

Is Contraception Really Safe?

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Abstract

Aim: On the background of media reports about serious harm to the health of thousands of women engaged in birth control and contraception, the paper aims at emphasizing the importance of the parameter safety in birth control and contraception.

Method: The method consists in an in-depth analysis of those sources of information that are most widely used by women and their health care providers, ie, packaging labels of manufacturers and statements by the FDA. In addition, the information contained in high-ranked scholarly journals which are most commonly accessed by health care professionals is analysed.

Results: Presently, women are not provided with information suitable for preventing harm and injury caused by contraceptive drugs and devices. Health care providers, frequently misled by journal articles, apparently fail to comply with the requirements of the principle of informed consent, despite urgings by manufacturers and the FDA.

Conclusion: At present it is difficult for women to obtain comprehensive, complete, and reliable information on the safety of all available methods of contraception.

Health care providers are frequently guided by economic principles and are also misled by editors who publish studies carried out by researchers who have to declare conflicts of interest. Due to this conflict vital information is withheld from the consumer so that detrimental consequences for her/his health loom large.

Key words: Safety; birth control; contraception; health care providers ; sterilization; long-lasting reversible contraception (LARC); oral hormonal contraception; and periodic abstinence.

Summary

In an introductory section, the article analyses the most recent complications encountered by patients using a contraceptive product that had been approved by the FDA in 2002 and was withdrawn from the US market 16 years later. It is argued that the central problem in the marketing and use of this product was failure to comply with the principle of informed consent, and the subsequent sections of the analysis examine as to whether or not the information provided by manufacturers of contraceptive pills and devices is sufficient to warrant safe use of these products

by the consumers. The examination includes the commonly used contraceptive options, namely permanent contraception through sterilization, oral hormonal contraception, Long Acting Reversible Contraception (LARC), Emergency Contraception (EC), and non-hormonal fertility awareness-based (periodic abstinence) methods.

Material and Method

Material

Information provided by manufacturers in packaging labels and by the FDA in pertinent publications. Scholarly articles published in leading journals with the highest impact factors.

Method

In-depth comparative analysis of information provided by various sources, such as manufacturers, FDA, scholarly articles, and popularizing publications emanating from academic institutions and clinics. Criteria for this analysis are completeness and accuracy of data.

Findings

The parameter safety is not adequately addressed, neither by manufacturers of products for contraception in their packaging labels, including the "information for the patient," nor by authors of articles in professional journals. Women do not obtain information as stipulated by the principle for informed consent due to failure on the part of health care providers. New avenues can be opened through the creation of information that summarizes in a synoptic fashion the parameters relevant for the clinical practice, as does the following table (Cf. Table 1).

In accord with most women's prerogatives, the following table gives priority to safety over efficacy and includes parameters which are of vital importance for the clinical practice, namely convenience and cost. (Cf. Table 1: Safety – Efficacy – Convenience – Cost Ranking, 2018).

Table 1: Safety – Efficacy – Convenience – Cost Ranking (SECCR), 2018.
(Based on WHO, 2017, FDA, 2013, and CTFailure table, 2011. Efficacy is indicated as percentage of women experiencing an unintended pregnancy within the first year of use).

Method	Safety (no harm in the sense of “nil nocere”)	Efficacy Perfect-Typical use	Convenience	Cost & Specifications
Symptothermal	High	0.4-24	High	No cost. Body temperature must be measured, cervical mucus must be observed (clear texture), cervix must be palpated (soft consistency and open).
Ovulation (based on cervical mucus)	High	3-24	High	No cost. Cervical mucus must be observed (“spinnbarkeit”)
TwoDay (based on cervical mucus)	High	4-24	High	No cost. Coitus must be avoided during fertile days. Fertile days determined by presence of cervical mucus (color and consistency). Coitus may be resumed after 2 consecutive dry days (or absence of secretion).
Standard Days Method (SDM) – based on calendar	High	5-24	High	No cost. Fertile period is tracked and coitus avoided (usually days 8-19 of each 26-32 day cycle).
Basal Body Temperature (BBT)	High	1-25	High	No cost. Fertile phase has passed when body temperature has risen (0.2-0.5° C) and remained such for 3 days. Conception is unlikely from 4th day following rise of temperature until next menstruation.
Calendar (rhythm) method	High	9-25	High	No cost. Menstrual cycle is monitored for at least 6 months. 18 is subtracted from shortest cycle (this is the estimated first fertile day). 11 is subtracted from the longest cycle (this is the estimated last fertile day). Caution when drugs are used (NSAID, certain antibiotics, anxiolytics, anti-depressants, etc.).
Male condoms	Moderate	2-18	High	Low cost. Protects against sexually transmitted diseases (STD) including HIV.
Female condom	Moderate	5-21	Moderate	Moderate cost. Prevents contact between sperm and egg. Protects against sexually transmitted diseases (STD) including HIV (according to WHO).
Implant (Small, flexible rod or capsule placed under the skin of the upper arm; contains progestogen hormone only).	Moderate	0.05-0.05	High	High cost. Implanted by clinician. Irregular vaginal bleeding common.
Mirena (LNG) Intrauterine device (IUD) (T-shaped plastic device inserted into the uterus; releases continuously small amounts of levonorgestrel).	Low	0.2-0.2	Moderate	High cost. Prevents contact between sperm and egg by thickening cervical mucus. Amenorrhea.

