Original Study

A Study of Myometrial Growth and Development

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A B S T R A C T

Study Objective: To evaluate myometrial growth and development.
Design: Thirty-five autopsy uteri, ranging from 10 weeks' gestation to age 18 years, acquired over 3 decades from 2 hospitals, were studied based on specimen availability, photographed for documentation, and reviewed at the end of the study. Most were embedded in toto, with 1 block and 1 slide per case. Some were immunostained for actin, CD10, MIB-1, and/or trichrome stain for collagen and muscle. Myometrial thickness was measured by ocular micrometry when sections were nontangential and analyzed by paired-sample *t* tests and bivariate linear regression.
Setting: Two university-affiliated hospitals.
Results: From 20 to 34 weeks, lateral wall corpus thickness increased 6-fold, with a 4- to 6-fold perinatal burst of growth ($P < .01$) and a drop in thickness after the neonatal period ($P = .013$). The corpus was thicker than the dome ($P < .01$) but less thick than the lower uterine segment ($P = .087$). The lower uterine segment was fully muscular in the second trimester, becoming more fibrous near term. Intramural, subserosal, and inframucosal myometaplasia were observed, as primitive stromal cells turned into muscle cells. Myometrial proliferation was brisk in the second trimester but greatly diminished in the perinatal period. Pressure effects from myometrial tone were observed during development. There was a pubertal burst of inframucosal myometaplasia.
Conclusions: Myometaplasia accounted for most myometrial growth, especially in the perinatal and pubertal bursts of growth. Pressure effects, related to myometrial tone, appeared to affect myometrial development. True endocervix, with a fibrous wall and mucinous epithelium, appeared late in development.
Key Words: Myometrium, Development, Myometaplasia, Lower uterine segment

Introduction

Despite Valdes-Dapena's pioneering work on uterine development several decades ago[1,2], myometrial growth and development has received very little study. Indeed, with the exception of our previous paper; neither the pioneering work, nor subsequent publications we have found on the subject, have appeared as peer-reviewed articles in medical journals[3–7]. Valdes-Dapena emphasized low power examination of myometrium. This project attempted a more thorough and detailed cytohistologic analysis of myometrial development at higher magnification.

In regard to myometrial growth, Valdes-Dapena analyzed uterine length, and measurements of corpus length vs. lower uterine segment[2]. The current study assessed myometrial growth by measurement of myometrial thickness using ocular micrometry.

Lastly, although myometrial hyperplasia has been established as a structural variation in adolescent uteri,[5] previous work has not explored pathologic lesions of myometrial development, which is not complete till about age 16. This study looked for myometrial pathology that might occur either before or after birth.

Materials and Methods

Twenty fetal uteri and 15 postnatal uteri were studied. Fetal uteri ranged in gestational age from 10 weeks to term (10, 15, 18, 20, 20, 21, 22, 22, 23, 24, 25, 28, 28, 29, 34, 39, and 40 weeks). Postnatal uteri ranged in age from 5 days to 18 years (5 days, 6 days, 9 weeks, 3, 3, 3, 4, 8, 12, 16, 17, 17, and 18 years). Full autopsy reports, often with detailed clinical information, were generally available, permitting clinicopathologic correlations.

The series was accumulated over 35 years from 2 institutions: Rochester General Hospital and Strong Memorial Hospital, in Rochester, New York. The initial samples were from Strong Memorial Hospital, from 1979 to 1989. Later cases were from Rochester General Hospital, from 1999 to 2013. All postnatal cases were from Strong Memorial Hospital, with autopsies performed by Dr Leon Metlay. In Rochester, critically ill neonates at Rochester General Hospital are transferred as soon as possible to Strong Memorial

Supported by a grant from the Rochester General Hospital Foundation and the Genesee Hospital Foundation. The authors indicate no conflicts of interest.
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1083-3188/$ - see front matter
http://dx.doi.org/10.1016/j.jpag.2014.12.002

Hospital, as are all critically ill infants, children, and adolescents.

Most fetal uteri were submitted in toto, with tubes and ovaries, facilitating evaluation of dome, cornu, and lateral walls and comparison of corpus to the lower uterine segment. This method predisposes to tangential sections. Nonetheless, only original hematoxylin and eosin–stained slides were evaluated, with no deeper sections. Thus, measurements of myometrial thickness were restricted to selected cases where tangential sectioning was excluded. Only 10 of 20 stillbirth uteri and 8 of 15 postnatal uteri were suitable. Statistical analysis was conducted by using paired-sample *t* tests, to compare mean differences in thickness of the lower uterine segment vs the lateral wall of corpus myometrium and the dome vs the lateral wall of the corpus myometrium. Bivariate linear regression was used to evaluate whether gestational age predicted thickness of the lateral corpus, and postnatal age predicted thickness of the lateral corpus in infants and children, compared with neonates.

