Emergency Contraception: History, Methods, Mechanisms, Misconceptions and a Philosophical Evaluation

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Abstract

Humans have attempted to disrupt the progression of pregnancy for a very long time. This dates back to the realization that it was a sexual activity which started the reproductive cycle. Folk methods for preventing pregnancy after unprotected sexual activity are physiologically unable to be effective and we now have chemical, mainly hormonal methods, and a mechanical method the intrauterine device which do work in the very early stages before conception can be diagnosed with certainty. These methods are impeded by those who worry that fertilisation of the ovum may have occurred, and that the method may then be abortifacient. Considering that it is possible to easily disrupt an established pregnancy by medical or surgical means depending on the duration, this would be no different than any other means of abortion induction. This evaluation takes the approach of viewing pregnancy as a 40 week continuum and that the approach to halting it after it has begun should simply be chemical or mechanical depending on duration and subject preference and clinical suitability as appropriate. There is no clinical reason to not be able to act in the early stages before the diagnosis of pregnancy is determinable. Clinicians may want to use the duality of conceived and non-conceived simultaneously if it helps to take action to interrupt the pregnancy continuum so that they may view their client as pregnant or is not pregnant enabling them to act accordingly. This could be viewed as the ‘uncertainty principle’ of emergency contraception. The methods available and their historical context and limitations are presented and examined.

Keywords: Emergency contraception; Reproductive cycle; Progression of pregnancy

Introduction

Emergency Contraception (EC) is also known as the ‘morning after pill’, less commonly the ‘morning after IUD’ or simply ‘morning after contraception’, ‘emergency contraception’ or more correctly but less politically correctly as post-coital contraception. The principal motivation for emergency contraception is to prevent pregnancy from becoming established after one or more episodes of intercourse which could potentially result in a fertilized ovum. In this situation the woman seeking the method was not using contraception or feels that the method she is using is for whatever reason deficient. Emergency contraception is controversial. Opponents feel that it is either always or at times abortifacient. Proponents feel that it is such a benefit to women and their health and wellbeing that it is either

Not true that it is an abortifacient or
It is and it does not really matter.

The mechanism of action is not fully known but the oral methods do appear to act by delaying ovulation [1]. The IUD is more controversial since it certainly at times stops implantation of a fertilised ovum and at other times clearly interrupts an early implanted ovum [2,3].

This paper is devoted to resolving these issues from a purely biological view not in terms of the dogma and fixed paradigms which the opponents and to some degree the proponents have. The role of emergency contraception in the pregnancy continuum is evaluated. Reversible contraception and irreversible contraception (sterilization) act to stop the pregnancy continuum from starting. Abortion (termination of pregnancy) acts to stop the pregnancy continuum after it has already become established, usually in the first or second trimester. Emergency contraception attempts to disrupt the continuum when it has either 1) almost, but not yet started or 2) just started.

Awareness of Pregnancy

It is logical that it is not possible to want to do something about avoiding pregnancy unless there is awareness that it is coitus which causes pregnancy. While this is obvious to virtually all humans at present, there is no evidence that any other species is aware of this. This being the case, there must have been a time in our evolution when we first made the connection between coitus and pregnancy. Even after this connection was made, the exact timing of the commencement of pregnancy was a complete mystery. Pregnancy appeared to begin when a number of factors lead a woman to believe that she was pregnant viz: the feeling of being pregnant, absent menstruation, frequent urination, breast and abdominal enlargement, feeling of moving in the abdomen (quickening). The term abortion as the term for the interruption of pregnancy was therefore coined when the determination of pregnancy was based on the above. It was the work of the 16th century anatomists including Gabrielle Fallopio and the 17th century invention of the microscope by Anthony Van Leeuwenhoek that would pave the way for the understanding of female genital anatomy and the mechanism of normal conception. It is somewhat ironic that science defying religious doctrinaires of the Middle Ages, are now happy to use the previously defied science to
move the definition of pregnancy to the microscopical rather than the macroscopical and of course changing the original definition of the word ‘abortion’. It was also not known at the time that a high percentage of conceptions fail to thrive at a very early stage, leading to miscarriage even before the awareness of pregnancy. Spontaneous abortion is therefore as natural as sustained pregnancy. The implications of this will be further considered when examining how effective emergency contraception appears to be [1].

