EXPERIMENTAL STUDY

Increased expression of estrogen receptor β in human uterine smooth muscle at term

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Abstract
Expression of the cx43 gene for the gap junction protein, connexin43 (Cx43), through activator protein (AP)-1 activity has been shown to be inhibited in human primary myometrial cultures pretreated with estrogen. In the present study, the primary myometrial cultures were shown to express predominantly ERβ, a subtype of estrogen receptor that inhibits AP-1 activity when bound to agonists. ERβ levels were decreased in the primary myometrial cultures after treatment with the phorbol ester, 1,2-O-tetradecanoyl-13 acetate, to stimulate AP-1 activity, and this effect is inhibited if cells were pretreated with estrogen. Two isoforms of ERβ were found in primary myometrial and leiomyoma cultured cells. Immunoblot and RT-PCR analyses indicated that ERβ expression was increased in human term myometrial tissue compared with non-pregnancy tissue. Immunohistochemistry localized ERβ to the nucleus in cells of term myometrial tissue samples that had high ERβ expression. ERβ was increased in term tissue in which Cx43 protein levels were low. In myometrial tissue in which Cx43 protein levels are greatest (e.g. during active labor), ERβ was barely detectable. Only low levels of ERβ were detected in non-pregnancy myometrial and leiomyoma tissues, and the lowest levels were found in tissues from mid cycle. In contrast, ERα was highly detectable in the non-pregnancy myometrial and leiomyoma tissues, but not in term myometrial tissue samples. This work indicates there is a dramatic switch from ERα to ERβ expression in the myometrium during pregnancy. The results suggest that, during gestation, myometrial ERβ may inhibit AP-1 activity and thus block induction of the cx43 gene and other labor-associated genes. Labor may ensue after a loss of myometrial ERβ expression.

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Introduction
Escalation of serum concentrations of steroid hormones, estrogens (17β-estradiol, estrone, and estriol), in women during gestation suggest that these hormones play an essential role during pregnancy in humans (1). Estrogens are found to be stimulatory to the initiation of labor in animals that experience progesterone withdrawal before parturition (2–4). In contrast, in animals such as guinea pigs, which do not have pre-parturition progesterone withdrawal, estrogen is inhibitory to the initiation of labor (4). The role of estrogen has not been determined in humans, who also do not experience pre-parturition progesterone withdrawal. One of the tissues targeted by estrogen during gestation is the uterine smooth muscle, the myometrium (5). Labor initiates as the myometrium ceases being quiescent and displays synchronous contractility. These physiological changes are believed to result from changes in myometrial gene expression.

Estrogen regulates gene expression in estrogen-targeted tissue through binding one of two members of the superfamily of steroid hormone nuclear receptors, the estrogen receptors (ER) (6). The two subtypes of estrogen receptors, ERα (67 kDa) and ERβ (60 kDa) are coded by separate genes (7, 8). They are expressed alone or together in several different tissues of the body (8, 9). ERα and ERβ have been demonstrated to have the same pharmacological responses through the estrogen response elements (EREs) in DNA promoters (10, 11). Estrogen receptors also modulate the expression and activity of transcription factors such as the proto-oncogene products, c-Jun and c-Fos (12–14). Jun and Fos family members regulate the expression of specific genes by binding to DNA elements known as activator protein (AP)-1 sites (15, 16). In contrast to the classical receptor-mediated transactivation from EREs, ERα and ERβ have opposite regulatory activity when mediated through the AP-1 promoter element (17): agonist-bound ERα activates AP-1 activity, whereas agonist-bound ERβ inhibits AP-1 activity. However, when bound by antagonists, both estrogen receptors activate transcription from AP-1 sites. The transactivation of ER through
AP-1 activity involves its interaction with Jun and Fos family members, and the outcome is sensitive to the member of the Jun/Fos family that is expressed (18).

cx43, the gene for the gap junction protein, connexin43 (Cx43), is a labor-associated gene that becomes highly expressed in the myometrium before the onset of parturition (5, 19, 20). Early expression of cx43 is associated with premature labor (20). Cx43 gap junctions assemble and promote intercellular communication, which is believed to synchronize labor contractions through the passage of molecules such as Ca^{2+} (5, 20). Regulation of cx43 expression probably reflects the regulation of other labor-associated genes in the myometrium, as AP-1 is a ubiquitous regulatory element.

