

Fibroids – link with sterility

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Objectives:

- The concept of the archimetra as the organ of human reproduction
- Adenomyosis and endometriosis as diseases of the inner myometrium
- Fibroids as related to the different layers of the myometrium

Summary

The archimyometrium or `junctional zone` or `inner myometrium` as the innermost of three myometrial layers surrounds the whole endometrium and is characterised by a predominantly circular arrangement of the muscular fibres (Werth and Grusdew, 1898, Wetzstein, 1965, Noe et al., 1999, Kunz et al., 2000). Unlike the two outer layers of the myometrium that develop late during ontogeny and therefore termed neomyometrium (Werth and Grusdew, 1898), the anlage of the archimyometrium can already be identified during the first trimester of gestation (hence its denomination). The ontogenetically early formation of the archimyometrium is pertinent to its function that results from the fusion of the two paramesonephric ducts and their mesenchymal elements to form the primordial uterus (Werth and Grusdew, 1898, Noe et al., 1999). The bipartition of the circular subendometrial myometrium in the upper part of the uterine corpus and its separate continuation through the cornua into the respective tubes is the morphological basis of directed transport capacities of the uterus during the menstrual cycle. (Kunz et al., 1996, Kunz et al., 1998b, Noe et al., 1999). The archimetra itself, consisting of the endometrium and the adjacent archimyometrium or junctional zone, is the organ responsible for basic reproductive procedures in human such as directed sperm and embryo transport and implantation of the blastocyst (Kunz et al., 1996, 1998, 2006, 2007). Thus

directed transport of sperm and preimplantation embryos into the tube or fundus-cornual region ipsilateral to the site of the dominant ovarian structure constitutes a genuine uterine function and results from both, the specific structure of the archimyometrium with its fundus-cornual bipartition of the circular fibers (Werth and Grusdew, 1898, Noe et al., 1999) and the effects of the utero-ovarian counter-current system providing an ipsilaterally increased input of hormones from the dominant ovarian structure into the uterine cornual region (Kunz et al., 1998b).

There is growing evidence that diseases of the inner myometrium such as adenomyosis represent an important factor in infertility. This has been shown in infertile women with endometriosis and in baboons with life-long infertility (Barrier et al., 2004, Kunz et al., 2005). Endometriosis and sterility are linked to the existence of adenomyosis and vice versa (Leyendecker et al., 1996, Kunz et al., 2000, 2005) and a number of studies have demonstrated an impairment of ovarian functions such as follicular development and oocyte quality and fertilization rates in women with diseases of the junctional zone (Toya et al., 2000, Garrido et al., 2002, Navarro et al., 2003).

As a consequence of these data regarding the association between fibroids and sterility it appears reasonable to assume that not only the different sizes of fibroids but the sites of their localization as related to the different layers of the myometrium might play an important role if the establishment of a successful early pregnancy and its further development is compromised.

Although the use of MR imaging with respect to the definition of size, number and localization of fibroids is still discussed controversially (Hricak et al., 1983; Brosens et al., 1995; Reinhold et al., 1998; Brosens et al., 1998, Tamai et al., 2006, Vercellini et al., 2006), everybody agreed that this imaging technique represents the best method to visualize the different compartments and their alterations of the non pregnant uterus non-invasively. However, by means of endovaginal sonography (EVS) fibroids can be documented highly reliable as well.

The physician dealing with reproductive disorders often encounters women suffering from infertility in association with fibroids. Besides problems including menorrhagia and pain fibroids are associated with infertility and pregnancy complications. Hence prior to the use of ART it has to be decided whether fibroids might hinder successful treatment and thus have to be removed. Before all fibroids are classified according to their topographical location into submucous, intramural and subseroid fibroids.

There is growing evidence that fibroids of the inner myometrium, i.e. submucous fibroids, have the most negative effects on successful human reproduction. These negative effects can be related to a distortion of the uterine cavity and to a disruption of the anatomical and functional continuity of the archimetra as the organ of menstrual cyclicality. It appears reasonable to assume that a subsequent dysfunction of the uterine organ archimetra by inner myometrium fibroids can be attributed to a dysfunction of a number of basal reproductive pathways. Fibroids of the inner myometrium negatively affect myometrial contractility during the menstrual cycle resulting in impaired directed sperm transport and embryo implantation. It has been shown by MR cinematography in women with submucous fibroids that the uterine peristaltic contractions were partly disrupted; however this could not be observed if the fibroids were located in other sites of the uterine wall. Either as a consequence due to an increased migration or to a delayed implantation and early growth retardation data from IVF cycles have provided evidence that fibroids of the inner myometrium or junctional zone have significantly decreased embryo implantation rates. It can be suggested that the decidual process is also linked to the archimetra with the junctional zone. It appears conceivable that disruptions of the inner myometrium by fibroids predisposes for impaired placentation and probably subsequent obstetrical complications.

Based on immunohistochemical findings it has to be assumed that fibroids of the inner myometrium differ from outer myometrial fibroids not only from their location and effect on reproductive physiology but from their aetiology. Recent studies and own data have shown that the steroid receptor expression in submucous fibroids is higher as compared to fibroids with different location. This correlates very well with data that a number of diseases of the inner myometrium such as adenomyosis, endometriosis and adenomyomas are closely related to a hyperestrogenism of the archimetra. Furthermore with respect to the incidence rates of all these diseases of the inner myometrium an evident correlation has been described. It has to be assumed that fibroids of the inner myometrium derive from distinct progenitor cells as compared to the fibroids of the outer myometrium. From yet unpublished data we have found evidence that fibroids of the inner myometrium exhibit a cyclically dependant steroid hormone receptor expression as the normal archimyometrium but not intramural or subserosal fibroids that may derive from the onto- and phylogenetically more recent neomyometrium. The different origin of inner myometrium fibroids is confirmed by the notion that these fibroids have fewer chromosomal abnormalities than outer myometrial fibroids.

Lecture summary

The modern view of the uterine muscular architecture differentiates between the inner myometrium or archimyometrium and the outer myometrium. While the outer myometrial layers represent the organ of pregnancy and delivery does the inner myometrium as a part of the onto- and phylogenetically older archimetra provide basic reproductive functions such as directed sperm and embryo transport, decidualization, implantation and placentation. Fibroids of the inner myometrium which differ in many aspects from those of the outer myometrium disrupt the continuity of the inner myometrium and thus compromise the physiology of early reproductive processes either during natural or during artificial cycles. While in fibroids of the outer myometrium size matters the inner myometrium fibroids should be considered to be removed surgically prior to the use of ART almost independent from the diameter as measured by imaging means.