Mifepristone Induction forFetal Demise (MIFD)

A Randomized Control Trial

Final Study and Analysis Protocol

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I Introduction

1.1 Background

The diagnosis of an intrauterine fetal demise is in itself a challenging moment. A patient can tell, almost immediately, that something is gravely wrong as the medical team is working to confirm the diagnosis and gather more information. Once diagnosed, a provider's goals are two-fold: first to provide appropriate emotional grievance support to the patient and her family; the second is to deliver the fetus in the safest and most expeditious matter [1, 2].

Current methods applied to the management of a late second and third trimester fetal demise incorporate similar techniques and pharmaceuticals that are utilized for the induction of a term viable pregnancy such as prostaglandin analogues, dilute oxytocin, mechanical cervical dilation with foley balloon, and amniotomy [3]. Despite the need for a safe and swift delivery, there have been few innovations that focus on the delivery of a non-viable fetus or practices that see to enhance the standard management of these patients over the last several decades [4, 5]. New research involving mifepristone has shown to be a promising addition to third trimester labor augmentation [6].

Mifepristone is a progesterone receptor modulator that is currently recommended by ACOG for use in management of first and second trimester medical abortions [27, 28]. Numerous publications have demonstrated the safety of this competitive progesterone receptor antagonist when utilized to induce labor in the second trimester or for cervical ripening and preparation prior to surgical dilation and evacuation[7-9]. The use of mifepristone, in addition to misoprostol, in second trimester medical abortions has shown that the addition of mifepristone decreases time to completion of abortion by 8 hours compared to misoprostol alone ($p<0.01$) [26]. Mifepristone has been shown to augment the effects of misoprostol not only in the first and second trimesters, but in the third trimester as well [26].

A recent study in India randomized women at a gestational age of 28weeks and greater, with diagnosed intrauterine fetal demise, to either receiving 200mg of mifepristone 24hours prior to initiation of induction with 100mcg of misoprostol every 4 hours or to receiving the misoprostol induction regimen alone. Results showed that induction to delivery in the combination group was 6.54 hours shorter than in the misoprostol group ($p<0.001$) and that significantly fewer doses of misoprostol were required for delivery completion in the combination group [30].

The delayed dosage intervals of >24 hours between mifepristone and misoprostol in previous publications does not reflect the care implemented at most United States hospitals [6, 13]. At the time of diagnosis of fetal demise, a woman is typically offered and requests same-day admission to the hospital and definitive management via an induction of labor. Utilization of mifepristone at the time of admission and initiation

of induction has not been studied in a prospective randomized trail. This is clinically relevant for the typical and practical management of fetal demise in the late second and third trimester where the standard of care in the United States is to ascertain the diagnosis and then implement management during that same day or admission. The information gained from physical exam and ultrasound are rarely able to identify exactly at what point in time thefetal death had occurred. However, ultrasound is a powerful and specific diagnostic tool, which can assure the veracity of the diagnosis when made. Women are offeredinduction of labor at the time of diagnosis to minimize their suffering, and mitigate potential complications such as: coagulopathy, sepsis, and hemorrhage [22].

In July of 2015, the CDC released the most updated statistical report on fetal and perinatal mortality. There were 23,595 documented fetal deaths in the year 2013, gestational age 20weeks and greater. Minority and marginalized women are disproportionately affected; with blackwomencomprising26% and Hispanic women comprising20% of the reported cases [34]. Our Bronx population includes these vulnerable populations, who stand to gain the most from evidence based protocols and improvements in the management of fetal demise. The community surrounding our Montefiore Weilerand Wakefield labor and delivery is identified as 45.3% Black and 58.4% Hispanic by US Census data [35]. Safely shortening the length of labor induction can greatly benefit the emotional and medical safety of our patients. A prolonged induction puts a woman at increased risk for:coagulopathy, sepsis, hemorrhage, and complications that require surgical intervention [22]. Mifepristone has a well-tested and known safety profile and has been proven to optimizethe effects of misoprostol, which is the standard medication for induction of labor in the setting of fetal demise [6].

