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Adverse Effects of Hormonal Contraception

R. Sabatini[1], R. Cagiano[2], T. Rabe[3]

With worldwide unintended pregnancy rates approaching 50% of all pregnancies, there is an increased need for the improvement of hormonal contraception acceptability, compliance and continuation. Despite the safety profile of current COCs, fears of adverse metabolic and vascular effects caused by estrogen component, and possible neoplastic effects of these formulations remain. Misperceptions and concerns about side-effects, especially those affecting the menstrual cycle and increased body weight, are often given as reason for discontinuation. Besides, severe adverse effects exist; perhaps they are very rare, but it might be that other cases were underestimated or ignored. It is important to take into account that COCs, as all medications, have some contraindications, which is mandatory to consider. The „pill" could be not for everyone. In any case, also mild or moderate adverse effects of COCs may impair the woman's quality of life. It is well known that even small increases in frequency of adverse effects, in COCs-users, could have a general critical health impact because of their widespread use, which is currently expanding to potential risk groups.

To avoid adverse events by COC use the exclusion of patients with known risk factors including patient history and family history is necessary. Furthermore the patient should be informed about possible side effects and side effects during OC use should be carefully monitored. Finally the risk benefit analysis for oral contraceptive pills which are worldwide used since more than 50 years for healthy patients is positive. Most women will benefit from additional non-contraceptive benefits such as improvement of acne vulgaris, dysmenorrhoea, stabilization of menstrual bleeding pattern, less ovarian cysts and finally a lower risk for ovarian and breast cancer, which persists even after withdrawl of COC for several years. **J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 130–56**

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■ Introduction

Combined hormonal contraceptives (COCs) are one of the most popular methods of birth control, worldwide. This reliable form of contraception, having a theoretical failure rate of 0.1% and, due to problems with compliance, an actual failure rate of 2–3%, may have several contraindications to use. In fact, COCs could induce adverse effects, most of them not serious but some which can be life threatening. The most serious risks associated with pill use include blood clots and venous thromboembolism, cerebral stroke, and heart attacks [1, 2]. These risks are increased in users who smoke, especially over age 35. In the early 1980s, the third-generation COCs were developed in an attempt to decrease the risk of cardiovascular disease (CVD) and to decrease androgenic side-effects such as weight gain, acne and adverse changes in metabolism of lipoproteins [3]. Although the third-generation 19-nortestosterone derivatives (gestodene, desogestrel) allowed reduction doses, the major disadvantage of these COCs, according with the majority of authors, is the increased risk of vascular effects [4]. In the last decade, with the aim to decrease the adverse effects COCs-related and to enhance the user's compliance, besides the dose reduction, other approaches have been performed such as the development of new steroids and the characterization of new schedules of administration. Ethinylestradiol (EE) and progestin (P) work synergically to inhibit ovulation. In addition, EE exerts its action, primarily dose-dependent, on the estrogen-target organs and tissues: endometrium, mammary epithelium, liver, haemostasis, and lipid metabolism. The androgenic action of progestins, reflected in reduction of HDL-cholesterol, is an important factor in occurrence of arterial accidents [5]. Experimental studies "in vitro" suggested that estrogens, inducing antioxidant effects on LDL, might be regarded as beneficial to arterial wall health [6]. Progestins could oppose the effect of estrogen in several systems, inducing LDL oxidation and consequent arterial wall injury [7]. The adherence to COCs is often poor, particularly in adolescents. Concerns about side effects, especially those affecting the menstrual cycle and the body weight, are often given as reason for discontinuation. Consequently, unintended pregnancy in adolescents remains a wide-spread social problem in all developed countries; in fact, five million of abortions carried out yearly, in the world, concern girls aged 15–19 [8]. Then, it is mandatory to provide for a safe method of birth control in this age group and to avoid the method discontinuation. However, the contraceptive management of these young women may encounter serious problems among those unaware carriers of the "factor V Leiden mutation" or of the other kind of diseases, especially affecting haemostatic system [4, 9–11]. Furthermore, there is an emerging evidence for requiring contraception in women aged 40 and older in which the occurrence of an unintended pregnancy might represent a significant problem. Although fertility naturally declines with advancing age, women in their forties wish to continue to be sexually active long beyond their desire for childbearing. Then, contraception becomes a great consideration during the last reproductive years. Recent researches indicated the safety of extending the use of combined hormonal contraceptives (COCs) to healthy women beyond the age of 40 and up to menopause without the need for replacement [12]. Women should still use con-

traception until one year after the last menstrual period because irregular ovulation may occur. Since well-designed studies proved an increased risk of thromboembolism with aging and with estrogen dose, it is wise to prescribe the lowest available dose of EE in the COCs, for adequately counseled couples [13]; although women's age, obesity and family history of hypertension are associated with an increase of blood pressure, independently from the contraceptive used [14, 15]. On the other hand, to continue COCs until premenopausal age and over could have a protective effect against cancer of ovary, endometrium and colorectum [16, 17]. The long-term cancer benefits might counter the short term harmful ones if they persist into the age, when most malignancies become common in women 50 years old or more [18]. It is necessary to make an accurate selection of the middle-aged women considering the high risk of adverse effects of this age group. Generally, disturbances COCs related, are mild or moderate in level; rarely, severe and only sporadic fatal cases are reported. Whatever the case, severe adverse effects exist; perhaps they are very rare, but it might be that other cases were underestimated or ignored [19]. It is important to take into account that COCs, as all medications, have some contraindications, which is mandatory to consider. The "pill" could be not for everyone. In any case, also mild or moderate adverse effects of COCs may impair the woman's quality of life. Besides, even small increases in frequency of adverse effects in COCs-users have a general critical health impact because of their widespread use, which is currently expanding to potential risk groups. In fact, women transplanted, depressed or suffering from cardiovascular diseases, diabetes, neoplasm, thrombophilic syndromes, rare diseases and/or smokers, today seek contraception [5, 20]. The medical history and the eventual risk factors of each woman, requiring contraception, should be carefully evaluated, before the prescription. In addition, for the management of these cases and the individual risk evaluation, specific knowledge is necessary about the particular pathologic entity and the possible contraceptive action. In fact, the inaccurate evaluation can lead to refuse a safe contraceptive method when suitable, or to prescribe a hormonal contraceptive when

hazardous [21]. These circumstances, at the worst, could be object of serious legal proceedings. Surveillance of the user's health and follow-up are needed. Consequently, an accurate contraceptive counseling, a good experience in this field and an optimal knowledge of each contraceptive method, together with its potential adverse effects, are mandatory for a modern contraceptive strategy. In conclusion, therapy selection should be individualized and based on the patient's specific needs and global related health risks.

■ 1. Mild Adverse Effects

The majority of women who use the birth control pill experience no side-effects at all; while, some of them experience mild side-effects such as spotting or breakthrough bleeding (BTB), nausea, headache, breast tenderness, weight gain, mood changes, low libido, and dermatologic problems. Mild and transitory disturbances are common in the first cycles of hormonal contraception and usually disappear after this period, without any problem [22]. However, these findings can also occur in the general population and during use of placebo, they can impact the users' lifestyle [23, 24]. Generally, COCs, with the highest progestin and estrogen potency and dose, are associated with the least number of bleeding days. Besides, it is well known that the ratio of the two steroids may affect bleeding [25]. In fact, menstrual disturbances are the consequence of both the prevailing levels of estrogens and the more or less suppressed endometrium [26]. Intermenstrual bleeding and amenorrhea cause worries about pregnancy and doubts about the method's effectiveness. Teens, in particular, have concerns about the menstrual irregularity and are more likely to discontinue hormonal contraception because of it. Providers understand that these side effects are minor and of little medical consequences but adolescent users may be ascribing great significance to these effects and may be declining these methods because of fear and misperceptions [27]. Inconsistency of use, chlamydial infection and smoking are factors that may have significant effects on rates of spotting and BTB. Frequency of intermenstrual bleeding, during the first three months of COCs use, seems highly influenced by regular-

ity of use. In regular users of monophasic COCs, containing ethinylestradiol 35 mcg/norgestimate 250 mcg, it was showed that the frequency of intermenstrual bleeding is below 2.6%. In Sunday start users the proportion of women with bleeding-free weekend increased to 47%, after the third cycle [28]. Comparing the degree of cycle control provided by various oral contraceptives is problematic. Clinical trials of OCs do not use standard terminology and definitions, making it difficult to analyze bleeding patterns of one preparation with those of another. Clinicians must alert pill-users to the possibility of intermenstrual bleeding and educate them with regard to the importance of continued, consistent oral contraceptive use to minimize this problem in their practice [29]. Several studies have confirmed an increase in intermenstrual bleeding associated with clamydial infection in pill-users. To evaluate the incidence of the problem, 65 women who had used OCs for more than 3 months and who presented with intermenstrual spotting, for which no readily demonstrable cause could be identified, were compared with 65 matched controls, without intermenstrual spotting, who were taking OCs and who had chlamydia testing because of one or more risk factors, and 65 matched controls seeking contraception. Nineteen of the 65 women (29.2%) taking OCs for more than 3 months and experiencing bleeding had positive tests, in contrast to seven of 65 matched controls (10.7%) who were also on OCs and who had had chlamydia testing because of vaginitis or new or multiple sexual consorts, and four of 65 women (6.1%) who were screened for C trachomatis before initiation of contraception [30]. Therefore, when spotting or BTB occur in women previously well regulated on OC, providers should consider causes other than OCs, very likely a chlamydial infection [25]. Smoking may increase unscheduled bleeding by interfering with estrogen metabolism. Consequently, women who smoke cigarettes and use OCs are more likely to have breakthrough bleeding than women who do not smoke [31]. OCs containing the new non-androgenic progestins and low-estrogen doses tend to effect acceptable bleeding patterns similar to those of the older low-dose EE-OCs. Women often discontinue hormonal contraception because of perceived weight gain [32]. Al-

though this suggestion affects, particularly, adolescents and young women preoccupied with body image. This teen's misperception is common reason of withdrawal or switching to other methods, often less effective than COCs. It has been known that adverse effects represent the main factors in determining acceptability and compliance with any hormonal contraceptive (HC) method. Several studies are carried out with the aim to clarify if weight increase, with hormonal contraceptives, is real or only a common misperception. The combination ethinylestradiol (EE) 20 mcg/levonorgestrel (LNG) 100 mcg seems to have no significant impact on body weight and body composition(fat mass, fat-free mass, total body water, intracellular water, extracellular water) [33]. A multicenter comparative study on norgestimate (NGM) 180/215/250 mcg/EE 25 mcg versus norethindrone acetate 1 mg/EE 20 mcg showed that only the 0.3% of users, in both groups, experienced a 10% increase in weight [34]. A randomized, prospective study evaluating the incidence of side effects in women using EE 20 mcg/LNG 100 mcg or EE 15 mcg/gestodene 60 mcg or vaginal ring(EE 15 mcg/etonogestrel-ENG 120 mcg) reported no significant weight gain, into three groups. Particularly, over 1 year of treatment, the maximum weight gain from baseline was 2,8 kg in the first group, 1,6 kg in the second group and 0,8 in the third group [35]. Another study which compared the formulations EE 30 mcg/chlormadinone acetate 2 mg and EE 30 mcg/Drospirenone 3 mg showed no significant increase in body weight in both groups of adolescents considered, as demonstrated in other trials [36–39]. In women with a tendency to weight gain under oral contraceptives because of water retention, the use of EE 20–30 mcg/drospirenone (DRSP) 3 mg seems to be the ideal method to avoid this problem [37, 40]. In addition, a cohort study on lower and middle class Brazilian copper-IUD users, during ten years, explains that these women tend to gain weight during their reproductive life, because of other factors [41]. So, although weight gain is perceived as a disadvantage of oral contraception, no real weight increase was reported in the majority of current investigations. It is found no decrease in the reporting of symptoms with the reduction of estrogen dose, nor with

use of third-generation progestins. Little variation between monophasic and triphasic formulations was reported [22]. Nevertheless, the fear of weight gain with oral contraceptives can lead to noncompliance and method discontinuation. Woman need reassurance to remove such misperceptions. In fact, lack of informative communications between gynecologist and user and mistaken knowledge may contribute to ignorance about HC and misperceptions, particularly in adolescents [42]. Some women may experience mood swings or depression, side effects that may influence their decision to continue in taking a birth control pill, particularly if they have a history of depression.

Cognitive-emotional factors, including the appraisal of stress, loci of control and self-integration, seem to be implicated with specific patterns of negative affect and much more so for hormonal contraceptive-users than for nonusers. However, for the most part, oral contraceptive use versus nonuse seems to influence the saliency rather than the nature of cognitive-emotional patterns [43]. In addition, it is believed that most women, using combined oral contraceptives (COCs), can expect minimal change in mood, but the percentage of women who reported depressive symptoms seems to decline as increases the number of years of COCs use [44, 45]. Really, few studies were focused on the depressogenic properties of the hormonal contraceptives (HC), in spite of the diffuse concern about mood changes [46]. Impairment of social functioning is a significant aspect of depression, distinct from the symptoms of depression [47]. A study hypothesized that changes in reproductive hormones, by affecting the synchrony or coherence between components of the circadian system, may alter amplitude or timing relationships and thereby contribute to the development of mood disorders in predisposed individuals [48]. Sporadic cases of panic attacks, in women who had previously experienced depression and who were COC users, have been reported; however, these reports regarded the COCs containing high doses of EE (50 mcg) and appeared when these users had stopped taking the pill [49]. Several biological conditions may be involved in the predisposition of women to depression, including genetically determined vulner-

ability, hormonal fluctuations and a particular sensitivity to such hormonal fluctuations, in brain systems, that mediate depressive states. In particular, several reproductive events may be related to depression as premenstrual syndrome (PMS), premenstrual menstrual dysphoric disorder (PMDD), pregnancy, postpartum, menopause, miscarriage, infertility, hormone-replacement-therapy (HRT) and hormonal contraceptive use [50, 51]. Progesterone and progestagens may induce negative mood, most probably via the GABA (A) receptor active metabolites. In humans, the maximal effective concentration of allopregnanolone, for producing negative mood, is within the range of physiological luteal phase serum concentrations [52]. It is known that neuroactive steroids, as the gamma-aminobutyric acid receptor agonists, are important in the modulation of affect and adaptation to stress [53]. Nevertheless, a recent study performed on adolescent girls treated with depot-medroxy progesterone acetate (DPMA), over a period of 12 months, showed that those do not present depressive symptoms [54]. Similar results were obtained by an Australian study carried out on 9.688 young women, aged 22 to 27, taking COCs. In fact, the odds ratio of nonusers, experiencing depressive symptoms, is not significantly different from that of COC users(OR = 0.90–1.21) [45].Therefore, it seems that healthy women without underlying mood or anxiety disorders, who were given a low-dose combined oral contraceptives, did not experience adverse psychological symptoms despite a significant reduction in neuroactive steroids. Another study reported that COC users have more negative mood impact than vaginal ring users, as well as irritability, is more frequent in COCs containing low-dose EE than in COCs containing very low-dose EE. However, irritability seems to decrease with duration of pill-use [35]. Some researchers have found in adolescent girls, taking COCs, a higher prevalence of positive mood than in MPA users [55]. A significantly higher number of cases of previous depressive episodes, PMS and PMDD in depressed patients, compared with nondepressed women, has been reported [56, 57]. A study analyzed data from 658 COC-users. In the overall sample, 107 women (16.3%) noted worsening of their mood on oral contraceptive, 81

