SUMMARY THESIS

Chapter I gives a general introduction and describes the outline of the thesis. We focused on the most common abnormalities of the uterus; fibroids and intracavitary abnormalities. Intracavitary polyps are focally growing abnormalities within the uterine cavity arising from the endometrium. Leiomyomas or fibroids are benign monoclonal tumours arising from the smooth muscle cells of the myometrium. These benign abnormalities can cause several symptoms including abnormal uterine bleeding and subfertility. More than half of the women will experience these problems during their life. Heavy menstrual bleeding can result in anaemia, interfere with daily activities and have a physical, emotional, sexual and social impact on daily live. Although the majority of fibroids are asymptomatic, up to 25% cause problems. Fibroids can have a negative impact on women's lives, cause a major public health-care burden and are worldwide still the leading cause for hysterectomy.

In gynaecology, (transvaginal) ultrasound is the most widely used modality to visualize the uterus. Abnormalities can be visualized and classified using ultrasound. Ultrasound is usually a two-dimensional image. With three-dimensional (3D) ultrasound a volume of the uterus can be stored and analysed directly on the machine or at a personal computer whenever needed. The advantage of 3D ultrasound above 2D ultrasound is that it allows examination of the uterus from any angle and in any plane. This potentially allows the examiner to more accurately classify abnormalities and measure its size and extent of protrusion into the uterine cavity. Imaging vascularity of the uterus can be of additional help in differentiating between abnormalities inside the uterus. A successful treatment is dependent upon the correct diagnosis. Part I of the dissertation deals with the imaging of intracavitary abnormalities using a 3D (gel/water contrast) ultrasound, and part II deals with the imaging of vascularity of fibroids using 3D power Doppler ultrasound.

In Chapter II we studied the interobserver and intraobserver variability of three dimensional gel infusion sonography (3D GIS) in the assessment of intrauterine abnormalities. Forty five 3D volumes were reviewed by two independent examiners and one examiner reviewed these samples twice with an interval of 1 month. Type, size and location of the abnormality were recorded together with image quality. We found an substantial to almost perfect interobserver and intraobserver agreement for 3D GIS in detecting the presence of an intracavitary abnormality. Agreement for both interobserver and intraobserver was lower but still moderate for fibroid classification. Quality of the 3D volumes was assessed as poor in 11 out of 45 cases. Reproducibility
increased when poor quality images were excluded. We concluded that interobserver and intraobserver agreement for 3D GIS in the diagnoses of intrauterine abnormalities was substantial to perfect.

In Chapter III we studied whether 3D GIS can improve diagnoses and preoperative planning (compared to 2D GIS). In a prospective cohort study, we studied whether the addition of 3D GIS to 2D GIS improves accuracy for the detection of polyps and fibroids. We were also interested to know if a higher accuracy would improve optimal planning of hysteroscopic procedures in terms of required equipment and expertise. In 110 women with a suspected intra-uterine abnormality, 2D GIS, 3D GIS and a hysteroscopy were performed. Diagnostic accuracy was calculated for the detection of fibroids and polyps with both histology and hysteroscopy as the reference standard. In comparison to 2D GIS, sensitivity increased by using 3D GIS for the detection of fibroids and polyps, without major interference of the specificity. Despite an improved accuracy after the addition of 3D GIS, the planning for hysteroscopic procedures did not improve substantially. We concluded that in daily practise the addition of 3D SIS improved accuracy slightly but hardly improved the planning of hysteroscopic procedures.

Chapter IV reviews the literature about the accuracy of 3D SIS. Thirteen studies (1053 women) reported the accuracy of 3D SIS for focal uterine abnormalities of which 11 studies (846 women) were suitable for meta-analysis and eight reported accuracy according to the type of focal abnormality. The design of the included studies seemed applicable. The main quality problem with the included studies was insufficient reporting of their methods resulting in unclear risk of bias for several of the quality domains assessed. Therefore the overall quality of the evidence was considered low. The summary estimate for sensitivity and specificity was higher for 3D SIS (96.9 % and 99.5%) than for 2D SIS (90.9% and 96.3%) though this difference was not statistically significant. We concluded that low quality evidence showed 3D SIS to be very accurate in detecting intracavitary abnormalities. Summary sensitivity and specificity are higher for 3D SIS but margins of improvement are limited since 2D SIS is already very accurate. 3D SIS is an alternative to 2D SIS where the technology and appropriate expertise is available. Both 2D SIS and 3D SIS should be considered an alternative to diagnostic hysteroscopy when intracavitary pathology is suspected in both subfertile women and those with abnormal uterine bleeding.

In chapter V we focused on 3D ultrasound without gel or saline instillation. GIS and SIS are very accurate in the diagnosis of submucous fibroids but more invasive than conventional 3D ultrasound. Therefore we investigated the accuracy and reliability of 3D ultrasound in classifying submucous fibroids. A prospective pilot study was performed,
including 14 consecutive patients undergoing hysteroscopic myomectomy or fibroid ablation (Sonata™). All patients underwent routine ultrasonography, prior to the surgical procedure. 2D, 3D, 2D SIS and 3D SIS images were stored and percentages of protrusion were estimated. In this pilot study, 3D ultrasound was not as accurate as 2D SIS or 3D SIS in estimating the percentage of protrusion. 3D was not more accurate than 2D in the total group. A moderate interobserver agreement for 3D and a good interobserver agreement for 3D SIS was found. There was a large variation in image quality of individual patients. In particular during the luteal phase, when the endometrium is thick, visibility of the uterine cavity improved. Based on these findings we concluded that refinement of the technique and timing of 3D ultrasound in the evaluation of fibroids should be performed before evaluation in larger studies and before conclusions can be drawn.