1.2 Hypothesis:

The addition of mifepristone, when compared to placebo, to the standard accepted methods of induction of laborwill expedite time to delivery of the fetus in womenwith intra-uterine fetal demise at 20 weeks gestational age and greater.

1.3 Objectives:

1. To compare time to delivery of fetus after administration of mifepristone or placebo at the onset of labor induction.
2. To calculate the duration of induction and hospitalization time among the two groups including time to delivery of placenta, duration of time on labor and delivery, time as an inpatient, and number of nights in the hospital.
3. To determine the number of women, in each arm of the study, who require surgical interventions due to a failed induction or retained products of conception.

4. To determine if administration of mifepristone augments misoprostol, oxytocin and mechanical cervical dilation.
5. To explore the overall incidence of complications and their association with mifepristone use, such as febrile morbidity, infection requiring antibiotics, or transfusion.
6. To assess whether simultaneous start of induction of labor with misoprostol after mifepristone administration versus subsequent administration or delays in the administration of misoprostol after mifepristone administration makes a difference in the time to delivery of the fetus and to assess the optimal lag time between the two medications.

1.4 Expected Outcomes:

It is expected that the addition of mifepristone will allow for more an expeditious delivery of the fetus among women who present with fetal demise greater than 20 weeks gestation age. It is the intention of the researchers that our results will be submitted for internal quality improvement assessment, scientific meeting presentation and peer review publication. We hope to impact our institutional practice as well as regional and national guidelines regarding the management of second and third trimester fetal demise.

II Study Design

2.1 Proposed Protocol:

We propose a double blinded, randomized, placebo-controlled clinical trial at the time of initiation of induction of labor for fetal demise at 20 weeks gestational age or greater.

1. Diagnose fetal demise: confirm absence of fetal heart motion by attending physician as per the institutional standards and protocols.
2. Confirm gestational age at presentation to labor and delivery based on available medical records and/or ultrasonography as per standard practice and institutional protocols.
3. Based on inclusion and exclusion criteria potential participants will be informed about the research, offered the opportunity to contribute, and trained research staff will complete the informed consent process. After documentation of consent and discussion of the research as indicated the participants will be randomized to the intervention or control arm. Both groups will receive emotional and physical support with induction of labor as per practice guidelines and standard of care by Montefiore physicians, faculty and staff irrespective of participation or assignment.

4. Interventional Arm: Ingest 200mg tab of mifepristone orally. This will coincide with or be implemented prior to the initiation of the induction of labor plan as delineated by the attending physician. The timing will be sensitive to the needs of the participant and the labor and delivery room staff.
5. Control Arm: Ingest a placebo tab orally with similar physical properties. This will coincide with or be implemented prior to the initiation of the induction of labor plan as delineated by the attending physician. The timing will be sensitive to the needs of the participant and the labor and delivery room staff.
6. Montefiore protocol for induction of labor:
    a. 12w0d-23w6d: Misoprostol 400 micrograms vaginally every 3 hours for 5 doses.
    b. 24w0d-28w6d: Misoprostol 400micrograms vaginally every 6 hours for 5 doses.
    c. 29w0d and older: Misoprostol 25-50mcg vaginally every 4 hours for 4 doses OR 100mcg vaginally every 12 hours for 4 doses.
    d. Induction methods and protocols will be at the discretion of the physician team and tailored to the clinical context.
7. Data: Patient data will be collected by the Labor and Delivery staff via electronic medical record or paper record that will be scanned into the electronic medical record. The investigators will use data abstraction tools to collect information such astime of medication administration, medications administered, time of delivery of fetus,duration of admittance to labor and delivery, and postpartum course, or complications from the electronic medical record.

2.2 Definitions:

1. Intrauterine Demise: Absence of fetal heart motion on bedside ultrasound; confirmed by two separate providers and the attending physician.
2. Mifepristone: A19-nor-steroid derivative of norethindrone that competitively binds to progesterone and glucocorticoid receptors, with antagonist effect. Mifepristone administration is the standard of care when providing medical management for first and second trimester terminations/abortions as per the American Congress of Obstetricians and Gynecologists.
3. Induction of Labor: The use of medications and other techniques to induce contractions and cervical change with the goal of effecting delivery and evacuation of all uterine contents.