(12.3 %) experienced mood improvement and 470 (71.4%) had no change in their mood [58]. In practice, the only consistent OC-related mood effects, experienced by most women, are beneficial, although a subgroup of women experienced negative mood changes. Future research must focus on expounding the individual difference and OC-related risk factors for negative mood swings [57]. Despite numerous studies on the topic, to date there is no consensus on the effects of oral contraceptives on mood or on the mechanisms by which they exert these effects. In conclusion, the problem of whether or not oral contraceptives affect the psyche function of the woman is still controversial. Furthermore, the widespread presence of the depression in the industrialized countries, increases the difficulty. It is suggested that the mood and behavioral effects of OCs might be attributed to different progestin compounds and, possibly, to their estrogen ratios [59]. Women with a history of depression should be attentive to potential mood changes after starting an oral contraceptive, but oral contraceptives are an important option for all women, including those with a history of depression. The changes in desire and sexual satisfaction, during hormonal contraceptive(HC) use, are important elements that may influence acceptability, compliance and method continuation. Little is known about the influence of HCs on sexual functioning. Sexual side-effects have been reported in women taking HCs, although no consistent pattern of effect exists to suggest a hormonal or biological determinant [60]. Overall, literature data show that women, during HCs use, experience positive effects, negative effects, as well as no effects on libido [61–64]. Anyway, current pill-users seem to discontinue their use for low libido less frequently than did users of higher dose pills [65]. In the past, an important trial reported evidence that mood and sexual desire are not associated suggesting that HCs can have direct effects on women's sexuality. Therefore, the negative effect on sexual interest found in this study was not just a result of HC induced negative mood changes [66]. Furthermore, a population survey, conducted among 1466 women who used different methods of birth control (oral contraceptives, intrauterine devices, condoms, natural family planning, sterilization),indicated

that combined oral contraceptives and sterilization have less negative impact on physical and psychological functioning than the other methods used [62]. This evidence is in contrast to what the general public often believes. Nevertheless, with the introduction of OCs very low-dose EE, sexual disturbances, due to vaginal dryness and low desire are problems which often come-up [63]. A study evaluated the effects on vaginal dryness, sexual desire and sexual satisfaction of the hormonal contraceptives. low-dose EE (20 µg EE/100 µg levonorgestrel (LNG) versus very low-dose (15 µg EE/ 60 µg gestodene or vaginal ring containing 15 µg EE/120 µg etonogestrel). After three cycles, 30.4% of the participants, taking oral contraceptive, containing very low-dose EE, reported vaginal dryness, while the same problem was reported in 12.7% of the COC low-dose EE users and in 2.1% of the women using the contraceptive vaginal ring. In the meantime, COC 15 µg EE users reported the highest rates of negative impact on sexual well-being and this data may be related to the free testosterone levels. In addition, this study reported a discontinuation rate of 22.3% with COC low-dose EE, 30.4% with COC very low-dose and 11.7% with vaginal ring [35]. Indeed, cycle control and sexual satisfaction seem to be good indicators of treatment adherence and continuation, although studies on the effects of sex-steroids on female sexual behavior have not yielded conclusions. With use of OCs combination there is an increase in sex hormone-binding globulin with resultant lower free testosterone levels. This could explain the decreased sexual desire in pill users, while vaginal dryness could be due to the low estrogenic dosage, with consequent arousal or enjoyment disorders [67, 68]. OCs could also cause emotional-affective, parasympathetic and psychosexual disturbances. From the biological point of view, androgen-level modifications and loss of estrogen fluctuations have to be taken into consideration. Both may act on sexual aspects of the subject, decreasing sexual desire and vaginal lubrication, respectively [69]. Many reports have established that sexual desire, in women, may be related to androgen levels; however, there are also reports showing that progestins with antiandrogenic effect in COCs do not affect sexual desire [35, 61, 63, 65]. In human popula-

tion, sexual behavior is not so simply determined by the level of sexual steroids. The difficulty arises from the complex interaction among different factors influencing female sexual function as sexual relationship type, menstrual irregularities, vaginal dryness, partner attraction and sensitivity, culture, economic status as well as life-style [67, 70]. Although sexual side-effects have been noted in various subgroups of women using hormonal contraception, no consistent pattern of effect exists to suggest a hormonal or biological determinant. Most likely, effects on sexual desire represent a complex and idiosyncratic combination of biological, psychological and social effects. Further researches are required to identify which factors may have the greatest effect. There are various adverse effects attributed to the use of OCs; however, in many instances, a casual relationship appears to be nonexistent, highly improbable or difficult to substantiate [71, 72]. The equilibrium of healthy skin and mucosa may be affected by pharmaceutical agents, as hormonal contraceptives (HC) causing different manifestations. Although combined HCs may be beneficial in certain androgen-dependent dermatoses, they can also affect the skin through their hormonal effects or through iatrogenic effects associated with their toxicity, in certain individuals [73]. The side-effects of the pill on the skin are probably more frequent and may have a potential to alter the quality of life of women who use it [74]. Cutaneous adverse effects as melasma, photosensitivity, bullous eruptions and monilias are frequently reported in women taking hormonal contraceptives [75]. Melasma or Chloasma, a dark brown hyperpigmentation, accounts for about 60% of all cutaneous side-effects of HCs and appears frequently in women who have heavily pigmented nipples and eyes [76]. It may occur in these women when not protected from sunlight and regress more slowly than after pregnancy, sometimes can be definitive. Progesterone activity changes the biochemistry and pH of the skin and sebacious glands, thereby contributing to eruptions of acne vulgaris [77]. However it is known that anti-androgen progestins and estrogen combinations are more effective than standard contraceptive combinations, without anti-androgen property, to trait the acne [78, 79]. Particularly, a study carried out

in 170 adolescent girls reported as very convenient the monophasic formulation containing ethinylestradiol 30 mcg and chlormadinone acetate 2 mg for the acne vulgaris management [36]. Even though many believe that combined oral contraceptives may cause hair loss, there is little evidence to support it. Alopecia is very rare and may even reflect a simple coincidence. Reactions of hypersensitivity or allergy to COC may include urticaria and eczema. Rarely, urticaria may be a life-threatening skin disease. The symptoms may range from pruritus to generalized skin eruptions, gastrointestinal and/or bronchial problems to systemic anaphylaxis and cardiovascular emergencies [80]. Dermatologic, vascular manifestations of HCs are dependent on the estrogens and include telangiectasias, angiomas and livedo reticularis. Although livedo reticularis or racemosa is commonly seen in women with antiphospholipid antibody syndrome or can be a nonspecific lesion of systemic lupus erythematosus [81, 82]. Several dermatological and systemic disorders may be aggravated by COCs as hereditary angioedema, herpes gestationis, porphyries, LES. Same condition for hidradenitis suppurativa, seborrhoea, and Fox-Fordyce disease [74].

■ 2. Moderate Adverse Effects

2.1. Hepatobiliary Complications
Hepatobiliary complications of combined oral contraceptives (COCs) are by far the most frequent and varied, among all moderate side-effects. However, the introduction of low-dose COCs led to an evident decline in their frequency [83]. Vascular symptomatology attributable to "pill" use includes the Budd-Chiari syndrome and the Peliosis Hepatis which are potentially serious, but often reversed with discontinuation of use [84–87]. COCs are inducers of certain hepatic enzyme systems causing generally little clinical effects, but also favor the formation of delta-aminolevulinic acid and should be avoided in case of Porphyry [88]. Intra-hepatic cholestasis may be induced by estrogens in pregnancy or in COCs treatment and, in clinical practice, it is indistinguishable from another cholestasis, aggravated or revealed by estrogens, such as primitive biliary cirrhosis. Reversible intra-hepatic cholestasis, as estrogen dependent

effect, in women with genetic predisposition, may induce pruritus, anorexia, asthenia, vomiting and weight loss without fever, rash or abdominal pain. Termination of COCs clears the condition without sequelae within 1–3 months, sometimes after a temporary worsening, in which abdominal pain and fever are the most common symptoms. This status is not related to the duration of use and disappears 5–15 days after COC use is terminated [89]. Despite their effect on the reduction of biliary excretion, COCs may provoke jaundice which is rare and apparently due to the estrogen and the progestin, both. Jaundice, usually, appears within the first six months of pill use and disappears, without sequelae, 1 or 2 months after termination of pill use. Half of these women, developing jaundice with COCs, have experienced intrahepatic cholestasis in pregnancy. They should be closely monitored when taking birth control pill. While, women with familial defect of biliary excretion, including Dubin-Johnson syndrome, Rotor's syndrome, and benign intrahepatic recurrent cholestasis should not take oral contraceptives [89]. Asymptomatic biliary lithiases is another possible clinical effect and it is twice common as in pill users as in the control population. Therefore, women taking COCs, almost always, have elevated cholesterol levels in their bile which probably explains the increased frequency of complications leading to cholecystectomy, in women receiving long-term estrogen treatment. It is important to know that the anomalies in the bile composition generally disappear when COCs use is stopped [90]. An asymptomatic lithiasis in a young OC user not necessarily require termination of COCs [89–92]. Patients with a past history of liver disease, in whom liver function tests have returned normal, may tolerate the oral estrogen. Although they need to be closely monitored for adverse reactions [89, 90]. Limited data from studies on chronic hepatitis or its sequelae suggest that COCs use does not affect the rate of progression or severity of cirrhotic fibrosis, the risk of hepatocellular carcinoma, in women with chronic hepatitis, or the risk of liver dysfunction, in hepatitis B virus carriers [93]. The role of estrogens in the genesis of hepatic adenomas is well established but it is more controversial with focal nodular hyperplasia [94–97].

2.2. Migraine-Headache
The classification of headache disorders of the International Headache Society clearly identifies an "exogenous hormone-induced headache" which could be triggered by an intake of combined oral contraceptives (COCs) [98]. The frequency of this symptom in women of reproductive age and the widespread use of hormonal contraception induce to consider the association as a relevant health problem [99]. A large cross-sectional population-based study, carried out in 46,506 women using COCs, proved that headache prevalence increases with age; in fact, it has been reported that are affected 22% of women aged 20–24, 28% aged 25–29, 33% aged 30–34 and as many as 37% of women aged 35–39. The same study showed a significant dose relationship between headache and estrogens while no significant association between headache and only-progestin contraceptives (COPs) was found [100].

Really, the effect of exogenous progesterone on headache and migraine is not well understood. It is known that headache can be related to estrogen exposure, during pill intake and after hormone withdrawal, in the pill free-interval [101–103]. It has been noted that migraines may occur during episodes of uterine bleeding in women taking progestogens even if ovulation is suppressed [104, 105]. However, it is unclear whether this effect is secondary to estrogen fluctuations, if due to incomplete suppression of the ovulation, or to increased prostaglandins within the endometrium [104]. Because progesterone-only methods may not suppress ovulation, estrogen fluctuations can occur. It has been observed that, in women taking progestogen-only pills, headache and migraine improve most often in those who have achieved amenorrhea [106]. However, even when ovulation is completely suppressed, estrogen fluctuations have still been noted in women using progesterone-only methods [107]. Third-generation progestogens may be associated with fewer headaches per cycle, compared with second-generation progestogens [108]. The newest formulations influence the headache course to a lesser extent than previous hormonal contraceptives, although these cannot completely avoid the possibility of an attack. A pilot study suggested that the use

of 50 μg estrogen patch during the pill free-interval may reduce the frequency and severity of migraine at that time [109]. Therefore, continuous regimen hormonal contraceptives (HCs) may represent a convenient strategy as preventive therapy reducing the frequency, duration and intensity of attacks [110, 111]. In any case, headache, associated with COCs, will typically improve as the use continues. Migraine-headache is undistinguishable from other benign headaches and recurring syndrome of headache, nausea, vomiting and/or other symptoms of neurologic dysfunction. Migraine with aura specifically describes a complex of neurologic symptoms that occur just before or with the onset of migraine/headache. Reevaluation or discontinuation of combined hormonal contraception is advised for women who develop a progressive severity and frequency of headaches, new-onset migraine with aura or nonmigrainous headaches persisting beyond 3 months of use [110]. Whatever, headache/migraine per se is not a contraindication for COCs use. Anyway, it is very important to remember that patients suffering from migraine with aura generally show a greater thrombotic risk than women with migraine without aura [112]. Other risk factors, as patient's age, tobacco use, hypertension, hyperlipidaemia, obesity, and diabetes must be carefully considered when prescribing COCs, in migraine patients. Migraine has been considered to be a benign, not life-threatening illness. In spite of this, several studies suggested it as a rare risk factor for ischemic stroke. A study reported six cases of migrainous stroke fully meeting the diagnostic criteria of the International Headache Society (HIS) and all patients had migraine with aura [113]. This association is still conflicting and seems to be restricted to particular subgroups as the women under 45 years of age with migraine with aura who smoke and use HCs. Furthermore, epidemiological studies disclosed the risk of stroke, raised in women who suffered from migraine in their younger time [112, 114]. Taking into account a baseline 10-years ischemic stroke rate of 2.7 per 10,000 young women (aged 25–29), COCs usage increases the risk up to 4.0. The risk might increase to 11.0 for women who have migraine with aura and to 23.0 for women with migraine with aura using COCs [115]. There are no available studies that directly compare the risk of stroke in migraineurs, with and without aura, using estrogen-containing contraceptive. The majority of the studies regarding stroke risk in women with migraine, using combined contraception, are retrospective case-controls. Thus, these data must be interpreted with caution [110, 116]. ACOG and the WHO state that the COCs may be considered for women with migraine headache only if they do not experience aura, do not smoke, are otherwise healthy and are younger than age 35 [117–119]. The IHS Task Force does not state that migraine with aura is an absolute contraindication to use of combined contraception and suggests an individualized decision regarding contraceptive choice [113].