ParaGard (copper IUD)	Low	0.6-0.8	Moderate	High cost. Copper component damages sperms.
Depo-Provera	Moderate	0.2-6	Moderate	High cost.
Combined oral contraceptives (COCs)= "the pill"	Moderate	0.3-9	Moderate	Moderate cost. Contains estrogen and progestogen.
Progestogen-only pill (POP) or "minipill"	Moderate	1-3 (10)	Moderate	Moderate cost. Thickens cervical mucus and prevents ovulation.
Evra patch	Moderate	0.3-9	Moderate	High cost.
NuvaRing	Moderate	0.3-9	Moderate	High cost.
Combined contraceptive patch and combined contraceptive vaginal ring (CVR)	Moderate	1-8(?) (Research on efficacy limited).	Low	High cost. Continuously releases a progestin and an estrogen directly through the skin (patch) or from the ring. Prevents ovulation, copper component damages sperms. Pharmaco-kinetic profile comparable to COCs.
Monthly injectables or combined injectable contraceptives (CIC)	Moderate	1-3	Low	High cost. Irregular vaginal bleeding. Injected monthly into muscle.
Progestogen-only injectables	Moderate	1-3	Low	High cost. Injected into the muscle or under the skin every 2 or 3 months, depending on product. Irregular vaginal bleeding; delayed return to fertility after use.
Diaphragm	Moderate	6-12	Low	High cost. Must be used for each coitus.
Emergency or post-coitus Contraception (EC)	Moderate - Low	1-15	High	Moderate cost. Pills (ulipristal acetate 30 mg or levonorgestrel 1.5 mg) must be taken twice to prevent pregnancy up to 5 days after coitus. Alternatively IUD (copper or levonorgestrel) to be inserted.
Lactational Amenorrhea (LAM)	High	1-2	Moderate	No cost. Effective in preventing ovulation as long as monthly bleeding has not yet returned. Requires exclusive breastfeeding day and night of infant less than 6 months old.
Male sterilization (vasectomy)	Moderate	<1 (after 3-months semen evaluation). 2-3 (without semen evaluation).	High	High cost. Surgical intervention. Permanent contraception by cutting vas deferens tubes which transport sperm from the testicles.

Female sterilization(tubal ligation)	Low	0.5-0.5	Moderate-Low	High cost. Surgical intervention. Permanent contraception by blocking or cutting the fallopian tubes.
Sterilization through creation of scar tissue (ESSURE)	Very low	?	Low	Device has been withdrawn from the market in several countries, including the U.S.
Sponge	Moderate	20-24 - parous women 9-12-nulliparous women	Moderate	Moderate cost. To be used for each coitus.
Spermicides	Moderate	18-28	High	Moderate cost.

Discussion

In reviewing the literature on birth control, family planning, and contraception, it appears that there is almost unanimous agreement on the safety of the methods most commonly used.

Thus, a highly pertinent article in one of the leading medical journals world-wide reiterates systematically statements on the safety of contraceptive devices. Among the clinical key points safety is stressed for both intrauterine devices and implants: “IUDs and hormonal implants are safe for almost all women, including adolescents, as well as women in the postpartum or postabortion period.”[1,p.461]

Concerning intrauterine devices, the authors affirm that they are safe for almost all women: “Almost all women can safely use IUDs. Exceptions include women who have hypersensitivity to copper, . . .” [1,p.462] For implants the same claim is made as for intrauterine devices: “Almost all women can safely use implants; exceptions are women who have hypersensitivity to barium or to the components of the implant.”[1, p.463]

Methods belonging to long-acting reversible contraception (LARC) are declared safe for almost all women: “LARC methods are safe for use in almost all women, including young and nulliparous women.”[1, p.465] The safety of LARC is ascertained also for postpartum and postabortion periods: “Both IUDs and implants are safe for use in the postpartum and postabortion periods, including immediately post partum and post abortion.”[1,p.465]

