ORIGINAL RESEARCH

Ease of termination of pregnancy in all trimesters with advent of mifepristone and prostaglandins in patients attending labor room and Gynaecology outpatient department of a tertiary care centre

[1]Dr. Ayushi Kumari Arya, [2]Dr. Kavita, [3]Dr. Bindu Arya, [4]Dr. (Prof) Mamta Singh

[1]PG Resident, [2]Associate Professor, [3]Assistant Professor, [4]Head of Department, Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India

Corresponding author
Dr. (Prof) Mamta Singh
Head of Department, Department of Obstetrics and Gynaecology, Nalanda Medical College and Hospital, Patna, Bihar, India

Received date: 23 January, 2024 Acceptance date: 26 February, 2024

ABSTRACT

Background–The combination of mifepristone (RU 486) and a prostaglandin analogue given either sublingually, orally or intravaginally is effective in terminating pregnancy, but the prostaglandin component of the regimen is cumbersome to administer and has side effects. We conducted this study to determine the efficacy& safety of 200 mg of mifepristone followed by a small dose of misoprostol, an orally active prostaglandin E_1 analogue, and Dinoprostone, a Prostaglandin E 2 analogue in gel form, for termination of pregnancy. Mifepristone(RU 486) is a potent antiprogesterone, a new class of pharmacological agent which antagonizes the action of progesterone. It is 19 Norsteroid which has greater affinity for progesterone receptors present on the myometrium of uterus than does progesterone itself, thus blocking action of progesterone and also increases the sensitivity of uterus to Prostaglandins .But when administered alone , termination of pregnancy is incomplete in 16 % women due to insufficient increase in prostsaglandin concentration in uterus. Mifepristone (RU-486) 200 mg given orally on day 1 . This is followed in 24 to 48 hours by sublingual, buccal or vaginal administration of 400 microgram of misoprostol(prostaglandin E 1) , or Local application of PGE2 gel form - Prepidil – available in 2.5 ml syringe for an intracervical application of 0.5 mg of dinoprostone. These are the effective method for termination of pregnancy in all trimesters as It is safe, effective and convenient method as well as privacy is maintained . **Aims–** To assess the safety &efficacy of medical termination of pregnancy using RU-486&prostaglandins. **Method -**This was a prospective observational study, conducted on 500 women attending Obstetrics and Gynaecology Department, Nalanda Medical college and hospital, Patna from Nov. 2022 - feb 2024. Firstly, early weeks pregnancy < 13 wks is confirmed by urine pregnancy test by kit method, measurement of serum concentration of Beta subunit of human chorionic gonadotropin (beta –HCG) and Ultrasonography. All women who want termination of pregnancy , 200 mg of RU-486was given on day 1 and then 24 to 48 hrs later 800 microgram of misoprostoloraly or vaginally given in first trimester, 400 microgram of misoprostol either sublingually, orally or vaginally given in second trimester. In third trimester, misoprostol 25 or 50 mcg p/v based on parity of women, primigravida 25 mcg &multigravida 50 mcg was administered for pregnancy termination . Dinoprostone gel 0.5 mg was also administered transcervically either alone or 24 to 48 hrs after miferpristone ,for induction of labor > 40 wks whose Bishop's score less than 6or termination of pregnancy > 28 wks with Intrauterine death . **Results -** The final assessment of 500 women was completed.140 women pregnant for <12 wks, 288women 13 wks to 27 wks pregnant, 52women >28 wks pregnancy with intrauterine death, 20 pregnant women was induced with this method who had > 40 wks pregnancy with Bishop's score less than 6. In present study 92 % women are 20 – 32 year age. Majority of women (80 %) are of 1st & 2nd para. Complete abortion in 96.4 %, Incomplete abortion in 3.5%. 92.3 % women expelled dead fetus within 48 hrs of induction with combined regimen and 90 % delivered vaginally within 24 – 48 hrs after induction of labor. **Conclusion**-The present study demonstrated the safety and efficacy of combinedMifepristone and prostaglandin therapy for Medical terminaton of Intrauterine pregnancy in Indian adult women.Mifepristone is an alternative to classic uterotonic agents for inducing labor in an unripe cervix and reduced the incidence operative procedure.

