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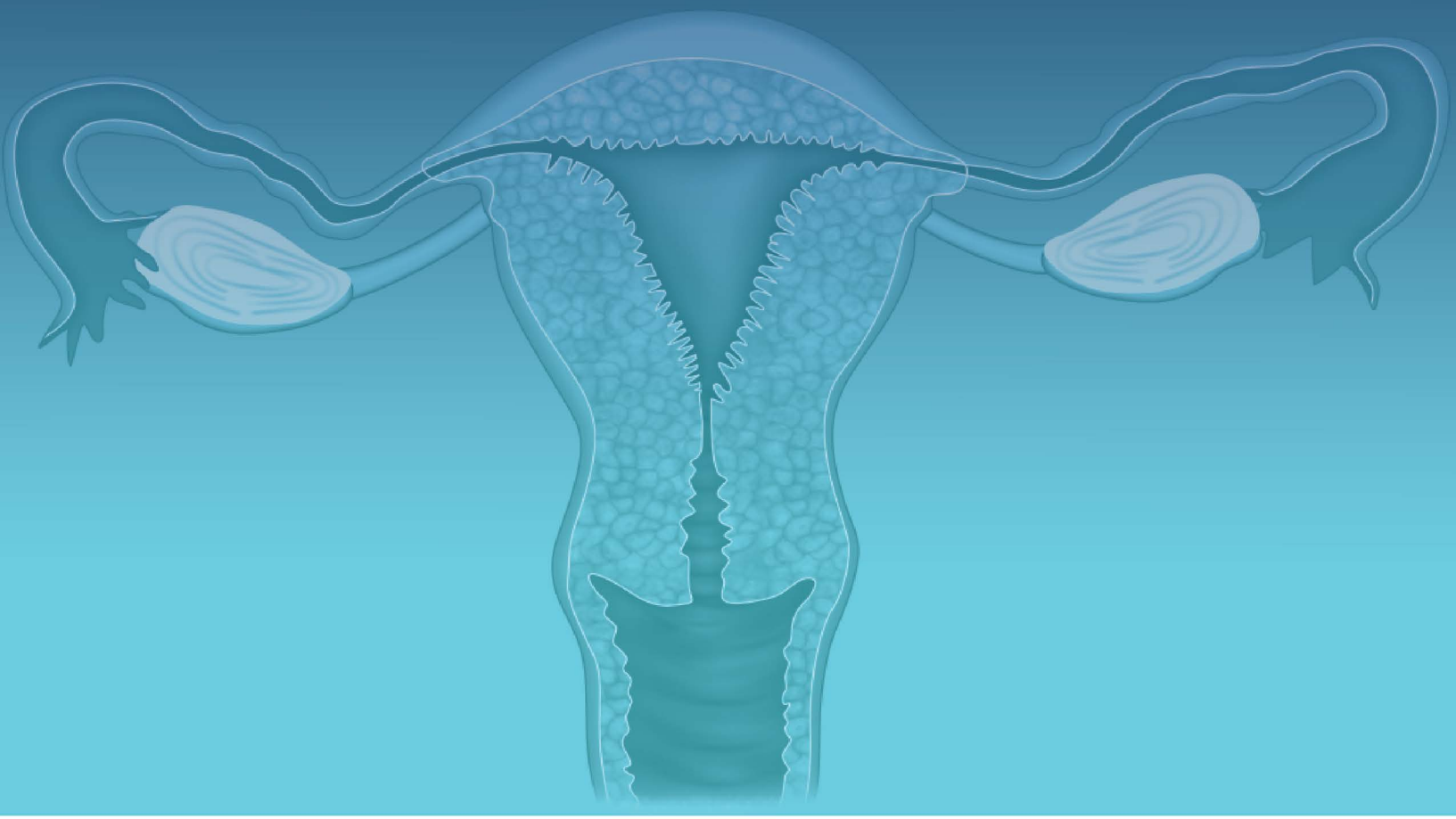
THE CERVIX



Editor
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4

CHAPTER

Effects of Drugs on Cervix

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ABSTRACT

There are many drugs which acts on both non-pregnant and pregnant cervix. But their mechanism of actions are still in gray zones. OC pills, clomiphene citrate, estrogen progesterone act on non-pregnant cervix and estrogen, progesterone, androgens and prostaglandins act in effacement of cervix in pregnancy. PGE2 gel has been widely used for preinduction cervical ripening. Misoprostol is a synthetic PGE1 analog. Intravaginal misoprostol causes first and second trimester abortion and cervical ripening and labor induction during term. Valethamate bromide (Epidosin), Drotaverine and Hyaluronidase are few other drugs widely used for effacement of cervix in labor induction or enhancing labor. Like many other scientific work, the work is in progress.

