OBSTETRICS

Direct electrical stimulation softens the cervix in pregnant and nonpregnant rats

Dajun Fang, MD; Shao-Qing Shi, MD; Leili Shi, DDS; Jinying Yang, MD; Huishu Liu, MD, PhD; Huimin Xia, MD; Robert E. Garfield, PhD

OBJECTIVE: The objective of the study was to determine the effects of electrical stimulation (ES) on cervical ripening in pregnant and nonpregnant rats.

STUDY DESIGN: Timed pregnant and nonpregnant Sprague-Dawley rats (n = 6–7/group) were used. Cervical ES for pregnant rats was performed in vivo on day 15 of gestation by inserting an electrical probe into the vagina in contact with the cervix. Parameters of ES varied from 0.1 to 0.2 mA, 10 pulses per second, 20 milliseconds pulse duration, and repeating pulses for 15, 30, 60, and 120 minutes for pregnant ES groups and similar times for sham control groups with electrode but without ES. Nonpregnant ES groups were stimulated with only 0.2 mA for 30 minutes. Cervical collagen was measured in controls and following ES at various times using light-induced fluorescence (LIF) of collagen. Photographs were taken following ES, and some rats were killed, the cervices were isolated, and cervical extensibility was estimated.

RESULTS: LIF values of pregnant rats are significantly lower ($P < .001$) and extensibility greater ($P < .05$) in the ES treatment groups compared with the control groups on days 16 and 17 of pregnancy. Similarly LIF is lower ($P < .05$) and extensibility values greater ($P < .05$) in nonpregnant rats treated with ES. No adverse effects, including altered delivery time, pup weights, or damage to cervix, were produced by low current levels of ES needed to soften the cervix.

CONCLUSION: The following conclusions were reached: (1) application of ES rapidly produces softening and ripening of the cervix in pregnant and nonpregnant rats; (2) ES treatment does not produce early delivery; (3) the exact mechanism for ES ripening is not yet known; and (4) ES might be used clinically to ripen the cervix when needed.

Key words: cervical ripening, cervix, electrical stimulation, induction of labor, parturition

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Softening, effacement, and dilation are critical and sequential steps included in the ripening process of the cervix to convert it from a rigid to an extensible state and are necessary for initiation of parturition and normal delivery. Cervical softening, a chronic event, usually occurs progressively during pregnancy and begins in early pregnancy, whereas effacement and dilation of the cervix are more acute changes that occur near term.[1,2]

The steps from softening to dilation provide a pliable and accessible pathway for delivery of the fetus. Generally, ripening that occurs too early can often lead to preterm birth and delay in ripening progresses to postterm pregnancy with complications including substantial increase in perinatal mortality and morbidity, such as meconium-stained amniotic fluid with aspiration, which sometimes proceeds to cesarean delivery.[3,4] In addition, a lack of sufficient cervical ripening can advance to gestational age increase or postterm pregnancy, which is associated with unexpected stillbirth.[5] Therefore, it is often desirable to artificially promote cervical ripening.

The cervix of all mammalian species, including humans, is composed of connective tissue and a small proportion of smooth muscle that is continuous from the uterus through the vaginal wall.[6,7] Changes in connective tissue and water content of the cervix are responsible for the softening process during pregnancy.[1,2,8] Concentrations of collagen, glycosaminoglycans, and hyaluronic acid decrease during pregnancy to result in a more pliable organ capable of effacement and dilation.[1,2,8] In humans, the concentration of collagen has been estimated at approximately 70% at 10 weeks of gestation and at term approximately 30% compared with that of nonpregnant patients.[1,2] Physiologically the softening process and ripening of the cervix are thought to be followed by

From St Joseph's Hospital and Medical Center, Phoenix, AZ (Drs S.-Q. Shi, L. Shi, and Garfield), Guangzhou Women and Children's Medical Center (Drs Fang, S.-Q. Shi, Yang, Liu, Xia, and Garfield), and Southern Medical University (Drs Fang, Yang, Liu, and Xia), Guangzhou, China.

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Corresponding author: Robert E. Garfield, PhD. drrobertgarfield@gmail.com

