Medical termination of pregnancy

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Medical Termination of Pregnancy

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List of Abbreviations

APLA - Antiphospholipid antibody

β-hCG - β-Human chorionic gonadotropin

BV - Bacterial vaginosis

CI - Confidence interval

CS - Cesarean section

CHD – Congenital Heart Defects

CMV – Cytomegalovirus

CVS – Chorionic Villous Sampling

DIC – Disseminated Intravascular Coagulopathy

IUFD – Intrauterine fetal demise

IUD – Intrauterine Device

IVF - In vitro fertilization

LAC - Lupus anticoagulant

MTP - Medical termination of pregnancy

NSAID- Nonsteroidal Anti-Inflammatory drugs

NTD – Neural Tube Defect

POC – Products of Conception

REPL - Recurrent early pregnancy loss

RM - Recurrent miscarriage

RPOC – Retained Products Of Conception

SD - Standard deviation

US - Ultrasound

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Summery

Abortions and stillbirths result from complex maternal and fetal factors, including genetics, hormones, immune and environment. Spontaneous abortions, or miscarriages, occur before 20 weeks, while stillbirths, or Intrauterine Fetal Demise, happen after 20 weeks, with causes ranging from maternal conditions like advanced age to fetal issues like chromosomal abnormalities.

The discussion talks about pregnancy termination methods, particularly medical abortion, which employs medications for safer induction. In the first trimester, a mifepristone and misoprostol combination effectively induce abortion by blocking progesterone action and inducting uterine contraction. While misoprostol alone is an alternative, it's slightly less effective, often requiring more follow-up procedures. Its advantages are the easiness of use and cost-effectiveness, make it preferable, especially in resource-limited settings where Mifepristone is often absent.

For second-trimester abortions, both medical and surgical methods are available, with some favoring surgical methods for safety. However, medications can still be used, sometimes in combination with surgery. Third-trimester abortions typically necessitate surgical procedures like dilation and evacuation due to associated risks.

While abortion induction carries risks like cramping and bleeding, severe complications are rare but necessitate immediate attention. Examples include incomplete abortion, infection, excessive bleeding, and uterine rupture, especially in scarred uteruses.

The debate on abortion worldwide involves a mix of ethical and legal viewpoints, with laws varying from strict to more tolerant. Over time, these laws have changed due to moral concerns and safety issues. Currently, around 60% of people live in places where abortion is allowed for various reasons. Despite progress in some areas, obstacles remain, affecting discussions and access to reproductive healthcare globally.

This thesis will provide an overview about indications for termination of pregnancy, methods for TOP with focus on medical aspect, complications of the procedures and eventually legal and ethical part with concentration on abortion laws.

Sažetak

Pobačaji i mrtvorođenja rezultat su složenih čimbenika koji se odnose na majku i fetus, uključujući genetiku, hormone, imunološki sustav i okoliš. Spontani pobačaji, ili spontani pobačaji, događaju se prije 20. tjedna, dok se mrtvorođenja, ili intrauterina fetalna smrt, događaju nakon 20 tjedana, s uzrocima koji variraju od majčinih stanja poput napredne dobi do fetalnih problema poput kromosomskih abnormalnosti.

Rasprava govori o metodama prekida trudnoće, posebno medicinskom pobačaju, koji koristi lijekove za sigurnije izazivanje. U prvom tromjesečju, kombinacija mifepristona i misoprostola učinkovito izaziva pobačaj blokirajući djelovanje progesterona i inducirajući kontrakcije maternice. Iako je misoprostol sam kao alternativa, nešto manje učinkovit, često zahtijeva više postupaka praćenja. Njegove prednosti su jednostavnost korištenja i ekonomičnost, što ga čini poželjnim, posebno u resursno ograničenim okruženjima gdje Mifepriston često nedostaje.

Za pobačaje u drugom tromjesečju dostupne su i medicinske i kirurške metode, pri čemu neki preferiraju kirurške metode zbog sigurnosti. Međutim, lijekovi se i dalje mogu koristiti, ponekad u kombinaciji s kirurgijom. Pobačaji u trećem tromjesečju obično zahtijevaju kirurške postupke poput dilatacije i evakuacije zbog povezanih rizika.

Iako indukcija pobačaja nosi rizike poput grčeva i krvarenja, ozbiljne komplikacije su rijetke, ali zahtijevaju hitnu pažnju. Primjeri uključuju nepotpuni pobačaj, infekciju, prekomjerno krvarenje i rupturu maternice, posebno u ožiljnim maternicama.

Rasprava o pobačaju diljem svijeta uključuje mješavinu etičkih i pravnih gledišta, pri čemu se zakoni razlikuju od strožih do tolerantnijih. Tijekom vremena, ti su se zakoni mijenjali zbog moralnih briga i sigurnosnih problema. Trenutno, oko 60% ljudi živi na mjestima gdje je pobačaj dopušten iz različitih razloga. Unatoč napretku u nekim područjima, prepreke ostaju, utječući na rasprave i pristup reproduktivnoj zdravstvenoj skrbi globalno.

Ova teza pružit će pregled indikacija za prekid trudnoće, metoda za prekid trudnoće s naglaskom na medicinski aspekt, komplikacija postupaka i konačno pravno-etičkog dijela s koncentracijom na zakone o pobačaju.

1. Introduction

Abortion is the termination of pregnancy by removal of the fetus or embryo, either spontaneously or via induction. Spontaneous abortions, also known as "miscarriage", account for 30-40% of pregnancy loss [1]. When actions are taken to end the pregnancy, it is called "induced abortion". If it occurs before 20 weeks' gestation (~ 10% of pregnancies), it is called *miscarriage* or *spontaneous abortion*. If it occurs after 20 weeks' gestation, it is called *stillbirth* or *intrauterine fetal demise (IUFD)* .

