INTRODUCTION

Post maturity

The normal length of pregnancy is from 37 to 41 weeks. Post maturity refers to any baby born after 42 weeks gestation or 294 days past the first day of the mother's last menstrual period. (1)

Post-mature births can carry risks for both the mother and the fetus, after the 42 weeks of gestation. The placenta, which supplies the fetus with nutrients and oxygen from the mother start aging and will eventually fail, (2) so post term pregnancy may be a reason to induce labor.

Incidence

The incidence of post-term pregnancy has been found to be as high as 14% in some conducted observational studies. (3) However, reports from different settings suggest that it varies between 3% and 14%, regardless of ethnicity. (4) This wide variation is likely to be the consequence of different policies of labor induction and methods for assessing gestational age. (5) Post-term pregnancy may be the most common indication for induction of labor. (6)

Causes and Risk factors

The etiology of post-term pregnancy is not unknown. Multifactorial causes have been postulated since explanatory models are unproven. However,

1- Post maturity is more likely when a mother has had one or more previous post-term pregnancies, primiparity, male gender of the fetus. (7)

2- Genetic factors;duration of pregnancy varies with ethnicity. The average length of pregnancy is found to be about 5days shorter in black populations than in white populations (7)

3- When there is a miscalculation (due dates are easily miscalculated when the mother is unsure of her last menstrual period), the baby could be delivered before or after the expected due date. When the menstrual period is irregular, post-mature births can also be attributed. it is very difficult to judge how and when the ova would be available for fertilization and subsequently result in pregnancy, so in reality the baby is not technically post-mature.(8) However, in most first world countries where gestation is measured by ultrasound scan technology, this is less likely. The use of ultrasound in early pregnancy for precise dating significantly reduces the number of post-term pregnancies compared to dating based on the LMP. (9)

4- Elevated pre-pregnancy weight (high maternal BMI) and maternal weight gain both increase the risk of a post-term delivery.(10)

5- Advanced maternal age is also a strong risk factor for prolonged pregnancy.(11)

Symptoms and Signs

Diagnose of post-mature birth based on the length of the mother's pregnancy and the baby's physical appearance after delivery, [12] before delivery:

1- Reduced fetal movement.
2- A reduced volume of amniotic fluid may cause a reduction in the size of the uterus.
3- Meconium-stained amniotic fluid may be seen when the membranes have ruptured.

After delivary:

1- The neonate has lower than normal amounts of subcutaneous fat and reduced mass of soft tissue.
2- The skin may be loose, flaky and dry.
3- Fingernails and toenails may be longer than usual and stained yellow from meconium.

Maternal risks

The maternal risks of post term pregnancy are often underappreciated.

Post-mature baby are larger than average size baby, so

1. Operative vaginal delivery **(**forceps or vacuum) may be used to resolve the difficulties at the delivery time and increase incidence of severe perineal injury(3.3% vs 2.6% at term).[13]

2. Cephalopelvic disproportion , shoulder dystocia and caesarean sections are encouraged if this happens.[14]

3. Other complications as postpartum hemorrhage increase progressively after 41 weeks of gestation.[15]

4. Maternal anxiety can increase when pregnancy progresses beyond term.

Neonatal and Fetal Risks

1. Reduced placental perfusion, once a pregnancy has passed the 40 week gestation period, physicians closely monitor the mother for signs of placental deterioration. Towards the end of pregnancy calcium is deposited on the walls of blood vessels and proteins are deposited on the surface of the placenta, which changes the placenta. This limits the blood flow through the placenta and ultimately leads to placental insufficiency, oligohydramnios and the baby is no longer properly nourished. [16] Induced labor is strongly encouraged if this happens.
2. Meconium aspiration is seen in higher rates in post term neonates.[17]
3. Post term is associated with higher incidence of fetal macrosomia (fetal weight ≥ 4,500g), and in turn high incidence of birth injury.[18]
4. Approximately 20% of post term fetuses have fetal dysmaturity syndrome, which describes infants with characteristics of chronic intrauterine growth restriction from uteroplacental insufficiency.[16]
5. Post term pregnancy is also an independent risk factor for neonatal encephalopathy[19] and for death in the first year of life.[20]

6. Compared with delivery at 40 weeks of gestation, delivery at 42 weeks or later has been shown to be associated with an increased risk of cerebral palsy.[21]
7. Sudden infant death syndrome, fetal and neonatal mortality rates increase after 40 weeks.[22]

Monitoring post-mature pregnancy

Once fetus is diagnosed post-mature, the mother should be offered additional monitoring as this can provide valuable clues that the fetus's health is being maintained.

