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Progress in the Application of Nitric Oxide Donors to Promote Cervical Ripening

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Abstract: We usually use drugs to promote cervical ripening before inducing labor to reduce the risk of induction failure and surgical delivery. The methods to promote cervical ripening are developed rapidly, and there are many types, each with its own advantages and disadvantages. In recent years, the role of nitric oxide (NO) donors in promoting cervical ripening has become a research hotspot. Its representative drugs are mainly isosorbide mononitrate; ISMN), glyceryl trinitrate, sodium nitroprusside, etc. This article analyzes and summarizes the historical background, mechanism of action and clinical application of NO donors to promote cervical ripening.

In the third trimester, in order to ensure the safety of the mother and fetus, it is necessary to terminate the pregnancy in a timely manner, and the correct application of cervical ripening drugs and labor induction drugs can greatly reduce the rate of cesarean section. Cervical maturity is directly related to the success rate and duration of labor induction in late pregnancy [1]. There are many ways to promote cervical ripening, and the most ideal way to promote cervical ripening is to promote its ripening process is basically similar to natural ripening, which does not cause excessive contractions, does not affect uterine blood flow, and does not adversely affect the safety of the mother and fetus [2]. At present, prostaglandin (PG) drugs are commonly used at home and abroad, but prostaglandins may induce excessive contractions while promoting cervical ripening, so they are not the most ideal pro-cervical ripening drugs [3]. According to literature reports [4], NO donors have the effect of promoting cervical ripening with few side effects, so this study reviews the application progress of NO donors to promote cervical ripening.

1. Historical Background of Nitric Oxide Donor Use to Promote Cervical Ripening

A 2013 American College of Obstetricians and Gynecologists (ACOG) [5] states that induction of labour can be an option of treatment when the benefits of immediate labour outweigh the continuation of pregnancy and the benefits of induction must be weighed against its potential harm to mother and baby. Therefore, when the conditions of the mother are not conducive to continuing the pregnancy, for example: a delayed pregnancy (up to 41 weeks) or a pregnant woman who has expired; maternal patients with serious diseases that require early termination of pregnancy, such as pregnancy with diabetes, pregnancy with hypertension, nephropathy, etc., can tolerate vaginal delivery; for those who do not have labor within 2 hours of premature rupture of membranes, we need to use drugs and other means to start labor before the mother naturally goes into labor to achieve the purpose of delivery. The success of induction of labour depends primarily on the maturity of the cervix. At present, the medical examination of the cervical maturity of pregnant women mainly uses the Bishop score, which can predict the time of delivery of pregnant women and whether they have begun to enter labor. If Bishop > = 6 points, we can give the woman oxytocin or artificial rupture of membranes for direct induction of labor, if Bishop < 6 points, we need to promote cervical ripening by medical or mechanical methods before inducing labor for women.

There are many methods to promote cervical ripening, such as pharmaceutical methods (oxytocin, misoprostol, denoprostone, resorcinol, scopolamine hydrochloride, atropine, lidocaine, diazepam, papaverine, etc.), mechanical methods (Foleys catheter, cervical COOK balloon, seaweed sticks, artificial rupture of membranes, etc.) and traditional Chinese medicine [6]. At present, the most widely used cervical ripening drugs at home and abroad are prostaglandins. In 2011, the World Health Organization recommended [7] induction of labour with low-dose misoprostol (prostaglandin E1 analogue), which has a better cervical ripening effect than denoprostone (a prostaglandin E2 analogue), shortens the time from initial dose to delivery, shortens the time from initial dose to the onset of labor activity, and reduces oxytocin use [8]. However, because prostaglandins also stimulate uterine contractions while promoting cervical ripening, they can have some adverse effects on the mother and fetus, such as uterine rupture and fetal damage [9]. The ideal agent to induce cervical ripening should produce sufficient cervical changes while minimizing fetal and maternal side effects [10]. A recently introduced agent for cervical ripening is a NO donor. Studies have shown that NO is involved in the process of cervical ripening in the third trimester, and topical application of NO donors may induce cervical ripening by rearranging cervical collagen and basic substances, thereby softening the cervix. Previous animal and human studies have shown [11] that NO donors are safe in pregnancy. The biggest potential problem with the use of NO donors is the risk of maternal hypotension due to NO's vasodilating effect. If severe, it can impair blood flow to the uterine placenta and cause fetal hypoxia [10]. In recent years, there have been reports of NO donors, such as isosorbide mononitrate, glyceryl trinitrate, and nitropruna that reduce cervical resistance and have been used for cervical ripening and/or induction of labour [12].