INTRODUCTION

Cervix plays many roles. In non-pregnant condition it affects fertility as well as can cause infertility. In pregnancy, it closes and holds the product of conception until term. If it opens in between, then preterm delivery occurs increasing fetal morbidity and mortality. It plays a vital role in the life of a woman, but its role till date is underestimated and gray areas still exists about cervix. Many drugs affects cervix, both non-pregnant and pregnant. The contraceptive pills as well as the fertility drugs both affect cervix, even the drugs given in the intrauterine life to the mother also affect the cervix. Drugs are used in pregnancy to dilate the cervix in first trimester operation and for effacement of cervix during labor.

DRUGS USED IN NON-PREGNANT CERVIX

OC Pills

It is known that viscosity of cervical mucus increases due to domination of progesterone throughout the second half of menstrual cycle. This increase in viscosity does not allow sperm penetration. Because of their progestin content, OCs also cause the same effect and this contributes to contraception. It is unclear which mucoprotein content change causes this effect in cervical mucus. The amount of MUC5B mucin in human cervical mucus varies during the menstrual cycle and peaks at ovulation, suggesting that this larger mucin species may be an important factor affecting sperm transit to the uterus. It has been suggested that MUC5B, owing to its hydrophilic structure, unexpectedly reduces the viscosity by keeping water so as to enhance sperm permeability through endocervix. It was expected that OC may change the MUC5B mucin levels in human cervical mucus in order to enhance its contraceptive efficacy and change the cervical mucus from thin to thick pattern. MUC5B is the main element responsible for the viscous and scanty structure of cervical mucus. This also contributes to the contraceptive efficacy of combined oral contraceptives. Some speculate that the OC-induced MUC2 increase in cervical mucus may be the underlying mechanism of OC-induced cervical carcinogenesis, although large-scale longitudinal studies are needed.[1]

FERTILITY INDUCING DRUGS

Ovulatory disorders are common causes of subfertility and infertility in women of reproductive age. Several pharmacologic agents are available to induce or augment ovulation, with varying rates of success. These medications include clomiphene citrate (a selective estrogen receptor modulator), aromatase inhibitors, urinary and recombinant gonadotropins, gonadotropin-releasing hormone (GnRH) analogs, and insulin-sensitizing agents. Clomiphene citrate is considered a first-line treatment because of its low cost, relative ease of use, and minimal side effects. It has been 50 years since the first clinical trial demonstrated that administration of clomiphene citrate induces ovulation in more than 75% of amenorrheic women. Asaad and Hipkin[2] have shown that, in untreated women there was a very strong tendency for CM quality to improve with rising plasma E2 levels and to worsen with rising plasma P levels. Similar results were found in CC-treated women, except that plasma E2 was very significantly higher and there was a significant inverse relationship between plasma E2 and CM quality. This reduced production of cervical mucus hampers the sperm migration which can lower fertility. This can be bypassed by IUI.

DIETHYLSTILBESTROL (DES)

Adenocarcinomas of the vagina and the cervix have been found in several instances with no apparent relation to transplacental or other DES exposure. A few cases of vaginal clear-cell adenocarcinomas were described in young women even before the introduction of DES in therapeutics. However, the risk for the general population without DES exposure is considered to be several orders of magnitude lower, compared with the data obtained from women with a history of intrauterine exposure. Therefore, the evidence on a causal relationship between DES exposure and clear-cell adenocarcinoma of the vagina or cervix seems conclusive.[3-5] Evaluating the available scientific data, the International Agency for the Research on Cancer (IARCWHO) has estimated that there is sufficient evidence for DES to be classified as a human carcinogen.[6]

Past human exposure for medicinal purposes was mainly in the context of threatened abortions and estrogen replacement therapies. There is sufficient evidence that intrauterine exposure of females to DES before the 12th week of pregnancy is causally associated with the appearance of vaginal and cervical clear-cell adenocarcinoma. Cancer appears usually after menarche, and at an age between 10 and 30 years. Cases become very rare after the age of 25.[7]

DRUGS USED IN PREGNANT CERVIX

Cervical Ripening Techniques

Cervical ripening in the presence of an unfavorable cervix (long, firm, closed, or minimally dilated) can be undertaken using either mechanical or hormonal methods. As long as there is no contraindication to labor, there should be no contraindication to using either oxytocin or a ripening agent. Mechanical techniques include the intracervical insertion either of rubber catheters with balloons (i.e. a single- or double-balloon 16- or 24-French Foley catheter) or of osmotic dilators. Examples of hormonal or biochemical methods that have undergone clinical investigation for cervical ripening include prostaglandins (PG), RU 486 (mifepristone), estrogen, DHEAS, glyceryl trinitrate and relaxin.[8]

Early Pregnancy

There has been increasing awareness of the potential hazards of metallic dilatation prior to suction curettage in first trimester termination, as such dilatation leads to an increased risk of incompetent cervix, spontaneous abortions and premature births in subsequent pregnancies. Termination beyond 10 weeks after metallic dilatation has been reported to lead to the risk of soft tissue trauma, hemorrhage, etc. Also incidence of complications have been recorded to rise steeply with increasing gestation weeks. The problem revolves round the internal OS, which is the point of greatest resistance during the process of dilatation. Recent investigations have shown that while cervices dilated to 10 mm or less show virtual full recovery to normal size when measured 6 weeks later at follow up, cervices dilated beyond 11 mm frequently did not, as the muscle fibers at the internal OS tend to tear off radially leaving behind a permanent damage. Thus, the method of dilatation assumes greater importance than the method of evacuation in preventing abortion morbidity both immediate and delayed.