Albeit the authors cannot deny the risk of expulsion, they simply compare risks for various time periods and recommend placement of the IUD at least six weeks post partum: “Although IUDs are generally safe for use in the postpartum period, the relative risk of expulsion of IUDs that are placed immediately post partum is higher than the risk with IUDs placed at 6 weeks post partum or later.”[1,p.466]

The authors also claim that the Centers for Disease Control (CDC) issues recommendations for safe use, which take into account various conditions or characteristics: “The CDC publishes

recommendations for the safe use of contraception, including IUDs and implants, for women with various conditions or characteristics.”[1, p.467] In the conclusion again, “the extremely high” safety is highlighted as one of the noteworthy properties of LARC methods: “All adolescents and adult women should be informed about the availability of LARC methods, given their extremely high effectiveness, safety, and high rate of continuation.”[1,p.467]

This tranquil scenario of safety of contraception and birth control depicted by scholarly articles has been brutally shaken in 2018 by events surrounding a contraceptive device for sterilization. This device had been approved by the FDA in 2002 and had to be removed from the market 16 years later in 2018 due to complaints about severe adverse events, including bleeding, perforation, and migration of the device. “But there have been reports women experienced changes in menstrual bleeding, unintended pregnancy, chronic pain, perforation and migration of the device, allergic reactions and immune-type reactions after being implanted with the device . . .”[2] Other media highlighted additional adverse events: “Patients have reported cases of pain, bleeding, allergic reactions and cases where the implant punctured the uterus or shifted out of place.”[3]

Not only health problems but also legal issues were the target of press reports, and it was reported that the device had given rise to approximately 16,000 lawsuits or claims because of severe injuries. “It has been the subject of an estimated 16,000 lawsuits or claims filed by women who reported severe injuries, including perforation of the uterus and the fallopian tubes. Several deaths, including of a few infants, have also been attributed to the device or to complications from it.”[4]

The troubled history of the device has brought to light two crucial issues in the area of birth control and contraception: first, the safety deficit of a contraceptive device that has been declared “safe” by the FDA; second, the lack of cooperation on the part of health care providers who failed to inform patients about adverse events and risks of the contraceptive device for sterilization.

According to media reports, the FDA went so far as to restrict the use of the device to those women who had signed a statement acknowledging familiarity with the risks and had received also their doctor's signature prior to implantation. "The Food and Drug Administration said only women who read and have the opportunity to sign a brochure about the risks of the device will be able to receive the implant made by Bayer. The checklist of risks must also be signed by the woman's doctor." [3]

As can be seen, the lack of cooperation on the part of health care providers has been criticised by both, the FDA and the manufacturer of the device. Apparently, women choosing the implant for permanent contraception were not adequately informed about adverse events, risks, and complications. "Despite previous efforts to alert women to the potential complications of Essure, we know that some patients still aren't receiving this important information," said FDA Commissioner Scott Gottlieb, in a statement. "That is simply unacceptable." [3]

As regards the FDA's statements attention must be drawn to the insistence on the safety and efficacy of the device. "Bayer announced that they will no longer sell or distribute Essure in the U.S. after December 31, 2018, for business reasons. This information does not change the FDA's understanding of the safety and effectiveness of the device; however, the FDA emphasizes that women with Essure should speak with their physician about any medical questions they may have." [3] The FDA's explanation on both safety and effectiveness makes it clear that physicians are called upon to meet their obligations, and there should be no doubt in their mind that safety in this context always refers to "no harm" as specified also by the bioethical principle "nil nocere."

In light of the issues brought to the forefront by the adverse events experienced by women who were using a "safe" device, it seems imperative to examine as to whether or not the topic safety is treated with the necessary precision and diligence in the pertinent literature, ie, scholarly articles and packaging labels furnished by manufacturers of products and devices.

The following discussion provides an analysis of these sources of information and aims at determining as to whether or not patients obtain adequate reliable information to make an "intelligent choice," as required by the bioethical principle of informed consent. [5].

Permanent contraception by means of sterilization

The mechanism of action of the device for permanent contraception is remotely comparable to tubal ligation. The implant made of a nickel alloy and a polyester-like fiber causes scar tissue to form and this tissue inhibits contact between the sperm and the ovum.