We have determined that the 5' flanking promoter region of the human cx43 gene contains an AP-1 site (21), the activity of which may be important for the induction of cx43 expression at term (22). We have shown that increased cx43 expression in human myometrium at term correlates with increased expression of c-Jun and c-Fos (22), and have demonstrated that stimulation of human myometrial AP-1 activity transiently increases c-Jun and c-Fos expression and induces cx43 gene transcription (22). This is true whether AP-1 activity is stimulated through protein kinase C activation after treatment with 12-O-tetradecanoyl-13-acetate (TPA) or through protein kinase A activation after incubation with 8-bromo-cAMP (21, and T Peresleni, J J Wu & J Andersen, unpublished observations). We have shown that estrogen antagonizes the induction of cx43 expression through AP-1 activity in primary myometrial cultures without significantly decreasing c-Jun or c-Fos levels (22). These published results suggested that the cultured uterine cells might express ERβ.

We previously analyzed the levels of ERα in term myometrium and determined that the levels of this receptor protein were negligible in pregnancy myometrium (22). With the availability of antibodies to ERβ, in the present study we analyzed the expression of ERβ in primary cultures of human myometrial cells and in term myometrial tissue. We found an inverse relationship between the levels of expressions of ERβ and cx43 in the term human myometrial tissue tested.

### Materials and methods

#### Tissue acquisition

Approval to utilize human tissue was given by the Stony Brook University Hospital Committee on Research Involving Human Subjects (No. 97–1224 and No. 95–1695). Human myometrial tissue from non-pregnant and postpartum women was obtained from surplus pieces of surgical specimens after hysterectomies. Uterine leiomyoma tissue was obtained in the same manner. After the patient gave written consent, term myometrial tissue was obtained from women during elective and indicated cesarean section (Table 1). Full-thickness strips of term myometrial tissue were excised from the upper margin of the transverse uterine incision. The tissue was snap frozen and reserved in liquid nitrogen.

Small aliquots of individual frozen tissue were quickly sliced on ice, placed in 5 vol. 8 mol/l urea, 5% SDS solution and processed as described by Brandon et al. (23) for immunoblot analysis. For immunohistochemistry, sections (5 μm) of frozen tissue were cut at −25°C and fixed to prepared glass slides.

#### Cell culture system

For cell culture experiments, myometrial tissue was processed and cultured as described by Zhao et al. (24) and Andersen et al. (25). The cultures were not passaged and were used within 2 weeks of the initial plating. Twenty-four hours before the experiments, the culture medium was changed to serum-free, phenol-red-free Dulbecco’s modified Eagle’s medium supplemented as

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### Table 1

Profile of women from whom term myometrial tissue was obtained during c-section and postpartum. Samples are ordered by increasing cx43 expression. The numbers were assigned to each sample as they were obtained.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Week†</th>
<th>Labor status</th>
<th>Dilatation (cm)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cs3</td>
<td>37</td>
<td>Pre-active</td>
<td>5</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>Cs8</td>
<td>38</td>
<td>None</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cs1</td>
<td>38</td>
<td>None</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cs9</td>
<td>40</td>
<td>None</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cs2</td>
<td>39</td>
<td>None</td>
<td>1</td>
<td>Breech</td>
</tr>
<tr>
<td>Cs6</td>
<td>39</td>
<td>Pre-active</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Cs10</td>
<td>38</td>
<td>None</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cs4</td>
<td>40</td>
<td>Pre-active</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cs5</td>
<td>39</td>
<td>Yes</td>
<td>8</td>
<td>Fetal distress</td>
</tr>
<tr>
<td>Cs7</td>
<td>40</td>
<td>Yes</td>
<td>4</td>
<td>Failed VBAC</td>
</tr>
<tr>
<td>Pp</td>
<td>40</td>
<td>Postpartum</td>
<td>–</td>
<td>Hemorrhage after delivery</td>
</tr>
</tbody>
</table>

† Estimated week of pregnancy. VBAC, vaginal birth after previous c-section.
described elsewhere (25, 26). All experiments with the primary cultures were performed using this defined serum-free medium. Ethynyl estradiol was added to the cultures in a concentration of 10 nmol/l for 48 h. TPA (Caltbiochem-Novabiochem Corporation, La Jolla, CA, USA) was added to the cultures in a concentration of 100 ng/ml for 3 h. Control samples were treated with vehicles, 0.1% ethanol and 0.03% dimethyl sulfoxide.