It is observed that prostaglandin both as vaginal suppository and intramuscular injections are successful (80–87%) in adequately dilating the cervix in late first trimester cases.[9,10] Prior medications can be accomplished by paramedical personnel, an added advantage as regards the subsequent procedures.

Though both the multiple doses 1.0 and 1.5 mg suppositories were successful in approximately 80% of cases, the latter gave rise to more gastrointestinal upsets. However, the interval needed to accomplish the desired effects imposes a problem on both the patient and the doctor. In contrast, the intramuscular injection regimes have been successful in a significant number of cases (86%)

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and within a much shorter interval (4 hours). The single prostaglandin dose schedule had a greater possibility of gastrointestinal upsets, due to a larger dose being injected at one time as compared to the two dose schedule.

Recent report from Karim suggests that 16 phenoxy PGE2 methyl sulphone given by intramuscular injection is highly efficacious with negligible side effects.[11] This compound used intramuscularly holds high promise, as it has no side effects with the same effectiveness. In order to reduce gastrointestinal disturbances prostaglandins were injected intracervically in smaller doses. The side effects were almost eliminated but it was found to be successful only in 63% of the cases. Subsequently the dosage was increased from 50–100, μgm each side. But even this failed to show any appreciable gain. However, Karim reported that intracervical injection of 16-16 dimethyl PGE2P-benzaldehyde semicarbazone ester was successful in 80% of cases of 180 nulliparous patients within 3 hours, an encouraging result.[12] The preoperative dilatation by prostaglandin has an additional advantage of minimizing the blood loss[13] during the procedure as the prostaglandin initiates uterine contraction which may also minimize chances of uterine perforation.

Isogel Tents

73% of the patients were adequately dilated with the Isogel tents. The tents appeared to be more efficacious at later gestation weeks, since the increasing vascularity at higher gestation results in increased glandular secretion and dilates the tents better. The success rate for cases around 12 weeks was 80%. The intracervical injections and the tents also have the disadvantage of an additional theatre procedure prior to routine curettage.

LATE PREGNANCY

Estrogen and Progesterone

There is a great deal of evidence concerning the actions of steroid hormones on the connective tissues of the pelvis. Most available data concern the effects of steroids on the cervix. The time course of cervical softening in rats, sheep and humans suggests the possibility that the changes in connective tissue biochemistry that underlie the physiological phenomenon of cervical softening are under hormonal control. Both estrogens and progestogens have been implicated in the control of cervical softening. However, recent experiments using inhibitors suggest that, cervical softening can be produced in both sheep and humans by progesterone withdrawal in the absence of high circulating concentrations of estradiol-17. Intravenous estradiol-17 has also been shown to produce a degree of cervical ripening in pregnant women at term[14] and extra-amniotic administration of a gel containing estradiol valerate also caused cervical ripening when assessment was made I8 hours later. Comparison of estrogens with prostaglandins in clinical studies on cervical ripening at term have shown both agents to be of approximately equal efficiency.[15,16] However, estradiol given vaginally has no effect on the cervix earlier in pregnancy.[17]

Intravenous injection of dehydroepiandrosterone sulphate also produces changes in the state of the cervix in late pregnant women. This treatment has been associated with increased levels of estradiol- 17α in biopsy specimens of human cervix taken during late pregnancy as we1l as with an increased production of collagenase by cervical explants[18-20] and release of estrogens from cervical biopsy material collected during labor. When used as an agent for cervical softening, the interval between the beginning of the DHAS treatment and delivery was again shortened, particularly in the primiparous group in which the greatest effect on the cervix was seen. Thus DHAS may also be acting indirectly on the cervix by way of an increase in myometrial contraction.

Given the seemingly unavoidable problem of the induction of uterine contractions as well as cervical softening by treatment with estrogens in late pregnancy, it is necessary to consider evidence drawn from other sources in order to determine the part played by estrogens in the control of cervical softening. Low circulating concentrations of estradiol-17 have been associated with the failure of intravaginal prostaglandin E treatment for cervical softening prior to induction of labor.[21] There was no similar relationship seen with progesterone or prolactin. Thus, estrogens might be involved in modulating the response of the cervix to ripening agents.[22] This suggestion is supported by the finding that some pregnancies complicated by placental sulphatase deficiency and low estriot excretion may result in a failure of the cervix to ripen at term.[23-26]