2. Mechanism of Nitric Oxide Donors Promoting Cervical Ripening

The human cervix is fibrous connective tissue composed of a large amount of collagen fibers, a matrix and water, and contains a small amount of elastic fibers and smooth muscle. The number of collagen fibers determines the stiffness of the cervix, and its main role is to keep the uterine mouth closed (Figure 1). Collagenases that cause collagen fiber degradation are Ca^{-} and Zn^{-}-dependent metalloproteinases derived from neutrophils and fibroblasts in the cervix from vascular infiltration

into the cervical stroma. Studies have shown that the histological changes of cervical ripening are swelling, curling, and rupture of collagen fibers, reduced content, increased stromal components, and obvious neutrophils and macrophages can be seen in all cervical tissues, similar to acute inflammatory phenomena [13].

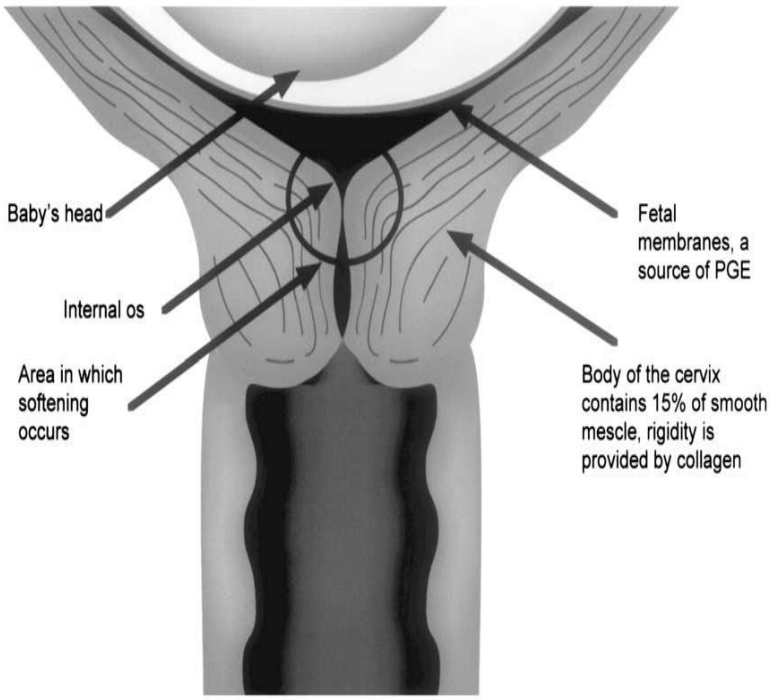

Figure 1. The internal os of the cervix, where ripening is thought to commence, lies in close proximity to the fetal membranes. The rigidity of the cervix is largely provided by collagen and thus collagenase is needed to soften it

Among the many current factors that regulate cervical ripening (mechanistic factors, estrogens, cytokines, and other inflammatory factors, etc.)(Figure 2), the role of prostaglandins is crucial, and NO appears to be involved in this process (Figure 3) [14].