Abortion, that was introduced already in ancient times, faced ongoing threats to its legality and accessibility from entities seeking to undermine women's basic rights. While efforts to decrease the need for abortion through education on contraception and increasing awareness, access to abortion remains very important to the well-being of millions of women all over the world [2].

Abortion regulations and their implementation have varied across different periods in history. Throughout much of the 20th century in the Western world, movements advocating for abortion rights achieved the reversal of abortion bans. Despite the legality of abortion in many Western countries, anti-abortion factions frequently fight this status [3].

Abortion in Europe varies considerably between countries and territories due to differing national laws and policies on its legality, availability of the procedure, and alternative forms of support for pregnant women and their families. In most European countries, abortion is generally permitted within a term limit below fetal viability, for example 12 weeks in Germany and Italy, or 14 weeks in France and Spain), although a wide range of exceptions permit abortion later in the pregnancy [4][5]. In Croatia, according to present law, abortion can be performed as an elective procedure until 10 weeks following conception, and in specific circumstances afterwards, all under the approval of the First Instance, consisting of a gynecologist, another physician, and a social worker or registered nurse [6].

Abortion can be preformed via medical or surgical methods. Medical methods, which is the administration of medications to terminate the pregnancy, usually uses Misoprostol in combination with Mifepristone, or the use of one of them solely. In specific cases, which will be

presented during this thesis, Methotrexate is also an option for induced abortion.
Surgical methods, which is the physical removal of products of conception from the uterus to end the pregnancy, include "Dilation & Curettage (D&C)" in earlier stage of pregnancy, and "Dilation & Evacuation (D&E)" in later stages of pregnancy, since D&E requires more surgical instruments to remove the tissue (like forceps) [7][8].

This thesis will give a review of the commonly known etiologies that can lead to abortion in the early and late stages of pregnancy, different methods will be discussed- pharmacological or surgical, as well as the legal and ethical aspect included in this subject.

2. Definitions

Pregnancy loss can occur with different presentations at different stages of pregnancy [9].

Before 20 weeks' of gestations:

- **Thretened abortion**- women presents with bleeding and cramping, sympyoms of an impending early pregnancy loss, however, the cervical os is closed and the embryo or fetus still appears viable on US. About 50% of these progress to an actual abortion [10].
- **Missed abortion**- the death of the embryo or fetus without symptoms or expulsion of the POC.
- **Inevitable abortion**- Women presents with bleeding and cramping, which are more severe than with thretened abortion, the cervical os is open and the embryo or fetus will be nonviable on US, followed by partial or complete passage of POC.
- **Complete abortion**- pregnancy loss with complete passage of all products of conception.
- **Incomplete abortion**- pregnancy loss with loss of some, but not all, products of conception.
- **Recurrent pregnancy loss**- The consecutive loss of multiple pregnancies, defined as ≥2 pregnancy losses occurring before 20 weeks' gestation [10].
- **Septic abortion**- An early pregnancy loss complicated by an intrauterine infection, which rarely occurs. Septic abortions occur most often in the setting of nonsterile abortion procedures [10].

After 20 weeks' of gestation:

- **Stillbirth**- also called **IUFD**, defined as the death of an embryo after 20 weeks' of gestation.

3. Indications

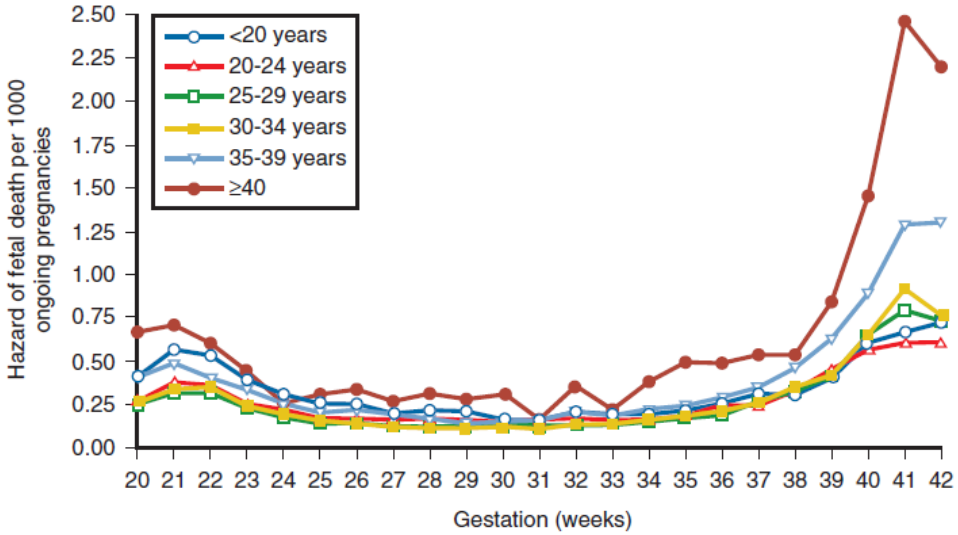
Although the causes of most miscarriages or stillbirths are unknown, they supposedly result from a complex interplay between maternal and fetal etiologies, such as parental age, genetic, hormonal, immunological, and environmental factors [11]. It is important to mention, of course, that any maternal comorbidities can complicate the pregnancy and affect the neonate, leading to morbidity and\or mortality. Here are some examples that can lead to fetal loss.

3.1 Maternal etiologies

Maternal age

Advanced maternal age, typically defined as 35 years and older at the time of delivery, is recognized one of the strongest risk factors for miscarriage and stillbirth. Older maternal age is associated with an increased risk of chromosomal abnormalities in oocytes, such as aneuploidy. Older mothers are more likely to have pre-existing medical conditions such as hypertension, diabetes, and obesity, which can increase the risk of pregnancy complications, including stillbirth. These conditions may impact placental function, fetal growth, and maternal-fetal blood flow, potentially leading to adverse pregnancy outcomes [12].