2.3 Protocol Amendments:

All amendments to the protocol by the primary research team will be delineated on handouts and distributed at participating Labor and Delivery Units at 8AM the following day. The same information

will be electronically mailed to resident physicians, attending physicians, physician assistants and nurse managers currently staffing the participating Labor and Delivery units.

III Drug Information

3.1 Study Drug Information

Mifepristone is a 19-nor-steroid derivative of norethindrone that competitively binds to progesterone and glucocorticoid receptors, with antagonist effect. The majority of the drug is absorbed through the gut (70%), it then undergoes demethylation and hydroxylation in P-450 microenzyme systems, namely CYP3A4 [18]. Subsequent monodemethylated, didemethylated and hydroxylated metabolites all maintain significant receptor activity[19]. Mifepristone and its metabolites are bound to alpha 1 acid glycoprotein in serum (AAG); saturation is reached with 100 mg of mifepristone. Peak plasma concentrations are reached within 1-2 hours of ingestion, with rapid distribution, alpha half-life of 1.4 hours, and a long beta half-life, elimination time of 20-30 hours [18]. Dosage regimens of 200 mg or more quickly saturate AAG and with the elaboration of metabolites nonlinear pharmacokinetics results in a large pool of biologically active substrates [19]. The physiologic effects of mifepristone include decidual detachment, necrosis, capillary regression, cervical softening and potentiation of myometrial contractions through the loss of progesterone's inhibitory effects [20]. This profile lends compelling support that mifepristone can confer tissue changes and procedural benefit within hours of administration.Of note, since Mifepristone is mainly metabolized by microenzyme CP3A4, the study will thoroughly review patients' medications/substances that may have the potential to induce/inhibit this enzyme. The safety and toxicity profiles of mifepristone are excellent. The FDA approved regimens for medication abortion in the US includes a dose of 800 mg and does not require any consideration or contraindication for women who are taking cytochrome inducing or inhibiting agents. It is not anticipated that many young, pregnant patients will be on such drugs; however, if a significant difference of patients' intake of such medications is noticed among the study arm compared to the control arm, the analysis of the outcomes will take that into account as a possible confounder, ie. exclude such patients in sub-analysis or control for this as a confounder.

The American Congress of Obstetricians and Gynecologists recommends the use of mifepristone in the management of labor induction for a woman with a first or second trimester fetal demise [27,28]. Clinical trials have proven mifepristone to be effective for cervical ripening for labor induction, shortening operative time in dilation and curettage procedures, decreasing length of completion of induced abortions, and augmenting the effects of misoprostol [26, 30-33]. These effects of mifepristone have not yet been studied in a real-time practical management of second and third trimester fetal demise. There is a dearth of information on how quickly the mifepristone augments the effects of cervidil,

oxytocin, and mechanical cervical dilation – all methods currently known to be safe and effective in augmentation of late second and third trimester fetal demise in medical institutions. The following proposed study will investigate if administration of mifepristone at the time of induction of labor will expedite delivery of a demised fetus. This finding would be a significant improvement to the existing management of fetal demise and a compelling surrogate for the potential morbidity associated with a protracted or failed induction of labor.

3.2 Study Drug Side Effects

The side effects of misoprostol are similar to those one would experience during a labor course: bleeding, abdominal cramping, diarrhea, nausea, vomiting, headache, dizziness, back pain, and tiredness. Any drug can cause an allergic reaction, which could be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat or trouble breathing.

