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From **KFOG**

Presidents message

Esteemed colleagues, beloved friends and dear students,

God gives life. Life as we are aware does not start at the moment of birth, but at the very second an ovum and sperm fuse to form the zygote.

I believe, we, the Gynecologists and Obstetricians are entrusted by God to ensure that human life is created and delivered on this planet the way God intended. This is how I define our profession and passion.

Over my decades of experience, I have seen that motherhood conquers all fear, pain, sorrow and misery of child birth. Being a Gynecologist and Obstetrician, its our sworn duty to preserve the thread of motherhood intact. 'Healthy Mother, Healthier Children'

Last year, KFOG focused on activities for Reduction of MMR as well as on the areas of Fetal Medicine, Genetics and Adolescent Health, in addition to taking critical steps to protect our fellow Gynecologists and Obstetricians against grave atrocities they face in the line of duty.

KFOG has been toiling to keep the Maternal Mortality Rate under check, as MMR is a performance indicator to improve 'Health and Safety' of pregnant women and new mothers.

"Walk the talk" was our anthem for last year, and KFOG conducted many CME's and Seminars throughout the State, which were focused to sensitize the Gynecologists and Obstetricians about the importance of Genetics and Fetal Medicine, for the health of the posterity is indebted to a healthy intra-uterine life as well, which is our ultimate responsibility.

Basic Genetic and Fetal Medicine CME's were conducted at Calicut, Ernakulam, Trichur, Kollam and Trivandrum. To expand our base, for the last one 1 year, KFOG is auditing 'Near Miss" case MDNMSR program is in the pipeline as we speak and will roll out soon.

KFOG envisions to decreasing MMR to 30 by the year 2020 and the only way to do it is by training, training and more training. Not just Gynecologists and Obstetricians, but our supporting nursing staff and paramedics too, as a cohesive knowledgeable team with us can create the desired miracles required to achieve our target.

Adolescent health education under the leadership of Dr. Suchitra was well taken up by Kannur, Trichur, Ernakulam, Kollam and Trivandrum societies.

To effectively perform our duties and responsibilities towards the society, we have to protect ourselves first against the miscreants, who either driven by ignorance or in most cases with maleficent intent, take law on to their own hands, and kill in a single stroke.For this, last year KFOG stepped into the social arena to fight the atrocities committed against doctors, especially us Gynecologists and Obstetricians, who are most susceptible to such attacks. All are well aware of the mental and physical torture that a young lady Gynecologist in Southern Kerala had to undergo, when her patient succumbed to an untimely death following anaphylactic shock due to antibiotics, after LSCS. After knowing the aftermath of the event, there was very strong interference from the part of KFOG, escalating the issue to the ministerial level, resulting in the arrest of one of the perpetrators who harmed the said lady Gynecologist and also for ensuring that she is not subjected to a media trail but a fair and just legal one wherein she gets an opportunity to prove her innocence.In spite of our sincere efforts at treatment, sacrificing our family and personal life, health and sleep, sometimes an inadvertent isolated unfortunate incident can ruin us mentally, physically, socially and financially. The public need to be educated regarding the umpteen numbers of complications that can occur at any time during pregnancy and child birth.

For that, we need to ensure the participation of parents

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and spouses during antenatal classes so that they can be sensitized to unexpected complications which can occur at any time during pregnancy and delivery. In this respect, I think short films by the Kannur Society and Cochin Society did spread this awareness in the general public and that can be taken up by other societies too.

Last year, our social responsibilities extended to newer areas. As you might be aware, Government Of India had taken steps to ban the drug Oxytocin, often a life saver for a mother in labour, and nowadays, sadly, that of the Obstetrician too. The manufacturing, distribution and sale of Oxytocin as well as its import by private companies were banned and a company named Karnataka Drugs & Pharmaceuticals was given the sole rights to manufacture Oxytocin, which would have naturally lead to creation of monopoly, artificial scarcity and black marketing of this life saving drug.

Many of our members made a social mark last year.Special mention of DrGracy receiving women empowerment award,Dr.Jose getting international recognition for his film Kharam,Dr.Aswath getting elected as FOGSI VP and DrShyjus for his KaminiRao oration at AICOG.

On that note, as the retreating president of KFOG, I request my dear young Gynecologists to stand together as a single fraternity and cultivate an avid enthusiasm for your work without being too much drawn by the money. Lakshmi Devi always followSaraswathi, and you can trust me on that. Be on your toes to update and do your work sincerely, passionately and with love. Make guidelines and protocols and follow them. Then, I believe, wealth and happiness would naturally follow suit.

In midst of all these busy schedules, don't forget to find time out for your family, friends and also a bit of "me time" for your own inner peace and growth.

"We are not now that strength which in old days
Moved earth and heaven, that which we are, we are,
One equal temper of heroic hearts,
Made weak by time and fate, but strong in will
To strive, to seek, to find, and not to yield"

With this I conclude my humble presentation before you and take this opportunity to wish all of you the very best in personal and professional life ahead. Thank you for the support and love extended to me during my tenure. May god be with you.

Thank you

Dr. Presannakumari Bhanumathy

SINCERE THANKS FROM TEAM KFOG 2018

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Expectant and Medical Management of ECTOPIC PREGNANCY

Dr. Presannakumari B

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Author is the current president of KFOG, very good leader, academician surgeon. This chapter is an except from her popular book for Postgraduates in Obstetrics and Gynaecology new edition.

Management of ectopic pregnancy has dramatically changed over the past few decades. Ectopic pregnancies leading to rupture, catastrophic internal haemorrhage and shock are presently rare. Technological advances in diagnosis and knowledge of the risk associated with ectopic pregnancy has resulted in diagnosis and treatment even before symptoms are experienced. An ectopic pregnancy can lead to tubal abortion, tubal rupture or spontaneous resolution.This article will elaborate only on expectant and medical management of ectopic pregnancy

Expectant management

Ectopic pregnancy generally requires either surgical or medical management as emergency. However, like a failing intrauterine pregnancy, a small number of ectopic pregnancies also will fail early so that no active interference is needed. These patients can be sorted out by careful trans-vaginal ultrasound and â-hCG measurement. Patients who are categorized as pregnancy of unknown location (PUL), can also be managed expectantly as TVS and â-hCG measurement cannot clearly distinguish between failed intrauterine pregnancy and resolving ectopic pregnancy. A small adnexal mass could represent an involuting ectopic pregnancy or an unrelated adnexal mass.

Selection of patients for expectant management

Patients who satisfy the following criteria may be chosen for expectant management

1. The β-hCG concentration is $\geq$ 1000 mIU/mL
2. No significant intraperitoneal haemorrhage
3. The patient must be aware and accept the risks, they should comply to treatment and should be available for follow up.
4. Ectopic mass size less than 4 cm.