Figure 1. Relationship of fetal death and maternal age across gestation. Adapted from figure references (1)



Uncontrolled Diabetes

Uncontrolled diabetes mellitus, whether it is type 1 or type 2, can significantly increase the risk of fetal death in utero due to a variety of factors. While both type 1 and type 2 diabetes can increase the risk of stillbirth if poorly controlled, some studies suggest that the risk may be slightly higher in women with type 1 diabetes due to the longer duration of the disease and the earlier onset of vascular complications [13]. One of the primary mechanisms is placental insufficiency, which can occur as a result of the vascular changes associated with uncontrolled blood sugar levels. These changes can impair blood flow to the placenta, reducing oxygen and nutrient delivery to the fetus and compromising fetal growth and development [14]. Additionally, uncontrolled diabetes often leads to fetal overgrowth, known as macrosomia, which can increase the risk of birth trauma and umbilical cord accidents during labor, ultimately contributing to fetal distress and stillbirth [15]. Furthermore, uncontrolled diabetes is associated with an increased risk of congenital anomalies, particularly cardiac defects and neural tube defects, which can further compromise fetal viability [16]. Polyhydramnios, or increased amniotic fluid volume, is another complication of uncontrolled diabetes that can raise the risk of umbilical cord accidents and fetal hypoxia [17].

Severe Preeclampsia and Eclampsia

Preeclampsia is a hypertensive disorder that occurs during pregnancy and is characterized by high blood pressure and proteinuria. Placental dysfunction is one of the main ways that preeclampsia can result in fetal mortality. Preeclampsia is hypothesized to interfere with the placenta's growth and function, making it less able to nourish and oxygenate the fetus. This placental insufficiency can result in fetal growth restriction (FGR) and fetal hypoxia, which can ultimately lead to fetal demise. Additionally, severe cases of preeclampsia may be complicated by placental abruption, a medical emergency in which the placenta prematurely separates from the uterine wall [18]. Placental abruption can cause sudden and severe fetal distress, leading to fetal death if not promptly addressed. Furthermore, maternal complications of preeclampsia, such as eclampsia (seizures) and HELLP syndrome (a combination of hemolysis, elevated liver enzymes, and low platelet count), can further compromise fetal well-being and increase the risk of adverse outcomes, including stillbirth. Early detection, close monitoring, and timely

intervention are crucial for minimizing the risk of adverse outcomes for both the mother and the fetus in pregnancies complicated by preeclampsia.

Antiphospholipid antibody syndrome (APLA)

One important cause of recurrent pregnancy loss, especially in the first trimester, is APLA syndrome. APLA stands as a significant cause of recurrent pregnancy loss in women, with studies indicating its association with adverse pregnancy outcomes [19]. This syndrome is characterized by the presence of antiphospholipid antibodies such as lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein I antibodies, all of which increases the risk for thrombosis and impaired placental function, which can ultimately lead to recurrent miscarriages. This syndrome come into consideration in women who have more than 2 pregnancy losses, and can be diagnosed by laboratory testing for the antibodies. Early identification and appropriate management of APLA are crucial in reducing the likelihood of recurrent pregnancy loss and optimizing maternal and fetal health outcomes [19]. It is important to note that APLA is associated with pregnancy loss, rather than having long term effects on infants. According to literature, six studies looking at a total of 277 infants born to APLA-positive mothers consistently found no cases of neonatal thrombosis, except for complications related to prematurity [19]. A rare complication, Perinatal thrombosis, has been reported in only 16 infants born to APLA-positive mothers, and most of these infants had at least one other prothrombotic risk factor present.

Table 1. Estimates of maternal risk factors and risk for stillbirth
Modified from the American College of Obstetricians and Gynecologists (ACOG).
Adapted from figure references (2)

CONDITION	PREVALENCE AMONG STILLBORNS	ODDS RATIO
General population	—	1.0
Previous growth-restricted infant (<10%)	7%	2-4.6
Previous stillbirth	1%	1.4-3.2
Multiple gestation:		
Twins	3%	1.0-2.8
Triplets	0.1%	2.8-3.7
Low-risk pregnancies	80%	0.86
Hypertensive disorders:		
Chronic hypertension	6%-10%	1.5-2.7
Pregnancy-induced hypertension		
Mild	6%-8%	1.2-4.0
Severe	1%-3%	1.8-4.4
Diabetes:		
Treated with diet	3%-5%	1.2-2.2
Treated with insulin	2.4%	1.7-7.0
Systemic lupus erythematosus	<1%	6 to 20
Renal disease	<1%	2.2-30
Thyroid disorders	0.2%-2%	2.2-3.0
Thrombophilia	1%-5%	2.8-5.0
Cholestasis of pregnancy	<0.1%	1.8-4.4
Smoking >10 cigarettes daily	10%-20%	1.7-3.0
Obesity (prepregnancy):		
Body mass index 25-29.9 kg/m^2	21%	1.9-2.7
Body mass index >30	20%	2.1-2.8
Advanced maternal age (reference <35 yr):		
35-39 years	15%-18%	1.8-2.2
≥40 years	2%	1.8-3.3
Black women compared with white women	15%	2.0-2.2
Low educational attainment (<12 yr vs. ≥12 yr)	30%	1.6-2.0

3.2 Fetal etiologies

Chromosomal Abnormalities:

Aneuploidy (trisomy or monosomy) is the most commonly identified chromosome abnormality in humans, occurring in at least 5% of all clinically recognized pregnancies [20].
These conditions arise from errors in chromosomal segregation during gametogenesis or early embryonic development [21]. Trisomies occur when an individual has three copies of a particular chromosome instead of the usual two, leading to a variety of developmental anomalies and medical complications. Increasing maternal age is the most important etiological agent associated with aneuploidy: for women in their 40s, as many as one-third of all clinically recognized pregnancies might be trisomic [20]. Chromosomal abnormalities, the common ones being trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome), and trisomy 13 (Patau syndrome), represent significant challenges in prenatal care and serious difficulties for those making termination decisions. They are associated with multiple congenital anomalies and high rates of neonatal mortality. Infants with these conditions often have severe developmental disabilities and may require intensive medical care for survival, but long-term outcomes are generally poor [21].

