The Uterine Junctional Zone

Faisal Kashgari [*], Ayman Oraif, Osamah Bajouh

Department of Obstetrics and Gynecology, Faculty of Medicin, King Abdulaziz University, Jeddah, Saudi Arabia
fkashgari@gmail.com

Abstract: Knowledge of prenatal and postnatal development of uterine development is very limited in humans. The female reproductive tract is initially formed as part of the urogenital system. The uterine corpus and cervix is differentiated by 12 weeks gestation. Development of the female reproductive tract begins during prenatal life with the formation and fusion of the mullerian ducts. Depending on the genetic sex of the gonads of the embryo, sex is determined with development of either the mullerian duct or wolffian duct. If the testes are absent, developmentof the mullerian duct continues with regression of the wolffian ducts. The basalis layer is not eroded during menstruation or after parturition. The basailis layer contains a zone of loose endometrial glands and stroma, and another zone where the glands terminate and stem cells reside. The basalis layer functions as a germinal compartment that provides stem cells to the functionalis layer each month to regenerate after menses. The uterine junctional zone is a very dynamic and an important structure within the uterus. More studies are needed to further identify the role of the junctional zone in various obstetrical and gynecological diseases.

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Introduction

Knowledge of prenatal and postnatal development of uterine development is very limited in humans. The female reproductive tract is initially formed as part of the urogenital system[1]. The human uterus is formed prior to 8 weeks gestation[2]. The uterine corpus and cervix is differentiated by 12 weeks gestation[2]. Development of the female reproductive tract begins during prenatal life with the formation and fusion of the mullerian ducts. Depending on the genetic sex of the gonads of the embryo, sex is determined with development of either the mullerian duct or wolffian duct. If the testes are absent, developmentof the mullerian duct continues with regression of the wolffian ducts.

The mullerian duct differentiates into the fallopian tubes, uterus, cervix and upper portion of the vagina[3]. Mullerian duct formation is similar between species, and differences in morphology results from differences in fusion of the mullerian ducts[4]. The degree of fusion is species-specific and defines the shape of the adult uterus. In Rodents, fusion is limited which results in formation of two uterine bodies. In animals, ducts fuse posteriorly, which results in a bicornuate uterus with a small common corpus with a single cervix and vagina[4]. Ducts of higher primates (humans) fuse more anteriorly, resulting in formation of a single uterus with a single cervix and vagina. Anatomical variations are observed within a species which results from different degrees of fusion[4].

Subsequent development of the uterus and vagina occurs in two phases: *Organogeniticand functional*[5]. The organogenitic phase occurs once during development and is irreversible. This phase is hormonal (estrogen and progesterone) independent. The epithelia of the mullerian duct are determined to be organ specific. Any insults during this stage affect subsequent function of the organ damages. In the *functional phase,* the epithelia changes each month during the menstrual cycle and is hormonal dependent.

The uterus is not fully developed at birth. Tissue histology is established during postnatal life in animals and presumably humans[4]. Development of the uterus involves: organisation of the endometrial stroma, differentiation of the myometrium, and development of the endometrial glands.

The fully formed human uterus consists of a single uterine body. The layers of the uterus have been traditionally divided into three layers: endometrium, myometrium and serosa. The endometrium is further divided into an *upper stratum functionalis*, which mostly contains glands surrounded by a loose stroma, and *lower stratum basalis,* which contains branching glands surrounded by dense stroma[6].

The basalis layer is not eroded during menstruation or after parturition[4]. The basailis layer contains a zone of loose endometrial glands and stroma, and another zone where the glands terminate and stem cells reside. The basalis layer functions as a germinal compartment that provides stem cells to the functionalis layer each month to regenerate after menses[7].

The Junctional Zone

The subendometrial myometrium and endometrium have a different embryonic origin (paramesonephric duct), to the outer myometrium (non-paramesonephric duct)[8]. These different origins of myometrium is reflected in the function of these 2 layers: The outer myometrium is responsible for the forces of labor[9]. The inner myometrium (junctional zone) is responsible for sperm transport and regulation of implantation and placentation. Differentiation of the junctional zone is under estrogen control and is independent of the outer layer.

The concept that the inner myometrial layeris a separate layer than the outer myometrium was first described in 1898 as the (archimyometrium)[10]. The junctional zone layer was only confirmed recently with the availability of high resolution ultrasound and magnetic resonance imaging (MRI). In 1983, Hricak et al. described this layer using MRI[11]. It was described as a distinct low signal separating endometrium in high signal from outer myometrium in intermediate signal. This zone corresponds to the inner most layer of myometrium and not to the basal layer of endometrium.

