DRUG METHODS FOR ARTEFICIAL TERMINATION OF UNWANTED PREGNANCY

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MEDIKAMENTOZNE METODE VEŠTAČKIH PREKIDA NEŽELJENE TRUDNOĆE

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ABSTRACT

All medical and surgical procedures are carried out in order to premature termnination of pregnancy, can be divided on medicament and surgical methods, according to the way of procedure.

Medications used today in order to break unwanted pregnancy are inhibitors of the synthetics of progesterone and antiprogesterone, prostaglandini and antimetabolite.

Mifepristone is a derivate of norethidrone, binds to the progesterone receptor with an affinity similar progesterone, but it does not activate them so as to act as an antiprogestine.

Metotrexat is an antimetabolite and is used in gynecology practice for more indication areas. It is used the most often in conservative treatment of ectopical pregnancy. Because of low price and accessibility in order to mifepristone, it was used for application in drug methods of inducative abortions.

Misoprostol is an anlogue PGE1, used in peroral pills.

The complication are very rare at aplication of mifepristone and misoprostole in the aim to the termination the early unwanted pregnancy. The appearance of more efficient procedure of drugs called out abortions, it does not mean taht decision for the abortion is more modest. The ease and safety should not help to make a decision.

Keywords: *medical abortion, mifepristone, metotrexate, misoprostole*

SAŽETAK

Sve medicinske i hiruške procedure koje se sprovode u cilju preterminskog prekida trudnoća, mogu se prema načinu izvođenja podeliti na medikamentozne i hiruške metode.

Medikamenti koji se danas koriste u cilju prekida neželjene trudnoće su inhibitori sinteze progesterona, antiprogesteron, prostagladini i antimetaboliti.

Mifepriston je derivat norethindrona; vezuje se za progesteronske receptore sa afinitetom sličnim progesteronu, ali ih ne aktivira tako da deluje kao antiprogestin.

Metotreksat je antimetabolit i u ginekološkoj praksi se koristi za više indikacionih područja. Najčešće se primenjuje u konzervativnom tretmanu ektopičnog graviditeta. Zbog male cene i dostupnosti u odnosu na mifepriston, pokušavana je njegova primena i u medikamentozno indukovanim pobačajima.

Mizoprostol je analog PGE1, koji se koristi u obliku peroralnih tableta.

Komplikacije su izuzetno retke kod primene mifepristona i mizoprostola u cilju terminacije rane neželjene trudnoće. Pojavljivanjem sve uspešnijih procedura medikamentima izazvanog pobačaja, ne znači da je odluka o prekidu trudnoće jednostavnija. Lakoća i bezbednost ne bi trebalo da pomažu u donošenje odluke.

Ključne reči: *medikamentozni abortus, mifepriston, metotrexat, misoprostol*

INTRODUCTION

The drugs methods of arteficial abortion are defined as a use drugs in order to call out the expulsions of unwanted pregnancy. The successful drug abortion is defined as complete remove of products concept, so that instrumental revision is not necessary. The drugs used today in order to abortion, are inhibitors of the synthesis of progesterone, antiprogesterone, prostaglandine and antimetabolite.(1).

The abortion called out of mifepristone and analogue prostaglandine are very effective options for early abortion. Since 1988. years when antiprogesterone has been

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showed RU 486 (mifepristone), the million of women all around the world had possibility to have abortion without use surgical method (2).

Mifepristone and Misoprostole

Mifepriston is a derivate of norethodrone, binds for the progesterone receptors with affinity similar to progesterone, but it does not activate them so as to act as an antiprogestine (3). In pregnancy it works that it causes necrosis deciduae and detachment of the embryo affects the reduction of the inhibitory effect of progesterone on the uterine muscules and increases the sensitivity of the uterus to endogenous and exogenous prostaglandine (4,5). Also affects the structural changes in the cervix in terms softening and thus helps in the process of expulsion.

Mifepristone is easily absorbed into digestive tract, actives a high level of serum for 2 hours from the application (6). It acts as inhibitor of ovulation and affects the hypotalame-pituitary-ovarial axis, even in small doses (7). The peak of contrentation in serum is identical to all womwn who have taken increasing doses per os from 100 to 800mg (8). Misoprostol is an analog PGE1, that is used in the form of oral tablets. It is stable at room temperature. In France (9) and Great Britain(10) the researches of mifepristone and misoprostole showed that they increased uterine activity in early prgnancy.

Pharmacokinetic studies of misoprostole have shown that at peroral application, the concentration of drug in serum was greater than in vaginal application (11, 12). But vaginal application of misoprostole has better clinical effect, that explained by the fact that probably applied vaginae, has direct effect on cervix and uterus.