The Natural History of Conception

The evidence shows that as many as 30% of conceptions abort spontaneously at a very early stage poses certain philosophical problems. When emergency contraception is being considered there is a 1 in 3 chance that the potential conception it is attempting to prevent may spontaneously demise. Therefore the provider certainly cannot be sure that the agent being provided is preventing a potentially viable conceptus. While pregnancy begins with implantation of a fertilised ovum (by definition), when life itself begins is not a scientific definition but a philosophical and theological one. In some instances emergency contraception may not stop conception but blocks the fertilised ovum from implanting in the endometrial wall-is that an abortion? If implantation has taken place and the emergency contraceptive method prises it off the uterine wall - is this an abortion? Finally does life begin as soon as maternal genes have fused with paternal or do we need to have a few mitotic divisions or gastrulation before we can say this constitutes abortion? It is against this background that the various emergency contraceptive methods will be examined.

Pregnancy as a Continuum

The pregnancy continuum begins with fertilization of the ovum by a given sperm and subsequent implantation and then extends for approximately 40 weeks or 280 days. It may become disrupted anywhere along this continuum either through internal or external factors. While the internal factors are not intentional the external factors may be unintentional e.g. trauma or intentional e.g. use of chemicals or instrumentation. In many countries it is legal to interrupt pregnancy during this continuum. While this would usually take place when the pregnancy was established more anxious women attempted to use douches post-coitally. The duration of gestation and thus the definition of pregnancy has taken place. This may not be true of all methods but may be true when misoprostal or the IUD is used. It is after fertilization and especially after implantation has taken place that it becomes problematic for certain schools of thought. The separation of methods for termination of the progress of a fertilized ovum into a ‘contraceptive’ and an ‘abortion’ phase, while appealing to certain religious or quasi-moral sensitivities, and the discontinuous mind-set is not scientifically rational. This is irrespective of the mechanism of action of the method.

Historical Efforts to Disrupt the Continuum

Historically many women have found themselves pregnant when they did not want to be. The reasons are many fold and obvious. This coupled with an inferior position in society sometimes led women to seek to attempt to disrupt the pregnancy continuum. While this would usually take place when the pregnancy was established more anxious women attempted to use douches post-coitally. In the early twentieth century Coca Cola was a favourite. Unfortunately the rapid progression of spermatozoa into the uterus and up the Fallopian tubes rendered these efforts as useless [4]. This is discussed in detail later.

Definition of Emergency Contraception

Emergency Contraception (EC) is usually described as the use of a method within 120 hours following unprotected sexual intercourse [1]. This restriction is sometimes modified to enable EC to be used up to 120 hours after the time of expected ovulation. There is no scientific rationale for this, simply a desire to act before the fertilized ovum has presumed to have become implanted i.e. approximately six to eleven days after conception [5]. This is a good example of science being impeded by religious and quasi-moral behaviour. It is no more rational now than it was in the time before van Leeuwenhoek.

Methods used for Emergency Contraception (EC)

There are two main methods of EC.  
- chemical - usually hormonal and taken orally and 
- mechanical - the insertion of a copper carrying intrauterine device (IUD).

There are a number of chemical compounds which have been evaluated since the 1960’s, only some of which remain in use. A summary is given in Table 1.

<table>
<thead>
<tr>
<th>Type of EC</th>
<th>Estrogen</th>
<th>Progestin or anti-progestin</th>
<th>Other</th>
<th>comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>non-steroidal</td>
<td></td>
<td></td>
<td>no longer used</td>
</tr>
<tr>
<td>Ethinyloestradiol (EE2)</td>
<td>steroidal</td>
<td></td>
<td></td>
<td>no longer used</td>
</tr>
<tr>
<td>Levonorgestrel (LNG)</td>
<td>steroidal</td>
<td></td>
<td></td>
<td>available without prescription and/or over the counter in most countries</td>
</tr>
<tr>
<td>EE2-LNG (Yuzpe)</td>
<td>steroidal</td>
<td>steroidal</td>
<td></td>
<td>disappearing slowly where LNG is available</td>
</tr>
<tr>
<td>Danazol</td>
<td>steroidal anti-progestin</td>
<td></td>
<td></td>
<td>no longer used</td>
</tr>
</tbody>
</table>
Evolution of hormonal methods of emergency contraception