Immunoblot analysis

The relative levels of ERα (67 kDa), ERβ (60 kDa) and Cx43 (43 kDa) proteins were determined for 100 μg of each of the tissue lysates through immunoblot analysis. Polyclonal antibodies (pAb) for ERα (rabbit polyclonal SC 543) and ERβ (goat polyclonal SC 6822) were purchased from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA). Antibody for Cx43 (mouse monoclonal mAb 3068) was purchased from Chemicon Internationals, Inc. (Temecula, CA, USA).

Preparation of cell lysates and immunoblot analysis using enhanced chemiluminescence (Amersham Life Science, Bucks, UK) were performed as previously described (24, 25). Prestained marker proteins (BioRad) were run in parallel. Cell lysates from HeLa cells (ATCC CCL 2), MCF7 breast cancer cell line (ATCC HTB 22) and the human metastatic prostate cell line, LNCaP.FGC (ATCC CRL 1740) were used as controls in the immunoblot analyses.

Immunohistochemical detection of ERβ

Immunohistochemical detection of ERβ in frozen myometrial tissue was performed as previously described (22) using the same anti-ERβ pAb that was used for immunoblot analysis. A section of frozen prostate tissue from a 66-year-old man with prostatic adenocarcinoma was also analyzed as a positive control for ERβ. Incubations with primary antibodies were performed overnight at 4 °C. Sections were also counterstained with light green, using standard protocols. Duplicate sections were stained with hematoxylin and eosin using standard procedures to facilitate identification of cellular elements and areas of necrosis (data not shown). Peroxidase activity was observed by light microscopy using a 25× objective and photographed using a Princeton Instruments Micromax cooled CCD digital camera. Evaluation of myometrial results was determined by comparison of staining in tissue sections that were incubated with anti-ERβ pAb with duplicate tissue sections that were incubated without primary antibody.

RT-PCR analysis

The relative levels of ERβ mRNA were analyzed in myometrial tissue using RT-PCR analysis. Total RNA was isolated from tissue as described elsewhere (24). Then 80 μg total RNA were reverse-transcribed with dT primers for 1 h at 37 °C, following standard procedures. cDNA was purified using phenol–chloroform extraction and precipitated with ethanol. PCR was performed to amplify the cDNA resulting from reverse-transcription of 1, 2 or 5 μg total RNA. PCR conditions were as described by Vladusic et al. (27). PCR products for β-actin and β2 microglobulin were generated to assess cDNA quality. PCR reactions using ERα and ERβ primers (27) resulted in 417 base pair and 435 base pair products, respectively. PCR products were analyzed by electrophoresis on 3% NuSieve agarose, 1% agarose gel containing ethidium bromide and compared with low-molecular-weight DNA marker, which was generated by digesting pBR322 with HaelII. PCR products from plasmids carrying either ERα cDNA or ERβ cDNA were used as positive controls.

Results

ERβ expression in human myometrial tissue at term

The relative levels of ERα and ERβ were determined by immunoblot in lysates from 10 cesarean section (c-section) myometrial tissue samples and one postpartum myometrial tissue (Table 1) and compared with the relative levels in non-pregnancy myometrial and leiomyoma tissue lysates from cycling women (Fig. 1). In addition, lysate from MCF7 breast cancer cells was analyzed as a positive control for ERβ; lysate from HeLa cells was analyzed as a negative control for ERα and ERβ. Also, because ERβ is expressed in prostate tissue (8, 10), lysate from the human metastatic prostate cell line, LNCaP.FGC, was analyzed.
However, the prostate cell line was negative for both subtypes of ER.