3. Severe Adverse Effects

3.1. Cardiovascular Effects

Large prospective studies on adverse effects of oral contraceptives (OCs) have revealed an increased risk of circulatory diseases, mainly thromboembolic events, which appears strictly associated with the dose of contained hormones. Nonetheless, greater safety has been sought through a progressive reduction of the ethinylestradiol (EE) dose, it was estimated a 3–4-fold increased risk of venous thromboembolism with current oral contraceptive use. In any case, the absolute risk seems to be very small and almost half that associated with pregnancy. Extensive researches suggest that contraceptive hormones have antiatheromatous effects but relatively little is known regarding their impact on atherosclerosis, thrombosis and arrhythmogenesis. There are inconsistent results from studies on chance of stroke in pill users. Existing data are mixed with regard to possible protection from OCs for atherosclerosis and cardiovascular events; longer-term cardiovascular follow-up of menopausal women with regard to prior OC use, including subgroup information regarding adequacy of ovulatory cycling, the presence of hyperandrogenic conditions, and the presence of prothrombotic genetic disorders is needed to address this important issue. Studies on heart attack found increased risk largely confined to smoker and older women, with an up to 34-fold higher risk for heavy smokers over 40. Generally in young healthy women, risk of heart attack resulted lower than that in term pregnancy. Since serious reactions, which have a relatively low incidence, are highly underreported (less than 10%), it is difficult to prove dose-dependent differences in the rates of cardiovascular diseases. Current guidelines advise that, as with all medication, contraceptive hormones should be selected and initiated by weighing risks and benefits for each individual patient. Women 35 years and older, prior to use, should be assessed for cardiovascular risk factors including hypertension, smoking, diabetes, nephropathy, and other vascular diseases, including migraine. This procedure can permit, to women of all reproductive ages including perimenopausal women, to realize many health benefits through oral contraceptive use together with an improved health status later in life.

3.1.1. Blood Hypertension

Short-term studies have been suggested that combined hormonal contraceptives may induce a mild rise in blood pressure [120, 121]. It seems that HCs induce hypertension in approximately 5 % of users of high-dose pill containing at least 50 μg estrogen and 1–4 mg progestin; however, small increases in blood pressure have been reported even among users of modern low-dose formulations [14, 122]. In fact, it has been reported that low-dose HCs may induce a mild elevation in blood pressure, about 4 mmHg systolic and 1.0 mmHg diastolic, in 1.5% of users. This increase is statistically significant but clinically unimportant and may result on discontinuation [123]. Blood pressure differences between HC users and non users tend to increase with age. Furthermore, obesity, family history of hypertension and previous hypertensive disorders of pregnancy seem associated with an increase of blood pressure during hormonal contraceptive use [123, 124]. It is very likely that blood pressure undergoes physiologic changes depending on hormonal fluctuations. Data on long-term and withdrawal effects of HC use on this outcome are, however, scarce. A recent prospective cohort study carried out on HC-users and past users aged 28–75 years, showed that hormonal contraceptives seem to increase blood pressure and urinary albumin excretion (UAE) and may be deleterious on urinary function in 6.3% of the users, although stopping

may result in correction of these effects. In fact, women who take HCs have an increased risk of developing new hypertension, which returns to baseline within 1–3 months of HC cessation [125]. Although, some cases of irreversible hypertension, kidney failure and malignant nephrosclerosis have been reported [126, 127]. Women, with pre-existing hypertension who take HCs, have an increased risk of stroke and myocardial infarction when compared with hypertensive women who do not [128–130]. Women who smoke have an increased risk of hypertension (2–3 times) when take HCs. Smoking increases the risk of vascular damage by increasing sympathetic tone, platelet stickness and reactivity, free radical production, damage of endothelium, and by surges in arterial pressure. Effectively, females with nicotine abusus, hypertension and hypercholesterolemia have a damaged endothelium. The effect of the combined hormonal treatment on the endothelium in these women might include decreased ability to release the strong vasodilator nitric oxide and as a consequence an impaired vasodilation [131]. Surprisingly, this increased risk declines on quitting cigarettes within 2–3 months [132]. Blood pressure elevations are usually attributed to the estrogen, but there is evidence of a progestin role as well [124, 125]. The mechanism by which some HCs users develop hypertension is poorly understood, but it may be related to changes in the renin–angiotensin-aldosterone system [133–135]. The raise of hypertension, often associated with raise of weight, might be the consequence of increased fluid retention in women taking hormonal contraceptives, especially if over 35 years. Androgenic progestins accentuate sodium retention, which may play an important role [134]. A short-term study showed in women aged 35–39, treated with gestodene 75 mcg/EE 20 mcg versus gestodene 60 mcg/EE 15 mcg, a non statistically significant mean increase of 4 mmHg for systolic pressure and 2 mmHg for diastolic pressure in the first group and corresponding increases of 3 and 2 mmHg in the second group [136]. Considering the role of renin-angiotensin-aldosterone system in the development of hypertension, it is possible to explain the absence of effects on hypertension exerted by progestins containing HCs with antiandrogenic properties and,

particularly of the drospirenone, an aldosterone-derivative [135–137]. Among women taking COCs, HDL cholesterol levels decline and LDL levels increase compared to nonusers. This effect was attributed to the estrogen, but there is evidence of a progestin role as well [124, 125, 138]. On the other hand, old women treated with estrogens have more favorable lipid profiles than do women of the same age not receiving estrogen [139]. Although the first problem is the HC prescription and following use with prevalence of uncontrolled hypertension [140]. In fact, women with hypertension should be cautioned about the effects of estrogen containing oral contraceptives which may cause a further elevation in systemic blood pressure. Women with hypertension are at increased risk for cardiovascular events [141]. HC users, who did not have their blood pressure measured before initiating HC use, were at higher risk for ischemic stroke and myocardial infarction, but not for hemorrhagic stroke or VTE, than HC users who did have their blood pressure measured [122, 128, 142, 143]. In the meantime, in order to evaluate the risk factors for VTE and cardiovascular disease, prior to the prescription of combined hormonal contraceptives, a full clinical, personal and family history, together with the measure of blood pressure and body mass index (BMI) may be advisable. In any case, the absolute risk seems to be very small and is half that associated with pregnancy. However, findings indicate that there is no increased risk of myocardial infarction or stroke associated with oral contraceptive use in healthy, non-smoking and normotensive women, the adoption of this procedure can permit to women of all reproductive ages, including perimenopausal women, to realize many health benefits through oral contraceptive use, including improved health status later in life.

3.1.2. Myocardial Infarction
Each year 1.7 cases of myocardial infarction (MI) per 1 million normotensive women, aged 30–34, are registered [144]. The incidence of MI was estimated of 2–5-fold for hormonal contraceptive(HC)-users compared with nonusers [143, 145]. The risk results dose-related, and increased also for women using low-dose pill. Coagulation factors, especially factors VII and fibrinogen, have been established as important cardiovascular

risk factors. Procoagulant alterations are observed in women taking hormonal contraceptives (HCs) and in those receiving estrogen substitution, but unlike HC users, such women appear to be protected by age-related increases in the level of antitrombin III [142, 146]. Smoking is an important influence-factor on the fibrinogen level, which probably explains part of the increased risk of MI among HC users. However, the majority of studies indicate hypertension as the primary risk factor for MI. In fact, the rate of this event was evaluated 10.2 per 1 million of hypertensive women aged 30–34 [144]. Both, smoking and hypertension substantially increase the risk among HC users and some data suggest further increased risk among those with diabetes, hypercholesterolemia or a history of pre-eclampsia or hypertension-pregnancy related. The role of the different types of progestagens used in HCs is still controversial [122, 128, 147].

Clinical trials on myocardial infarction have found inconsistent results, possibly because of differences in the prevalence of risk factors, particularly smoking and elevated blood pressure, in the populations studied. In the absence of a history of smoking and other conventional risk factors, current users of modern COCs probably do not have an increased risk of myocardial infarction; neither are former users at risk [141]. Evidence for important differences in the risk of myocardial infarction between formulations is weak and contradictory. However, the risk could be highest in the first year of use and increased in women with a previous venous thrombosis and with age. In the past years was demonstrated, on 219 death from myocardial infarction, that the frequency of use of combined oral contraceptives, during the month before death, was significantly greater in the group with infarction than in the control group and that the average duration of use was longer [148]. The lowering of both estrogen and progestin content, since the introduction of the pill in 1960, clearly didn't reduce the risk of myocardial infarction; although current opinions are conflicting [149, 150]. Some studies reported that the risk of MI does not appear to depend on coagulation abnormalities. However, a study carried out on 217 women with a first myocardial infarction before the age of 50 years and 763 healthy control women, found

that the risk is substantially elevated among women with various inherited clotting factor defects [151]. The overall odds ratio for myocardial infarction, in the presence of a coagulation defect, was evaluated 1.1. The combination of a prothrombotic mutation in smokers seems to increase the risk of MI 12-fold compared with non-smokers, without a coagulation defect. Among women who smoke cigarettes, it was found that factor V Leiden presence versus absence increases the risk by 2.0, and prothrombin 20210A mutation presence versus absence by 1.0 [1]. Besides, the risk seems to be highest in the first year of HCs use. The effects in COC users of other risk factors for venous thrombosis tend to be less pronounced and more inconsistent. A number of studies have found higher relative risk among current users of low estrogen dose COCs, containing desogestrel or gestodene, than among users of similar products containing levonorgestrel [150]. A number of explanations have been proposed for these clinically small differences but evidence is weak. A transnational study comparing women, aged 18–44, 182 with MI and 635 without MI, reported overall odds ratio for MI, second generation COC users versus no current users of 2.35 and third generation versus no current users of 0.82. A direct comparison between third generation users and second generation users yielded an OR of 0.28. Among users of third generation COCs, the OR for current smokers was 3.75; while among second generation users was 9.50 [149]. In conclusion, myocardial infarction in women taking combined hormonal contraceptives remains rare; in fact, it has been estimated that the population attributable risk is less than three events in one million women years [145]. A logical hypothesis to explain the development of myocardial infarction would be an interaction between the hypercoagulability induced by COCs and the risk factors, known or unknown, in the users [152]. It is interesting to remember that antibodies to synthetic steroids (EE and P) and circulating immune complexes were found in the serum of 30% of HC users and their titres are significantly higher in 90% of women who develop vascular thrombosis unrelated to atherosclerosis [153, 154].

In the last years, sporadic cases of myocardial infarction associated with hormonal contraceptive use have been reported [154–156]. Women can minimize, and possibly entirely eliminate, their arterial risks stopping smoking and by having their blood pressure checked before using a COC, in order to avoid its use if elevated blood pressure is discovered. The users may decrease their venous thromboembolic risk by their choice of COC preparation although the effects will be modest. Thus, reducing the hormone dosage of COCs and performing better screening of patients are needed to further reduce the frequency of cardiovascular complications.

3.1.3. Stroke

Hormonal contraceptive(HC) users have a low background incidence of the major cardiovascular diseases. In fact, current users of low estrogen dose-HCs have a small increased risk of ischemic stroke, if they haven't other risk factors, notably hypertension, age, smoking, and a history of migraine [157–159]. Particularly, the risk of ischemic stroke, among current users with a history of hypertension, was evaluated 10.7 (OR) [160]. Similarly, the use of the HCs seems to increase the risk of hemorrhagic stroke in women aged over 35 (OR > 2) and, when they have a history of hypertension, this risk is 10–15-fold compared with women who did not use HCs s and did not have a history of hypertension [161]. Besides, HCs users who carried the D allele of ACE I/D polymorphism, predisposing to hypertension, could have a potential risk allele for stroke, especially for hemorrhagic stroke [162]. Current users who are also current cigarette smokers compared with women without these characteristics, have odds ratio (OR) > 3. Past users of HCs do not seem to have an increased risk for stroke. The risks are similar for subarachnoid and intracerebral hemorrhage [163]. After the introduction of low-dose oral contraceptives, a decline in cerebral thromboembolism, among young women, has been reported [139]. However, cerebrovascular occlusion in young women may be caused by hormonal contraceptive use when unsuspected free protein S or protein C deficiency, coagulation factor XIII gene variation or inherited thrombophilia exist [164–167]. The role of inherited prothrombotic conditions, as factor V Leiden, and prothrombin mutation in the pathogenesis of ischemic stroke is not well established; although it seems

that carriers of the factor V Leiden mutation might have a 11.2-fold higher risk of ischemic stroke than women without either risk factor [168, 169]. A prospective cohort study on 44,408 women on low-dose oral contraceptives and 75,230 with an intrauterine device (IUD), followed during three years, reported a higher incidence of hemorrhagic stroke than ischemic stroke (34.74 vs 11.25 per 100,000 woman years) for HC users. The relative risk (RR) for hemorrhagic stroke was 2.72 times compared with that in the IUD users. Furthermore, the RR of current users of HC was 4.20 and still reached 2.17 among past users after they stopped taking HC for more than 10 years [170]. While, other studies have found no statistically significant increase in the risk of stroke among HC past users, without other risk factors. In fact, for past users compared with never users the odds ratio was evaluated 0.59 [19]. Current users of low-dose oral contraceptives seem to have a risk for stroke similar to that of women who have never used these medications and the results did not appreciably differ between Hemorrhagic stroke and ischemic stroke. Although other studies reported that the incidence of total stroke among 18–44-year-olds was 11.3 per 100,000 women years, with the rate of hemorrhagic stroke higher than the rate of ischemic stroke as: 6.4 versus 4.3/100,000 women-years. Compared with women who had never used COCs, current users of low-dose had estimated odds ratio of 0.93 for hemorrhagic stroke and 0.89 for ischemic stroke [171–173]. There is insufficient information to determine whether major differences in the risk of ischemic stroke exist between different HC formulations. Data examining the risk of hemorrhagic stroke in current COC users with other risk factors are very sparse, as are those relating to the hemorrhagic stroke risk associated with particular COCs. Literature data are scarce and sometimes showed methodological limitations It is important to remember that we define stroke as the rapid onset of loss of cerebral function that lasted at least 24 hours and could not be ascribed to subdural hemorrhage or to other diseases: neurologic, neoplastic, infection, or multiple sclerosis. The stroke may be venous or arterial in origin and the second may be hemorrhagic, ischemic or provoked by other cause as