The contradictions posed by the data presented above might be resolved by studies of the receptor populations of the cervix during pregnancy. The non-pregnant human cervix has been shown to contain specific estrogen-binding proteins. the numbers of which may increase in response to oral contraceptive regimes, although they do not vary during the menstrual cycle.[27] The identification of receptors for estrogens within tissue taken from the cervix during pregnancy would suggest that this group of steroid hormones might have some direct action on the cervix during labor. The theory that progesterone withdrawal is the key event in the initiation of parturition has been the subject of considerable interest since 1956.[28] Although most

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studies have concentrated on the relationship between progesterone concentrations and myometrial contractility the possible involvement of progesterone in the control of cervical softening has also been examined. Results of early studies were mostly negative. In the rat, the increase in cervical weight in response to treatment with estrogen or relaxin was not reduced by concurrent treatment with progesterone, neither administration of progesterone to late pregnant rats nor withdrawal of progesterone from the hormone replacement regime used to maintain pregnancy following ovariectomy caused any increase in cervical extensibility. The increase in cervical compliance seen in sheep after induction of labor could not be inhibited by treatment with progesterone(s) although uterine activity was effectively abolished by the progesterone treatment.

The effects of progesterone on the human cervix are poorly understood. Progesterone treatment during early and mid-pregnancy has been shown to be ineffective in preventing abortion and premature labor, suggesting that neither myometrial contractility nor cervical ripening can be inhibited by progesterone. Specific binding of progesterone has been measured in specimens of non-pregnant human cervix,[29] indicating that the cervix may be a target organ for this hormone. However, there are no reports of progesterone receptors being identified in cervical tissue from pregnant women.

Androgens

The cervix undergoes continuous remodeling during gestation to adapt to the expanding pregnancy. The regulation of this process is poorly understood, although it is believed to be under hormonal regulation. Both estrogens and progesterone have been shown to regulate cervical fibroblast function in vitro. Although clinical evidence suggests that androgens play a role in regulating cervical function, few studies have evaluated the role of androgens in cervical remodeling. In load-bearing tissues such as the tendon and cartilage, the extracellular matrix, consisting of collagen and proteoglycans, is responsible for biomechanical tissue properties. Proteoglycans are the main molecular component of the ground substance in the cervix. Their structure and function is poorly understood. The endocrine environment of pregnancy changes throughout its duration. A number of agents, including relaxin, progesterone, estrogen, nitric oxide, and prostaglandins, are known to alter cervical function. Recent data suggest that androgens are also important mediators of cervical function during pregnancy. It has been recognized that androgen precursors, such as dehydroepiandrosterone sulfate (DHEAS), can induce cervical ripening when given in the third trimester. Two clinical risk factors that have been associated with preterm delivery also effect androgen metabolism. Male fetal sex is recognized as a risk factor for prematurity, with male fetuses over representing preterm births in a number of population-based studies. Male preterm newborns produce higher levels of androgenic precursors than female newborns. In addition, periodontal disease has also been recognized as a risk factor for preterm delivery. The mechanism has yet to be established, although specific bacterial species (e.g. *Prevotella intermedia*) have been associated with both preterm delivery and increased 5_- reduced androgen production. Although not direct evidence, both suggest a role for androgen metabolism in preterm delivery. Cervical tissue expresses some of the highest levels of androgen receptors within the body. The function of these receptors has not been determined. In other tissues, including bone and cartilage, androgens regulate biomechanical responses by altering both composition and structure. Dailey et al[30] hypothesize that androgens directly regulate cervical remodeling by altering both collagen structure and proteoglycan composition. To begin to test this hypothesis, they evaluated the role of flutamide (an androgen receptor antagonist) on cervical biomechanics, structure, and composition. Cervical resistance has been shown to decline with advancing gestational age. This decline in resistance has not been explained, although many have speculated that this is due to changes in the hormonal milieu. Increases in circulating progesterone and estrogen are commonly cited. Evidence suggests that androgens are likely to play a role in the gradual decline in cervical resistance. Androgen receptors are highly expressed in the cervix. Dailey et al demonstrated in their studies that DHT (a 5_-reduced androgen) is able to accelerate the decline in cervical resistance, whereas the androgen receptor antagonist, flutamide, is able to inhibit this decline.

PROSTAGLANDINS

Prostaglandins consist of 20 carbon compounds synthesized in all cells. Exogenous prostaglandins have been administered orally, intravaginally, intracervically, or extra-amniotically to ripen the cervix and induce labor. Each of these routes has drawbacks. The application of prostaglandins in the upper vagina or in the cervical canal is more effective than a placebo with less total dose than when given systemically, thereby decreasing the total dose, maternal systemic effects, and uterine hyperstimulation. PGF_2 is not available as a cervical ripening agent, because it requires 10 times the equivalent dose of PGE_2 for equal efficacy and results in more systemic side effects. The primary pharmacologic method for cervical ripening is synthetic prostaglandins, namely prostaglandin E1 (PGE1) or misoprostol and PGE2 or dinoprostone.

