Ultrasound and Doppler Study of Uterine and Subendometrial Blood Flow Anatomical Landmarks of Intrauterine Contraceptive Device

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Abstract:
Previous studies reported changes in the local vasoactive substance production within the endometrium with a subsequent increase in vascularity as a possible mechanism of intrauterine contraceptive device (IUCD)-induced heavy menstrual bleeding. This review investigates the role of power Doppler velocimetries of the uterine arteries as a predictor of IUCD-induced heavy menstrual bleeding.

Keywords: Doppler, Uterine, Subendometrial, Blood Flow, IUCD.

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Introduction:

The uterus is located in the lesser pelvis between the urinary bladder and the rectum. Although generally a midline structure, lateral deviations of the uterus are not uncommon. The broad ligaments extend from the uterus laterally to the pelvic side walls. They contain the fallopian tubes and vessels. The uterosacral ligaments serve to keep the uterus in an anterior position. They arise from the upper cervix posteriorly and extend to the fascia over the second and third sacral vertebrae. The round ligaments arise anterior to and below the fallopian tubes and cross the inguinal canal to end in the upper portion of the labia majora **(1)**.

The normal adult uterus measures approximately 7-9 cm long, 4.5-6 cm wide and 2.5 3.5 cm deep (anteroposterior dimension). Its corpus-to-cervix ratio is 2:1**(1)**.

The blood supply to the uterus is via the uterine artery, a branch of the internal iliac artery. This vessel enters the uterus at the cervico-corporal junction and ascends along the lateral aspect of the uterine body to the cornua. At the uterine cornua an adnexal branch originates which supplies the ipsilateral ovary and anastomoses with the ipsilateral ovarian artery **(2)**.

From the uterine artery arise perforating branches which extend through the serosa. The uterine arteries anastomose through the anterior and posterior arcuate vessels. These vessels are located in the outer one-third of the myometrium, between the exterior longitudinal muscle fibers and the inner oblique muscle fibers **(3)**.

Endometrium:

Sonographically, the endometrium is one of the most dynamic structures in the body. During the reproductive years of a normal female, the uterus undergoes ultrasonographically detectable alterations characterized by cyclical changes in the echo pattern of the endometrium. In fact, it is possible to infer the approximate day of a normal woman's menstrual cycle by the sonographic appearance of the endometrium**(4)**.

From the first day of the menstrual cycle until the mid-cycle, the normal endometrium progressively thickens and develops sonographically detectable strata. This appearance can be described as layered, trilaminar or 5-line (my term of preference). Past the mid-cycle, the normal endometrium brightens and progressively thins. These sonographic endometrial patterns appear to be related to the changes in the glandular and vascular elements of the endometrium during the menstrual cycle **(5)**.

Fleischer et al. determined that the endometrium is thickest during the secretory phase (3.6 ± 1.4 mm), less thick during the proliferative phase (2.9 ± 1 mm) and thinnest during menstruation **(5)**. These values are for the half-thickness as measured from the endometrial canal to the endometrial-myometrial junction. Full thickness measurements ranged from 4 to 12 mm, with an average thickness of 7.5mm.

The endometrium will either slough if no pregnancy occurs or will undergo various changes in the event of a pregnancy.

The blood supply to the endometrium is derived from branches of the uterine arteries. Emanating from the arcuate arteries (vide supra) are the radial arteries. These vessels run through the myometrium to just outside the endometrium where they form terminal branches of two types: straight and coiled. The straight branches, also known as the basal arteries, supply the basalis layer of the endometrium. The coiled branches, also known as the spiral arteries, traverse the endometrium and supply the functionalis layer. The spiral arteries, like the endometrium and unlike the basal arteries, are responsive to the hormonal changes of the menstrual cycle **(6)**.

In preparation for implantation, the endometrium undergoes transformations influenced by the ovarian hormones produced during the early secretory phase. These modifications include: an increase in the rate of blood flow, an increase in the number of cells populating the stroma and epithelium, an increase in uterine oxygen consumption, an increase in oxygen diffusion into the uterine lumen and a generalized edema **(7)**.

The spiral arteries respond to the hormonal changes of the menstrual cycle and undergo transformations, as well **.**These responses include: proliferation of the endothelium, thickening of the wall and coiling. These vessels play an important role in implantation. The chances for a normal implantation may be reduced if the spiral arterioles are inadequately developed **(8)**.

Ultrasound Imaging of Intrauterine Contraceptive Device (IUCD):

Imaging has an important role in the evaluation of IUD, not only to check that an IUD is in the correct position to be effective but also to assess for associated complications. Sonography is the commonly used method to evaluate IUDs because it is easy to perform, is cost effective and lacks a risk of radiation. When an IUD is not found on sonogram, a plain radiograph of the abdomen (plain x-ray) is helpful to determine its location, computed tomography and magnetic resonance imaging are not commonly used for assessment of an IUD but IUD may be seen when these imaging studies are performed for other indications **(9).**

The routine use of trans-vaginal ultrasound (TVU) to assess the position of IUCD after insertion has been advocated. There is much evidence that shows the high accuracy of three dimensional (TVU) in assessment of the location of any type of IUCD **(10)**.

