighted Ssh-Turbo Spin Echo (TSE) on uterus proper long axis. Functional sequence was added, consisting of a SENSE Single shot echo-planar imaging (sshEPI) on parasagittal plane, with diffusion-sensitized gradients (b=600 mm²/s) along 16 directions, that determined main diffusion directions reflecting fibre orientation (Fig. 1).

Parameters of sshEPI are reported in table 1 (Table 1).

Diffusion weighted ssh-EPI images were processed on a dedicated workstation for data pre-processing with a deterministic free software. Tracking was continued until the stop criteria were satisfied. To help fibre visualization in the final fibre tracking a minimal FA of 0.2 and a maximal angle change of 10° per integration step were used. Fibres underlining the preferential water movement used a reference vector color-coded map (assigning red, green and blue to each orthogonal directions). The feasibility of the techniques above described has been validated in previous studies on nulliparous volunteers and volunteers with previous vaginal deliveries (10). In reliance on the numbers, the dimension and the localization of different region of interest (ROIs) drawn, it could be possible to obtain at first the global uterus architecture and secondarily specific fibre orientation and distribution (Fig. 2). In order to identify longitudinal fibres, different ROIs were placed on the uterus, particularly on the isthmus anterior segment (Fig. 3 and 4).

Scar was classified by TVU and MR on morphological sequence as linear (if endometrial profile was not altered) or retracting (if endometrial profile was altered or in the occurrence of dehiscence at the site of the uterine scar). Endometrial and myometrial thickness were measured at scar level, upstream and downstream the scar in both modality. Moreover
3T MR-DTI fibre tractography elaboration was performed, providing not solely qualitative reconstruction of fibre orientation but also quantitative results, described as the eventual reduction of the number of longitudinal fibres that run through uterine scar (on the anterior isthmus) compared to the posterior wall at the same level.
Fig. 1: 3T MR-DTI protocol consisted of morphological and functional sequences. a. Axial T2 weighted SE. b. Sagittal T2 weighted SE on uterus long axis. c. Para-sagittal T2 weighted ssh-TSE on uterus proper long axis. d, e, f. Example of SENSE single shot echo-planar imaging (sshEPI) on parasagittal plane, with diffusion-sensitized gradients (b=600 mm2/s) along 3 directions.

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Table 1: Table illustrates parameters used for sshEPI on parasagittal plane, with diffusion-sensitized gradients (b=600 mm²/s) along 16 directions.

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Fig. 2: Previous study conducted on nulliparous volunteers and volunteers with previous vaginal deliveries. a. 3T MR-DTI ssh-EPI imagine on parasagittal plane of non-caesarean uterus. b. Example of ROIs drawn in order to obtain whole uterus architecture: the green was been placed on sagittal plane, the blue on axial plane and the red on coronal plane. c. 3T MR-DTI with 3D tractography reconstruction illustrated global uterus fibre architecture.

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Fig. 3: Previous study conducted on nulliparous volunteers and volunteers with previous vaginal deliveries. a. 3T MR-DTI ssh-EPI imagine of non-caesarean uterus depicted on the axial plane. Two ROIs were drawn parallel, one on the anterior isthmus and the other on the posterior wall at the same level. b. 3T MR-DTI with 3D tractography reconstruction illustrated the circular fibres running between the two ROIs chosen, superimposed on uterine anatomy. These fibres constituted part of inner layer of myometrial uterine wall (stratum subvascolare). c. 3D imagine of the same circular internal fibres seen through the axial plane. d. 3D imagine of circular fibres running between two ROIs chosen on the axial uterine plane, without the anatomic uterus visualization.

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**Fig. 4:** Previous study conducted on nulliparous volunteers and volunteers with previous vaginal deliveries. a. 3T MR-DTI ssh-EPI imagine of non-caesarean uterus depicted on the sagittal plane. Two ROIs were drawn parallel, the green on the anterior isthmus and the red on the posterior wall at the same level. b. 3T MR-DTI with tractography reconstruction illustrated the longitudinal fibres running between two ROIs chosen, superimposed on uterine anatomy. These fibres constituted part of external layer of myometrial uterine wall (stratum supravascolare). c. Drawing ROIs of minor dimensions (the green on anterior isthmus and the red on posterior wall), a less number of longitudinal fibres could be depicted, superimposed on uterine anatomy. d. 3D imagine of longitudinal fibres running between two ROIs chosen, without uterine anatomy superimposed.

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Results

All volunteers underwent to the two examinations without any complications.