- **Fetal movement recording:**

Regular movements of the fetus are the best sign indicating that it is still in good health. The mother should keep a "kick-chart" to record the movements of her fetus. Less than 10 movements in 12 hours is not a good sign and could indicate placental deterioration. [23]

- **Obstetric ultrasound**

It is an imaging technique that uses high-frequency sound waves to produce images of the fetus in the uterus. The purpose of a wellbeing ultrasound varies including: [24]

- Assessment of gestational age.
- Evaluating the growth and health of the fetus.
- Confirming the fetus position and presentation.
- Measuring the size of the fetus and estimating fetal weight.
- Evaluation movements of the fetus.
- Measuring the amount of amniotic fluid by estimation the amniotic fluid index.

- **Nostress test**

A cardiotocograph is used to monitor the fetal heart rate. It is done by monitoring the baby's heart rate with a small device that is placed on the mother's abdomen. The device uses sound waves (ultrasound) to measure changes in the baby's heart rate over time, usually over a period of 20 to 30 minutes. [25] Normally, the baby's baseline heart rate should be between 110 and 160 beats per minute and should increase above its baseline by at least 15 beats per minute for 15 seconds several times during the test. The test is considered reassuring (reactive) if two or more fetal heart rate increases (acceleration) are seen within a 20 minute period. Further testing may be needed if these increases are not observed after monitoring for 40 minutes. [26]

Vibroacoustic stimulation can wake the fetus, and is sometimes used to speed up the test or to facilitate further evaluation of a nonreactive nonstress test.

- **Contraction stress test**

A contraction stress test (CST) can also be done to assess fetal health. It involves giving an intravenous medication (oxytocin) to the mother to induce uterine contractions. The fetus' heart rate is monitored in response to the contractions. A fetus whose heart rate slows down during a CST may require an emergency cesarean delivery. [27]

Biophysical profile

A biophysical profile (BPP) score is calculated to assess the fetus' health. It consists of five components, nonstress testing and ultrasound measurement of four fetal parameters: fetal body movements, breathing movements, fetal tone (flexion and extension of an arm, leg, or the spine), and amniotic fluid volume. Each component is scored individually, 2 points if normal and 0 points if not normal. The maximum possible score is 10. Amniotic fluid volume is an important variable in the BPP because a low volume (called oligohydramnios) may be a sign of changes in the feto-uteroplacental circulation. Amniotic fluid level can become reduced within a short time period, even a few days. [28]

- **Doppler flow study**

Non-invasive technique for assessment of placental and fetal circulation. It measures the amount of blood flowing in and out from the placenta. It has been used for studying most of the major fetal circulatory systems, including the umbilical artery (UA) umbilical vein, aorta, heart and middle cerebral artery. Doppler sonography provides a unique opportunity to investigate human fetal hemodynamics and to use these findings for fetal surveillance. Umbilical artery Doppler is an effective test for improving perinatal mortality and morbidity. [29]

Management of post term pregnancy

Compared with waiting indefinitely or waiting at least one week for labor to occur spontaneously, labor induction after 41 weeks of gestation is associated with fewer perinatal deaths. Labor induction can help reduce the need for additional monitoring of women and reduce the duration of hospitalization, especially in settings where women need to be hospitalized earlier in pregnancy to avoid this situation in which they are unable to reach the hospital in an emergency. [30] A studies showed that induction of labor in women with post-term pregnancy is a safe management option and a reasonable way of avoiding Cesarean section.[31]

Post-term pregnancy is best managed in health care settings where there is capacity for patient monitoring and facilities exist for the treatment of complications. In the absence of such capacity induction of labor becomes risky. However, since many women in developing countries do not have access to such health care facilities, post-term pregnancy remains an important health problem. In isolated settings that are far from hospitals in developing countries, induction of labor is often undertaken with home remedies and folk medicines. Many plant extracts have been shown to have uterotonic effects. [32]

Induction of labor

Inducing labor is artificially starting the labor process by using medication and other techniques. Labor is usually only induced if there is potential harm on the mother or fetus.

