The controversy concerning mechanisms of action of post coital pills

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Abstract

In December 2012, an allegedly raped woman was refused admission by two Catholic hospitals in Cologne. This lead to a public discussion about the availability of the Morning-After Pill (MAP). The consequence was the approval of the MAP in case of rape by Cardinal Meisner who consulted particular expert organisations of gynaecologists. They stated that the MAP only inhibits ovulation. In this case, they referred to the pill ellaOne® (on the market since 2009) which contains Ulipristal Acetate (UPA) and would replace the Morning-After Pill with LNG.

The investigations on which this essay is based show clearly and ufndoubtedly, that apart from ovulation inhibition, UPA has got a nidation inhibiting mode of action. As selective progesterone receptor modulator (SPRM) it repeals the effect of progesterone in the female internal genitalia, changing the function of the tubes and the endometrium, in a manner that the nidation of the embryo cannot take place. Not only in references, but the protagonists themselves gave contradicting statements of a mere ovulation inhibition of UPA, which in fact confirm the nidation inhibition. Besides, there are clear statements of the companies Watson and HRA Pharma who sell ellaOne® concerning the nidation inhibiting effect of UPA.

The question of a timeframe where UPA could be given without the risk of nidation inhibition must be answered by a clear no, according to INER (Institute for natural conception regulation), for it is theoretically possible, but in practice it is not feasible, because according to NER criteria the nidation inhibiting effect can never be excluded.

1 Reasons for the Approval of the 'Morning-After Pill' (MAP) in case of rape

1.1 The occasion of the approval

In December 2012, an allegedly raped woman was rejected by two Catholic hospitals in Cologne for the securing of evidence. At that moment she probably had already got the pill by the doctor who called the hospitals.

In the public the rejection was explained with the negative position of the Catholic Church concerning the 'Morning-After Pill'. Later we learned that none of the hospitals had the permission to execute a securing of evidence; only five hospitals in Cologne have that permission. That was the real reason for not admitting the woman.

What lead to the release of the Morning-After Pill?

As a consequence there was a high public and political pressure on Cardinal Meisner: the health minister of North-Rhine-Westphalia threatened to examine and possibly revoke the accreditation of Catholic hospitals. In the media the Catholic Church was presented as an antiquated organization with regard to scientific standards.

1.2 Advisors of Cardinal Meisner

BVF, DGGEF, both said: The "Morning-After Pill" is a contraceptive, not abortifacient, it has got *only and exclusively ovulation inhibiting and no nidation inhibiting* modes of action. They cited a *study of Kristina Gemzell et al., since four years president of FIAPAC,* the International Federation of Professional Abortion and Contraception Associates.

1.3 Message of Cardinal Meisner on the 31st of January, 2013

> *"If after a rape a preparation is used whose principle of action is the inhibition of a procreation, in order to prevent the fertilization, in my opinion this is acceptable. If a preparation is used whose mode of action is the inhibition of nidation, in order to prevent the nidation of the already fertilized ovum, this is not acceptable, because this removes actively the livelihood of a fertilized ovum and its granted protection of human dignity."*[1]

Explanation given by the Press office of the Archdioceses Cologne:

> *"The statement given by the Archbishop of Cologne considers new findings with regard to the so-called 'Morning-After Pill'. It does not refer to the abortion pill Mifepristone (RU 486, 'mifegyne') which is still to be rejected according to Catholic perception.*
>
> *To date it was often presumed, that the nidation inhibiting effect would be the central mode of action of those preparations called 'Morning-After Pill'. […] Obviously, this is no longer the state of science. But Church has always to consider the scientific findings when making evaluations."*[2]

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1 www.domradio.de/themen/ethik-und-moral/2013-01-31/kardinal-meisner-erlaubt-form-der-pille-danach

2 Ibid.

2 Overview of 'Morning-After Pill' data

2.1 Preparations and active substances available at the moment

Preparation	Active substance and dose per pill
Unofem	LNG (1500 µg)
Duofem	LNG (2 × 750 µg)
Vikela	LNG (1500 µg)
PiDaNa	LNG (1500 µg)
NorLevo	LNG (1500 µg)
Levogynon	LNG (750 µg)
Postinor	LNG (1500 µg)
Tetragynon (no longer on the market)	LNG + EE2[3]
ellaOne	UPA (30 mg = 30.000 µg)
Mifegyne a) CH and D only for abortion b) Russia and China also as post-coital pill	Mifepristone (200 mg)

Table 1: Preparations of MAP available at the moment

1) The post-coital pill, today also in the medical sector mostly called "Morning-After Pill", is a preparation used only in case of need, in contrast to hormonal contraceptives.
2) In ethical terms there is one decisive main question: Has the 'Morning-After Pill' only a life preventing effect or also a life destroying one? In this regard the following must be stated: Independently of an ethical evaluation of measures to suppress or prevent ovulation, all those measures belong to the category of preventing life, blocking the procreation of a new human. Fundamentally different are considered those measures, which attack directly or indirectly already generated life.

Summarily, a preliminary statement can be given: Ovulation inhibition has certainly nothing to do with the destruction of life. Ovulation inhibition without exception, only *prevents* life.

In contrast, nidation inhibition is an indirect attack on emerging life, it does not destroy the embryo directly, but deprives it of the necessary living conditions leading it as a consequence to death. The death of embryos in the first days of an early pregnancy normally occurs without the knowledge of the mother.

But for an ethical evaluation it is completely irrelevant if an artificially induced death is realized by a person or not. It is equally irrelevant, how present the sensitization and problem awareness of the population is regarding that kind of life destruction.

The study made by Kristina Gemzell et al. especially refers to the ovulation inhibiting effect of ellaOne® (UPA) and PiDaNa®, Vikela® respectively Norlevo® (LNG)[4]. But in that study the nidation inhibiting effect is neglected, essential studies to that effect are not mentioned or omitted.

1.1 Frequency of use

Regarding the frequency of using post-coital pills the following numbers may give an example (see Table 2).

Region	Use per year	Year/tendency	Prescription requirement
Switzerland	107.000	2012[5]	No
Germany	400.000	increasing[6]	Yes
World	12.000.000	2012/increasing[7]	Nearly everywhere not required

Table 2: Frequency of using MAP

3 Ethinylestradiol, the most used synthetic oestrogen in ovulation inhibitors.
4 K. GEMZELL-DANIELSSON ET AL., 2013.
5 HLI Switzerland, own calculation, not published; (based on three sources, see References)
6 T. Rabe/C. Albring C. 2013: DGE (Dt. Gesellschaft für Endokrinologie): Hormone und Stoffwechsel, 10.04.13, www.endokrinologie.net/ presse_130410.php
7 "Emergency contraceptive use has steadily increased, with about 12 million packages sold last year, according to IMS Health and the SymphonyIRI Group, health information and market research companies."

The MAP available on the market since ca. 2000 (France 1999) Norlevo (CH), Vikela® (A), Postinor® (A) respectively PiDaNa®, Unofem®, Levogynon® (Germany) contains the gestagen Levonorgestrel (LNG) which also is known for inhibiting ovulation. But at the same time it has got a nidation inhibiting effect confirmed in many cases by literature[8], although today it is alleged that it hasn't got that effect[9]. As the cited literature shows too less case numbers or lacks in design, this won't be explained in detail here. Besides, today ellaOne® (UPA) is clearly preferred. UPA shall replace LNG as the following statement proves:

> *"In contrast to LNG, UPA can still postpone the ovulation at already increasing LH level and a follicle size of 18 mm. So, because of that superior effectiveness, UPA is the first choice for emergency contraception."*[10]

In most of the European countries, the LNG containing MAP is no longer available only on prescription, with the exception of Poland and Italy (Germany: over the counter since the 15th of March, 2015). The dose of the LNG pill is fifty times higher than the POP containing LNG. In several countries, the UPA ellaOne® is only available on prescription.

The current literature especially considers the SPRMs and especially UPA. It is practically preferred to LNG everywhere and is considered the new standard method. Though, ellaOne® is twice or triple as expensive.

2.3 Security of LNG

How sure is the prevention of a pregnancy with LNG?[11]

Time of use after sexual intercourse	Success rate / prevention of pregnancy
First 24 h	95 %
24–48 hours	85 %
48–72 hours	58 %

Table 3: Security of LNG

2.4 Security of UPA

The timeframe of the UPA effectiveness with the "successful" intake to 120 hours after the sexual intercourse cannot only be based on the ovulation inhibition. The higher security rate of UPA vs. LNG speaks for nidation inhibition. The pregnancy rate with UPA could be reduced from 5.5 % to 1.8 % and with LNG from 5.4 % to 2.6 %[12].

2.5 What is Ulipristal Acetate?

– Chemically, it is a follow-up compound of Mifepristone – RU 486 = Antiprogestin:
– RU 486 = SPRM, first generation
– UPA = SPRM, second generation = CDB-2914
– Both compounds are so-called selective progesterone receptor modulators (SPRM)

Comparison of the structural formulas of Mifepristone and UPA (see Table 4):

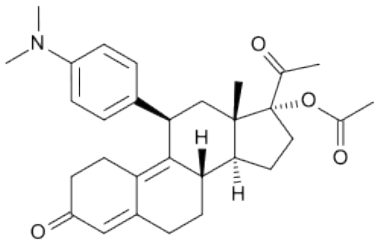	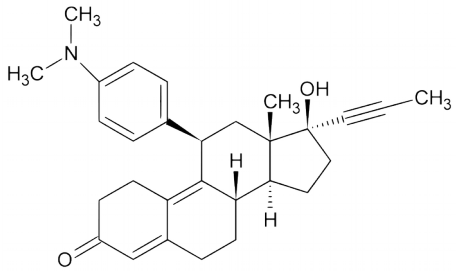
Ulipristal-Acetate = UPA[13] = SPRM 2. Generation = CDB-2914 = Anti-Progestin = post-coital pill	Mifepristone[14] – RU 486 = SPRM 1. Generation = Anti-Progestin = abortion pill

Table 4: Comparison of the structural formulas of Mifepristone and UPA

8 Cf. for example A. CORBIN 1998; W. RELLA 2008.

9 G. BENAGIANO/H. VON HERTZEN: Comments. Towards more effective emergency contraception? In: Lancet, 2010; 375, 527–528: "Levonorgestrel and mifepristone, in an in-vitro model, have different mechanisms of action, because **levonorgestrel has no effect on implantation** whereas **mifepristone can prevent it,** which **might also apply to ulipristal**." (Emphasis RE)