During follow up, if the β-hCG levels are increasing or there are signs of tubal rupture, the patient might need either medical or surgical interference. The upper level of β-hCG below which a patient can be treated expectantly is not yet established by studies. When the cut of was taken as >1500mIU/mL, 28% of women subsequently

needed medical management and 13% required surgery. The success rate for expectant management reported by various studies ranges from 48-100%.

Follow up

Patients treated expectantly should be properly counseled and closely monitored. She should be within easy reach from the hospital. β- hCG level should be monitored every 48 hours till it is found declining and then weekly until it is normal. Rapidly declining hCG level suggests favorable outcome. Tubal rupture is very unlikely when the β-hCG has become normal. Patients who develop significant abdominal pain should be re-evaluated and might need interference. Following expectant management, tubal patency of the affected tube is reported to be 93%. Subsequent intrauterine pregnancy rates of 63 – 88% have been reported.

Medical Management

Since most ectopic pregnancies are presently diagnosed early in gestation, medical management is widely preferred. The use of methotrexate to treat ectopic pregnancy was first cited in 1982 by Tanaka et al. Since then, numerous prospective studies were carried out using methotrexate as an alternative treatment of ectopic pregnancies. Methotrexate is a folic acid antagonist that competitively inhibits the conversion of di-hydro folic acid to folinic acid thus reducing the active metabolite intracellularly. This leads to diminished DNA synthesis, which adversely affect fast growing tissues. Hence it is used for the treatment of trophoblastic disease and ectopic pregnancy. The drug can be used orally, intravenously, intramuscularly or can even be directly injected into the ectopic sac. The most commonly used route at present is intramuscular. Before administering methotrexate, it is important to exclude an intrauterine pregnancy. Methotrexate should not be used with a presumptive diagnosis of ectopic pregnancy or in situation where the ectopic is non-viable and can be treated conservatively by simple observation. Since a large number of women undergo early surveillance with β-hCG and TVS, the number of diagnostic errors will increase. This occurs especially while treating women for infertility. Ultrasound examination need not be done in an asymptomatic woman before 49 days of gestation, when one does not expect to see an intrauterine gestation. Such early evaluation can mislead the clinician by non definitive and false findings leading to more tests and diagnostic errors. If the patient is clinically stable and the ultrasound does not give a definitive diagnosis of ectopic gestation, a repeat ultrasound can provide confirmation of diagnosis, even if the β-hCG is above the discriminatory zone. Non specific findings like a sac-like object in the uterus or the adnexa should be followed up rather than hastily treated with methotrexate. Studies have shown that in many cases where serial β-hCG values suggests abnormal gestation, the pregnancy ultimately grew to a viable gestation when the initial β-hCG value was very low (500 IU/L). Over-surveillance can lead to unnecessary intervention.

There are multiple regimens for the use of systemic intramuscular methotrexate including 'single-dose', 'multi-dose' and 'two dose protocol'.

The ideal candidates for MTX treatment

1. Hemodynamically stable
2. No severe or persistent abdominal pain
3. Willing for follow up till beta hCG is normal.
4. Normal liver and renal function test results.
5. Pre-treatment hCG concentration less than 5000 mIU/mL.
6. Ectopic mass size of less than 3 - 4 cm and no cardiac activity.

Before the first dose of MTX women should be screened with complete blood count, liver function tests and renal function tests. Chest X-ray should also be taken if the woman gives a history of pulmonary disease. Folic acid supplements should be stopped as it will decrease the effective-ness of treatment.

Contraindications to methotrexate

1. Abnormal renal or liver function tests - Since methotrexate is cleared by the kidney, women who have renal failure can develop pancytopenia due to bone marrow suppression, acute respiratory distress syndrome or bowel ischemia with even a single dose of methotrexate. Women who have hepatic or renal disease may not be able to clear MTX and hence MTX is contraindicated in such women.
2. Active pulmonary disease, peptic ulcer, immunodeficiency.
3. Hypersensitivity to MTX

4. Heterotopic pregnancy with coexisting viable intrauterine pregnancy which need to be continued.
5. Breastfeeding
6. When the woman is not willing to comply with treatment or she has no timely access to institutional management in case rupture occurs.

Factors that lower efficacy

1. High β-hCG concentration – when the β-hCG concentration is 5000 mIU/mL or more, failure rate statistically increases. Women who are most suitable for Methotrexate treatment are those with hCG concentration less than 3000 IU/L. A systematic review found out that for every 10 women treated, there would be one more failure if the hCG level is 5000-9999mIU/L than there would be if the hCG level is 2000- 4999 mIU/L.
2. Presence of fetal cardiac activity is significantly associated with treatment failure.
3. Large ectopic size. When the ectopic size is more than 3.5 cm. it has been found that success rate is less
4. Peritoneal fluid – blood in the peritoneal cavity may be due to tubal abortion. In a large case series, it was found that peritoneal fluid confined to the pelvis was not associated with increased medical treatment failure. Hence it is prudent to try medical treatment if the blood is confined to the pelvis
5. High pre- treatment folic acid level.
6. Rate of β-hCG rise prior to or within several days following treatment.

Routes of Administration

MTX can be given intravenously, intramuscularly or orally. It can be injected directly in to the sac. Intramuscular MTX administration is the commonly used method of treatment for tubal pregnancy. Since local injection of MTX in to the sac necessitates laparoscopy, it is rarely resorted too.

Pre treatment evaluation

1. hCG estimation – To establish baseline level for monitoring the effect of therapy.
2. TVS – For evaluating the size of the sac, cardiac activity and the amount of blood in the peritoneal cavity.
3. Blood group and Rh type – Rh negative women should be given anti - D immunoglobulin.
4. Complete blood count, liver and renal function test.

There are 2 commonly used regimes for MTX treatment. Single dose and multiple dose protocol.

Single Dose

- MTX at a dose of 50 mg/ m2
- β-hCG repeated on day 4 and day 7
- If the β-hCG fall between day 4 and day 7 is less than 15 % of that on day 1; the day of MTX administration, a second dose of MTX is administered on day 7
- If hCG does not decrease after two doses, consider surgical management

Multi Dose

- MTX is given at a dose of 1mg/kg on days 1, 3, 5, 7 withLeucovorin 0.1 mg/kg on days 2, 4, 6, 8
- β-hCG should be repeated before each Methotrexate injection.
- Methotrexate is repeated until β-hCG falls by 15% from its peak concentration.

Two Dose

- MTX at a dose of 50 mg/ m2 on day 1
- Administer second dose of MTX at a dose of 50 mg/ m2 intramuscularly on day 4, if the β-hCG did not decrease by 15% by day 4.