Induction of labor is common in obstetric practice. According to the most current studies, the rate varies from 9.5 to 33.7 percent of all pregnancies annually. Approximately 20% of pregnant women have their labor induced in the UK and the USA each year.

Although there is no ideal predictor of successful induction of labor, cervical status is now accepted as the most useful characteristic. (33)

In the absence of a ripe or favorable cervix, a successful vaginal birth is less likely. It is recommended that a cervical ripening agent should be used before labor induction. (34) Therefore, cervical ripening or preparedness for induction should be assessed before a regimen is selected.

Cervical ripening

Cervical ripening, clinically diagnosed by softening, effacement, and dilatation of the uterine cervix, is commonly stimulated pharmacologically before induction of labor to reduce the risk of prolonged labor, failed induction, cesarean section, and maternal and fetal morbidity.

The human cervix consists of smooth muscle cells (10–15%) and connective tissue (85–90%) (35) The columnar epithelium lining of the endocervical canal contains large branched glands. (36) The underlying stroma consists predominantly of extracellular connective tissue, mainly type I and III collagen bundles. In addition, type IV collagen is present in smooth muscle cells and blood vessel walls. Collagen bundles provide a rigidity that can be removed rapidly by collagenases; the source and control of collagenases are not yet fully understood.(36) The matrix consists of water, glycosaminoglycans and proteoglycansas well as dermatane sulfate, hyaluronicacid and heparin sulfate. Elastic fibers with functional elastin are located between the bundles of collagen fibers in a thin band under the epithelium . The ratio of elastin to collagen is highest in the area of the internal os. (37)

The cervix undergoes changes in two phases: ripening and dilation. Cervical ripening is an integral part of the conditioning phase of parturition, and it occurs independently of uterine contractions. (38)

The uterine cervix has a pivotal role in the physiology of gestation and parturition; it has to be firm enough to retain the conceptus throughout pregnancy and, on the other hand, have the ability to soften before and during labor to enable the birth of the infant. The human uterine cervix undergoes biochemical as well as structural changes that can detect clinically resulting in softening, effacement and dilatation of cervix during the last weeks of pregnancy. (39)

Mechanism of cervical ripening

In the human, physiological cervical ripening at term is an active biochemical process. It has been described as an inflammatory process accompanied by the infiltration of white blood cells, marked tissue edema, and rearrangement of the cervical collagen fibers. (40) Therefore, cervical ripening is associated unavoidably with changes in local cytokines, prostaglandins, metalloproteases and other bioregulators that play roles in inflammation and collagen metabolism. (41)

Cervical ripening characterized by inflammatory events, such as extravasation of neutrophils and macrophages (42) and an increased cervical level of pro-inflammatory cytokines such as interleukin (IL)-8. (43)

Progesterone, essential for the maintenance of pregnancy, and glucocorticoids have anti-inflammatory properties [44] Placental production of progesterone and adrenal synthesis of glucocorticoids [45] increase markedly during human pregnancy. Progesterone and cortisol regulate the human placental corticotropin-releasing hormone (CRH) gene. [46] Placental CRH, synthesized in abundance in the human placental syncytiotrophoblasts and trophoblasts has been proposed to be a key regulator for human parturition through interactions with adrenal steroids and estrogen. [47]

Prostaglandins are a group of lipid compounds that are derived enzymatically from fatty acids and have important functions in the human body. Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.