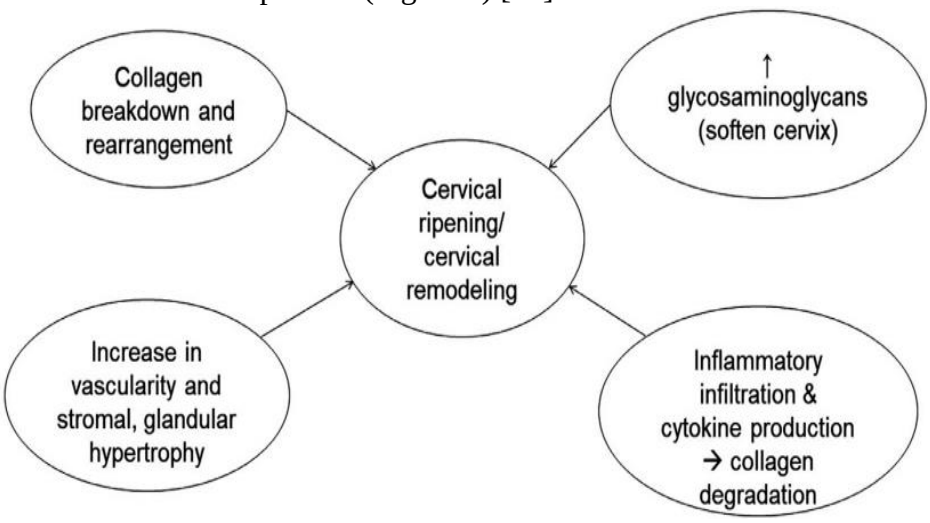

Figure 2. Biochemical processes that lead to cervical ripening

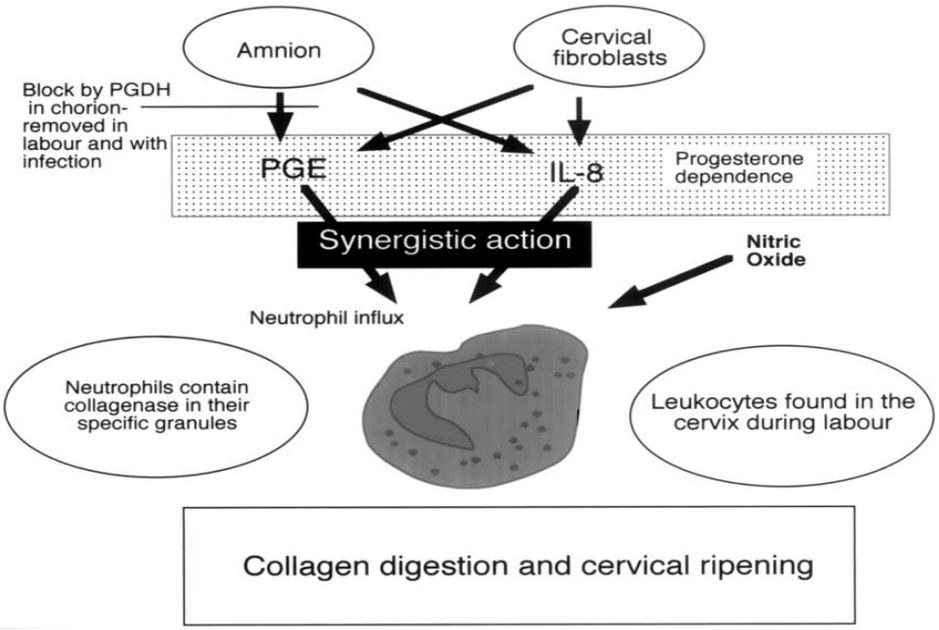

Figure 3. Neutrophil entry into tissue is mediated by a synergistic action between a chemokine such as IL-8 and a vasoactive substance such as PGE. Nitric oxide, another vasoactive substance is also implicated but the direct effects on neutrophil entry are unknown

The production of NO in vivo is divided into two pathways: endogenous and exogenous(Fig. 4) . The endogenous pathway is that under the catalysis of NO synthase (NOS), the guanidine nitrogen atom of L-arginine (L-ARG) oxidizes to produce L-guanidine and NO, and the exogenous pathway is that certain nitro compounds react with sulfhydryl-containing substances in the body to produce an unstable s-nitrosomercaptan, which decomposes itself to form NO [15]. The NO donor is administered vaginally through the exogenous route to produce NO locally in the cervix and play a role in promoting cervical ripening.(Figure 4)

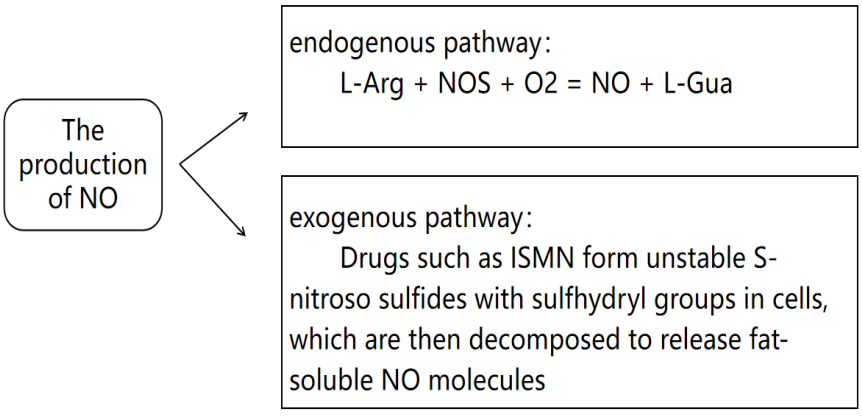

Figure 4. Two pathways of the production of NO in the body

There are many methods to promote cervical ripening, but their common feature is an increase in the concentration of local prostaglandins. Uldbjerg's study [16] showed an increase in concentrations of almost 20% Sul-fated glycosaminoglycans in patients taking prostaglandin cervix. The increase in these polysaccharides is consistent with histological alterations, i.e., an increase in