The junctional zone has been shown to contain myocytes with morphologic characteristics different from typical myocytes of outer myometrium[12]. The junctional zone myocytes present a greater nuclear area, looser extracellular matrix, and lower water content which decrease the signal of this zone on MRI. Architectural arrangement of the junctional zone is unique with a concentric arrangement of smooth muscle fibers in contrast to longitudinal orientation of smooth muscle fibers of outer myometrium.

Physiological Changes of the Junctional Zone

During premenarche, pregnancy, or postmenopause, the junctional zone is not well seen on MRI.

In the postmenopause, the outer myometrium approaches theintensity of junctional zone because of dehydration of the smooth muscles with fibrous involution of extracellular components. Prepubertal, the Junctional zone is not measurable due to the lack of estrogen. During pregnancy, the junctional zone is poorly visualized, reappears 15 days postpartum and is clearly defined 6 months after delivery. During these stages of the reproductive cycle, the junctional zone cannot be properly assessed[9]. The junctional zone disappears during pregnancy and becomes visible 6 months postpartum[13].

The hormonal variation in the reproductive cycle is one of the major factors contributing to changes in the thickness of junctional zone. Maximal thickness is reached during menses. In contrast, the outer myometrium has no dependence on hormonal stimulation and there is no variation in thickness during menstrual cycle.

One study provided evidence for junctional zone hormonal responsiveness by demonstrating that the junctional zone was thinner in patients using the birth control pill[14]. GnRH agonist therapy creates a similar MRI appearance of the uterus and junctional zone to that of postmenopausal women[15]. Hormonal replacement therapy in postmenopausal women results in reappearance of the junctional zone.

Junctional Zone Contractions

The use of ultrasound with video recording and MRI revealed the contractions of the junctional zone. One study showed that these contractions correlate with phase of menstrual cycle[16]. Video recordings showed the contractions to have a speed of 1.2–1.7 millimeter/second with a frequency of 3–5 contractions/min[17].

Uterine peristaltic activity originates exclusively from the junctional zone[9]. Transvaginal ultrasound allows detection of contraction wavesand recording is carried out over a period of 3-5 minutes. Contractions direction, strength and frequency change in relationship with the phase of menstrual cycle[18].

In the follicular and early luteal phase, contraction waves have a cervix to fundus orientation. The amplitude and frequency of the contractions steadily increases around time of ovulation and is directed toward ovulatory site. These contractions participate directly in transport of sperm toward ovum as reported by Kunz et al.[19]. Sperm has been detected in fallopian tubes a few minutes after vaginal placement. After ovulation,the junctional zone becomes more quiescent but baseline random contractions are present all the time.

Functions of the Junctional Zone

During the luteal phase of the menstrual cycle, uterine activity decreases under the influence of progesterone. Reduced contractions might help the embryo by facilitating supplies of nutrients and oxygen[20]. Reduced uterine activity may also help with the embryo implanting near the uterine fundus[20]. In several studies, conception cycles are associated with a reduction in overall contractility when compared with non-conception cycles[21,22].

The uterus must balance its status for successful implantation and placentation, so that it becomes receptive to invasion of the trophoblast but is still able to control and stop this process. There is increasing evidence that the junctional zone has a role in implantation and placentation though the activity of uterine natural killer cells[23].

Junctional zone contractions might have a role in controlling menstrual flow. Loss of contractions with inner myometrial distortion may be a factor in AUB and dysmenorrhea[24].

Normal Values of the Junctional Zone

In earlier studies, Junctional zone thickness between 2-5 mm was considered to be normal. These values have been revised recently with the availability of better imaging tools. Currently, *Thickness of up to 8 mm is considered normal*[25].. A junctional zone thickness measuring >= 12 mm is highly predictive of histological adenomyosis[26].

Junctional Zone and Gynecological Diseases

Adenomyosis and the Junctional Zone

Adenomyosis is presence of endometrial glandular cells more than 2.5 mm from endometrium-myometrium interface[27]. Involvement of myometrium can include be *diffuse adenomyosis*, or focal. An *Adenomyoma*is a localized confluence of glands forming a mass. The exact prevalence of adenomyosis is unknown[25] but prevalence has been reported to be from 5% to 70%

Transvaginal Ultrasound and MRI are the main investigational tools in confirming suspected cases of adenomyosisThickening of the junctional zone on MRI is consequence of inner myocyte proliferation or hyperplasia[28]. .