Trans-vaginal Doppler ultrasound is the gold standard in the evaluation of female internal genital organs and it provides information about the vascular characteristics of these organs. It can evaluate any abnormalities of these organs. The conditions that can be examined include:

- The endometrium of women with infertility problem or who complaining of abnormal uterine bleeding.
- Chronic pelvic pain, congenital malformation of the ovaries or uterus, ovarian cysts and tumour, uterine mass, myoma and polyp.
- Pelvic inflammatory disease, bladder abnormalities.
- It can also detect complications of IUDs including a low position, associated infection, myometrial migration, uterine perforation and fragmentation of IUD**(11).**

The three-dimensional ultrasound could be proposed as a good tool for assessing the proper position of an IUCD in situ by measuring either IUCD. Fundal distance (IUCD-FD) or IUCD. Endometrial distance (IUCD-ED) **(12).**

Uterine artery blood flow in normal menstrual cycle:

The general pattern of uterine blood flow throughout the menstrual cycle is that perfusion increases in response to rising plasma estrogen and progesterone and decreases with the periovulatory fall in estrogen **(13)**. The lowest Pulsatility Index (PI) values are seen around Days 8 and 21, while the highest values are seen around Days 1 **(14)**. Significant changes in diastolic blood flow at the different times of the cycle may not be noted **(15)**. In general, the index values for the uterine artery ipsilateral to the ovary containing the dominant follicle are lower than the contralateral artery **(4)**.

Goswamy and Steptoe (16) found waveforms were continuous in most multiparous patients throughout the cycle, except for a few days immediately after ovulation and during menstruation but were only continuous in nulliparous patients immediately before ovulation.

Steer et al. (17) found that uterine artery PI and S/D ratio values differed significantly between abdominal ultrasound and vaginal ultrasound during the normal cycle.

Yaseen et al. (18) studied circadian rhythm in uterine artery blood flow. They found a nadir in PI following sleep, which was unrelated to changes in oestradiol, progesterone, Luteinizing Hormone (LH), or Follicle Stimulating Hormone (FSH). The increased blood flow which they found following sleep may have been the result of overnight bed rest, since a similar improvement is seen in pregnant patients who have been at bed rest continuously for several days.

Dickey (19) who used abdominal ultrasound to measure uterine blood flow, found no differences in blood flow at different phases of the cycle **.**

Scholtes et al. (20), using a 4.25 MHz vaginal transducer, found little variation in PI in the phases of the cycle and additionally found no difference in PI on the side of the dominant follicle or corpus luteum. However, **Steer et al. (17)**, using vaginal ultrasound with a 6 MHz transducer, found marked variation in uterine artery PI during the cycle in 23 patients, 20 of whom were nulliparous, which was similar to that reported by **Goswamy and Steptoe (16)** for multiparous patients.

Spiral artery, as well-as-the uterine artery, PI and TAMV were measured throughout the cycle with vaginal ultrasound using a 5 MHz transducer by **Sladkevicius et al. (21)**. Continuous diastolic flow in the uterine artery was present in all examinations. Spiral artery PI was much lower than uterine artery PI (0.8-1 versus 2.4-3.4), but mirrored the changes in average values for the uterine arteries throughout the cycle. Values for PI were lowest for the spiral and uterine artery on days 7 and 12 post-ovulation and highest 2 days after the LH surge. Velocity was highest for the spiral artery on days -1, +7 and +12 from the LH peak, and highest in uterine arteries on day -2. These authors found marked differences between the dominant and non-dominant ovary side in mean uterine artery velocity, and to a lesser extent in PI, in the peri-ovuiatory and early luteal phase. Spiral artery and uterine artery PI and RI were measured during the peri-ovulatory period in 27 patients with spontaneous cycles and 51 patients with stimulated cycles by **Kupesic and Kurjak (22)**. All had male factor infertility, but parity was not stated. Results from right and left uterine arteries were averaged when they found no consistent differences between the side with the dominant follicle and the contralateraral side.

Relationship to estrogen and progesterone:

Several researchers have measured serum oestradiol and progesterone, as well as blood flow during the normal cycle **(16)** noted that uterine blood flow increased with rising concentrations of oestradiol and progesterone and decreased when oestradiol fell immediately following ovulation. In marked contrast, **Steer et al. (17)** found that maximum uterine artery PI values, indicating highest impedance to blood flow, occurred on the day of serum oestradiol peak, and then fell by 25% to a mid-cycle nadir 2 days following the urine LH peak, rose again the next day for 1 day only before falling again to an even lower mid-luteal phase nadir 10 days after the LH peak, while oestradiol concentrations were still high and progesterone concentrations were high.

