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Article

A Multi-Institutional informed consent proposal as a prevention tool for Combined oral contraceptive intake and thrombotic risk

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Abstract: Background: Combined oral contraceptives are among the most widely used contraceptive methods in the world today. Despite the different changes in terms of estrogen/progestogen combinations and dosages, the thromboembolic risk for a woman who takes combined oral contraceptives persists to date. Methods: the review of relevant literature and international guidelines on prescription of combined oral contraceptives made it possible to create a proposal for informed consent to be used for prescribing. Results: The several section of our consent proposal are been designed according to a rationale in order to cover all the aspects presented by worldwide guideline: how to take, adverse effects, advertisements, extra-contraceptive benefits and effects, checklist for condition at risk of thromboembolism, signature of woman. Conclusions: An informed consent to standardize combined oral contraceptives prescription can improve women eligibility, mitigate thromboembolic risk and assure legal protection to healthcare providers. In this paper in particular we refer to Italian medical-legal scenario, to whom our group of researcher belong. However the model proposed is designed in the respect of main healthcare organization guidelines and it could be easily use by any center in the world.

Keywords: oral contraceptive; contraceptive informed consent; thrombosis risk, venous thromboembolism.

1. Introduction

The use of combined oral contraceptives, also known with the acronym COC or simply as "pill" in common languages, is today one of the most discussed and constantly developing topic. In 1981 Mclure et al, first, stated that COC has the lowest Pearl Index (PI), corresponding to 0.1, in comparison with the other existing contraceptive methods, like in example progesterone only minipill (PI 1-2), intrauterine devices (PI 1-3), condom (PI 0.4-1.6) or lactation for 12 months (PI 25) and coitus interruptus (PI 9) [1]. Still nowadays COC represent the most effective birth control method, comparable only to tubal ligation (PI 0.04) and vasectomy (PI 0.1), which however are surgical procedure and irreversible [1,2]. This is the reason why to date COC are one of the most use contraceptive method all over the world, mostly in developed countries, like USA, Australia and European Union [3-5]. In Italy the most common is the condom (prevalence 39.1%), but, the main contraceptive method still remains the pill (prevalence 25.9%), as the most adopted method in all groups of women considered, in pairs or not. Also noteworthy is the constant greater use of pills and condoms among women who are not in couples (34.9% and 33.4%), compared to those who are (21.3% and 16.1%), maybe according to the different maternity projects in the two groups [6].

This phenomenon reflects the additional health effects of COC, which let them prescribed as therapy as well as mere contraception. The main extra-contraceptive benefits of combined hormonal contraception are divided in three categories: effects on symptoms of the menstrual cycle (dysmenorrhea, heavy menstrual bleeding, premenstrual syndrome, menstrual headache, hyper-androgenic symptoms); improvement of gynecological pathologies such as adenonomiosis or endometriosis and related consequences [7]; preventive effects of pathological conditions (pelvic inflammatory disease, extra-uterine pregnancy, ovarian/endometrial/colorectal and other cancers) [8,9].

Despite the many advantages, some physicians and even more women have still doubts about the possible side effects COC intake related [10]. Actually the most feared one is the thrombosis risk, still existent, as claimed by many health worldwide organization [11]. The COC-related thrombotic diathesis mostly occurs as venous thromboembolism (VTE), a nosological entity including deep venous thrombosis, commonly in the thigh or lower leg – or pulmonary embolism. While VTE is a rare event in young women of reproductive age (incidence 1–5/10,000 woman-years), COC increase the overall risk of VTE, increasing its incidence approximately up to 10–15/10,000 woman-years [12-16].

However, VTE risk due to COC intake is still very low and is much lower than the risk during physiological conditions, like pregnancy (approximately 5–20/10,000 woman-years) and the postpartum period (40–65/10,000 woman-years) [17]. COC-related VTE risk is also lower than the corresponding VTE risk with other contraceptive methods (Figure 1A), which also promote an increase of blood clots, like transdermal patch or vaginal ring [18,19].