10 T. Rabe: www.endokrinologie.net/presse_130410.php (Translation: A.L.)

11 Information sur les produits pharmacéutiques en Suisse, mot clef NorLevo®Uno.

12 A.F. GLASIER ET AL. 2010.

13 Admission of UPA: 2009.

14 Admission of Mifepriston: 1988 in France; in the rest of Europe in the nineties.

Concerning the close relationship between UPA and Mifepristone there are several statements:

> *"Thus, UPA is similar to the compound Mifegyne® which is authorized for medical abortion."*[15]

> *"Morning-After Pill: New compound ellaOne® has got an effect similar to the abortion pill."*[16]

Regarding the structural formulas it is apparent how both compounds resemble. One can ask, why the older compound Mifepristone is not used as "Morning-After Pill". The following citation may give an answer:

> *"Mifepristone is widely used to terminate pregnancy and as such is commercially available in many countries. The negative abortion-related image of Mifepristone has clearly limited the involvement of major pharmaceutical companies in the development of Mifepristone as well as other SPRMs as contraceptive drugs."*[17]

For Mifepristone, in the three dimensional cell culture model a nidation inhibiting effect is clearly proved, but not for LNG[18]. The close relationship to Mifepristone leads to the extrapolation of that model to UPA:

> *"Ulipristal has similar biological effects to Mifepristone, the antiprogestin used in medical abortion and marketed for emergency contraception in China and Russia. When used correctly, Mifepristone is also an effective emergency contraceptive."*[19]

So Mifepristone is used as a MAP, not in the Western countries (because of its negative reputation as an abortion pill), only in China and Russia.

3 Controversy: Mode of action of UPA

The rape case in Cologne was a dramatic event for the question which modes of action the new MAPs have got relating to the MAP dramatically boosted the question about the mode of action of emergency contraception compounds. Until Up to now the normal common opinion was that those compounds also may result in early abortion were amongst others early abortifacients. Now Cardinal Meisner and the German Bishops Conference refer to information according to which asserts that there are new drugs which are only ovulation inhibitors. The evidence is clear that the LNG-MAP, which has been on the market for more than 13 years, has a nidation inhibiting effect although latterly only an ovulation inhibiting effect is propagated.

It is important to examine the mode of action of the less known new MAP, ellaOne® (on the market since 2009) which contains UPA, in order to clarify and allow a proper evaluation of the facts.

For that purpose the statements of the two expert organisations which advised Cardinal Meisner are presented in the introduction:

(1) ***"24th of January 2013 – The 'Morning-After Pill' is contraception, no abortion – press release by the BVF and the DGGEF Munich/Heidelberg. The modern `Morning-After Pill´ prevents or delays the ovulation.*** *When the* ***ovulation has already taken place****, the ovum has left the ovary and is in the tube or in the uterus****, the 'Morning-After Pill' neither inhibits the fertilization of that ovum nor the nidation in the uterus.*** *It does not cause an artificial menstruation, a so-called withdrawal bleeding, by which an embryo already nidated in the uterus would miscarry.*

> *This is valid for both drugs authorized in Germany as 'Morning-After Pill', LNG as well as UPA. Hence, both drugs do not interfere in the development of an already generated human being. They are to be considered* ***contraceptives and not abortifacients****. They are not comparable to drugs used to release the endometrium and for a medical abortion.*

> *The background: After the ovulation, an ovum can be fertilized within 12 up to max. 24 hours. Sperms on the other hand, can survive three to five days in the cervix, the uterus or the tube. Both available 'Morning-After Pills' prevent ovulation or delay it until the survival time of the sperms is exceeded. UPA has got a longer effectiveness than LNG and therefore offers a higher security to women. Inspite that LNG is authorized up to three days and UPA up to five days after an unsafe sexual intercourse, studies show that it is important to prescribe the drug as soon as possible."*[20]

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15 B. HINNEY 2010.

16 www.imabe.org/index.php?id=1366

17 N.N. SARKAR 2011: www.egms.de/static/en/journals/gms/2011-9/000139.shtml (GMS German Medical Science 2011, Vol. 9, ISSN 1612-3174)

18 P.G.L. LALITKUMAR ET AL. 2007.

19 G. BENAGIANO/H. VON HERTZEN 2010.

20 C. ALBRING/T. RABE 2013; (Translation A.L.). (Dr. med Christian Albring, president of the occupational union of gynecologists in Germany [BVF]; Prof. Dr. med. Thomas Rabe, president of the german society for gynecologicel endocrinology and reproduction medicine [DGGEF]).

(2) The joint statement (2011) given by DGGEF and BVF:

> ***"Ovulation inhibition:** The current data situation indicates that the clinical relevant mode of action is **only based on the inhibition of ovulation."***[21]

3.1 Mode of action of UPA – including pharmacodynamic considerations

As mentioned above, UPA is a SPRM, i.e. it means that it occupies selectively the progesterone receptors in the body of the woman and prevents the binding of the body's own progesterone to these receptors. Already attached progesterone is displaced. There is a ***"high-affinity binding to the human progesterone receptor. Main effect mechanism: Inhibition or delay of the ovulation."***[22]

Here, the inhibition of ovulation is indicated as ***main** effect mechanism* and **not** as ***only** effect mechanism!* So it is correct, when Wikipedia summerizes:

> *"Ulipristal is a SPRM: It prevents the binding of the body's own sexual hormone progesterone so that it cannot become effective. The ovulation is inhibited or delayed.* ***The formation of proteins necessary for the beginning and maintenance of a pregnancy is suppressed."***[23]

Here, there is an indication concerning ovulation inhibition and also concerning an influence on the existence of a pregnancy, consequently nidation inhibition. According to Brache et al.[24] ovulation is postponed or inhibited by use of UPA when LH increases, but only in 79 % of the cases; thus, there are 21 % "breakthrough ovulations"[25] where nidation inhibition could become effective.

In the **tube** – the smooth muscles and secretory cells of the tube[26] – there is **a high concentration of progesterone receptors (PR)**. According to Karbowski et al. the steroid receptors play an important role for the transport of the ovum in the tube[27].

But under influence of UPA these receptors are blocked, with a consequent dysregulation of tube motility and secretory function (desynchronization of these processes). Thereby not only the composition of the tube secretion is changed but the restraining effect of the natural progesterone on the tube muscles is neutralised, too. This blocking effect results in **a to fast transport of the embryo into the uterus where he finds an insufficiently prepared endometrium to nidate.** Because of the receptor blockage the lining of the endometrium is not developed**,** the nidation cannot take place and the embryo dies.

Plaintext, UPA as SPRM deprives the female internal genitalia of the progesterone effect, this means for the tubes and the endometrium: **By preventing the progesterone effect with UPA the embryo is deprived of livelihood – without progesterone respectively progesterone effect there is no nidation and no maintenance of a pregnancy!** These very important facts in the natural physiology are confirmed by HRA Pharma, the producer of PiDaNa and ellaOne®:

> *"Referring to the background of Ulipristal Acetate, Progesterone plays a pivotal role in reproduction in many species. It is involved in the control of ovulation, implantation, and maintenance of pregnancy."*[28]

3.2 Scientific literature on nidation inhibition

It is interesting to see that **several authors often** describe the nidation inhibiting effect **without naming it nidation inhibition.** They describe – besides an ovulation inhibition respectively postponement[29] – a delayed endome-

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21 T. Rabe: Work group "post-coital contraception" 2011.

22 D. Dörfler 2012.

23 http://de.wikipedia.org/wiki/Pille_danach (Translation A.L.) (Emphasis RE).

24 V. BRACHE ET AL. 2010.

25 In this paper the ovulations which take place despite the UPA effect are called "breakthrough ovulations", in analogy to the use of ovulation inhibitors.

26 F.A. LEIDENBERGER ET AL. 2009.

27 B. KARBOWSKI ET AL.: Licht- und Elektronenmikroskopie der Steroid-Rezeptoren in Tube und Uterus, 1993: „Our investigations show, on the light level as well as on the electron microscopy level, that the variations found in the expression of the steroid receptors must be understood as expression of a partly reversible cell damage, which coincides with a functional impairment during the transportation of the ovum. Our results indicate a participation of the steroids and their receptors in the complex and in detail still poorly understood regulation of the ovum transportation." (Translation A.L.)

28 Advisory committee for reproductive health drugs, 2010.

29 V. BRACHE ET AL. 2010; and: Ellaone® (UPA) : Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) *: "UPA is an orally effective SPRM with binding to human progesterone receptor. As effect mechanisms the inhibition or delay of the ovulation and an influence on the endometrium are cited. It is not possible to give a statement with regard to the safety if the drug is used during an existing pregnancy. So, before using it a pregnancy must be excluded."* (Translation A.L.)

trial maturation[30/31/32], a missing secretory transformation of the endometrium[33], a lower endometrium thickness[34] and the disturbance of the endometrial synchronisation[35] or other *"influence on the endometrium"*[36/37], among other statements they describe *a reduction of important molecular markers of implantation*[38].

The fact that nidation inhibition by UPA has frequently been described in scientific literature without naming it as such, suggests that there has been a linguistic cover-up. The processes described are all processes with nidation inhibiting or preventing effects we also know from Mifepristone as `Morning-After Pill´ and interceptive. So, **UPA must be called a partial interceptive, too!**

Few authors concretely talk about the nidation inhibition effect of UPA and say that it must be ethically evaluated in different manner[39/40], some of them even give more weight to that effect than to the ovulation inhibiting effect[41]. With that evaluation they coincide with former authors who wrote about nidation inhibition by interceptives[42]. It is also assumed that »**As *a nidation inhibitor Ulipristal has a stronger effect than Levonorgestrel.* *This could explain its longer effect.«***[43]

They also write that drugs which partially prevent the nidation might be inaccessible for women in many countries or not be accepted by them[44].

One author established the timeframe of UPA "up to 120 hours ***after possible fertilization"***[45]. So she clearly presumes a nidation inhibiting effect as main effect!