INTRODUCTION

Now a days we are encountering increasing number of indications for termination of pregnancy owing to greatly improved detection of antenatal malformations, Intrauterine death, genuine indications of Medical termination of pregnancy .In country like India, clinical research on medical abortion is important because of the large population and the need to provide an acceptable service for women. As surgical abortion is frequently conducted with anaesthetia, medical abortion is effective and safe, it may be a better alternative for many women. In India, termination of pregnancy has been legal for many years so it has provided good chances for clinicians to accumulate experience in this procedure. Women prefer medical method for termination of pregnancy using medical pill as it make the process more accessible, less traumatic and less expensive. It has increased access to safe abortion, easy induction and reduces induction to delivery time hence reduces maternal mortality.

Tab Mifepristone, also known as RU – 486 (RousselUclaf -486) is a 19- Norsteroid, which is a potent antiprogesterone, when administered alone will terminate early pregnancy in 80% of cases. RU 486 at low doses, blocks progesterone by competitively binding to its intracellular receptor present on myometrium of uterus. It also enhance sensitivity of uterus to prostaglandins which ultimately leads to improvement in consistency of cervix and causes cervical ripening.

Prostaglandins are potent oxytocics agents and that have physiological role in abortion and labor. Misoprostol is synthetic prostaglandin E1 analogue (PG E1), absorbed from vaginal, oral, and buccal route and causes contractions of smooth muscles of uterus along with ripen the cervix leading to expulsion of fetus .Uterine tachysystole is the side-effect which causes meconium - stained amniotic fluid.

DINOPROSTONE–synthetic prostaglandin E2 Analogue (PG E2) available in three forms: gel, time–release vaginal insert and a 20 mg suppository. Gel and vaginal insert used only for cervical ripening before labor induction . 20 mg vaginal suppository is used for termination of pregnancy between 12 to 20 weeks gestation and for evacuation of uterus after fetal demise upto 28 weeks. Local application of PG E2gel form ie. PREPIDIL is available in 2.5 ml syringe for an intracervical application of 0.5 mg of dinoprostone . A 10 mg dinoprostone vaginal insert ie . CERVIDIL– a thin , rectangular polymeric wafer held within a white mesh polyester sac ,which has a long tail for easy removal from vagina . It is placed in posterior vaginal fornix which releases medication slowly at the rate of 0.3 mg / hr . Uterine tachysystole which is defined as > 5 contraction in 10 minute period accompanied with fetal heart rate abnormality is the main complication. Dinoprostone can be used in women with glaucoma and asthma with caution.

The combined treatment of mifepristone with low doses of prostaglandin analogs appears to be an effective and safe method for termination of pregnancy under medical supervision, with a high success rate of 92-97% and less side effects observed with prostaglandins.

MATERIAL AND METHODS

This study was a prospective observational study conducted in the Obstetrics &Gynaecology Department of Nalanda Medical College and hospital, Patna . This study was conducted from Nov 2022 to feb 2024.Pregnant female fulfilling the inclusion criteria attending our Obstetrics outpatient or emergency were recruited for the study after taking informed consent. The study was approved by the Institutional Ethical committee.

INCLUSION CRITERIA

- Women with ultrasonically confirmed pregnancy with IUDs
- Women with ultrasonically confirmed gross congenital malformations
- Women opting for MTP within safe time slot .
- Women with early pregnancy failure that had prior uterine surgery
- Women with term (≥ 40 wks) pregnancy with cephalic presentation .
- Women have adequate pelvis
- Liquor adequate.