"The Essure implant consists of two small coils made of a

nickel alloy and a polyester-like /sic!/ fiber. It is placed through the vagina into the fallopian tubes, and is designed to create an inflammatory response that causes scar tissue to form, blocking the tubes." [4] In contrast to laparoscopic sterilization, this device does not require general anaesthetic or surgery. "It does not require general anaesthetic or surgery, unlike laparoscopic sterilisation." [4]

Obviously, the underlying physiological reasoning is avoidance of fertilization, ie, contact between sperms and ovum. Physiologically speaking, 50-100 sperms reach the ovum, and many of them contact the zona pellucida, a membranous structure that surrounds the ovum. "This is followed by the acrosomal reaction, the breakdown of the acrosome, the lysosomelike organelle on the head of the sperm. Various enzymes are released, including the trypsin-like protease acrosin." [6, p.12]

The aversion of this process through a scar tissue that prevents contact between the ovum and the sperm has given rise to severe adverse reactions. Concerning the physiological reasoning which underlies the mechanism of action the question arises as to whether the infliction of a wound is an ethically justifiable procedure. The manufacturer argues that the necessary information about adverse events had been provided and that health care providers had been urged to inform patients accordingly.

In fact, the FDA offers comprehensible information by identifying the population for which the device might be suited and by insisting on its efficacy and safety. The reader can be expected to understand that the device is a permanent form of birth control, which is not appropriate for all women of child-bearing age. The FDA also specifies for whom the device might be a suitable option, namely for those women who do not plan to have any more children, who desire not only a reversible but a permanent form of birth control, who prefer a sterilization procedure that does not require an incision or general anesthesia (some gynecologists may administer a local, ie, numbing anesthetic to reduce potential discomfort during the implantation), and those women who are interested in a permanent birth control which does not include hormones. [7]

The FDA also warns that the implanted device is not immediately effective in preventing pregnancy. Thus, another form of birth control must be implemented to prevent pregnancy until a confirmation test has been performed. This confirmation test -- verifying that the inserts are positioned correctly -- is performed three months subsequent to Essure placement. [7]

In addition to the FDA, the manufacturer provides comprehensive information on the confirmation test and on long-term risks. As one of the Essure Confirmation Tests (a modified HSG) necessitates an x-ray, the patient is informed that

she will be exposed to very low levels of radiation. According to the manufacturer, some patients can experience nausea and/or vomiting, dizziness and/or fainting, cramping, pain or discomfort. In rare cases, it is specified, a patient will experience spotting and/or infection.[8]

As to the long-term risks, the manufacturer explains that pain (acute or persistent) of varying intensity and duration can occur and persist subsequent to placement of the device. Women with a history of pain are more likely to experience such discomfort. The manufacturer also mentions reports according to which the insert had been located in the lower abdomen and pelvis. In such a case, the contraceptive efficacy of the device can no longer be guaranteed. Allergic reactions are also mentioned. "Patients with known hypersensitivity to any of the components of the Essure system may experience an allergic reaction to the insert. In addition, some patients may develop an allergy to nickel or other components of the insert following placement." [8] Symptoms in women using the device may be associated with an allergic reaction including hives, rash, swelling and itching. One of the most serious adverse events that might occur is ectopic pregnancy, ie, pregnancy outside the uterus, and the manufacturer appropriately stresses the life-threatening character of such a condition: "This can be life-threatening. If insert removal is indicated, surgery will be necessary." [8]

In addition to emphasizing compliance with FDA requirements, the manufacturer also issued special safety information. In a warning, attention is drawn to some severe adverse events, including perforation of the uterus and/or fallopian tubes, localisation of the device in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions. "If the device needs to be removed to address such an adverse event, a surgical procedure will be required. This information should be shared with patients considering sterilization with the Essure System of Permanent Birth Control during discussion of the benefits and risks of the device." [9]

As can be seen, the manufacturer endeavors not only to explain possible adverse events but also requests that there be intensified communication between patient and health care provider to discuss all pertinent issues. Concerning adverse events, the manufacturer appropriately mentions the life-threatening condition of an ectopic pregnancy: "This can be life-threatening. If insert removal is indicated, surgery will be necessary." [8]

In light of the information provided by the manufacturer, patients should in fact be able to make an intelligent choice, especially if there is additional counseling by their physician. It is precisely this counseling, however, that has become the target

of critique. If the blame put on the health care providers is in fact justified the forensic proceedings will have to address this issue. From the clinical practice there seems to be evidence to sustain this blame so that health care providers will have to be prepared to justify their lack of compliance with legal and ethical requirements. This justification might include time urgency, cost-effectiveness, and other economic principles as embraced also by doctors in the European Union (EU).[10]

Oral hormonal contraception

Oral hormonal contraception is the most commonly used method of contraception world-wide. Concerning its safety, a considerable number of products have to be analysed, including combination oral contraceptives, the micropill, and the minipill. The following discussion focuses in a paradigmatic fashion on the most frequently used products.

