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Ph.D. értekezés

# The role of MRI in the diagnostics of the uterinal diseases

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Introduction

In magnetic resonance assay of the anatomy of human body the laminar structure of the uterus wall was detected: a layer different from the external myometrium, the junctional zone (JZ) was circumscribed directly near to the endometrium.

JZ is MR-morphologically defined as a zone with a low signal intensity and harmonic appearance covering the inner one third of myometrium, externally surrounding the endometrium having a high signal intensity on T2-weighed images. In light microscopy the myometrium is a homogeneous structure of smooth muscle cells. The muscle fibres are arranged mainly in a circular system in the junctional zone. Despite the fact that no histological differences between the junctional zone and the myometrium could be confirmed in light microscopy, the two layers are in fact different in respect of both structure and function.

From the aspect of evolution both the endometrium and the junctional zone derive from the Müller tube, while the external myometrium is of mesenchymal origin. This is the embryonal origin with the common progenitor cell, which may develop into either endometrium stroma cell or junctional zone muscle cells, and may explain several functional similarities between the two layers. For example the cyclic changes of the appearance of the oestrogen and progesterone receptors are similar in the junctional zone to those detected in the endometrium. At the same time the external myometrium does not show cycle depending changes in the expression of the steroid hormone receptors. Additional factors also indicate that the differentiation of the inner mezenchimal cells into smooth muscle cells is under oestrogen control, and is independent from the differentiation of the external mezenchimal layer.

Pathological phenomena occurring in the junctional zone: adenomiosis and its different forms of appearance, dismenorrhea, subendometrial myoma, endometrium carcinoma infiltration, postoperative lesions.

The number of Caesarean sections has dramatically increased in the recent years: a frequency of Caesarean sections of 25-27% was registered in Hungary and in the West European countries in 2007.

Caesarean sections as all other operative procedures involve operational risks, and well regulated indications are used for them accordingly. After Caesarean sections the patients are exposed to many sever or even life threatening complications: e.g. abscess, scar opening,

ovarian venous thrombosis. In their study MR has a leading rule against CT and UH. Since with its excellent tissue resolution and the ability to circumscribe simultaneously a great volume MR plays a primary role in the imaging assay of the small pelvis, it was reasonable to apply it for the description of the normal and pathological status of the small pelvis after Caesarean sections. It is generally assumed that at least 6 months are required for the healing process to end with the overall dehydration of the scar tissue.

In pregnancies after Caesarean sections it is a general issue to decide on the method of labour. In comparison to a vaginal birth a Caesarean section naturally assumes an operational anaesthesia, requires prolonged hospital care and involves a higher risk in respect of placenta previa in the next pregnancy. Increased respiratory morbidity has been also observed in neonates. Ectopic pregnancy may also occur due to the operational scar. The risk of scar opening is slightly higher after one previous Caesarean section, and significantly higher after three ones if attempt is made to give a vaginal birth.

Objectives

1. Study of the MR anatomy and physiology of the junctional zone in comparison to the international literature to decide how JZ may be considered a vital phenomenon.

   Including *in vitro* study of JZ (quasi post mortem organi).

   My additional aim is to find a new technical solution, which allows us to asses the perfusion of the uterus wall more accurately than before.

   Review of the pathology of JZ as an independent functional unit in the light of the literature, with the use of own images.

   Drawing of a proposal for MR diagnostics of adenomyosis
2. MR assay of myometrial scar after Caesarean section, with a special regard to its measurable thickening, as an additive factor affecting decisions on the method of the next birth.

   Including comparison of the labour practice of Erzsébet Training Hospital of Sopron Town of County Rank with the international tendencies.

   Characterisation of operational scars older than one year

   Clarification of the nature of N (complication contra normal post-operative phenomenon)

   Examination if there is a prognostic correlation between the scar thickness and the method of the next birth.

## Patients and methods

### Studies for a more thorough assessment of the nature of JZ

I examined retrospectively the images of 135 female patients (15 to 85) appearing for MR assay of the small pelvis between 01.12.1995 and 01.03.1997 at the X-ray and Isotope Diagnostics Department of Erzsébet Kórház of Sopron Town of County Rank. The assays were made with a superconductive magnet with low field strength (0.5T) (Toshiba Flexart, Japan), and T2-weighed, sagittal plane images were analysed among the recorded sequences. I excluded 35 patients from the study due partly to technical reasons (claustrophobia, artefacts), and partly to a post-hysterectomy state. Due to the nature of the retrospective sampling I had no information on the menstrual cyclic phase. I examined the images of 100 female patients to assess if the zonal anatomy remained unchanged, or was affected by some (actual or former) progress of disease.