There is a very interesting essay about the nidation inhibiton effect of UPA, written by Miech with regard to the timeframe from ovulation until 24 hours after ovulation. He describes three nidation inhibition mechanisms:

"(1) failure of the decidua[46] to develop and become receptive to implantation of the blastocyst,

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30 G. BENAGIANO/H. VON HERTZEN 2010: "A delay in endometrium maturation was seen after ulipristal at 10, 50, and 100 mg. Furthermore, menstruation is delayed by 1–2 weeks in 30 % of the cases after 100 mg, 27 % after 50 mg, and 9 % after 10 mg doses. These results are similar to those described after mifepristone."

31 P. STRATTON ET AL. 2010: "With a single late-follicular dose, luteal phase endometrial maturation was delayed in 70 % of biopsy specimens at each dose of CDB-2914 (10, 50, and 100 mg) compared with 17% in the placebo group (25). A delay in ovulation and suppression of E2 levels was less frequently observed and was dose dependent. Similarly, 100 mg mifepristone given from days 10 to 17 delayed both ovulation and endometrial maturation (26)."

32 N.N. SARKAR 2011: "The SPRMs which are developed at the moment unfold their effect by inhibiting the ovulation and delaying the endometrial synchronisation. Low doses of progesterone antagonists delay the endometrial maturation without impairing the ovulation."

33 T. RABE ET AL., work group 2009: "The development of the secretory endometrium during the luteal phase is inhibited, independent from the dose. The threshold value of the morphologic change of the endometrium seems to be lower than the value for the inhibition of the ovulation."

34 D. DÖRLER 2012.

35 N.N. SARKAR 2011: "Currently developed SPRMs are derivatives of steroid compounds with mild or potent antiprogestogen activity. SPRMs may exert a contraceptive activity by different mechanisms such as inhibition of ovulation and disruption of endometrial synchronization." //

"In the field of contraception, SPRMs have shown contraceptive potential by suppressing follicular development, delaying surge of luteinizing hormone (LH), retarding endometrial maturation and promoting endometrial bleeding. Mifepristone, a best known SPRM, showed a strong intercepting action." Cf. also : P. STRATTON ET AL. 2010.

36 Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ)

37 B. HINNEY 2010:"As effect mechanism they indicate the inhibition or delay of the ovulation and an influence on the endometrium."

38 P. STRATTON et al. 2010: "In contrast to histologic dating, molecular markers of implantation and P action and endometrial thickness were reduced by CDB-2914 in a dose-dependent fashion."

39 G. BENAGIANO/H. VON HERTZEN 2010. http://www.faz.net/aktuell/wissen/medizin/pille-danach-arzneimittelstreit-um-die-notfallverhuetung-1983357.html. "Both active substances inhibit the ovulation and impair the maturation of the endometrium. The new active substance suppresses the effect of the progesterone, the older one the release of the luteinising hormone. But Benagiano and von Hertzen presume the UPA as nidation inhibitor which has got a greater effect than LNG, what could also explain the longer effect. But as a nidation inhibitor, the new 'Morning-After Pill' should be evaluated in ethically different manner, when compared to a product which especially takes influence in the ovulation."

40 G. PIAGGIO/H. VON HERTZEN 2010, op.cit.: "If levonorgestrel is effective up to and including the fourth day, it would be ill-advised to replace its use, for women presenting before the fifth day, with a costly progestogen-receptor modulator. Such drugs, which may act in part through prevention of implantation, might not be accessible or acceptable to women in many countries."

41 Stratton, P. et al. 2010: op.cit.

42 For example H.D. TAUBERT/H. KUHL, 1995; and very clearly A. TEICHMANN, 1991, p. 165: "Ethical concerns against the use of that form of in general so-called **post-coital interception** measures are justified, for they do not make a principle difference between an abortion and the nidation inhibition which mostly is the base of these methods."

43 BENAGIANO, G./H. VON HERTZEN, 2010; (Emphasis RE).

44 G. PIAGGIO/H. VON HERTZEN, 2010.

45 B. SPANIER 2010.

46 'Decidua' means the changing endometrium. It is formed under the influence of the luteal hormone and gives for example a nutrition basis for the nidating embryo, by storage of nutritions (glycogens, lipids).

(2) failure of secretions of uterine glands in the decidua to maintain an implanted embryo, and

(3) the return of spontaneous uterine contractions."[47]

Moreover, in his opinion, there are possibly additional immunological rejection reactions of the trophoblast cells of the blastocyst which occur during the first 5–10 days after fertilization. It seems that to date there very little attention has been given to the immunopharmacology of Ulipristal.

4 Process of effect mechanism of UPA with regard to ovulation and nidation inhibition

4.1 Pharmacodynamics

Principally: **Occupation of PR receptors by UPA**, antagonistic and partially agonistic effect:

1) Ovary: **Ovulation inhibition** (OH) respectively **postponement,** agonistic effect on the progesterone receptors. By negative backcoupling the release of LH is reduced and the LH peak prevented (hypothalamus pituitary axis). OH eventually also by direct effect on the ovary[48].
2) Tube: Blocking of PR receptors in the tube in the consequence dysregulation of tube motility and secretory function (desynchronisation of these processes): among other things **too quick transportation of embryo** into the uterus and **change of composition of tube secretions.**
3) Endometrium still not ready for nidation, because **endometrial synchronisation is delayed or prevented by blocking the PR receptors (missing phase concordance)**: The **maturation,** that is the **secretory transformation of the endometrium is prevented.**
4) **Nidation inhibition respectively prevention**.

Normally, these statements should not give reason to doubts concerning the nidation inhibiting effect of UPA because they are part of the basic knowledge of every physician and pharmacologist – it is propaedeutics. The German pharmacology course book "Mutschler Arzneimittelwirkungen", the most famous standard book for more than 40 years now, says that the knowledge about nidation inhibition (also as a result of normal ovulation inhibitors/contraceptives) is "basic knowledge"[49].

But there are also critical voices concerning the ovulation inhibiting effect of SPRMs, especially with regard to their use as contraceptives:

"Progesterone antagonists can block the follicle development, the LH secretion and the maturation of the endometrium; these facts give the substances the potential of oestrogen-free contraceptives. But nevertheless ***progesterone antagonists*** *are only conditionally useful as contraceptives because* ***they possibly have got a teratogenic and/or embryotoxic effect.*** *SPRMs are no effective LH secretion blockers and that is why they are not eligible as contraceptives."*[50]

Reimann also talks about a potential embryotoxic effect from UPA:

"The effects of using Ulipristal with nevertheless occurring pregnancy are not safe enough, so a possible embryotoxic effect couuld not be excluded."[51]

A similar statement is given by the AkdÄ. But H. Kaulen goes further:

»In this respect we know little about this active compound [i.e. UPA] It kills growing embryos in animal experiments.«[52]

The "arznei-telegramm" advises a pregnancy test before using UPA even on the part of the authors of the »arznei-telegramm«, a pharmaceutical industry independent publication, mention the potential nidation inhibiting effect of UPA!

Reimann says concerning the post-conceptual effect:

"Based on a present letter of HRA Pharma and the communication to expert circles (43) and patients (44) we can presume that the pharmaceutical industry wants to position ellaone® as 'modern Morning After Pill' and

47 R.P. MIECH 2011.
48 S. NALLASAMY ET AL. 2013.
49 E. MUTSCHLER ET AL. 2005, p. 218.
50 www.pharmawiki.ch/wik/index.php?wiki=Progesteronrezeptor_Liganden
51 A.L.G. REIMANN 2013.
52 H. KAULEN 2010.

thus as a 'third generation product'. It is still open for discussion if that positioning on the German market would be enhanced or weakened by an interest-based omission of possible post-conceptual effects."[53]

Additionally, the following statement must be taken into consideration, too:

"For under age women the safety and efficiency of the new active substance has still not been proven because this age did not take part (with very few exceptions) in the clinical studies."[54]

In the public nobody mentions this fact, but ellaOne® is also given to women under age! Furthermore, it is remarkable that to date, despite the post-coital contraception, no reduction of abortions could be achieved[55]. According to the DGGG, Germany is, to some extent, an exception: between 2002 and 2001 they reported that the number of abortions has decreased by 16.5 %, and in the group of minors even by 45 %[56].

4.2 Which are the arguments for a nidation inhibiting effect of UPA?

- The high safety inspite of "breakthrough ovulations";
- This is especially significant in the case of "breakthrough ovulations" on the level of increasing LH, LH peak and also decreasing LH where no 100 % OI is granted and, in increasing manner, only nidation inhibition can be effective.
- Longer efficiency than LNG: according to scientific literature, LNG has no longer an ovulation inhibiting respectively postponing effect at increase of LH;
- "Safety" consistent up to 5 days (also at LH peak) in contrast to LNG (fast decrease of effect);
- UPA = SPRM, takes the progesterone effect from the internal genital: **With no progesterone respectively no progesterone effect no nidation;**
- There are many indications for a nidation inhibiting activity of UPA (apart from the ovulation inhibition) in pharmacokinetics and pharmacodynamics.

Additionally, there are are more statements that underline this, as for example those by Reimann[57]:

"Simultaneously it is underlined that ***progesterone is necessary for a successful nidation."***

"... other authors who at least take into consideration an ***effect on the endometrium*** *and an immunmodulatory effect on the interaction between zygote and endometrium and thus* ***as a result a nidation inhibition as further mechanism of action after post-ovulatory use.*** Another consideration is the pharmacological relationship as an agonist / antagonist (`modulator´) with the progesterone antagonist Mifepristone. ***An effect on the endometrial physiology could also be shown with therapeutically used doses.*** The ***meta-analysis*** of both approved studies mentioned above show a possible ***post ovulatory mechanism***. The effects of Ulipristal use in case of an emerging pregnancy are not sufficiently secured, a possible embryotoxic effect cannot be excluded."

Watson-Pharma, the producer and seller of ellaOne® in the USA, also confirms nidation inhibition mechanisms in the endometrial region[58].

HRA-Pharma mentions that UPA in animal experiments resulted in a "preimplantation loss". The numbers stated there prove a significant embryo loss after using UPA[59]. Additionally, changes in the endometrial region are also described[60].

4.3 Effect on the ovulation under consideration of the sperm survival time

Figure 1 (effect of a 'Morning After Pill' containing UPA on the ovulation) follows the representation in "Notfallkontrazeption – ein Update" from 4th of February, 2013[61].