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Cervical changes described in physiologic cervical ripening and spontaneous labor are reproduced with exogenous prostaglandins. Electron microscopic studies of cervical tissue following PGE2 have shown a dispersal and disintegration of the collagen fibers and a pronounced increase in the amount of ground substance.[31] A dissolution of collagen, increase in glycosaminoglycans, and increase in fibroblast activity have been described in early gestation in humans and late pregnancy in rabbits. Although these ripening effects may occur without contractions, prostaglandins are known to enhance myometrial sensitivity to oxytocin. Prostaglandins have been reported to accelerate gap junction formation leading to more coordinated uterine contractions. Myometrial strips taken from the fundus during spontaneous labor have been reported to be stimulated with PGE2, while smooth muscle of the lower uterine segment and cervix are inhibited by PGE2.

Maternal systemic effects occur very infrequently when low doses of prostaglandins are applied topically. Reported systemic effects include fever, vomiting, and diarrhea, all of which are very uncommon (usually <1%), dose dependent, mild, and reversible, either with removal of the preparation or with expectant management. Caution has been expressed about use of any prostaglandin product in cases of glaucoma, severe hepatic or renal impairment, and asthma. Bronchial constriction or significant blood pressure changes have not been reported after low doses of PGE2 and asthma is not a contraindication for its use. Increasing experience has been gained from use of low-dose prostaglandins after prior cesarean sections. Continuous monitoring is recommended among inpatients, and risk of a rupture must be explained beforehand.

Neonatal outcomes following prostaglandin cervical ripening compare favorably with those of oxytocin induction alone. Closure of the neonatal ductus arteriosus is not delayed despite low-dose intrapartum PGE2 therapy. Infant follow-up at 2 and 6 months of age has shown no unusual sequelae from the use of PGE2 gel.

PGE1 (MISOPROSTOL)

Misoprostol is an antiulcer medication containing a PGE1 analogue. It has gained widespread use for cervical ripening, despite lack of Food and Drug Administration (FDA) approval for this indication, because of its much lower cost. Each 100 μg or 200 μg tablet is stable at room temperature and easy to administer. Each tablet is usually divided into 25 or 50 μg doses, and then placed intravaginally every 3 or 4 hours. Any contractions are usually mild, but they may be sustained. Hyperstimulation of the uterus is dose dependent and occurs in 3–5% of cases.

Misoprostol is an effective agent for cervical ripening and labor induction when used judiciously and cautiously. Multiple trials have proved that misoprostol is an effective agent, as compared with oxytocin or prostaglandin E2, for cervical ripening and labor induction in term pregnancy however, investigations continue regarding the optimal dose, dosing regimen, and route of administration.

In November 1999, the American College of Obstetricians and Gynecologists recommended the 25 μg dose, given vaginally every 3 hours. Unlike trials where 50 μg of misoprostol was used, the 25 μg dose administered intravaginally as frequently as every 3 hours was not associated with an increase in uterine tachysystole, hyperstimulation, or meconium passage when compared with PGE2.

Uterine contraction abnormalities are often found in association with higher misoprostol doses. Some trials also indicate increased frequencies of meconium passage, neonatal acidemia, and cesarean delivery for fetal distress in women receiving higher doses of misoprostol. Overall, most trials fail to demonstrate a significant change in the cesarean delivery rate with the use of this agent.

PGE2 (DINOPROSTONE)

Local applications of PGE2 causes cervical ripening by three mechanisms: (1) Alteration of extracellular grounds substance of cervix by increasing collagenase, elastase, glycosaminoglycans, dermatan sulfate, and hyaluronic acid levels, (2) Relaxation of smooth muscle of cervix, (3) Gap junction formation leading to initiation of uterine contractions. Dinoprostone is available in two vaginally administered FDA approved formulations. It is available as a 10-mg vaginal insert that releases PGE2 (dinoprostone) at 0.3 mg per hour during the recommended 12-hour dosing period. Uterine contractions are gradual and usually peak several hours after insertion of the medication. The risk of hyperstimulation is approximately 5–10%, making outpatient use inadvisable. Continuous fetal heart rate monitoring is recommended, although there is no evidence to support this. A string attached to the insert allows for easy removal.

The controlled-release PGE2 intravaginal insert is associated with the initiation of cervical ripening and active labor during the 12-hour dosing period, frequently without the need for oxytocin. In this regard, approximately one-third of all women had the intravaginal insert removed before the end of the 12-hour dosing period because cervical ripening and active labor had been initiated. The cesarean section rate for induction failure following the administration of an intravaginal insert was very low (3.3–4.5%), and the vaginal delivery rate was similar to or

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greater than rates obtained with either placebo or multi dose PGE2 gels.