I studied MR anatomy of the uterus also *in vitro* (de facto post mortem organi). 1997.01.01. 7 uteruses removed between 01.01.1997 and 01.03.1997 were *in vitro* studied. The studies were made within 30-90 minutes from the hysterectomy, with a surface roll, and sagittal plane T2-weighed images were made. Since *in vivo* both the junctional zone and the cervix stroma have a very low signal intensity with the given weighing, I studied if this similar signal intensity was identifiable also *in vitro*.

With the help of my gynaecologist colleague I made transvaginal power Doppler tests on seven female patients between 01.06.1998 and 15.07.1998 (continuous frequency of 6-8 MHz, intracavity transducer, SonoAce, Medison, Korea). During the study the power Doppler was used after the assessment of the endometrium with 2D ultrasound test and circumscription of the subendometrial halo signal. We also examined if a circulation signal could be detected in myometrium neighbouring the endometrium, and if so, what was its size in comparison to the neighbouring external myometrium.

To assess the circulation of the junctional zone I applied an unpublished procedure independently developed with the help of my colleagues. A sagittal plane T1-weighed dynamic fat suppressed sequence was made during intravenous administration of MR contrast (T1 TSE FS; 5 mm slice thickness, 0.2 gap, TR 23 ms, TE 11 ms, FA 150°, band width: 196 Hz/pixel, FOV 250x250 mm, a-p direction of phase coding,

matrix: 157x192 pixels, voxel size_ 1.6x1.3x5.0 mm, spectral fat suppression, Siemens Medical Solutions, Erlangen, Deutschland, 10 ml Multihance iv., 4 ml/s flow). Imaging is started already in the native phase, then is continued at least for two minutes (but this may be optionally prolonged). A measurement of three slices is made in 6 seconds. Three video files are made from the obtained raw images via post-processing, which present the layers of the uterus with the feeling of a movie, enabling us to assess the perfusion.

2008.06.01. In period between 01.06.2008 and 31.08.2008 I applied the procedure on a voluntary woman free from complaints (age: 34, nullipara, no external hormone was administered) to assess the layers of the uterus in all phases of the menstrual cycle.

Examinations for the assessment of the scar of the Caesarean section

Our patients were from two in-patient institutions: partly the gynaecological and radiological documentation of female patients giving birth via Caesarean sections between 1st January 1997 and 31st December 2007 in Erzsébet Training Hospital of Sopron Town of County Rank and subsequently examined for the small pelvic with MR, and partly 01. radiological images of female patients examined for the small pelvic with MR between 1st January 1997 and 31st March 2008, and having Caesarean sections in their history were scientifically processed. 96 female patients met the criteria of selection ($n_{Sopron}$=85, $n_{Eisenstadt}$=11). The average age at the time of MR assay was 35.2 (between 27 and 51). Their history included one Caesarean section in 87 cases, and 2 in 9 cases. One MR assay was made on 82 female patients, two on 11, and three on 2 (totally 110). Averagely 6.2 years were between the MR assay and the (last) Caesarean section (between 0.3 and 26 years). The indication neither for MR assay nor for the Caesarean section was examined by me. Due to the specific nature of the retrospective data collection there is no information in which cyclic phase the female patient was at the time of the assay. In all cases the Caesarean section was a lower transverse section. I used the images of the sagittal plane T2-weighed sequence for the purposes of the study (Siemens Symphony Maestro Class 1.5 T, Siemens Medical Solutions, Erlangen, Deutschland).

In all cases I studied the biometric characteristics of the uterus: the thickness of the anterior myometrium, the thickness of the cervix wall, the height of the endometrium, the length of the uterus, as well as the minimum thickness of the operational scar in

millimetre. Average and standard deviations were calculated for all diameters on the basis of the obtained data.

I studied the operational scar also from qualitative aspects: it was classified into three classes on the basis of the signal intensity (low signal intensity, low and high signal intensity, high signal intensity).

I also studied if the niche can be differentiated.

I studied the patients with a special regard to the scar thickness depending on time lapsed since the (last) operation. From this aspect I classified the patients into three groups of almost identical numbers of patients: 1. group 1 – between 1 and 3 years ($n_1$=29); group 2 – between 4 and 6 years ($n_2$=29); group 3 – beyond 6 years ($n_3$=41).