53 A.L.G. REIMANN 2013.
54 www.faz.net/aktuell/wissen/medizin/pille-danach-arzneimittelstreit-um-dienotfallverhuetung-1983357.html
55 E.G. RAYMOND ET AL. 2007.
56 DGGG 2012, cited in: Kommentar der pro familia, Bundesverband.
57 A.L.G. REIMANN 2013.
58 WATSON-PHARMA, USA 2011.
59 Advisory committee for reproductive health drugs, 2010.
60 Ibid.
61 T. RABE/C. ALBRING ET AL. 2013, p. 3

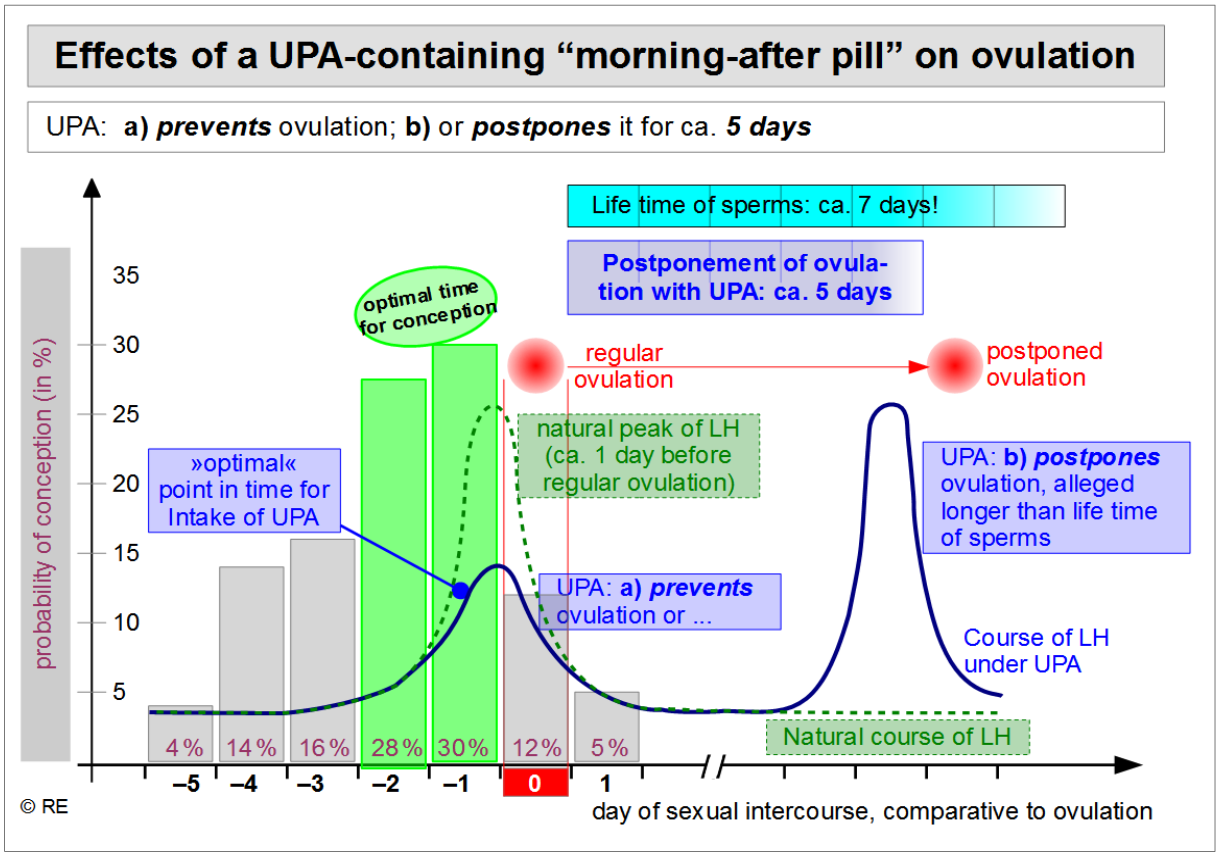

Figure 1: Effect on the ovulation of a 'Morning-After Pill' containing UPA.

The authors explain it in the following manner:

> *"Figure 2. In case of use shortly before ovulation (with increasing LH level) only UPA is able to delay the ovulation by reducing the LH level. In the two days before ovulation when the conception risk is at highest level, with LNG the ovulation can no longer be avoided."*[62]

4.3.1 Postponement of the ovulation

According to Brache et al. the postponement of ovulation is 5 days, the survival and fertilization ability of the sperms is, according to DGGEF, BVF and Rabe/Albring only 3-5 days[63]/[64]. According to the rules of natural conception regulation (NER), spermatozoa are able to survive and to fertilize up to 6 days[65].

H. Kuhl, and C. Jung-Hoffmann, specify a significantly longer survival period:

> *„The fertile phase of a cycle starts 6 days before ovulation and ends on the day after ovulation. The relatively high probability of a fertilization before the ovulation is based on the long survival time of the sperms in the cervix, which is up to 7 days."*[66].

4.3.2 What are the consequences?

1) According to that, after the ovulation postponement of 5 days there are still functional spermatozoa in the genital tract of the woman, and evidently, after 3 days, too.
2) These spermatozoa are still able to fertilize the ovum after 5 days postponement of ovulation.

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62 Ibid.

63 Ibid.: "But sperms can, under optimized conditions, survive three up to five days in the cervix, the uterus or the tube."

64 Ibid.: "The delayed ovulation occurs about five days later. That is enough to close the fertile timeframe, because the sperms have got a survival time of 3-5 days in the female genital tract (according to Behre and Nieschlag 2000)."

65 J. RÖTZER/E. RÖTZER 2010, p. 27: "Fertilization ability of spermatozoa. How long spermatozoa are able to fertilize in the liquefied cervical mucus, depends on the duration of the cervix mucus secretion and the quality of the cervix mucus. The often heard statement that the fertilization ability of spermatozoa in the body of the woman endures about three days is, in that general manner, not correct. Depending on the woman, this period can be shorter (sometimes only a few hours) or longer (perhaps up to 6 days). Such a long period of fertilization ability rarely occurs. Besides, the woman is able to recognize that possibility by existence of a longer phase of cervical mucus in good quality."

66 H. KUHL/C. JUNG-HOFFMANN 1999, p. 18. Cf. also: A.J. WILCOX ET AL. 1995.

3) With a half-life period of 32,4 ± 6,3 hours (after single dose of 30 mg)[67], UPA is still effective in the sense of nidation inhibition after 5 days.
4) This also means that after an ovulation delay of five days there are still tube and endometrial changes in the sense of nidation inhibition because the progesterone receptors in tube and endometrium are still occupied by UPA.
5) As UPA shows potential embryo toxicity, there is in addition a danger of damaging the embryo if the nidation inhibition has no effect.

The indications of BVF und DGGEF show consequently a possible misinterpretation or misinformation with serious consequences! The above mentioned statement of Rabe and Albring is therefore misleading:

»The postponed ovulation occurs five days later. This is sufficient to close the fertile window given the maximal survival time of sperms in the woman's genital tract (i.e. uterus and tubes) of 3–5 days.«

In many cases the fertile window is not closed because sperms can survive up to seven days.

Moreover, the optimal time for the UPA uptake at a rise of LH is not linked to a 100 % ovulation inhibition, but only a 79 %, thus with a 21 % »breakthrough ovulation rate« (Brache et al., see also Figure Ovulation/Nidation inhibition with UPA) and thus accordingly, a possibility for fertilization. This is not mentioned at all but only faded-out. Not even theat at a follicle size of >18 mm a ovulation inhibition takes place in only about 60 % of cases (Brache et al.). On the contrary, it is widely propagated – with respect to LNG –, that even at a rise of LH there is an ovulation inhibition. Indeed, ovulation is inhibited, but not to 100 %. Thus, this is merely half of the truth.

If UPA is given at the LH peak (for example in case of rape or after unprotected sexual intercourse at any time of the cycle), the ovulation can take place within 72 h (32.3 %; = 1,54 ± 0.52 d), for the woman at a time period with the highest probability for fertilization! Hence, fertilization is very likely to happen! As a consequence, there is a high probability for nidation inhibition!!

This can certainly occur on the part of the reliability of UPA, given that as a rule through the action of nidation inhibition, there is even a warranty that the pregnancy is not carried out. The whole is sold as an 'exclusive ovulation inhibition', though not by Brache et al.

4.4 Ovulation inhibition- / Nidation inhibition under UPA:

Figure on the basis of Brache et al., 2010[68], und Stratton et al., 2010[69]
[see following page]

4.4.1 Ovulation postponement in the course of the cycle

- With UPA before LH peak significant longer = 6,85 ±1,42 d
- With UPA at LH peak = 5–10 d in 67.6 % of cases
- But: With UPA at LH peak = 1,54 ±0,52 d ovulation in 32.2 %

Ovulation within 72 h, similar to placebo[70]. Hence, fertilization is possible because sperms are still able to fertilize ***(according to H. KUHL/C. JUNG-HOFFMANN up to 7 days and not up to 3–5 days, as postulated by Rabe und Albring)!! From that moment on, the nidation inhibition mode of action is active!***

Administration of 30 mg UPA[71]:
UPA 1–5 refer to the numbers in purple in the Figure above

UPA 1: before rise of LH = 100 % ovulation inhibition (8 cases!)
The significance of this data is critical due to the small number of cases (only 8 cases)

UPA 2: at follicle size >18 mm = 60 % ovulation inhibition

UPA 3: at increase of LH, but before LH peak = 78.6 % ovulation inhibition

UPA 4: at LH peak: 68 % ovulation postponement/OI, but in 32.2 % of cases ovulation **(!) within 72 h**