Combination with other medications

- Oral Mifepristone 600mg combined with methotrexate 50mg/m2
- Gefitinib can be combined with methotrexate

Single dose protocol:

In single dose protocol, MTX is given at a dose of 50 mg/ m2 after measuring β-hCG titre. Patient should be under observation since there is risk of rupture even after administering MTX. β-hCG should be repeated on day 4 and day 7. On day 4 beta hCG may not fall significantly or may even increase. If the β-hCG fall between day 4 and day 7 is less than 15% of that on day 1; the day of MTX administration, a second dose of MTX is administered on day7. ?-hCG should be repeated every 7 days till it is normal. The success rate of single dose treatment reported was 87% if the initial β-hCG is between 5000 IU/ L to 9999 IU/L and 82% if the initial β-hCG is between 10000 IU/ L and 14999IU/L. Since a high initial β-hCG decreases the success rate of single dose treatment, it should be reserved for patients with less initial β-hCG concentration.

While on medical therapy if symptoms of rupture develop medical therapy should be abandoned and surgical management should be resorted to. Patients can experience slight abdominal pain within 7 days of starting therapy. This usually subsides within a few hours. If the pain is severe and persistent it could be due to rupture and hence needs urgent evaluation and management.

Multiple dose protocol:

The multiple dose protocol was the initial regimen used. In the multiple dose protocol MTX is given at a dose of 1mg/kg alternating with Leucovorin 0.1 mg/kg. βhCG should be repeated before each Methotrexate injection. Methotrex-ate is repeated until β-hCG falls by 15% from its peak concentration. Nearly 50% of patients will not require the full 8 day treatment. The success rate reported was 92.7%. This is significantly higher than that achieved with single dose treatment. Multiple dose protocol is specially preferred for interstitial pregnancies as well as cervical pregnancies.

Two dose protocol:

It has been demonstrated that the single dose protocol has a higher failure rate than multi dose protocol, which has higher side effects. In order to reduce the failure rate of single dose regimen, a two dose protocol was designed where methotrexate is administered on day 0 and day 4 and additional doses if needed are given on day 7 and / or day 11 if β-hCG levels did not decrease by 15% during the follow-up period. A report on this regimen found a success rate of 87%, lesser side effects and high patient satisfaction.

Combination with other medications

Mifepristone

Methotrexate in combination with mifepristone has been investigated in two randomized trials. Oral mifepristone 600mg combined with methotrexate 50mg/m2 was compared with methotrexate alone. The success rate was lower with methotrexate alone – 61% versus 72%. There were no differences in tubal patency. Further studies are necessary before advising additional mifepristone. Another agent studied is gefitinib. Gefitinib selectively inhibits tyrosine kinase. Further studies are needed before gefitinib can be used to treat ectopic pregnancy.

Precautions during therapy

1. Avoid pelvic examinations during surveillance due to the risk of tubal rupture.
2. Avoid intercourse.
3. Avoid sun exposure to decrease the risk of MTX dermatitis.
4. Avoid foods containing folic acid.
5. Avoid non steroidal anti-inflammatory drugs as significant drug interaction can occur if both drugs are taken together.

Pain during treatment

Mild to moderate abdominal pain can occur but usually it is of short duration. However severe pain may be due to rupture and hemoperitoneum. Hence patients with severe pain should be evaluated and might need surgical interference.

Consequences of inappropriate use of methotrexate.

Inappropriate use of methotrexate can result in disastrous consequences. There are several reports of methotrexate being used in presumed ectopic pregnancy when later an on-going intrauterine pregnancy was diagnosed. If the pregnancy is allowed to continue it can result in a live born infant with craniofacial, skeletal, cardiovascular and gastrointestinal malformations and IUGR.

Subsequent pregnancy

Literature on toxicology recommends 4-6 months as wash out period if methotrexate is given. This may be because residual methotrexate may be present in the liver and kidney for about six months. Even though there is no evidence of teratogenic risk among women who conceive soon after methotrexate therapy, it is safer to advise pregnancy after about six months of treatment. These women should be advised routine pre-conceptional folic acid. There is no evidence of adverse effect of methotrexate on subsequent pregnancy following methotrexate treatment for ectopic pregnancy.

ASSISTED REPRODUCTIVE TECHNIQUE How to Improve Results

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Introduction

ART – Assisted Reproduction Technique involves those procedures in which both gametes, both sperm and ovum are handled outside the body. It involves procedures like IVF(In Vitro Fertilisation) , ICSI (Intracytoplas- mic Sperm Insemination) , GIFT(Gamete Intra Fallopian Transfer), ZIFT (Zygote Intra Fallopian Transfer)etc. Because of more invasive procedures involved, most of the centers now do IVF & ICSI only.

IVF/ICSI : The basic difference between conventional IVF and ICSI is that, in IVF each ovum retrieved is mixed with about 10 – 20 thousand sperms in vitro and allowed to fertilize and form embryo. But in ICSI each oocyte cumulus complex retrieved is first denuded and one sperm is injected to it using a micro-manipulator.

The 5 basic steps of IVF & ICSI are the same . They are :

- ✓ Controlled Ovarian Super Ovulation
- ✓ Ovum Retrieval
- ✓ Sperm Extraction
- ✓ Fertilization
- ✓ Embryo Transfer

ART OUTCOME :

First IVF baby Lousie Brown was born on July 25th 1978 from a natural cycle. In last 40 years ART specialists have been trying to improve the success rate. Even in best centers in worldwith good embryos,over all implantation rates is less than 50 %. The different aspects to improve ART outcome will be discussed below

1) **Improve Ovarian Stimulation and Ovum Pick –up**

   The main factors affecting the Ovarian stimulation are :

a) **Age** : Success rate of ART treatment decreases as age increases. Most of the studies have proved

that maternal age is the most important factor, and above the age of 35 years the success rate decreases significantly.

b) **Indications**: Among the different female indications ART done for tubal factor has got the maximum success rate. These patients usually has better oocyte quality and good receptive endometrium. Among the male indications, obstructive azoospermia has got the best results because usually they present early and their sperms are usually genetically normal.In cases of severe OAT (oligoasthenoteratozoospermia) and azoospermia it is recommended to do karyotyping to rule out any Chromosomal abnormalities , either it can be numerical or structural defects. The importance is that they can result in fertilization defects or abnormal embryos or even recurrent abortions. Also it is recommended to do PCR (Polymerase Chain Reaction) for identifying 'Y' deletion. The important is that if there is 'Y' deletion, the resultant male offspring can inherit the same defect as the father. In unexplained infertility, ICSI is preferred over Conventional IVF. This is because ICSI has got better fertilization rates. So we can select better embryos for implantation

In cases of severe endometriosis and frozen pelvis, it is better to go for prolonged pituitary Suppression before stimulation. In cases of adenomyosis if it is large, it is better to go for adenomyomectomy and if small for prolonged suppression before starting stimulation.

