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Application of Mifepristone and Misoprostol During the First Trimester of Pregnancy

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Abstract

About 100 million sex acts occur every day in the world with 910,000 cases of conception. 10% of these pregnancies terminate in induced abortion. Objective was to study the clinical factors for choosing medical abortion with Mifepristone and Misoprostol and show their efficacy in the first trimester of pregnancy. A total of 153 pregnant women treated with Mifepristone and Misoprostol were examined in the first trimester of pregnancy in comparison with 157 pregnant women who underwent surgical technique. Our study revealed a considerable prevalence of medical termination of pregnancy over the surgical method. The prevalence of complications in women who have used surgical method of abortion was 14 times higher compared to medical methods.

Keywords

Pregnancy; First trimester; Mifepristone; Misoprostol; Medical abortion; Ultrasonography; Blood-tinged discharge; Missed abortion

Introduction

The widespread use of contraception is one of the main strategic plans of modern healthcare in relation to reproductive health of women [1]. Women of Kazakhstan currently have a great opportunity to use qualitative methods of contraception. However, the problem of abortion is urgent and requires us to continue the research policy on the distribution of contraceptives. Given the fact that none of the methods of contraception is sufficiently reliable, the problem of unwanted pregnancies remains topical for today and the women are forced to undergo an abortion [2].

Abortion for unwanted pregnancy is one of the most important medical and social factors having a negative impact on women's reproductive health [3].

The World Health Organization (WHO) has recognized abortion as a serious problem of women's reproductive health in many countries [4].

Abortion is allowed under the law in almost all countries of the world. This procedure is not prohibited in many countries in order to preserve physical and mental health of women. Kazakhstan is one of 275 countries that adhere to the principles permitting abortion on a woman's desire as well as on medical and social indications [2].

Annually half a million women die from causes related to pregnancy all over the world [5]. It was found that half of all pregnancies which resulted in maternal mortality were undesirable ones.

Half of maternal mortality in Latin America is related to illegal abortions. These are women with postabortion complications who are occupying more than half of the beds in the gynecological hospitals [6].

In women who underwent abortion in the first pregnancy at the age of 20-24 yrs the incidence of breast cancer increased two times.

At the current moment there is still a high level of abortions and a high rate of related complications — more than 70% of women suffer from inflammation of the female genitalia, high levels of endocrine disorders, miscarriage, infertility [7].

The World Health Organization has made a number of recommendations on the use of nonsurgical method of performing

abortion and concluded that, first, the therapeutic methods of performing abortion increase choice options and may contribute to the improvement of reproductive health, and, second, further studies are necessary to improve the modern medical methods of abortion through identification of new pharmaceuticals with characteristics superior to currently marketed drugs, or with other mechanism of action [8].

Despite the fact that programs of sexual education of adolescents and young people have been implemented in many countries, and they are included in the program of a healthy lifestyle and family planning, there is a mixed picture of the number of abortions for every 100 known pregnancies in different countries in women younger than 20 yrs [9].

The problem of abortions still requires solutions despite the steady tendency in the decrease in their number. They are the leading cause of maternal death and lead to inflammatory diseases of the genital organs, infertility, as well as adversely affect the course of subsequent pregnancies and births, increasing the frequency of miscarriage, maternal, and perinatal pathology [10].

When considering epidemiology of artificial abortion, efficacy and safety of the methods and organization of abortion services, WHO has made a number of recommendations including the following: "develop nonsurgical, nontoxic for women and nonteratogenic (in case of effective dose using) method of performing abortion that reliably provides the complete expulsion of the products of conception. The method should be suitable for using in nonclinical conditions and economically acceptable for women in all countries" [11].

In addition, WHO Scientific Group has formed a number of recommendations on this issue and concluded that, first, medical methods of abortion increase the number of options and may

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contribute to the improvement of reproductive health. And, second, further studies are needed in order to improve the modern medical methods of abortion through identification of new pharmaceuticals with characteristics superior to currently marketed drugs, or having other mechanism of action [12].

In this regard, the main objective of the study was to investigate clinical factors for choosing the medical abortion with Mifepristone and Misoprostol for termination of early pregnancy.