In cases when vaginal birth followed a previous Caesarean section, I compared the method of birth, and in case of a repeated section I compared the operational report on the scar line to the scar thickness measured in MR assay. The operating surgeon had no information on the measured thickness of the scar line, and on the other hand the operational report was not available for me before the measurement of the scar line. My stock included 14 female patients (average age: 32.3; between 28 and 39), who gave birth either via vagina (n=4) or a repeated Caesarean section (n=10) after a previous Caesarean section, and MR assay was made for the small pelvis either between the two births (n=9) or after them (n=5). One female patient gave birth via vagina after the Caesarean section, so 15 births were given totally. MR assay was made on all female patients giving vaginal birth after the vaginal birth. In addition, MR assay was made on one female patient after the birth, following a repeated Caesarean section. In 9 cases MR assay was made between the two births (in these cases only repeated section was made). I documented the biometrical characteristics of this group of patients similarly to the above. In addition, I studied the morphological characteristics of the operational scar on the basis of the operational report and the method of birth. I classified the patients by the fact if during MR assay the operational scar was thicker or thinner in comparison to two specified values. The first specified value is the arithmetical mean of the measured scar thicknesses (5.8 mm), the second is 3.5 mm.

## Discussion

### A more detailed assessment of the nature of the junctional zone

In my patients the zonal anatomy of the uterus expressed regular stratification in the majority of the cases (81%): with T2-weighing the junctional zone having a low signal intensity and surrounding the endometrium having a high signal intensity in the form of a belt occupied the inner third of the myometrium, while the signal intensity of the external myometrium was moderate. In a smaller but not negligible part of the patients (19%) the junctional zone did not express or only partly expressed a typical appearance. In *in vitro* and *in vivo* tests the anatomy of the uterus was identically circumscribed in general. The only essential difference was that the junctional zone could not be distinguished *in vitro*. The signal intensity of the junctional zone is expressly low *in vivo*, similarly to the stroma of cervix, while it is moderate *in vivo* just as in the case of the external myometrium. At the same time the signal intensity of the cervix stroma expressly rich in fibres remained significantly low.

In transvaginal power Doppler tests circulation signals in the form of bands were detected subendometrially in the majority of the cases, but in narrower zones in the inner third of the myometrium, which directly proves the increased blood supply of the subendometrial region.

Kinetic contrast MR assay seemed to be suitable for the testing of the blood supply of the uterus, i.e. its perfusion. This procedure confirms observations considering the junctional zone a special zone of the uterus wall with increased water supply. There is a logical and theoretical correlation between the increased perfusion and biological role of this zone, since it functions as the "blood supplier" of the endometrium in pregnancy. The "coronial" accumulation in the uterus wall from inside to outside - which I could circumscribe with the use of video reconstruction first as far as I know - can be explained also with this functionality: Centripetally running branches of the uterine artery coming from the periphery penetrates the external myometrium without directly supplying blood to it, thus blood rich in oxygen and nutrients feeds directly the junctional zone and the endometrium. Such increased perfusion of the junctional zone can be more or less observed in all phases of the menstrual cycle with the exception that the perfusion of the directly subendometrially positioned junctional zone reduces in the

late secretion phase (logically to prepare the separation of the endometrium), and the interface between the endometrium and the junctional zone is irregular.
Detection of the accumulation area for a prolonged period in the fundus of the uterus during menstruation was a clear surprise to me. The fact that this wall part does not express any anatomical or pathological deviation in the later phases indicates that it is presumably a physiological phenomenon correlated with menstruation: e.g. I can imagine that the intramural pressure increased during a contraction, and this prevented blood from entering the region in question.

According to the morphometrical analysis of 110 tests of 96 female patients meeting the selection criteria the average scar thickness was 5.2 mm.
While the fresh operational scar undergoes intensive changes in size and signal intensity during the first year, the thickness of the old scar does not change on the basis of my data. At the same time the scar thickness was 3.2 mm in cases of repeated sections.
The signal intensity of the scar of the lower transverse incision was low or mixed (both low and high), while that was high in 1.8% of the cases. This observation can be easily explained with the fibrotic nature of the scar line, which indicates low cell and water contents. At the same time it calls the attention to the fact again that the original structure of the uterus wall does not reinstitute at the place of the Caesarean section in the majority of cases. Reinstitution of the original zonal anatomy was observed only in one female patient.
Niche was circumscribed in 90.9% of the patients, which is above frequency given in the literature.
I tried to find correlation between the thickness of the scar line and the method of the next labour.
Scar lines thicker than 5.8 mm were confirmed by MR assay in two cases, and thinner ones in two cases in VBAC group.
The scar was thinner than 5.8mm in four cases, however, was thicker in two cases when scars found thinned out during the operation were observed as thinned out in MR assay. Within the latter cases one of the women was MR assayed within 4 months from the Caesarean section. Since the final thickness of the mature scar develops during the first post-operative year, MR assay cannot be considered informative in this case. In the second case, when the scar line was thicker than 5.8 mm, Caesarean section was made

due to contractions and spatial disproportionateness during the repeated birth, this can explain why the incision scar thinned out according to the operational report.