Several signs of adenomyosis have been described using MRI:

*Microcysts*Areas of cystic ectopic endometrium (2-8mm) within the junctional zone accompanied by a cystic glandular dilatation[25].

*Adenomyoma*an adenomyoma is a focal consolidation ofglands located within the junctional zone or entire myometrium. It manifests as a myometrial mass distinct from the junctional zone. An adenomyoma is rarer than both focal and diffuse adenomyosis. It is often confused with fibroids. One differentiating feature is thatan adenomyoma does not have large blood vessels at the periphery while fibroids do[25].

Thickness of the junctional zoneA thickness of > 12 mmis most accepted criterion in establishing presence of adenomyosis. Thickening could be diffuse or localised. When thickness is greater than 12 mm, adenomyosis may be diagnosed with a diagnostic accuracy of 85% and a specificity of 96%[26,29].

Focal thickening of JZ of greater than 12 mm is a strong indicator of adenomyosis. *A blurred interface of JZ* with outer myometrium. The uterus may be globally enlarged which is indicative of the presence of adenomyosis.

Adenomyosis and Age

Adenomyosis typically affects older, multiparous women, but junctional zone thickening is not an uncommon finding in young women. One study reported an incidence of 54% of junctional zone hyperplasia in subfertile patients complaining of menorrhagia or dysmenorrhoea[30]. The mean age of women was 34 years, and 71% were nulliparous.

Thickening of the junctional zone associated with adenomyosis alters the peristaltic activity of inner myometrium. Studies have demonstrated a loss of coordinated fundo-cervical contractions during menstruation and of cervico-fundal peristaltic activity in late proliferative phase when compared with controls[28]. These could affect sperm transport and contribute to fertility problems. Disruption of peristaltic waves has been linked to other symptoms, such as dysmenorrhoea and menorrhagia[9].

Endometriosis and the Junctional Zone

Some Studies showed endometriosis have shown a higher prevalence of thickened junctional zone and endometriosis[19]. Studies also showed increased basal tone, frequency and amplitude of uterine contractions with endometriosis[31]. Aberrant junctional zone peristalsis may play an integral part in pathogenesis of endometriosis by facilitating retrograde menstruation.

Junctional Zone Fibroids

Fibroids are associated with many gynecological problems which includes abnormal uterine bleeding, chronic pelvic pain, infertility and early and late obstetrical complications[9]. Fibroids are classified according to location into submucous, intramural, and subserousfibroids. The Impact of fibroids on fertility is thought to be related to the location. Submucous fibroids have the most impact and the Subserous has the least. It is unclear what impact might the intramural fibroids have on fertility and the evidence has been conflicting.

Submucosal fibroids originate from the junctional zone[9]. A study demonstrated that uterine peristaltic movements are affected by submucous fibroids[32]. Junctional zone fibroids might also interfere with gametes migration, embryo transfer or implantation by altering normal uterine contractility or endometrial blood supply.Major anatomical distortion caused by junctional zone fibroids might also affect fertility[33].

A study demonstrated a decreased expression of endometrial HOX gene, a molecular marker of endometrial receptivity, in women with submucous fibroids[34]. Such decrease was seen on endometrium overlying fibroids as well as in healthy endometrium, pointing towards a global effect of submucous fibroids.

Yoshino et al. showeda detrimental effect of intramural fibroids which do not distort the cavity on fertility. Altered contractility has been demonstrated, and MRI shows a higher frequency of uterine peristalsis during mid-luteal phase with intramural fibroids which may lead to decreased pregnancy rates[35]. Another plausible infertility mechanism is possible disruption of JZ which can affect embryo invasion and placentation with subsequent adverse pregnancy outcomes.

In the same study by Yoshino et al.[35] in 51 women desiring fertility who were examined by MRI and had intramural fibroids, There was increased uterine peristalsis which might be a factor in decreased pregnancy rates. In women with high frequency of contractions (>=2 contractions/3minutes), myomectomy reduces the frequency of contractions and improve pregnancy rates.

Studies of in vitro fertilization and junctional zone fibroids have shown significantly lower implantation and pregnancy rates[36]. Estrogen receptors and Progesterone receptor expression is significantly higher in junctional zonefibroids when compared to outer myometrial fibroids. This may explain the higher proliferative activity of these fibroids and their increased responsiveness to GnRH agonist therapy[9].