UPA 5: after LH peak: 8.3 % ovulation inhibition

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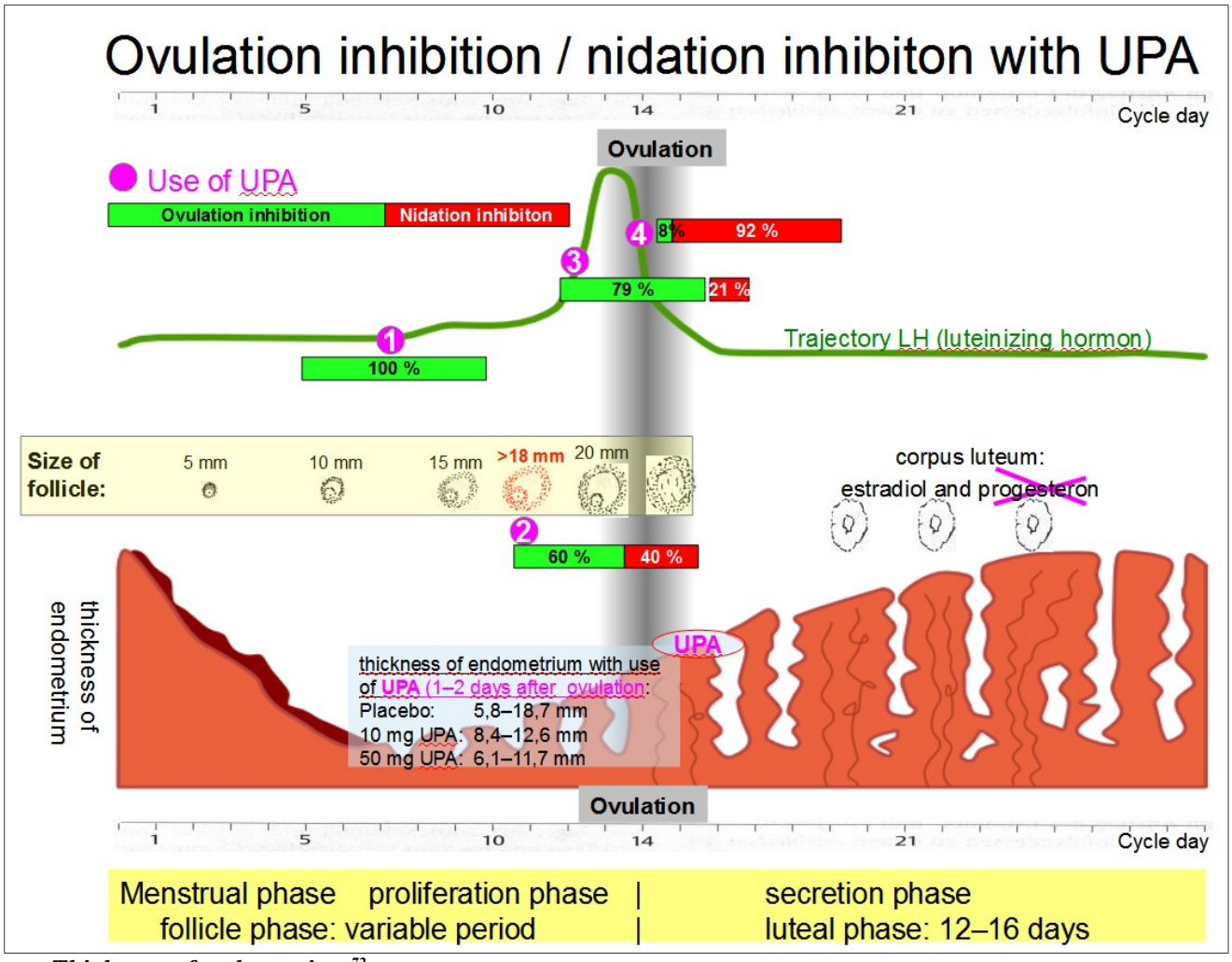
67 "The terminal half-life period of UPA in the plasma after single dose of 30 mg was 32,4 +/- 6,3 hours." www.pharmazie.com/graphic/A/51/0-91551.pdf
68 V. BRACHE ET AL. 2010.
69 P. STRATTON ET AL. 2010.
70 V. BRACHE ET AL. 2010.
71 Ibid.



Thickness of endometrium[72]

It is very restricted, even with a low UPA dosis (10 mg), see graphic.

Thus there is a high percentage of 'breakthrough ovulations' from the rise of LH on with a chance for fertilization!

Nevertheless, the high contraceptive effectiveness is mantained! This can only be achieved by an additional mechanism, namely nidation inhibition!

The great weak point of Brache et al. is that they always refer to ovulation inhibition with UPA, but the high percentage of breakthrough ovulations is not commented. *Though the authors do not deny them, but they only refer partly to the* ***possibility of fertilization*** *and there is no mention of what happens to the fertilized egg cells, namely nidation inhibition (except for 3 of 20 'luteinized unruptured follicles' = LUF, i.e. unruptured follicles turned to corpus luteum)*[73].

The statement of the authors comprises that UPA causes a significant ovulation postponement respectively inhibition even if it is given at LH increase. Based on LNG this might be correct, because at that moment it does not cause an OI any longer![74/75]

Nevertheless, the nearly exclusive propagation of ovulation inhibition with UPA still at an increase of LH, where LNG no longer causes an ovulation inhibition, is not justified, because it is not the whole truth. Ovulation is inhibited respectively postponed, but only in 79 %, in 21 % of the cases there is a breakthrough ovulation. That is a point of maximum fertilization probability, besides, the ability of spermatozoa to survive and to fertilize is also significantly higher. In practice, this is of great importance!

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72 Ibid.

73 Ibid.

74 N.N. SARKAR 2011: "Thus, ulipristal acetate could delay follicular rupture if taken immediately before ovulation. This SPRM as EC could perhaps prevent pregnancy when given in advanced follicular phase at the onset of LH surge, a time when LNG EC is no longer effective in inhibiting ovulation [29]." (Emphasis RE)

75 T. RABE (DGGEF e.V.)/C. ALBRING, (BVF E.V.) Notfallkontrazeption – ein Update, vom 4.2.2013: "Abb. 2 Bei Gabe kurz vor der Ovulation (im ansteigenden LH-Spiegel) kann nur Ulipristalacetat durch Senken des LH-Spiegels den Eisprung noch verzögern. **An den beiden Tagen vor der Ovulation, wenn das Konzeptionsrisiko am größten ist, kann der Eisprung mit Levonorgestrel nicht mehr verhindert werden.**" (Emphasis RE)

The same can be observed for the ovulation inhibition of 60 % at a follicle size >18 mm. There are no comments on the 40 % breakthrough ovulations. It cannot be argued that the exclusive mode of action is ovulation inhibition.

Obviously, it is not appropriate to indicate the percentage of ovulation inhibition and to omit to mention the breakthrough ovulations with their possible consequences including nidation inhibition and to pretend that they are practically non existent. At the same time they they refer to the ovulation inhibition as the exclusive mode of action.

This procedure is not justifiably selective and as such scientifically unacceptable.

One gets the impression, that the reader of the statements of Rabe et al. und Albring et al. has been deliberately deceived! He should get used to the thought that the main effect is ovulation inhibition, and possibly the only effect. The reader is deliberately kept off the ethical problem of the destruction of life by nidation inhibition. Perhaps this happened to Cardinal Meisner on the expert advice!

It is clear after the presentation of the weak points that it is a deception to make believe that the high effectiveness of UPA is exclusively due to ovulation inhibition.

4.5 Establishment of a time frame for a risk-free use of UPA

Especially in the case of rape the question arises if and when UPA can be given without the risk of nidation inhibition. We would not have this problem if Cardinal Meisner had not been advised in the sense that the modern 'Morning-After Pill' has only ovulation inhibiting effect. Given the case, such a pill could be given without any hesitation and at any time in the cycle, because there would be no risk of nidation inhibition. Now we have seen that ellaOne® shows an ovulation and a nidation inhibiting effect. As a consequence, we need to determine a time frame in the cycle where only ovulation inhibition could occur. This would require a careful examination of the evidence.

4.5.1 What are the necessary requirements?

- *Knowledge about the cycle process: at least evaluation of the cervical mucus to restrict the fertile phase;*
- *Vaginal ultrasound to determine the follicle size or an eventual corpus luteum and the endometrial thickness (but here there is a relatively high range);*
- *LH in urine quick test (not yet possible to test in the blood);*
- *Progesterone quick test* (already in use in veterinary medicine to establish the ideal time for mating; the transfer of this method to humans is doubtful[76])

4.5.2 Questions and concerns from the woman's point of view

- How many women go to the police or to a physician immediately after a rape? Very often a lot of time is lost!
- Which woman knows the days until ovulation?
- How many women know their cycle (cervical mucus, basal temperature curve). Only the assessment of the cervical mucus would be important!
- It is not adequate to presume a schematic cycle, for example 28 days and not even ovulation on the 14th day.
- It is the more important to have an intensive anamnesis!
- Which woman would accept a vaginal ultrasound after a rape?
- Quick LH test = serial test, it has to be done at least twice with an interval of several hours = it needs time!
- Progesterone quick test: see above.

4.5.3 The cycle control in practice?

We presume:

- A vaginal ultrasound would be possible, with a small follicle (upper limit: 14 mm diameter[77])
- The LH test would correspond to several pre-ovulation days
- The Progesterone quick test would clearly show that ovulation has taken place, thus the' `Morning-After Pill' as an ovulation inhibitor would not be necessary.
- Observed "Signs of fertility" before the rape.

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76 www.vetpharm.uzh.ch/reloader.htm?tpp/00000000/V0064-XX.htm?inhalt_c.htm

77 Because in the study of Brache et al. there was an ovulation at a proband after follicle size of <18 mm. The proband was excluded from the study. This example shows that the processes of fertilization don't follow a fix scheme and with regard to the risk of nidation inhibition a very great security distance must be kept.

This problem was presented for examination to **experts from INER (Institute for natural conception regulation**, **Prof. Dr. med. Rötzer**). Due to their holistic approach they can evaluate the facts in objective manner.

The **Episcopal Vicar for Marriage, Family and Life, Dr. Helmut Prader (St. Pölten, Austria)**, besides a respected expert concerning natural conception regulation, has intensively examined the question as he already did with the LNG pill. These are the conclusions of the examination:

"In summary, in most of the cycles there is one up to three days where – after a rape – the use of UPA would result in an ovulation inhibiting or postponing effect. In practice it is not applicable because even women who know their cycle and keep records do not know how that traumatic event will affect the cycle. Besides, it is uncertain if a woman would immediately consult a doctor or the police. From experience we know that it takes several days until she does. Therefore, it will hardly be the case, following a responsible handling of the situation, that the administration of the pill would be acceptable. This due to the impossibility to ensure the exclusive ovulation inhibition or postponement. In the second part of the cycle and during the first days of the cycle the intake of the pill is unnecessary because a pregnancy can be excluded (second part) or the probability is very low (0,2 % during the first 6 days).