Structural Abnormalities:

Structural abnormalities encompass a wide variety of physical malformations or defects in the growing fetus. These abnormalities can have an effect on numerous organ systems, consisting of the central nervous system, cardiovascular system, genitourinary system, and musculoskeletal system. Presented below are some of the common, known abnormalities:
Neural tube defects (NTD), such as spina bifida, result from incomplete closure of the neural tube during embryonic development, leading to spinal cord and vertebral malformations [21].
Severe form of NTD is Anencephaly, characterized by incomplete development of the brain and skull. Infants with anencephaly are typically stillborn or die shortly after birth due to the severity of the condition since it is incompatible with life [21].
Congenital heart defects (CHD) are structural abnormalities of the heart and great vessels that occur during fetal development. While many CHDs can be managed with surgical intervention after birth, certain complex or severe defects may be incompatible with life or associated with

significant morbidity and mortality. Abnormalities can range from mild defects such as patent foramen ovale, to severe defects such as hypoplastic left heart syndrome or tetralogy of Fallot. Conditions that involve abnormalities in the formation of the heart structures, impairing cardiac function and circulation, can lead to devastating consequences for the infant, and even death if not corrected soon after birth.

The severity of these abnormalities varies widely, ranging from mild to severe, and may significantly impact the prognosis and quality of life of the affected individual. In cases where structural abnormalities are deemed incompatible with postnatal survival or result in significant morbidity and suffering, termination of pregnancy may be considered as a compassionate option.

Genetic Disorders:

Genetic disorders result from mutations or abnormalities in the DNA sequence of specific genes, leading to altered protein function or expression. These disorders may be inherited from one or both parents or arise de novo in the affected individual. Examples of genetic disorders that may be consider for termination of pregnancy include cystic fibrosis, Tay-Sachs disease, Huntington's disease and Duchenne muscular dystrophy. Most of these disorders will ultimately cause severe disabilities, some of which can present even in utero, or in the first year of life, and will be terminated with death. Prenatal genetic testing, such as chorionic villus sampling (CVS) or amniocentesis, allows for the detection of the genetic abnormalities in the developing fetus, providing parents with important information about the health status of their unborn child [24]. When genetic testing identifies a severe or life-limiting genetic disorder, parents can be suggested the termination of the pregnancy.

Fetal Infections:

Infection is an important cause of stillbirths worldwide. In low-income and middle-income countries, 50% of stillbirths or more are probably caused by infection. By contrast, in high-income countries only 10–25% of stillbirths are caused by infection [25]. Fetal infections have a significant risk to the developing fetus and may result in adverse outcomes, including congenital malformations, neurodevelopmental disabilities, and fetal demise. Viral, bacterial, parasitic, and fungal infections can all potentially affect the fetus during pregnancy, either through vertical transmission from the mother or environmental exposure [25]. Common examples of fetal

infections associated with spontaneous abortion include variola, Salmonella typhi, Campylobacter fetus (Vibrio fetus bacterin), malaria, cytomegalovirus, Brucella, Toxoplasma gondii, Mycoplasma hominis, Chlamydia trachomatis, and Ureaplasma urealyticum [27]. These infections can have devastating consequences for fetal development, leading to conditions such as microcephaly, Fetal growth restriction, hydrops fetalis and organ dysfunction. Diagnosis of fetal infection often involves a combination of maternal serological testing usually preformed in the first trimester checkup, ultrasound imaging, and amniotic fluid analysis. In cases where fetal infection is confirmed and is associated with a high risk of severe complications, termination of pregnancy may be considered as a means of preventing further harm to the fetus and reducing the likelihood of long-term disability. In addition, intrauterine fetal demise can occur, due to fetal stress and as a consequence of the infection [25].

Incompatible with Life Conditions:

Incompatible with life conditions refer to severe fetal abnormalities or anomalies that are incompatible with postnatal survival or result in profound suffering and distress for the affected individual. These conditions may include severe Anencephaly (as mentioned above), bilateral renal agenesis, where the kidneys fail to develop, leading to oligohydramnios and pulmonary hypoplasia, or severe skeletal dysplasias, where skeletal abnormalities impair respiratory function and mobility. All of these abnormalities can be a part of different syndromes (Eg, Down syndrome), a sequence (Eg, Potter sequence), or isolated. In either way, when the prognosis for the affected fetus is poor and the condition is deemed incompatible with a meaningful quality of life, parents are suggested to terminate the pregnancy to spare the unborn child unnecessary pain and suffering [26]. However, even if the parents decide to continue with the pregnancy, most of these pregnancies will be terminated spontaneously, either by spontaneous abortion, or in later stages, as stillbirth.

4. Methods

After discussing the different etiologies for spontaneous, as well as artificial termination of pregnancy, we will now focus on the methods themselves. Women who need to have an abortion should be counseled about all methods available as well as the risks, advantages, disadvantages, and the different features of these options. In the following section, we will focus on abortion via the pharmacological side, also known as medical abortion, or, medical termination of pregnancy, also known as medication abortion. Medical abortion is a method of a TOP involving the use of medicines rather than surgical methods (ie, uterine aspiration) to induce an abortion with high success rates and fewer complications, due to its safeness and effectiveness. In the following discussion, we will discuss the process, how it varies between the trimesters, what are the different drugs and protocols used to induce abortion, highlighting their mechanisms of action and relative advantages, as well as side effects.