Another preparation of PGE2 (dinoprostone) is a 2.5 mL gel that contains 0.2 mg of PGE2. The patient is encouraged to remain supine for at least 30 minutes following gel installation to minimize leakage of the gel. Careful fetal heart rate monitoring is recommended for at least 30 minutes after instillation (American College of Obstetricians and Gynecologists, 1995). At least 6 hours should elapse before either the dose is repeated or intravenous oxytocin is administered. More than a single dose is often necessary, and the manufacturer recommends a maximum of three doses during 24 hours.[32]

Other Pharmacotherapy

Valethamate bromide (Epidosin) is an ester and is a potent rapidly acting anticholinergic spasmolytic and musculotropic agent which accelerates labor by improving cervical dilation.[33-35] A 50% reduction in duration of labor has been reported with Epidosin with mean rate of cervical dilation after 3 cm dilation to be 3.0 cm per hour in primigravida women.[36-38]

Drotaverine, an isoquinolone derivative, has a powerful spasmolytic action on smooth muscle cells by altering the membrane potential and permeability. Peak plasma concentration appears between 45 and 60 min and elimination occurs in 16 hours.[39,40] It facilitates dilation of cervix and shortens the labor in dose of 40 mg i.v. or i.m. with no other complication and no increase in cesarean delivery rate. It has been used in the third stage of labor too.[41,42]

HYALURONIDASE

During ripening, marked biochemical changes take place in the cervix, causing it to become soft and dilatable at the time of parturition. The most striking of these changes is the decrease in concentration of collagen and GAGs, together with a marked increase in HA concentration.[43,44] HA is synthesized by 3 related isoenzymes, named hyaluron synthase 1, 2, and 3.[45] Evidence derived from animal models of cervical ripening that demonstrated a sharp and sudden increase in cervical HA levels during spontaneous and induced labor, as well as a temporal increase in the transcription of cervical hyaluron synthase 2 (HAS2) proximal to the onset of labor, supports the important role of HA in the process of cervical ripening. However, equally important is that the functional role of HA in the process of cervical ripening and remodeling is determined in part by the size and structure of this GAG. A previous study in humans showed an increase in the concentration of HA in cervical secretions of women in labor.[46] The amount of HA correlated significantly with the levels and activity of HAase. Earlier studies suggested a positive effect of HAase on cervical ripening[47,48] and demonstrated significant morphologic and morphometric cervical changes following treatment.[49,50] Spallicci et al[51] performed a randomized double-blind trial in 168 pregnant women at term comparing intracervical injection of HAase vs placebo and found a significantly higher Bishop score, shorter duration of labor, and larger chance of vaginal delivery with the HAase-treated women. Furthermore, the latest Cochrane review concluded that intracervical injections of HAase for cervical ripening appears beneficial, but further research should be sought.[52] For obvious reasons testing the mechanisms of action of HAase in humans may be difficult.

Though there was no dilatation achieved with intracervical hylase at a dose of 3,000 IU the cervix appeared remarkably softened and gave the operator a subjective feeling of markedly reduced resistance during metallic dilatation. Increasing the dosage of 4,500 IU dilated the cervix to approximately 7 mm, but the results have been rather inconsistent. Being protein in nature, it stands a theoretical chance of giving rise to allergic manifestations in case of intravasation. Given that HAase treatment and performance of a cervical biopsy under a research protocol may prove ethically challenging. Yet, the results of current studies provide novel biomechanical evidence in support of HAase. It could be one of the most important regulators in the process of cervical ripening and that it may be clinically useful.

MECHANICAL MODALITIES

a. *Hygroscopic dilators:* These are natural or synthetic rods inserted through the cervical os and left in situ for a particular time wherein because of their osmotic properties they absorb endocervical and local tissue fluids. This swelling causes a controlled dilatation of the cervix along with releasing prostaglandins. Natural dilators are obtained from the seaweed Laminaria japonicum
b. *Balloon devices:* Foley's catheter or designer balloon devices when inserted intracervically can facilitate cervical ripening. Once properly placed (beyond the internal os) balloon or the catheter is inflated.

CONCLUSION

There are many drugs which acts on both non-pregnant and pregnant cervix. But their mechanism of actions are still in gray zones. OC pills, clomiphene citrate acts on non-pregnant cervix and estrogen, progesterone, androgens and prostaglandins acts in effacement of

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cervix in pregnancy. PGE2 gel has been widely used for pre-induction cervical ripening. PGE2 should be used in preference to intracervical preparations as they are equally effective and administration of intravaginal PGE2 is less invasive of the vaginal preparations. Tablets should be preferred over the gel as they are more cheap and equally effective. Mioprostol is a synthetic PGE1 analogue. Studies showed that intravaginal misoprostol causes first and second trimester abortion and cervical ripening and labor induction during term. Valethamate bromide (Epidosin), Drotaverine and Hyaluronidase are few other drugs which are widely used for effacement of cervix in labor induction or enhancing labor. Like many other scientific work, the work is in progress.

