Limitation of medical treatment of endometriosis

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Combined oral contraceptives (COCs) & VTE:

- Millions of women have given preference to the use of combined oral contraceptives (COCs) since its introduction in the 1960s.
- Over the last 60 years, efforts have been made to reduce the risk of venous thromboembolism events associated with combined oral contraceptives
- Today, all strategies seem to be moving towards the safe use of these products.
- With novel formulations on the market, estradiol- and estetrol-based combined oral contraceptives, the association of ethinylestradiol with levonorgestrel should no longer be the only option for minimizing the risk of venous thromboembolism associated with combined oral contraceptives use.

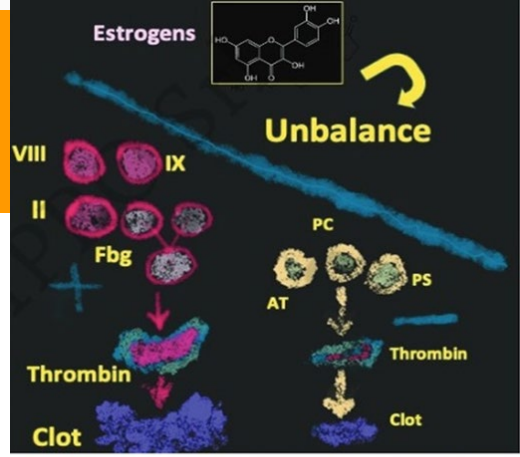


Figure 1 - Hemostatic changes in women taking the oral contraceptive pill
Fbg: fibrinogen; AT: antithrombin; PC: protein C; PS: protein S.

- Thrombosis risk with estrogen-containing compounds increases with increasing systemic dose of estrogen.

- While progesterone-only–containing products are not associated with thrombosis, when paired with estrogen in combined oral contraceptives, the formulation of progesterone does impact the risk.

- When contemplating **hormonal contraception** or **hormone replacement therapy**, clinicians must consider a **variety of factors** including hormone type, dose, route, personal ,family history of thrombosis, and other prothrombotic risk factors to make informed, personalized decisions regarding the risk of venous thrombosis

Hormone replacement therapy:

- **Hormone replacement therapy** is associated with higher risk of thrombosis and is further elevated with certain patient charateristics including increased **age**, **BMI**, and **elevated baseline bio markers such as D-dimer**.
- It is uncertain if the formulation of estrogen influences thrombotic risk.

- **Topical and transdermal routes of administration of estrogen have no associated increased risk of VTE**

- While **avoiding** potent synthetic estrogens dramatically reduces thombotic risks for those with and without underlying risk factors, benefits of estrogen may outweigh risks.

- Conversely, progestins and transdermal and vaginal estradiol, with progestin **endometrial protection** when needed, are safe in nearly all individuals.

- The identification of an individual risk profile is helpful to define the better strategy for each woman.

- In this meta-analysis suggest that **progestin-only contraceptive (POC)** use is not associated with a **increased risk of developing various cardiometaboli outcomes.**

- Based on limited evidence, suggest that an **increased risk of VTE** might be present for **injectable POCs**, as well as some indication for an **increased diabetes risk**.

- There is some indication that an **intrauterine levonorgestrel device** might be a safe choice with regard to VTE risk.

- Women whose **blood pressure** was not measured before starting the use of **OCP** showed **increased risk of acute myocardial infarction (AMI).** Therefore, their blood pressure must be measure before starting the use of the method

- The second **most prevalent contraindication** was **smoking** and age ≥ 35 years together.

- The risk of AMI in women who smoke and have less than 35 years is **10 times greater** than that of those who do not smoke , and this risk in women older than 35 is **higher regardless of smoking.**
- The contraindicated use of OCP is also a cardiovascular risk factor, especially in women **over 30 years old**. are the cardiovascular system diseasesd .

- Use of combined contraceptives accelerate the cascaded of coagulation and fibrinolysis
- They could describe an increasing of various markers of hemostasis and fibrin turnover as a result of the pro coagulatoric effects of oestrogens an **especially ethinyl estradiol**.
- The action of **ethinylestradiol** on **hepatic** and **vascular function** is well documented by the rise of sex hormone-binding globule (SHBG) .

- The combined drugs (COC) **progestogens with pronounce androgenic properties**, e.g., **levonorgestrel,** may counteract estrogen-induced changes in the **hepatic synthesis of hematological factors.**

- Women with **obesity** have **physiological changes** compared to normal weight individuals such as modifications in the **cardiac output** or alteration of **the liver enzymes functions**.