One of the first studies, that describe mifepristone (RU486) and misoprostole as aborifacient drugs, was published in France in 1993(13). Administered dose is 600mg mifepristone, after 36 to 48 hours practiced 400μg misoprostolefor the purpose of termination of pregnancy of 49 days of gestation (7 weeks gestation). If the expulsion has not occurred within 4 hours of application misoprostole, dose is repeated. Application of this protocol with 895 women induced abortion complete in 99% cases.

Immediately after the publication of these results was counducted in the USA multicenter study 1994. and 1995. in wich was investigated the application similar protocol but gestational period of 63 days (9 weeks of gestation) with only one per oral dose of mifepristone of 400μg. The results showed that successfully challenged the medicament abortion occurred in 92% cases of women with gestational age of pregnancy was less than 49 days, 83% pregnancy age 50 to 56 days (8 weeks of gestation) and 77% pregnancy age 63 gestation days (14).

Thanks to some other researches, FDA approved in 2000. the use mifepriston in the USA. It is also approved the use mifepristone in a dose of 600mg at pregnancy less than 49 days in hospital ad out-patient conditions with peroral use of misoprostole after 36 to 48 hours in a dose of 400μg. After approval FDA for usemifepristone and misoprostole in induction of abortion, where taken many studies about this drugs. Some authors showed that dose of mifepristone could reduce on 200mg and it could reach the same effects as with a dose of 600mg (15,16,17,18,19,20,21). After that it was turned out that the vaginal application of misoprostole was more effective than peroral drug aplication, specially in pregnancy age between 50-63 days gestation(22,23,24). Schaf at al. published that women were trained, in their studies to apply indipendently the tablets of misoprostole at home, and there isn`t important difference if misoprostole is used one, two or three days after application mifepristone (20). Their protocol is considered the practicing 200mg mifepristone, at pregnancy less than 63 gestation days, in ordination, and after in period of one , two or three days, women would apply in vagina four tablets misoprostole (800μg) at home. On the 4th and 14th day control was done with patient in ordination, as it could confirm the success of procedure. In researches done in the USA, it was always use ultrasound diagnostics as a confirmation of success procedure. It was showed useful application prescribed level of serum beta HCG-a.

Using recommended procedure, complete abortions are realized depending of authors in a span of 95% to 98%. In 1% cases are diagnosed intact pregnancy (25,26,27,28).It cites more factors that influence the high level of failure, as the greater gestational age of 50 and 63 days, less expirience of doctors, specially in the cases of ample bleeding from uterus or strong patients` pains (27,29). If the gynecologist is trained well to recognize and set the ample bleeding, side effects and regularly explains ultrasounds findings, than the level of instrumental intervention was less. Some studies showed that the women who had delivery and the women who had diltation and abortion, they have greater risk for faliure procedure than nulipar (27,30,31). It is possible that every pregnancy remains persistent changes in the cervix structure, in sense of the relationship of muscule and connective tissue components in favor of the latter.

Complications are extremely rare in the application of mifepristone and misoprostole for the purpose of early researching this combination of drugs in the USA, 80 000 women are exposed by drug abortion, but only 139 (0.19%) are registered to FDA that they had unwanted - 13 patients was carried out blood transfusions for bleding and 10 patients received antibiotics for an infection and 6 women had an allergic reaction. Fifty patients (0.063%) were diagnosed pregnancies intact and them was later conducted suction abortion. Also 50 patients was mode instrumental revision or suction abortion due bleeding.It is recorded 5 ectopic pregnancies, and 1 death for shattered tube with ectopic pregnancy (33). It is estimated that the level of less serious complication higher but they were not reported to official organs.

Bleeding and crampy expected consequences of a successful medically induced abortion and patiens should be advised of this, esperially during and immediately after the expulsion of products of conception. If the bleeding is

heavier and it is considered to be more abundant when in the course of an hour's blood and filled fwo standard napkins and it takes longer than 2 hours, then it is necessary to examine the patient and check the necessary parameters.

Side effects of a single dose of mifepristone are rare and more side effects registered during this procedure comes from the systemic effects of misoprostole, and they are usually transient and they do not require additional intervention. Of these symptoms are the most common nausea (34%-72%), vomiting (12%-41%), diarrhea (3%-26%), and higher temperature followed by chills (34).