the arterial dissection. The aneurysmal bleeding was defined as a hemorrhagic stroke. The role of hormonal contraceptives (HCs) as a risk factor for cerebrovascular pathology is still discussed but other prospective and retrospective studies, to establish the casual relationship between HC use and stroke, are still necessary [174]. A recent study found that women using HCs had a relative risk for cerebrovascular accidents of 1.5. The risk was increased at higher doses and for some specific progestins. No evidence supports a relationship between atherogenic disease and use of COCs. Former users of HCs do not have an increased risk of ischemic stroke [174]. In addition, it is important to evaluate the relationship between migraine and stroke considering the high prevalence of migraine in young women [114]. It is reported that a significant association between migraine with aura and juvenile stroke in women exist with odds ratio of 2.11 in women aged under 46 years and 3.26 under the age of 35 [112, 175]. Migraine with visual aura was associated with an increased risk of stroke; particularly, in women who smoke and with other medical associated conditions; when those take oral contraceptives markedly increase their risk [112, 175]. Evidence from six case-control studies suggested that COC users with a history of migraine were 2 to 4 times as likely to have an ischemic stroke as nonusers with a history of migraine. The odds ratios for ischemic stroke ranged from 6 to almost 14 for COC users with migraine compared with nonusers without migraine. Some studies that provided evidence on hemorrhagic stroke reported low or no risk associated with migraine or with COC use [176]. There is insufficient information to determine whether major differences in the risk of ischemic stroke exist between products. Current users appear to have a modestly elevated risk of hemorrhagic stroke, mainly in women older than 35 years; former users do not. Cases of transitory ischemic attacks in women with migraine have been reported, also with progesterone-only preparations [177]. In most cases of myocardial infarction or stroke, one or more risk factors were identified [114, 178]. Cerebral vein and sinus thrombosis may occur in COC users affected by congenital thrombophilia, especially if prothrombotic conditions like hyper-homocysteinemia, nephrotic syndrome,

or if unknown, dural arteriovenous malformations are present [156] Fortunately, these findings are reported only in sporadic cases. It is essential to provide the preventive diagnosis with the aim to avoid a probable high risk for the woman; therefore, recent research has shown the influence of the type of progestin. Despite the limited data, it seems that progestin-only-contraceptive does not increase the risk of heart attack and stroke. Until now, no sufficient literature data exist about combined hormonal contraceptives delivered by a different route (transdermal patch, vaginal ring, subdermal implant). Although, a cohort study reported no stroke relief among 49,048 women-years of transdermal contraceptive system exposure, and 10 among users of norgestimate containing oral contraceptive [179]. In conclusion, current available studies indicate that there is no significant increase in the risk of ischemic stroke or acute myocardial infarction associated with the use of low-dose estrogen COCs in women properly screened before use, and who have no pre-existing cardiovascular risk factors.

3.1.4. Arterial Accidents
Among women taking combined hormonal contraceptives (COCs), arterial accidents rarely occur and isolated cases are reported also in women taking only-progestin preparations (POP). In the meantime, the lowering of the ethinylestradiol dose (EE) in COCs, accompanied by a steady decline in venous accidents, clearly did not reduce the risk of arterial accidents [168]. Furthermore, arterial thrombosis seems to be unrelated to the duration of use or past use of COCs [139, 143]. Several studies have indicated that smoking and age with hypertension, diabetes and, hypercholesterolemia are most important risk factors as well as thrombophilia [114, 147, 173, 178, 180]. Mortality from arterial diseases was estimated 3.5 times higher than from venous diseases, in women under 30 years, taking COCs, and 8.5 times in those 30–44 years old. Moreover, COCs containing second generation-progestagens seem to confer a smaller increase of the risk of venous diseases and a higher increase of the risk of arterial events, compared with COCs containing third generation-progestagens [181, 182]. In addition, epidemiologic studies suggest that arterial disease risk in young women decreases within

5–10 years of smoking cessation [183]. Nevertheless, it is believed that COC use, per se, does not cause arterial disease, it can synergize with subclinical endothelial damage to promote arterial occlusion. The prothrombotic effect of the hormonal contraceptive estrogen intervenes in a cycle of endothelial damage and repair which would otherwise remain clinically silent, or would ultimately progress because of presence of smoking, hypertension or other factors, up to atherosclerosis [182, 183]. Therefore, the risk of arterial diseases does not seem to increase in healthy non smoker women under 35 years [184]. However, a study performed on 152 women with peripheral arterial disease (PAD) and 925 control women (age 18–49 years) affirmed that all types of COCs were associated with an increase risk of PAD [185]. The same result was obtained from a rigorous meta-analysis of the Literature from 1980 to 2002 [170]. The effects of COCs on the haemostasis and inflammation variables, resulting in an increased thrombosis risk, show large differences in the women's response and the polymorphism in the estrogen receptor-1 (ER1) gene may explain part of this inter-individual response. However, a recent research evidenced that the haplotype ER-1, does not have a strong effect on the estrogen-induced changes in haemostasis and on inflammation risk markers for arterial and venous thrombosis. In fact, no significant link between the different doses of ethinylestradiol and the effect was found [186]. In the Literature, some cases of isolated or multiple artery occlusions in young women who smoke and who take oral contraceptives have been reported [182, 187, 188]. Scarce data are available on involvement of progestins in the coagulation patho-mechanisms. However, likely the vascular effects of progestins are mediated through progestin receptors as well as through down-regulation of estradiol receptors [189, 190]. Estrogen and progestin receptors are localized in endothelial and smooth muscle cells of the vessel wall, but there are differences in the response of vein and arteries to sex-steroids. In the arteries, the progestin may inhibit the endothelium dependent vasodilatator action of estrogens; while, in the veins progestin may increase the capacitance resulting in a decreased blood flow. Modifications in haemostasis parameters seem to depend

on the type and dose of progestogen, the presence of estrogen compound and the duration of use. The risk of combined formulation could be a consequence of vascular action of progestins. In fact, it seems that some progestins may up-regulate thrombin receptor expression, while other progestins did not [191, 192]. Definitive conclusions about the significance of these findings have not yet been achieved. In this light, the prudent choice of hormonal regimen could be recommended. Using progestins with minimal vascular toxicity may lead to the safety of estrogen-progestin preparations for pre-menopausal women also with Hereditary Hemorrhagic Telangiectasia (HHT). In fact, COC use seems to be a promising alternative to usual treatment of nosebleeds, also as a first-line option in women HHT-affected. In the meantime, this management avoids the risk of pregnancy [193]. Further studies are required to establish the role of progestins on haemostasis [194]. No differences between second and third generation oral contraceptives on the risk of arterial wall disease were found. In most cases of myocardial infarction or stroke, one or more risk factors were identified. Two of the most relevant risk factors are smoking and the absence of blood pressure control without forgetting the thrombophilic syndromes, particularly when unrecognized [195]. When COCs are prescribed to women with known risk factors for arterial thrombotic disease such as smoking, diabetes, hypertension, migraine with aura, family disposition of acute myocardial infarction or thrombotic stroke, a low-dose pill with a third generation progestins may have an advantage, particularly over 30 years. In conclusion, women who smoked and had used OCs have case-fatality rates 2–3 times greater than women in other groups. The relative risks of OC use seems to be lower for the incidence of 1st event of arterial disease than for death in affected users. Caution is needed in prescribing OCs for women who smoke and an effort to induce smoking cessation should be made first.

3.2. Cancer Risks
3.2.1. Introduction
Fear from increased cancer risk is one of the most significant causes for low acceptance and low compliance of hormonal contraceptive (HC) methods. Effec-

tively, the Agency for Research on Cancer declared that combined HC are carcinogenic to humans, based on an increased risk for hepatocellular carcinoma, breast and cervical cancer [196, 197]. Many studies have examined the potential association between oral contraception and cancer; however, many questions are still raised concerning this possible connection [198, 199]. The evidence suggests that current users of combined oral contraceptives have an increased risk for cancer of the breast, cervix, and liver compared with non-users. While, it was generally reported that current users of combined oral contraceptives have a reduced risk of cancer of the endometrium, ovaries, and, possibly, colorectum [16, 17]. The risks for breast, endometrial and cervical cancer seems to decline after stopping oral contraception, returning to that of non-users within about 10 years [200, 201]. The long term cancer benefits might counter the short term harmful ones if they persist into the age when most malignancies become common in women 50 years or more [18].

3.2.2. Breast Cancer Risk
Breast cancer is, worldwide, the leading cause of cancer in women. Therefore, the clinical impact of the association between hormonal contraceptives use and breast cancer risk is very important considering the widespread HCs use. It was estimated that more than a quarter of a million women are diagnosed as having breast cancer in the United States, annually [202]. Major risk factors increasing the relative risk (RR), more than 4-fold, are: family history, increased breast density, previous diagnosis of atypical hyperplasia and thoracic radiotherapy. Other factors act with a relative lower increase risk, estimated less than a 2-fold, including endogenous and exogenous hormones [203]. Experimental data strongly suggest that estrogens have a role in the development and growth of breast cancer. Estrogens promote the development of mammary cancer in rodents and exert both direct and indirect proliferative effects on cultured breast cancer cells. The role of progestins is more controversial. It has been reported that they can play either anti-proliferative or proliferative effects, very likely depending on the phenotype of the cell, the micro-environment and the species [204]. In the last decades, the age of the

first full term pregnancy(FFTP) has dramatically changed in western world and oral contraceptives (OC) are used thus much longer prior FFTP than in past. There is a serious concern that OC could be responsible, in part, for the burden of breast cancer. The FFTP promotes differentiation of breast tissue, which can be protective against potentially carcinogenic substances, especially if it occurs early in the life [205]. According to the age and the state of breast tissue, OC may exert different effect when they are used. In practice, the RR could increase with a young age (< 20 years) at start [206]. Women who are currently combined oral contraceptives (COCs) users or have used them in the past 10 years are at a slightly increased risk of having breast cancer during the next 10 years. Besides, the cancers diagnosed in these women tend to be localized to the breast and to have a better differentiation than the cancers diagnosed in those who have never used HCs [207]. Only a few researches have addressed potential impact of OC on different histological types of breast cancer. Case-control studies did not find any increase related to OC use for lobular and ductal cancers as well as for ER+ and ER- [208, 209]. However, OC use was not associated with risk of breast cancer in situ (BCIS) it seems that a significant increase in risk could be observed in former users but not in current users [206, 210]. The study of Hannaford including 46,000 women followed up since 1968–1969, did not find an increased risk of breast cancer among ever users In this study, 75 % of the ever users had used an OC containing 50 μg ethinylestradiol (EE) and 63.6 % of the women were below 30 years when they started using OC [18]. Similarly, the Oxford Family Planning Association (FPA) study, including 17,032 women 25–39 years between 1968 and 1974,has not observed any increase in the RR of gynecological cancers among ever users of oral contraceptives compared with never users [211]. The Women's Contraceptive and Reproductive Experiences (Women's CARE) study did not observed any increase in the RR in the whole cohort [212]. Interestingly, more than 2500 women had begun using OC before the age of 20 and no increase in the RR was observed in users. In this study, most of the women used newer OC formulations than in the studies analyzed in the Oxford meta-

analysis, which could explain the difference in the results. In conclusion, the data available suggest that the protective effect of OC is maintained in formulations with < 50 μg EE, just as in low-dose formulations with < 35 μg [206]. Some researchers have suggested that there may be an increase in the risk of breast cancer associated with a prior induced abortion in users or past users of HCs. The risk, if present, may vary according to the duration of the pregnancy in which the abortion occurred, or to a woman's age or parity at that time, or the age at menarche, and to have used oral contraceptives for an extended period of time. The breast cancer relative risk (RR) in those with one or more induced abortion was 1.2-fold to women with no history of abortion and it was reported to be greatest (2.0) among nulliparous women whose abortion occurred prior to 8 weeks' of gestation [213]. This risk was slightly higher when the abortion was performed before 20 years or after 29 years of age with a relative risk (RR) of 1.5. The data from these studies neither permit a causal interpretation at this time, nor do they identify any particular subgroup of women with induced abortion histories at enhanced risk of breast cancer [213, 214]. In general, no association has been found between spontaneous abortion and the risk for breast cancer [198, 215]. Multiparous women who have used OC before the FFTP had an (OR = 1.44 (95% CI: 1.28–1.62), higher than those who started after the FFTP (OR = 1.15; 95% CI: 1.06–1.26). Duration of use > 4 years before FFTP was associated with an OR = 1.52 (95% CI: 1.26–1.82). Nulliparous women had no increase of the risk irrespective of the duration of use. The results of this study suggest that pregnancy could enhance breast cancer risk promoted by OC. This meta-analysis used only case-control studies and crude odd ratio, which could have increased the RR values. In most studies, mortality rates from breast cancer diagnosed in OC users were lower or equivalent to non-users [216, 217]. An association between breast cancer and long-term HC use among young women, beginning close to menarche, suggests that at puberty, a time when breast epithelial cells are undergoing considerable proliferative activity, these are more susceptible to genetic damage than in adult life. In addition, the frequency in this age group of imbalances of adrenal-ovarian

maturation might have importance [218, 219]. Although, it seems that in younger women baseline risk for breast cancer might be extremely low [16]. Scarce data are available to assign a risk for progestin-only pill [218]. However, the effects of medroxyprogesterone acetate (MPA) as well as norethisterone (NET) were investigated in the presence of a growth factor mixture and/ or estradiol in normal and neoplastic human epithelial breast cells, and it seems that MPA may increase breast cancer risk in women when used in long-term treatment. In this respect NET reacts neutral. The mitosis of pre-existing cancerous cells may be partly inhibited by the addition of both progestogens [220]. Thus, these results indicate that it is necessary to differentiate between normal and malignant breast cells concerning the assessment of progestogens as a risk factor for the breast. Data regarding injected or implanted hormonal contraceptives are limited. However, it seems that implants could induce higher risk for breast cancer than injected preparations (OR 8.59); while, associations between injected HC use and breast cancer in women are consistent with modestly increased risk among recent users and for ER (estrogen receptors) negative tumors. Based on a small number of users of subdermal implant contraceptives, a significant increase in breast cancer risk was observed; therefore, surveillance of implant users may be warranted [221]. Particular interest was devoted to predisposed women as the BRCA1/2 mutation carriers. Although there are some indications of increased breast cancer risk in some subgroups of women, recent international studies reported in those no evidence that the current use of combined oral contraceptives (COCs) might be associated with a risk more strongly than in the general population [222, 223]. Early breast cancer and ovarian cancer screening are recommended for women with BRCA1/2 mutations. Inherited breast and ovarian cancers account for 10 % of all breast and ovarian cancers [224]. Relative to association of breast and ovarian cancers, these cancers tend to occur at an earlier age and grow more aggressively than the others. Identification of patients with the mutation is therefore crucial, because preventive measures such as prophylactic bilateral mastectomy, prophylactic bilateral salpingooophorectomy and chemopreven-

tion with Tamoxifen can prevent breast and ovarian cancer [225, 226]. Likewise, genetic counseling prior to testing is mandatory, considering the major impact of the test results on the individual's life [227, 228]. No absolute recommendation is made for or against prophylactic surgery; these surgeries are an option for mutation carriers, but evidence of benefit is lacking, and case reports have documented the occurrence of cancer following prophylactic surgery [229]. Many women would prefer fewer bleeding episodes while taking oral contraceptives. For this reason and with the intention of reducing menstruation-associated symptoms, an extended-cycle contraceptive is often considered. The results of a study "in vitro" indicate that continuously administered ethinylestradiol may not increase breast cancer risk in comparison to intermittent application [230].