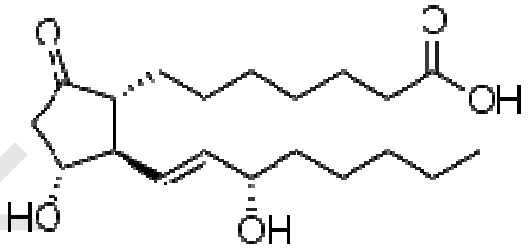

Figure (1): Prostaglandin molecule

Prostaglandins are mediators and have a variety of strong physiological effects, such as regulating the contraction and relaxation of smooth muscle tissue.[48] Prostaglandins are not endocrine hormones, but autocrine or paracrine, which are locally acting messenger molecules. They differ from hormones in that they are not produced at a discrete site but in many places throughout the human body**.** Prostaglandins alter the extracellular ground substance of the cervix, increases the activity of collagenase in the cervix. They cause an increase in elastase, glycosaminoglycan, dermatan sulfate, and hyaluronic acid levels in the cervix, leading to relaxation of cervical smooth muscle facilitates cervical dilation. Finally, prostaglandins allow for an increase in intracellular calcium levels, causing contraction of myometrial muscle. [48]

Cyclo-oxygenases are enzymes that convert arachidonic acid to prostaglandins. It has been found to exist in a constitutive isoform (COX-1) and an inducible isoform (COX-2).The constitutive isoform accounts for the formation of prostaglandins involved in the regulation of physiologic functions ,whereas COX-2 is typically involved in the production of prostaglandins at the site of an inflammatory process . The COX enzymes are down regulated by cortisol in human decidua, myometrium and cervix. [49]

Platelet-activating factor (PAF) is a lipid pro-inflammatory mediator, involved in several reproductive processes, i.e. parturition [50] PAF is synthesized by some leukocytes, blood platelets and vascular endothelial cell[51] The PAF receptor contains estrogen responsive element within its promoter region, enabling regulation by estrogens. [52] The activation of PAF-R is associated with cytoskeletal remodeling and expression of pro-inflammatory modulators, such as COX-2, IL-6 and IL-8.Thus, PAF-R and COX enzymes have been widely demonstrated as factors involved in the events promoting and proceeding parturition, yet their cell origin in the human uterine cervix remains to be clarified. [53]

Nitric oxide (NO) is synthesized intracellularly from the amino acid L-arginine through the activity of specific synthase enzymes (NOS). [54] NO stimulates PGE_2 release from human cervical tissue, and stimulates Cyclo-oxygenases expression by a cGMP-independent mechanism. Thus, increasing local PGE_2 concentrations in inflammatory tissues [55]

The degree of ripening at the time of active labor is a decisive importance as regards its course and duration of labor.Various scores have been proposed for quantitative assessment of cervical ripening. Bishop score is one of most commonly used ones. [56] Also, the modified bishop score is another method of assessment.

The Bishop Score

The Bishop Score is a measure help to predict whether or not an induction is likely to succeed or fail. [57] During vaginal examination evaluation the degree of:

- cervical dilation
- cervical effacement
- cervical consistency
- cervical position
- fetal station

Each factor is "graded" on a scale of 0-2 or 0-3. The maximum possible score is 13.

Table (1): The Bishop Score

Parameter\Score	**0**	**1**	**2**	**3**
Position	Posterior	Intermediate	Anterior	-
Consistency	Firm	Intermediate	Soft	-
Effacement	0-30%	31-50%	51-80%	>80%
Dilation	0 cm	1-2 cm	3-4 cm	Cm >5
Fetal station	-3	2-	0,1-	,2+ +1

Interpretation

The exact cut-offs used differs by source, but generally a score of 5 or less indicates the woman is unlikely to go into labor spontaneously at that time, and that an induction is likely to fail. A score of 8 or more indicates that an induction is more likely to succeed. [56]

Modified Bishop Score

According to the Modified Bishop's pre-induction cervical scoring system, effacement has been replaced by cervical length in cm. [58]

Table (2): The Modified Bishop Score

Parameter\Score	0	1	2	3
Position	Posterior	Intermediate	Anterior	-
Consistency	Firm	Intermediate	Soft	-
Cervical length	>3 cm	>2 cm	>1 cm	0 cm
Dilation	0 cm	1-2 cm	3-4 cm	Cm >5
Fetal station	-3	2-	0,1-	,2+ +1

Another modification for the Bishop's score is the modifiers. Points are added or subtracted according to special circumstances as follows:

- One point is added for:
  1. Existence of pre-eclampsia
  2. Every previous vaginal delivery
- One point is subtracted for:
  1. Postdate pregnancy
  2. Nullparity
  3. PPROM(preterm premature rupture of membranes)

Methods of cervical ripening

A-Non pharmacologic methods

Non pharmacologic approaches to cervical ripening and labor induction have included herbal compounds (primrose oil and red raspberry leaves), castor oil, hot baths, enemas, sexual intercourse, breast stimulation, acupuncture, acupressure, transcutaneous nerve stimulation. These modalities have been recommended for cervical ripening ,however till now have not proven efficacy for cervical ripening or induction of labor [59] and no evidence supports the use of these modalities as viable methods for cervical ripening or labor induction. A surgical method of cervical ripening is considered as effective non - pharmacologic method.