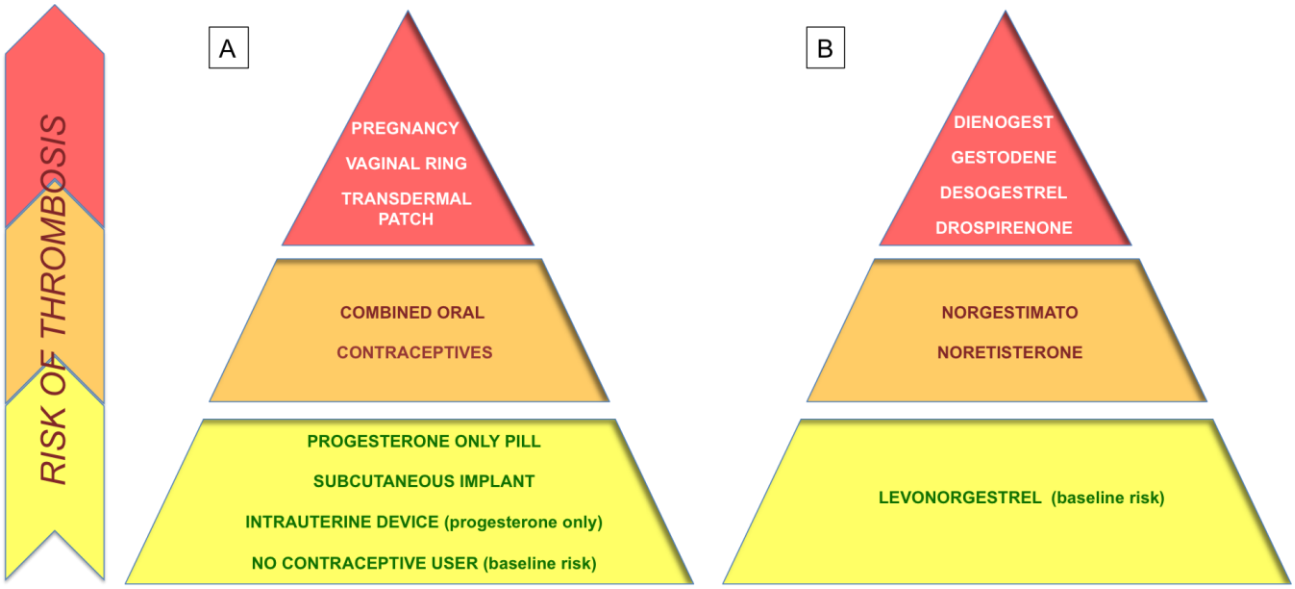

Figure 1. Contraceptive methods and thrombosis risk: The pyramid on the left (Figure A) groups the different contraceptive systems, including physiological conditions such as pregnancy, classifying them according to the corresponding risk of thrombotic events (highlighted by the change in color, from yellow to red); the pyramid on the right (Figure B) represents the various progestin components of the combined oral contraceptives available on the market, classified according to their risk of thrombotic events.

In order to mitigate this risk it is fundamental that the prescription of COC consist in an exhaustive and complete counselling with the woman, focusing on two main topics. First, the women should know signs and symptoms of VTE, like swollen or painful calf or shortness of breath, being able to early recognize them and to consult a healthcare provider as soon as possible to improve prognosis. Secondly, the physician should be sure to detect any possible individual woman's current risk factors, which could contraindicate prescription of hormonal contraceptive [12,16]. In this article our research group suggest the use of an informed consent for COC prescription in order to mitigate VTE risk, making safer COC intake.