From the time that seminal fluid was known to be the cause of pregnancy a variety of methods have been used to attempt to block it from commencing the pregnancy continuum. We have evidence that attempts to prevent pregnancy after sexual intercourse go back as far as 1500 BC. Methods advocated for this have included many forms including making violent body movements. Loranos of Ephesus (98-138 AD) advised women to hold their breath at the time of ejaculation, and to draw the body back so the seminal fluid could not get into the uterus. After this she was supposed to get up and to sit with bent knees and sneeze and then carefully wipe out the vagina and drink cold water. Some sages added to this by advising to then blow the nose, have a good shake and jump backward seven or nine times to dislodge the semen. Even as late as the nineteenth century the American physician RT Trall recommended similar methods.

Useless oral preparations have also been tried since ancient Egyptian days. Mixtures of grease, herbs and ale were used by the ancient Egyptians. In the fourth century AD wine and cabbage blossoms were recommended by Oribasius. Fiji islanders have used infusions of leaves and roots. Cabbage blossoms and seeds have also been used in many years. Douches of various kinds have also been used for many years. Douching was very popular in the nineteenth and early twentieth centuries when it was promoted by the American physician Charles Knowlton. He suggested using douches containing alum, zinc sulphate, sodium bicarbonate, vinegar and salt. While some of the above are indeed spermicidal, the problem is that spermatozoa enter the cervical canal in seconds and the Fallopian tubes within minutes of ejaculation. Vaginal douching appears to be the main surviving folklore post-coital method still being used, at least to a modest extent as of a 1980 survey [4]. Its use is certainly on the decline now as easier access to emergency contraception has become available and as a better understanding of the physiology of conception becomes more widespread.

Evolution of hormonal methods of emergency contraception

The first attempts at using hormones as post coital or emergency contraception dates back to the early 1960’s [6]. This is not very long after the introduction of the combined oral contraceptive for birth control in the late 1950’s. Initially Diethylstilbestrol (DES) and ethinyl estradiol (EE2) were used. DES is a synthetic non-steroidal estrogen and EE2 is a synthetic steroidal estrogen. Initially DES 50 mg was given post coitally for 4-6 days. Later DES 25-50 mg daily for 5 days or EE2 0.5 mg to 2 mg for 5 days post-coitally was used [6,7]. In the early 70’s Yuzpe and colleagues began evaluating the combination of EE2 and dl - Norgestrel (NG). This was based on the knowledge that a single dose of 0.05 mg EE2 and 1 mg of NG produced endometrial changes. They settled on a dose of 0.2 mg EE2 and 2 mg NG administered in two divided doses 12 hours apart. This method was much better tolerated than the previous estrogen regimes. It appeared to be as effective using the clinical evaluation methodology of the time [8]. Currently since 50 µg (0.05 mg) EE2 birth control pills have been generally replaced by pills containing 30 µg and even lower doses of EE2 and dl - norgestrel has been replaced by the active isomer levonorgestrel (LNG) the Yuzpe regime consist of 2 divided doses of 120 µg EE2 and 0.6 mg LNG (4 tablets of the standard 30 µg EE2/150 µg LNG birth control pills). This method avoids the potential serious side effects e.g. deep vein thrombosis of the estrogen only methods. It was the first method to become available without prescription in some countries.

Earlier research into progestin only methods was rekindled in the late 1980’s leading to studies of the use of 0.75 mg LNG in two divided doses 12 hours apart and finally to the use of 1.5 mg LNG as a single dose taken within 72 hours and even up to 120 hours after unprotected intercourse, but it is more effective the earlier after unprotected intercourse it is taken [9,10]. The LNG method appears to be twice as effective as the Yuzpe and appears to work mainly by the inhibition of ovulation or the production of dysfunctional ovulation [11]. There is reasonable evidence that LNG is not effective if ovulation has occurred, but not all researchers are in agreement and some suggest it may still have a residual effect by virtue of its effect on the endometrium [1]. Those who are concerned about whether emergency contraception is an ‘arbitrarily’ happy about this. Those who just want to prevent an unwanted pregnancy and have no religious inclination see this as a deficiency and a limitation of the method. The safety profile of LNG is such that it has become the mainstay of oral emergency contraception and is available over the counter with varying degrees of freedom and without prescription in many countries.

