European Journal of Obstetrics & Gynecology and Reproductive Biology 144S (2009) S70–S76

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Cervical ripening and insufficiency: From biochemical and molecular studies to *in vivo* clinical examination

Dietmar Schlembach [a,b,*], Lynette MacKay [b], Leili Shi [b,c], William L. Maner [b,c], Robert E. Garfield [b,c], Holger Maul [b,d]

[a] Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria
[b] Department of Obstetrics and Gynecology, Division of Reproductive Sciences, University of Texas Medical Branch, Galveston, TX, USA
[c] Department of Obstetrics and Gynecology, St. Joseph's Hospital and Medical Center, Phoenix, AZ, USA
[d] Department of Obstetrics and Gynecology, University of Heidelberg, Heidelberg, Germany

ARTICLE INFO

Keywords:
Cervical insufficiency
Cervical ripening
Cervical collagen
Light-induced fluorescence
Preterm labor

ABSTRACT

To understand cervical ripening and especially the pathophysiology of cervical insufficiency, it is important to know the cervical composition: the cervix is dominated by fibrous connective tissue, consisting predominantly of Type I collagen (70%). Despite many studies of the cervix, we still rely upon relatively crude methods for clinical evaluation of the cervix. If the amount of cervical collagen plays a role in cervical insufficiency and in success of or length of induction of labor, then measurements of cervical collagen may provide an objective means of establishing the diagnosis or prognosis.

We have established and reported a non-invasive means, called Collascope, to measure collagen cross-linking using light-induced fluorescence (LIF), and which is specifically designed to assess cervical ripening, and functions by measuring the natural fluorescence of non-soluble collagen in the cervix. Studies conducted in animals and humans in a variety of settings indicate that cervical function can be successfully monitored using the Collascope during pregnancy: LIF correlates negatively with gestational age and positively with time-to-delivery interval, and is predictive of delivery within 24 h. Additionally LIF is significantly lower in women with cervical insufficiency.

We suggest that the Collascope might be useful to better define management in cases of spontaneous preterm or induced term cervical ripening. From our studies and others, it is clear that in forecasting (pre-)term cervical ripening, the capability of the technologies and bioassays that have been generally accepted into clinical practice are limited. Any devices shown to be superior to the clinically accepted tests currently used should be quite useful for clinicians. The Collascope offers an objective measurement of both the function and state of the cervix, by directly measuring collagen cross-linking using LIF.

1. Introduction

Parturition is a complex process involving two different "compartments," with changes occurring both on the maternal side (myometrium and cervix) and on the fetal side (fetus itself, fetal membranes), and leading to delivery of the fetus. The interrelationship between these compartments is not well understood. Further, the currently used methods to monitor myometrial and cervical changes involved in parturition are crude, and only the end points can be detected reliably. Uterine contractions, cervical changes, and changes in fetal membranes occur at different times [1]. Early changes, such as increased electrical conductance between uterine smooth muscle cells, or the degradation of cervical collagen leading to softening of the cervix, are not taken into account, unless one relies on only subjective and not well-reproducible methods such as digital palpation of the cervix. Table 1 summarizes the current methods and their accuracy used in patient monitoring or screening of labor (Table 1).

Preterm delivery remains one of the most important issues in obstetrics, resisting solution and yielding its secrets slowly and reluctantly. Because of the frustration associated with our inability to predict and prevent preterm birth, many varied methods have been proposed, in an attempt to determine the risk of the problem, to detect its precursors and early stages, and to treat various degrees of early labor and/or cervical dilatation [3,4].

The incidence of preterm labor and preterm delivery has been slightly increasing in the last years, and is now up to 12.7% [5]. It varies widely with different populations and risk factors, such as

* Corresponding author at: Department of Obstetrics and Gynecology, Medical University of Graz, Auenbruggerplatz 14, A-8036 Graz, Austria.
Tel.: +43 316 385 2401; fax: +43 316 385 3199.
E-mail address: drschlembach@gmx.net (D. Schlembach).

0301-2115/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejogrb.2009.02.036

Table 1
Current methods used in uterine monitoring or screening of (preterm) labor [Garfield et al. [2] reproduced with the permission from Blackwell publishing].

	Accuracy	Invasive
Monitoring of contractions in combination with pelvic examination	Moderate	No
Monitoring the state of the cervix	Moderate	No
Symptomatic self monitoring	Low	No
Intrauterine pressure monitoring	High	Yes
Tocodynamometer (external uterine monitor)	Erratic	No
Ultrasound, remote sensing, temperature monitoring, blood flow monitors	Mixed	No
Endovaginal ultrasonography	High negative predictive values	No
Fetal fibronectin	High negative predictive values	No
Salivatory estriol test	High negative predictive values	No

low maternal pre-pregnancy weight, socio-economic status, racial and ethnic factors, maternal education, maternal work patterns, physical effort during pregnancy (especially during the third trimester), maternal sexual activity, tobacco use, interval between pregnancies, bacterial vaginosis, and other types of bacterial colonization, uterine abnormalities, number of fetuses, and more.