Surgical methods

1. Stripping of the Membranes

The membranes are stripped by inserting the examining finger through the internal cervical os and moving it in a circular direction to detach the

inferior pole of the membranes from the lower uterine segment .Stripping of the membranes causes an increase in the activity of phospholipase A_2 and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) as well as causing mechanical dilation of the cervix, which releases prostaglandins. Risks of this technique include infection, bleeding, accidental rupture of the membranes, and patient discomfort. [60]

2. Amniotomy

It is hypothesized that amniotomy increases the production of, or causes a release of, prostaglandins locally. Risks associated with this procedure include umbilical cord prolapse or compression, maternal or neonatal infection, FHR deceleration, bleeding from placenta previa or low-lying placenta, and possible fetal injury. [59]

3-Balloon catheter

A 30-mL to 50-mL Foley catheter filled with saline is effective in inducing cervical ripening and dilation. The catheter is placed in the uterus, and the balloon is filled. Direct pressure is then applied to the lower segment of the uterus and the cervix. This direct pressure causes stress in the lower uterine segment and probably the local production of prostaglandins. [61]

B-Pharmacologic Cervical Ripening

1-Prostaglandins

Prostaglandins are the current method used for the labor induction [62] Prostaglandin E1 (Misoprostol) and Prostaglandin E2 (dinoprostone) is the preferred agents and is usually administrated into the posterior fornix of vagina; it is act on the cervix to enable ripening by a number of different mechanisms, leading to relaxation of cervical smooth muscle facilitates cervical dilation and contraction of myometrial muscle, [63]. Risks associated with the use of prostaglandins include uterine tachysystole, hypertonus and uterine hyperstimulation, other side effects such as nausea, vomiting, diarrhea, fever and accompanying FHR changes. [64] Uterine rupture in women with previous cesarean section is also a possible complication, limiting its use to women who have a uterine scar. [65.66]

2- Mifepristone

Mifepristone (Mifeprex) is an antiprogesterone agent. Progesterone inhibits contractions of the uterus, while mifepristone counteracts this action. It shown that women treated with mifepristone are more likely to have a favorable cervix within 48 to 96 hours. [67] However, little information is available about fetal outcomes and maternal side effects; thus, there is insufficient information to support the use of mifepristone for cervical ripening. [68]

3- Relaxin

The hormone relaxin is thought to promote cervical ripening. But insufficient support for the use of relaxin in cervical ripening or induction of labor. [96]

4-Oxytocin

As pregnancy progresses, the number of oxytocin receptors in the uterus increases (by 100-fold at 32 weeks and by 300-fold at the onset of labor). Oxytocin activates the phospholipase C-inositol pathway and increases intracellular calcium levels, stimulating contractions in myometrial smooth muscle. Oxytocin is the preferred pharmacologic agent for inducing labor when the cervix is favorable or ripe. [63]

Nitric oxide

The discovery of an endothelium derived relaxing factor[70], and its later identification as nitric oxide (NO) have to be considered as among the most exciting discoveries in medicine in the 1980s. [71] Therefore, it was science's "molecule of the year" in 1992, and its discovery was rewarded with the Nobel Prize in 1998.