EXCLUSION CRITERIA

- Suspected/ confirmed ectopic pregnancy
- Known hypersensitivity to Mifepristone or Prostaglandins .
- Sepsis
- Severe anemia
- Cephalopelvic disproportion
- Undiagnosed adnexal mass
- Intra uterine devices in-situ
- Ongoing spontaneous miscarriage
- Intra Uterine Growth Restriction
- Medical co-morbidities like hepatic, cardiovascular or renal dysfunction
- Chronic adrenal failure
- Current long term corticosteroid use
- Clotting disorder / anticoagulant therapy
- Severe Uncontrolled Asthma
- Inherited porphyria
- All women underwent detailed history, clinical examination, and counseling and routine biochemical investigations including coagulation profile. USG was done to confirm the diagnosis. All subjects were admitted for close observation. Their haemoglobin was measured at baseline and at the end of termination of pregnancy.
- For first trimester with gestational age ≤12 wks gestational age-single dose of tablet mifepristone 200 mg per orally given on day1. Then all

patients were closely monitored for their vitals including BP, pulse rate, pelvic pain and any bleeding per vaginum. On day 2, tablet misoprostol 800 mcg was administered per vaginum on posterior fornix.

- For second trimester with gestational age 13 – 27 wks gestational age – tablet mifepristone 200 mg was given per orally on day 1 then first dose of tablet Misoprostol 400microgram was administered per vaginally on posterior fornix 24 hrs apart .
- Women were monitored for vitals, uterine contractions and any bleeding per vaginum.
- Next dose of drug was omitted if sufficient uterine contraction was present or cervical dilatation ≥ 1 cm was achieved.
- If expulsion of product of conception was not achieved at the end of 4 hours of misoprostol, a second dose of tablet misoprostol 400 mcg was given per vaginally on posterior fornix .
- Follow –up done after 1 week of expulsion included bimanual pelvic examination and repeat Ultrasonography for retained product of conception .
- Successful termination of pregnancy was defined as complete expulsion of conceptus without need for additional surgical intervention. Continuation of pregnancy, incomplete expulsion & hemorrhage requiring surgical procedures were considered as failure.
- Termination of pregnancy in case of intrauterine death after 28 wks with intrauterine death achieved by applying tablet misoprostol 50 microgram per vaginally. Next dose was doubled to 100 mcg and then to 200 mcg after 4 hours consecutively , when no cervical changes seen or < 2 uterine contractions in 10 minutes was present . Maximum 6 doses was given
- When delivery did not occurred after 24-32 hrs, the Dinoprostone gel 0.5 mg applied transcervically and still if there was no cervical dilatation mechanical method for induction was applied .
- Women with prior cesarean delivery , tab misoprostol 25 to 50 mcg p/v given and dose was not doubled after 4 hr to prevent uterine rupture .
- Women with term pregnancy wks ≥ 40 wks with intact membrane , adequate liquor and pelvis and Bishop's Score less than 6 , single dose of Tablet Mifepristone 200 mg given . Fetal heart rate was monitored continuously at 1 hr interval . If fetal heart rate was reassuring ,wait and watch for progress of labor for 24 -36 hrs . When FHR was with in normal range and cervix become favourable ,augmentation of labor done with oxytocin .
- If cervix is still unfavorable after 36 hrs or fetal heart rate not reassuring , cesarean section done .
- For labor induction in women at or near term with premature rupture of membrane but liquor adequate and cervix favourable , 25 mcg of misoprostol given sublingually , dose repeated for inadequate labor after 6 hrs .
- If labor induced 4 hrs after 2nd dose of misoprostol, augmentation of labor done by 2 units of oxytocin infusion and if not induced then cesarean section done .
- In women with pregnancy > 40 wks, 0.5 mg Dinoprostone gel (Prepidil or cerviprime gel) was applied transcerically via 2.5 ml syringe. Women were monitored for vitals, uterine contraction, FHR and Bishop's score. Dose repeated after 6 hrs and maximum 3 doses given. Delivery occur within 24 hrs. When FHR was reassuring but uterine contraction is <2 contraction in 10 minutes, Bishop's score is still less than 6 or any time when FHR was not reassuring, termination of pregnancy done by cesarean section.