However, it remains unknown whether this long-term treatment is associated with a different breast cancer risk from that of the usual treatment. Several unclear questions remain regarding the eventual breast cancer risk of hormonal contraceptive users and the role of progestins. A study assessed „in vitro" the effects of progesterone (P), testosterone (T), chlormadinone acetate (CMA), medroxyprogesterone (MPA), norethisterone (NET), levonorgestrel (LNG), dienogest (DNG), gestodene (GSD) and 3-ketodesogestrel (KDG) in normal human breast epithelial MCF10A cells and in estrogen and progesterone receptor positive HCC1500 human primary breast cancer cells. The results showed that MPA and CMA, with growth factors (GFs), induced proliferation of MCF10A cells. While P, T, NET, LNG, DNG, GSD, and KDG had no significant effect. In HCC1500 cells, MPA and CMA with GFs had an inhibitory effect, whereas LNG, DNG, GSD, KDG and T enhanced the proliferative effect of GFs. P had no significant effect. No progestogen could further enhance the stimulatory effect of E2 on HCC1500 cells, but KDG inhibited it. MPA, GSD, T, CMA and NET had an anti-proliferative effect on the mitotic GF and E2 combination. P, LNG, DNG and KDG had no significant effect. So, some progestogens may induce proliferation or inhibit growth of benign or malignant human breast epithelial cells inde-

pendently of the effects of growth factors and E2 [231]. Therefore, some experimental studies suggested that the choice of progestin for hormone therapy could be important in terms of influencing possible breast cancer risk; however, clinical studies are necessary to prove these results obtained in vitro. Further researches are necessary to clarify the role of the different progestins and their dosages in the development of breast cancer.

3.2.3. Ovarian Cancer Risk

The incidence of ovarian cancer in the world is 6.6% but Europe has one of the highest incidence rates of ovarian cancer in the world, making it an important public health issue. The incidence of this disease seems to be reduced by pregnancy, lactation, tubal ligation and oral contraceptives [232]. The role of sex hormones seems important for ovarian carcinogenesis. Epidemiological observations and experimental data from the animal model indicate that estrogens may have an adverse effect, while progesterone/progestins reduce the effect directly on the ovarian epithelium. There is evidence that oral contraceptive use provides substantial protection against ovarian cancer and that the longer HC use offers the greater reduction in ovarian cancer risk (p < 0.001) [225, 233]. However, the eventual public-health effects of this reduction will depend on how long the protection lasts after use ceases. Women who have used oral contraceptives for 5 years or longer, have about half the risk of ovarian cancer compared with never users [234–236]. Recently, the Collaborative Group on Epidemiological Studies of Ovarian Cancer (Oxford) reported from a re-analysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls that this reduction in risk persisted for more than 30 years after oral contraceptive use had ceased. However, it became somewhat attenuated over time; the proportional risk reductions per 5 years of use were 29% for use ceased less than 10 years previously, 19% for use ceased 10–19 years previously, and 15 % for use ceased 20–29 years previously. This effect is not dose-dependent considering the similar proportional risk reduction from the 1960s onwards [237]. The incidence of mucinous tumors (12% of the total) seemed little affected by oral con-

traceptives, but otherwise the proportional risk reduction did not vary much between different histological types. These findings suggest that oral contraceptives have already prevented some 200,000 ovarian cancers and 100,000 deaths from the disease, and that over the next few decades the number of prevented cancers will rise to at least 30,000 per year [226, 237]. The reduction of risk does not seem related to androgenicity of the hormonal contraceptives [235, 238]. Low estrogen dose oral contraceptives confer a benefit, regarding ovarian cancer risk, similar to that conferred by earlier high estrogen dose formulations [239–241]. While, current available data suggest that long-term use of estrogens may slightly increase the risk, especially of endometrioid type of ovarian cancer [202, 238]. The protective effect of combined oral contraceptive pill, was confirmed in multiple studies; however, it is unclear whether this protection also covers women with a genetic predisposition to ovarian cancer or perimenopausal women. About 5% of all ovarian-cancer cases are caused by a genetic predisposition, in particular as a component of the autosomal dominant hereditary breast-ovarian-cancer syndrome. Women with this germline mutations in the cancer susceptibility genes, BRCA1 or BRCA2, have up to an 85% lifetime risk of breast cancer and up to a 46 % lifetime risk ovarian cancer [228, 239, 240]. Ovarian and endometrial cancer also occur in families with Lynch/ hereditary non-polyposis colorectal cancer syndrome (HNPCC). The syndrome is caused by germline mutations in DNA mismatch-repair genes. Women at high risk of gynecological cancer based upon familial clustering of disease or a demonstrated pathogenic germ-line mutation are candidates for surveillance with annual gynecological examinations, including vaginal echoscopy and serum carcinoma antigen CA125 testing. Prophylactic surgery in the form of adnexectomy leads to a marked, but not complete, reduction of ovarian-cancer risk in high-risk cases [225, 226, 242]. There is insufficient evidence to advise against, the use of oral contraceptives or hormonal substitution after adnexectomy for healthy women with a genetic predisposition to breast cancer. Recommendations for surveillance and prevention should be given only after genetic-risk counseling, based on a detailed fam-

ily study and DNA-based diagnosis [225, 226, 240]. There is emerging evidence that familial breast cancer, including BRCA1 and BRCA2 mutations, could be estrogen sensitive. Therefore, endogenous and exogenous estrogens, such as hormonal contraceptives, may increase the risk of breast cancer in BRCA1 mutation carriers. So, HCs, especially, in older women should be used with caution in BRCA1 or BRCA2 mutation carriers [243].

3.2.4. Endometrial Cancer Risk

Combined oral contraceptives (COCs) use was associated with a decreased risk in endometrial carcinoma, related with duration of use (RR = 0.28 after 5 years of use). However, the estimated protective effect seems to be reduced becoming statistically non-significant when allowance was made for weight and parity [244]. In fact, it was only clearly evident in women who had less than 3 live-births and who had BMI less than 22 kg/m^2 [245]. Overall, progestin effect results not dose-dependent; in fact, high progestin potency COCs did not confer significantly more protection than low progestin potency HCs (OR = 0.52). However, among women with a body mass index of 22 kg/m^2 or higher, those who used high progestin potency oral contraceptives had a lower risk of endometrial cancer than those who used low progestin potency oral contraceptives (OR = 0.31); while, those with a BMI below 22.0 kg/m^2 did not [245, 246]. A reduced risk of endometrial carcinoma with COCs use was present only among users of five or more years duration [247]. Oral contraceptives present a chemopreventive opportunity for endometrial and ovarian cancer. In fact, the risk is dramatically lower among women who have used these preparations than among those who have not [245, 246]. Therefore, the highest protective effect was produced by preparations with the lowest estrogen and the highest progesterone content. Endometrial cancer risk is not elevated when combined therapy is given in a cyclic manner with progestin administered only part of the time and it is reduced when both estrogen and progestin are administered on a daily basis [248]. In most cases, the endometrioid adenocarcinoma is preceded by hyperplasia with different risk of progression into carcinoma. A study reported that 2% of the cases with complex hyperpla-

sia (8/390) progressed into carcinoma and 10.5% into atypical hyperplasia. 52% of the atypical hyperplasias (58/112) progressed into carcinomas. In the case of progestogen treatment (n = 208 cases) 61.5% of the treated women showed remission confirmed by re-curetting, compared with 20.3% of those without hormonal treatment (n = 182; p < 0.0001). Endometrial hyperplasia without atypia may be effectively treated with progestagen; however, in post-menopausal women, total hysterectomy could be preferred [249].

Endometrial and ovarian cancer are the fourth and fifth most common malignancies in women, with approximately 40,000 new endometrial and 25,000 new ovarian cancers expected to be diagnosed in the Unites States, per year. Combined oral contraceptives reduce the risk of endometrial cancer about 50%. The risk of carcinomas decreases with an increasing duration of oral contraceptive use and this reduced risk lasts for 10–15 years after cessation. A significantly lower risk of developing an endometrial carcinoma can be observed for contraceptives with a high progestin and a low estrogen concentration. Due to the protective effect, the use of oral contraceptives is a useful means of chemo-prevention in women at high risk of endometrial cancer [250].

Intrauterine progesterone therapy has been proposed as a potential uterine-sparing treatment for atypical endometrial hyperplasia and adenocarcinoma. Although was reported a rare case of a woman with atypical endometrial hyperplasia, treated with the levonorgestrel-releasing intrauterine system, who developed, six months after the IUS use, an increasing endometrial thickness on ultrasonography, and the progression of the previous lesion to adenocarcinoma [251, 252].

The levonorgestrel-releasing intrauterine system (LNG-IUS) has profound morphologic effects on the endometrium, including gland atrophy and extensive decidual transformation of the stroma. These findings confirm that the stromal compartment of the endometrium undergoes changes consistent with decidualization for at least up to 12 months after insertion of an LNG-IUS [253].

3.2.5. Cervical Cancer Risk

In some studies HCs have been associated with an increased risk of cervical abnormalities and cervical cancer, but there might be alternative explanations for these epidemiological associations: HC users can start having sexual intercourse at an earlier age, they have more sexual partners, and they rarely use barrier methods of contraception [253, 254]. Nevertheless, combined oral contraceptives are classified by the International Agency for Research on Cancer as a cause of cervical cancer. As the incidence of cervical cancer increases with age, the public-health implications of this association depend largely on the persistence of effects long after use of oral contraceptive has ceased. Among current users of oral contraceptives the risk of invasive cervical cancer increased with increasing duration of use (relative risk= RR for 5 or more years' use versus never use, 1.90) [255]. The risk declined after use ceased, and by 10 or more years had returned to that of never users. A similar pattern of risk was seen both for invasive and in-situ cancer, and in women who tested positive for high-risk human papillomavirus (HPV). Relative risk did not vary substantially between women with different characteristics. Ten years' use of oral contraceptives from around age 20 to 30 years is estimated to increase the cumulative incidence of invasive cervical cancer by age 50 from 7.3 to 8.3 per 1000 in less developed countries and, from 3.8 to 4.5 per 1000 in more developed countries [256–258]. Recent studies suggest that long duration use of oral contraceptives increases the risk of cervical cancer in HPV positive women. Cervical cancer is caused by specific types of the human papillomavirus (HPV) but, not all infected women develop cancer. It was hypothesized that HC can act as a promoter for HPV-induced carcinogenesis [259, 260]. Available data showed an increase in the transcription of high-risk HPV by 16alpha–hydroxylation of estrogens and this finding explains the increased cervical carcinogenesis risk for long-term contraceptive using, HPV-infected women [201, 260]. Results from published studies were combined to examine the relationship between invasive and in situ cervical cancer and duration of use of hormonal contraceptives, with particular attention to HPV infection [261, 262]. Twenty-eight eligible studies were iden-

tified, together including 12,531 women with cervical cancer. Compared with never users of oral contraceptives, the relative risks of cervical cancer increased with increasing duration of use: for durations of approximately less than 5 years, 5–9 years, and 10 or more years, respectively, the summary relative risks were 1.1, 1.6, and 2.2 for all women, respectively. The results were similar for invasive and in situ cervical cancers, for squamous cell and adenocarcinoma [263]. The risk was found to increase with use of HCs for more than 7 years beginning after age 25 [264]. Recently, was affirmed that compared with non-users, women who had ever used or currently users HC users had an increased risk of cervical carcinoma. (OR 1.45).

However, the risk was not statistically significant. Considering the duration of use, women who had used OC for 3 years or less did not have an increased risk of cervical cancer (OR 0.78). Nevertheless, the odds ratio of oral contraceptive pill use for more than 3 years was 2.57 which was statistically significant. So, long-term use of oral contraceptives might be a cofactor that increases the risk of cervical carcinoma by up to 4-fold in women who are positive for cervical HPV [261–263]. For this reason, many U.S. gynecologists refuse prescription of hormonal contraceptives in women without cervical cancer screening [264]. Although the World Health Organization does not recommend any change in oral contraceptive use [265]. So, a risk-benefit analysis supports the continuation of contraceptive use among women who have abnormal smears but also, who have access to educational counseling and clinical surveillance [266]. Cervical cytological studies reported the significantly high frequency of squamous intraepithelial lesions (SILs) in the early stages of contraception with Norplant insertion, but after 1 year a progressive decline of them was found and after 3 years no SIL was seen [267]. Data suggest that in adolescents and young women HPV infections and their sequelae, squamous intraepithelial lesions (SILs) occur more commonly among human immunodeficiency (HIV)-infected girls because of the HIV associated CD4+T-cell immunosuppression [268]. However, the risk of developing the HPV-associated precancer high-grade squamous intra-

epithelial lesion (HSIL) in HIV-infected adolescent is unknown. It seems that the use of hormonal contraceptives, either combined oral contraceptives or intramuscolar MPA, high cervical mucous concentrations of interleukin-12, a positive HPV test, and a persistent low-grade squamous intraepithelial lesion (LSIL) were significantly associated with the development of HSIL [269].