IV Participant Selection

4.1 Recruitment

Patients will be recruited at the time of admission to the Labor and Delivery units at the Montefiore Hospitals – Einstein Campus at Weiler and Montefiore North, at which there are approximately 60 and 30, respectively, fetal demises diagnosed annually. Firstly the diagnosis of fetal death will be ascertained as per the standards of the unit by the attending physician. The medical team will counsel the patient on the induction of labor plan. Based on inclusion and exclusion criteria potential participants will be informed about the research, offered the opportunity to voluntarily contribute, and trained research staff will complete the informed consent process.The timing of consent will be sensitive to the needs of the participant. The research and therefore voluntary aspect of care will be clearly delineated. After documentation of consent and discussion of the research as indicated the participants will be randomized to the intervention or control arm. Both groups will receive emotional and physical support with induction of labor as per practice guidelines and standard of care by Montefiore physicians, faculty and staff irrespective of participation or assignment.

Patients in the interventional arm will ingest 200mg tab of mifepristone orally. This will coincide with or be implemented prior to the initiation of the induction of labor plan as delineated by the attending physician. The timing will be sensitive to the needs of the participant and the labor and delivery room staff.

Similarly, patients in the control arm will ingest a placebo tab orally with similar physical properties without the active ingredient. This will coincide with or beimplemented prior to the initiation of the

induction of labor plan as delineated by the attending physician. The timing will be sensitive to the needs of the participant and the labor and delivery room staff.

In an effort to optimize recruitment, participation and the diversity of the participants, no parental consent will be obtained. This is consistent with other research that involves youth and addresses reproductive health needs, with the goal of protecting privacy and eliminating a potential sampling bias (Martinez-Garcia 2014, Reed 2008). The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research and the Society of Adolescent Medicine have advised that parental consent can be waived for minimal risk research that involves care that is legally rendered in the state (reproductive health services) and it is difficult to obtain parental consent (National Commission 1997, Santelli 2003). Pregnant teens are emancipated in New York State and are often faced with socially complex and unstable home environments (Alperen 2013, Malee 2013). They may not have a guardian who accompanies them to their clinic visits or accompany is present with them in the hospital during the admission for management of fetal demise.

4.2 Inclusion Criteria

1. Women ages 16-50
2. Women whose primary language is English
3. Intrauterine fetal death as confirmed by absence of cardiac motion on ultrasound by Attending physician at the time of admission to the hospital.
4. Estimated gestational age greater than 20 weeks
5. Hemodynamically stable
6. Women with one prior low transverse cesarean delivery

4.3 Exclusion Criteria

1. History of 2 or more low transverse cesarean deliveries
2. Prior classical cesarean delivery
3. History of abdominal myomectomy
4. Known or suspected allergic reaction to mifepristone
5. Known or suspected adrenal gland disease
6. Known or suspected bleeding diatheses or coagulopathies
7. Known or suspected use of QTc-prolonging medication
8. Known maternal medical or physical conditions that prohibits vaginal delivery
9. Patients in active labor, with cervical dilation greater than 6 cm.

4.4 Participant Timeline

1. The patient receives a diagnosis of intrauterine fetal demise at 20 weeks gestational age or greater.
2. Patient must meet inclusion and exclusion criteria of study.
3. Patient verbally consents to the delivery plan and is a candidate for induction at a Montefiore labor and delivery (Wakefield or Weiler-Einstien Hospitals).
4. Participants will be informed about the research, offered the opportunity to contribute, and trained research staff will complete the informed consent process.
5. After documentation of consent and discussion of the research as indicated the participants will be randomized to the intervention or control arm. Both groups will receive emotional and physical support with induction of labor as per practice guidelines and standard of care by Montefiore physicians, faculty and staff irrespective of participation or assignment.
6. With prior assignment based on the randomization scheme medications will be maintained in secure medical dispensing equipment consistent with Montefiore standards (labor and delivery Pyxis will be used). Medications will be individually placed in sequentially numbered, sealed opaque containers. Research team will source and dispense medication to participants.
6. Patient's labor course is routinely monitored and documented in EMR by all participating providers.