As observed previously, ERβ protein was barely detectable in the term myometrial tissue by immunoblot. In contrast to ERα (Fig. 1, top panel), ERβ was detected at levels significantly greater (2.5–13 times) than those in the non-pregnancy tissue (Fig. 1, bottom panel; compare ERβ results in lanes Mf, Lf, MI, LI (non-pregnant tissue) with results in c-section lanes 6, 10, 4 and 7 and lane Pp (postpartum tissue). The RT-PCR analysis of the levels of ERα and ERβ mRNAs in the myometrial tissue was consistent with the immunoblot results (data not shown). Both myometrial and leiomyoma tissues from non-pregnant women appeared to express relatively low levels of ERβ protein, and these levels were further suppressed during mid cycle (not all data shown).

Two protein bands were observed for ERβ in the immunoblot. Both of these bands are easily seen in Fig. 1 in the lane containing lysate from cultured myometrial cells (lower panel, lane m), as indicated by dashes). The faster moving form of ERβ was the predominant form observed in the analysis of cultured leiomyoma cell lysate (data not shown). The reason for the difference in mobility between the two ERβ isoforms has not been examined.

**Localization of ERβ to the nucleus in term myometrial tissue**

Immunohistochemistry was used to detect ERβ protein in the same tissue as was analyzed by immunoblot (Table 1). The same anti-ERβ pAb was used in both the immunoblot and immunohistochemistry analyses. Figure 2 shows representative immunohistochemical results. Clear nuclear staining was observed in the term myometrial tissue that had increased levels of ERβ as determined by immunoblot (compare Fig. 1 lanes Pp

![Figure 2](https://example.com/figure2.png)

**Figure 2** Location of ERβ in the nucleus of term human myometrium with high expression. Representative immunohistochemical staining using anti-ERβ pAb. (A) Postpartum myometrial tissue; (B) c-section 7 myometrial tissue; (C) c-section 6 myometrial tissue; (D) myometrial tissue from luteal phase; (E) prostate cancer tissue as a positive control; (F) non-immune control of postpartum tissue. Arrows point to positively staining nuclei in panels A, C, and E. See Table 1 for profiles of the pregnant patients.
and CS 6 and with Fig. 2 panels A and C, respectively). Nuclear staining was also observed for prostate tissue from a 66-year-old man diagnosed with prostatic adenocarcinoma (Fig. 2, panel E). This is in contrast to that observed in the prostate cell line (Fig. 1, lane P). No nuclear staining was observed for non-pregnancy myometrial tissue (Fig. 2, panel B) or for the term tissue (CS 7) taken from a woman in active labor (Fig. 2, panel B). These results confirmed those obtained by immunoblot and indicated that ERβ is found in the nucleus of cells in myometrial tissue with a relatively high degree of expression. In contrast, in tissue with relatively low ERβ expression, no nuclear staining was observed (Fig. 2, panels B and D).

Relationship between ERβ and Cx43 expressions in human myometrium at term

Immunoblot analysis was used to measure the relative levels of ERβ (Fig. 3A) in term myometrial tissue samples that had previously been used to analyze levels of Cx43 and ERα (22). Lysates from HeLa cells, MCF7 breast cancer cells and non-pregnancy myometrial tissue were also analyzed (Fig. 3, lanes marked H, B and m, respectively). The numbers at the top of each CS lane in Fig. 3 designate the c-section sample number listed in Table 1. samples (Fig. 3A, CS lanes 3, 8, 1, 9, 2, 6, [10], 4, 5, 7) having been placed in order of increasing expression of Cx43 (compare with Fig. 3B; technical difficulties occurred with application of sample 10). The samples that had the greatest levels of Cx43 protein also had significantly greater levels of c-Jun and c-Fos (22). It is evident that ERβ levels decreased in the c-section samples as Cx43 levels increased. In addition, ERβ levels were increased in the postpartum myometrial tissue (Fig. 3, Pp), and these tissue samples had reduced Cx43 protein levels compared with those observed in the c-section tissue (Fig. 3, lanes CS). It is interesting that, in general, the slower-moving form of ERβ was found in tissue from women in pre-active labor or in postpartum tissue samples (Fig. 3A, compare mobility of ERβ in samples CS 8, 1, 9, 2 [and 10 in Fig. 1] with mobility in samples CS 6, 4 and Pp).