Regarding morphological evaluation, endometrial thickness was similar in both assessments (p=0.036) (Fig. 5). Thickness of myometrium was found higher at 3T MR evaluation than TVU at scar level (7.1±1.7 mm versus 5.6±1.9 mm, p=0.004), upstream the scar (13.2±2.8 mm versus 9.3±2.1 mm, p=0.001) and downstream the scar (10.3±1.7 mm versus 7.8±1.7 mm, p=0.002).

Regarding scar morphology in 4/18 women uterine scar description was discrepant between 3T MR and TVU: in 3 subjects it was assessed as "linear" at TVU and "retracting" at 3T MR, in 1 subject as "retracting" at TVU and "linear" at 3T MR, whereas in the remaining 14 volunteers the two methods agreed in the evaluation of uterine scar's morphology. 3T MR in comparison to TVU showed a higher thickness of the myometrium at scar level in the presence of linear scar (p=0.01) whereas no difference was found between the two techniques in retracting scar (p=0.5) (Fig. 6). 3T MR overestimated thickness of myometrium upstream the scar in comparison to TVU on linear and retracting uterine scars (p=0.002 versus p=0.003) whereas no difference was found between the two techniques in downstream scar assessment whether linear or retracting (p=0.1 and p=0.5). These values are summarized on the table 2 (Table 2).

Histological specimen of the ex-vivo uterus accurately showed the altered fibre architecture as it could be appreciated on 3T MR pre-surgery morphological images and at tractography microstructural reconstruction, with a reduction of myometrium thickness, altered fibre architecture and irregular fibre direction (Fig. 7).

3T MR-DTI with 3D tractography reconstruction analysis provided quantitative data that showed a reduction in the number of longitudinal myometrial fibres that run through uterine scar in the anterior wall at isthmus level respect to the posterior wall at the same level in all three groups. In particular, the decrease of longitudinal myometrial fibres was greater in I group composed by women with two previous caesarean sections (-62±37%) than in III group composed by women with a previous caesarean section and subsequent vaginal delivery (-59±37%); whereas the lower decrease of longitudinal fibres that run through uterine scar respect the posterior wall was seen in II group composed by women with only one pCS (-31±55%) (Fig. 8).

As describe in our previous studies (10) 3T MR-DTI confirmed uterine fibre anisotropy: inner circular layer (stratum subvascolare) and the external longitudinal layer (stratum supravascolare). This highly arranged architecture is not preserved at scar level in the caesarean volunteers. 3T MR-DTI imaging of caesarean scarred uteri showed that the previous surgery in the anterior isthmus segment caused fibre disruption and that within the scarred tissue there is a varying degree of muscle fibre disruption.
The volunteer (group II) with the most fibre disruption and the highest reduction of longitudinal myometrial fibres within the anterior isthmus region respect to the posterior wall (decrease of 95%) developed placenta previa during her subsequent pregnancy, leading to programmed caesarean delivery. The other volunteer (group II) had a vaginal delivery at second pregnancy and her decrease of longitudinal fibre in the anterior isthmus was of 4%, as quantified by 3T MR-DTI with 3D tractography approach. It seems likely that the amount of disruption of fibres in number and orientation caused by surgery varies within different women and maybe be associated to placental mal-insertions at the following pregnancy as reported in general literature (3) (Fig. 9 and 10). These of course are preliminary data, limited by the small volunteer population.

The added information provided by 3T MR-DTI study of caesarean scarred uterus respect to TVU may highlight women with a high risk of placental complications at subsequent deliveries. This new added information could change the management of pregnancies when it came to choices: closer observation throughout pregnancy, best modality of delivery and planned conservative therapies, such as uterine artery embolization to prevent a hysterectomy.
Fig. 5: 40 years-old volunteer with one previous caesarean delivery (group II). Scar described as "retracting" by both TVU and MR, with myometrial thickness reduced and minimum dehiscence of endometrial profile at the site of the surgical section. Endometrial thickness was found similar in both assessments (p=0.036). a. Example of endometrial thickness measured on transvaginal ultrasonography; the value is 9.9 mm. b. Measure of endometrial thickness on 3T-MR T2 SE imagine on sagittal plane is 9.45 mm, similar to that on TVU.