Methods

We have examined 153 pregnant women in the main group being in the first trimester of pregnancy and treated with Mifepristone and Misoprostol. The comparison group consisted of 157 pregnant women who used surgical technique.

The main and the control groups were comparable by age and duration of gestation. Ultrasound examinations in dynamics were performed in all women before the abortion and on Days 3-4 after the abortion. In this case, the contents of the uterus were assessed for the presence of residues of the fetal ovum, blood; also the endometrial thickness was measured.

Medical abortion in the first trimester of pregnancy was carried out as follows: Mifepristone 200 mg per os followed by Misoprostol 0.2 mg in 48 h every 15 min No. 5. Manufacturer Zizhi Pharmaceutical Co., Ltd, China. LLP "InterFarmaceutical" is an exclusive distributor in Kazakhstan.

Results

Clinical data

The research work and particularly assessment of reasons for choosing surgical or medical abortion showed that it is the reliability of the method that is the most important thing for women who had chosen surgical abortion. For women who prefer medical abortion, it was the desire to avoid surgery-related complications to be the most important option. In the second place for women undergoing the surgical abortion, there was a motive of using this method of abortion previously. For women who had chosen medical abortion the second most important reason was the safety of the method. On the third place for women who had chosen surgical abortion was less time-consuming motive, on the fourth – affordability, on the fifth – contraindications for the use of other methods of abortion. Recommendations of this particular method by the doctor for women who had chosen medical abortion were on the third place.

We have developed indications and contraindications of the early abortion using Mifepristone at the end of the studies performed.

The main indication is the presence of intrauterine pregnancy of up to 49 days of amenorrhea relative to the first day of the last menstrual period. One should take into account the psychological status of the pregnant woman because medical abortion is indicated for more passive, depressed women with the lack of a high nervous tension, increased anxiety, low confidence, and a high emotional arousal. The medical abortion is the most preferable option in nulliparous patients and those seeking to avoid the surgery-related complications. Also, we took into account conditions that were necessary for the implementation of medical termination of pregnancy.

Due to the fact that there are different recommendations for the dosage regimen of Mifepristone in the literature (from 200 to 600 mg

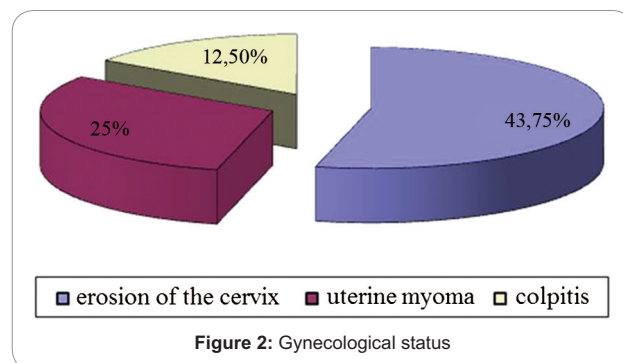
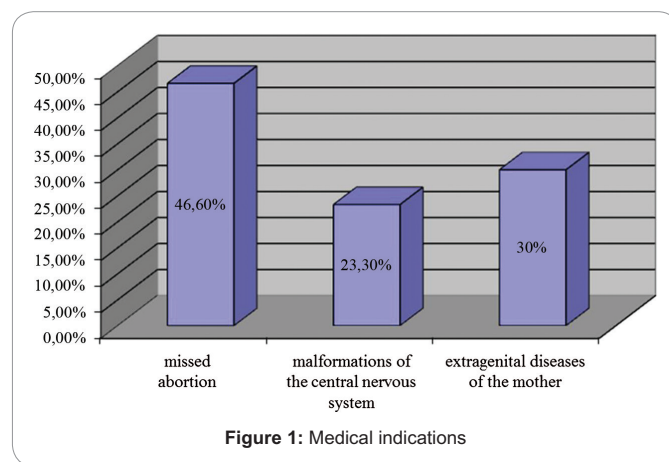
regular dose and 10 mg for emergent contraception – using the data of experimental studies in pregnant animals), we have established that the dose of 100 mg per animal shows 100% abortion effect (Mifegyn, Mifepristone, Pencroftone). At the same time, ten-fold reduction in dose down to 10 mg per animal did not show an abortive effect.