4.1 First Trimester

In the first trimester, medical abortion is considered up to 10 weeks gestation. During these weeks, MTP primarily involves the use of mifepristone, followed by a prostaglandin analogue such as misoprostol [28]. *Mifepristone* is a selective progesterone receptor modulator that binds to the progesterone receptor with an affinity greater than progesterone itself, but does not activate the receptor, thereby acting as an antiprogestin[29], hence interfering with the continuation of pregnancy. Mifepristone dilates both the cervical and uterine vessels, leading to cervical softening, increased uterine contractility (similar to menstrual period) and increased prostaglandin sensitivity [30]. *Misoprostol* is a prostaglandin E1 analogue that causes cervical softening and uterine contractions, and has a wide range of reproductive health applications, including induction of labor, management of spontaneous and induced abortion, and prevention and treatment of postpartum hemorrhage [49]. Misoprostol can be used either in combination with mifepristone or on its own. The combination of this two effectively induces abortion by blocking progesterone action, leading to decidual degeneration and detachment of the

placenta, followed by uterine contractions to expel the products of conception [31]. This combination is 97% effective during the first 63 days of pregnancy [32]. Mifepristone alone is less effective, resulting in abortion within 1–2 weeks in anywhere from 54% to 92% of pregnancies, according to review of 13 studies [33]. If mifepristone is unavailable, then a misoprostol-only regimen can also be used as an alternative [34]. The success rate of misoprostol alone for terminating pregnancy found to be 93%, which is nearly the same as the mifepristone-misoprostol combination. However, 15% of the women using misoprostol alone required a surgical follow-up procedure, which is significantly more than the mifepristone-misoprostol combination [35]. Misoprostol alone is more effective at inducing abortion in pregnancies that have stopped developing, rather than inducing abortion (TOP) in a normal pregnancy. Due to the ease of handling and storing it, its non-invasiveness and proven cost-effectiveness, the use of misoprostol within abortion care offers several advantages. It reduces the need for skilled surgical abortion providers, while offering a non-invasive and highly acceptable option to pregnant individuals [49]. For these reasons, and some other unmentioned advantages, misoprostol is particularly useful in low-resource settings [49]. To conclude, combined mifepristone–misoprostol regimens are recommended as the preferred therapy for medication abortion because they are more effective and with less risk for complications than misoprostol-only regimens. If a combined mifepristone–misoprostol regimen is not available, a misoprostol-only regimen is the recommended alternative.

In terms of administration, Mifepristone is given orally. With Misoprostol, the liver's first-pass lowers the drug bioavailability, and oral misoprostol is the least effective medication for achieving a complete abortion. Because the drug can be immediately absorbed into circulation by vaginal and sublingual route of administration, since they are bypassing the liver's first-pass effect, they yield higher efficacy and longer durations of action.

The dosage can vary between countries, but the normal, acceptable dosages depend on the availability of Mifepristone:

1. If mifepristone is available- the prescribed mifepristone is single dose of 200 mg [36] plus one of the suggested options:

a. Misoprostol 800 mcg vaginally administered once at any point 1–3 days later. (Administering misoprostol 6–8 hours after mifepristone appears to be equally effective [37]).
b. For women with a pregnancy of ≤49 days who prefer the oral route of administration, misoprostol may be administered as a 400 mcg oral dose 2 days after mifepristone [38].
c. Misoprostol 800 mcg sublingually 2 days after mifepristone is another option for women who prefer to avoid vaginal administration, but they should be counselled about increased side effects [39].

2. If mifepristone not is available, women with undesired pregnancies ≤63 days of gestation should be offered the following regimen: Misoprostol 800 mcg vaginally repeated every 24 hours up to three doses.

It is important to note that Complete abortion rates with all regimens are highest at earlier gestational ages. Medication abortion failure (defined as the need for uterine aspiration because of ongoing pregnancy or retained tissue) increases with advancing gestational age through 70 days of gestation, although failure rates remain low even at this point [37][38][39].

When considering the side effects, nearly all women using the Mifepristone-Misoprostol regimen experience abdominal pain, uterine cramping, and vaginal bleeding or spotting for an average of 9–16 days. Other less common side effects included nausea, vomiting, diarrhea, dizziness, fatigue, and fever [36]. Pain management during medication abortion is an important consideration because many patients report pain that requires analgesia [40], and Nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the recommended drugs. Other, more serious and rarer side effects and complications will be discussed in detail later in the "complications" section. In addition, women must be evaluated clinically for potential contraindications to medical abortion, including ectopic pregnancy, cervicitis or upper genital tract infection, presence of an IUD, or any contraindication to use of the specific medications [37]. Moreover, many studies excluded women with severe medical problems such as heart and liver disease or severe anemia [55].

Another important drug to mention is Methotrexate, which is commonly used for the medical management of ectopic pregnancy. Ectopic pregnancy is a potentially life-threatening condition where a fertilized egg implants outside the uterus, most commonly in the fallopian tube. Methotrexate acts by inhibiting the enzyme dihydrofolate reductase, which disrupts DNA synthesis and cell division, leading to the dissolution of trophoblastic tissue and termination of the ectopic pregnancy [41]. In the past, this drug was used as a combination with Mifepristone for abortion induction. However, during recent years, Misoprostol has proven better results with less side effects. Therefore, Methotrexate is no longer used for TOP in pregnancies located inside the uterus [42].
Clinical guidelines recommend methotrexate for hemodynamically stable patients with ectopic pregnancies, where rupture has not occurred and β-hCG levels are below a certain threshold (The optimal cutoff is unclear as values vary in the literature. What is clear is that success rates of medical management decrease with higher β-hCG values ≥ 5000 mlU/mL) [43]. This treatment has been proven to be cost-effective and avoid risks associated with surgery and anesthesia [44]. Methotrexate is typically administered as a single intramuscular injection, with dosage adjusted based on factors such as gestational age and serum -hCG levels [45]. Common side effects of methotrexate therapy include nausea, vomiting, abdominal pain, and mild hematologic abnormalities, though serious adverse reactions such as hepatotoxicity and bone marrow suppression are rare [46]. Overall, methotrexate offers a non-invasive alternative to surgical interventions for ectopic pregnancy, with high success rates and minimal long-term sequelae.