In cases with PCOD with oligo or anovulation usually they respond better with controlled ovarian Hyperstimulation. But precautions must be taken to prevent OHSS. With better results with Frozen Embryo transfer techniques, in patients with high E2 values on day of HCG, embryos can be cryopreserved and utilized for subsequent cycles, therebydecreasing the chances of OHSS.

c) **Drugs** : There are different studies about different protocols and drugs used for controlled ovarian hyperstimulation. Among these long and short protocols using GnRh analogues is preferred many centers. GnRh antagonist protocol is stated by few studiesas having many benefits especially in poor responders. Also GnRh antagonist is used in hyperresponders and oocyte donors, as we can use agonist trigger instead of HCG, which will decrease OHSS significantly. Among the Gonadotropins even though there are conflicting reports, recombinant FSH is found to be giving better results in our experience.

2) **Good Laboratory Techniques :** Among the different aspects of a laboratory not only the standard specification but even the location of the lab in a pollution free environment is found to be important. The different culture medias used are having short half-life and are very costly. They must be transported and stored maintaining the cold chain. The disposables used even though are costly, must be of standard specification and pyrogen free. Experienced embryologist and a co-ordination between the staff is most vital in the success of ART treatment.

3) **Embryo Transfer :** The embryo transfer is usually done on the 2nd or 3rd day. It is the procedure by which the embryos are transferred into the uterine cavity without disturbing the endometrium, there by facilitating the further growth of embryo. Even though it is a simple procedure, it must be done atraumatically using special catheter . Usually it is done under ultrasound guidance. Out of the many embryos developed in the laboratory, the best are selected by the embryologist. The embryos are graded in the laboratory based on the appearance under microscope and the better dividing ones are regarded as the best.

Usually two or three good embryos are transferred during embryo transfer to increase the chance of pregnancy. But this definitely increases the incidence of multiple pregnancy. In few western countries now the rule is to go for single embryo transfer, this definitely decrease the chance of multiple pregnancy, but also decrease the chance of pregnancy in a single cycle. With improved facility of embryo cryopreservation, the excess embryos can be cryopreserved and can be thawed and transferred in the in subsequent cycles.

4) **Factors to improve improve Implantation :**

a) **Hysteroscopy** : Even before the start of suppression by doing a base line TVS (Trans Vaginal Sonography) if you are suspecting any

uterine pathology it is better to do hysteroscopy. Also in cases of previous endometrial procedures and in failed cases it is better to do a hysteroscopy to rule out any endometrial pathology and adhesions. It is the procedure by which the potential space of the uterine cavity is distended using fluid and directly visualized using hysteroscope. Not only diagnosis of the uterine cavity lesions, but also treatment of the same can be done using hysteroscope.

b) **Hydrosalpinx** : Hydrosalpinx is the condition in which secretions are collected in the tube resulting in disruption of the anatomy and function of the tube. The secretion from the hydrosalpinx is found to be embryo toxic and interfere with implantation. So it is recommended to remove the hydrosalpinx or disconnect the damaged tube from uterus, before going for ART procedure.

c) **Prolonged suppression** : In cases with multiple small myomas, endometriosis, adenomyosis it is better to give prolonged suppression of Hypothalamus pituitary ovary to improve the results. This has found to improve the implantation in these patients.

d) **Blastocyst** : If facilities are available like Triple Gas Incubator and special medias, we can grow embryos even upto blastocyst stage. The advantage is that we can select the better multiplying and better quality embryos and transfer fewer embryos which will reduce the multiple pregnancy and improve the take home baby rate

e) **Assisted Hatching** : By making a small hole in the outer zone of embryo either by using Laser, Chemical or Mechanical methods, is found to improve the implantation especially in cases of unexplained infertility.

f) **Laser in ART**: Even though Laser is a very expensive tool, because of its precision it has got varied use in ART and found to improve the results significantly.

1) Immobilization of the sperm : Laser can be used affectively to immobilize the sperm by crushing the tail before ICSI
2) Assisted Hatching : Compared to mechanical or chemical methods used for Assisted Hatching Laser helps to make precise defect in the zona without injuring the embryo.
3) Embryo Biopsy : Laser Assisted Embryo Biopsy for PGD is better than other techniques

g) **Preimplantation Genetic Diagnosis** (PGD) : In the blastomere stage, each cell is totipotent. So even if we take a single cell , the remaining embryo will grow into a healthy foetus. So at this stage if we do an embryo biopsy and by doing FISH (Fluorescent in Situ Hybridization) or PCR (Polymerase Chain Reaction), we can exclude aneuploidies and transfer only unaffected embryos during the embryo transfer.

h) **Vitrification:**This method of freezing embryos gives very good recovery of embryos after thawing, which has increased the cumulative pregnancy rates per ovum pick up and planning freezing of embryos in hyperstimulation.

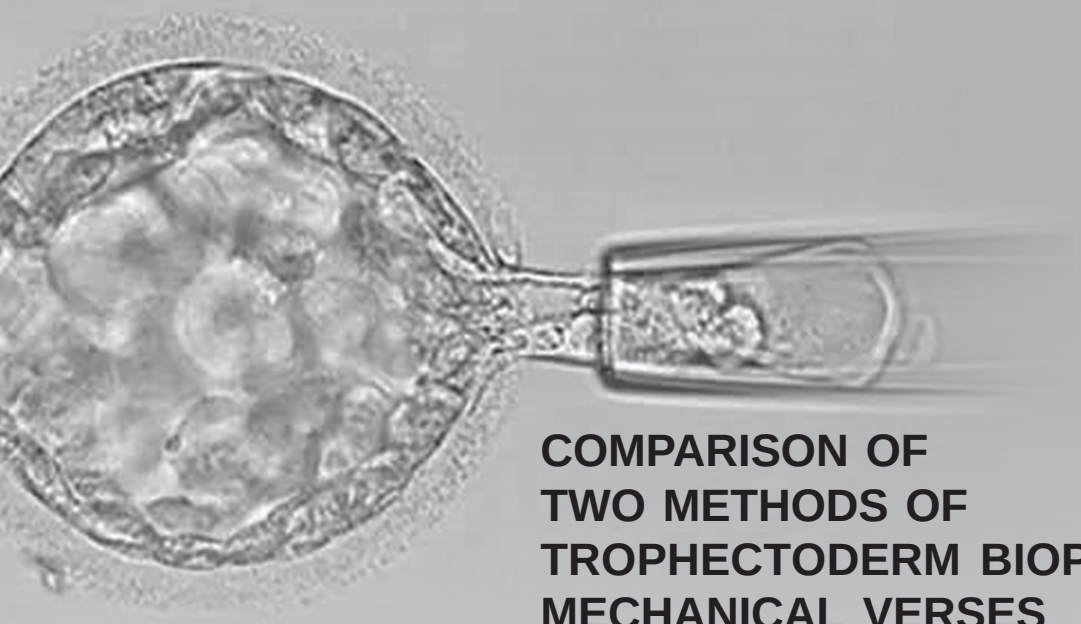
5) Luteal Phase Support : All the pregnancy resulting from induced ovarian cycle must be supported in the luteal phase by progesterone. This is a must in all ART cycles using progesterone either by injectable or vaginal or oral route.

