PROSTAGLANDIN E_2 IN CERVICAL SOFTENING IN MEDICALLY INDICATED LABOR INDUCTION AT/OR NEAR TERM

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by

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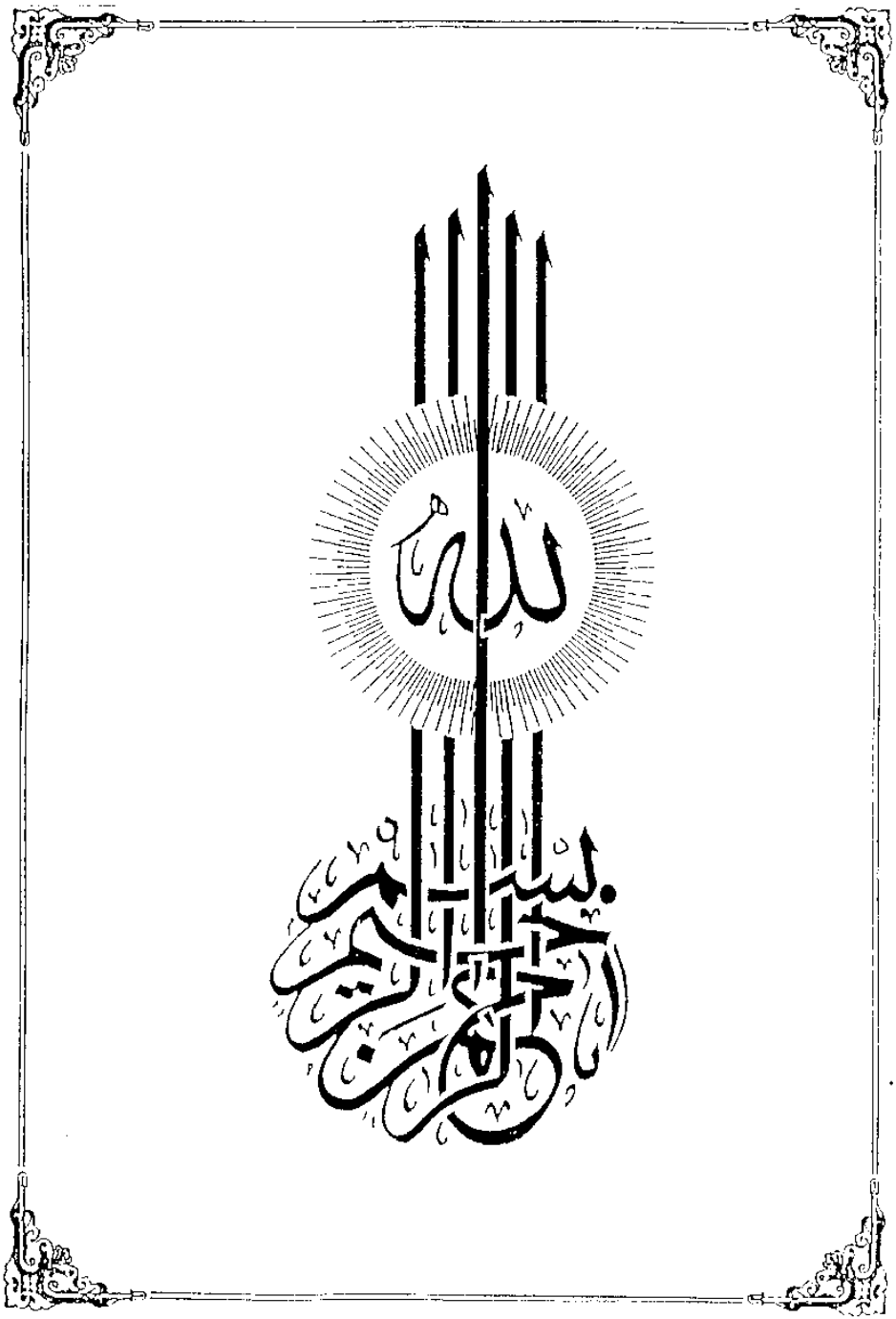
ABSTRACT