The development of an effective means to prevent or reduce the occurrence of preterm delivery depends on the understanding of the conditions that initiate labor. In fact, despite intensive investigation, the rate of preterm births has not declined in several decades. The key issue, for successfully delivering during preterm labor, is the ability of the rigid or soft cervix to withstand the pressure induced by uterine contractions. In addition, preterm cervical ripening may result in cervical insufficiency, and may contribute to the occurrence, enhancement, and maintenance of uterine contractions by mechanisms only partially understood.

On the other hand, with increasing frequency, labor is induced using drugs that enhance cervical ripening and support uterine contractions in order to aid delivery and to prevent complications for mothers and newborns that would otherwise be associated with continuation of pregnancy. Labor induction has become a common procedure in obstetrics, but is unfortunately accompanied by a number of potential complications, such as uterine overstimulation, uterine rupture, and fetal compromise.

2. Cervical ripening – biochemical and molecular mechanisms

2.1. Composition and function during pregnancy

The cervix is composed of smooth muscle (about 10%) and connective tissue (90%), consisting of collagen, elastin, and macromolecular components that make up the extra-cellular matrix [6–11]. Many biochemical and functional changes occur in cervical connective tissue at the end of pregnancy [9–24]. This three-step process of cervical ripening consists of (and results in) softening (a "chronic" process throughout pregnancy, normally beginning weeks before labor or delivery), effacement, and finally, dilation of the cervix (both of the latter are really acute events, occurring within hours). During pregnancy, the cervix is normally firm and closed. At the end of pregnancy, the cervix becomes softer and dilates as the uterine contractions increase during labor.

Indeed, many biochemical and functional changes occur in cervical connective tissue during pregnancy, and are summarized by the term "cervical ripening" [8–11]. These changes precede the clinical symptoms that are currently evaluated, that is, uterine contractions and cervical dilatation.

The cervix, which is dominated by fibrous connective tissue, is composed of an extra-cellular matrix consisting predominantly of collagen (70% Type I and 30% Type III), along with elastin and proteoglycans, and a cellular portion consisting of smooth muscle, fibroblasts, epithelium, and blood vessels [25]. Throughout most of gestation, the cervix remains rigid and closed in order to secure the products of conception. A dramatic functional shift occurs during parturition as the cervix dilates through a "destructive" process [1]. Cervical collagen is known to play a major role in regulating cervical function [26–28]. Recently, a decrease in Type I collagen has been reported to be associated with cervical ripening [29]. This finding is in accordance with our preliminary results on cervical light-induced fluorescence (LIF) measurements. LIF decreases significantly as gestational age increases [30].

2.2. Hormonal influences and biochemical changes

Many studies show that hormones seem to control cervical ripening, although the mechanisms and effects on each step in ripening are not clear. In animal models, the physiologic decrease in the concentration of progesterone during the third trimester of pregnancy initiates a cascade that is analogous to an inflammatory response, with an influx of polymorphonuclear cells [31] and a release of matrixmetalloproteinases into the cervical stroma, culminating in the degradation of collagen [25]. In humans, a functional decrease of progesterone concentration is mostly probably due to decreased sensitivity of the hormone receptor.

Matrixmetalloproteinases (MMP) and tissue inhibitors of metalloproteinases play a major role in cervical ripening and dilation. MMP-1 degradates Type I and III collagen, MMP-8 mostly Type I collagen. An increase in matrixmetalloproteinases (MMP-8 and MMP-9) has been found in women with cervical dilation in term and preterm delivery, suggesting a role of MMP's in cervical dilation [32].

Because anti-progestins induce cervical ripening, this process seems to be controlled at least in part by hormones, including progesterone and estrogen [33], relaxin [34] and androgens [35]. "Knock-out" mouse models have demonstrated failure to deliver, owing to failure of cervical ripening [36,37].

Autocrine and paracrine mediators, like cytokines [38], prostaglandins [37], platelet activating factor [39], and nitric oxide [40], produced by different isoforms of its synthases [41], have been shown to take part in physiologic or pathologic cervical ripening, thereby forming a complex and poorly understood network with short-circuits and parallel pathways, widely influenced by hormones and their sensitivities [42]. Similarly, lipopolysaccharides are well known for triggering the cascade model described above. Therefore, these factors may also be operative in premature cervical ripening associated with genital tract infection [43]. Additionally, the nervous system has significant involvement in the process of reproduction, and could also be involved in cervical ripening. Sensory, sympathetic, and parasympathetic fibers are numerous in the cervix [44]. These nerves synthesize neurotransmitters such as vasoactive neuropeptides, calcitonin gene-related peptide, substance P, and secretoneurin. These are locally released in the cervix and act through their receptors to induce inflammatory-like cervical changes in vasodilatation, vascular leakage, and plasma and leukocyte extravasations.

Despite all of these studies, the complete cascade responsible for the process of cervical ripening, which finally enables uterine contractions to efface and dilate the cervix, is still not fully understood.

3. Cervical insufficiency

The incidence of cervical insufficiency is very difficult to determine, because there are no clear clinical criteria for the diagnosis. Rather, the diagnosis is made by exclusion of other causes of preterm delivery. Cervical insufficiency is probably an