RESULTS

A total of 500 pregnant women were included in this study. 140women belongs to first trimester pregnancy loss ≤ 12 wks gestational age , 288 women in second trimester between 13 – 27 wks that want termination of pregnancy due to some congenital malformation or genetic defect in fetus or sudden IUD due to uncontrolled diabetes in mother. 52 women had >28 wks pregnancy with intra uterine death and 20 women had >40 wks pregnancy with Bishop score < 6. The mean age of study population was 26 ± 6 years. Complete abortion seen in 134 women, 6 failure in first trimester, 279 women successful complete abortion in 2nd trimester and 7 incomplete abortion that require D& E , ongoing pregnancy in 2 women in second trimester . In women with > 28 wks with intrauterine death , 48 women expelled dead fetus with in 48 hrs while 4 underwent CS as these women had previous cesarean history and 18 women with pregnancy > 40 wks with bishop score < 6, delivered 24- 48 hrs after induction with mifepristone or prostaglandins that include misoprostol and dinoprostone gel while 2 underwent Cesarean section as 1 had meconium stained liquor with fetal distress and 1 had fetal distress due to tachysystole . Complete abortion was in 96 . 4% women and incomplete abortion in 3. 03 % , ongoing pregnancy in 0.46 % , 90 % women delivered vaginally after induction and 92.30 % had expulsion of dead fetus with in 48 hrs .

Overall success rate was 95.2 % (95% CI; 94.1-97.7%). Among those with successful outcome, mean duration between administration to expulsion of conceptuous was 12 ± 36 hours. Overall there were 20 failures cases (4 %), ongoing pregnancy in 2 (0.69 %), incomplete expulsion in 4 (7.69 %) and hemorrhage requiring hemostatic curettage in two (1. 42 %) women.

All females had uterine bleeding regardless of the outcome of drug administration. The mean duration of bleeding was from 1 – 14 days , lasted 12 or fewer days in 85% of women opting for medical abortion .

There was a fall in hemoglobin concentration at the end of expulsion from 11.8± 1.0 g/dl to 10.1 ± 1.0 g/dl($p<0.001$).

TABLE SHOWING DOSES OF MIFEPRISTONE AND MISOPROSTOL REQUIRED AND ITS EFFECT ON FIRST AND SECOND TRIMESTER ABORTION

Gestational age	No. of patients to which Tab.Mifepristone 200mg given orally on day 1	Dose of Tab.Misoprostol given 24 – 48 hrs after mifepristone	Complete abortion	Number of cases in which further management required	Ongoing pregnancy
≤ 12 wks	140	800 mcg p/v	134	6	Nil
13– 27 wks	288	400 mcg p/v	279	7	2
28 wks with IUD	52	50 mcg p/v	46	4	Nil
>40 wks with bishop ' s score	20	25 mcg in primigravida 50 mcg in multigravida	18	2	Nil

DURATION OF ABORTION AFTER INDUCTION IN FIRST AND SECOND TRIMESTER

Duration of induction to delivery interval	Trimester	No. of patients
< 6 HR	1st trimester	22
6- 12 HR	1st trimester	34
12 – 18 HR	1st trimester	87
18 – 24 HRS	1st trimester	115
24 – 32 HRS	2nd trimester	121
32 – 36 HRS	2nd trimester	98
36 – 48 HRS	2nd trimester	23

MEASUREMENT OF BISHOP 'S SCORE

CERVIX	SCORE			
	0	1	2	3
POSITION	Posterior	Mid-position	Anterior	■
CONSISTENCY	Firm	Medium	Soft	■
EFFACEMENT	0-30 %	40 – 50 %	60- 70 %	>80 %
DILATATION	Closed	1-2 cm	3-4 cm	>5cm
BABY'S STATION	-3	-2	-1	+1, +2