3.2.6. Colorectal Cancer Risk

The association between oral contraceptive use and colorectal cancer have yielded conflicting results. The analysis from a multicenter case-control study, conducted in 6 Italian regions in 1992–96 with data from a 1985–91, yielding a total of 803 women with colon cancer (median age 61 years), 429 cases of rectal cancer (median age 62 years), and 2793 controls (median age 57 years) showed that the protection conferred by oral contraceptives (HC) use was similar when the origin of the neoplasm was in the ascending, transverse, or descending colon. An inverse association was also found between use of HCs and rectal cancer (OR = 0.66), but there was no association with duration of OC use. For colon and rectal cancers combined, a 36% reduction in cancer risk was present among combined oral contraceptive (COC) users (OR = 0.64). These findings are consistent with the descriptive epidemiology of colorectal cancer, and experimental findings on estrogen receptors and the colorectal cancer pathway [17]. Other researchers reported that oral contraceptive use showed no significant influence, while users of hormone replacement therapy had a reduced risk of rectal cancer (OR = 0.56). Thus, the association of colorectal cancer with reproductive and menstrual factors is neither strong nor consistent [270]. Similar results were obtained from a large study on 118,404 women which supports as the current or past of oral contraceptives use did not appreciably alter the risk of colorectal cancer [271]. Adenomatous polyps (adenomas) are precursors of colorectal cancer. Parity, history of spontaneous or induced abortion, infertility, type of menopause, age at menopause, use of oral contraceptives, and use of menopausal hormone replacement therapy were not associated statistically, with significant adenoma risk, although some possible trends were observed [272]. Colorectal adenomatous polyps, as recognized precursor lesions to colorectal cancer, have been studied to enhance knowledge of colorectal cancer etiology. Although most of the known risk factors for colorectal cancer are also associated with the occurrence of colorectal adenomas; cigarette smoking has had a strong, consistent relationship with colorectal adenomas but is generally not associated with colorectal cancer. The explanation for this paradox is unknown [273]. It is also suggest that the major effect of smoking on the colorectal adenoma-carcinoma sequence occurs in the earlier stages of the formation of adenoma and the development of carcinoma in situ.

There is little overall association between colon cancer and oral contraceptive use, parity, age at first birth, hysterectomy or oophorectomy status, or age at menopause. Use of contraceptive hormones at or after age 40, was associated with decreased risk of colon cancer (OR = 0.60), particularly among women with more than five years of use (OR = 0.47). While, results from previous studies showed as inconsistent any protective effect against colon cancer. Would be important given the continuing debate over its potential risks and benefits [274]. Evidence from epidemiologic studies suggests a possible role of exogenous and endogenous hormones in colorectal carcinogenesis in women. However, with respect to exogenous hormones, in contrast to hormone replacement therapy, few cohort studies have examined oral contraceptive use in relation to colorectal cancer risk. A recent study performed on 88.835 women affirmed that use of oral contraceptives was associated with a modest reduction in the risk of colorectal cancer (OR = 0.83). No trend was seen in the ratios with increasing duration of oral contraceptive use. The results are suggestive of an inverse association between oral contraceptive use and colorectal carcinogenesis [275]. Previous findings on the associations between oral contraceptive (OC) use and reproductive factors and, risk of colorectal cancer have been inconclusive. Women who had used OCs for 6 months to < 3 years had a relative risk of 0.61 relative to never users, with little additional decreased risk being seen with longer duration of use (p for multivariate trend = 0.09). No significant association was observed between reproductive factors and colorectal cancer risk. These findings provide some support for a potential role of HCs in reducing risk of colorectal cancer [276]. These data are consistent with a role for estrogen in altering susceptibility to diet and lifestyle factors possibly, via an insulin-related mechanism [277].

It is hypothesized that estrogen up-regulates insulin-like growth factor (IGF-I) receptors and insulin receptor substrate (IRS-I) levels in the colon, which in turn increases susceptibility to, obesity-induced, increased levels of insulin. It was further hypothesized that androgens may have similar effects in men given the decline in colon cancer risk associated with BMI with advancing age. The association between body mass index (BMI) and colon cancer has been reported to be different for men and women. Scarce literature has examined if estrogen influences these differences [278]. Epidemiologic and experimental reports suggest that female hormones protect against the development of colorectal cancer, but studies are limited. It was described a case of a patient, in the placebo arm of a 4-year primary chemoprevention trial, who developed adenomatous polyps and then had eradication of polyps after the administration of oral contraceptives. No change in the prostaglandin levels in the colonic mucosa was noted after polyp elimination, making nonsteroidal anti-inflammatory drug ingestion unlikely as a cause. This report represents the regression of colorectal adenomas with the use of estrogen/progesterone compounds [279]. Ever users of oral contraceptives do not benefit from a long-term reduction in colorectal cancer, although current and recent use may obtain some protection. Women who have used HRT appear to have important reductions in their risk of colorectal cancer, especially while using these hormones. Further studies are needed in order to determine how long any benefits last and whether these are stronger in women exposed to both classes of exogenous hormones [280].

3.2.7. Skin Cancer Risk

Skin expresses estrogen, progesterone and androgen receptors.

Steroid hormones, such as those contained in oral contraceptives, affect skin cell cycle control. Consequently, they

can induce increase of epidermal growth factor signaling, expression of proto-oncogenes, inhibition of apoptosis, DNA replication and, potentially can promote tumor development. Available evidence suggests the skin „sensitivity" to estrogens, progestins, and androgens, even though these relationships do not significantly increase the risk of developing skin cancer, when estrogen exposure is not excessive. The question of whether oral contraceptives increase the risk for the development of skin cancer, particularly melanoma is still an area of concern [281, 282]. Several studies confirmed that ever being pregnant, age at first pregnancy, current use of hormonal contraceptives, duration of their use, and age at first use of oral contraceptives have an absence or no consistent association with melanoma [283–285]. On the contrary, women who have had three or more children seem to be significantly protected as compared to nulliparous ones. In fact, seems that women with both earlier age at first birth (< 20 years) and higher parity (≥ 5 live birth) have a particular lower risk than women with later age at first birth (≥ 25 years) and lower parity [286–288]. However, other factors could act, such as excessive sun exposure in beach holidays for 3 weeks or more [287]. In fact, history of sunburn and intensive sun-UV exposure, both might be important factors for the development of melanocytic nevi and, indirectly for melanoma [281, 288, 289]. Intermittent and intense sun exposure, during the life, could increase the risk, while prolonged exposure, as during outdoor works, seems not associated with the same risk [290, 291]. Evidence suggests that there is no causal link between oral contraceptive use and melanoma or with benign melanocytic nevi, nor has a specific subgroup of women been consistently implicated, as being at increased risk of this disease due to use of oral contraceptives [281, 288, 289]. However, based upon small numbers of cases, there was evidence that changes in nevi during recent pregnancy could be a risk factor for melanoma (OR = 2.9) [281, 288].

Reproductive hormonal factors may have a potential role in cutaneous melanoma but oral contraceptive use does not increase the risk of developing melanoma, and generally skin cancer, when estrogen exposure is not excessive [291–

294]. Furthermore, women who reported experiencing hyperpigmentation of facial skin during prior pregnancy seem to have a lowered risk for all cutaneous melanoma. Similarly, women who reported use of acne medication [286, 294].

These aspects should be further studied. These data suggest an overall lack of effect of oral contraceptives on cutaneous melanoma risk, in the women population. Although it was evaluated that the relative risk, associated with oral contraceptives use for a long period (5 years or longer) which had begun at least 10 years before the melanoma, is 1.5 (OR) [291]. In conclusion, modern hormonal contraceptives seem to have not influence on melanoma and skin cancer development. On the other hand, the rates of European mortality from cutaneous malignant melanoma (CMM) tend to decline since 1990s and this improvement resulted particularly favorable in young women [74, 295].

3.2.8. Liver Cancer Risk
Liver cell adenomas are rare benign tumors whose incidence has been increasing since 1970 [296]. They generally occur in otherwise healthy women over age 30, who have used hormonal contraceptives (HCs) for five years or longer [297, 298]. In fact, evidence proved the link between the raise of incidence of hepatic adenomas and the widespread and prolonged use of the "pill" [299–301]. Not rarely benign liver tumors are incidental findings on echography. Liver cell adenomas are not premalignant and may undergo reversible change after withdrawal of causative agents, such as oral contraceptives [302–304]. However, these tumors which regress when OC use stops, can reoccur if HC use is reinstituted or if pregnancy occurs [299, 305]. The most extensive complication of hepatic adenoma is intratumoral or intraperitoneal hemorrhage, which occurs in 50–60% of patients [306]. The risk of developing adenoma is increased with duration of oral contraceptive use, and in larger tumors, the hemorrhagic risk is also increased in pill users [298, 306]. Adenoma also occurs in people with Type Ia glycogen storage disease, and is associated with insulin dependent diabetes [306]. Some authors believe that liver cell adenomas are potentially premalig-

nant and could degenerate into hepatocellular carcinoma but there is very few well documented reports of this transformation [306–308]. Although a recent report shows that 10% of hepatic adenoma progress to hepatocellular carcinoma [307].

Really, seems that the transformation might be come from areas of dysplasia in the context of liver cell adenoma. In fact, liver adenoma can regress, while dysplasia is an irreversible, premalignant change and will eventually progress to hepatocellular carcinoma [309–311]. It is generally believed that focal nodular hyperplasia (FNH) having a wider age distribution, is not associated with the use of oral contraceptives [94, 95]. However, a large proportion of women with FNH (50–75%) are HC users, as previous clinical observations affirmed [312]. In long-term HC users it was emphasized the need of surveillance with ultra-sonography. It is known that sex hormones and anabolic-androgenic steroids are implicated in the development and progression of hepatic adenomas. The human liver expresses estrogen and androgen receptors and, experimentally both androgens and estrogens have been implicated in stimulating hepatocyte proliferation and may act as liver tumor inducers or promoters. In humans, receptors are present and may mediate the action of sex steroids or androgenic steroids on hepatic adenomas and adjacent liver, but in less than one third of patients. This evidence may have therapeutic implications [313, 314]. A paradigmatic case of liver adenoma in a young women affected from Polycystic ovary syndrome associated with high levels of androgen and following a high dose hormonal therapy has been reported [315]. So, surveillance can be advised also for women with hormonal imbalance treated with high doses of hormonal therapy. However, the increased risk for hepatocellular carcinoma in the absence of hepatitis B viruses, is the only established evidence of a direct association between HC use and cancer risk, which led an International Agency for Research on Cancer Working Group to classify combined hormonal contraceptives as carcinogenic to humans in 1998 [16]. The role of estrogens in the genesis of hepatic adenomas is well established, but is more controversial with focal nodular hyperplasia [95, 312]. The ap-

pearance of low-dose HCs does not seem to have decreased the incidence of benign liver tumors. Therefore, several studies have demonstrated that the risk of adenoma increase with the duration of treatment. In the mean time. benign liver tumors are very rare and should not affect prescription of HCs. Focal nodular hyperplasia of liver is less dangerous than hepatic adenomas but still necessitate stopping use. This pathological entity had been reported in women prior to widespread use of the pill, but HCs use appear to favor its growth. Some cases of subhepatic vein thrombosis or the Budd-Chiari syndrome, associated to focal nodular hyperplasia as well as adenoma have been reported [87, 316, 317].

3.2.9. Pancreatic Cancer Risk

Incidence rates for pancreatic cancer are consistently lower in women than in men. Previous studies suggested that reproductive factors, particularly parity, may reduce pancreatic cancer risk in women. A study on 115,474 women (follow-up : 22 years) identified 243 cases of pancreatic cancer. Parity seems to be an important risk factor. It was reported that a relative risk of pancreatic cancer was 0.86 for women with 1–2 births, 0.75 for 3–4 births, and 0.58 for those with 5 or more births, compared with nulliparous women. However, after adjusting these results for other factors, the analysis for linear trend indicated a 10% reduction in risk for each birth. Other reproductive factors and exogenous hormone use were not significantly, related to pancreatic cancer risk [318]. Compared with women who were premenopausal at baseline, postmenopausal women were at significantly increased risk of pancreatic cancer (OR = 2.44).

Age at first live birth, parity, age at menarche, use of oral contraceptive, and use of hormone replacement therapy (HRT) were not associated with altered pancreatic cancer risk in studies population. However, among parous women, later age at first full term pregnancy, significantly seems to increase the risk of this cancer (adjusted OR = 4.05). Other than the increased risk among postmenopausal women, this cohort study provides little support for associations with hormonal factors. Additional prospective data are needed. However, growing epidemiological evidence that as-

pects of reproductive history and hormonal exposure could be associated with risk of this disease could induce to support the hypothesis that pancreatic cancer is, at least in part, an estrogen dependent disease [319]. Prolonged lactation and increased parity seem associated with a reduced risk for pancreatic cancer [320]. In a parallel fashion, risk of pancreatic cancer was decreased for women with intact ovaries compared to those who have had oophorectomy: hazard ratio was 0.70. These results indicate that older age at menopause could be associated with reduced pancreatic cancer risk, but further research is warranted [321]. It was observed no association between any other reproductive factors examined (age at first birth, menarche, or menopause; type of menopause; diethylstilbestrol [DES] or duration of oral contraceptive or estrogen replacement therapy use) and pancreatic cancer mortality [322].

In summary, literature data support the observation that high parity is associated with lower risk of pancreatic cancer but do not show a linear trend with increasing parity. Furthermore, it was found no evidence that other reproductive factors may be associated with pancreatic cancer mortality [323]. It is of interest to report that clinically attainable concentrations of Medroxyprogesterone acetate (MPA) can inhibit the growth of some human pancreatic carcinoma cells, in vitro, by inducing apoptosis, probably through their PR, in association with the phosphorylation of bcl-2 [324].

3.2.10. Neurofibromas Growth

Neurofibromas are benign tumors of the peripheral nerve sheath, which may occur sporadically and, in association with the common familial cancer syndrome, neurofibromatosis type 1 (NF1) [325]. NF1 is a hereditary disease caused by mutations of the NF1 gene at 17q11.2. Loss of the NF1 gene product in Schwann cells leads to the development of benign nerve sheath tumors [326, 327]. There are intriguing links between the growth of neurofibromas and the levels of circulating hormones. In fact, dermal neurofibromas usually arise during puberty, increase in number and size during pregnancy, and shrink after giving birth [328]. The majority (75 %) of neurofibromas express progesterone receptors (PR), whereas only a minority

(5%) of neurofibromas express estrogen receptors (ER). Consequently, it has been suggested that hormones may influence the neurofibromas of patients with NF1 and may increase potential for malignant transformation of plexiform tumors. It has been showed "in vitro" that in neurofibromas, progesterone-receptors are expressed by non-neoplastic cells and not by neoplastic Schwann cells. Therefore, the progesterone might play an important role in neurofibroma growth and antiprogestins might be useful in the treatment of this tumor [329–331]. These observations lead to ask: do hormonal contraceptives stimulate growth of neurofibromas? Evidence suggested that oral contraceptives do not seem to stimulate the growth of neurofibromas and thus may be used by NF1 patients. Although, high doses of progesterone might stimulate the growth of neurofibromas and deserve closer observation [331].