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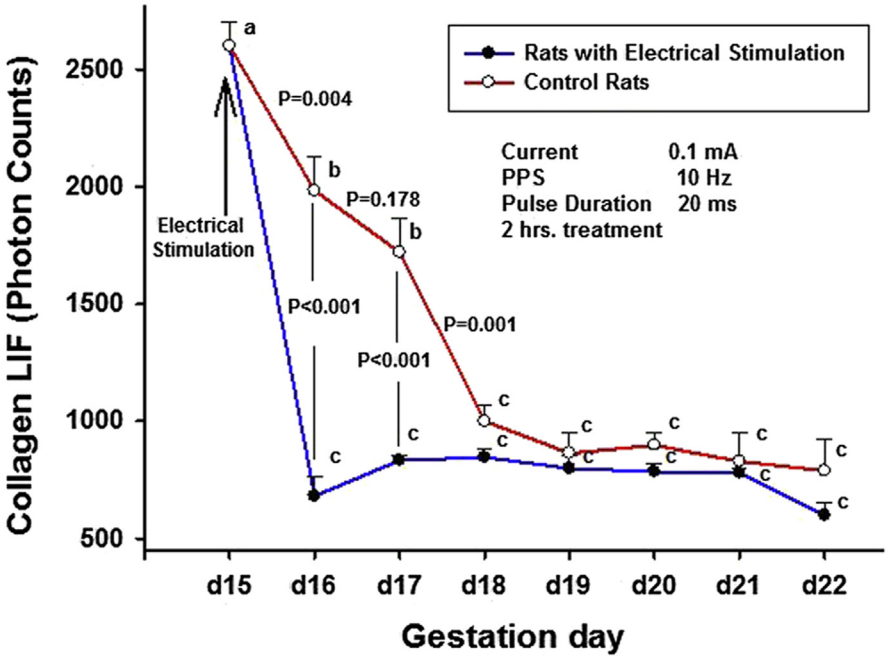
FIGURE 1
Cervical collagen fluorescence (LIF) in control and ES-treated pregnant rats from day 15 of gestation until term (day 22)



Shown are the mean values (±SEM) of LIF (in photon counts). ES was applied only on day 15 of gestation for 2 hours. Stimulation parameters are shown. Note that in control rats the cervical fluorescence progressively declines to low levels on days 18–22 of gestation, indicating normal softening of the cervix. ES on day 15 produces low fluorescent levels on day 16 and 17 of gestation compared with controls ($P < .001$), and the levels remain low, but not significantly different from controls, until day 22. Different letters next to mean values indicate significant differences ($P < .05$) between the mean values of control vs ES-treated (n = 7 rats/group).

ES, electrical stimulation; *LIF*, light-induced fluorescence.

Fang. Electrical stimulation ripens the cervix of rats. Am J Obstet Gynecol 2015.

uterine contractions of labor. Therefore, it is desirable to have a soft cervix before the uterus begins to forcefully contract to accomplish the delivery process.

In animals the process of cervical ripening also proceeds as in humans but on a shorter time frame, depending on the length of gestation. Many studies of rats, with a gestation period of 22 days, have shown that the cervix of pregnant animals in early gestation is softer than that of nonpregnant animals and slowly becomes more extensible until term.[9,10] Many approaches have been used to promote or delay cervical ripening in various species.[9,11-13]

Clinically, various mechanical or pharmacological methods, including the use of mechanical devices such as a Foley catheter, hygroscopic and osmotic dilators, and pharmacological agents such as misoprostol, dinoprostone, oxytocin, and nitric oxide donors[14-22] are frequently applied to ripen the rigid cervix and induce labor in humans during pregnancy when it is indicated. However, some of them have undesirable side effects to the mother and/or fetus.

Different methods of softening the rigid cervix are also used in nonpregnant patients when entry into the uterine cavity is clinically relevant. Ideally a method that ripens the cervix should soften the cervix without causing unnecessary pain and have minimal side effects on the mother or fetus. It is generally agreed that a better method for ripening the cervix would lead to a reduction in the number of cesarean deliveries.

Electrical stimulation (ES) is well known to elicit responses in a variety of excitable tissues, such as nerve, skeletal, and cardiac muscle. ES has also been studied for action on various types of smooth muscle, including cervical, airway, bladder, myometrial, gastrointestinal, and other smooth muscle tissues.[23-32] In addition, ES (transcutaneous electrical nerve stimulation) has been used in obstetrics to relieve pain during labor[33,34] as well for a diversity of other treatments including bone and tissue repair and collagen synthesis.[35-39] Therefore, we suspect that ES may be safely used for cervical ripening by physically or chemically changing the composition of the cervix.

The aims of this study were as follows: (1) to determine whether ES would ripen the cervix in pregnant and nonpregnant rats; (2) to confirm that ES softens the cervix by measuring changes in cervical extensibility; and (3) to examine the effects of ES on the timing of parturition and damage to the cervix and determine any fetal effects.

Materials and Methods

Animals

Timed-pregnant Sprague-Dawley rats (240–280 g) from Charles River Laboratories (Wilmington, MA) were delivered to our animal care facilities on day 13 of gestation (day 1 being the day when a sperm plug was observed). The rats were randomly divided by a technician blinded to the study design into groups (n = 6–7 per group). The animals were housed separately, with free access to food and water and maintained on a constant 12 hour light-dark cycle.

During ES the rats were lightly anesthetized with intraperitoneal injections of a mixture ketamine (Ketalar; Parke-Davis, Morris Plains, NJ) and xylazine (Gemini; Burns Veterinary Supply, Inc, Rockville Centre, NY) to keep the rats quiet and immobilized during treatments. Similarly, a limited number of non-pregnant rats (n = 6 per group) were also used, at indeterminate stages of the estrus cycle, to estimate the effects of ES. The rats were killed by CO_2 inhalation after delivery or treatment.