Contraindications for drug abortion with mifepristone are: confirmed or suspected ectopic pregnancy, intrauterus napkins, chronic systemic corticosteroids application, insufficiency adrenal gland, coagulopathy, allergy to the mifepristone and hereditary porphyria. It is not clinically approved that mifepristone affects to bronchial asthma, but many patiens use corticosteroids in therapy, what is the contraindication for mifepristone application.

Contraindications for mizoprostole application are: alleggy drug, epilepsy and acute inflammatory diseases of the digestive tract. The special precantions are necessary with patiens who are at serious anemia, sever liver damage, kidney and lungs, uncontrolled hypertension and cardiovascular disease angina pectoris, valvular disease, arrhythmia or cardiac waekness.

Metotreksat-Misoprostole

Metotreksat is an antimetabolite and in gynecological practise is used for more induction area. IT more aften applies in the conservative treatmenent of ectopic preagnancy. Because of the low price and availability in relation to the mifepristone, it was attempled its application and in medically induced abortion. One dose of 50 mg per square meter of surface patient is administered orally or intramuscularly. After three to seven days it is applied 800μg misoprostole vaginal. Using this sheme, Creinin and associates are made a success in 1995 (32) on the level of 88% to 98 % depending on the size of pregnancy. The termination of pregnancy in slower, so that almost 10-30% women had complete abortion after three or four weeks. Wiebe an associates (33) showed, on the sample of 1042 women that there is not a significant difference in the rate of success at women who received combination of mifepristone and misoprostole and women who received combination of metotrksat and mizoprostole. The success of bolth procedures was about 96% and the frequency of side effects was similar. Buth, it is evident that the groub of womwn who received mifepristone, abortion accured more quickly and this is in any case more preferable for patients.

Misoprostole

Misoprostole is used alone to induce artefitial abortion. The first researches, made by patiens have shown the low level of success, what is about 5% to 11% if it's applied in dose at 400μg per per oral (34). Later studies in which misoprostole administered vaginally in a dose of 200-800μg, showing success in a range of complete abortion of 20% to 60% (35, 36). Unlike these first studies some autors as Carbonell and associates (37) and Esteve and associates (38) have shown the rate of 90% complete abortion repeated intravaginal application of moistened tablets misoprostole in total dose of 800 μg at pregnancy less than 56 of 63 gestation days. Ngai and associates (39) compared the effects of moistened intravaginal tablets misoprostole and dry, and theycame to the result that the moistened tablets lead to 85% success of abortion and to the 65% abortion, but that difference is not ststistically significant (p=0.43).

Randomized study of women over 250 that Jaina and associates (40) hare done, showed that vaginal aplication moistened misoprostole in daily dose of 800 μg during theree consecutive days, aachired the success rate on 88% compared to standard combination of mifepristone and misoprostole, in which the rate of success 95.7% what is statistically significant better.

Dimitrijevic and associates showed that vaginal aplication moistened misoprostole in daily dose of 1000 μg during theree consecutive days, aachired the success rate on 92,8% compared to standard combination of mifepristone and misoprostole, in which the rate of success 95.7% (42-44). And another authors showed the similar results used the same doses of misoprostole (48)

Based on an analysis, of previous studies on the use of misoprostole, it ca be concluded that repated doses od 800 μg moistened tablets misoprostole, intravaginal, at pregnancies less than 63 gestation days (9 gestation week) show the efficacy in 85% to 90% of cases (45, 46, 47). Adminis - tered in this way and these doses, misoprostol alone has lower degree of success than the standard procedure in the combination with mifepristone or metotrexat.(32,33,41)

CONCLUSION

Drug abortions are safe and effective alternative to surgical abortions.

Mifepristone in a dose of 200 or 400 μg, after which the vaginally administred misoprostole in a dose of 800 μg are the most effective combination available women who decided for abortion. These drugs can cause safely expulsion in pregnancies less than 63 gestation days (9 gestation week). The main side effects of using these drugs are gastrointestinal discomforts. The bleeding is variable, but it lasts more often two or theree weeks. Instrumental revision (suction or abortion) is rarely needed as emergency procedures. By aplication of drugs, dilatation of cervical canal is mosthy completed so that the instrumental revision facilitated.

The therapists are required to comply with the will with their patients. Howerer gynecologist who proposed manner of termination of unwanted pregnancy must be completely sure that the patient is sure of hes decision. Appearing all more successful procedures drug inducted

abortion, it does not mean that the decision for abortion easier. When the decision on the abortion is made by the patient, gynecologist proposes the ways of termination of pregnancy, but it is necessary that the patient makes a decision which of methods will be applied. Depending on each specific case, gynecologist is the on who offers alternative. The selection method is recommended by gynecologist, and a final decision is made by patient.

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