Effect of treatment with estrogen or TPA on ratios of ERα and ERβ in cultured myometrial cells

We observed previously that treatment with estrogen antagonized TPA induction of Cx43 expression in the uterine cells (22). In the present study, we analyzed by immunoblot the relative levels of ERα and ERβ in cultured luteal-derived myometrial cells after treatment with estrogen, TPA, or both. Untreated myometrial cells expressed both ERα and ERβ (Fig. 4A, lane 0). Treatment with TPA (100 ng/ml) (Fig. 4A, lane TPA) resulted in the down-regulation of the expression of both receptors. Treatment with 10 nmol/l ethynyl estradiol for 48 h (Fig. 4A, lane E) resulted in upregulation of ERβ expression. However, in cells pretreated with the estrogen and then treated with TPA, ERα expression was downregulated and ERβ was upregulated (lane marked TPA/E). Pretreatment with estrogen altered the ratio of ERβ to ERα in cells treated with TPA compared with that found in cells treated with TPA alone (compare ERα and ERβ in lanes marked TPA and TPA/E).

For comparison, levels of Cx43 were examined in the same cells as shown in Fig. 4A. Treatment with estrogen alone caused upregulation of Cx43 expression through an unknown mechanism. Treatment with TPA alone upregulated the expression of Cx43 and resulted in a greater ERα:ERβ ratio. Treatment with TPA in cells exposed to estrogen downregulated Cx43 expression and resulted in a lower ERα:ERβ ratio. As ligand-bound ERβ antagonizes AP-1 activity, the downregulation of ERα and upregulation of ERβ in the myometrial cells may account for the antagonism by estrogen of TPA induction of Cx43 gene expression.

Discussion

Uterine smooth muscle is the primary tissue involved in labor. At term, the myometrium changes from a quiescent...
Human term myometrium has increased ERβ

In cultured myometrial primary cells, two forms of ERβ protein separated after gel electrophoresis. The reason for the change in protein mobility is unknown. Shifts in protein mobility may occur because of differential mRNA splicing or post-translational protein modifications such as phosphorylation (29). A post-translational modification of a protein may enhance or conclude from the results of both techniques that ERβ expression is very low in the non-pregnancy myometrium and leiomyoma tissues, compared with term myometrium.

Expression of ERβ in leiomyoma tissue suggests that leiomyoma pathobiology may play a greater part than does a heightened response to estrogen. We have previously reported that ERα has increased expression in leiomyoma tissue compared with myometrial tissue, particularly during the follicular phase (26). In contrast, ERβ levels in both myometrial and leiomyoma tissues vary similarly during the menstrual cycle, being lowest at mid cycle. The major characterized difference between the two subtypes of ER involves their trans-activation functions in the context of AP-1 elements and in the ability of different ligands to affect this function (10, 11, 17). Gene expression in the tumor may be affected adversely by an inappropriate ratio of the two estrogen receptors at the beginning of the menstrual cycle, when ERα levels are abnormally increased. AP-1 activity, for example, may not be under normal control as a result of the altered ERα:ERβ ratio. This is significant, as AP-1 activity is a primary pathway used to control cell growth (15, 16).

Our recent studies clearly demonstrate that increased AP-1 activity is involved in the induction of cx43 expression in term myometrium (21, 22). Myometrial AP-1 activity involves activation of c-Jun and c-Fos proteins, the factors that bind to AP-1 sites in DNA. A proximal AP-1 site in the human cx43 promoter functions to induce cx43 transcription in primary cultures of uterine smooth muscle cells after activation of AP-1. Our work points to the possibility that increased AP-1 activity may also have a role in the induction of the other labor-associated genes.

The involvement of the AP-1 activity in the induction of cx43 expression in human myometrium at term suggests that, during pregnancy, estrogen may down-regulate cx43 expression by controlling the activities of c-Jun and c-Fos proteins through interaction with ERβ. One possibility is that ERβ interacts with the AP-1 binding proteins and interferes with their transactivation functions, thus keeping the induction of cx43 expression in check. The cx43 gene is then one of the first genes to be identified that may have this regulation. In support of this, there appears to be an inverse relationship between the expression of ERβ and the expression of cx43 in term myometrium. It appears that, as ERβ expression decreases, cx43 gene expression increases. Loss of ERβ expression or function appears to tip the scales in favor of cx43 expression.