Obstetrical Disorders and the Junctional Zone

The junctional zone is involved in implantation and placentation[28]. During pregnancy, decidualization occurs first in the endometrium and then in the junctional zone. The endometrium is not normally adhesive and must acquire a receptive phenotype which starts in the junctional zone to allow invasion of the embryo. MRI in the peri-implantation period shows appearance of a low-signal mass located in the junctional zone, presumably at future site of implantation, with disruption of the junctional zone at this site. Of notice, disruption of the junctional zone is seen with miscarriages but not observed in patients with ectopic pregnancies[37].

Disruption of the junctional zone prior to pregnancy may have profound effects on deep placentation and pregnancy outcome. One study reported that adenomyosis which is associated with thickening of the junctional zone, is an important risk factor for Preterm labor and Preterm premature rupture membranes[38]. Two recent studies demonstrated that endometriosis, which is associated with junctional zone thickening, is a major risk factor for pre-term birth[28].

Deep placentation involves full conversion of both endometrial and myometrial segments of the spiral arteries into large, remodelled utero-placental vessels. Incomplete remodelling of the spiral arteries is associated with obstetrical complications, ranging from miscarriage and preterm labor to fetal growth restriction and pre-eclampsia[28].

The primary site of vascular pathology in pregnancies lies in the junctional zone. Defective remodelling was first described in patients with pre-eclampsia. Similar observations were described in association with abruption, sporadic miscarriage, preterm labor and Preterm premature rupture membranes[28].

In severe pre-eclampsia with fetal growth restriction, the junctional zone segment of spiral arteries are characterized by obstructive intimal hyperplasia and atherosis[28].

Advanced maternal age is associated with structural changes in the junctional zone, which might explain the increased risk of pregnancy complications. One study measured the thickness of the junctional zone by MRI and found a gradual increase in diameter of the junctional zone starting in the third decade of life, which is accelerated in women > 34 years[28].

Normal pregnancy induced structural changes of JZ spiral arteries do not completely resolve following a first delivery. Histological studies have shown that changes in internal elastic lamina of junctional zone spiral arteries persist following first pregnancy which provides an explanation for higher birth weight in subsequent pregnancies[28].

Junctional Zone Contractions and Assisted Reproduction Techniques

Junctional zone contractility is exaggerated in IVF cycles when compared with a natural cycle, but follows a similar pattern: maximum at time of oocyte retrieval and decreasing daily thereafter[39]. During IVF, embryos are exposed to an even more mobile endometrium.One study showed that increased junctional zonecontractility just before ET significantly reduced success rate when compared with a minimal number of contractions[40].

Embryos often relocate from uterine cavity after IVF/ET. The ectopic pregnancy rates after IVF ranges from 2.1% to 9.4% after IVF[39]. There is evidence that this is consequence of Junctional zone contractions during Embryo transfer. Experimental studies of mock ET in humans have demonstrated expulsion of methylene blue in 57% of transfers and movement of contrast media towards cervix/vagina in 38% and 21% respectively[39].

Atraumatic Embryo transfer is more frequently associated with a successful outcome[41]. There is a strong correlation between ET technique and junctional zone contractility. Even minimal stimulation of the uterus such as touching uterine fundus with catheter is capable of generating contractions[39], which can relocate embryos towards cervix or fallopian tube. Reducing depth of catheter insertion and not touching the uterine fundus significantly improves pregnancy rates[39].

One study showed that a thickened JZ is a failure predictive factor for embryo implantation in IVF. Analysis of IVF results showed more than 74%

of failure if the JZ > 7 mm. MRI examination for IVF patients may be required with repeated failures[42].

Recurrent Pregnancy Loss and the Junctional Zone

A study evaluated JZ by 3D TVS in women with RPL as compared to normal fertile controls[43]. Thickness and morphology of JZ were evaluated in midluteal phase, in period that coincides with time of embryo implantation. Measurements of thickness of JZ were performed in 60 patients with RPL due to different causes. Control group included 23 fertile women without history of miscarriages and pelvic disease, referred for a routine scan. Patients with RPL showed a JZ thickness significantly increased with respect to that observed in control group (5.8 vs. 5.0 mm). Significantly increased values of the JZ thickness were found among patients with Idiopathic RPL (6.0 mm). 3D TVS of JZ could represent a promising useful tool for screening women with a history of RPL. Thickened JZ may represent an important contributing factor to some causes of RPL and may represent an independent indication of the risk of pregnancy loss.

Conclusion

The uterine junctional zone is a very dynamic and an important structure within the uterus. More studies are needed to further identify the role of the junctional zone in various obstetrical and gynecological diseases.

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