Compared to surgical methods, medical termination in the first trimester is less invasive and can be performed on an outpatient basis, providing greater privacy and autonomy for women.

4.2 Second trimester

The majority of abortions occur in the first trimester of pregnancy before 12 weeks of gestational age. Abortion in the second trimester, after 12 weeks of gestational age, is less prevalent but still occurs in both developed and developing countries. They are are associated with both increasing age and parity and higher education [47]. As with first trimester abortion, both medical and surgical methods can be used. However, according to research preformed in 2002, Dilation and evacuation (D&E) is safer than medical abortion for second-trimester pregnancy termination [48]. When considering medical abortion, the process is similar to that of the first trimester, using the same drugs combination, typically including mifepristone and a prostaglandin analogue such as misoprostol [49]. Compared to first trimester MTP, second trimester procedures may require higher doses of medications, multiple visits to healthcare providers, and more careful follow ups due to the increased gestational age and size of the pregnancy [50].

Side effects of second trimester MTP may include nausea, vomiting, diarrhea, abdominal cramping, and vaginal bleeding, which can be more pronounced than in the first trimester due to the larger volume of uterine contents, however, Serious adverse maternal events associated with second trimester medical abortion with the combination regimen are uncommon [51]. Moreover, with MTP in second trimester there is an increased risk of incomplete abortion, and the need for surgical intervention, such as dilation and evacuation (D&E), in cases where medical termination is unsuccessful or complications arise [52].

4.3 Third trimester

Third trimester abortion, also referred to as late termination of pregnancy, describes the termination of pregnancy by induced abortion during a late stage of gestation. Most apply the term late to ≥ 24 weeks' gestation. However, "late" is not precisely defined, and different medical publications use varying gestational age thresholds. Feticide, also called induced fetal demise, encompasses actions leading to the termination of a fetus and is often associated with legal implications. In medical contexts, it specifically denotes procedures where a healthcare provider deliberately induces fetal death, either as a precaution during abortion to prevent potential live births or as an independent intervention in cases of selective reduction. Third trimester abortion is very rare, mainly because after this time the fetus, with special care, has the potential to survive on its own. All countries in Europe permit abortion later in pregnancy only if specific circumstances are present, generally when the pregnancy represents a serious danger to the life, or to the physical or mental health of the woman, or when a serious malformation or anomaly of the fetus is diagnosed [54]. In these cases, surgical procedures such as dilation and evacuation (D&E) is preferred over medical methods. The use of medications for MTP in the third trimester is limited and carries significant risks, including uterine rupture, hemorrhage, and incomplete abortion, which can have serious threats to maternal well-being.

Eventually, the method of choice for induction of abortion, whether it is pharmacological or surgical, is individualized. Each woman can choose which procedure is better for her, considering her wishes and other comorbidities, as well as contraindications if present.

Table 3. Chart of recommendation on medical management of abortion. Adapted from references (49)

RECOMMENDATIONS	COMBINATION REGIMEN (RECOMMENDED[a])		MISOPROSTOL-ONLY (ALTERNATE)
	MIFEPRISTONE ⟩⟩ 1–2 DAYS ⟩⟩	MISOPROSTOL	MISOPROSTOL
1A. INCOMPLETE ABORTION < 13 WEEKS	None	Use misoprostol-only regimen	600 µg PO[b] or 400 µg SL[b]
1B. INCOMPLETE ABORTION ≥ 13 WEEKS	None	Use misoprostol-only regimen	400 µg B, PV or SL every 3 hours[b]
2. INTRAUTERINE FETAL DEMISE ≥ 14–28 WEEKS	200 mg PO once	400 µg PV or SL every 4–6 hours[b]	400 µg SL (preferred) or PV every 4–6 hours[b]
3A. INDUCED ABORTION < 12 WEEKS	200 mg PO once	800 µg B, PV or SL[b]	800 µg B, PV or SL[b]
3B. INDUCED ABORTION ≥ 12 WEEKS	200 mg PO once	400 µg B, PV or SL every 3 hours[b]	400 µg B, PV or SL every 3 hours[b]
	TIMING OF POST-ABORTION CONTRACEPTION		
	IMMEDIATE INITIATION		
4A. HORMONAL CONTRACEPTION	Immediately after the first pill of the medical abortion		
4B. IUD	With assessment of successful abortion		

B: buccal; PO: oral; PV: vaginal; SL: sublingual

[a] Combination regimen is recommended because it is more effective.

[b] Repeat doses of misoprostol can be considered when needed to achieve success of the abortion process. In this guideline we do not provide a maximum number of doses of misoprostol. Health-care providers should use caution and clinical judgement to decide the maximum number of doses of misoprostol in pregnant individuals with prior uterine incision. Uterine rupture is a rare complication; clinical judgement and health system preparedness for emergency management of uterine rupture must be considered with advanced gestational age.

5. Complications

Any known medical intervention, whether it is pharmacological or durgical, is not without risks. As mentioned earlier, most women that will use the pharmacological pathway for abortion induction will have cramping and bleeding same as, or heavier, than a menstrual period. Other adverse effects may include nausea, vomiting, fever, chills, diarrhea, headache, dizziness or hot flashes. There are symptoms considered as "red flags", which patients should we aware of, and if present, should immediately approch medical services [56]:

- Severe, heavy bleeding (enough blood to soak through four sanitary pads in 2 hours)
- Abdominal pain, nausea, vomiting, diarrhea, fever for more than 24 hours after taking mifepristone
- Fever of 38 °C or higher for more than 4 hours

A systematic review preformed in 2013 which included 45,000 women who used the 200 mg mifepristone followed by misoprostol combination found that less than 0.4% had serious complications requiring hospitalization and/or blood transfusion [57].