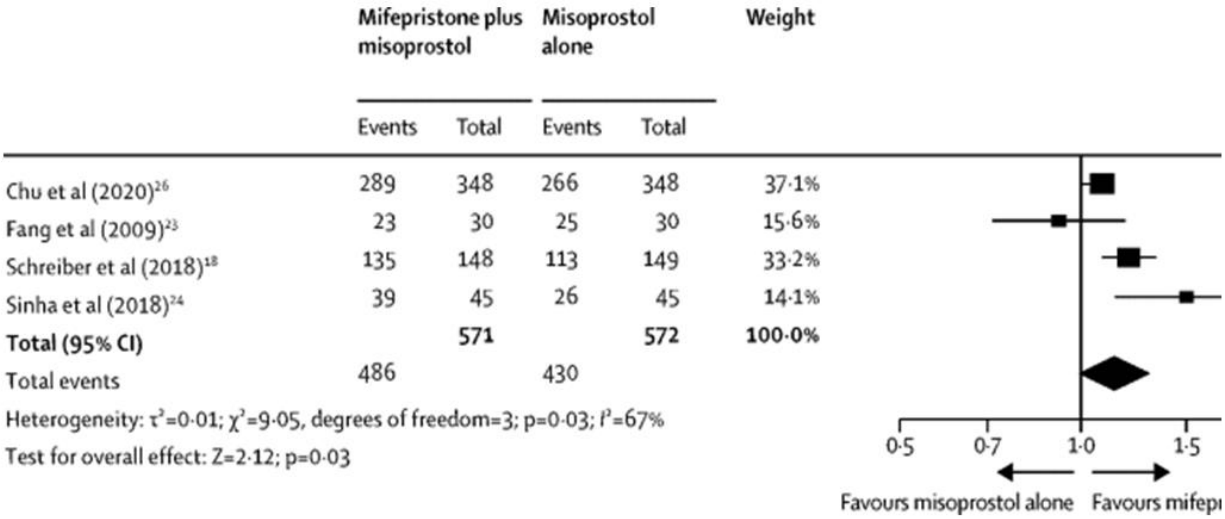
TERMINATION OF PREGNANCY IN FULL TERM PREGNANCY (> 40 WKS) WITH BISHOP'S SCORE < 6

Mode of induction	Number of patient delivered successfully	Percentage
Single dose of Tab mifepristone 200mg	2	10 %
Single dose of tab misoprostol 25 mcg	5	25%
Two doses of tab. misoprostol 25 mcg 6 hrs apart	3	15 %
Single dose of cerviprime gel	6	30 %
Two doses of cerviprime gel 6hr apart	2	10 %

DURATION OF DELIVERY AFTER INDUCTION WITH MIFEPRISTONE OR PROSTAGLANDINS REQUIRE FOR TERMINATION OF >40 WEEKS PREGNANCY

Dose of drug	Duration of delivery	No. of patients delivered
Single dose of tab mifepristone	6- 8 hrs 8- 12 hrs 12 - 24 hrs >24 hrs	Nil Nil 1 2
Single dose of tab .Misoprostol	6-8 hrs 8- 12 hrs	1 2

	12 -24 hrs	2
Two doses of misoprostol 25 mcg 6 hrs apart	6-8 hrs 8- 12 hrs 12 -24 hrs	Nil 1 2
Single dose of Cerviprime gel	6-8 hrs 8- 12 hrs 12 -24 hrs 24 – 36	Nil 2 3 1
Two doses of cerviprime gel	6-8 hrs 8- 12 hrs 12 -24 hrs 24 – 36	1 1