Four days before ovulation and three days after ovulation the pills cannot be taken because it also has a nidation inhibiting effect.

In theory there are at most 3 days for a legitimate use of the pill. But the premises are so substantial that these few days can only be determined afterwards, considering all the facts presented above."

4.5.4 Practicability

We can see that in theory there are up to 3 days for a reasonably risk-free use of UPA where a nidation inhibition is not to be expected.

In practice, these 3 days cannot be delimited properly because it is hardly possible to determine whether the nidation inhibiting effect is in place. This ia indicated in the study of Brache et al. among others the exclusion of a proband who had an ovulation at a follicle size of < 18 mm. In case of a study such exclusions are feasible but in real life not!

The vaginal ultrasound can determine the size of the follicle but cannot say anything about certain symptoms as for example the quality of the cervical mucus which is essential for fertility evaluation. Similarly, the LH test without considering the quality of the cervical mucus is insufficient.

How can an emergency doctor recognize a correct and responsible timing with regard to these circumstances? He will give UPA 'just for safety reasons', because according to Brache et al. In 60 % of the cases the ovulation (follicle size >18 mm) would be delayed or prevented! This relatively high probability could move the physician to administer UPA. The cases of 40 % nidation inhibition after a breakthrough ovulation are easily overlooked!

5 Discussion

5.1 Contradicting statements referring to the mode of action of UPS – language use

The cited statements of Rabe et al. and of BVF and DGGEF decidedly emphasize the exclusive ovulation inhibition of UPA (and also LNG).

Under the title "Mode of action of UPA" numerous statements from current scientific literature have proven that besides the ovulation inhibiting there is also a nidation inhibiting effect.

Further revision of references revealed following statements which on the one hand elucidate the UPA mode of action and on the other hand make us take notice of contradictions.

To start with the first reference of Rabe et al. 2009 in an article presented for the new approval of Ulipristal Acetate:

»The development of the secretory endometrium during the luteal phase is inhibited, independently from the dose. *The threshold value for the morphologic change of the endometrium seems to be lower than the value for the inhibition of ovulation.«*[84]

The mechanisms of action described by Rabe et al. are clearly of nidation inhibition!

In a second reference Rabe et al. **2011** depict clearly the mechanisms of nidation inhibition but weaken the significance by concluding that the contraceptive effect on the endometrium is not proven:

"Luteal phase and endometrium

In a placebo controlled comparative study the effect of 10, 50 and 100 mg UPA in the early luteal phase was investigated. There was a ***significant delay of endometrial maturation.*** *This effect was especially significant on* ***endometrial biopsies 4-6 days after ovulation after administration*** *of* ***higher doses of 50 and 100 mg (61).*** *The*

> ***treatment with UPA** resulted in a **significant decrease of endometrial thickness**, **dependent on the dose** and in an increase of progesterone receptors in the endometrium. But a **contraceptive effect on the endometrium is not proven for the current doses of emergency contraception with UPA (30 mg).”***[78]

The denial of a “contraceptive effect on the endometrium” in the interpretations by Rabe et al. is striking, because the histological finding showed a ***“significant delay of the endometrial maturation”***, which underlines with no doubt the nidation inhibition. The authors refer to the dependence of the dose (30 mg) by stating: ***»However, a contraceptive effect on the endometrium is not proven for the current dosages of emergency contraception with UPA (30 mg).«***

Though they have not tested UPA 30 mg but only 10, 50 and 100 mg. It is very strange that the dose of **UPA 30 mg** is mentioned explicitly in this context. Did they know the research results of other authors that they left UPA 30 mg out of the test? Namely Stratton et al. 2010 had already shown a **delayed endometrial maturation with one and only UPA dose of 10 mg. According to Stratton et al.** the **ovulation postponement depended on the dose.** These authors consider that these endometrial effects, including a reduced endometrial thickness, are the reason for the UPA effectiveness as an emergency contraceptive, even in absence of effects on the ovary and the menstruation cycle[79].

The University Hospital of Gynaecology of Vienna takes the same view concerning the reduced endometrial thickness.[80]

Stratton et al. did not confirm the exclusive ovulation inhibiting effect of UPA postulated by Rabe et al. In 2009, Rabe et al. presented a completely different statement when describing the significant nidation inhibiting mode of action of UPA: ***The development of the secretory endometrium is inhibited, independently from the dose*[81]*.*** Here, there is no statement about a not proven contraceptive effect; quite the contrary: ***They mention an inhibition of the development of the secretory endometrium independently from the dose”. This is another contradiction in a series of contradictions!***

In other words, the secretory transformation is even inhibited with a lower dose of UPA, thus including 30 mg UPA in ellaOne®. Besides, Rabe et al. indicate that the ***“threshold value for the morphologic change of the endometrium […] is lower than the value for the inhibition of the ovulation”*[82]*.*** That is the clearest definition of a nidation inhibiting effect in comparison to the ovulation inhibition.

Stratton et al. confirmed:

> ***“Thus, the threshold for changes in the endometrial morphology was lower compared to the changes in folliculogenesis.”***[83]

It is interesting that the statements given by Rabe et al. 2009 and by Stratton et al. 2010 practically conform to each other and lead to the assumption that the ovulation inhibition of UPA is subordinated to the nidation inhibition!

This corresponds to the statement of Narendra Nath Sarkar 2011:

> *“Currently developed SPRMs are derivatives of steroid compounds with mild or potent antiprogestogen activity. SPRMs **may exert a contraceptive activity by different mechanisms such as inhibition of ovulation and disruption of endometrial synchronization.”***[84]

Hence, there is no doubt concerning the nidation inhibiting mode of action of UPA – all the more at a dose of 30 mg contained in ellaOne®.

In a third reference 2012, there is another striking contradiction: **On 1st of February 2012, the BVF and the DGGG communicated on the website “Frauenärzte im Netz”:**

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78 T. Rabe et al. 2011.

79 P. Stratton et al. 2010: “In summary, decreased endometrial thickness and decreased L-selecting ligands expression may be the earliest features of the antiprogestational effect of CDB-2914 in the luteal phase, heralding other endometrial changes. In our studies, endometrial maturation appeared to be more vulnerable to a small, single dose given in the follicular phase than with a single dose given in either early luteal or midluteal phase. Whether this is a direct endometrial effect or a result of an ovarian effect is not known. Taken together, these endometrial effects in the absence of ovarian and menstrual cycle effects suggest mechanisms by which CDB-2914 might be effective as an emergency contraceptive (28).”

“With a single late-follicular dose, luteal phase endometrial maturation was delayed in 70% of biopsy specimens at each dose of CDB- 2914 (10, 50, and 100 mg) compared with 17% in the placebo group.”

“Thus, the threshold for altering endometrial morphology was lower than that for altering folliculogenesis, ...“

80 D. Dörfler 2012.

81 T. Rabe et al. 2009.

82 Ibid.

83 P. Stratton et al. 2010.

84 N.N. Sarkar 2011.

> ***"The 'Morning-After Pill' prevents or delays the ovulation so that no fertilization can take place. If a fertilization has already taken place, it prevents the nidation in the uterus."***[85]

Herein both associations confirm again plainly the nidation inhibiting effect of the Morning-After Pill. But that was not all, in a fourth reference **2013**, there is again an enhanced pleading for the exclusive ovulation inhibiting effect and against a possible postovulatory mode of action of UPA: *"neither the fertilization of that ovum nor the nidation in the uterus" is prevented.* Indeed, the fertilization is not prevented after an ovulation, it takes place. The progesterone receptors in the cervix are also occupied and blocked by UPA preventing the thickening effect of progesterone on the cervical mucus. Hence, the sperms can get into the uterus and the tubes and fertilize an eventually present ovum even more effortlessly.

However, this work presents numerous references from different studies which confirm that the nidation of the fertilized ovum in the endometrium is definitely prevented. This is corroborated by the high efficacy of UPA, which can harldy be ensured by the partial effect of ovulation inhibition.

The effect of blocking the progesterone receptors in the tube and in the endometrium has already been mentioned above. In addition, it must be noted that with UPA uterus contractions occur more often[86] (Miech, Fn 49). This because of the lack of the restraining effect of the progesterone on the uterus muscles, which would have another negative effect on a possible pregnancy.

Bernward Büchner, a former judge of Freiburg (D) and since 1985 chairman of the Pro-life Lawyers Association in Cologne alerted about the contradiction of Rabe on February 2, 2013 during a heated discussion over the Morning-After Pill and gave following verdict on him:

> *"What could have contributed to this* ***Copernican revolution?*** *There are no publications which undoubtedly prove that LNG and UPA have exclusively got an ovulation influencing effect, but there are publications that question more or less strongly a further reaching effect. Do we have to believe that purely scientific findings are decisive here?"*

Another of Büchner's interventions is noteworthy:

> *"Professor Thomas* ***Rabe is*** *as the president of DGGEF a rewarded lecturer and as* ***a member of industries in connection with several pharmaceutical industries, among others with HRA Pharma****, the pharmaceutical enterprise respectively the manufacturer of the compounds PiDaNa und ellaOne."*[87]

5.2 What do the pharmaceutical enterprises say?

The description of the UPA effects by Watson-Pharma, the licensed enterprise for selling ella in the USA (ellaOne® in Europe):

> "*How does* ***ella*** *work?*
> ***ella*** *is thought to work for emergency contraception primarily by stopping or delaying the release of an egg from the ovary. It is possible that* ***ella*** *may also work by preventing attachment (implantation) to the uterus."*
>
> *"Mechanism of Action ...*
> ***ella*** *postpones the follicular rupture. The likely primary mechanism of action of Ulipristal Acetate for emergency contraception is therefore inhibition or delay of ovulation; however, alterations to the endometrium that may affect implantation may also contribute to efficacy."*[88]

As mentioned above, HRA-Pharma also confirms a significant "preimplantation loss" of embryos in animal experiments[89].