V Randomization

Allocation methods will be variable block randomization (blocks of 2&6, by computer generated random number sequence. Best practices will be implemented to assure the maintenance of randomization and blinding. The randomization scheme will be kept at a separate secure research site and researchers will not have access to this scheme until the analysis phase, following completion of the data collection process and enrollment. The Montefiore research pharmacy will be involved in the storage, packaging, monitoring and utilization of both placebo and study medications. The placebo and study medications will be maintained in secure medical dispensing equipment consistent with Montefiore standards (labor and delivery Pyxis). Medications will be individually placed in sequentially numbered, sealed opaque containerswith a unique participant identifier that will correspond with the patient identifier the participant receives upon enrollment. Participants, research staff, and the data collection and analysis teamswill be blinded to contents of each pill. The mifepristone and placebo tablets will be obtained from Danco pharmacies where the placebo has been specifically developed to have similar physical properties to the mifepristone tablet.

VI Data Collection

The hospital staff will maintain medical records as per standard of care. The research team will assigna unique numerical participant identifier with enrollment and allocation of participants. As previously mentioned this identifier will correspond with the information on the sealed medication envelop. Case report forms (CRF) will capture relevant data such as: medication administration time points, clinical events and secondary outcomes. Nursing, pharmacy and medical records will be reviewed to assure accuracy and completeness. Data proofing and collection will be completed by persons blinded to treatment assignment. Intake measures will include: age, socio-economic status, gestational age, method of attainment of gestational age, insurance, gravidity and parity, previous cesarean deliveries, medical history, most recent hemoglobin and hematocrit. Admission data will include cervical exam, membrane intact or rupture status, and vital signs. Secondary outcomes, additional interventions, and adverse events will be captured on the CRF. Due to the fact that participants will be inpatient for the duration of their induction and post-partum course, we do not anticipate any significant withdrawals, deviations or incomplete data sets. Patient identifiers will be secured in locked and protected environments. The CRF and abstracted data will not have any patient identifiers.

VII Statistical Guidelines

7.1 Sample Size:

Based on a review of the literature, institutional charts and clinician experience, the mean time to delivery of fetus is projected to be 24 hours with a standard deviation of 6 hours. To detect a change in 4 hours, with a two-sided alpha of 0.05 and power of 0.8: 37 persons would be needed in each group for a total of 74 persons enrolled in the study.The effect of 4-hour reduction is chosen because it is considered a clinically significant reduction.

7.2 Analysis:

An intention to treat analysis will be completed. Two sample t-test and Wilcoxon rank sum test will be calculated for the primary outcome of time to delivery of fetus. Other secondary outcomes will be described with descriptive statistics and compared with ANOVA or Chi square analysis.

VIII Ethical Consideration

8.1 Confidentiality:

The participants, providers, and research team will all be blinded for the duration of the study. The patients' medical information is protected under HIPAA, therefore only staff directly involved in the

patients' care and the primary research team will access the participants' medical records. All personal identify information will be removed from CRF. A unique participant identifier will be utilized for all data collection and analysis. In a separate locked and secured location the consent forms will be secured with a log of participants enrolled in the research.

8.2 Dissemination Policy:

Data collected during the study by labor and delivery team is confidential and protected by HIPPA. Abstracted data without patient identifier will be entered into CRF. The data will then be analyzed and reported.

8.3Declaration of Interest:

The investigatorshave nothing to declare. Our purpose is to enrich the current body of knowledge on induction of labor for an intrauterine fetal demise in the second and third trimester.

8.4 Potential Benefits:

If Mifepristone expedites the delivery of the demised fetus, women in the control of the arm of the study will benefit tremendously from participating in the study as their induction will be shorter. This outcome has important consequences as it will avoid secondary complications from long inductions such as maternal infections and surgery. Additionally, a quicker induction time may ameliorate the emotional suffering of the patients.

8.5Adverse Event and Safety Monitoring Board:

A safety monitoring board will be identified consisting of two clinician scientists who are familiar with scope of clinical practice but are not directly involved in the research. These physicians will review adverse events and work closely with the principle investigator and research team to assure that safety and reporting standards are maintained at a high level. The principle investigator will also actively review all outcomes for the patients throughout the course of the study, and will remained blinded to their treatment.Data will be abstracted within 72 hours of enrollment from the electronic medical record onto case report forms for the majority of participants. Timing regarding abstraction of serious adverse events onto case report forms is delineated below. The PI will review all CRFs and cross check to the medical record for accuracy every 6 weeks. There will be quarterly communications between the PI and monitoring board regarding adverse events and a written annual reports of these communications will be compiled regarding the review and assessments by the monitoring board. The PI and research team will

convene weekly for the first few months and then monthly thereafter to assure that the application of the protocol, recruitment and data collection practices are all in compliance. All adverse event and case report forms will be available to the monitoring board, and reports of this information will