Combination oral contraceptives

The designation "combination oral contraceptives" denotes several contraceptive drugs containing varying components of hormones. Two of the most frequently used and extensively described by the manufacturers are discussed in the subsequent section.

Norethindrone /ethinyl estradiol containing tablets [11]

An analysis of the information provided by the manufacturer of Norethindrone /ethinyl estradiol containing tablets [11] shows that the reader finds extensive information on contraindications, adverse events and risks, including the possibility of death through intra-abdominal hemorrhage in association with hepatic adenomas. Whether all women will be capable of finding the information necessary for making an intelligent choice, as required by informed consent, remains to be seen. After all, some readers might be at a loss if they encounter the expression "Bud-Chiari syndrome" without being told that this terminus designates a hepatic vein occlusion due to idiopathic thrombosis, tumor, or other causes, resulting in hepatosplenomegaly, jaundice, ascites, and portal hypertension.

Levonorgestrel and ethinyl estradiol containing tablets [12]

An analysis of the information provided by the producing company of levonorgestrel and ethinyl estradiol containing tablets, shows that an impressive amount of information is offered to the reader in a 44-page packaging label. What deserves particular attention is the explicit warning of a lethal event due to blood clots. "Blood clots and blockage of blood vessels are the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the legs can cause thrombophlebitis and a clot that travels to the lungs

can cause a sudden blocking of the vessel carrying blood to the lungs.”[12,p.32]

A similar warning is expressed with respect to heart attacks and strokes: “Oral contraceptives may increase the tendency to develop strokes or transient ischemic attacks (blockage or rupture of blood vessels in the brain), angina pectoris, and heart attacks (blockage of blood vessels in the heart). Any of these conditions can cause death or serious disability.”[12,p.33]

The producing company also presents, similar to other producers, the table containing data on the “annual number of birth-related or method-related deaths associated with control of fertility per 100,000 nonsterile women, by fertility-control method and according to age.” In interpreting this table it is stated: “In the above table, the risk of death from any birth-control method is less than the risk of childbirth, except for oral-contraceptive users over the age of 35 who smoke and pill users over the age of 40 even if they do not smoke.”[12,p.35]

In contrast to other producers, the producing company of levonorgestrel - ethinyl estradiol includes as side effects also exacerbations of systemic lupus erythematosus, aggravation of varicose veins, cataracts, cystitis-like syndrome, hemorrhagic eruption, and optic neuritis which can lead to partial or complete loss of vision.[12, p.13]

Desogestrel/ethinyl estradiol and ethinyl estradiol tablets:[13]

The producing company of desogestrel/ethinyl estradiol and ethinyl estradiol tablets provides a 39-page document which contains contraindications, warnings, and precautions in addition to the admonition to read the directives provided. Besides a brief summary of the patient package insert, a “Detailed Patient Package Insert” is provided. What is also contained is the table indicating “percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year, United States.”[13]

Mention is made about death-bearing sequelae of benign hepatic adenomas. “Rupture of rare, benign, hepatic adenomas may cause death through intra-abdominal hemorrhage.”[13] A similar warning is expressed for blood clots. “Blood clots and blockage of blood vessels are one of the most serious side effects of taking oral contraceptives and can cause death or serious disability. In particular, a clot in the leg can cause thrombophlebitis and a clot that travels to the lungs can cause a sudden blockage of the vessel carrying blood to the lungs.”[13] The risks of these side effects, the producing company admits, may be greater with its own desogestrel-containing oral contraceptives, “than with certain other low-dose pills.”[13]

The producing company also refers to estimates for oral contraceptive users in general. “It has been estimated that in women between the ages of 15 and 34 the risk of death due to a circulatory disorder is about 1 in 12,000 per year, whereas for non-users the rate is about 1 in 50,000 per year. In the age group 35 to 44, the risk is estimated to be about 1 in 2,500 per year for oral contraceptive users and about 1 in 10,000 per year for nonusers.”[13]

The producing company also mentions that oral contraceptives may increase the tendency to develop strokes, angina pectoris and heart attacks. “Any of these conditions can cause death or serious disability. Smoking greatly increases the possibility of suffering heart attacks and strokes. Furthermore, smoking and the use of oral contraceptives greatly increase the chances of developing and dying of heart disease.”[13]