6) Ante Natal Care : Good Antenatal Care is a must for completion and better outcome of an ART treatment . Just getting the pregnancy is not the end result, but getting a healthy baby must be the ultimate aim and success of ART treatment for both treating physician and patient.

Recent Advances : Cytoplasmic transfer: This is a recent introduction in ART where especially in elderly females, the cytoplasm of the oocyte is replaced with that of younger individuals, retaining the nucleus. This is still in research state.

ICMR : In Indiathere is no specific law governing ART centers and treatment. But Indian Council for Medical Research has come out with guidelines for ART treatment in India. Government of India is planning to come out with a law controlling ART centers and treatment based on these guidelines. They are also planning to start accreditation for the ART centers.

Conclusion: Even after evolution of ART in last40 years there is a limitation for success of ART treatment. Success of ART treatment depends on systematic analysis and meticulous approach to each case and proper co-ordination by the ART team. Also success can be improved by up gradation of knowledge and implement-ation of latest techniques and gadgets.



COMPARISON OF TWO METHODS OF TROPHECTODERM BIOPSY MECHANICAL VERSES LASER - ASSISTED

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ABSTRACT

Background

With the current development of IVF Technologies such as PGD/PGS techniques, low oxygen tension culture system, and vitrification techniques have encouraged blastocyst stage biopsy which promised more safe approach and more cells obtained than cleavage stage biopsy. There are two distinct methods to do TE-biopsy , laser assisted and mechanical technique. The study aimed to compare the impact of mechanical verses laser assisted trophectoderm biopsy on murine embryo development and determine the difference in time taken to perform the procedures.

Methods:

Embryos n= (146) were cultured and assisted hatched prior to hatching blastocyst biopsy. Embryos were divided into three groups: Mechanical biopsy (group A; n=50), laser assisted biopsy (group B; n=50) and control (n=46)

Results

Embryo viability proportion after biopsy in group A was 82%, whilst in group B was 80%. There was no statistical difference in embryo viability rate post biopsies between biopsy groups (p=0.7542) or between biopsy groups and control group (p=0.9804). The average time taken to do the mechanical biopsy method was 103.3 seconds (95% CI 83.18-123.4), faster compared to 130.9 seconds (95% CI 109.7-152) with laser assisted biopsy method. 100% successful retrieval of TE cells was achieved in group A while 98% retrieval rate was achieved in group B.

Conclusions

There is no difference in embryo development and viability following mechanical or laser -assisted TE biopsy . Mechanical biopsy technique is favourable for being 'easy' and faster. Mechanical biopsy can be promising choice of biopsy method in hatching stage blasatocysts.

POSTABORTION CONTRACEPTION

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INTRODUCTION

Contraceptive selection requires consideration of patient preferences and medical factors. For women who have undergone an abortion and desire contraception, additional issues include when to start the method and whether or not back-up contraception is necessary. Prompt initiation of postabortion contraception increases utilization and continuation and thus reduces the risk of future unintended pregnancy.

WHEN TO START POSTABORTION CONTRACEPTION

The first ovulation post abortion occurs between a mean of 21 to 29 days after the procedure with a reported range of 8 to 103 days . As the resumption of ovulation can be rapid and unpredictable, we advise women who desire contraception to begin the method at the same time the abortion occurs (ie, immediate start).

Advantages of immediate initiation of contraception include that the woman is known not to be pregnant, an additional visit is not required, and the woman leaves with a contraceptive plan in place, although a plan to use condoms or short-acting reversible contraceptives is not likely to be as reliable as immediate initiation of long-acting reversible contraception.

CONTRACEPTIVE OPTIONS

Postabortion women can safely use any contraceptive option that is compatible with their medical comorbidities

Long-acting reversible contraception

Long-acting reversible contraception (LARC) has a low failure rate, high continuation rate, and high ease of use .

LARC includes the copper intrauterine device (IUD), levonorgestrel-releasing IUDs, and the etonogestrel implant.

Progestin-only implant

The progestin-only etonogestrel implant is 99 percent effective at preventing pregnancy , has a high continuation rate , and has no risks specific to post abortion women . The etonogestrel implant can be inserted after any type of abortion (induction, medication, spontaneous, or surgical) regardless of gestational age at pregnancy termination

Intrauterine contraception

Either copper or levonorgestrel-releasing IUDs can be inserted immediately after abortion in women with

no evidence of uterine infection. Post abortion intrauterine contraception is 99 percent effective , associated with fewer subsequent abortions, and associated with higher rates of continued use when compared with short-acting contraceptive methods . Immediate IUD insertion has been reported to reduce subsequent abortions by 50 to 70 percent compared with interval IUD insertion (ie, insertion at a follow-up visit), but immediate insertion is also associated with higher rates of expulsion than interval insertion .

Short-acting hormonal contraception

Estrogen-progestin contraceptives (oral pill, transdermal patch, and vaginal ring) can be initiated after first- and second-trimester abortions . Short-acting progestin-only contraceptives (oral progestin-only pills, depot medroxyprogesterone acetate injection) can be started immediately after an abortion, with no limits on gestational age .

Barrier contraception

Barrier methods include the diaphragm, cervical cap, sponge, and condoms (male and female). Advantages include contraception only when needed and lack of hormones.

Ï%Diaphragms are available in two forms: a round device that must be fit Ï%The FemCap is a cervical cap that is available in three sizes. The choice of size is determined by the woman's reproductive history.

Ï%Other barrier methods (male condom, female condom, sponge, and spermicidal agents) can be used as soon as coitus is resumed.

Sterilization

Women who desire sterilization can proceed with a laparoscopic method (eg, silastic band, bipolar electrocoagulation, titanium clip, or salpingectomy). Laparoscopic sterilization can be performed concurrently with a surgical abortion procedure . Hysteroscopic sterilization is contraindicated immediately after abortion.