In order to detect the influence of preinduction intracervical prostaglandin E_2 (PG E_2) gel on cervical ripening and labor in patients at/or near term with an unfavorable cervical state, 0.5 mg PG E_2, suspended in a viscous gel, was instilled into the cervical canal in 25 patients with unripe cervices (Bishop score $\leq$ 5) to accelerate ripening before planned induction with oxytocin titration. The patients treated with the gel were compared to 25 similar untreated controls. Among patients given the PG E_2 gel, 50% had induced labor, delivering without further stimulation within 12 hours whereas this occurred only in 4% of the controls; the difference is statistically significant. Patients undelivered after treatment with PG E_2 gel achieved a considerable and statistically significant improvement of cervical score ($P < 0.001$) whereas in the controls there were also significant changes in cervical score ($P < 0.05$) registered but still not as remarkable as in the treated patients. Thus, the cervical score changed from a mean of 2.7 prior to treatment to a mean of 7.5 within 12 hours after treatment. In the controls, the corresponding means were 2.4 and 3. The mode of delivery seems to show that there is a tendency to reduce the number of cesarean section, being 16.7% in the treated group and 40% in the controls, but it did not reach statistical significance. No maternal side effects were observed and there were no adverse effects on the fetuses. Pretreatment with intracervical PG E_2 gel reduces the risk of failed induction, with success rates of 95.8% in the treated patients and 56% in the controls, and provides the mother with an experience similar to spontaneous labor without harming the fetus.



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DEDICATION

This thesis is dedicated to my father; my sister, Samia; and my mother who is not alive to share our happiness. Their continual love and support made this work possible.

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CHAPTER 1

THE MORPHOLOGY OF THE HUMAN CERVIX

Unlike other structures, the cervix has no fixed morphology. Indeed, the dramatic changes that occur in response to pregnancy and labor appear to be unique in the human body (Danforth, 1983).

In considering the form and structure of the cervix, two distinct systems would ordinarily be discussed: 1) its mucous membrane, including the squamous epithelium that covers the portio vaginalis, the squamocolumnar junction, and the mucosa of the endocervix, all of which undergo changes at the different stages of the menstrual cycle, of pregnancy and of labor, and 2) the wall, or substance of the cervix, which determines its shape or form. The integrity of the first system is vital to the appropriate migration and transport of sperm (Danforth, 1983), but this is a subject with which we are not now concerned. The second system, the characteristics of the wall of the cervix, permits it to carry out its vital functions of acting as a barrier to retain the conceptus and opening at an appropriate time to permit the conceptus to be expelled from the uterus (Conrad and Ueland, 1976; Danforth, 1983). Here we will discuss the morphologic characteristics of the wall of the cervix.

1.1 The Nonpregnant Cervix

1.1.1 Gross Characteristics and Attachments

The normal human cervix is about 2.5 to 3 cm in length. Its anteroposterior diameter is about 2 to 2.5 cm, the lateral diameter about 2.5 to 3 cm. Their difference is due to the shape of the cervical canal which in the sagittal plane is straight and in the frontal plane, spindle shaped. The wall of the cervix is about 1 cm thick throughout its length.

The cervix is divided into two portions, the portiovaginalis and portio supravaginalis, according to the segments that lie respectively below and

above the vaginal reflection. The vaginal reflection is located at about the junction of the inferior and middle thirds of the cervix. The uterine supports (the pubocervical fascia anteriorly, the uterosacral ligament posteriorly, and of most importance, the transverse cervical or cardinal ligaments laterally) are attached to the cervix immediately superior to the vaginal reflection. In the nonpregnant woman, they stabilize the cervix in approximately the center of the pelvis, and during pregnancy they are the "guy ropes" the uterus pulls upon to expel the baby in the second stage of labor (Danforth, 1983).

1.1.2 The Fibrillar Composition of the Cervix

1.1.2.1 Collagen

The human cervix is composed predominantly of fibrous connective tissue, which is demonstrated by contrast stains to be almost entirely collagen (Danforth, 1947, 1954 and 1983; Hughesdon, 1952). The uterine cervix from fertile nonpregnant women contains 80% water (Liggins, 1978). Collagen can account for as much as 50% of the total dry weight, as Danfort et al (1974) demonstrated in the human cervix. As a proportion of total cervical protein, collagen represents 82% (Danforth and Buckingham, 1973).