In referring to the table about mortality, the producing company explains: “It can be seen in the table that for women aged 15 to 39, the risk of death was highest with pregnancy (7 to 26 deaths per 100,000 women, depending on age). Among pill users who do not smoke, the risk of death is always lower than that associated with pregnancy for any age group, although over the age of 40, the risk increases to 32 deaths per 100,000 women, compared to 28 associated with pregnancy at that age. However, for pill users who smoke and are over the age of 35, the estimated number of deaths exceeds those for other methods of birth control. If a woman is over the age of 40 and smokes, her estimated risk of death is four times higher (117/100,000 women) than the estimated risk associated with pregnancy (28/100,000 women) in that age group.” [13]

The producing company also explains extensively drug interactions and specifies that drugs can interact with birth control pills “to make them less effective in preventing pregnancy or cause an increase in breakthrough bleeding. Such drugs include rifampin, drugs used for epilepsy such as barbiturates (for example, phenobarbital), phenytoin (Dilantin® is one brand of this drug), phenylbutazone (Butazolidin® is one brand), and possibly certain antibiotics.”[13]

Additional contraception is recommended as these drugs can make oral contraceptives less effective.

“Birth control pills may interact with lamotrigine, an anticonvulsant used for epilepsy.”[13] Given an increased risk of seizures, so the advice, the physician may adjust the dose of lamotrigine.[13] Among the medicines that reduce the efficacy of birth control pills, the following are mentioned: Barbiturates, Bosentan, Carbamazepine, Felbamate, Griseofulvin, Oxcarbazepine, Phenytoin, Rifampin, St. John’s wort, and Topiramate.

The “micropill”

As early as 1987 use of the micropill, which contains less than 50 microgram of ethinyl estradiol, has been advocated, and it had been recommended that women of all age groups should attempt to use the “micropill”--either the combination-type or the trimest formulations--in order to minimize risks. “Only a few indications are left for the primary prescription of high-dose combination-type, sequential and step-up preparations as well as for the progestogen-only ‘minipill’. With ‘micropill’ becoming the oral contraceptives of the first choice, also rational reasons for changing formulations have become rare.”[14]

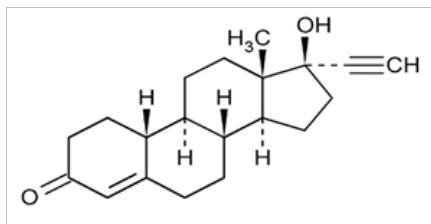
The “minipill:”

Numerous studies have been devoted to the minipill or progestin-only pill which contains norethindrone.[15]

Chemical Name: 17-hydroxy-19-nor-17 α -pregn-4-en-20-yn-3-one

Molecular Wt: 298.42 Molecular Formula: C₂₀H₂₆O₂

Structural Formula



Concerning information provided by the producing company of the progestin-only pill, the possibility of a lethal outcome in the case of benign liver tumors is mentioned: “These benign liver tumours can rupture and cause fatal internal bleeding.”[15]

In addition to information provided by the producer, health agencies and clinics offer advice on the minipill. Trustworthy information emanates from such institutions as the Mayo Clinic. [16] This information includes warnings about side effects, such as “irregular menstrual bleeding, acne, breast tenderness, decreased sex drive (libido), depression, headaches, nausea, and ovarian cysts.”[16]

In reviewing other studies on progestin-only pills and combination oral contraceptives it becomes obvious that one of the pivotal topics is drug interaction, especially in societies where polypharmacy goes rampant.[17] Drug interaction is less relevant for the most effective of all contraceptive pills and devices, namely implants and intrauterine devices designated as Long-Acting Reversible Contraception (LARC).

Long Acting Reversible Contraception (LARC)

Implants

An analysis of the information provided by the producing company of the etonogestrel-containing implant shows that possible complications and adverse events are well-described, even those that can be death-bearing, namely ectopic pregnancy and blood clots. Ectopic pregnancies, it is specified, can result in severe “internal bleeding, infertility, and even death.”[18]. Blood clots, on their part, can lead to heart attack or stroke, and “it is possible to die from a problem caused by a blood clot . . .”[18]

Whether the information provided by the manufacturer of the implant is too lengthy, too technical or confusing remains controversial because the readers have varying levels of educational background and degrees of intelligence. What can be ascertained, however, is the effort made by the producing company to warn also about the most hazardous complications. These complications together with the question of cost-efficiency might deter some patients who otherwise would be inclined to choose the implant for contraceptive pursuits.