HOW TO START POSTABORTION CONTRACEPTION

After surgical or induction abortion

Women who undergo surgical (ie, dilation and evacuation) or induction abortion can start any medically appropriate contraceptive method on the day of the procedure and do not need a period of abstinence or back-up contraception . Back-up contraception or a period of abstinence of seven days is advised for women who start contraception up to seven days from the procedure.

Management of women who start contraception more than seven days from a surgical or medication abortion is presented below.

After spontaneous or medication abortion

The optimal contraceptive start time is less clear for spontaneous and medication abortion compared with surgical or induction abortion because the amount of time required for uterine evacuation is unpredictable. For women with a spontaneous abortion, the pregnancy may have lost viability days or weeks prior to the passage of tissue. In medication abortion, the woman must take two different medications at specified times. All of these issues can create confusion as to when to start contraception.

For women who undergo medication or spontaneous abortion, the contraception start times and need for back-up contraception or a period of abstinence vary with the contraceptive method :

Ï%**Intrauterine device**

Intrauterine devices can be inserted once the uterus is determined to be empty by either the clinical history or ultrasonography. No back-up contraception or abstinence period is needed following insertion of a copper IUD because it also functions as an emergency contraceptive . In contrast, seven days of abstinence or back-up contraception are advised following insertion of a levonorgestrel-releasing IUD.

Ï%Etonogestrel implant

For women undergoing medication abortion, the etonogestrel implant can be inserted on the day of mifepristone administration . If the implant is placed more than three days after mifepristone administration, back-up contraception or abstinence is required for an additional seven days

For women who have a spontaneous abortion, the etonogestrel implant can be inserted after the abortion is completed. If implant insertion occurs more than three days following spontaneous abortion, back-up contraception or abstinence is required for an additional seven days

Ï%**Depot medroxyprogesterone acetate (DMPA) injection**

DMPA injections can be initiated up to seven days after mifepristone administration. An additional seven days of abstinence or back-up contraception are

generally advised , but may be avoided if DMPA is initiated within three days of mifepristone use . For women who initiate DMPA on the day of mifepristone administration, the risk of ongoing pregnancy appears to be higher than for women who start the medication after the abortion is completed (3.6 versus 0.9 percent) . Thus, we counsel women that combined start of mifepristone and DMPA is more convenient but the medication abortion may be more likely to fail.

DMPA injections can be initiated after a spontaneous abortion has been completed . An additional seven days of abstinence or back-up contraception are advised.

Ï%**Combined estrogen-progestin contraception**

Combined estrogen-progestin contraception (ie, oral pill, patch, or vaginal ring) can be started within seven days of mifepristone administration or spontaneous abortion . Back-up contraception or abstinence is advised for an additional seven days.

Ï%**Progestin-only pills (POPs)**

POPs can be started within seven days of mifepristone administration (for medication abortion) or spontaneous abortion . In contrast with other methods, the Center for Disease Control and Prevention advises two days of back-up contraception or abstinence because the rapid impact of the drug on cervical mucous takes more than two days unnecessary.

DELAYED CONTRACEPTIVE START (>7 DAYS POSTABORTION)

For women who delay starting contraception for more than seven days from the abortion and present after having had unprotected sexual activity, exclude pregnancy and assess the need for emergency contraception.

Ï%Exclude pregnancy

A new pregnancy is excluded by history or laboratory testing. Human chorionic gonadotropin (hCG) levels will typically take two to four weeks, but sometimes longer, to resolve after abortion. Of note, hCG levels are highest in the first trimester and therefore may take longer to resolve after a first-trimester abortion compared with a later gestation . If pregnancy testing is positive in this setting, the woman is encouraged to use back-up contraception (eg, condom) while serial quantitative serum hCG levels are assessed. If levels are clearly declining, the desired method of contraception can be started

COMPLICATIONS

Contraceptive complications generally do not differ among post abortion or nonpregnant women. As discussed above, there may be an increased rate of IUD expulsion after late first-trimester or second-trimester abortions.

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1. Stoddard A, Eisenberg DL. Controversies in family planning: timing of ovulation after abortion and the conundrum of postabortion intrauterine device insertion. Contraception 2011; 84:119.
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FERTILITY 'IN-STORE' for a better tommorow !

DR SHYJUS P.

An infertility specialist laparoscopic surgeon orator organiser leader dancer singer and much more. He is currently the secretery of Kannur OG Society

Around 2% of women of reproductive age suffer from invasive cancer and thus are at risk of ovarian failure due to the gonadotoxic treatments in the form of chemotherapy and radiotherapy. From a time where cancer equated to morbidity and mortality, we have reached a day when the chance of surviving from most cancers, is around 80%. Hence many women have started to focus on 'quality of life' after treatment and the possibility of having their own children comes high up, in their priority list .Thus the concept of 'fertility preservation' is focused on saving gametes in girls and young women who run the risk of losing the entire pool of ovarian follicles either due to cancer or a genetic disease. Furthur areas which are getting explored are for women who wish to delay childbearing or to postpone menopause.

Till recently, cryopreserved oocytes or embryos from IVF treatment were considered the only option. The major disadvantage for this method was the fact that it couldn't sustain long-term fertility including support of functioning ovulatory cycles. It also requires upto two weeks of ovarian stimulation, which may be incompatible with an urgent cancer treatment.

Cryopreservation and transplantation of ovarian tissue has now come into being, to overcome these shortcomings. It could restore menstrual regularity and thus the patient gets the possibility of a spontaneous conception too. This method can even be performed in cases where chemotherapy has already been initiated, in contrast to IVF treatment.

Chemotherapeutic agents causes a reduction in the number of primordial follicle, reduces ovarian weight and augments ovarian atrophy. The extent of damage depends on the regimen used and the age of the patient. Ovaries of young girls contain a larger number of follicles and hence are more resistant to the effects of chemotherapy. Alkylating agents including cyclophosphamide and busulfan are more gonadotoxic than other chemotherapeutic agents {Odds ratio of 4, for premature ovarian insufficiency (POI)}. Radiotherapy interrupts the normal cellular proliferation cycle and causes extensive cell damage. It has been estimated that a radiation exposure of 20 Gy fractionated over 6 weeks in younger women causes sterility with 95% confidence.