In our previous work (21, 22), we examined the levels of ERα in term myometrial samples and were surprised to find very low levels at term. In the present study, we found that ERβ, the newly found estrogen receptor subtype, was expressed in relatively high levels in the myometrium from women undergoing elective and indicated c-section, compared with that in myometrium and leiomyoma tissues from non-pregnant women. Our results indicate that, whereas ERα is the predominant estrogen receptor subtype in non-pregnancy myometrium, ERβ is the predominant estrogen receptor subtype in term myometrium.

Pedeutour et al. (28) recently reported detecting ERβ expression in human non-pregnancy myometrium and uterine leiomyoma tissues using RT-PCR. Our detection of ERβ mRNA in non-pregnancy tissue using the RT-PCR method is in agreement with our detection of the relative levels of ERβ protein by immunoblot. We
decrease its activity, or may alter the half-life of the protein (30). A shift in protein mobility to the slower form of ERβ correlated with increased cx43 expression and a decrease in ERβ levels. The reason for the change in ERβ mobility may reveal a regulatory mechanism for ERβ that is important to its function. The mobility of ERβ in term myometrial tissue changed according to labor status. Regulation of ERβ protein may be part of the switch that allows for changes in myometrial gene expression at term. Downregulation of ERβ function or levels would lift the inhibition of AP-1 activity and allow for subsequent induction of labor-associated genes that are regulated through AP-1. It is important to characterize the modification and decipher its role in the function of ERβ in regulating gene expression.

Although cultured myometrial cells are derived from the tissue of non-pregnant women, they have a number of the morphological and physiological characteristics of term myometrium. For example, Cx43 protein was not detectable in normal non-pregnancy myometrial tissue by immunohistochemistry or by immunoblot, but, when cultured, the myometrial cells derived from non-pregnancy tissue expressed high levels of Cx43 protein (compare references 22 and 25). The primary myometrial cells have high expression of other labor-associated genes such as thrombospondin-I (31). Like term myometrium, and unlike non-pregnancy myometrium, cultured myometrial cells derived from non-pregnancy tissue express ERβ. They also express relatively high levels of functional prostegestrone receptor, in common with term tissue (22, 24). Primary myometrial cells from non-pregnancy tissue contain oxytocin receptors and respond to oxytocin with transient calcium oscillations that are not distinguishable from those from myometrial cells derived from pregnancy tissue (32). The reason that the cultured myometrial cells were so similar to pregnancy myometrium may be due to the use of fetal bovine serum or the thinning out and stretching of the attached explant pieces during culturing. Nonetheless, their similarity with pregnancy myometrium makes them a useful in vitro system for studying the myometrial-specific regulation of human genes such as cx43 and ERβ.

Previously, we had screened for expression of an alternative estrogen receptor in term myometrium by binding fluorescein-conjugated estradiol to the tissue. Negative results using this technique made us conclude that at that time that an alternative estrogen receptor was not expressed at high levels. Interestingly, Pullkkinen & Hämiäiläinen (33) and Perrot-Applanat et al. (34) also found low estrogen binding in human term myometrium. In contrast, using specific antibodies to ERβ, we found that expression of the newly found ERβ was increased in term myometrial tissue. It may be that endogenous estrogen bound to ER in situ created an artifact in the first study by blocking the binding of the fluorescein-conjugated estradiol. This appears to be an intrinsic weakness of the method.

Our new results are significant for two reasons. Firstly, finding relatively high levels of ERβ in term myometrium supports the concept that estrogen plays a significant role in regulating myometrial gene expression at least during the last trimester. Secondly, the observation that expression of ERβ is inverse to that of cx43, one of the labor-associated genes, suggests that ERβ may play an important biological role during late pregnancy in downregulating expression of labor-associated genes in uterine smooth muscle cells. Our study supports the concept that estrogen, like progestosterone, plays an essential role in pregnancy maintenance in humans. It would be interesting to see if ERβ is also expressed in the term myometrial tissue of animals such as guinea pigs, which do not have progestosterone withdrawal before parturition. Perhaps these animals would be better models for human parturition than sheep or rats (4).

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References

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