An adverse event is any symptoms, sign, illness or experience that develops or worsens in severity during the course of the study. A number of adverse events are expected in the course of the management of fetal demise and induction of labor including, painand bleeding. Information as noted in the medical records will be abstracted in the CRF and compiled as secondary outcomes. Events that are determined to be both unexpected and related to the study medication will be entered into the CRF as well as a separate adverse event form. All serious adverse events will be reviewed by the PI, data safety monitoring board and submitted to the IRB within 48 hours. Other adverse events will be reviewed by the PI, data safety monitoring board, and submitted within one week. Events that meet International Conference on Harmonization (ICH) criteria for a serious adverse event include volunteers who experience any of the following during the course of their enrollment: death, life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, occurrence that results in persistent or significant disability in capacity, congenital anomaly/birth defect, or other important medical event (may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above).An important medical event is one that may not be immediately life threatening, but is clearly of major medical significance. It may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. All serious adverse events will be reviewed by the PI, regardless of causality assessment. Serious adverse events will be reported to Montefiore Medical Center, the FDA, and Danco Laboratories, Inc. All information related to data and adverse events will be monitored by the principle investigator, Jessica Atrio.

XI Consent

Following diagnosis, counseling and support patients will be offered the opportunity to go through the informed consent. Physician researchers will be sensitive to the context for some women this may be a relatively short interval (closer to 30 minutes) and for others who need time to process the diagnosis with family and in consultation with other persons they may be offered participation after a more lengthy counseling process (closer to several hours). Women will be approached during their admission for their induction while in the obstetric triage area or in labor and delivery. Standard of care will be maintained. When women are given this diagnosis, the standard recommendation is to admit to the hospital for induciton of labor. All physician researchers will respect the emotional needs of women and will offer participation and informed consent after women have received counseling and support.

