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## ABSTRACT

**Introduction:** The in-utero phase of uterine development is not fully understood. While it is known that the uterus develops from fusion of the Mullerian ducts, the morphologic evolution post-fusion is not well established. Beyond simple scientific curiosity, understanding the development of various components of the fetal uterus could potentially enhance our understanding of pathologic disorders.

**Design:** A total of 41 fetal uteri from autopsies performed at our institution between 2004 and 2010 were included in the study. The fetuses ranged in age from 19 to 37 weeks. Each uterus with attached adnexa was sectioned along their long axis to display the full thickness of the uterine wall. The thickness of the endometrium (surface epithelium and stroma) was compared to the myometrial thickness. Various immunohistochemical stains were performed on the uteri to confirm stromal and myometrial thickness and identify potential proteins/pathways involved in uterine development.

**Results:** Up to week 20, the endometrium, composed of purely stroma and a single layer of surface epithelium, and the myometrium had essentially the same thickness. Past 20 weeks the epithelium had shallow invaginations into the stroma, but true glands were not formed. During this time the stroma remained the same thickness as the myometrium. In cases over 30 weeks, the ratio of endometrium to myometrium decreased from 1:1 to 1:4. CD10 was consistently expressed in the uterine stroma while desmin and smooth muscle actin were expressed in the myometrium. Estrogen receptor (ER) was expressed predominantly in the stroma while the progesterone receptor (PR) was expressed in the epithelium and myometrium. As seen in the post-menarchal uterus, the epithelium was CK7 positive and CK20 negative.

**Conclusions:** Up to week 30 of gestation, fetal uteri have an endometrial/myometrial ratio of 1 (E/M=1) compared to a ratio of nearly 1/10 in the adult uterus. The adult endometrium has surface epithelium, glands and stroma, while fetal endometrium is composed of a single layer of epithelium overlying pure stroma. As the absolute thickness of both the stroma and myometrium is greater in the adult uterus, a differential rate of growth is probably responsible for the transformation in the E/M ratio under the influence of cyclic hormones.