2. Materials and Methods

A thorough search of relevant scientific literature has been carried out on multidisciplinary databases (PubMed, Scopus, Research Gate, Google Scholar) and article that were published up to 2021 with corresponding updates. The search keys used were: combined oral contraceptive, pill, hormone therapy, estrogen, progestin, contraception, thrombotic risk, deep vein thrombosis. Papers centered around cases and instances in which COC intake were not linked to thrombotic occurrence were disregarded. Moreover several studies have been found by sifting through the references of the selected papers and an additional search was conducted on institutional websites for reports, guidelines, opinions and recommendations released by international and national institutions, like: World Health Organization, Centers for Disease Control and Prevention, Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologists, Royal College of Obstetricians and Gynecologists, American College of Obstetricians and Gynecologists, National Institute for Health and Care Excellence, Italian Society of Gynecology and Obstetrics, Italian National Institute of Health.

The search was limited to English and Italian languages and all articles have been independently delved into by three of the authors in order to make sure about their relevance within the framework of the present paper; only those articles deemed to be relevant by at least two of them and with the agreement of the others authors have been ultimately selected.

3. Results

In the last 12 years, 14 of the 57 articles concerning the problem object of our study (COC and thrombotic risk), have been selected by the main scientific search engines as they are considered the most complete and up-to-date. Evaluating the current literature, we identified seven manuscripts that refer to guidelines, practical recommendations or information notes from world health organizations. These guidelines have been the basis for the realization of our informed consent [3,12,16,17,20-22]. These international guidelines agree that the assessment of medical eligibility fro COC prescription should not routinely include any blood exams, including testing for thrombophilia/hyperlipidaemia/diabetes mellitus/liver function or pelvic/breast examination and cervical screening, however the strength of recommendation is, instead, mandatory to assess the following aspects: medical conditions, lifestyle history, drug history (any prescribed or non-prescribed drug that could affect COC/itself be affected by COC), a recent blood pressure recording (strength of recommendation C) and BMI evaluation (D) [12,20-22]. Our informed consent (Supplementary Figure S1) could be a useful tool, which allows to define at the best and standardize COC prescription and, thus, the corresponding woman's counselling.

A complete contraceptive counselling should focus on three main goals: giving detailed and exhaustive information's on the chosen method of contraception; helping and professionally supporting woman's decision-making process [23]; avoiding a managerial approach in favour of an individualized one, respectful and attentive to the preferences, needs and individual values of woman. Our informed consent has been designed in the respect of worldwide guidelines could guarantee both a good clinic-anamnestic evaluation and a good patient information, reaching both a primary and secondary VTE risk prevention. Its application could easily stratify the target of women with low thromboembolic risk and adequately selecting COC prescription, making an objective proof of it, without need of doing any blood exams. The main section which are made of our informed consent are on: how to take COC; specific warnings to know before assumption; possible adverse effects; signs and symptoms whose appearance during COC intake requires a timely clinical evaluation; extra-contraceptive health benefits and effects; woman's data including checklist of possible VTE risk conditions; woman signature.

3.1 The informed consent for Combined Oral Contraceptive: our proposal

The possible informed consent, will be address to the following points, as reported in Supplementary Figure S1:

I-) HOW TO TAKE IT: Taking combined hormonal contraception (COC), from 1 day of Menstrual Cycle ensuresimmediate effectiveness. Wanting to start taking at any time of the cycle, it is recommended to use an additional contraception for 7 days and, only with the pill with Estradiol Valerate (EV) +Dienogest (DNG) in the formulation 26+2, for 9 days.

II-) WARNINGS: The first week of taking contraception, either EP or POP, inhibits ovulation. Delays or forgetting to take pills considerably increases the chances of pregnancy during the first week of the pack. The allowed intake delay is 12 hours, after 24 hours it is

advisable to take two pills together. Risk of ineffectiveness in case of vomiting within 3 hours or profuse diarrhea after 4-6 hours of intake. First clinical check-up after 12 months from the beginning of therapy.Control of blood pressure within 6 months of starting therapy. COC use should be discontinued 4 weeks before major surgery.