DISCUSSIONS

The combination of mifepristone and a prostaglandin results in the complete and safe termination of early pregnancy, as demonstrated previously[4,6-9,20] and as confirmed by the results presented here. The Vaginal or oral administration of prostaglandin appears to be an improvement over intramuscular prostaglandin administration for the medical termination in women who have had amenorrhea for less than 50 days. Misoprostol is more convenient than any other prostaglandin, because it is given orally, and compliance is good. The drug is inexpensive, and it can be stored at room temperature.The side effects in the women who received misoprostol were neither more frequent nor more severe than those reported after any other prostaglandin. No woman in either study had a cardiovascular accident. Misoprostol is generally considered to be a safe drug,[25-27] and larger doses (often 800 µg daily) have been given for long periods for other, mostly gastrointestinal indications in patients who are more likely to be smokers or to be at risk for cardiovascular accidents than healthy pregnant women, however, caution should be exercised in using this agent in women at risk for cardiovascular accidents. In any case, the administration of misoprostol alone (not preceded by mifepristone) in order to induce abortion (a practice strongly disapproved of by the distributing company) is particularly unsuitable, since the woman would be exposed to the double risk of insufficient abortive action and embryonic abnormalities[28-30].

Most common indication for induction was past dates . Dinoprostone gel is efficient in achieving cervical ripening and successful labour with reduction in latent phase of labur and total delivery time when applied transcervically .

In spite of the satisfactory results reported here, we wish to emphasize that the abortion procedure should continue to be medically supervised[14]. Pregnancy constitutes an empirical risk for women, whether they choose to continue or to terminate it, and medical assistance is a woman's right in either case. In particular, the woman should be examined initially to determine the duration of pregnancy and to exclude ectopic pregnancy and any other medical or surgical contraindication to any method of abortion. Ectopic pregnancy is difficult to detect very early, and its possible occurrence makes a follow-up visit 8 to 15 days after the treatment mandatory, whether pregnancy is terminated by pharmacologic or surgical methods. It is too early to determine whether it will become possible to use the mifepristone-misoprostol method, under medical control, outside specialized centers.

CONCLUSION

We found in the studies reported here that, for the termination of pregnancy, orally administered

misoprostol, in conjunction with mifepristone, is at least as successful and as well tolerated as other prostaglandins given parenterally or vaginally. This new regimen is simpler and potentially allows greater privacy than any other abortion method. We suggest that mifepristone followed 24 hours later by misoprostol is a convenient and safe regimen for the early termination of pregnancy, but the possibility of rare accidents cannot be excluded, and caution should be exercised .. Given the relatively high rate of Caesarean section inIndia of more than 50% , it is important to measure and reportthe effectiveness, side effects and safety of medical regimens in thispatient group. Also, it would be useful to estimate the costeffectiveness of medical versus surgical termination in the Indian setting for women with and without previous Caesarean section . This study was conducted to evaluate the efficacy and safety of medical management using mifepristone along wih misoprostol and othr prostaglandins for termination of pregnancy in any trimesters .Even though mifepristone is expensive, as it can be administered on outpatient basis & significantly less need for hospital stay, thereby reducing overall cost. It can be used safely as uterotonic agents for induction of labor in previously scarred uterus . Dinoprostone gel application is efficient in achieving cervical ripening and successful labour in nulliparous as well as multiparous. Secondary application of PGE2 gel significantly improves the chances of cervical ripening in unfavorable cervix and so there is an improvement in Bishop's score but strict vigilance is required for both maternal and fetal parameters specially in cases of second applications .

REFERENCE

1 Athawale R, Acharya N, Samal S , Hariharan C . Effect of mifepristone in cervical ripening for induction of labour . Int J Reprod Contracept Obstet Gynecol. 2013 ; 2 (1) :35-8 .

2 Raymond EG, Grimes DA. The comparative safety of legal induced abortion and childbirth in the United States. Obstet Gynecol. 2012;119:215–219. doi: 10.1097/AOG.0b013e31823fe9.]