One scar found non-thinned out according to the operational report was thicker, and 3 ones were thinner than the arithmetical mean. In one of the latter cases the operation was made due to the unfavourable positioning of the skull and multiple sclerosis of the mother, in the second case the Caesarean section was made due to gestosis in week 38 of the pregnancy, and in the third case the repeated Caesarean section was indicated due to the breech presentation. In these elective Caesarean sections presumably the lower uterinal segment did not well develop.

In case of comparison to 3.5 mm the scar was thicker in three cases, and was thinner only in one casein VBAC group. One of the scar lines found thinned out during the operation was thinner than 3.5mm, and five were thicker. Two scars found non-thinned out during the operation were thicker, two were thinner than 3.5mm in MR assay. Based on this no correlation may be detected between scar thickness of 3.5mm and the operational and VBAC data. At the same time sufficient correlation between the thickness of the scar and the operational report on the scar in case of - partly - a vaginal birth following a Caesarean section and - partly - of a repeated Caesarean section.

Facts

The junctional zone was circumscribed differently *in vivo* and *in vitro*, while the anatomical parts of the uterus were similarly circumscribed, which indicates the vital nature of JZ. This is in compliance with several observations already known from the literature or newly published (e.g. subendometrial accumulation, uterinal peristalsis). The subendometrial circulation may be confirmed also with transvaginal power Doppler tests, however, the thickness of the affected wall part does not fully meet that of JZ.

Video file developed by me with the help of my colleagues from kinetic T1-weighed contrast assays makes it possible to asses the perfusion of the uterus wall with the feeling of a movie. It is possible to characterise the perfusion with an accumulation curve.

JZ is a layer of the uterus wall with increased blood supply, its magnetic resonance appearance is fundamentally vital, and can be hardly explained with the increased nucleus/cytoplasm ratio or the smaller extracellular space. Additional prospective

studies are required for a more thorough study of the physiology and pathophysiology of the perfusion.

Recommendation for AM MR diagnostics:
Timing of the assay: 2. menstrual week.
Sequences: two T2-weighed sequences with perpendicular planes

→ if JZ ≤ 8 mm, there is no AM

→ if JZ is > 12 in a circumscribed or diffuse way, T1-weighed native measurement is required

→ if JZ is homogenous for both T2 and T1, repeated asses is required for the assessment of the dynamics; constant thickening indicates AM

→ if → AM cystosus lesion is circumscribed in JZ with or without blood degradation products → AM

→ „pseudowidening" of EM and/or linear strias are detected → AM (Cave! EM-carcinoma differential diagnosis)

→ if it is 8 mm < JZ ≤ 12 mm, then clear signals of AM must be found: cystosus formulates, linear strias, pseudowidening

Increased precaution is required if AMY increases despite the therapy, since the possibility of EM carcinoma exists in AMY.

The rates of Caesarean sections, of vaginal births after section and of repeated Caesarean sections at the Obstetrical and Gynaecological Department of Erzsébet Training Hospital of Sopron Town of County Rank are in proportion to the international tendencies. The rate of uterus rupture/scar opening is lower than data published in the literature.
The average scar thickness of patients studied by me is greater than that given in certain literature references.
The thickness of the operational scar does not change beyond one year.
In accordance with the fibrotic nature of the operational scar its signal intensity is fundamentally low with T2-weighing
Niche can be confirmed with a higher frequency in patients studied by me in comparison to the literature, therefore I think that it can be considered a normal post-operative phenomenon instead of being a complication.

I could not confirm the prognostic role of scar thickness of 3.5mm given in the literature (established among other terms of assay). At the same time - accepting the literature - I think that scar thickness of 3.5 mm or above this value measured with MR assay may represent a higher risk in case of VBAC.

Based on my data, in case the scar thickness is above 5.8 mm VBAC cannot be considered a higher risk, provided that there is no indication for resection due to the foetus or the mother. Additional prospective studies are required to confirm this.