In Chapter VI we evaluated the interobserver agreement and discriminating value of three-dimensional Power Doppler ultrasound (3D PDUS) in patients with fibroids. 3D PDUS was performed in 19 patients with fibroids and 3D volumes were evaluated by three independent examiners. The following vascular parameters were studied: Vascular Index (VI), Flow Index (FI) and Vascular Flow Index (VFI) of the fibroid, the vascular capsule and of its highest vascular area. Both manual and automatic contour modes were used to calculate the vascular parameters. We found that in the manual contour mode, the VI of the fibroid and the VI of the vascular capsule had the highest interobserver (almost perfect) agreement. Both parameters seem to have good discriminating values, given the large range of these parameters between different fibroids, independent of their volume. We concluded that VI assessed by 3D PDUS was reproducible in the assessment of fibroid vascularisation with good discriminating abilities.

In Chapter VII we evaluated the influence of the cardiac cycle and different gain settings on 3D PD parameters in the assessment of fibroid vascularisation. In 40 patients, 3D PD US was performed using 3 different gain settings: a fixed predetermined gain (50dB), a higher gain (65dB) and an individualised subjectively most optimal gain. Two consecutive 3D PD sweeps were taken to evaluate the effect of the cardiac cycle. For offline measurements, one reviewer recorded the most favourable method of volume calculation and shell size in every fibroid. Volume calculation using the manual mode was preferred over the automatic mode in the majority of cases. A shell of 0.5 cm was most adequate to calculate vascularisation of the fibroids’ capsule. To determine vascularity using 3D PD US in uterine fibroids a predetermined fixed gain can be used. By performing a scan of more than 10 seconds, the potential influence of the cardiac cycle on the VI seems limited.
Chapter VIII describes a prospective cohort study were patients with fibroids were followed over time. The objective was to analyse fibroid vascularisation measured with 3D Power Doppler in relation to absolute fibroid volume change during 12 months follow up and in relation to fibroid growth rate per year. In total 66 premenopausal women diagnosed with a maximum of 2 fibroids with expectative management were consecutively included. 3D ultrasound including Power Doppler was performed at baseline, 3, 6 and 12 months. Volume and vascular parameters were calculated using VOCAL software. Baseline fibroid vascularisation (VI) measured with 3D Power Doppler was correlated with fibroid volume at 12 months \( (p = 0.02) \). An increase of 1% in VI at baseline was associated with a 7.00 cm\(^3\) larger fibroid volume at 12 months. Furthermore, vascularisation was also associated with fibroid growth rate per year \( (p=0.04) \). We concluded that in women with uterine fibroids without therapy , baseline vascularisation (VI) measured with 3D Power Doppler is correlated with absolute fibroid volume change at 12 months and with fibroid growth rate per year.

In Chapter IX we evaluated fibroid vascularisation in relation to symptoms and health related quality of life using 3D Power Doppler parameters in women with expectative management. A prospective cohort study was performed among 53 premenopausal women diagnosed with a maximum of 2 fibroids. 3D sonography including Power Doppler was performed at baseline, 3, 6 and 12 months follow up. Participants were asked to complete PBAC and UFS-QOL questionnaires at baseline and after 3, 6 and 12 months of follow-up. We found that baseline vascularisation (VI) is associated with bleeding symptoms (PBAC score) over time; a 1% higher VI at baseline leads to an 14.6 point increase in PBAC score \( (p=0.04; \text{95\% CI 0.62 – 28.46}) \). When adjusted for fibroid volume at baseline and type of fibroid association was not significant. Fibroid volume at baseline and heavy menstrual bleeding over time are also associated; a 10 cm\(^3\) larger fibroid volume at baseline is associated with a 5.6 point higher PBAC score over time \( (p=0.03, \text{95\% CI 0.05 – 1.07}) \). Subgroups analyses for type of fibroid (submucous, intramural and subserosal) showed a statistically significant association between baseline VI and PBAC score at 12 months follow up for intramural fibroids \( (\text{regression coefficient 15.4; p = 0.004; 95\% CI 6.8-24.0}) \). This study demonstrates an association between fibroid vascularisation and heaviness of menstrual bleeding. Vascularisation is also associated with other fibroid related symptoms and quality of life.

In Chapter X we discuss the main results, implications and future perspectives. We demonstrated good reproducibility for 3D GIS in the presence of an intracavitary abnormality. We found 3DSIS to be more accurate than 2DSIS but margins of improvement are limited since 2D SIS is already very accurate. Currently, the clinical relevance seems limited. The use of 3D ultrasound without contrast in classifying fibroids is feasible but
still needs improvement before its value in the diagnostic pathway can be determined in future studies. 3D power Doppler is accurate and feasible. The vascular index (VI) is reproducible in fibroids and is related to volume change over 12 months in women without therapy. Vascularisation may also help us to predict increase of symptoms over time. Future research is required for defining the best method of quantifying vascularity, for estimating treatment effect and possibly also for the differentiation of fibroids and sarcomas.