3 ACOG Practice Bulletin No. 135: Second-trimester abortion. Obstet Gynecol 2013; 121:1394. Reaffirmed 2019. doi:10.1097/01.AOG.0000431056.79334.c

4 Bhattacharya S, Prescott GJ, Black M, Shetty A. Recurrence risk of stillbirth in a second pregnancy. BJOG. 2010 Sep;117(10):1243-7.

5 Norman JE, Heazell AEP, Rodriguez A, Weir CJ, Stock SJE, Calderwood CJ, Cunningham Burley S, Frøen JF, Geary M, Breathnach F, Hunter A, McAuliffe FM, Higgins MF, Murdoch E, Ross-Davie M, Scott J, Whyte S., AFFIRM investigators. Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial. Lancet. 2018 Nov 03;392(10158):1629-1638

6 Kawasaki K, Kondoh E, Minamiguchi S, Matsuda F, Higasa K, Fujita K, Mogami H, Chigusa Y, Konishi I. Live-born diploid fetus complicated with partial molar pregnancy presenting with pre-eclampsia, maternal anemia, and seemingly huge placenta: A rare case of confined placental mosaicism and literature review. J Obstet Gynaecol Res. 2016 Aug;42(8):911-7

7 Feroz A, Ibrahim MN, McClure EM, Ali AS, Tikmani SS, Reza S, Abbasi Z, Raza J, Yasmin H, Bano K, Zafar A, Siddiqi S, Goldenberg RL, Saleem S. Perceptions of parents and religious leaders regarding minimal invasive tissue sampling to identify the cause of death in stillbirths and neonates: results from a qualitative study. Reprod Health. 2019 May 10;16(1):53.

8 Siassakos D, Jackson S, Gleeson K, Chebsey C, Ellis A, Storey C., INSIGHT Study Group. All bereaved parents are entitled to good care after stillbirth: a mixed-methods multicentre study (INSIGHT). BJOG. 2018 Jan;125(2):160-170.

9 Kerns JL, Ti A, Aksel S, Lederle L, Sokoloff A, Steinauer J. Disseminated Intravascular Coagulation and Hemorrhage After Dilation and Evacuation Abortion for Fetal Death. Obstet Gynecol. 2019 Oct;134(4):708-713.

10 Ovadia C, Seed PT, Sklavounos A, Geenes V, Di Ilio C, Chambers J, Kohari K, Bacq Y, Bozkurt N, Brun-Furrer R, Bull L, Estiú MC, Grymowicz M, Gunaydin B, Hague WM, Haslinger C, Hu Y, Kawakita T, Kebapcilar AG, Kebapcilar L, Kondrackienė J, Koster MPH, Kowalska-Kańka A, Kupčinskas L, Lee RH, Locatelli A, Macias RIR, Marschall HU, Oudijk MA, Raz Y, Rimon E, Shan D, Shao Y, Tribe R, Tripodi V, Yayla Abide C, Yenidede I, Thornton JG, Chappell LC, Williamson C. Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses. Lancet. 2019 Mar 02;393(10174):899-909

11 Battarbee AN, Sinkey RG, Harper LM, Oparil S, Tita ATN. Chronic hypertension in pregnancy. Am J Obstet Gynecol. 2020 Jun;222(6):532-541

12 Merc MD, Lučovnik M, Bregar AT, Verdenik I, Tul N, Blickstein I. Stillbirths in women with pre-gravid obesity. J Perinat Med. 2019 Apr 24;47(3):319-322.

13 Cruz AS, Pinto jm, Valerioo . PGE2 –gel for enhancement of priming and induction of labour at term in patients with unfavourable cervix . Europr j Obstet Gynaeco Rerod Biol. 1985;20 :331-6 .

14 American College of Obstetricians and Gynaecologists. Induction of Labour. Washington DC: ACOG. 1999;10.