More recently the Progesterone Receptor Modulator (PRM) Ulipristal acetate has become available with prescription in some countries. It is marketed under the trade name Ella-One®. It may be given in a 30 mg dosage up to 5 days (120 hours) after unprotected intercourse and appears to work by delaying ovulation and/or by preventing follicle rupture for up to 5 days [12]. This accounts for its longer window of use compared to LNG. There is also some evidence that alters endometrial cytology but it is not known if this is part of its clinical action.
Other chemical methods

Danazol, an androgenic and progestogenic steroid which is used for treating endometriosis has been used as an emergency contraception with limited efficiency and its use for this purpose has been discontinued [1]. Mifepristone (RU-486, Mifigyne®) which is used in conjunction with misoprostol for first trimester medical abortions has also been used as an emergency contraceptive [1]. Mifepristone binds to progesterone receptors and prevents ovulation, and may also disrupt luteal function and prevent endometrial development if given after ovulation. A single 10 mg dose is given within 120 hours of unprotected intercourse. It is more effective than the Yuzpe regime and as effective as 1.5 mg of LNG [13]. The antiprogestogen gestrinone which is also used for treating endometriosis as well as mifepristone. While the mechanism of action of the Yuzpe method and LNG and Ella’ (or Ella-One as it is also known) is disputed to some extent viz: it is uncertain whether they act after fertilization or not, there is no doubt that mifepristone and gestrinone can disrupt the newly implanted conceptus as they are both potent abortificients [13].

Meloxicam a COX-2 inhibitor anti-inflammatory agent had also been studied as an emergency contraceptive. When meloxicam is given for 5 days in the late follicular phase of the cycle it interferes with luteal function but does not produce other hormonal changes. It increases the ability of 1.5 mg LNG to prevent follicle rupture [1].

Side Effects of Oral Agents Used As Emergency Contraception

There is no evidence that any of the hormonal methods viz: Yuzpe, LNG, or Ella’ have any effects on a pre-existing pregnancy [1]. Minor side effects include a 20% incidence of nausea and vomiting [1]. Depending on when the vomiting occurs the medication may need to be re-administered or given vaginally. Menstrual cycles may be altered. The length of the cycle may be shortened if treatment is given early in the cycle. If given later in the cycle there is a tendering for prolongation of menstrual bleeding during the next period [1].

Efficiency of Hormonal and Non-Hormonal Oral Emergency Contraceptive Pills (ECP)

The early hormonal emergency contraceptive studies were non-comparative. Placebo controlled studies were not conducted then and to this day there have been not any. For ethical reasons they are unlikely to ever take place. However, we now have an idea of the probability of pregnancy occurring on any given day of the menstrual cycle. It is now possible to compare the observed versus the expected number of pregnancies to get an estimate of the efficacy of the method [14].

Many women are not sure of their cycle day and so the efficacies of early hormonal methods were over-estimated [1]. Some women who ask for the emergency contraception are not even sure if they were definitely exposed to pregnancy because of confusion, possible intoxication etc. These situations are known to inflate and overestimate the efficacy of the method.

Yuzpe and Progestin only Methods

The Progestin only regime (LNG 1.5 mg in a single or divided dose) appears to prevent about 50% of expected pregnancies. The Yuzpe regime is not as effective and probably prevents 30% of expected pregnancies [1].

Ulipristal acetate (Ella’)

A single 30mg dose of Ulipristal acetate is the most effective ECP pill option and has a pregnancy rate 40-60% lower than LNG depending when it is given. The reason for this is that it appears to be more effective in postponing ovulation when the follicle size is over 18 mm. All of the hormonal methods are less effective in women with a higher Body Mass Index (BMI). In women with BMI of 26 kg/m² and over LNG is very much less effective, and is probably only marginally effective. Ulipristal acetate efficacy is also reduced, less dramatically but is also somewhat marginal at a BMI of 35 kg/m² or greater [15]. Given the present trends of obesity in women of reproductive age this has important implications for the future utility of this method.

