Opinion on the use of Mifepristone (RU 486). Report.

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Opinion

The Opinion of the National Consultative Ethics Committee is requested in very specific circumstances and is given in the context of existing law.

Several members of the Committee have expressed reservations since their personal convictions do not allow them to accept induced abortion. Such reservations have been duly noted.

An Opinion from the National Consultative Ethics Committee has been requested on the use of Mifepristone (RU 486). One of the properties of the molecule is that it is an antiprogestin. It can therefore be used as an abortifacient. As a result, induced abortion performed in this manner is totally non-surgical.

Whilst recognising this as a fact, the Committee wishes to take this opportunity of formulating certain general observations. However beneficial and intrinsically salutary, a new product cannot be allowed for use in violation of existing law.

Since only a single dose of Mifepristone is required, those involved might well contravene articles of the law dated 17th January 1975, as modified by the law dated 31st December 1979, on induced abortion. In fact, these articles respond to general imperatives which do not simply vanish when a new substance appears.

Consequently, it is important that use of such a substance should only be authorised within the context of existing law and under medical supervision. Although it may help to avoid the need for surgery, it should not, because of that, lead to an increase in the number of induced abortions.

These being the issues, the Committee feels it must as of now insist that prescription and use of this product be only authorised from the outset in highly specialised centres.

This should not be difficult since such centres already exist.

Report

A therapeutic test was proposed to the Cochin hospital (Paris), and the hospital's Ethics Committee was consulted. The committee considered the matter to be far-reaching and beyond its purview. It therefore passed the case on to the National Consultative Ethics Committee.

Our opinion is therefore requested on a very specific multicentric trial. The text of this opinion is given below after this report, but we consider that it should be preceded by introductory remarks and followed by considerations regarding the future.

The test submitted to us for opinion is connected with abortion. It therefore seems important to underline at the start that for a number of French men and women, abortion is at present experienced as a defeat.

It is only justified by the notion that it is the lesser of two evils. The 1975 law which authorises it in certain particular circumstances was voted in that belief.

However, each year, 40 to 50 million abortions are performed world wide.

In France, their number has diminished in the last two years, but in 1985 there were still 173 000 abortions.

In the light of such figures, methods of abortion which are safe, which do not endanger a woman's life, and which bring about the least possible physical sequelae, are an absolute necessity.

RU 486 might well, in specific cases, be one of these safe methods. It seems to induce abortion which closely resembles spontaneous miscarriage and avoids the complications inherent to surgery.

The experimentation we are being asked to consider is an attempt to verify that hypothesis.

This study can be divided into three parts as follows :

technicalities

French law on induced abortion

ethics.

Technicalities

A brochure containing scientific data pertaining to RU 486 is attached to the test protocol

It includes the following points :

1) RU 486 is part of the group of anti-hormones,

- One of the RU 486 properties is that it is *an antiprogestin.* It is the result of cooperation between Roussel-Uclaf and Professor Baulieu. This is the first time that such a product is available for clinical purposes.

RU 486 is an antiprogestin since it prevents the body from using progesterone.

Progesterone acts by binding in the nuclei of cells called target-cells, to specialised receptors. This "progesterone-receptor" binding causes specific modifications to take place in tissues.

RU 486 which is obtained by modifying a synthetic progesterone molecule, has an affinity for progesterone receptors which is six times stronger than real progesterone. It occupies the receptors, induces no activity, but prevents progesterone from being active for lack of receptors.

Progesterone is a hormone which is essential for the continuation of pregnancy. It is secreted by the ovary up to the second month of pregnancy, after which the placenta continues to produce it until birth.

Hence the proposal to use RU 486 as an abortifacient. Since RU 486 occupies the progesterone receptors, progesterone ceases to be active. The egg is unable to develop and expulsion follows.

- The product is also *an anti-glucocorticoid* . This property has been examined in other experiments.

2) The following studies of RU 486 have been made :

- Galenic, pharmacologic, pharmocokinetic, and toxicologic animal studies. In particular, no teratogenic effect on rat or rabbit foetus has been observed.

- Kinetic pharmacology and bioavailability studies in humans.

- The anti-glucocorticoid effect has been examined very carefully. At dose levels used in the experimental conditions submitted to us, the effect does not seem to be in evidence.