It is an important biological mediator in human beings[72], it mediates a wide range of physiologic processes that include the inhibition of platelet aggregation, smooth muscle relaxation, [73] neurotransmission,[74] and it is also generated by phagocytes (monocytes, macrophages, and neutrophils) as part of the human immune response. [75]

NO a small, highly reactive, free radical gas with a half-life time of a few seconds. [76] It diffuses freely across membranes, these attribute to make nitric oxide ideal molecule for a transient paracrine and autocrine signaling. It is soluble both in water and lipids. [77] It is a key vertebrate biological messenger, playing a role in a variety of biological processes. It is a known bioproduct in almost all types of organisms, ranging from bacteria to plants, fungi, and animal cells. [74]

Synthesis

Nitric oxide is synthesized endogenously from amino acid L-arginine, oxygen molecule , and nicotinamide adenine dinucleotide phosphate (NADPH) by the action of various nitric oxide synthase (NOS) enzymes Utilizing NADPH as an electron donor and heme, tetrahydrobiopterin, calmodulin, and flavin adenine mono- and dinucleotides as cofactors through a reaction that consumes five electrons. The overall reaction consists of a two-step oxidative conversion of Larginine to NO and L-citrulline via Nwhydroxy- L-arginine as an intermediate with monooxygenase I and monooxygenase II, in each step a mixed function oxidation taking place. [78] (Figure 2)

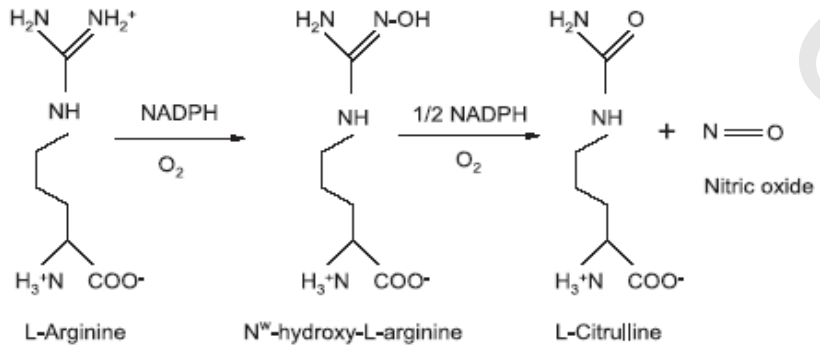

Figure (2): Nitric oxide synthase

Nitric oxide synthase (NOS) is expressed in three isoforms. Their syntheses are regulated by genes located in chromosomes 12, 17 and 7, respectively. [79]

1. Endothelial NOS is primarily expressed in vascular endothelial cells [80] and platelets. [81]
2. Neuronal NOS is expressed in the neurons, cerebullem and skeletal muscle. [82]
3. Inducible NOS, which becomes expressed in inflammation, it is calcium independent and is induced by different cytokines and endotoxins, thereafter it has been demonstrated in various human cells including macrophages. [76]

Nitric oxide is rapidly converted to stable NO metabolites; nitrate and nitrite (Nox) which can be assayed both in vitro and in vivo by means of the Griess reaction in physiological fluids e.g. plasma, urine and peritoneal fluid.[83,84] Vaginal fluid has also been assayed for Nox, [85] and all of these isoforms are present in the various cells of the uterine cervix. [86] Griess reagent forms azo dye with nitrite, which can be spectrophotometrically measured. [87]

General role

NO is an important intra- and intercellular signaling molecule involved in the regulation of diverse physiological and pathophysiological mechanisms in cardiovascular, nervous and immunological systems[88] It relaxes vascular smooth muscles, inhibits platelet aggregation, stimulates angiogenesis, reduces blood pressure and transmits neuronal signals. It also activates macrophages mainly through iNOS[89] On the other hand, it can act as a cytotoxic agent in inflammatory disorders[88], NO may also play a role in asthma[89] and interestingly, patients with asthmatic symptoms but normal lung function have also been shown to have increased alveolar and bronchial NO concentrations[90] In summary, NO is involved on a very large scale in human physiology.

Reproductive role

In females, circulating Nitric oxide is increased during follicle development and decreased immediately after ovulation [92].NO regulates endometrial functions such as endometrial receptivity, implantation and menstruation. [93] In early preimplantation embryonic development NO regulates mitotic division and mediates spiral arterial changes in decidualization [94] and promotes embryo implantation. [95]In addition to the above, NO production is essential for maintaining pregnancy. [96]

Placental perfusion is also controlled in part by NO [91] and fetal membranes are rich in NO, and oxytocin stimulates NO release in fetal membranes at term. [96]

In preeclampsia, Endothelial function changes occur before the clinical development of preeclampsia , [97] [98] Recent studies have revealed that there was NOS gene polymorphisms in women at risk of preeclampsia , which implies a primary role of NO deficiency in preeclampsia. [99]

In myometrial tissue all three NOS isoforms have been found .[100] NO produced by the trophoblast and placenta plays a significant role in maintaining uterine quiescence and blood flow [101] and inhibits uterine contractility during pregnancy, [102] the decreased production of NO, as well as the decreased sensitivity to NO close to term, may promote

the initiation of labor. [103] In conclusion, NO appears to be a key element in reproduction and pregnancy.