The Intrauterine Device (IUD) as an Emergency Contraceptive

The copper T IUD was first used as an emergency contraceptive by Lippes et al. in 1976 [16]. This was shortly after the concept of adding copper to an IUD was proposed by Zipper [17]. The IUD has been used in the west since being introduced by Richter in 1909, and subsequently by Grafenberg, both in Germany. Grafenberg introduced the IUD into the USA. The rationale for the use of the IUD as an emergency contraceptive is that implantation takes place after ovulation about 6-12 days after fertilization [5]. If the IUD is inserted before implantation takes place the copper on the device releases ions into the endometrium which then becomes hostile to successful implantation. Since the IUD does not delay ovulation, fertilization undoubtedly takes place on some occasions. IUDs are very effective as emergency contraceptives [2].

The current recommendations of many authorities are that they may be inserted up to 5 days after unprotected intercourse. However some agencies e.g. Centre for Disease (CDC), Atlanta, the World Health Organisation (WHO), Geneva and the Faculty of Sexual and Reproductive Health Care, London, United Kingdom specify that the IUD may be used up to 5 days after ovulation if the day of ovulation can be determined with reasonable accuracy. Their position is that if it acts before implantation it is a contraceptive rather than an abortifacient. There is evidence that it may be effective and safe even after implantation has occurred [2]. Its use in this situation is disturbing to some sensitivities but this is a philosophical issue not a prejudice based on scientific evidence. This sensitivity may often unjustifiably place limits on the IUD as an emergency contraceptive. This method is not advised often enough and is the method of choice in women with a BMI of over 30 kg/m² where hormonal methods have reduced efficacy [15]. Only copper IUDs have been extensively studied although some plastic IUDs were included in the earlier studies. There is as yet no evidence that a LNG releasing IUD (Mirena) would be effective in this situation and for that reason it is not recommended as an emergency contraceptive.

Limitation of Oral Emergency Contraception

The successful use of emergency contraception is limited by two main factors. The first is the limitations of the methods themselves. The hormonal methods are known to be effective for up to 120 hours after unprotected coitus. This applies to Ulipristal acetate, the most effective oral agent available but the two other commonly (and more
widely available methods) the Yuzpe estrogen-progestagen or the LNG only regime have only limited efficacy beyond 72 hours. The Yuzpe regime is a two divided dose method and also requires more compliance. The second type of limitation is the limitation of provision. Ulipristal acetate is generally available only by physician prescription. If a physician is unwilling to prescribe it for religious or ‘moral’ reasons this is a limiting factor of availability for the method. Some providers may be concerned that it is an ‘abortifacient’ and prevents implantation of the fertilized ovum or causes blastocyst demise. These conditions cannot be observed and are at odds with the evidence that Ulipristal delays ovulation and/or follicle rupture. While the LNG and Yuzpe methods are available without prescription in most countries this does not ensure that they are necessarily available. They may be available on the open pharmacy shelves depending on local regulations and may also not be available behind the counter if the pharmacist chooses not to stock them. Some pharmacies may demand the type of identification which the prospective buyer does not have. The pharmacist may have religious or moral objectives to stocking these products or in filling physician prescriptions for Ulipristal.

Only the women seeking emergency contraception is at risk of pregnancy. The physicians and pharmacists who do not approve of the methods should not be allowed to ‘counsel’ women who request this method, only explain the potential pharmaco logical side effects and potential method problems as their only type of counsel is likely to be negative indoctrination.

The Limitations of the IUD as an Emergency Contraceptive

The IUD is a very effective emergency contraceptive [2]. We do not really know the limits of its efficacy but it is clearly at least 7 days from conception and possibly longer [2]. Currently most providers limit its use to 5 days after unprotected intercourse or 5 days after the expected date of ovulation if there has been only one episode of unprotected intercourse in that cycle. These restrictions are not scientifically based but are put in place in order to make sure that the IUD is not being used to disrupt an implanted conceptus. Since the evidence suggests that its action is up to 7-10 days after unprotected sex this limitation is to avoid causing what is a possible ‘mini-abortion’ in some viewpoints [2].