Let's focus on number of possible serious complications:

Incomplete Abortion

One of the main, known complications of MTP is incomplete abortion, which is defined as the retention of fetal or placental tissue in the uterus [58]. Incomplete abortions usually happen in small percentage of patients, since MTP medications such as Mifepristone and prostaglandins have high efficacy and effectiveness [58]. This complication can lead to persistent vaginal bleeding and hemodynamic instability. In addition, the retained products of conception result in release of thromboplastin into the systemic circulation and can lead to disseminated intravascular coagulationcan (DIC) which is a life threatning condition. This situation may require additional interventions, such as repeat doses of medication or surgical procedures like dilation and curettage (D&C), to remove the retained tissue [49].

Infection

Infection is a rare but potentially serious complication following medical abortion. Infections related to abortions are often caused by an ascending bacterial infection such as chlamydia,

gonorrhea, mycoplasma and bacterial vaginosis (BV) that proceeds from the lower genitals and moves through the cervix to the uterus [60] or if proper aseptic techniques are not followed during the procedure [61]. It can manifest as endometritis or pelvic inflammatory disease (PID), and, if untreated, can spread to the fallopian tubes and may lead to infertility. Infection may present with symptoms such as fever, abdominal pain, and abnormal vaginal discharge and requires prompt diagnosis and treatment with antibiotics to prevent complications. Antibiotics prophylaxis (such as doxycycline or metronidazole) are not routinely given with MTP [62]. However, they are typically given before surgical abortion procedures [63] as they are believed to substantially reduce the risk of postoperative uterine infection [64].

Excessive Bleeding

While uncommon, excessive bleeding or hemorrhage can occur following medication abortion, particularly in cases of incomplete abortion or uterine atony . Patients should seek medical evaluation if they soak through two pads per hour for two consecutive hours, which is suggestive of severe hemorrhage [65]. If the physical examination does not reveal a readily apparent source (eg, vaginal laceration), pelvic ultrasound should be performed to evaluate for RPOCs, uterine blood or other sources. Excessive bleeding may necessitate blood transfusions or surgical procedures, to control hemorrhage and ensure patient safety.

Uterine Rupture

Uterine rupture, although extremely rare, has been reported following medical abortion, particularly in cases of uterine scarring from previous surgeries such as ceserean section (CS) or structural conditions such as uterine fibroids [66]. As the rates of cesarean deliveries rise, leading to more women with scarred uteruses seeking abortions, clinicians providing second-trimester medical abortions need to remain alert for the possibility of uterine rupture in order to promptly diagnose and manage this serious complication. Uterine rupture poses significant risks to both the woman and the fetus and may require emergent surgical intervention to mitigate complications. Although uncommon, uterine rupture can occur with second-trimester medical abortion even in an unscarred uterus [66], therefore there should be a low threshold for suspicion for this complication.

Long term infertility

Many women are likely to desire and experience a future pregnancy after having had an abortion. Abortion has been investigated for its potential effect on secondary infertility, ectopic pregnancy, spontaneous abortion, stillbirth, and other pregnancy complications that can lead to adverse maternal or fetal health [59]. In a resereach preformed in 2016, first-time mothers with a prior abortion were significantly less likely to be treated for infertility compared with women in their first pregnancy (1.95 versus 5.14 percent, $p < .0001$), thus suggesting that there is no association between abortion and secondary infertility [59].

To conclude, while medical termination of pregnancy is generally safe and effective, it is essential to be aware of potential severe complications. Healthcare workers should thoroughly counsel patients on the risks and benefits of the procedure, monitor them closely during and after the process, and be prepared to manage any complications that may arise to ensure the well-being of patients.

6. Ethics and legal aspect

Human opinion on abortion tends to be divided. While some contend it's the taking of an innocent life, others feel abortion should be a woman's freedom to make her own decisions. The question of whether it is legal or illegal to end a pregnancy is complicated and has wide-ranging effects on people, societies, and healthcare systems. The motivations behind seeking an abortion can be diverse, ranging from health issues and financial concerns to personal situations or simply a woman's autonomy over her body. The problem lies in the debate over the legality of this procedure. The legality of abortion often hinges on moral and ethical beliefs. People have varying opinions on when life begins and whether a fetus has the same rights as a born person. Abortion laws vary widely among countries and territories, and have changed over the time. Such laws range from abortion being freely available on request, to regulation or restrictions of various kinds, to outright prohibition in all circumstances. Many countries and territories that allow abortion have limits for the procedure, depending on the reason. The majority of countried approve abortion by request being up to 12 weeks, up to 24 weeks for rape, incest, or socioeconomic reasons, and more for fetal impairment or risk to the woman's health or life. In contrast, other countries, particularly those with strong religious or conservative influences, maintain highly restrictive abortion laws, prohibiting or severely limiting access to abortion services even in very understandable cases such as rape or incest.

Historically speaking, discussions regarding abortion were frequently linked to issues with property rights, social order, and producing citizens for the state. In the 19th century, Western countries began codifying abortion laws, motivated by moral objections and concerns about safety. Despite legal restrictions, illegal abortions persisted, leading to public health risks and privacy violations. By the 20th century, some countries began liberalizing abortion laws, particularly for cases endangering a woman's life. The Soviet Union was the first to legalize abortion on request in 1920, viewing it as a social issue stemming from economic inequality. Other countries followed the decision, with varying degrees of legalization and restrictions. For example, the United Kingdom's Abortion Act of 1967 legalized abortions up to 28 weeks, while countries like Germany and those governed by Sharia law, which is a body of religious law that forms a part of the Islamic tradition, have more specific legal frameworks with

differing limitations and punishments.