amorphous substances between collagen fibers, which may be newly synthesized proteoglycans. Therefore, it is believed that in the process of prostaglandins promoting cervical ripening, the content of aminopolysaccharide sulfate or the change of its pattern and the physicochemical interaction of collagen play a major role. Topical vaginal NO donors produce NO through exogenous pathways, and studies have shown that this NO product reacts with soluble guanylate cyclase, and its products increase the concentration of cyclic guanylate (cGMP) in cells. cGMP can cause dephosphorylation of myosin light chains within smooth muscle structures, leading to relaxation, thereby promoting cervical ripening(Figure 5) [17].

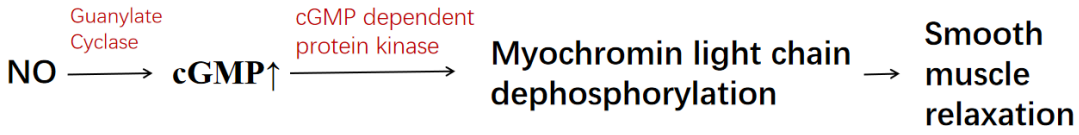

Figure 5. L-Arg-NO-cGMP pathway

3. Clinical Effect of Nitric Oxide Donor in Promoting Cervical Ripening

Currently commonly used clinically as a NO donor to promote cervical ripening is ISMN, and in most clinical studies using ISMN to promote cervical ripening, the formulation of ISMN used is designed for oral administration. Experiments have shown [18] that vaginal administration has a lower serum drug concentration and better local cervical absorption than oral administration, resulting in fewer systemic side effects. Experimental comparisons of oral administration of ISMN and intravaginal administration of ISMN found [10] that the timing and concentration of plasma ISMN peak levels after the two methods of administration differed. The highest serum level after oral or intravenous injection of 20 mg of ISMN is 425 ug/L and peaks 2 hours after administration. After vaginal administration of 20mg of ISMN, the highest serum level of ISMN was only 144ug/L, and the peak level was at least 6 hours, or even longer. Although we cannot determine whether true peak serum levels have been reached, peak concentrations observed after vaginal administration are less than half of the peak concentrations after oral or intravenous administration [19]. This is due to the fact that vaginally administered ISMN may experience a single uterine passthrough effect, giving preference to the drug being transported from the vagina to the uterus [20]. This results in much higher concentrations of ISMN in the uterus than in serum, although we are not yet able to formally test the concentration of ISMN in utero. Because large amounts of the drug are delivered to the uterus, the amount that can be absorbed into the bloodstream is reduced, which may explain the lower serum levels of ISMN and fewer systemic side effects after vaginal administration compared with oral or intravenous administration [18]. Therefore, clinically we recommend that ISMN be administered vaginally to promote cervical ripening [21].

Experiments have found that the concentration of vaginal ISMN and the concentration of serum ISMN after administration also have dose-dependent effects, that is, 40 mg of ISMN taking 40 mg of ISMN in full-term pregnancy has a more obvious inhibitory effect on maternal blood pressure than 20 mg [10]. Experimental data [22] suggest that plasma ISMN levels gradually increase as the dose of intravaginal ISMN increases to 40 mg. And when the dose of intravaginal ISMN is increased to more than 40 mg, plasma ISMN levels hardly increase again. Further studies involving pharmacokinetic changes associated with larger doses of ISMN are needed to further explore this hypothesis.

Given the evidence of misoprostol's efficacy, many experts prefer misoprostol to promote cervical maturation, however, it may cause maternal and fetal complications due to uterine hyperstimulation [23]. NO is considered the main mediator of cervical ripening, which does not

cause hyperstimulation of the uterus during this process. Therefore, ISMN is often used clinically in combination with misoprostol to promote cervical ripening in women with preterm or term pregnancy. According to the results of the current study: the combination of ISMN with misoprostol has a greater effect on cervical ripening and delivery than misoprostol alone, and can increase the success rate of vaginal delivery in pregnancy. (The cesarean section rate was 6.6 percent in the misoprostol plus ISMN group and 13 percent in the misoprostol plus placebo group) [24]. The results of Masoumeh and Abdellah et al. [25] showed that the mean time (9 hours) from cervical expansion to Bishop score > 6 in the misoprostol plus ISMN group was significantly shorter ($P<0.05$) than in the misoprostol plus placebo group (12 hours), but the mean time interval from induction of labour to delivery (61 hours) in the misoprostol plus ISMN group was longer ($P<0.05$) than in the misoprostol plus placebo group (49 hours).