Due to this fact and to the data of world literature, we have used the following drug scheme for termination of early pregnancy: Mifepristone – 200 mg per os (1 tablet of 200 mg) and then administration of Misoprostol after 48 h in the dose of 1,000 mg (0.2 mg per 15 min).

It is important to note that among all causes of abortion medical indications constitute 1/2 among 153 surveyed women with the major percentage (46.6%) related to developing pregnancy, with every third patient having an extragenital disease. The second reason was reluctance of continuing the pregnancy in 1/3 of women, while only 9 out of 153 surveyed had social indications (Figure 1).

During the study of obstetric and gynecological history, two-third women were recognized as being gynecological healthy. A thing of particular attention is the presence of cervical erosion in three women and the presence of uterine fibroids in every fourth patient (Figure 2).

Much attention in the research process was devoted to the time of bleeding occurrence and its duration on the background of Mifepristone using. This question is of great scientific and practical significance: according to the current literature [13], 60-65% of patients suffer blood-tinged discharge before the administration of prostaglandins. Given the importance of this symptom in the clinical picture of early pregnancy abortion, we have performed the detailed analysis of the time of blood-tinged discharge occurrence after administration of Mifepristone.



It was established that on the background of Mifepristone blood-tinged discharge developed in 5.2% of women on the first day and in 62.74% on the second day. Thus, in the majority of the surveyed women blood-tinged discharge developed on the second day. This is slightly higher than the WHO data on the use of Mifepristone. However, the time of blood-tinged discharge occurrence does not indicate the fact of the expulsion of a product of conception (concept), as evidenced by our data from clinical and ultrasound examination in dynamics: before abortion, on Days 3-4 after abortion on the background of Mifepristone and prostaglandins using. Given the lack of information on the time of beginning of expulsion of the products of conception after administration of prostaglandin, we have shown that in each third patient this process takes place during the first hour and in two-third of women – in 2 h after prostaglandin administration. An average time of the beginning of expulsion of the products of conception occurs within 28 min.

According to our data in the vast majority of the surveyed women (98.14%), an expulsion of the products of conception occurred after 2 h.

Ultrasound examination data (ultrasonography)

Ultrasound data which should include determination of the presence or absence of fetal ovum, uterine examination in order to detect residues of the ovum and blood, and measurement of the uterine size in three projections have a great importance for monitoring the effectiveness of early term abortion. Ultrasound investigation must be mandatory on Days 3-4 with simultaneous determination of endometrial thickness and nature of the contents of the uterus in order to ascertain the complete expulsion of the products of conception and exclude the presence of ongoing pregnancy.

During the measurement of the uterine size in three dimensions and the thickness of the endometrium, we have calculated the “volume of the uterus” and the “size of the uterus” in conventional units.

We have considered the volume as a product of the standard measurements in three dimensions, while the size was considered as an integral index obtained by the method of principal components.

This method allows to describe 73% of the observed variability of the linear dimensions of the uterus. In this case, 65% is considered to be sufficient in order to develop a formula for determining the size of the uterus which indicates an exact gestational age, efficiency of the medical drugs used for abortion, as well as the probability of predicting possible complications.

Hence, in case of uncomplicated postabortion condition, uterine sizes were consistent with the period: before abortion – 79.28 ± 0.57 ; on Days 3-4 after abortion – 91.42 ± 0.57 . Uterine volume was: before the abortion – $104,197 \pm 2,502$; on Days 3-4 after abortion – $154,500 \pm 3,402$.

We have identified patterns of the increased size and volume of the uterus in arbitrary units on Days 3-4 after medical abortion.

In addition, it is necessary to take into account the length of the ovum (LO) which was equal to 10.39-11.52 mm on the average according to our data.