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Fig. 6: Comparison between TVU and MR on "linear" and "retracting" scar. 34 years-old volunteer with caesarean and subsequent vaginal delivery (group III). a. TVU imagine illustrates linear scar with endometrial profile not altered. Myometrial thickness was measured upstream the scar (blue line), at scar level (white line) and downstream the scar (red line). b. 3T-MR T2 SE imagine on sagittal plane confirms linear morphology of uterine scar. With the same modality, myometrial thickness was measured upstream the scar (blue line), at scar level (white line) and downstream the scar (red line) and the values measured were compared to those obtained on TVU. 3T MR in comparison to TVU showed a higher thickness of the myometrium at scar level in the presence of linear scar (p=0.01). 42 years-old with one previous caesarean delivery (group II) and occurrence of placenta previa at subsequent delivery, leading to programmed second caesarean delivery. c. TVU imagine illustrates retracting scar with myometrial thickness reduced and endometrial profile concave, retracted by uterine scar. Myometrial thickness was measured upstream the scar (blue line), at scar level (white line) and downstream the scar (red line). d. 3T-MR T2 SE imagine on sagittal plane confirms the retracting morphology of uterine scar. With the same modality myometrial thickness was measured upstream the scar (blue line), at scar level (white line) and downstream the scar (red line) and the values measured were compared with those obtained on TVU. We did not found difference on myometrial thickness at scar level between the two techniques in retracting scar (p=0.5).
Table 2: Table illustrates "p values" of myometrial thickness measured on TVU and MR at scar level, upstream and downstream the scar. 3T MR in comparison to TVU showed a higher thickness of the myometrium at scar level in the presence of linear scar (p=0.01) whereas no difference was found between the two techniques in retracting scar (p=0.5). 3T MRI showed statistically significant differences in measuring myometrial thickness upstream the scar in comparison to TVU on linear and retracting uterine scars (p=0.002 versus p=0.003) whereas no difference was found between the two techniques in downstream scar assessment whether linear or retracting (p=0.1 and p=0.5).

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Fig. 7: 38 years-old volunteer with two previous caesarean deliveries (group I) and occurrence of in-situ cervical carcinoma, undergone to hysterectomy. a. The section of histological uterus shows "retracting" scar morphology with myometrial thickness reduced and clear dehiscence of endometrial profile at the site of the surgical sections. b. 3T MR-DTI ssh-EPI imagine with 3D tractography reconstruction shows complete interruption of myometrial fibres at scar level. c. Particular of complete interruption and disarray of myometrial fibres at scar level. The fibres upstream and downstream the scar depicted with 3D tractography approach show a severe disarray and muscle fibre disruption.
Fig. 8: 29 years-old volunteer with one previous caesarean delivery (group II) with "retracting" scar. a. TVU imagine shows a retracting scar and dehiscence of endometrial profile at the site of the surgical section. b. 3T-MR T2 SE imagine on sagittal plane confirms the same scar morphology "retracting" with myometrial thickness reduced and endometrial profile concave, retracted by uterine scar. c. 3T MR-DTI ssh-EPI imagine shows hypointensity area at scar level. d. 3T MR-DTI with 3D tractography reconstruction illustrates few longitudinal fibres running through axial plane between ROIs placed upstream and downstream the scar. Quantitative analysis demonstrate a discrete reduction of longitudinal fibres in the anterior isthmus respect the posterior wall (decrease of 53%).
Fig. 9: 31 years-old volunteer with caesarean and subsequent vaginal delivery at second pregnancy (group III). a. MR image demonstrates "linear" scar with endometrial profile not altered. b. 3T MR-DTI ssh-EPI image with 3D tractography reconstruction shows fibres at scar level. c. 3D tractography visualization with uterus on 3 planes illustrates longitudinal fibres running through uterine scar along axial plane, between ROIs placed upstream and downstream the scar. Quantitative analysis demonstrate a reduction of longitudinal fibres in the anterior isthmus only of 4% respect the posterior wall.

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**Fig. 10:** 42 years-old with one previous caesarean delivery (group II) and occurrence of placenta previa at subsequent delivery, leading to programmed second caesarean delivery. a. 3T-MR T2 SE imagine on sagittal plane shows "retracting" scar with significant reduction of myometrial thickness at scar level and endometrial profile depressed, retracted by uterine scar. b. 3T MR-DTI ssh-EPI imagine shows hypointensity area at scar level. c. 3T MR-DTI ssh-EPI imagine with 3D tractography reconstruction shows few longitudinal fibres running through uterine scar long axial plane between ROIs placed upstream and downstream the scar. Quantitative data demonstrate high significant reduction of longitudinal fibres in the anterior isthmus respect the posterior wall (decrease of 95%).

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Conclusion

Morphological assessment of uterine scar shows that 3T MR overestimates myometrial thickness around the scar in comparison to TVU, maybe related to the more objective measurement possible with such imaging technique. Moreover, 3T MR-DTI with 3D tractography approach can depict uterine microstructural fibre architecture and quantify the specific reduction of fibres in women with different caesarean deliveries. In the future, 3T MR-DTI will hopefully become a useful clinical tool to look for potential variation in uterine structure, especially in women with caesarean sections helping to improve the in-vivo non-invasive insight into uterine structure, with better management of a physiological event such pregnancy is.