3.2.11. Unclear Cancer Risks

Literature data no reported significant association of age at menarche, parity, age at first birth, and exogenous hormone use with bladder cancer risk. Findings suggest that menopausal status and age at menopause may play a role in modifying bladder cancer risk among women [332]. For postmenopausal women, early age at menopause (≤ 45 years) compared with late age at menopause (≥ 50 years) was reported associated with a statistically significant increased risk of bladder cancer (incidence rate ratio = 1.63). The association between age at menopause and bladder cancer risk could be modified by cigarette smoking status [198, 333]. Greater incidence of thyroid cancer in women than men, particularly evident during the reproductive years, has led to the suggestion that female hormones may increase the risk for this disease. A study estimating the relative risk of papillary thyroid cancer among users of exogenous hormones among 410 women aged 45–64 years, found no association of use of hormonal contraceptives (HCs) or HRT with risk of papillary thyroid cancer. Among women less than 45 years of age, the risk of papillary thyroid cancer seems to be reduced in those who had ever used HCs (OR = 0.6); beyond the relation with ever-use, there was no further association with specific aspects of exposure such as estrogenic potency,

latency, recency, age at first or last use, or use at the reference date. Therefore, the data do not support the hypothesis that use of exogenous estrogens increases the risk of female thyroid cancer [334].

The role of exogenous hormones in the development of meningioma is unclear. Little evidence of association between meningioma and exogenous hormone exposures in women was found but did suggest that some hormonal exposures may influence tumor biology in those women who develop meningioma [335].

■ 4. Other Severe Side Effects

4.1. Angioedema

Literature data suggest a close relationship between female hormones and angioedema. In fact, it is well known the variation in overall frequency of angioedema symptoms related to the different female life stages of childhood, puberty, menses, pregnancies and menopause. According to sporadic reports, hormonal contraceptives can induce or exacerbate symptoms of hereditary angioedema (HAE), type I and type III or idiopathic angioedema [336, 337]. However, many women with these diseases may use oral contraceptives without having any effect on their angioedema [338]. The main symptoms include sudden swelling and reddening of the skin which can improve after the hormonal contraceptive (HC) cessation [339]. Although in rare cases, patients, presenting severe abdominal pain and laryngeal edema, can have airway obstruction and even death [340]. Therefore, angioedema is a potentially life threatening condition and may be inherited or acquired . After COC discontinuation the evidence showed a remarkable improvement with increase of C1-INH. Several studies reported that HCs may play an iatrogenic role in the etiology of chronic angioneurotic edema or urticaria [341]. Hormonal measurement demonstrated that the number of attacks is significantly higher in female with high progesterone levels while a significantly lower attack frequency, during 1-year follow-up, was reported in patients with a higher (40 nmol/l) SHBG level [342]. Recurrent angioedema is biochemically characterized by reduced C1 inhibitor level and/or function and, genetically, by a heterogeneous group of

mutations in the C1 inhibitor gene that have an autosomal dominant mode of transmission [343]. Recently, a new type of hereditary angioedema (type 3) has been reported. This occurs only in women and is characterized by normal C1-INH levels and severe attacks of angioedema, which are clinically indistinguishable from the classic form [344–346]. Acquired forms of angioedema are estrogen(both endogenous and exogenous) dependent, although it seems that progesterone-only contraceptives may also induce attacks of this disease [339, 345]. The patients report, during the first year or later after starting contraception, relapsing swelling of the lips, hands, larynx and abdomen. The affected women have normal serum C4 and C1 inhibitor (C1Inh) antigen but a lowered C1Inh activity. The suppression of the pill was associated with the regression of the edema and normalization of C1Inh function. The mechanism is unknown but it could be due to a modulation of C1Inh expression upon androgens or to an imbalance between coagulation proteins favoring C1Inh cleavage by its target proteases. The relationship between female hormones and angioedema appeared to be even clearer when the type III hereditary angioedema was recognized. This HAE mostly affects women. It was initially described as recurrent angioedema without quantitative or functional C1Inh abnormalities [347, 348].

In 2006, two mutations in the F12 gene (gene encoding for Hageman factor), associated with type III HAE, were identified; although only 15–20% of the patients, suffering from type III HAE, had one of these mutations [349, 350]. In conclusion, the majority of the Angioedema patterns result EE-dependent or sensitive. It is advisable that clinicians should not administer estrogen-containing contraceptives to women known to have hereditary angioedema (HAE), in whom C1-esterase inhibitor (C1 INH) deficiency was demonstrated. In fact, it was reported that combined hormonal contraceptives (COCs) can exacerbate symptoms of HAE in 63–80% of the affected women [339, 351].

4.2. Peliosis Hepatis

Possible hepatic effects of oral contraceptives (OCs) include tumors, intrahepatic cholestasis, Budd-Chiari syn-

drome and a less well known vascular lesion such as peliosis [352]. Peliosis hepatis (PH), firstly described in 1950 by Zak, is a rare liver condition, sometimes fatal, characterized by multiple congestive cavities, measuring a few millimeters to about 3 cm in diameter [353]. The lesions consist of areas of hepatocellular necrosis, secondarily cystic, filled with blood . The cysts of PH often lack a cell lining and are surrounded by hepatocytes; furthermore, these may be voluminous and subcortical creating a risk of hemoperitoneum. All these lesions may be associated with a benign or malignant liver tumor. This rare disease is most commonly found in the liver but can also develops in organs belonging to the mononuclear phagocytic system (spleen, bone marrow, lymph nodes);however, a paucity of studies indicated that other organs such as lungs, parathyroid glands, and kidneys may be affected, too [354]. Initially, PH is an asymptomatic disorder, when only focal hepatocellular necrosis is present, sometimes hemorrhagic. Mild cases may be incidentally detected during imaging tests done because liver function test results are slightly abnormal or for other reasons, Ultrasonography or CT can detect cysts. While, in the severe and fatal cases, portal hypertension with varices and ascites, liver failure and/ or hemoperitoneum with shock, secondary to intraperitoneal rupture, were reported [355]. Some studies have described the prevalence of PH in patients with associated conditions, which include pulmonary tuberculosis, carcinomatosis, HIV infection, aplastic anemia, systemic lupus erythematosis treated with high-dose glucocorticoids, and patients who underwent renal transplantation. PH is also associated with use of hormones as anabolic steroids, oral contraceptives, glucocorticoids, and tamoxifen. In the past, HP was a mere histological curiosity, occasionally found at autopsies but has been increasingly recognized with wide ranging conditions from AIDS to the use of anabolic steroids. Some cases of Peliosis hepatis have been reported in women taking oral contraceptives. In this circumstance, regression of the initial lesions is possible with termination of the etiologic agent [84, 85, 356]. Although, rare cases of focal hemorrhagic necrosis of the liver and generalized peliosis hepatis have been reported

[356, 357]. The epidemiology of peliosis hepatitis is incompletely understood since most patients are asymptomatic and remain undiagnosed. There are several hypotheses, such as, its arising from sinusoidal epithelial damage, an increased sinusoidal pressure, due to obstruction in blood outflow from the liver, or hepatocellular necrosis [90, 358]. Peliosis hepatis is usually asymptomatic, but occasionally a cysts rupture could result in an hemorrhage and sometimes causing death. Some patients develop overt liver disease, characterized by jaundice, hepatomegaly, and liver failure. Nonetheless, the peliosis hepatis could be rare and usually asymptomatic, at least initially. Mild cases may be detected incidentally during imaging tests. Caution is mandatory in the management of combined hormonal contraceptive users, especially if long-term users [356, 357].

4.3. Ophthalmologic Effects

Ophthalmologic effects of oral contraceptives (OCs) have been reported; although their role has not always been confirmed. Adverse ocular reactions from OCs rarely occur and their incidence was estimated to be 1 in 230,000 users [359]. Neuroophthalmologic complications may result from cerebral vascular accidents responsible for visual field deficits, accidents affecting the cerebral trunk or ischemic events resulting from obstruction of the internal carotid artery [360]. The role of OCs in cerebral vascular accidents is controversial; although it is generally agreed that OCs use may increase thromboembolic risk in women over 35 who smoke and those with risk factors for atherosclerosis. While, severe adverse vascular accidents of the eye are exceptional in women under 40 years and without risk factors [361]. Spasm of the central retinal artery, generally precedes occlusion and requires immediate ophthalmologic examination and discontinuation of COCs. On the contrary, this event lead to loss of sight and functional recuperation in unusual [362–364]. Since estrogens have been implicated in the etiology of thromboembolic disease, smaller doses of these steroids are recommended. However, low-dose oral contraceptives can still cause thromboembolic disorders with serious neurologic or ocular disabilities. Before treatment with OCs commences, a thorough medical examination is necessary. if the family history reveals prominent cardiovascular risk factors, testing for thrombophilia is recommended. Even nowadays, patients should be warned of the risk of visual field as a potential side-effect associated with oral contraceptives [365]. In fact, acute retinal arterial vascular occlusive disorders represent the more important cause of blindness or serious impaired vision; although, their pathogenesis is hitherto a controversial issue [363, 366]. The prognosis for retinal emboli is mediocre. Problems in color vision initially affecting blue have been described in OCs users and may be a function of the duration of use. This condition seems to be especially prevalent in users with diabetes. Pregnancy appears to accelerate the loss of visual field in some women with pigmentary retinopathy. For this reason some ophthalmologists recommend that they avoid OCs. Venous occlusion occurs less suddenly and involves a less extensive loss of sight. The prognosis depends on the affected area. Symptomatology of the ophthalmic vein thrombosis may be variable: unilateral proptosis, hemorrhagic retinopathy and increase in intraocular pressure can be differently associated. There is a complete resolution of the vein thrombosis and eye signs and symptoms with the discontinuation of the hormonal contraceptive [367]. In any case, these worned vascular effects in women taking hormonal contraceptives are very rare [368]. The risk is affected by smoking, irregular lipid and/or glucose metabolism and hypertension. Although ocular complications are unusual, they should be kept in mind and women with a history of vascular problems, visual problems, or migraines should be excluded before COCs are prescribed. Particularly, migraine should be considered a warning signal [369]. Retinal disorders have been more common in women who complained of headache. However, the incidence of these complications seems to lesser with the estrogen-dose reduction and the use of third generation progestins [370]. Other conditions, as the isolated retinal bleeding and vascular papillitis, are reversed on termination of COCs use. The more rare macular edema has been reported but the data result insufficient to permit a casualty relationship with COCs. Retrobulbar optic neuropathy in young women may be considered as the first manifestation of a sclerosis. Ophthalmic migraines are, also reported in sporadic cases [366]. Intolerance to contact lenses has been reported and vision may deteriorate in myopic patients, but prospective studies have not demonstrated a link. In addition, experimental studies on the ocular effects of oral contraceptives in animals showed only increased permeability of the lens and possibly vascular dilatation [360]. Other ocular problems have been observed in OC users but no link has been proven and the only evidence is anecdotal such as the effect on cataract, lacrymal secretion, diabetic retinopathy, and age-related macular degeneration [370]. In summary, ocular effects or complications are rare, nonspecific, occur after a short or long duration of use, and may be serious or minor. Vascular complications are the most serious effects identified but few prospective and comparative studies have been performed to confirm the relationship [364]. Therefore, no link has been proven between ocular effects and COCs, but several anectodal reports suggest caution. Even nowadays, women, taking COCs, risk the danger of vascular occlusions especially if they suffer from arterial hypertension, diabetes mellitus, coagulation anomalies or if they are chronic smokers. Possible etiopathogenetic interrelations between hormonal contraceptives and ocular side-effects are still controversial; however, when the HC-user reports a vision decrease or persistent or recurrent headache it is convenient that hormonal contraception is discontinued [371].

4.4. Vasculitis

Some studies affirmed that hormonal contraceptives, sometimes may provoke vasculitis. Since Kussmaul and Maier described the index case of vasculitis in 1866, the field has seen many changes but many mysteries remain [372]. Vasculitis represent such a heterogeneous group of disorders which may involve small arteries, arterioles, capillaries, and venules [373, 374]. Cutaneous vasculitis may be confined to the skin or may be part of an associated systemic disease [375]. Oral contraceptives (OCs) can affect the skin through their hormonal effects or through iatrogenic effects associated with their toxicity in certain individuals. Toxic effects of OCs are rare but potentially serious; they should be diag-

nosed early and require permanent termination of OC use. The clinical manifestations are variable and not specific to the medication. The most frequently reported manifestations are allergic vascularities which may lead to serious renal complications, fixed pigmented erythema, urticaria, and lichenoid eruptions [73]. Associations between markers of allergy (eosinophils, IgE and atopy) and hormonal dependent events in women (premenstrual asthma, menopause and oral contraceptive use) have been found [376]. In women, combined steroid contraceptives may cause a decrease in antibody formation and complement levels and may exhibit an immunosuppressive effect "in vitro" on lymphocyte activation by nonspecific mitogens. In vivo, the immunosuppressive effect on lymphocytes is evident after approximately 2 years of contraceptive use and remain for several months after discontinuation of the drug. In women with rheumatoid arthritis who used steroid contraceptives, an improvement in symptoms occurred; in unaffected women, the risk for acquiring the disease was decreased by half. There is an improvement in the symptoms of chronic bronchial asthma, but there are also some cases of allergic manifestations 1 to 2 months after beginning contraceptive use [377]. Contradictory results were reported on the effect of steroid contraceptives on allergic diseases in women. Clinical manifestation ranging from vessel hypersensitivity and allergic angitis to other forms of vasculitis indistinguishable from classical systemic forms as Wegener's granulomatosis, polyarteritis nodosa or Churg-Strauss syndrome [378–380]. Half of the patients with Wegener's granulomatosis develop skin lesions due to the systemic vasculitis. Differential diagnostic considerations may present several difficulties and a skin biopsy is necessary for establishing the diagnosis. Antineutrophil cytoplasmic antibodies with antigen specificity for proteinase 3 (PR3-ANCA) supports the diagnosis of Wegener granulomatosis [381]. Wegener's granulomatosis is an organ- and/or life-threatening autoimmune disease of as yet unknown etiology. The classic clinical triad consists of necrotizing granulomatous inflammation of the upper and/or lower respiratory tract, necrotizing glomerulonephritis, and an autoimmune necrotizing systemic vasculitis affecting predominantly small vessels. The detection

of antineutrophil cytoplasmic antibodies directed against proteinase 3 (PR3-ANCA) is highly specific for Wegener's granulomatosis. ANCA positivity is found only in about 50% of the patients with localized Wegener's granulomatosis (which is restricted to the respiratory tract and affects 5% of the patients), whereas PR3-ANCA positivity is seen in 95% of the patients with generalized Wegener's granulomatosis [382]. Vasculitis is an independent risk factor for diffuse endothelial dysfunction and may be a consequence of TNF-alpha action on endothelial cells [379, 380]. Polyarteritis nodosa has been progressive illness resulting in a systemic necrotizing vasculitis which may affect the kidneys, gastrointestinal tract, skin, nerves and muscles. Churg-Strauss is a hypereosinophilic syndrome inducing systemic vasculitis [380]. The subjects affected may be tested for the presence of the FIP1L1-PDGRFA mutation [383]. In conclusion, hormonal contraceptives may induce allergic vascularities. It is hypothesized as possible etiology a reaction of cell-mediated immunity. Affected subjects may present cutaneous involvement alone or life-threatening systemic involvement, which may result in severe and sometimes fatal illness. Although, oral contraceptives when implicated could induce generally mild vasculitis, however, a rare case of vasculitis with cutaneous necrosis, in a woman taking COC containing levonorgestrel 0.15 µg and ethinylestradiol 0.03 mg has been reported [384].