3) *RU 486 was tested for the first time for its abortive properties on women by Herman in Geneva in 1983.* Experimentation has continued since then under the aegis of WHO, the Population Council, and the Roussel/Uclaf company.

In the last three years, more than 850 women have used the substance for that purpose world-wide, in particular in France, Nordic countries, the Netherlands, and China.

The following conclusions have been drawn from these trials :

- Taken orally, a single 600 mg dose seems to be the most effective.

- In 90% of cases, RU 486 interrupts pregnancies of up to 35 days since the last menstrual period, and is effective in 85% of pregnancies less than 41 days since the last menstrual period.

- Effectiveness is reduced to 60% in pregnancies of 6 weeks.

- RU 486 induces miscarriages resembling spontaneous miscarriages. As in the latter, metrorrhagia occurs. Two thirds of patients describe it as heavy or very heavy.

Haemorrhage requiring therapy has been infrequent (2.5% of cases). Such incidents occurred early in the trials at a time when the substance was not fully investigated. It seems to be connected to expulsion and not to the product which does not modify coagulation tests.

- RU 486 at this dose is very acceptable clinically and biologically.

- RU 486 does not seem to have any ill effect on later fertility since women who have had induced abortions with the drug have subsequently produced normal children.

Test submitted to the Committee's appreciation

Roussel/Uclaf, on the basis of earlier experimentation, proposes in this study to "define effectiveness of and tolerance to RU 486 in the termination of pregnancy of an age equal or less than 41 days since last menstrual period, within the framework of the French law on induced abortion".

1) The trial is multicentric, carried out by 25 centres with 10 cases per centre which may be increased since the ultimate aim is to arrive at 400 cases over three months.

2) *Technical criteria for inclusion* are age of pregnancy equal or less than 41 days since last menstrual period, verified by :

physical examination,

HCG assay. This hormone, secreted by the egg, can be assayed 2 or 3 days after implantation of the egg in the lining of the uterus, i.e. around the 8th to 10th day after fertilisation before any interruption of menstruation takes place; pregnancy can be confirmed by this procedure,

by pelvic ultrasonography which does not confirm pregnancy since an egg is not always visible at this point, but a more advanced pregnancy can be diagnosed.

3) *Criteria for exclusion* are essentially anemia, conditions producing abnormal coagulation, liver or adrenal failure, cortisone therapy;

4) *Regimen* : three tablets swallowed fasting or about three hours after ingesting a meal, at the hospital in the presence of the prescribing physician.

A detailed list of drugs which should not be used simultaneously is attached to the protocol.

5) *Biological supervision* is provided by two work-ups :

one before RU is taken,

another 10 days after RU was used.

They cover blood count, platelets, and liver tests.

6) *Results are evaluated* 7 to 10 days after tablets are ingested.

Effectiveness is evaluated by interview, physical examination, assay of HCG, and pelvic ultrasonography.

- Complete evacuation of the uterus is rated a success.

- Failure is the necessity of surgery for :

persisting pregnancy,

pregnancy termination without expulsion,

egg retention,

heavy uterine bleeding requiring hemostasis by curettage.

Tolerance covers :

- bleeding
- pain
- changes in laboratory test results.

7) The brochure given to *researchers* for proper management of the trial contain *numerous recommendations :*

- be on call by telephone around the clock,

- active follow-up of patients and if necessary, contact them by telephone if they do not attend an appointment.

Finally, and this is a new departure, the Roussel laboratories will appoint an inspector who will follow the experiment so as to check on the quality of clinical tests .

"Observation and source documents will be reviewed in detail by the inspector on each visit to the centre. The team of researchers will cooperate fully with the inspector and supply any missing information whenever possible".

In so doing, the Roussel laboratories are following, it would seem, the Ministry's recommendations. However, should violation of medical confidentiality not be a concern since the inspector may not be a physician ?

In scientific terms, therefore, necessary precautions are being observed. However, the National Committee requests that the inspector be a physician.

Comparison between other induced abortion techniques and RU 486

1) The technical advantages of RU 486 compared to other abortion techniques should be investigated.