- Women over 34 years, separated/divorced, with private health plan, and low education level presented higher prevalence of contraindication to the use of OCP

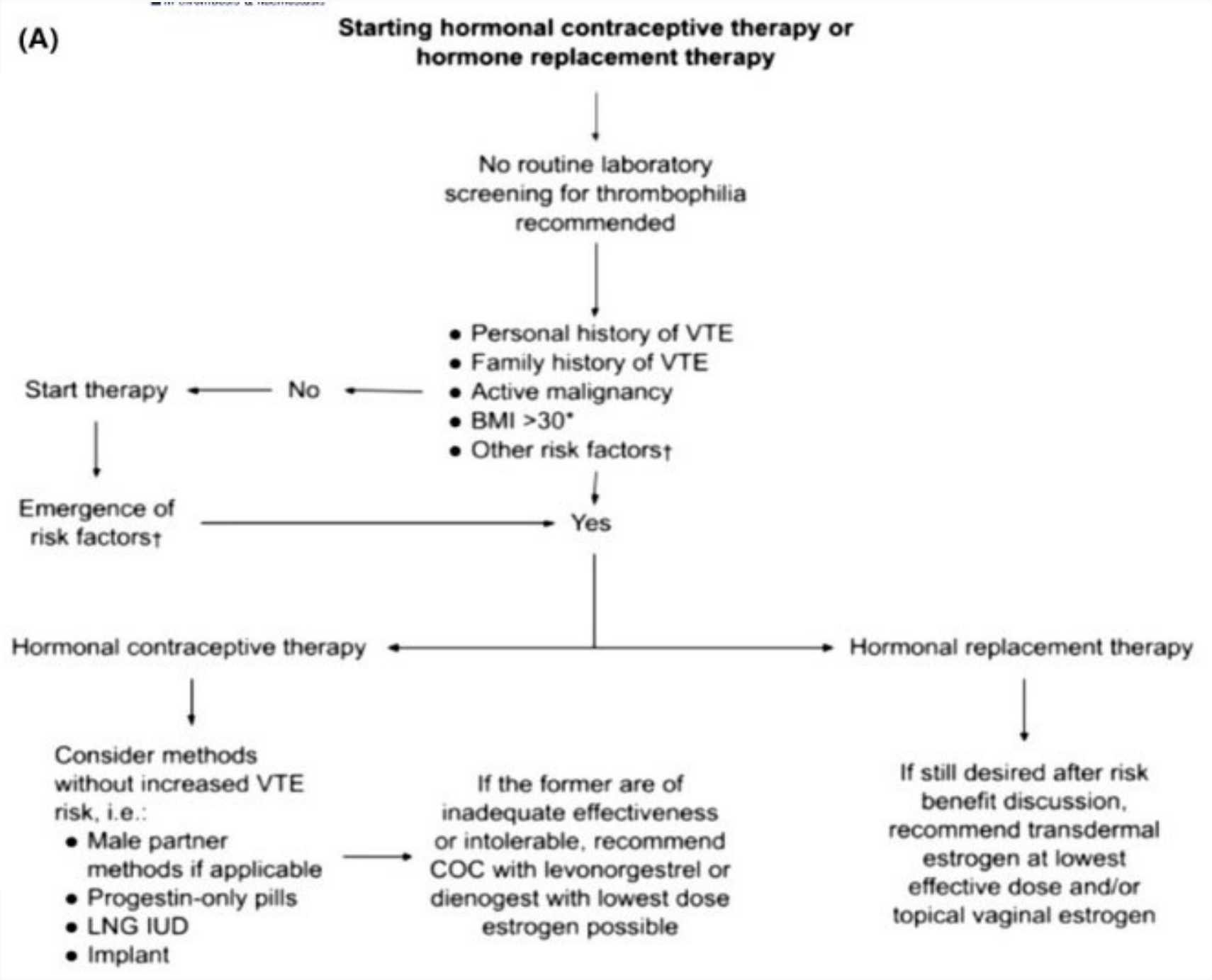
- **The education level is expected to improve the proper choice of OCP**

- **Some important contraindications to the use of OCP**, such as thromboembolism and migraine with aura