■ 5. Hormonal Contraception in Female Transplant Recipients

In the last decades, organ transplantation has become the universally accepted treatment of end-stage organ failure. The technological progress has led to progressive increase of number and survival-time of female transplant recipients, many of whom are in reproductive age [385].

Therefore, there is a growing interest about the quality of life of female transplant recipients, including sexuality and childbearing. The National Transplantation Pregnancy Registry advises female organ transplant recipients to wait from 18 months to 2 years after transplantation, before attempting to

conceive, allowing the time to recover from surgery, graft function to stabilize and immunosuppression to more likely be at maintenance levels [386]. Therefore, it is advisable that women wishing to have children should avoid conceiving in that time following transplantation [387, 388]. Family planning counseling and consideration of a suitable contraceptive method are essential after transplantation. Contraception is indicated in couples who do not wish to have children, and/or in those who wish to delay pregnancy, in order to improve their health status or social condition. However, if future fertility is not desired, it should be discussed with the patient prior to discharge from the hospital after transplantation. In fact, planning of pregnancy is very crucial in avoiding maternal and fetal risks and deleterious effects on graft function and survival rate. Until now, there are not many reports, in female transplant recipients, studying the different types of contraceptives used, their side-effects, as well as success and failure rates. Consequently, an appropriate and safe contraception, following transplantation, remains hitherto an unsolved issue [389]. However, the choice of the contraceptive is best determined by the efficacy of the method and the likelihood of patient adherence [390]. Menstrual irregularity and infertility are common in women with advanced kidney chronic diseases, but most regain their reproductive function soon after transplantation, showing ovulatory cycles in 72% of them [385, 391, 392]. In fact, females resume ovulatory cycles within 1–2 months and achieve fertility within an average of six months following kidney transplantation [393]. Pregnancy soon after renal transplantation may be successful, but must be regarded as at high risk because of the increased risk for hypertension and preeclampsia, intrauterine growth retardation and prematurity. It is best delayed until 1–2 years after grafting. Close monitoring of immunosuppressant levels in the blood is crucial during pregnancy to avoid inappropriately low levels of immunosuppression [394]. The mean interval between transplantation and conception is three years [387]. Therefore, renal transplantation offers the best hope for patients with end-stage renal disease who wish to have children. The choice for an optimal contraception

risk-free is difficult in these women, even though successful renal transplantation restores normal menstrual cycle and fertility [389]. Post-transplant diabetes, osteonecrosis, cataracts and nephrotoxicity may be directly related to the various immunosuppressive drugs used. The lowest dose compatible with graft acceptance should help to reduce the incidence of these not fatal but significant complications. Patients with a lower GFR are more susceptible to the development of secondary hypertension which could worse graft survival [395]. The development of the graft nephroarteriosclerosis, as a consequence of hypertension, may accelerate the progression of the nephropathy [396]. In spite of these contraindications to hormonal contraception, in women showing stable graft function and without other risk factors, an effective hormonal contraception may be considered [387]. A study, carried out on twenty six women with mean serum creatinine of 1.3 mg/dl, taking combined oral contraceptives (20–35 mcg EE and 3rd generation of progestins) versus contraceptive patch (20 mcg EE and 150 mcg norelgestromin) reported good cycle control and high acceptability. Oral contraceptives were discontinued in two cases: in one because of deep thrombophlebitis and, in the other, because of liver function deterioration. No other side-effects were reported until the end of study (18 months). Hormonal contraception did not significantly influence body mass index, blood pressure, serum creatinine or other biochemical parameters [385], although in the first year post-transplant, blood pressure may be a non-immunological risk factor for long term graft survival [389]. A recent, preliminary study evaluated 17 women (9 renal and 8 liver transplant recipients) treated with vaginal ring releasing an average of 120 mg etonogestrel and 15 mg ethinylestradiol, daily. The duration of treatment was 12 cycles. At the onset of therapy all patients showed at least 6 months of stable graft function with no signs of allograft rejection. The mean post-transplant follow-up was 4 ± 3.6 and 5.3 ± 2.1 years for women with renal and hepatic transplantations, respectively. The immunosuppressive therapy was not changed for any patient. Estrogen-related adverse events as nausea and breast tenderness were reported in two patients. Only one patient experienced significant bleeding related to thrombocytopenia. Nevertheless, by cause of the paucity of the cases, these findings might suggest that vaginal administration, diminishing the chance of drug interactions, could be safer for these patients [397]. Adequate counseling on contraception is imperative in order to avoid unwanted pregnancies and to delay parenthood for at least 1 year. Premature delivery is the major problem in these patients and can be avoided by maintaining adequate graft function and controlling hypertension and infections [398]. Despite the presence of relative contraindications to hormonal drugs in female renal recipients, administration of combined low-dose contraceptive pill should be taken into account as highly effective contraceptive method that, additionally, regulates menstrual bleeding, protects from ovarian cysts development and improves patient's quality of life. In any case, combined pills are among the lowest failure rate contraceptives, but they interact with cyclosporine and are contraindicated in patients with thromboembolism and deep vein thrombosis. Successful liver transplantation not only treats the underlying liver disease, but also restores libido and fertility in female recipients. Although reports of successful pregnancy in female liver transplant recipient continue to increase, these pregnancies are considered at high-risk because associated with an increased materno-fetal morbidity [398]. A study assessed, retrospectively, tolerability and safety of hormonal contraceptives (HCs) in 15 liver transplant recipients, aged 24–35 years, who used HCs for a time not shorter than 12 months. The period from grafting to administration of hormonal contraceptives varied from 6 months to 7 years. Biochemical parameters of liver function, fasting glucose levels, body mass index (BMI) as well as blood pressure were monitored at baseline and every three months of therapy. No case of pregnancy or graft rejection was observed. Changes of biochemical parameters were not significant. Blood pressure and BMI remained stable in the group. None of the patients discontinued therapy for medical indications. Hormonal contraception was administered as soon as liver transplant function became stable. It was effective, well tolerated and did not seem to impair graft function. However, a long-term prospective study is necessary to assess the safety of hormonal contraception in transplant recipients [399]. As liver transplantation leads to restoration of normal menstruation, female patients of reproductive age must be counseled about the possibility of pregnancy and the use of contraception. In conclusion, pregnancy should be avoided for at least 6 months after liver transplantation. With specialized care and attention, pregnancies are generally associated with good outcome [394, 400]. Despite substantial advances in mechanical circulatory support, cardiac transplantation remains the "gold standard" treatment option for eligible patients with class D end-stage heart failure [401]. Transplant survival rates have progressively improved with 55% of recipients now surviving 10 years after transplantation, although most of the mortality aversion is in the first 6–12 months [402]. Younger female patients without serious coexisting conditions, who undergo heart transplantation, have a probability of almost 90% of survival during the first year. Almost 65% of those will survive the next ten years and are likely to have an excellent quality of life. It has become evident that reproduction after organ transplantation is possible. The desire to become pregnant is common and normal in women in childbearing age, including recipients of cardiac transplants. The risk for complications is not higher than for pregnancies of renal or liver transplant recipients, to which pregnancy is not invariably advised against. Despite a greater frequency of complications during pregnancy, successful delivery of a healthy infant is the rule, without any detectable long-lasting adverse effects on both mother and offspring. However, cardiac transplant recipients, who wish to become pregnant, should be counseled on possible complications [403]. Generally, reproductive function improves after transplant and many cases of pregnancy had been reported in this time. Even though different cases of successful outcomes are reported, pregnancy soon after cardiac transplantation is considered a high-risk condition and remains contraindicated [404–406]. When the couple has completed the familial nucleus or does not desire off-springs, it is important to realize whether safer method of contraception

is advisable in such women. Counseling for contraception, when sterilization is not desired, is mandatory. The new low-dose hormonal contraceptives can provide suitable birth control in these women but accurate and correct information about both risks and advantages is mandatory [407]. It is obligatory that the choice of a contraceptive takes into account the possible development of arterial hypertension, often associated to immunosuppressive therapy, and the possible effects of the combined formulation on coagulation, carbohydrate and lipid metabolisms. However, a study carried-out on twenty-four female patients, with congenital heart defects, reported no side-effects during combined oral contraceptive use, without the need to increase the doses of antihypertensive drugs [408]. In practice, low-dose gestagen preparations might be indicated for high risk patients, while low-dosage combined preparations might be indicated for low risk cardiac patients [407, 409]. The use of oral contraceptives, at present, is more controversial because of their effects on lipid and carbohydrate metabolism, on arterial pressure, and coagulation. However, the new types of OCs, with less than 30 mcg of ethinylestradiol, do not seem to alter coagulative homeostasis or increase the risk of thromboembolism. Nonetheless, doubt, hesitance and fear hamper the use of COCs. Probably, in the near future, large prospective studies on the topic will encourage the hormonal contraceptive use also in female heart transplant recipients.

■ 6. Conclusion

The world population is expected to increase by 2.6 billion to 9.1 billion in 2050 [410]. Particularly, the developing countries contribute to this growth with consequent increase of their social and economic problems. So, this overpopulation stresses the discrepancy between developed and developing states. The report "The Evolution of the Family in Europe 2008" declares that over 1.16 million of legal abortions are performed each year in Europe. The real global incidence is unknown and each supposed percentage results underestimated. Besides, an estimated 19 million unsafe abortions occur worldwide each year, resulting in the death of about 70,000 women. The majority of these abortion

occur in under-resourced settings as sub-Saharan Africa, Central and Southeast Asia, Latin America, and the Caribbean. The causes include inadequate delivery systems for contraception, restrictive abortion laws, cultural and religious influences [411–413]. With worldwide unintended pregnancy rates approaching 50 % of all pregnancies, there is an increased need for the improvement of hormonal contraception acceptability, compliance and continuation. Currently, pharmacological methods of contraception are reversible contraceptive steroids formulated in pills, patches, intravaginal rings, subdermal implants and injections [414, 415]. Despite the safety profile of current COCs, fears of adverse metabolic and vascular effects caused by estrogen component, and possible neoplastic effects of these formulations remain. Misperceptions and concerns about side-effects, especially those affecting the menstrual cycle and increased body weight, are often given as reason for discontinuation. However, these disorders are not clinically significant they can lead to erratic method use or even to discontinuation [408].

Much of the woman's dissatisfaction because of menstrual changes can be averted by careful counseling prior to method prescription. Open dialogue explaining the potential for bleeding irregularities is crucial in this time, in order to avoid the discontinuation that places the woman at risk of unwilling pregnancy. The hormonal contraceptive prescription in some women at risk might be considered a hazard, but an expert individualized evaluation of gynecologist may consent it. Most women with congenital cardiac disease can safely use oral contraceptives, especially low-estrogen combinations or progestin-only preparations [416]. Clearly, oral contraceptives should be avoided in all patients at particular risk of thromboembolic complications because of pulmonary hypertension, Eisenmenger syndrome, rhythm disturbances, reduced ventricular function, serious arterial hypertension, infectious complications (endocarditis) or hyperlipidemia. Intrauterine devices-releasing progestin which are very effective, have no metabolic side effects and merely carry a small risk of endocarditis [87]. Other medical conditions require our attention. During hormonal contraceptive use, some cases of subhepatic vein throm-

bosis or the Budd-Chiari syndrome, associated to focal nodular hyperplasia as well as adenoma have been reported [316, 417]. In the meantime, it is mandatory to avoid combined hormonal contraception in SLE patients with high levels of antiphospholipid antibodies and, in those with active nephritis [418, 419]. In fact, these women, when use combined oral contraceptives are at high risk of thromboses (St. Thomas' Hospital-London) [418, 419]. Progress in the area of female reproduction is showing great promise for identifying new contraceptives drug targets [420]. Today, the properties of Selective progesterone receptor modulators (PRMs) and progesterone antagonists (PAs) open up new applications in contraceptive strategies introducing the new concept of "Endometrial Contraception" [421]. In the meantime, there is necessity to develop newer, possibly nonsteroidal and non hormonal contraceptives. Recent advancements in our understanding of ovarian endocrinology, coupled with molecular biology and transgenic technology, have enabled identification of several factors that are functionally critical in the regulation of female fertility.

Large investments are being made focalized on prevention of unwilling pregnancy and sexually transmitted disease in several countries, but the relevance of the problem requires the interest at international political levels. Contraception is a crucial human right for its role in health, development and quality of life. In spite of shortcomings of currently available male contraception, almost 35% of the couples that use contraception worldwide rely on male methods, suggesting that the development of a safe, effective, reversible and affordable contraceptive method for men would meet a critical need [422]. Because rates of unintended pregnancy, abortion and unintended birth are very high among adult women in the world, it is important to identify interventions that can increase contraceptive use in the population, such as vaccines. Currently, vaccines are still experimental and until now were mainly tested in animal and in women of developing countries [423, 324]. A research plan that rigorously assesses the impact of different approaches to increasing contraceptive use among adult and young women, should be an integral part of any long-term effort to prevent unintended pregnancy [425].

■ Conflict of Interest

R. Sabatini and R. Cagiano: no conflict of interest. **T. Rabe** has held talks for Jenapharm, Bayer-Schering Pharma, HRA, and MSD, receiving payment and in some cases travel expenses. Some advisory board activity.

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