When the law legalising induced abortion was voted in 1975, the medical profession in France had no experience at all of "legal abortion". They only knew of the appalling complications of clandestine abortion.

In the circumstances, doctors felt it was their duty to comply with the law, but wondered about what procedures to use and possible complications of these procedures.

At present in France, vacuum aspiration is generally considered to be the safest method : after mechanical dilatation of the cervix which impedes access to the uterus, its contents are aspirated with a suction cannula.

Anesthesia is required, depending on the physician's decision :

- general anesthesia with a stay in hospital of between 6 and 48 hours, according to the surgeon's preferences,

- local anesthesia with the patient remaining at the clinic for 3 hours.

2) The vacuum aspiration technique has undeniably eliminated almost all the major complications which were the result of clandestine abortion.

- *Almost total disappearance of mortality and of severe complications*

Professor Goulon, who heads a resuscitation unit, recalls that between 1965 and 1975, 120 women were admitted for life-threatening complications of abortion : 60 for toxic shock, 30 for air embolism, 42 for renal failure, 2 for endocarditis, and 5 for severe cases of phlebitis. 18 women died. Between 1975 and 1985, no requests for admission to the unit for that reason were made.

- Almost total disappearance of tubal infection sequelae leading to infertility.

At the present time, 80% of tubal infertility is caused by sexually transmitted diseases (STD)

3) This is an outstandingly good outcome, but not perfect because despite all the skill and care physicians may display, as in any surgical procedure, there are residual risks which rise steeply with the age of the pregnancy after 8 weeks since last menstrual period.

We do not have any national statistics which is a pity and we must use data from other countries using the same techniques, in particular the USA

- Fatalities :

infinitesimal, but not nil.

Before 6 weeks of pregnancy, 0.5 for 100 000, according to American statistics. Two thirds of theses deaths are due to accidents connected with anesthesia which was required for surgery.

- Immediate serious complications :

Risks occur mainly under general anesthesia :

Perforation of the uterus, 0.29%, sometimes severe, possibly requiring resection of the small intestine.

Internal hemorrhage, 0.05%

Uterine hemorrhage, 0.54%

Laceration of the cervix, 1.73%

Total, 2.61%.

With local anesthesia, there is less risk, 1.05%

- Delayed complications :

Risks are extremely difficult to evaluate :

Continued pregnancy : extremely rare (at the Hôtel Dieu Hospital in Paris, 1 case out of 4500 induced abortions).

Retention of placenta requiring further surgery. 1% is the generally accepted figure.

Infection leading to infertility. The risk is minimal but not nil, although sexually transmitted diseases are much more of a threat in this respect (80%).

Adhesion of the walls of the uterus (synechia), causing infertility. This is rare and easily dealt with, but surgery is required.

Incompetent cervix causing premature birth. This has not been finally proven, but cannot be entirely excluded.

4) RU 486, which brings about a medical abortion, should eliminate all the above complications of surgery.

With this treatment, the uterus is not forced open. It opens of its own accord and expels its contents as in spontaneous miscarriage. No mechanics are involved and uterine physiology remains intact.

This type of abortion as we have already noted, does introduce some risk. Oncoming trials should help us to define it.

- Serious risks :

Failure rate of 10 to 15% with attendant risk of foetal deformity if pregnancy persists. In the near future, combining RU 486 and prostaglandin may improve results.

It should be emphasised that in order to evaluate the results of treatment with RU 486, neither an interview with reports of bleeding, nor physical examination revealing a too small for age of pregnancy uterus, are entirely reliable. Other means of investigation must always be used such as pelvic ultrasonography or HCG assay.

Frequently heavy metrorrhagia, very rarely hemorrhage. However, this possible complication justifies close monitoring of patients, and this will certainly be the case in the trials submitted to us for an opinion since the protocol requires a doctor to be on call night and day.

However, these two problems : infinitesimal risk of failure to end pregnancy so that sophisticated means of investigation are needed to detect such cases, and low but existing risk of hemorrhage, lead the Roussel laboratories to believe that use of this substance should be restricted to countries in which sophisticated medical technology is available, and that it should not be used in developing countries.

- Minor risks :

Painful uterine contractions which only rarely require the use of pain-killers.

Termination of pregnancy with no expulsion so that surgical evacuation is required. In the near future, prostaglandins may medically induce evacuation.