REFERENCES

1. Aksoy M, Guven S, Tosun I, Aydın F, Kart C. The effect of ethinyl estradiol and drospirenone-containing oral contraceptives upon mucoprotein content of cervical mucus. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2012;164:40-3.
2. Asaad M. Hipkin L. The effect of clomiphene citrate treatment on cervical mucus and plasma estradiol and progesterone levels. Fertility and Sterility. 1993;59(Issue 3):539-43.
3. Herbst AL. Diethylstilbestrol and clear cell vaginal carcinoma. Am J Med. 1987;83: 375-6.
4. Noller KL, O'Brien PC. Diethylstilbestrol and clear cell vaginal carcinoma. Am J Med. 1987;83:374.
5. Swan SH. Diethylstilbestrol and clear cell vaginal carcinoma. Am J Med. 1987;83:372-4.
6. International Agency for Research on Cancer IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Supplement 7, Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs. 1987;142:273-8.
7. Marselos M, Tomatis L. Diethylstilboestrol: I. pharmacology, toxicology and carcinogenicity in humans. J Steroid Biochem. 1987;27(4-6):1029-34.
8. Sanborn BM, Held B, Kuo HS. Hormonal action in human cervix—II. Specific progestogen binding proteins in human cervix. Steroid Biochem. 1976;7:665-72.
9. Borell A, Leader V, Lundstrem JN, Martin PK. Green. "Induction of first and second trimester abortion by the vaginal administration of 15 Me P; F2a Methyl ester" in Advance in Prostaglaldins ExThromboxane Research (eds. B Samuelsson and R. Paoletti), Raven Press; 1976. p. 693.
10. Bygdeman I, AC Ganguli K. Kinoshita V. Lundstrom K. Green and S. Bergstrom: Development of a vaginal suppository for single administration for second trimester pregnancy. Contraception. 1977;15:129.
11. Karim S, Choo ST, Lim AL, Yeo XC, Patnam SS. Termination of second trimester pregnancy with intramuscular administration of 16 phenoxy 17, 18, 19, 20 tebanor P3E2 Methyl I:u:fonylamide. Prostaglandins. 1972;15: 65.
12. Karim S, Ratnam SS, Selvariurai B, Wun W, Prasad RNV. 16, 16 Dimethyl PU; E2 p-benzaldehyde semicarbazone ester prior to vacuum aspiration in first trimester nulliparae; Prostaglandlns. 1977;13:333.
13. Raote V, Krishna UR, Navrekar MR, Purandare VN. Blood loss in medical terminations of pregnancy. The Journal of Obstetrics and Gynaecology of India. 1979;XXIXNo.3:609-12.
14. Gordon AJ, Calder AA. Oestradiol applied locally to ripen the unfavorable cervix. Lancet. 1977;ii:1319-21.
15. Stewart P, Kennedv JH. Barlow DH, Calder AA. A comparison of oestradiol and prostaglandin E2 for ripening the cervix. Br J Obstet Gynaec. 198l;88:236-9.
16. Tromans PM, Beazley JM, Shenouda PI. Comparative study of oestradiol and prostaglandin E, vaginal gel for ripening the unfavourable cervix before induction of labour. Br Med J. 1981;282 I:679-81.
17. Anthony GS, Fisher J. Coutts JRT, Calder AA. The effect of exogenous hormones on the resistance of the early pregnant human cervix. Br J Obster Gynaec. l984;91:1249-53.
18. Mochizuki M, Honda T, Tojo S. Collagenolytic activity and steroid levels after administration of dehydroepiandrosterone sulfate. Inl J Gynaec Obstet. 197X;16:248-53.
19. Mochizuki M, Tojo S. Effect of dehydroepiandrosterone sulfate on softening and dilatation of the uterine cervix in pregnant women. In Dilatation of the Uterine Cervix (Edited by F. Naftolin and PG Stubblefield). Raven Press: New York; 1980. pp. 267-86.
20. Sasaki K, Nakano R, Kadova Y, Iwao M, Shima K, Souwa M. Cervical ripening with dehydroepiandrosterone sulphate. Br J Obstet Gynaec. 1982;89:195-8.
21. Tahara R, Yanaihara T, Araki H, Nakayama T. Steroid concentrations in human cervical tissue in relation to cervical ripening. Acra Obstet Gynec Jn. 1985;9:1924-30.
22. Mackenzie IZ, Jenkins G and Bradley S. The relation between plasma oestrogen, progesterone and prolactin concentrations and the efficacy of vaginal prostaglandin E2 gel in initiating labour. Br J Obstet Gynaec. 1979;86:171-4.
23. France JT, Liggins GC. Placental sulfatase deficiency. J. clin. Endocr Metab. 1969;29:138-41.
24. France JT, Seddon RJ, Ligeins GC. A study of a pregnancy with low oestrogen production due to placental sulfatase deficiency. J Clin Endocr Merub. 1973;36:l-9.
25. Oakey RE, Cawood ML, Macdonald RR. Biochemical and clinical observations in a pregnancy with palcental sulphatase and other enzyme deficiencies. Clin Endocr. 1974;3:131-48.
26. Bedin M, Alsat E, Tanguy G, Cedard L. Placental sulfataste deficiency: clinical and biochemical study of 16 cases. Eur J Obsret Gynaec Reprod Biol. 1980;10:21-34.
27. Sanborn BM, Held B, Kuo HS. Specific estrogen-binding proteins in human cervix. J Steroid Biochem. 1975;6:1107-12.
28. Csapo A. Progesterone block. Am J Anat. 1956;28:273-92.
29. Sanborn BM, Held B, Kuo HS. Hormonal action in human cervix III: specific progestagen binding proteins in human cervix. J Steroid Biochem. 1976;7(66):5-672.
30. Dailey TL, Long V, et al. Androgen-regulated cervical ripening: a structural, biomechanical, and molecular analysis. Am J Obstet Gynecol. 2008;198:543.e1-543.e9.