Options available for preserving fertility in females are:

1. **Hormonal suppression**: Co-treatment with GnRH analogs was expected to protect the ovaries from the harmful effects of chemotherapy. But no good evidence is available at present to support this.
2. **Cryopreservation of mature oocytes and embryos**is an effective method. The primary drawbacks of this technique are the time required for stimulation, the cost and the risk of ovarian hyperstimulation syndrome. In comparison to a delay of around 2-4 weeks (with the GnRH agonist cycle) between an IVF cycle and starting anticancer treatment, GnRH antagonist based protocols have significantly reduced this waiting period.
3. **Cryopreservation of ovarian tissue**
   The majority of the primordial follicles are located in the outermost 1-2 mm of ovarian cortex, which can be easily isolated from the rest of the ovarian tissue. When frozen, this can be stored in liquid nitrogen for years, allowing time for the patient to recover from the disease. This tissue is then re-transplanted in these women, allowing it to grow and thereby re-establish a cyclical hormonal milieu.
4. **Aspiration of small antral follicles &invitro-maturation (IVM)**
   This technique has the advantage of avoiding the risk of transmitting malignant cells when re-implanting frozen-thawed ovarian tissue

All these available options provides our women with an opportunity to achieve a pregnancy with their own cells, in an era where cancer diagnosis doesn't at all mean… 'The End' !

SNIPPETS from FIRST QUARTERLY CRMD MEETING on 11.03.2018 at SAT Thiruvanathapuram

COMPILED BY: **DR BETSY THOMAS**
CHEERFUL PROFESSOR AND ABLE COORDINATOR AND CURRENTLY PROFESSOR IN OG AMALA INSTITUTE OF MEDICAL SCIENCES TRICHUR.

33 cases of maternal deaths were discussed maintaining absolute anonymity. The causes are given in the following table.

Cause	Number
PPH	6
Cardiac illness	5
AFE	4
Suicide	3
Eclampsia	3
Guillain Barre syndrome	2
Sickle cell anemia	2
Pulmonary embolism	2
Sepsis	1
Trauma	1
Dengue fever	1
AFLP	1
Abruption	1
IUD with sepsis	1

Observation: Out of six PPH cases two were LSCS and the rest were following vaginal delivery. One Patient had broad ligament hematoma following LSCS and was referred to higher centre after 2 1/2 hours where she reached in a moribund state .

Recommendation : This shows the importance of close post op monitoring and tackling traumatic PPH at the earliest. Separate Haemostatic angle sutures are recommended during Caesarean.

Observation : Out of four cases of PPH following vaginal delivery , three reached the higher centre in a moribund state .

Recommendation: Practise AMTSL in all deliveries. Once PPH , Manage vigorously.

AMTSL:

1. Oxytocin 5 units added to 5ml normal saline and given taking 5 seconds, at the delivery of anterior shoulder or within one minute of delivery of the fetus. It should be ensured that there is no additional fetus inside. Immediately give 10units oxytocin IM. If there is excess bleeding or risk for it, give additional oxytocin- 20 units added to 500 ml saline and given at the rate of 4 ml per minute or methergin 0.2 mg IM (after excluding hypertension) or PG F2 alpha IM (after ruling out h/o asthma)
2. Early cord clamping, usually in about one minute.
3. Early placental delivery without waiting for signs of placental separation, by pulling on the cord while applying counter pressure on the contracted uterus. If the uterus is not contracted, do not pull on the cord.

AMTSL should always be documented too. Transvaginal uterine artery clamp and Suction cannula are first aid measures in Atonic PPH.

Observation : There were five deaths due to cardiac illness. Two were Eisenmenger's syndrome.

Recommendation : Eisenmenger's syndrome patients should be counselled against conception. Mortality rates are above 50% . Planned elective LSCS with Cardiac and Anaesthetic support would be a better option than vaginal delivery. Patients with prosthetic valves should be switched over to Heparin after 36 weeks. All infections should be aggressively treated in such women including upper respiratory infection and UTI .

Observation: There were four deaths due to suspected Amniotic fluid embolism. One patient had received Inj. Epidosin.

Recommendation : Though the use of Epidosin has definitely come down in our state , our CRMD team expressed concern that some of our Obstetricians are routinely using in active labour. Once AFE is suspected , all resuscitatory efforts have to be initiated immediately. Attending Quality Standards training programme will definitely help our Obstetricians in tackling such emergencies.

Observation : There were two deaths due to Sickle cell anemia . Sickle cell anemia rampant in Wayanad belt can be fatal especially in the setting of Sickle cell crisis.

Recommendation : Prompt diagnosis and treatment with hydration , analgesics ,O2 therapy , antibiotics and thromboprophylaxis is recommended.

Observation: There was one death due to dengue fever.

Recommendation : Special care should be given to pregnant women with Dengue. **Fluid resuscitation** is the cornerstone in managing Dengue as the phase of capillary leakage is associated with hypotension and hemoconcentration as evidenced by increasing hematorit and MODS. Delivery is indicated only for obstetric indication. Recurrent Dengue is associated with high mortality.

Other recommendations :

Stick to MgSO4 dose recommended by KFOG in eclampsia patients.

Identify Sepsis early and start broad spectrum antibiotics. Fluid replacement should be aggressive once the patient goes into severe sepsis.

Thromboprophylaxis should be initiated in all indicated cases at the right time. **Caesarean section + one risk factor** is an indication.

No pre transfusion steroids or antihistamines before blood transfusion.

CRMD meeting was followed by Maternal Near Miss meeting .

SNIPPETS from Fourth QUARTERLY CRMD MEETING on 08/12/2018 at IMCH Kozhikode

SNIPPETS from the fourth QUARTERLY CRMD MEETING on 8th and 9th December 2018 at IMCH Kozhikode : 35 cases of maternal deaths were discussed maintaining absolute anonymity. The causes are given in the following table.

Cause	Number
PPH	6
Hypertensive disorders	3
AFE	2
Suicide	2
Anaesthetic cause	2
VTE	1
HELLP syndrome	1
CVT	1
Pan hypopituitarism	1
Sepsis	1
Leptospirosis	1
Sickle cell anemia	1
SLE	1
Status epilepticus	1
Pontine haemorrhage	1
Extrahepatic portal vein obstruction	1
Synovial sarcoma	1
Natural calamity	1
Bowel perforation	1
Unknown	6

From the last meeting onwards , it was decided to classify these deaths into two more categories , based on the *Delay* factor and whether these deaths were *avoidable or not* . We analysed each of these deaths and subcategorised into the following :

Type of delay	**Number**
1. Delay from the part of patient and family	9
2. Delay in reaching the institution Not identified	
3. Delay after reaching the institution	17
4. No delay identified	3
5. Cannot comment	5
Avoidable or Not	**Number**
1. Unavoidable	6
2. Avoidable in an average medical setting	19
3. Avoidable only in the best settings	7
4. Cannot comment	3

Observation: A 30 year old G4P1L1A2 had a normal delivery and underwent PPS next day. Developed fever ,abdominal pain and abdominal distension from 2nd day. Erect X-ray showed gas under the diaphragm. Shifted to surgery ward and managed conservatively with Antibiotics for 2 days. She developed dyspnoea and saturation fall on day 5; laparotomy done , a 1x1 cm perforation in the ileum 30 cm from the ileocaecal junction with gross peritoneal contamination. Expired next day.