Immunostains for muscle markers (muscle-specific actin [MSA], smooth muscle actin [SMA], desmin) were done to assess whether primitive-appearing cells were undergoing myometaplasia, to assess whether endometrial stromal cells away from the endomyometrial junction were undergoing myometaplasia, to detect when inward bulges of the endometrium were due to accrual of mature muscle cells bulging up from the endomyometrial junction, or when muscle was present in the lower uterine segment.

MIB-1 stains were applied only in the late second to early third trimester and at the burst of perinatal myometrial growth near term. CD10 stains were done in term or near term cases where excess stromal nuclei with scant cytoplasm were seen in the inner myometrium.

Trichrome stains for collagen were used to distinguish fibrous tissue from muscle tissue in the lower uterine segment. They were also used to demonstrate myometrial scarring in cases of hypoxia in utero.

Each case was photographed and/or measured at the time of initial study, but the collection of photographs and measurements was collectively analyzed only at the end of the study (2013-2014), when additional study was only feasible for the most recent cases.

Results

Normal Myometrial Development

The earliest specimen, from a spontaneous abortion in the first trimester, was at 10 weeks. Only primitive stromal cells were seen in the wall,[3] and there was only a flat surface epithelium, with no epithelial invaginations (Fig. 1A). At 15 weeks (early second trimester), subtle changes were seen in the outer wall, farthest from the flat surface epithelium. Some outer wall nuclei become parallel to the flat surface epithelium, with scant cytoplasm and a spindle shape. This may be the first sign of myometaplasia (stromal cells turning into smooth muscle cells).

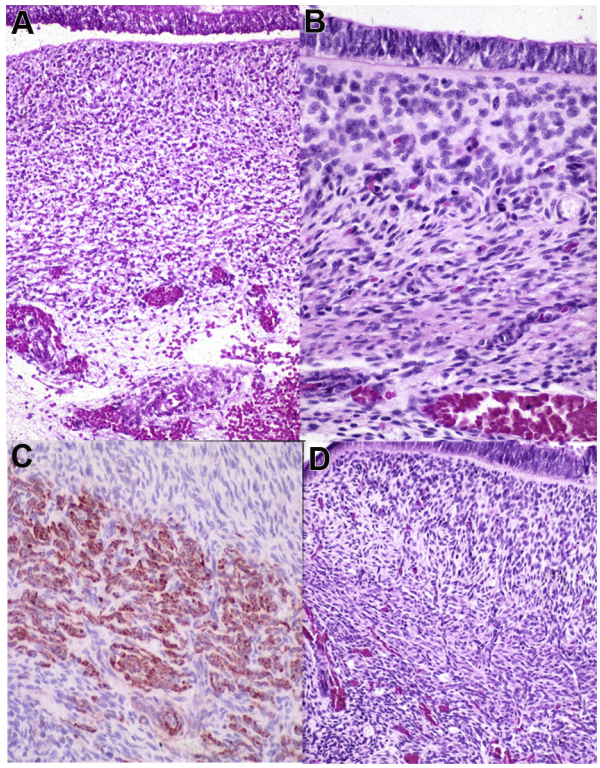

Fig. 1. A, A 10-week fetal uterus has no identifiable smooth muscle. All stromal cells appear primitive. B, An 18-week fetal uterus with definite outer wall smooth muscle. C, Actin (MSA) stain of 20-week uterus shows some parametrial cells with actin-positive cytoplasm. Endometrial stromal cells above the endomyometrial junction (top) have nuclei vertical to the endomyometrial junction. D, A 20-week uterus has compact endometrial stromal cells just beneath the flat surface epithelium, deeper edematous endometrial stromal cells with plump nuclei, and vertical spindle-shaped nuclei at the endomyometrial junction. Nuclei in the outer myometrium tend to be parallel to the endomyometrial junction. Outermost are primitive parametrial stromal cells.

By 18 weeks, definite smooth muscle cells with ample eosinophilic cytoplasm, low nucleus:cell ratio, and nuclei parallel to both the endomyometrial junction and flat surface epithelium were clearly evident in the outer wall (Fig. 1B). This is referred to as intramural myometaplasia. Like gastrointestinal, vascular, and urinary tract smooth muscle, these cells develop myometrial tone[8] that may cause pressure effects in the developing uterus (see later).

Another pattern of myometaplasia first observed in the second trimester was termed subserosal myometaplasia. The subserosal zone in the corpus can be quite thick.[3] Just outside the myometrium, in either the subserosa or in the lower parametrium, the mesenchyme could be very cellular, with some cells having nuclei parallel to the endomyometrial junction and scant MSA-positive cytoplasm (Fig. 1C). Desmin stains were similar to MSA stains but much weaker in intensity and contributed no additional information.

A third pattern first seen in the second trimester was termed inframucosal myometaplasia. This was restricted to the corpus, particularly in the anterior and posterior walls. Myometaplasia of endometrial stromal cells occurred at the endomyometrial junction. Three layers of endometrial stromal cells were detected. The innermost layer consisted of crowded cells with small dark nuclei. Farther from the