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31. Wingerup L, Ekman G, Malmstr Gm A, Ohlsson B, Ulmsten U. Biochemical changes in cervix uteri following local application of PGE2. (In Swedish) Transactions of the Swedish Society of Physicians. (Acta Societas Medicorum Suecanae) 1979;88(3):491.
32. Ulmsten U, Wingerup L. Cervical ripening induced by prostaglandin E2 in viscous gel. Acta Obst and Gynec. (suppl) 1979;84:1-18.
33. Kuruvila S, Jasper P, Peedicayil A, Mathai M. A randomized controlled trial of valethamate bromide in acceleration of labor. Int J Gynecol Obstet. 1992;38:93-6.
34. Kaur D, Saini AS, Lata S. Effect of intravenous infusion of Epidosin on labour. J Obstet Gynecol Ind. 1995;45:708-10.
35. Puri M, Rathee S, Garg R. Effect of Epidosin on cervical dilatation during labour. J Obstet Gynecol Ind. 1998;38:427-30.
36. Prakash HT, Shah SK. Role of valethamate bromide in cervical dilatation. J Obstet Gynaecol Ind. 1987;38:746-66.
37. Ambiye VR, Alwani CM, Sinha R. Valethamate bromide for acceleration of labour. J Obstet Gynaecol Ind. 1985;35:852-4.
38. Sharma JB, Pundir P, Kumar A, Murthy NS. Drotaverine hydrochloride vs. valethamate bromide in acceleration of labor. Int J Gynecol Obstet India. 2001;4:43-8.
39. Suranyi S. Use of spasmolytic agent drotaverine for the assistance of labour. Medikus Univ. 1972;22:202-11.
40. Blasko G. Pharmacology, mechanism of action and clinical significance of a convenient antispasmodic agent drotaverine. J Am Med Assoc Ind Physicians Update. 1998;1:63-9.
41. Blasko ST, Demeter J. The effect of intramuscularly administered drotaverine on the dilatation stage of uncomplicated deliveries. Obstet Gynecol Today. 1998;3(12):723-37.
42. Bolaji O, Onyeji CO, Ogundaini AO, Olugbade TA,Ogunbona FA. Pharmacokinetics and bioavailability of drotaverine in humans. Eur J Drug Metab Pharmacokinet. 1996;21:217-21.
43. El Maradny E, Kanayama N, Kobayashi H, et al. The role of hyaluronic acid as a mediator and regulator of cervical ripening. Hum Reprod. 1997;12:1080-8.
44. Rajabi MR, Quillen EW Jr, Nuwayhid BS,Brandt R, Poole AR. Circulating hyaluronic acidin nonpregnant, pregnant, and postpartum guinea pigs: elevated levels observed at parturition. Am J Obstet Gynecol. 1992;166:242-6.
45. Itano N, Sawai T, Yoshida M, et al. Three isoforms of mammalian hyaluronan synthases have distinct enzymatic properties. J Biol Chem. 1999;274:25085-92.
46. Obara M, Hirano H, Ogawa M, et al. Changes in molecular weight of hyaluronan and hyaluronidase activity in uterine cervical mucus in cervical ripening. Acta Obstet Gynecol Scand. 2001;80:492-6.
47. Berlingeri D. Use of hyaluronidase in treatment of the secondary uterine inertia in spastic cervix. Attual Ostet Gynecol. 1959;5:189-205.
48. Green PS. Intracervical injection of hyaluronidase: effect on dilatation and length of labor. Am J Obstet Gynecol. 1967;99:337-40.
49. Li WJ, Li ZL, Ha KW. Effect of hyaluronidase on cervical ripening. Chin Med J (Engl). 1994;107:552-3.
50. Gupta T, Verma NK, Sood A. Effects of intracervical injection of hyaluronidase in primigravidae during labour. J Indian Med Assoc. 1994;92:47-8.
51. Spallicci MD, Chiea MA, Singer JM, et al. Use of hyaluronidase for cervical ripening: a randomized trial. Eur J Obstet Gynecol Reprod Biol. 2007;130:46-50.
52. Kavanagh J, Kelly AJ, Thomas J. Hyaluronidasefor cervical ripening and induction of labour. Cochrane Database Syst Rev. 2006; CD003097.

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