The cyclical changes reflected by the flow velocity waveforms and index values appear to be mediated by the reproductive hormones**.** Patients with inactive ovaries on transdermal estradiol and vaginal progesterone therapy were studied using transvaginal ultrasound technique. These patients received their medications on a 28 day regimen. The baseline evaluation (pre-treatment) demonstrated a narrow systolic spectral flow pattern with a mean PI of 5.2 +/- 0.4. Evaluations performed on Days 13-14, showed a spectral tracing that was broader with an uninterrupted diastolic component. The mean PI was 1.5 +/- 0.2. On Days 26-27', no significant differences were noted (mean PI = 1.7 +/- 0.3) **Cacciatore et al., (23)**

Steer et al. (17) found a significant correlation between mean right and left uterine artery PI measured in the mid-luteal phase and endometrial thickness in normal patients (r=-0.85), those with unexplained infertility (r=-0.84), endometriosis (r=-0.90) and anovulation (r=-0.77) and also a lesser correlation with tubal infertility (r = -0.37).

Cacciatore et al., (23) found a significant correlation between mean right and left uterine artery PI and both oestradiol (r = 0.37) and progesterone (r = -0.32), but not endometrial thickness on the day of embryo transfer. None of these authors speculated about methods of treatment to increase uterine blood.

Effect of IUD on uterine and subendometrial blood flow:

De Souza and Geber (24) studied the influence of an IUD on uterine artery blood flow using Doppler assessment and concluded that the presence of an IUD does not interfere with the vascular resistance of the uterine arteries that can shown by Doppler assessments 1 month after insertion.

Jarvela et al. (25) evaluated the effect of copper IUD on uterine artery blood flow during midluteal phase and on the first day of the menstrual cycle and the concluded that copper IUD does not induce any major changes in the resistance of the uterine artery blood flow, although during menstruation in patients with increased menstrual pain after IUD insertion there seems to be a decreased in uterine artery PI.

Mirela et al. (26) studied the effect of the copper IUD on subendometrial vascularaization and uterine artery blood flow, using power Doppler energy and ultrasonography pulsed color Doppler during the midlueal phase, and they found that the copper IUD modified the subendometrial vascularaization of those patients who presented with IUD-induced side effects (dysmenorrhea or menorrhagia), as evidenced by power Doppler analyses. Uterine artery blood flow and subendometrial vascularaization were not altered after IUD insertion, as evidenced by RI and PI using pulsed colour Doppler ultrasonography and power Doppler analyses.

Zalel et al. (27) studied the effect of levonorgestrel intrauterine system on the uterine vasculature and the endometrium and they concluded that there is no effect in the main uterine artery blood flow. While subendometrial floe in the spiral artery was significantly reduced.

Uterine artery blood flow:

After IUCD insertion, there is an increase in the mean uterine artery PI in the mid-luteal phase, with no change PI during menstruation **(28)**. The extent of increased in the PI correlated with the serum levonorgestrel concentration. The circulating concentrations of levonorgestrel have a tendency to decline during the use of IUCD.

According, the increase in PI may be only temporary.

The subendometrial vascular changes observed in IUCD users include thickening of the arterial walls, suppression of spiral arterioles and capillary thrombosis**.** Because the PI reflects vascular impedance downstream from the point of measurement. this leads to increased vascular impedance more proximally in the vasculature, such as in the main branch of the uterine artery. Also the uterine arteries have usually high concentrations of progesterone and estrogen receptors**(23)**.

So, the effects of hormones become apparent more easily and rapidly and with amplified responses in the uterine arteries compared to other arteries. The IUCD users, resistance to blood flow is attenuated during menstruation, as the endometrium, with vasoconstrective changes in the spiral arterioles and capillaries is shed (**23**).

Endometrial effects:

The endometrial is constantly changing due to the effect of cyclic ovarian hormones. The development of the endometrial layers is regulated by complex mechanism involving these steroid hormones, their receptors and local molecular systems which mediate their action. The presence of the IUCD causes profound changes within the endometrium down to the hormonally non-responsive basalis **(29)**.

Local biochemical factors are important in the processes of cellular atrophy within the endometrium. These include an alternation in the dynamic of growth factor mechanism, an increase in apoptosis or programmed cell death within the endometrial glands and the suppression of a gene coding for a receptor for thrombin. These all have a role although their relationship remains unclear **(30)**.

Insulin-like growth factor system modulates the effect of estrogen. There are two main types of factor, IGF_1 which when stimulated by estrogen stimulates the endometrial to proliferate, and IGF_2 which causes and maintains differentiation within the endometrial. Endometrial stromal cell produce IGF_1 and IGF_2 and their binding proteins $IGFBP_1$ and $IGFBP_2$ **(30)**. Women using LNG IUS have been shown to have an increase in $IGFBP_1$ and a subsequent decrease in IGF1 activity. There is also a rise in IGF_2 **(31)**. This will result in a weak proliferation of the endometrium, which is well differentiated and maintained.

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