Intrauterine devices

The producing company of the intrauterine device warns appropriately about the severity of some risks, including the deadly outcome of some conditions, as for example pregnancy. Patients becoming pregnant with an IUD in place run the risk of a septic abortion. “. . . septic abortion—with septicemia, septic shock, and death—may occur.”[19]. Another condition with a lethal potential is sepsis due to Group A streptococcal sepsis (GAS) with pain occurring within few hours of insertion and subsequent sepsis. “Because death from GAS is more likely if treatment is delayed,” the producing company recommends speedy intervention in such a case. Particular stress is laid on pelvic inflammatory disease, which can have deadly sequelae. “PID can cause tubal damage leading to ectopic pregnancy or infertility, or infrequently can necessitate hysterectomy, or cause death.”[19]

Whether the information provided by the manufacturer of the intrauterine device is too lengthy, too technical or confusing is difficult to prove. What can be ascertained, however, is the fact that the scientific literature does not reflect the producing company’s concerns about safety. On the contrary, the parameter safety is treated with considerable negligence, as can be seen from one of the recent studies (2016) on LARC. This study claims that “almost all women can safely use IUDs.”[1,p.462] In light of warnings about serious adverse events and even

death, issued by the producer, the statement on the safe use seems irreconcilable with good ethical practice in research. It is worthwhile mentioning that such an empirically unverifiable emphasis on safety frequently stems from authors who have to declare conflict of interest. Editors of scientific journals as well as authors declaring conflict of interest should be aware that health care providers who read statements downplaying the issue of safety can be misled into neglecting the warnings issued by the manufacturer. The ensuing lack of compliance with informed consent might result in severe threats to the health of patients.

Neglect of information provided by the manufacturer can have particularly severe consequences for a method of contraception that has received increasing attention during the last years, namely the so-called emergency contraception. Emergency, or better post-coitus, contraception is of course no invention of the 21st century, since the “morning-after-pill” and mifepristone (RU-486), which binds to the progesterone receptor and blocks the binding of progesterone, have been known since the last century.

Post-coitus (Emergency) Contraception

At present, there seems to exist sufficient evidence to sustain the claim that Emergency Contraception (EC) can be considered as one of the most convenient forms of birth control, especially for women whose sexual activity is diminishing, because it requires administration of pills only twice within 12 hours and thus avoids the burden of daily administration.[20] In addition, it does not require the intervention by a health care provider. Several forms of EC have been described, namely oral administration of ulipristal acetate, oral administration of standard contraceptive pill, and intrauterine devices.[21] Estimates on the efficacy of EC have been included in studies on the efficacy of contraceptives.[22]

Ulipristal acetate

“Ulipristal acetate is a 20-oxo steroid obtained by acetylation of the 17-hydroxy group of (11beta,17alpha)-17-acetyl-11-[4-(dimethylamino)phenyl]-3-oxoestra 4,9-dien-17-ol”. [23] Being a selective progesterone receptor modulator it is employable as an emergency contraceptive. “It is a 3-oxo-Delta(4) steroid, a steroid ester, an acetate ester, a 20-oxo steroid and a tertiary amino compound. It derives from an estradiol.”[23]

Pharmacology

Ulipristal Acetate, an orally bioavailable acetate salt of ulipristal, is a selective progesterone receptor modulator with anti-progesterone activity. It binds to the progesterone receptor (PR) and thus inhibits PR-mediated gene expressions and interferes with progesterone activity in the reproductive system. As a consequence, it may suppress the development of uterine

leiomyomatosis. Due to its ability to inhibit or delay ovulation and to alter endometrial tissue, ulipristal acetate can be used as post-coitus contraception.

Concerning the efficacy of EC, attention must be drawn to the WHO table of 2017 which indicates an estimate of 99% efficacy by stating: “If all 100 women used progestin-only emergency contraception, one would likely become pregnant.”[24] In the same vein, German authors argued as early as 2000 that the efficacy of post-coitus contraception by means of “interceptive pills” is as effective as 99% in case of perfect use.[25,p.82]

Interestingly enough, this claim made in 2000 and the WHO estimate of 2017 do not correspond to the findings presented by the Food and Drug Administration (FDA) in a survey of contraceptive methods.[26] This survey, which appeared in 2013, indicates 85% efficacy in case of perfect use and 87.5% efficacy in case of typical use: “7 out of 8 women would not get pregnant after using Emergency Contraceptives”. [26] Unexpectedly, according to the FDA survey, typical use (87.5%) would be more effective than perfect use (85%).