Determination of the contents of the uterus using ultrasound examination on Days 3-4 is extremely important, as normal ultrasound picture of the uterus can be obtained in two-third patients in these terms. At the same time in every third patient, we have found ultrasound signs of blood and in 2.33% residual products of conception. It seems that in 30% of women the presence of blood in the uterus may be

caused by the lack of the prostaglandin effect on contractile activity of the myometrium. This has been studied in experimental studies in rats.

It is possible that this is caused by peculiarities of the action of Mifepristone and Prostaglandin on the receptors of blood vessels of the uterine endometrium. This is indirectly confirmed by the increased uterine size by 7-8 mm on Days 3-4 according to ultrasound investigation.

We have performed the first comparative evaluation of endometrial thickness in terms of medical and surgical abortion. It was found that the difference in the average value of endometrial thickness is 4 mm between medical and surgical methods of abortion (12.32 mm vs. 8.0 mm, $p < 0.001$). This probably indicates a physiological effect on the endometrium of the medical abortion on the background of Mifepristone use. In the study of the duration of bleeding in terms of a medical abortion in the early term pregnancy, our data does not differ from the literature. It is clearly observed (statistically significant, $p < 0.001$) that longer duration of bleeding is associated with medical abortion.

Thus, the duration of bleeding for 6-7 days during medical abortion is less by 19% as compared with the surgical technique; with the duration of 8-10 days – 6%, with the duration of 11-14 days – by 13% ($p < 0.001$). With the duration of bleeding more than 14 days, there was no significant difference between two groups.

During the adoption of new technologies in the termination of pregnancy, an issue of great importance belongs to the detailed analysis of short- and long-term complications of the abortion. In case of medical termination of pregnancy in one of 153 examined women, we have found such complications as endometritis (0.65%) and ongoing pregnancy (0.65%).

At the same time in case of surgical abortion in 39 observed patients, there were various kinds of complications: endometritis – in 7 patients; ongoing pregnancy – in 5 patients; remnants of the fetal ovum – in 17 patients.

Thus, we revealed a highly significant 14 times prevalence of the complications in the group with surgical termination of pregnancy ($p < 0.001$) indicating significant benefits for medical termination of early term pregnancy. The clinical efficacy of medical abortion was observed in 98.14% cases. The highest percentage of efficiency (36.8%) had Misoprostol used in the dose of 1,000 μg .

We have attempted to identify risk factors based on the data of obstetric and gynecological history and characteristics of the clinical course of medical abortion.

The study used methods of correlation analysis and did not reveal any correlation between the presented risk factors and complications that can occur with medical and surgical methods of abortion.

Discussion

We have carried out exploration of medical histories and found out significant benefits for medical termination of early term pregnancy compared to surgical methods. Our findings are based on experimental studies in pregnant rats [4], on the study of abortive action of Mifegyn, Mifepristone, and Pencroftone, as well as the study of the characteristics of clinical course of medical abortion.

- Choice by a woman of medical or surgical method of abortion depends: (a) on the social and psychological characteristics; (b) characteristics of motivations and emotional sphere; (c) priority of the importance of reproductive health in the system of

life values. Thus, women who chose medical abortion belong to the age group from 19 to 34 years. This may indicate greater susceptibility of young patients to innovations; most of the women are married, their educational level is above the average, they have at least one child, they have made the decision on abortion together with their partner.

- During the study of the value orientations of women who had chosen medical abortion, we revealed that health is mostly important for them – it was on the first place. For the group with surgical abortion health was on the third place of importance. This is equally true for the evaluation of other areas of life.
- For women who had chosen surgical abortion, the most important factors were the following: the reliability of the method and the motive of using this way of abortion previously by the woman. In case of the surgical method of abortion the motive of less time consuming is on the third place by importance, affordability – on the fourth place, contraindications for other methods of abortion – on the fifth place.

Analysis of the mental state of women who had chosen medical abortion shows that these women are less likely to be passive, before the procedure of abortion they often experience low mood, and rarely experience high levels of stress, less often heightened to situational anxiety. In this group there are more women with a low confidence. However, before an abortion these women rarely experience strong emotional arousal. The level of well-being in groups of women who chose medical or surgical abortion is present in approximately equal proportions.