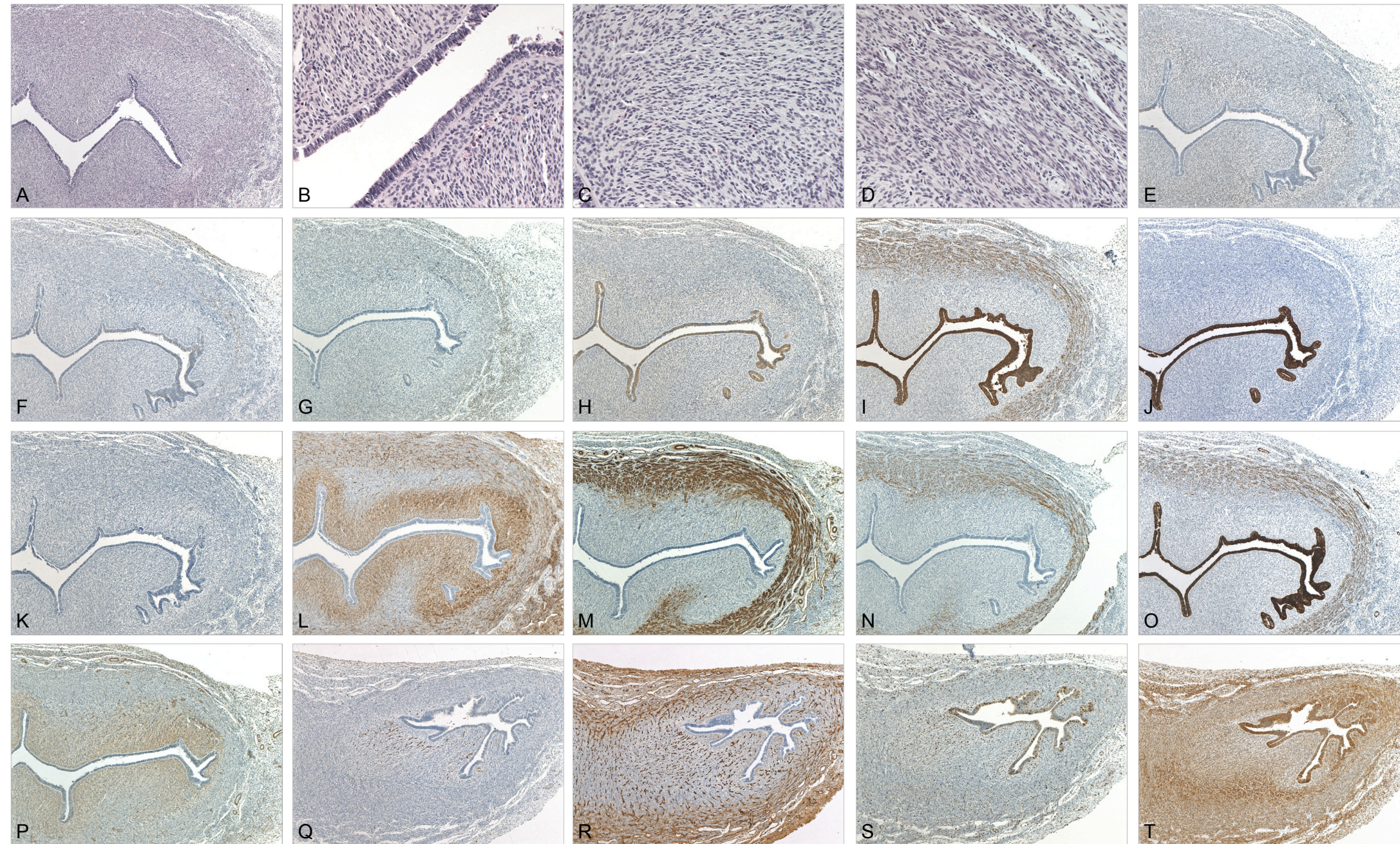
## INTRODUCTION and METHODS

- It is known that the uterus develops from the fusion of the Mullerian ducts, but following that fusion it is unclear how the three components of the uterus (endometrium, stroma, and myometrium) evolve to the post natal stage.
- The autopsy service of our department was searched for fetal uteri. A total of 41 were collected ranging from 19 weeks to 37 weeks. The three components of the uterus were examined by H&E and a panel of immunostains.

## RESULTS and CONCLUSIONS

- At 20 weeks the uterus consisted of a one cell layer thick endometrium with no invaginations or glands and a stroma and a myometrium of equal thickness. By the end of gestation the endometrium had started to invaginate and the myometrium was four times the thickness of the stroma.
- Although the Ki67 index is similar in the stroma and myometrium, Bcl2 is more highly expressed in the myometrium, suggesting more proliferation.

## FIGURE 1



At 25 weeks the uterus (A) has a single layer endometrium with rare invaginations and no gland formation (B). The stroma (C) is the same thickness as the myometrium. (D) Immunostains (E-T) reveal: E. Focal positivity for estrogen receptor (ER) in the stroma, F. Progesterone receptor (PR) in the nuclei of the epithelium and myometrium, G. Androgen receptor (AR) with patchy positivity in the outer myometrium, H. Her-2 along the cell membrane of the epithelium, I. Pancytokeratin AE1/AE3 in the epithelium and the myometrium, J. Cytokeratin 7 (Ck7) expressed only in the epithelium, K. A lack of cytokeratin 20 (Ck20) in all three components, L. Strong and diffuse expression of CD10 in the stroma with focal expression in the myometrium, M. Smooth muscle actin (SMA) limited to the myometrium and vasculature inside and outside of the uterus, N. Desmin limited to the myometrium, O. Strong expression of Cam 5.2 in the epithelium, myometrium and vasculature, P. Diffuse but weak staining of vimentin in the stroma, Q. Limited, but strong, expression of cKit in some cells of the stroma, R. Strong expression of CD34 in the vasculature of the uterus and surrounding tissues, but no expression in the endometrium, stroma, or myometrium, S. A Ki67 index of 30% in the epithelium and 20% in the stroma (predominantly sub-epithelial) and myometrium, T. Strong and diffuse expression of Bcl2 in the epithelium and myometrium with more focal expression in the stroma.