1.1.2.2. Elastic Tissue

Elastic tissue has been demonstrated in the cervix, but there is difference of opinion as to the amounts normally present and its physiologic significance in terms of the changing morphologic characteristics of the cervix in pregnancy and labor (Danforth, 1983). In Danforth's specimens (1947), stains for elastic tissue showed the presence of minute and, in his opinion, insignificant amounts of these fibers. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. They were most abundant in and around the walls of the large blood vessels. Elsewhere they constituted but a fraction of 1% of the total fibrous tissue of the cervix. More recently, Leppert et al. (1982) demonstrated the presence of elastin

in the cervices of two human cesarean-hysterectomy specimens, the biopsy material of one human nonpregnant fibroid uterus after delivery in two women with incompetent cervices, and cervical tissues from six cycling and six castrated monkeys. Although the amounts and concentration of elastin were not determined, a photomicrograph of one of the human cervices appeared to demonstrate a greater number of elastic fibers than were found in Danforth's specimen (1947). Leppert et al. (1982) concluded that although the amount of elastin appeared to be low, its presence might account for the rapid dilatability of the cervix in labor and the rapid return to normal shape after delivery.

1.1.2.3 The Fibromuscular Junction

The transition from myometrium of the corpus to connective tissue of the cervix is quite variable from one specimen to another. Its characteristics can often be discerned by gross examination of the stained slide held before a light or view box, the contrast in color between myometrium (red) and the collagenous cervix (blue in Masson, green in Milligan trichome) is readily apparent. Microscopic examination is usually needed to determine the exact point of transition from predominantly muscle to predominantly collagen. In most cases, the transition occurs over the course of 2 or 3 mm, in some less so. When a line is drawn across the critical area of transition it is sometimes wavy (Danforth, 1983).

1.1.2.4 Muscle

As noted by Hughesdon (1952), outside the mucosa the outer quarter or third of the wall is muscular like the corpus: the inner and major part consists of moderately cellular connective tissue, rich in collagen and containing some bundles of immature muscle fibers. He referred to the outer muscle layer as the extrinsic muscle of the cervix, since it forms part of a continuous layer running from fundus to vulva. The branch of this layer

which splits off and arches over the fornix is also seen. Its extent of penetration into the portio seems to vary but is generally most marked anteriorly. The muscle bundles of the extrinsic muscle occupy the outer quarter to third of the cervical wall and run, here as elsewhere throughout the uterus, in every possible direction. Between them lie broad loose collagenous septa, as in the outer and corresponding part of the corpus. The muscle bundles branching off, and arching over the fornix, are just visible. Internally, forming the bulk of the cervix, lies a broad mass of fibrous connective tissue. It contains a variable proportion of scattered muscle bundles, to which he referred as the intrinsic muscle of the cervix. The distinction is not absolute, however, as muscle size falls off gradually from above downwards. Danforth (1954) found no consistent distribution pattern of cervical muscle in the fringe or most peripheral areas of the portio supravaginalis where rather uniformly there appeared moderate to heavy strands of smooth muscle, the bundles of which ran in all directions and were separated from one another by considerable amounts of collagen. These strands were better developed laterally, about the uterine vessels, than either anteriorly or posteriorly. The author found these thin, scattered, attenuate muscle strands embedded in this heavy collagen matrix entirely dissimilar from the powerful, closely packed, collagen-sparse corporeal musculature. He suggests that this attenuate muscle may serve the purpose of protection for the uterine vessels during pregnancy and labor, and also that it may be concerned in the prompt return of the cervix to its normal contour immediately after the conclusion of labor.

The studies of the contractile ability of the nonpregnant cervix have been made by Najak et al. (1970) in vitro. They found that the nonpregnant cervix showed spontaneous contractility. However, in their study only the outer contractile layer was used. The same was found by Hughesdon (1952)