III-) SIDE EFFECTS: The COC are associate with an increase risk of venous thromboembolism (VTE) but it should beconsidered that, in most women, the benefits associated with using COC far outweigh the risk of serious side effects. Possibility of water retention that can cause an increase in weight of not more than 2kg, totally reversible to the suspension of the method. However, the available literature is not sufficient to determine the effect of COC on weight. Sensation of heavy legs, headache while taking or during the break period, mastodynia, nausea, rarely vomiting, changes in sexual desire. Most side effects are reduced already from the second cycle, often resolving spontaneously within 5 months. Occasional bleeding may occur. Have specialized medical assessment in the case of side effects of any entity. Please note: COC exposes to an increased risk of venous and arterial thrombosis ranging from 5 to 12 per 10,000 women each year depending on the type of COC taken, therefore it is recommended to alert the doctor and to go to the emergency department if there are signs or symptoms attributable to this event (swollen arms or ankles, legs tingling, lower extremity edema, erythromelalgia, dyspnea, etc). In this regard, it is recommended a periodic re-evaluation of individual risk factors such as age, smoking, obesity, etc.

IV-) SYMPTOMS OR DIAGNOSES REQUIRING CLINICAL ASSESSMENT DURING COC.

a-) *Urgent action*: chest pain, shortness of breath, hemoptysis, pain in one leg (usually the calf or inner thigh), swelling in the leg or arm, numbness or weakness on one side of the body, sudden change in your mental state.

b-) *Outpatient care*: breast node, secretion from the nipple, nipple inversion, changes in the breast skin; new onset migraine, new sensory or motor symptoms in the hour preceding the onset of migraine; persistent atypical vaginal bleeding; arterial hypertension, increase in body mass index (>35 kg/m2) (BMI >35), migraine or migraine with aura, deep venous thrombosis or pulmonary embolism, blood clotting abnormality, antiphospholipid antibodies positivity; angina, heart attack, stroke or peripheral vascular disease, atrial fibrillation, cardiomyopathy; mutation of the gene BRCA1-2 or breast cancer, liver tumor, gallbladder calculus.

V-) EXTRA-CONTRACEPTIVE BENEFITS: Hormonal contraception exerts a protective effect on genital integrity and fertility achieving overall a benefit in terms of reproductive health. Reduction of dysmenorrhea and heavy menstrual bleeding, premenstrual syndrome, menstrual headache, hyperandrogenic symptoms, endometriosis, ectopic pregnancy, Pelvic Inflammatory Disease(PID), prevention of ovarian, endometrial and colorectal cancers.

4. Discussion

With the aim to suggest our informed consent as a preventive tool for VTE during COC intake, we focused on several point. First of all we designed a checklist including all the possible contraindications, described by the main international guidelines mentioned above. They are 21 anamnestic criteria, which represent an absolute contraindication to COC intake, because they all are attributable at almost one of the following conditions, which alone or together plus pill show an additive and synergic pro-thrombotic effect,

according to well known pathophysiologic mechanism: hepatic dysfunction, cancer, proflogistic conditions, pregnancy, breastfeeding and vasculopaties of any types. The checklist make the physician sure to have collect all the needed anamnestic data at the time of prescription [24]. Secondly in our informed consent we decided not only to add several recommendation on how to correctly take the pill, but also a well detailed description of any possible signs or symptoms needing clinical evaluation. Specifically in the consent it is distinguished between urgent conditions, which have to be evaluated in the emergency room, and conditions whose evaluation can be deferred and must be done in an outpatient setting. This allows the woman to be more aware of her therapy, stratifying possible side effects by relevance, avoiding unnecessary and excessive worries for the woman and, at the same time, improper hospital access [24].