It has been demonstrated that cervical NO production is very low in post term pregnancy .Thus, it has been suggested that reduced cervical NO release may contribute to prolonged pregnancy. [104]

The human data and those from animal and in vitro, imply that in pregnancy nitric oxide has a role in physiological process of cervical ripening.[105]

The expression of NOS isoforms and the release of NO in the cervix have been shown to increase with advanced gestational age and during cervical ripening. [106] Commencement of uterine contractions was found to be increased level of cervical NO metabolites. [107]

In cervical ripening immunological mediators play a crucial role in this process. NO is involved in the acute inflammatory response and amplifies the cytokine cascade stimulated during this response. [108] Potential mechanisms of action of NO in the ripening process are via interactions either with prostaglandin biosynthesis or with lytic enzymes such as matrix metalloproteinases. Nitric oxide is known to stimulate cyclooxygenase to increase the production of pro-inflammatory prostaglandins. [109]The action of NO on cervical ripening appears to be accomplished by effects on connective tissue and smooth muscle cells. [110]

Nitric oxide donors

Nitric oxide donors are class of drugs that exert their action by librating nitric oxide in vivo. They include sodium nitroprosside ,nitroglycerin and isosorbide dinitrate and isosorbide mononitrate(IMN) .The vasodilatory effects of nitric oxide are widely used in the treatment of angina and cardic failure.

In obstetrics and gynecology

Nitric oxide donors are effective in:

1- Cervical ripening in humanbeing in first trimester of pregnancy [111], at term [112] and cervical ripening in non-pregnant. [113]
2- Management of preterm labor, [114] and improvement of fetal blood flow.[115]
3- Acute uterine relaxation to facilitate fetal extraction, manual removal of placenta. [116]

Side effects

Nitric oxide donors are safe and have no major side effects on the fetus or mother,[116] the most common side effect:

1. **Hypotension and Tachycardia:** nitric oxide donors have a small effect in depression of maternal blood pressure and increase the maternal heart rate. Thus, it has no clinically significant effect in hemodynamics . [112]

2. **Headache** is one of the most frequent symptoms. [117]

In clinical trials, several NO donors such as isosorbide mononitrate (IMN), glyceryl trinitrate (GTN), and sodium nitroprusside were reported to reduce the cervical resistance before uterine evacuation in patients undergoing termination of pregnancy in the first trimester. [118,119] vaginal administration of IMN in combination with gemeprost resulted in earlier second-trimester abortion compared with gemeprost alone. [120]

Vaginal administration of nitric oxide isosorbide mononitrite induce cervical ripening at term [121,122] without inducing uterine hyperstimulation, or abnormal fetal heart rate until the active phase of labor started. Thus, it can be administrated in outpatient maternal preference for outpatient cervical ripening and labor induction in uncomplicated pregnancies, thereby potentially improving patient convenience and reduced hospital costs.[123]

The combined use NO donor and a PG analog may be synergistic and lead to more effective cervical ripening with less frequent episodes of uterine hyperactivity [124], because the smooth-muscle-relaxant properties of IMN may result in a reduced incidence of the side effects attributable to PG-associated gastrointestinal and myometrial contractions.[125] However, Wolfier study demonstrated that vaginal application of IMN plus dinoprostone appeared to be no more effective than placebo plus dinoprostone for cervical ripening and labor induction at term. [126]

The ideal agent for cervical ripening would induce adequate cervical ripening with minimal adverse effects to the mother and the fetus, [127] an increasing body of evidence indicates a pivotal role of nitric oxide (NO) in the process of cervical ripening; many investigators have proposed that NO donors might be such agents. [128]