Altered expression of activin, cripto, and follistatin in the endometrium of women with endometrioma

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Objective: To evaluate the expression pattern of activin A, activin receptors, and activin modulators messenger RNA (mRNA) in the eutopic endometrium of patients with endometriosis at different phases of the menstrual cycle and to evaluate the mRNA expression of the same proteins in endometriomas during the menstrual cycle.
Design: Prospective study.
Setting: University hospital.
Patient(s): Women with and without endometriosis.
Intervention(s): Samples of endometrial and endometriotic tissue from women with endometrioma (n = 48), and endometrial samples from women without endometriosis (controls) (n = 48).
Main Outcome Measure(s): Quantification of activin A, activin B, activin receptor II, nodal, cripto, inhibin α, and follistatin expression by real-time reverse-transcriptase polymerase chain reaction (RT-PCR).
Result(s): The eutopic endometrium of patients with endometriosis showed [1] higher activin A mRNA expression in the proliferative phase and a lack of late secretory phase peak, [2] a lack of endometrial cycle-related variations of cripto and inhibin α mRNA expression, and [3] an inverse expression pattern of follistatin mRNA. Endometriomas showed similar variations in the expression of activin-related protein mRNA during the menstrual cycle as eutopic endometrium.
Conclusion(s): The disturbed expression of endometrial activin A, cripto (activin receptor antagonist), and follistatin (activin-binding protein) suggests a dysfunction of the activin pathway in endometriosis. Endometriomas showed similar changes of activin-related proteins during the menstrual cycle, which supports a common biology for eutopic and ectopic endometrium in endometriosis. (Fertil Steril® 2011;95:2241–6. ©2011 by American Society for Reproductive Medicine.)

Key Words: Activin A, activin B, activin receptors, cripto, endometriosis, follistatin, inhibin α, nodal

Endometriosis is a pathologic gynecologic entity typical of women in reproductive age, associated with pelvic pain and infertility (1). The disease can manifest in three clinically distinct forms: pelvic endometriotic implants, ovarian endometriomas, and deep endometriotic nodules (1, 2). These variants of the same disease have in common histologic features as chronic bleeding and signs of inflammation (1, 2).

Endometriotic tissue proliferates in the peritoneal environment and maintains a histologic similarity to eutopic endometrium (2). Indeed, ectopic implants seem to remain functionally responsive to sex steroid hormones but with differences in their protein production and receptor expression (3). Endometriotic cysts express matrix metalloproteinases (MMP) and angiogenic factors in higher amounts with respect to eutopic endometrium, suggesting that the endometrial tissue undergoes modifications that enable its implantation in the peritoneal cavity and pelvic organs (4). Moreover, ectopic endometrium has a decreased expression of relaxin and urocortin messenger RNA (mRNA) expression, which supports a difference with eutopic tissue (5, 6). Expression of estrogen and progesterone receptors is quantitatively altered in endometriotic tissue and biologically significant quantities of progesterone and estrogen are produced locally in endometriotic tissue through an abnormally active steroidogenic cascade (2). Molecular and biochemical studies also have revealed that the eutopic endometrium of patients with endometriosis shows differences in comparison with healthy women, which suggests a role of endometrial dysfunction in infertility (7–9); $\alpha v\beta$ integrins in particular are reduced at the time of implantation (7, 10).

Transforming growth factor β (TGF-β) and its family members are expressed by human endometrium, acting on cell proliferation, differentiation, immune function, apoptosis, and tissue remodeling and playing a role in the menstrual cycle, decidualization, and early pregnancy (11, 12). The TGF-β superfamily includes activins and inhibins, which are closely related dimeric glycoproteins (13, 14). Activin A (βA βA) is produced by the endometrium (15, 16), with the highest mRNA expression in the secretory phase (17) under progesterone and interleukin 1 (IL-1) modulation (18); it plays a possible role in the process of decidualization (19, 20). Activin B (βB βB) is also expressed by the endometrium (16), is related to the degree of endometrial decidualization, and is reduced in tubal ectopic pregnancy (21).

The biologic effects of activins are mediated by specific receptors (ActR), encoded by different genes, ActRI and ActRII, that initiate the Smad phosphorylation cascade (22, 23) and are localized in human

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