XII References

1. MacDorman MF, Kirmeyer S. Fetal and perinatal mortality, United States, 2005. *Natl Vital Stat Rep* 2009,**57**:1-19.
2. Perinatal Moratality 2007: United Kingdom. In: *CEMACH*. Edited by Health CEiMaC; 2009.
3. Gawron LM, Kiley JW. Labor induction outcomes in third-trimester stillbirths. *Int J Gynaecol Obstet* 2013,**123**:203-206.
4. Gregory EC, MacDorman MF, Martin JA. Trends in fetal and perinatal mortality in the United States, 2006-2012. *NCHS Data Brief* 2014:1-8.
5. Macdorman MF, Kirmeyer S. The challenge of fetal mortality. *NCHS Data Brief* 2009:1-8.
6. Hapangama D, Neilson JP. Mifepristone for induction of labour. *Cochrane Database Syst Rev* 2009:Cd002865.
7. Borgatta L, Kapp N. Clinical guidelines. Labor induction abortion in the second trimester. *Contraception* 2011,**84**:4-18.
8. Perritt JB, Burke A, Edelman AB. Interruption of nonviable pregnancies of 24-28 weeks' gestation using medical methods: release date June 2013 SFP guideline #20133. *Contraception* 2013,**88**:341-349.
9. Perritt JB, Edelman AB, Burke AE. Controversies in family planning: management of lethal fetal anomalies in the third trimester. *Contraception* 2012,**86**:93-95.
10. Wagaarachchi PT, Ashok PW, Narvekar NN, Smith NC, Templeton A. Medical management of late intrauterine death using a combination of mifepristone and misoprostol. *Bjog* 2002,**109**:443-447.
11. Vayrynen W, Heikinheimo O, Nuutila M. Misoprostol-only versus mifepristone plus misoprostol in induction of labor following intrauterine fetal death. *Acta Obstet Gynecol Scand* 2007,**86**:701-705.
12. Jannet D, Aflak N, Abankwa A, Carbonne B, Marpeau L, Milliez J. Termination of 2nd and 3rd trimester pregnancies with mifepristone and misoprostol. *Eur J Obstet Gynecol Reprod Biol* 1996,**70**:159-163.
13. Fairley TE, Mackenzie M, Owen P, Mackenzie F. Management of late intrauterine death using a combination of mifepristone and misoprostol--experience of two regimens. *Eur J Obstet Gynecol Reprod Biol* 2005,**118**:28-31.
14. Panda S, Jha V, Singh S. Role of Combination OF Mifepristone and Misoprostol Verses Misoprostol alone in Induction of Labour in Late Intrauterin Fetal Death: A Prospective Study. *J Family Reprod Health* 2013,**7**:177-179.
15. ACOG Practice Bulletin No. 102: management of stillbirth. *Obstet Gynecol* 2009,**113**:748-761.
16. The combination of mifepristone and misoprostol for the termination of pregnancy. *Int J Gynaecol Obstet* 2011,**115**:1-4.
17. Late intrauterine fetal death and stillbirth. In: *Green-top guidelines*. Edited by (RCOG) RCoOaG; 2010.
18. Sarkar NN. Mifepristone: bioavailability, pharmacokinetics and use-effectiveness. *Eur J Obstet Gynecol Reprod Biol* 2002,**101**:113-120.
19. Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clin Pharmacokinet* 1997,**33**:7-17.
20. Im A, Appleman LJ. Mifepristone: pharmacology and clinical impact in reproductive medicine, endocrinology and oncology. *Expert Opin Pharmacother* 2010,**11**:481-488.
21. Administration FaD. New Drug Application Approval Letter Mifeprex (Mifepristone). In. United States; 2000.
22. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, *et al.* Stillbirths: Where? When? Why? How to make the data count? *Lancet* 2011,**377**:1448-1463.
23. Community Needs Assessment of Maternal and Infant Health in the Bronx 2013. In: *Bronx Health Link*; 2013.
24. County Health Rankings. In. Edited by Institute UoWPh; 2014.
25. Summary of Vital Statistics New York City. In. Edited by Hygiene DoHaM; 2010.
26. Kapp N, Borgatta L, Stubblefield P, Vragovic O, Morena N. Mifepristone in Second-Trimester Medical Abortion. *Obstet Gynecol* 2007, **110**: 1304-1310.
27. ACOG Practice Bulletin No. 143: Medical Management of First-Trimester Abortion. *Obstet Gynecol*2014, **123**: 676-692.
28. ACOG Practice Bulletin No. 135: Second-Trimester Abortion. *Obstet Gynecol* 2013, **121**:1394-1406
29. Mifepristone U.S. Postmarketing Adverse Events Summary through 4/30/2011.

30. Panda S, Jha V, Singh S. Role of Combination of Mifepristone and Misoprostol verses Misoprostol alone in Induction of Labour in Late Intrauterine Fetal Death: A Prospective Study. *Journal of Family and Reproductive Health* 2013, **7**: 177-179.
31. Fox, MC, Creinin, MD, Harwood B. Mifepristone and vaginal misoprostol on the same day for abortion from 50-63days gestation. *Contraception* 2002, **66**: 225-229.
32. Ashok PW, Flett GMM, Templeton A. Mifepristone versus vaginally administered misorpsotol for cervical ripening before first-trimester termination of pregnancy: A randocmized control study. *Am J Obstet Gynecol* 2000, **183**:998-1002.
33. Shaw KA, Shaw JG, Hugin M, Velasquez G, Hopkin FW, Blumenthal PD. Adjunct mifepristone for cervical preparation prior to dilation and evacuation: a randomized trial. *Contraception* 2015, **91**: 313-319.
34. MacDorman MF, Gregory ECW. Fetal and Perinatal Mortality: United States, 2013. *National Vital Statitics Reports*2015, **64**: 1-23.
35. United States Census Bureau, Bronx County, NY. August 2015.