The nidation inhibiting effect of UPA cannot be expressed more clearly, especially by sources who should know and who would never admit this effect if it would not exist. This should even dispel the very last doubt!

It is surprising that neither Rabe nor Albring refer to these statements of the producers and sellers of UPA, HRA-Pharma and Watson-Pharma!

5.3 Abortions as early as possible?

The purpose of the combined effects of UPA – inhibition of the ovulation and **nidation inhibition**– also corresponds with a statement of Albring from 1998:

> *"Let abortions take place as early as possible to avoid getting into conflict by killing a born-alive child or killing a child before birth."*[90]

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85 B. Büchner 2013 cites that statement.
86 R.P. Miech 2011.
87 B. Büchner 2013.
88 Watson-Pharma, USA 2011.
89 Advisory committee for reproductive health drugs, 2010.
90 C. Albring 1998.

Indeed, it is hardly possible to destroy a young embryo earlier than with UPA! That objective seems to be achieved with the development of the SPRM Ulipristal Acetate.

In fact, this has already been the case with the market launch of the abortion pill RU 486 (Mifepristone) at the end of the eighties. Apart from the function as an abortion pill (up to the 49th day [after last menstruation]) it is also used as a 'Morning-After Pill'[91] - though, as already mentioned, not in the West but in China and Russia[92]. The negative image of RU 486 as an abortion pill prevented the major pharmaceutical companies from developing it to a 'Morning-After Pill', as already referred to above.[93]

Hence, research turned towards chemically related compounds, especially SPRMs, among which UPA was the most promising. Finally, in 2009, after 10 years of development, ellaOne® was launched on the market[94]. The great similarity between UPA and Mifepristone has already been discussed[95].

With regard to the close relationship between both substances it should be allowed to deduce the reverse – that UPA, of course in higher doses, also might be a suitable abortion pill.

This possibility is also considered by Keenan[96] who defined – because of the structural similarity of UPA and Mifepristone – a ***"contragestive versus a contraceptive"*** active post fertilization mechanism. He remarks:

> *"Ulipristal Acetate administration is contraindicated in a known or suspected pregnancy; however, it* ***could quite possibly be used as an effective abortifacient. Health-care providers should inform patients of the possibility of both mechanisms of action with use of this drug."***[97]

IMABE also confirms: *"Compared to Vikela ellaOne outweighs the fact that even a nidated embryo could be aborted (rejection due to endometrium damage)."*[98]

This effect concerns on the one hand the too fast transport of the embryo in the tube and on the other hand the endometrium which is not prepared for nidation. The reason is a *missing phase concordance between tube and endometrium respectively a disturbed synchronization!*

Thus the expressed objective of Albring would effectively be achieved: ***"Let abortions take place as early as possible"***, in China and Russia with Mifepriston and in the West with UPA, so to speak, globally.

5.4 More successful marketing by means of language manipulation

The **nidation inhibiting** effect was a problem for the marketing of UPA (see the mentioned problems with Mifepristone). In view of the bad reputation in the West of Mifepristone as an abortion pill, it was not likely that it could be introduced as the Morning-After Pill. This bad image had to be avoided for , UPA. Therefore, it had to be marketed speckless, i.e. as an exclusively ovulation inhibitor. There was too much at stake.

Reimann describes this very frankly:

> *"As a great part of the German public might have a more indifferent position towards a possible early abortion effect, the assumption of an interest-guided argumentation concerning the effect mechanism is not mandatory. On the other hand,* ***doubts concerning the post conceptive ineffectiveness of the compound might prevent a quick penetration of the South American market*** *where 'Catholic positions' can still be important."*[99]

About 500 million Catholics live there who would reject UPA under this aspect. Here, Reimann addresses a **problem which has accompanied the hormone contraceptives and interceptives for decades and goes through their history like a thread.** We are reminded of the statement of Christopher Tietze from Planned Parenthood and Population Council (see citations above and footnote 99).

He proposed 1964 at the Population Council Symposium as Public Relation-Trick:

> *"not to trouble those people for whom this question [i.e.: about a possible abortifacient effect of compounds for birth control] is of major importance..."*"[100]

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91 H. Huldi et al. 1993.

92 G. Benagiano/H. von Hertzen 2010.

93 N.N. Sarkar 2011: "Mifepristone is widely used to terminate pregnancy and as such is commercially available in many countries. The negative abortion-related image of mifepristone has clearly limited the involvement of major pharmaceutical companies in the development of mifepristone as well as other SPRMs as contraceptive drugs (21)." (Emphasis RE).

94 B. Hinney 2010.

95 Ibid.

96 J.A. Keenan 2011.

97 Ibid.

98 IMABE 2010.

99 A.L.G. Reimann 2013.

100 www.all.org/article.php? Id=10678; "At the 1964 Population Council symposium, Dr. Samuel Wishik pointed out that acceptance or rejection of birth control would depend on whether it caused an early abortion. Dr. Tietze, of Planned Parenthood and the Population Council suggested, as a public relations ploy, '*not to disturb those people for whom this is a question of major importance.'*"

"Tietze added that *theologians and jurists have always taken the prevailing biological and medical consensus of their times as factual,* and that »*if a* ***medical consensus develops and is maintained that pregnancy, and therefore life, begins at implantation****, eventually* ***our brethren from the other faculties will listen.*** *"*[101]

It is important to know that, according to the formulation of Tietze, not only the pregnancy begins with the nidation but also life itself! This audacity has not taken hold to date. It remains to hope that we will be spared of it by the findings in the IVF technology, as it aims specifically the fertilization of the egg by the sperm and thus a new life is created with its immanence. It will hardly come to mind to a reproductive scientist to implant the egg and the sperm separately, i.e. without prior fertilization, in the uterus, because there will be no success.

It suits the concept of Tietze, that latterly even LNG is defined only as ovulation inhibiting, although it contradicts earlier scientific literature. The fact that LNG is not only ovulation inhibiting is confirmed by following citations:

"Levonorgestrel […] has on many levels got a contraceptive effect. […] The contraceptive effect of Levonorgestrel is confirmed also by the fact that it can interrupt a pregnancy by influencing the endometrium / blastocysts."

"The fertility inhibiting effects of LNG are furthermore confirmed by its ability to interrupt an existing pregnancy by disturbing the endometrium / the blastocyst."[102]

Even the pharmaceutical company which sells "Plan B" (LNG containing 'Morning-After Pill') writes in its own information brochure:

"In addition, it may inhibit implantation (by altering the endometrium)."[103]

Another citation concerning NorLevo® Uno (Kreapharma):

"But we think that, in comparison to the classical abortions executed after several weeks or months of pregnancy, it is 'not an abortion' or ***just a very very weak one."***[104]

This is a really grotesque paraphrase of such important facts like an abortion even if it is "only" a nidation inhibition. The life of the embryo is nevertheless at stake.

The semantic problem was already a matter in **1959** at a Planned Parenthood and Population Council Symposium[105]. These and other considerations prepared the statement of the ACOG (American College of Obstetrics and Gynaecology) from **1965**: ***"Conception is the implantation of a fertilized ovum."*** [106] It was the reaction of the ACOG to the following publication of the U.S. Department of Health, Education and Welfare from **1963:**

"Abortion: All measures which impair the viability of the zygote at any time between the instant of fertilization and the completion of labor."

By that new definition, as mentioned above, a pregnancy does no longer begin – as before – with the fertilization but *with* the nidation of the embryo in the endometrium. As a consequence, the period between fertilization and nidation was completely unprotected and the embryo was in danger of being killed!

This definition has been followed by medical associations and many law makers as the example of Germany shows.[107] Tough nothing has changed genetically by the nidation, it is the same embryo as after fertilization, which is the biological beginning of life! The essence is the beginning of human life and not an arbitrary fixation of the beginning of pregnancy.

At those times, the nidation inhibiting effect of the contraceptive coil was the reason for that semantically new definition of when pregnancy begins. Afterwards the so-called ovulation inhibitors followed. And today the modern 'Morning-After Pill', where the nidation inhibiting effect is denied because of vested interests, despite the overwhelming scientific evidence. *Such a denial can only be described as brazen!*

The bioethics scientist Tham et al. write about this development:

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101 Ibid. (Emphasis RE)

102 A. CORBIN/M. GAST 1998.

103 GEDEON RICHTER LTD., 2009.

104 http://www.kreapharma.ch/gesundheit/verhuetung/pille-danach.htm (Emphasis RE)

105 Pro-Life Physicians: "With biology such a stubborn thing, pill promoters turned to semantics for a solution. Swedish researcher Bent Boving, at a 1959 Planned Parenthood/Population Council symposium, noted that: *"Whether eventual control of implantation can be reserved the social advantage of being considered to prevent conception rather than to destroy an established pregnancy could depend upon something so simple as a prudent habit of speech."*

106 ACOG 1965.

107 The german Criminal Code says (§ 218, StGB, Abs. 1, Satz 2, StGB):"Acts with effects on the the fertilized ovum before its nidation in the uterus is completed are not regarded as an interruption of pregnancy as defined by this law." ("Handlungen, deren Wirkung vor Abschluß der Einnistung des befruchteten Eies in der Gebärmutter eintritt, gelten nicht als Schwangerschaftsabbruch im Sinne dieses Gesetzes.") www.gesetze-im-internet.de/stgb/__218.

> *"The results of the study show that the current research in the field of birth control is mainly directed* ***towards products with an abortifacient action*** *and* ***that there is an attempt, also by the international literature, to make the public opinion accept them, by disguising or mystifying the 'abortion' aspect****. In a situation like this semantic and scientific concordance is more necessary than ever, otherwise people can be subject to manipulation while they think they are free."*[108]

If we compare and analyse the statements of Rabe et al. with the newer literature it becomes evident that there was no new scientific evidence between 2009 and 2013 which would speak against the nidation inhibition of UPA. It is quite the opposite: Most of the authors confirm an ovulation inhibiting and a nidation inhibiting effect of UPA!

It can hardly be assumed that the publication 2009 to the "new approval of Ulipristal Acetate for emergency contraception" was so badly founded after 10 years of research, that it had to be turned to the opposite within two years (2011). On the contrary, the facts were confirmed 3 years later with a citation of February 1, 2012.