However these risks following the use of RU 486 car be kept completely under control with high quality medical supervision. Therefore true progress seems to be achieved by the use of RU 486 since the physiology of the uterus is untouched, the resulting abortion closely resembles spontaneous miscarriage, and the procedure is non-surgical which eliminates all attendant mortality and morbidity.

Sociological repercussions

1) It is thought by some that abortion with RU 486 is too easy so that it could be used as a contraceptive.

The same argument was used by the opponents of the law on induced abortion in 1975. The law has been in force for ten years and we find, on the contrary, that the number of induced abortions is decreasing in spite of better census taking methods, and that France is a country in the lead as regards the use of so called modern methods of contraception.

From a woman's point of view, experience proves that it is not easy to take an abortifacient,

and that it is not easy to face alone an abortion procedure which last 2 or 3 days, and is accompanied by heavy bleeding and pain.

Many patients, given the choice of methods, i.e. RU 486 or aspiration, preferred aspiration since they did not need to take any abortive action personally. The abortion procedure was over in about 15 minutes and took place in a reassuring hospital environment.

Finally, RU 486 does entail a fair amount of technical constraint, such as HCG assays, and ultrasonography, which are not pleasant experiences.

2) Can such a simple method for abortion bring about a lower birth rate ?

In France and the rest of Europe, birth rates began to fall well before the second world war at a time when induced abortion was severely penalised.

Legislation on induced abortion in France did nothing to change birth rates. The same is true of all European countries when such laws were passed at different times.

Countries such as Spain and Belgium, where elective abortion was not authorised, also had falling birth rates. Certain developing countries are an excellent a contrario example of that trend. In spite of the adoption of modern methods of contraception and legislation authorising induced abortion, their birth rates persist unabated.

In fact, despite the technicalities, couples parent the number of children they actually want. Medical technology can only, as it improves, help to avoid mortal or otherwise severe accidents connected with birth control.

In conclusion, we feel that a favourable opinion may be given on experiments to investigate an innovative product which may serve to eliminate morbidity arising from surgical uterine evacuation and which are conscientiously conducted from a scientific point of view.

Elective abortion using RU 486 and the law (known as the "loi Veil)

This protocol complies with the law.

The French law requires that :

1) The age of pregnancy be less than 12 weeks of amenorrhea.

We are well below that limit : 5 weeks.

2) Abortion must be performed in a public or private hospital in accordance with article L. 179.

RU 486 will be ingested in a public hospital which has been approved for practising induced abortions by the Ministry of Health : the Port-Royal Hospital in Paris.

"Abortion must be performed by a physician".

RU 486 will be swallowed in the presence of a medical practitioner.

It should be remembered that when the law was voted, legislators had insisted on these two conditions so that abortion could be a fully medical procedure. Patients will be under very thorough medical supervision.

3) Patients must have attained the age of legal majority, or if not, be authorised by their parents.

The protocol specifies "women of at least 18 years of age or provided with parental authorisation".

4) The patient must have counseling.

At the preliminary visit, before absorbing RU 486, legal induced abortion formalities will be set in motion.

5) The legal time specified for reflection - 8 days - before the second medical visit when the patient signs a request for induced abortion, is the only point which might be questioned.

It can be complied with since up-to-date pregnancy tests make it possible to detect pregnancy as early as 10 days after fertilisation.

Thus a test can be performed two days after delayed menstruation, that is on the 32nd day of amenorrhea. After the 8 day reflection period, amenorrhea is 32 + 8 = 40 days, within the experimental calendar.

Conclusion

It therefore seems that in legal terms, there is no reason why approval of the trial should be withheld.

Perhaps, however, we ought to raise the problem - not of the principle of time for reflection since experience proves that it is essential - but of its 8 day duration.

Some women might, because of the time constraints, be prevented from using RU486 since the drug's effect is very short lived. They would then have to fall back on surgical abortion.

In fact, the law includes a provision to the effect that in an emergency, the doctor may decide to shorten the time limit.

It could therefore be considered that in this particular case - dead line for RU 486 to be effective - there is an emergency and the limit might be reduced by a few days.

In this way, one could be certain that the principle of the time for reflection is observed.