In discussing safety of combined EC pills, short duration of exposure and low content of hormone is emphasized. “Given the very short duration of exposure and low total hormone content, combined ECP treatment can be considered safe for women who would ordinarily be cautioned against use of combined oral contraceptives for ongoing contraception.”[21,p.8]

In the comprehensive review of 2017 on Emergency Contraception safety is defined with reference to death or serious complications: “No deaths or serious complications have been causally linked to emergency contraception. According to the U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC), there are no situations in which the risks of using combined, progestin-only or ulipristal acetate ECPs outweigh the benefits.”[21,p.8] As can be seen, in this context the terminus “safe” is used with a comparative component, where the risks are compared to the benefits. Whether such a relativistic definition contributes to a deeper understanding of the terminus “safe” remains to be seen. Most women might want to know precisely how safe a pill or device is in terms of adverse events, such as perforation, migration, surgical intervention for removal, pelvic inflammatory disease, etc. It is apparently this understanding of “safe” that underlies the statement accentuating the short duration of exposure and the low total hormonal content” . . . combined ECP treatment can be considered safe for women who would ordinarily be cautioned against use of combined oral contraceptives for ongoing contraception.”[21,p.8]

One of the central questions is safety in case of ECP use over a longer period of time, especially in view of the frequently encountered warning that emergency contraception should not

be implemented as a regular form of contraception.[25,p.82] "However, a pharmacodynamic study of repeated use of UPA EC (every 7 days for 8 weeks) showed no safety concerns, indicating that UPA can be safely used more than once per cycle." [21,p.9]

Studies indicating that UPA can be used safely more than once per cycle and studies suggesting no special safety concerns for the use of ECPs by women with particular medical conditions or personal characteristics support the claim that post-coitus contraception can be considered as one of the most convenient contraceptive options available, appropriate also for averting unintended pregnancy and abortion.

Non-Hormonal (fertility awareness based = periodic abstinence = natural family planning) methods

Despite incontestable advantages of Long Acting Reversible Contraception, of pills for oral hormonal contraception, of post-coitus contraception, adverse events, risks and complications can be severe. It is understandable, therefore, that certain women might be willing to venture into birth control only under the condition that risks can be avoided. Such avoidance seems in fact possible owing to the extensive study of non-hormonal methods during the last century.

At present nonhormonal contraception is recommended officially also by pharmaceutical companies encouraging women to use non-hormonal methods in certain instances: "You may also need to use a nonhormonal method of contraception during any cycle in which you take drugs that can make oral contraceptives less effective." [13] In addition to such recommendations by pharmaceutical companies, studies on quality of life in users of contraceptive pills might convince women to avoid hormonal contraceptives.[27]

The so-called "fertility awareness-based" methods (FAB) -- also designated as periodic abstinence or natural family planning -- receive increasingly attention, especially in European countries, where some of them originated.[25,pp. 61-64] In 1927, Van de Velde from the Netherlands delineated the Basal Body Temperature method. Between 1932 and 1933, the Japanese Ogino and the Austrian Knaus developed the Calendar method (designated misleadingly also as "rhythm"). In 1964, the Australian neurologist John Billings described the Ovulation or Cervical Mucus method after performing research on fertility. The latter was then integrated into other methods and defined as symptothermal method by Rötzer, an Austrian practitioner. An in-depth analysis of these methods and their assessments has been presented recently in a scholarly investigation[28] which draws attention to the neglect of informed consent, a neglect whose

repercussions have reached world-wide dimensions recently owing to the troubled history of the sterilization device discussed at the beginning of this article.

Conclusion

In light of the foregoing analyses it can be concluded that the problem of safety in contraception and birth control is by no means resolved. Manufacturers of contraceptive drugs and devices frequently fail to inform adequately about the risks associated with the use of their products. The FDA approves products as safe although they can cause severe side effects or even death. Health care providers subscribe to economic principles of cost-effectiveness rather than complying with the bioethical principle of informed consent. Editors of journals, even those with highest impact factors, publish articles whose authors have to declare conflict of interest and consequently do not unveil shortcomings of products marketed by their stipend- and grant-providers. The victims of this fatal constellation are women in search of suitable contraceptive options. They can only be advised to take extremely seriously all the information provided by manufacturers and give highest priority to those methods that are top-ranked with regard to safety.

Implications

In view of the evidence of threats to the health of patients who engage in contraceptive pursuits it is suggested that manufacturers make every effort possible to inform patients in a comprehensive and comprehensible fashion about all the risks possible. The FDA is expected to protect consumers from any harm and apply stringent requirements in procedures for the approval of a product. Health care providers are called upon to sense not only a legal obligation to avert lawsuits but also a bioethical imperative to assist their patients in preventing harm and injury. Editors of journals should show heightened sensitivity to the problem of conflict of interest and refrain from publishing articles where such a conflict is prevalent.

Conflict of interest – The author declares no conflict of interest

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