Abortion laws differ greatly throughout the world. Countries are classified into several groups according to their legal status and access limitations. Abortion is strictly prohibited in about 24 nations in the world. These include Andorra, Malta, El Salvador, Honduras, Senegal, Egypt, the Philippines, and Laos, where it is outright prohibited. In these countries, activists are still protesting for the easing of limitations, especially when it comes to situations of rape, anomalies in the fetus, or dangers to the woman's life. More than 50 nations, including Nigeria, Venezuela, Iran, Indonesia, Libya, and others, only allow abortions in certain situations, such as rape or fetal abnormalities, or when the woman's health is in danger. On the other hand, abortion regulations are more permissive in countries like Japan, India, Canada, and most of Europe, where over half of women of reproductive age can obtain an abortion upon request or on the basis of general societal or economic factors. Latin American nations including Colombia, Argentina, and Mexico have recently made progress toward broader reproductive freedoms by decriminalizing abortion after intensive advocacy campaigns. Comparably, legalization and decriminalization of abortion have been implemented recently in Ireland, resulting in notable modifications to their respective abortion legislation. In addition, New Zealand decriminalized abortion in 2020, removing the previous limitations that required the consent of two doctors and expanding the legal window to 20 weeks of pregnancy. As of 2022, countries that legally allow abortion on request or for socioeconomic reasons comprise about 60% of the world's population.

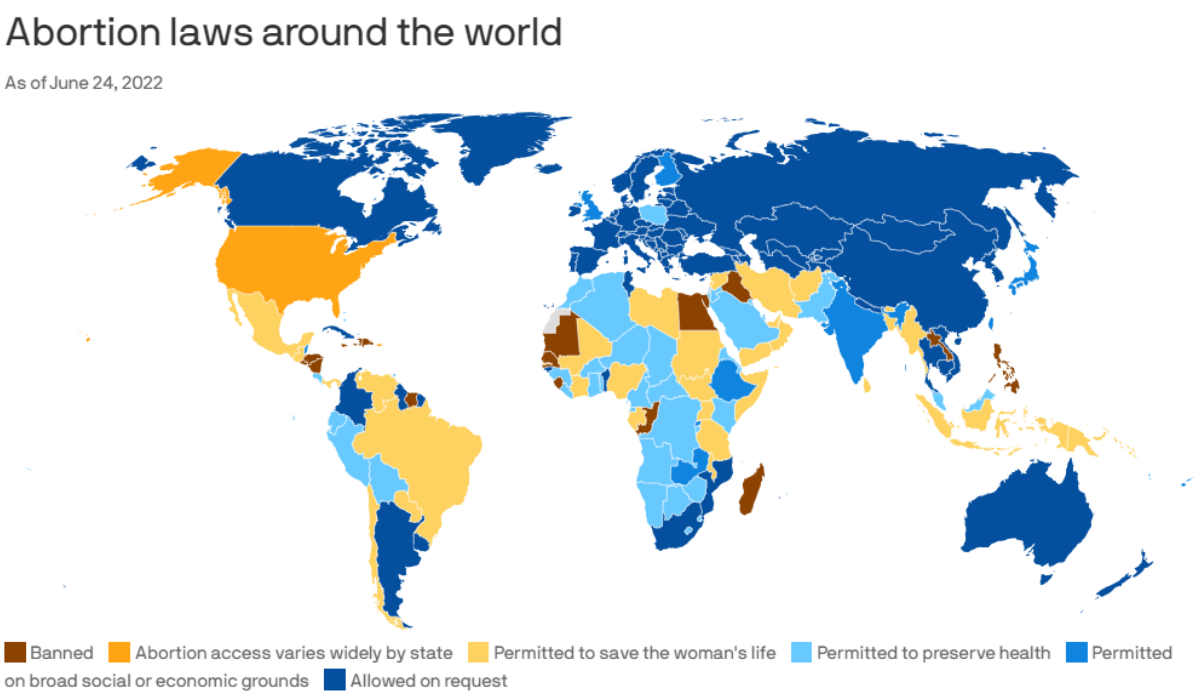


Figure 3. Abortion lows around the world. Adapted from "Center for reproductive rights."

In conclusion, the abortion debate reflects diverse ethical and legal perspectives worldwide. The abortion laws vary from strict prohibition to permissive access, with significant activism aimed at expanding reproductive freedoms, as well as women's choices. Currently, countries vary widely in their approach to abortion, with ongoing conflicts and changes in legislation. Overall, the complex legal and ethical issues surrounding abortion have a profound impact on worldwide conversations and people's ability to access reproductive healthcare.

7. Conclusion

The issue of abortion is a controversial and has stirred the world since historical days. Although today most countries of the world allow abortion without many prohibitions, there are still several countries that do not allow abortion even if the reason is justified. Understanding the reason for miscarriges, or stillbirth and the different ways to end the pregnancy by induced abortion is an important subject, especially for reproductive healthcare. Even though using medicine instead of surgery for ending pregnancy is effective and sometime safer, healthcare providers have to be careful for possible complications such as incomplete abortion, which is not very rare, as well as infections, excessive bleeding or even uterine rupture in rare cases.

Providing comprehensive guidance, selecting appropriate candidates, and closely monitoring them throughout and following the drug prescription are essential strategies for minimizing risks and ensuring favorable outcomes. Despite the challenges in this matter, ensuring universal access to safe abortion services constitutes a significant facet of reproductive healthcare. By prioritizing patient well-being, facilitating informed decision-making, and demonstrating compassion, Doctors can adeptly navigate the complexities associated with terminating pregnancies while upholding fundamental principles such as patient autonomy and beneficence.

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10. Biography

Reut Baram was born on April 26, 1996, in Holon, Israel. Graduated from Rotberg high school in Ramat Hasharon. Completed 2 years of military service in the IDF prior to starting medical school in the university of Zagreb and received the Dean's award for the 2nd year of medical school.