Recommendation : Careful opening of the peritoneum ; careful closure of abdominal wall so that an accidental bite through the bowel can be avoided . Earlier laparotomy might have saved this lady. Contrast CT would be the investigation of choice. Biopsy of the perforation site would help to distinguish between a pre existing lesion and an operative bowel complication.

Observation : A 27 year old underwent elective LSCS for previous LSCS. After 5 hours developed tachycardia and hypotension; USS showed free fluid .Relap done ; 1.5 litres hemoperitoneum ; Left broad ligament hematoma extending to pelvic side wall upto mesentery. Subtotal hysterectomy with LSO done. Tachycardia and tachypnoea worsened , shifted to MCH, but expired soon.

Recommendation: It is an avoidable death. Technique of Caesarean section has to be revisited including separate angle sutures. Vigilant Post op monitoring would have picked it up earlier.

Observation : 2 Anaesthesia related deaths were reported. One was due to cardiac arrest immediately after extraction of the baby. The second one was a case where the patient developed severe pain in the buttocks soon after spinal was given. Had seizures on the way to the higher centre , caesarean was done in the higher centre , baby asphyxiated, mother succumbed.

Recommendation : High alert drugs should be double checked before administration. Continuous monitoring after giving Anaesthesia is a must. It is not the machine but the man behind the machine who is important. In the second case undue haste in shifting the undelivered unstable mother to a higher centre could have been avoided.

Observation: 32 year old conceived after IVF , At 32 weeks c/o dyspnoea ; treated with Dexona, Deriphyllin and Duolin nebulisation. Next day had saturation fall , cardiac arrest and declared dead within 75 minutes. Cause of death : Pulmonary embolism.

Recommendation : Don't advise bed rest for flimsy reasons in pregnancy. Encourage walking for atleast 30 minutes daily. Avoid unnecessary drugs. No role for foot end elevation. An early echo is advisable when a pregnant lady presents with dyspnoea.

Other recommendations :

Proper periconceptional counselling in pre existing disease like SLE, sickle cell anemia, liver diseases etc.

MgSO4 is the drug of choice for eclampsia and not any other antiepileptics. Stick to the dose recommended by KFOG in eclampsia patients.

History of Psychiatric illness should be specifically asked for during first antenatal visit itself.

No role for sublingual Nicardia for hypertension and sublingual PGE1 for induction.

Elective IOL only after 39 completed weeks .

No role for albumin infusion or IV fluids in oligoamnios.

Low threshold for decision of obstetric hysterectomy in PPH.

Don't shift patients in a moribund state.

CRMD meeting was followed by Maternal Near Miss meeting .

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MISOPROSTOL-ONLY RECOMMENDED REGIMENS 2017

<13 weeks' gestation	13–26 weeks' gestation	>26 weeks' gestation[8]	Postpartum use
Pregnancy termination[a,b,1] 800µg sl every 3 hours *or* pv*/bucc every 3–12 hours (2–3 doses)	**Pregnancy termination**[1,5,6] 13–24 weeks: 400µg pv*/sl/bucc every 3 hours[a,e] 25–26 weeks: 200µg pv*/sl/bucc every 4 hours[f]	**Pregnancy termination**[1,5,9] 27–28 weeks: 200µg pv*/sl/bucc every 4 hours[f,g] >28 weeks: 100µg pv*/sl/bucc every 6 hours	**Postpartum hemorrhage (PPH) prophylaxis**[i,2,10] 600µg po (x1) *or* **PPH secondary prevention**[j,11] (approx. ≥350ml blood loss) 800µg sl (x1)
Missed abortion[c,2] 800µg pv* every 3 hours (x2) *or* 600µg sl every 3 hours (x2)	**Fetal death**[f,g,1,5,6] 200µg pv*/sl/bucc every 4–6 hours	**Fetal death**[2,9] 27–28 weeks: 100µg pv*/sl/bucc every 4 hours[f] >28 weeks: 25µg pv* every 6 hours *or* 25µg po every 2 hours[h]	**PPH treatment**[k,2,10] 800µg sl (x1)
Incomplete abortion[a,2,3,4] 600µg po (x1) *or* 400µg sl (x1) *or* 400–800µg pv* (x1)	**Inevitable abortion**[g,2,3,5,6,7] 200µg pv*/sl/bucc every 6 hours	**Induction of labor**[h,2,9] 25µg pv* every 6 hours *or* 25µg po every 2 hours	
Cervical preparation for surgical abortion[d] 400µg sl 1 hour before procedure *or* pv* 3 hours before procedure	**Cervical preparation for surgical abortion**[a] 13–19 weeks: 400µg pv 3–4 hours before procedure >19 weeks: needs to be combined with other modalities		

References

a WHO Clinical practice handbook for safe abortion, 2014
b von Hertzen et al. Lancet, 2007; Sheldon et al. 2016 FIAPAC abstract
c Gemzell-Danielsson et al. IJGO, 2007
d Sääv et al. Human Reproduction, 2015; Kapp et al. Cochrane Database of Systematic Reviews, 2010
e Dabash et al. IJGO, 2015
f Perritt et al. Contraception, 2013
g Mark et al. IJGO, 2015
h WHO recommendations for induction of labour, 2011
i FIGO Guidelines: Prevention of PPH with misoprostol, 2012
j Raghavan et al. BJOG, 2015
k FIGO Guidelines: Treatment of PPH with misoprostol, 2012

Notes

1 If mifepristone is available (preferable), follow the regimen prescribed for mifepristone + misoprostol[a]
2 Included in the WHO Model List of Essential Medicines
3 For incomplete/inevitable abortion women should be treated based on their uterine size rather than last menstrual period (LMP) dating
4 Leave to take effect over 1–2 weeks unless excessive bleeding or infection
5 An additional dose can be offered if the placenta has not been expelled 30 minutes after fetal expulsion
6 Several studies limited dosing to 5 times; most women have complete expulsion before use of 5 doses, but other studies continued beyond 5 and achieved a higher total success rate with no safety issues
7 Including ruptured membranes where delivery indicated
8 Follow local protocol if previous cesarean or transmural uterine scar
9 If only 200µg tablets are available, smaller doses can be made by dissolving in water (see www.misoprostol.org)
10 Where oxytocin is not available or storage conditions are inadequate
11 Option for community based programs

Route of Administration

pv – vaginal administration
sl – sublingual (under the tongue)
po – oral
bucc – buccal (in the cheek)

* Avoid pv (vaginal route) if bleeding and/or signs of infection

Rectal route is not included as a recommended route because the pharmacokinetic profile is not associated with the best efficacy

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