Because NO donors and PGs have different mechanisms of action, their combined use may work synergistically and lead to more efficient cervical ripening. At the same time, they have antagonism on the myometrium, PG can stimulate myometrium contraction, and NO donors can relax it, so the combination of the two can prevent excessive uterine contraction before induction of labor [26]. It has been hypothesized [4] that combining ISMN with misoprostol reduces the side effects associated with either drug, as the smooth muscle relaxation properties of ISM reduce the incidence of gastrointestinal contractions associated with PG effects. Compared with ISMN alone, combination therapy significantly reduces the incidence of headache, but does not reduce the occurrence of palpitations. However, the addition of ISMN did not reduce the incidence of abdominal or pelvic pain associated with misoprostol alone. In addition, combination therapy did not reduce the incidence of meconium contamination in amniotic fluid and the incidence of abnormal FHR associated only with the use of misoprostol.

However, the combination of ISMN with prostaglandins has been shown to lead to a cumulative level of systemic drug absorption with a clinically significant risk of side effects [22]. Therefore, the optimal combination dosage and frequency of administration scheme need to be further studied.

4. Nitric Oxide Donors Promote Cervical Ripening, Insufficient and Worried

There are different theories about the mechanism by which NO donors promote cervical ripening. The latest study shows that the NO donor acts on the cervix and reacts with soluble guanylate cyclase, and the reaction products increase the concentration of cyclic guanylate (cGMP) in cells. cGMP can also cause dephosphorylation of myosin light chains in the smooth muscle structure of the cervix, resulting in cervical relaxation, thereby promoting cervical ripening [17]. It has also been suggested that NO promotes the synthesis of prostaglandins by activating intracervical cyclooxygenase, leading to cervical ripening. As mentioned earlier, prostaglandins can cause uterine contractions while promoting cervical ripening, if NO donors can promote the synthesis of prostaglandins during use, then how is the function of NO donors to inhibit uterine contractions reflected? Or can NO donors promote the synthesis of prostaglandins by activating cervical cyclooxygenase, and can also activate matrix metalloproteinases to cause the degradation of collagen fibers, and the latter has a greater effect on counteracting the contractile effect of prostaglandins on the uterus? Therefore, the exact mechanism of NO donor to promote cervical ripening needs to be studied in depth from the aspects of histology and histochemistry.

Because nitric oxide has a vasodilating effect, the main accompanying symptoms associated with the clinical use of ISMN are hypotension, headache, and palpitations. However, these effects have not been shown to be clinically important, as none of the treated pregnant women will require treatment for hypotension, headache, or palpitations [24]. This may be due to induction of labour after a relatively short clinical duration of treatment. Another aspect of nitric oxide donors is the

relaxation effect on the uterine body. In vitro studies have shown that NO has the effect of relaxing the myometrium, leading to decreased uterine muscle tone, thereby increasing the amount of blood loss during delivery. However, in the clinical study of Masoumeh et al. [24], none of the women who lost more than 600 ml of blood during surgery required blood transfusion. However, due to the small number of women in the study trials, no conclusive statements can be made about the safety of vaginal administration of ISMN. However, we can conclude that ISMN can promote cervical ripening during preterm or term pregnancy by increasing tissue expandability without causing serious clinical maternal or fetal side effects. Thus, the use of NO donors to induce cervical ripening before induction of labour may be a major therapeutic advance [12].

5. Conclusion and Outlook

Numerous clinical trials have demonstrated that intravaginal ISMN is well tolerated by pregnant women and newborns, and therefore, we conclude that ISMN can promote cervical ripening during term pregnancy by increasing tissue dilation without causing serious clinical maternal and infant complications. Therefore, the use of NO donors to induce cervical ripening before induction of labor is currently the main clinical treatment progress [12].

In short, with the deepening of research, there are more and more methods to promote cervical ripening, but the most ideal method is still to be discovered. Because the mechanisms of action of various drugs to promote cervical ripening vary, the simultaneous application of two or more methods may be more effective than a single method. Therefore, at present, the combination of NO donors and prostaglandins is more often used clinically as a method to induce cervical ripening before labor. With the opening of the two-child policy, the search for a more natural delivery process, effective, safe, and patient-acceptable methods to promote cervical ripening, improve vaginal delivery rates, and minimize cesarean section rates are currently the biggest challenges facing obstetricians.

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The author states that this article has no conflict of interest.

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