In experiments on pregnant rats we have found that all tested antiprogesterins (Mifegyn, Mifepristone, Pencroftone) at the dose of 100 mg per animal had 100% abortifacient effect.

At the dose of 10 mg per animal the named drugs were not able to terminate the pregnancy. However, antiprogesterins (Mifepristone and Pencroftone) at the dose of 10 mg/animal in combination with prostaglandin (Misoprostol) in the dose of 4 µg per animal have a more pronounced effect than Mifepristone. Abortion-induced effect of antiprogesterins develops on the background of increasing uterine activity in pregnant rats. Prostaglandin (Misoprostol) improves motor activity of the uterus on the background of administration of antiprogesterins [4].

The incidence of complications of medical abortion was 1.3% versus 18.4% for the mini-abortions performed by vacuum aspiration. The structure of complications of medical abortion included marked endometritis and progressive pregnancy followed by vacuum aspiration. In surgical abortion, there were following complications: remains of the fetal ovum, ongoing pregnancy, endometritis.

On the basis of the literature data and the data of our own research, we have identified advantages and disadvantages of medical abortion as compared with vacuum aspiration of the fetal ovum (mini-abortion).

The advantages were primarily associated with:

1. Exclusion of intrauterine intervention, thus avoiding the associated complications.
2. As a result, medical abortion will normalize menstrual function.
3. The method is safer for both the physical and psychological health of women.

Disadvantages are

1. Stretched in time (takes 3-4 days on the average), and requires more careful planning of life during this period. In case of vacuum aspiration disability is limited to one day.
2. Discomfort during the expulsion of the fetal ovum. An intake of prostaglandin causes painful uterine contractions, and often nausea, vomiting, and diarrhea.
3. Exit of the ovum and prolonged bleeding from the genital tract have a negative impact on the emotional state of women.

Conclusion

There are several unanswered research questions regarding medical methods for abortion in the first trimester. The use of therapeutic schemes with mifepristone need more well-designed studies to determine the optimal dose of misoprostol administered via sublingual (more side effects) or buccal route in order to minimize side effects while maintaining the efficacy. It would be nice to get more data comparing oral and vaginal route of Misoprostol administration after Mifepristone in early pregnancy (≤ 49 or ≤ 56 days) in order to have a clear idea about the relative efficacy of these regimens in this gestational age [14].

As is noted in the Cochrane Review, additional studies are needed to compare the efficacy of Mifepristone and Methotrexate. As a part of one “non-blind” study it was found that both schemes are equally effective, although it took significantly longer to complete the abortion with Methotrexate [15].

While Mifepristone is not available at affordable price, it is necessary to conduct additional research in order to improve the scheme with Methotrexate and Misoprostol including oral Methotrexate. It is also necessary to evaluate alternative routes of Misoprostol administration. While these studies are of little importance for countries where Mifepristone is available, they are of great importance for developing countries, where it is not available. It is also difficult to perform these studies in countries with restrictions on legal abortion. Similarly, it is necessary to conduct well-designed studies in order to evaluate medical methods of abortion at the end of the first trimester (between 9 and 12 weeks of gestation) in order to increase access to this service in those sites where there are few specialists that are able to perform surgical abortion [14].

Additional research activity is also needed in order to reveal how you can simplify the regimen of medical abortion (regardless of the drug) for conditions of limited resources for healthcare. A recent randomized controlled trial has found that the interval between Mifepristone and vaginal administration of Misoprostol may be shortened to 6-8 h without affecting its efficacy (27), so more research with different intervals (including Misoprostol without any time intervals) will be hailed. Randomized trials have demonstrated safety, efficacy, and acceptability of Misoprostol and Mifepristone at home-based conditions (28-30). However, further research is needed for prospectively evaluate the definition of gestational age and the completion of abortion by clinical picture without the use of ultrasonography, and possibly the use of test strips for the diagnosis of pregnancy with low sensitivity to confirm the success of abortion. We also need properly designed studies of the treatment schemes for incomplete abortion including trials to assess the utility of repeated doses of Misoprostol [16-29].

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