There were no pregnancies in nearly 2000 women who used the TCu380A as emergency contraceptive irrespective of cycle day of insertion of the IUD. The IUD is thus safe and effective if used any time during the menstrual cycle. Any woman who has a negative high sensitivity pregnancy test is therefore a candidate for an emergency IUD.

At this stage (10-14 days after coitus) both the woman herself is aware of being pregnant and there are as yet no tests that can determine if she is indeed pregnant. Her ‘pregnancy’ is invisible and is just a human meme. Two genetically different strands of DNA may or may not have joined. Instead of using modern day knowledge to save herself from something she does not want at this stage (a pregnancy) whether she of her advisers or both are paralysed by a kind of scientific medievalism. Modern day humans have truly in some instances been hoisted by their own petard. This method is therefore limited by the sensibilities of the women herself in 1) her willingness to have the IUD inserted at this or any other time 2) the willingness of the person she consults in providing the method. The IUD is also useful as a regular form of contraception and gives providers the opportunity of providing emergency contraception and long acting reversible contraception (LARC), the most effective form of contraception [18], at the same time.

The willingness of providers to advise the IUD for emergency contraception is limited not only by moral and religious prejudices but also by prejudices and lack of knowledge of the method. This includes, i) only wanting to insert IUD during menses, ii) fear of insertion, iii) non-suitability for nulliparous women, non of which are currently considered as contraindications for the method. Often the real reason providers so not want to advise the copper IUD is because they are not comfortable with some or all the technical aspects of the method. Facilities which provide the IUD as an emergency contraceptive should ensure that they have staff who are familiar with and extremely competent in IUD insertions, especially in situations where there is pressure to insert the device successfully to avoid unwanted pregnancy.

Pregnancy as a Theoretical Concept - what can we Learn from Schrodinger’s Cat?

Schrodinger’s ‘cat’ is part of a thought experiment in quantum physics. It is an attempt to explain the concept that quantum physical particles can remain in two (or more) states at once. Many modern day electronic appliances are based quantum physics where in certain instances it is advantageous to deal with both states simultaneously, rather than determine the actual state. In dealing with pregnancy as a continuum this approach may be useful in that part of the continuum where pregnancy cannot be confirmed.

Currently we are happy to deal with unconformed pregnancy up to 5 days or 120 hours after unprotected intercourse. This is usually termed ‘emergency contraception’, in the hope that conception, however defined can be prevented. As discussed this may be extended up to 120 hours after expected ovulation in the case of the IUD. The IUD has been used up to 10 days (240 hours) post-coital, in the absence of confirmation of pregnancy [2,15,19,20]. There is thus a hiatus from approximately day 10 to day 27 or 28 of a 28 day cycle in which it is usually not possible to determine pregnancy. From day 28 or so the presence of pregnancy can be detected and the women can then elect to keep or abort the pregnancy. Schrödinger’s method would allow us to determine that a woman was both pregnant and not pregnant during the hiatus, and manage her problem using a definition which best suited both parties. Mifipristone has been used for both emergency contraception [21] and medical termination of first trimester pregnancy. It would be possible to establish the dose required for which it would work during days 10 - 28 of the cycle where a women was beyond 5 days (120 hours) post-coital. Mifipristone in this circumstance could be viewed as either an emergency contraceptive or an abortifacient simultaneously for women who could simultaneously be considered both pregnant and not pregnant. This would allow us to close the pregnancy continuum so that options would be available for interrupting pregnancy from possible conception up to the latest legal date in the women’s particular jurisdiction.

Conclusion

Emergency contraception deals with the earliest part of the pregnancy continuum immediately or just after it is established. The time from day 1 to approximately day 10-15 are most difficult to
manage as the pregnancy is not clinically or chemically detectable. This period of uncertainty could be treated as in physics by assuming the duality of pregnant and not-pregnant or ‘conceived’ and non-conceived simultaneously and managed accordingly so as to comply with the wishes of the woman seeking help to avoid an unplanned and unwanted pregnancy.

*Schroedinger was a famous Austrian physicist and was attempting to explain the paradox of subnuclear particle’s being able to be in two places or two states simultaneously

References