Therefore it must be presumed that Rabe et al. were very aware of the nidation inhibiting effect of UPA[109], when they published the statements concerning an exclusively ovulation inhibiting effect[110]. This can be interpreted as a conscious deception of Cardinal Meisner and the German Bishops Conference, in the sense of what Christopher Tietze said in 1964.

This is all the more grave because **these linguistic distortions do not concern dead material but the life or death of children before birth!** Mitchell says with regard to those facts: *"Semantics don't change truth."*[111] Inspite of it, the beginning of human life and pregnancy with fertilization remains the truth! Bernard Nathanson pointed out to these dangerous linguistic problems by saying: ***"Verbal engineering always precedes social engineering."***[112]

5.5 Pharmaceutical industry and interest groups

Concerning the ***relation between pharmaceutical industry and interest groups***, we read in the Deutsche Ärzteblatt (German magazine for physicians)[113]:

> *"There are numerous, well-founded studies which prove that not only the ovulation inhibition respectively postponement achieve the effect but that there is also a nidation inhibiting effect. It is difficult to understand that in contrast to scientific evidence, undifferentiated assertions are put in place. It is more understandable* ***when we consider the interests of some ideological groups and the interests of the manufacturers****, which try to avoid any ethical discussion and aim to sell as many `Morning-After Pills´ uncritically as possible. Thus, apart from the ideological-political groups, it is the manufacturers who work against the prescription obligation of these high-dose hormone compounds and are official sponsors e.g. of the DGGEF. The German medical magazine often acts thankfully against those relations between the interests of the pharmaceutical industry and medical recommendations. It is in fact important to disclose such relations."*[114]

We have nothing to add here.

5.6 UPA is threatening life

Based on the scientific facts we can affirm: **UPA is life-threatening because it shows**

- **Inhibition of ovulation = preventing life**
- **Inhibition of nidation = destroying life**
- **Potential foetal damage***

* Concerning the ovulation delay and consequently later ovulation there is a risk of damage to the child which cannot be excluded after an unsafe sexual intercourse with possible fertilization (following UPA usage).

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108 J. THAM ET AL. 2008, p. 900 (Emphasis RE).

109 T. RABE ET AL. 2009.

110 C. ALBRING/T. RABE 24.01.2013; see also: BVF und DGGEF, p. 7/8; and: T. RABE (FEDERFÜHREND) ET AL., in: J Reproduktionsmed Endokrinol 2011.

111 E. MITCHELL 2010.

112 www.pro-leben.de/abtr/taktiken_nathanson.php. In 1968 he founded NARAL (National Abortion Rights Action League)., a pro-abortion-organization which also financed the *Roe vs. Wade* cause and forced the legalization of abortion in the USA. After having aborted about 75.000 children he became a pro-life activist and brought many NARAL materials along, e.g. the widespread Film "Silent Scream", which shows an abortion.

113 The article from 2009 by Kothé Blanka only deals with the LNG containing pill, but the date of publication of the commentary 2013 by Rowik indicates that the author also means UPA, as well as the literature indications cited in the consequence of the commentary which practically exclusively refer to UPA.

114 aerzteblatt.de, 26th of March 2013, 13:21, Rowik: Commentary on the article mentioned in FN 133 by Kothé Blanka.

5.7 Moral theological aspect

Here, Tham et al. leave no doubts as to the moral theological aspect:

> *"...If, after appropriate testing, there is no evidence that conception has already taken place, it is licit to treat with medications that* ***prevent ovulation, sperm capacitation or fertilization. However, it is not permissible to induce or to recommend treatments that aim or have as a direct effect the removal, destruction or obstruction of the implantation of a fertilized ovum."***[115]

If anyone has the least doubt concerning the nidation inhibiting effect of UPA he can abide to the statement of the auxiliary bishop Andreas Laun:

> *"Only the possibility of such an effect leads to a categorical 'No' on the level of moral (...) If (nidation inhibition) happens only possibly, then anyone who propagates contraception as a means against abortion must arise with at least the same intensity against all abortive 'contraceptive' compounds."*[116]

5.8 Future of 'Emergency Contraception'

Kristina Gemzell-Danielsson et al. give an interesting outlook concerning the future of emergency contraception:

> *„Taken together, there is still a need to develop more effective EC [Emergency Contraception] methods. To ensure the highest efficacy and to cover the entire window of fertility,* ***the ideal agents for EC also need to target the endometrium and should be possible to use on demand pre- or postcoitally."***[117]

Here, the endometrium is explicitly named as the target organ for future research on methods before and after conception, which undoubtedly would involve nidation inhibition. Gemzell means probably the inclusion of the endometrium among others specifically in the inmunopharmacology and molecular biological research , as it was mentioned earlier by Miech and Stratton et al.

UPA lies therefore exactly in the finishing line of Gemzell-Danielsson, scientific research should provide more perfect results. It is doubtful whether they will manage without nidation inhibition.

5.9 Update of the inhibiting effect of nidation of 'the Morning After Pill'

There is a trend emerging in connection with last year's results regarding the 'Morning-After Pill' which demands a comment.

Meanwhile it seems that the assertion of the purely ovulation inhibiting effect of Norlevo® (LNG) and ellaOne® (UPA) as well as the hormonal coil Mirena® and Jaydess® (both LNG) is gaining wider and greater ground. Thus, the AIFA (Agenzi italiana del farmaco = Italian medicine agency) has allowed in an announcement[118] to remove following formulation from the package leaflet of the 'Morning-After Pill' containing LNG: *„The medication can also inhibit the nidation of the fertilized egg",* which implies that the embryo would be hindered in its existence and in its development. The text of the package leaflet says simply: „It inhibits or delays the ovulation". Five Catholic organisations[119] protested against it with an appeal to the TAR (Tribunale Amministrativo Regionale = Regional administrative court) Latium. Die AMCI[120] (ASSOCIAZIONE MEDICI CATTOLICI ITALIANI = Association of Italian Catholic doctors) refers on February 21, 2014 to the incompatibility of the resolution of the AIFA with the scientific evidence in international literature regarding and termed the procedure an inadmissible manipulation! The package leaflet should mandatorily at least consider the abortifacient potential of the pharmacon and the associated implications of ethical, scientific nature and of therapeutical use. AIFA requests an immediate scientific examination of the matter by the by the regulatory body!

Moreover, a review about the mode of action of Plan B (Morning-After Pill containing LNG in the USA)[121] concludes that the primary effect mechanism of LNG administered preovulatory – in the fertile window – takes effect mainly postovulatory, namely through nidation inhibition.

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115 J. THAM et al. 2001.

116 A. LAUN, 1991.

117 K. GEMZELL-DANIELSSON ET AL.: op.cit. (Emphasis RE).

118 17.12.2013, published 4.2.2014 in Gazzetta Ufficiale.

119 L'Associazione giuristi per la vita, l'Unione cattolica farmacisti italiani, il Forum delle associazioni familiari, l'Associazione italiana ginecologi e ostetrici cattolici e l'Associazione Pro Vita

120 COMUNICATO AMCI (ASSOCIAZIONE MEDICI CATTOLICI ITALIANI), Roma 21 febbraio 2014, Prof. Filippo M. Boscia, Presidente Nazionale AMCI e Direttivo Nazionale.

121 Plan B Approved For All Girls 15 And Older, By Wendy Sue Swanson, MD, MBE on April 30. 2013 (http://seattlemamadoc.seattlechildrens.org/plan-b-approved-for-all-girls-15-and-older/); and: The State of the Science: Why Catholic Hospitals Should Not Dispense Plan B, By Patrick Yeung Jr., M.D. and Donna Harrison, M.D. By Kathleen Berchelmann M.D. on May 1st, 2013 http://www.catholicpediatrics.com/articles/state-science-why-catholic-hospitals-should-not-dispense-plan-b-patrick-yeung-jr-md-and-older/

Regarding ellaOne® (UPA) a recently published work by Mozzanega et al[122] confirm also clearly the nidation inhibiting character of the compound with the evidence of nidation inhibition as the main effect.

The assertion of a purely ovulation inhibiting effect of several emergency and other contraceptives seems to have system, as it spreads increasingly worldwide, without scientific evidence. The above mentioned assuption that this is based on vested economic interests which mainly aim the South American market[123] may have in this light an increased significance.

Resume

Finally it can be concluded, that **there is no doubt about the nidation inhibiting effect of UPA! There is no 'Morning-After Pill' with exclusively ovulation inhibiting effects.** Unfortunately, Cardinal Meisner and the German bishops were misinformed.

The advocates of a time frame for a risk-free use of UPA must also be disappointed because according to the criteria of NER such a frame cannot be determined with a clear conscience. There are too many uncertainties so that the risk of a nidation inhibition can never be excluded.

Based on the clear scientific evidence, added to the contradictions in the statements of BVF and DGGEF, especially by Rabe and Albring and the statements of the manufacturers and sellers of these pills, HRA-Pharma and Watson-Pharma, we can only agree with the Büchner's conclusion:

> *"Those findings support the suspicion **that the new publications** concerning the effect of both 'Morning-After Pills' could be **influenced by an interest-based procedure. Hence, the Catholic Church should be very reserved towards them** and seek the advice of competent, independent scientists whom they can trust, before they again give statements on the effects of the 'Morning-After Pills' with the necessary consequences. If the Church trusts the new voices in science too easily, the past resiliance against the 'Morning-After Pill' will be broken and the world-wide triumph to the delight of the pharmaceutical industry and the abortion and contraception lobby can no longer be prevented."*[124]

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Most parts translated by Alexandra Linder

122 B. MOZZANEGA ET AL. 2014.

123 A.L.G. REIMANN 2013.

124 B. BÜCHNER 2013 (Translation A.L.) (Emphasis RE).

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Little glossary

LNG	Levonorgestrel
UPA	Ulipristal Acetate = CDB- 2914
RU 486	Mifegyne / Mifepristone = abortion pill
SPRM	Selective Progesterone Receptor Modulator
PR	Progesterone Receptor
EE2	Ethinylestradiol: the most used estrogen in the pill (COC)
OI	Ovulation inhibition
OP	Ovulation postponement
DO	Delayed Ovulation
BO	Breakthrough Ovulation
LH	Luteinizing Hormone
LUF	»luteinized unruptured follicle« = luteinization of ovulatory follicle without releasing an oocyte
US	Ultra Sonographie
WT	Waking Temperature