Finally the reference to the extra-conceptive effects of COC is useful for two main reason. On one hand the woman who choose COC as her contraceptive method is reassured and encouraged on this type of drug, improving her compliance and, thus, COC effectiveness. In fact in the past COC assumption was interrupted due to disinformation on COC and oncological risk linkage, then discredited by more recent literature [25,26]. On the other hand the physician should specify on the consent if the COC prescription is not only for a contraceptive aim but it is a therapy for a gynecological conditions, because this affects the type of COC chosen and the associated VTE risk. As a matter of fact each type of COC has its own VTE risk according to its estrogen-progestin qualitative and quantitative composition. According to guidelines COC containing ≤30 μg EE (ethinylestradiol) in combination with levonorgestrel (LNG) is a reasonable first-line choice of COC as mere contraception, in order to minimize cardiovascular risk [12,16,20-22]. Actually VTE risk is estrogen dose-related, but the metabolism of EE varies significantly both between individuals and within the same individual. Ranging EE bioavailability around 38%-48% has to be done the minimum effective dose [27]. LNG, instead, belongs to the second generation of progestins and is the one with the lowest VTE risk in association with EE in comparison with the other combinations with the same estrogen component (Figure 1B) [22,28]. However, when COC represent a therapy, despite the higher relative risk of VTE, the physician is authorized to choose a different combination of COC. In example Dienogest is the progestin component of choice for endometriosis, despite its relative risk with EE is 1,6 times greater than LNG. Instead drospirenone, like other fourth generation progestins, could be choose for patient with clinical and/or biochemical hyperandrogenism, ranging its relative risk with EE around 1,5-2,0 more than LNG [22]. Further on-going studies will define the VTE risk of other combination of COC, in example with estradiolo-2-valerato, to reduce as much as possible relative risk in COC therapeutic regimens and combinations.

The idea and design of our informed consent has been arose not only from literature and epidemiological relevance, but also from Italian medical-legal scenario, to whom our researchers group belong. But at the same time we created a tool valid allover the World. The Italian legislation specifies that the doctor must provide clear and complete information to the patient on the risks and benefits of therapy. The drugs used for contraceptive purposes are not strictly therapeutic in almost all cases. Therefore the risk / benefit ratio must be carefully calibrated on the needs and personal will of the patient. The benefit is to protect the conscious choice of having a pregnancy. In this sense, it can be broadly understood as the benefit of preventing damage to health (psychological, physical, social) resulting from an unwanted pregnancy. Those that are the risks have already been described in this article. In general, the prescribing physician needs to be updated on scientific advances, knowing individual benefits and risk factors.

The medical doctor is autonomous in the choice of therapy, even being able to deviate from the guidelines if these are not applicable to the specific case, as reaffirmed in Italy by the Gelli-Bianco law. Therefore, the first element to be evaluated must be the suitability of the proposed therapy to the needs of the case. After making sure of the suitability of the therapy, it is necessary to evaluate the safest treatment options for the patient among the

available treatment options. The conduct of the doctor who prescribes, albeit with diligence, a therapy involving greater risks for the patient, if it then materializes in damage, is considered negligent, as he has discarded other therapeutic options suitable for the specific clinical condition and such as to avoid the determination of the harmful event (sentence n.8875 of 08.09.1998 of the Cassation Criminal Section III). The doctor proposing the therapy must actively investigate what the patient's risk factors are. Therefore, diagnostic investigations are useful in case of doubts. Communication with the patient must address both the personalized risk and the benefit of the therapy. This communication must be in writing and sufficiently clear, as well as appropriate to the patient's cultural level.

5. Conclusions

Consequently, generic or too technical consent forms are not valid, such as not to be understandable to the patient. Therefore, although some generic information can be written on a pre-filled consent form, it is necessary to leave room for the personalization of the information on a case-by-case basis, making sure that the written consent form is clear in all its fundamental parts: (i) therapeutic purposes, (ii) therapeutic alternatives and their risk profile, (iii) general and specific side effects, (iiii) Behavioral measures to be taken in order to avoid therapeutic failure or the onset of complications.

Supplementary Figure S1. Proposal of informed consent targeted to COC prescription.

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