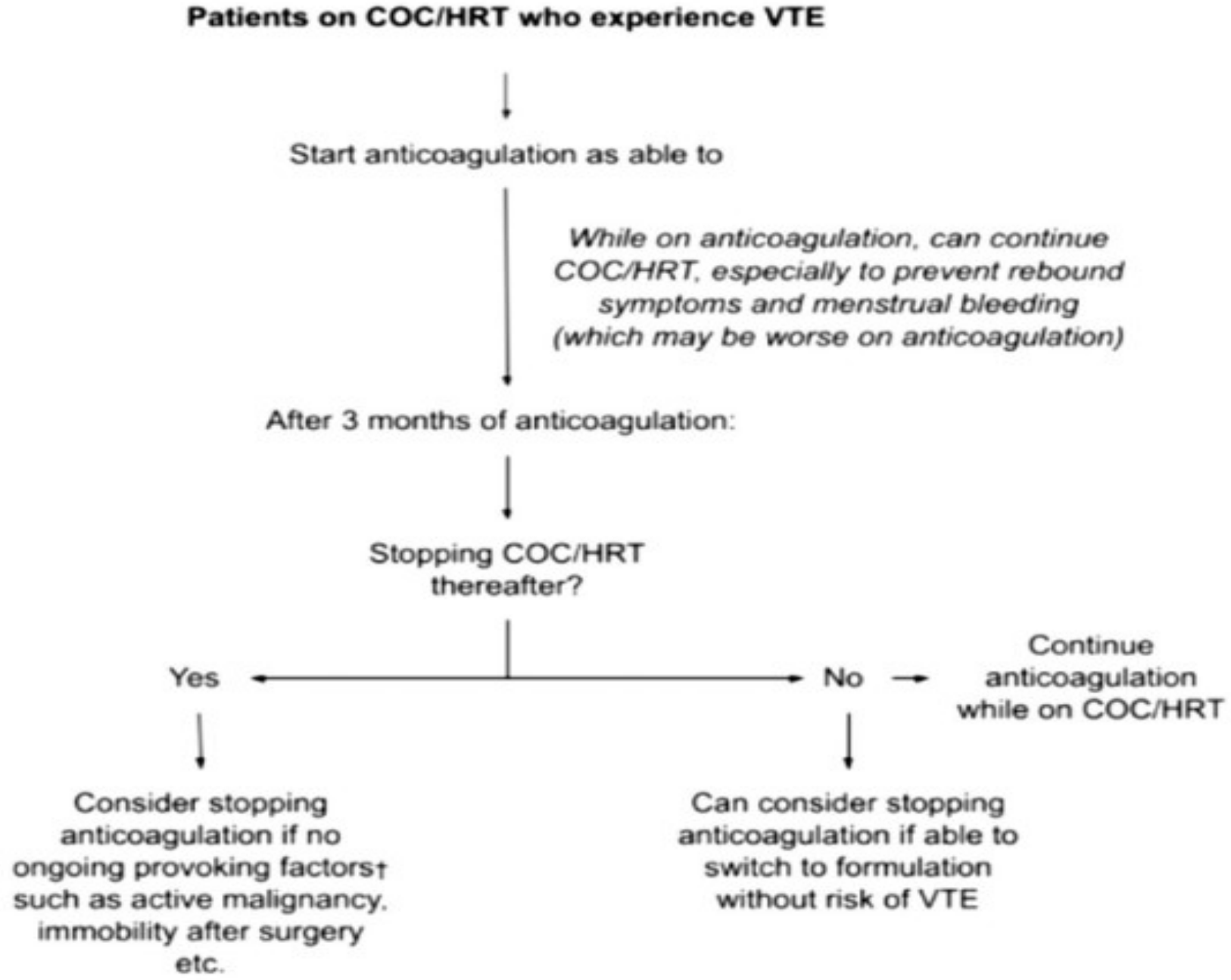
- The use of combined oral contraceptives (COCs) is a well-established risk factor for venous thromboembolism (VTE), **increasing the risk two- to four-fold** compared with non- use.
- In COCs, the estrogen component, mainly ethinylestradiol (EE), induces a hypercoagulative state

- **Progestins** seem to **modify the overall effect depending on androgenic activity**.
- The risk of VTE appears dose- dependent on EE and varies according to the progestin component.

- Continuous exposure to the combined oral contraceptive containing **ethinylestradiol + dienogest enhanced in vitro thrombin generation** compared with **estradiol valerate + dienogest**, suggesting that the substitution of ethinylestradiol with estradiol valerate in combined oral contraceptives may beneficially lower coagulation potential.


(A)
Starting hormonal contraceptive therapy or hormone replacement therapy
No routine laboratory screening for thrombophilia recommended
• Personal history of VTE
• Family history of VTE
• Active malignancy
• BMI >30*
• Other risk factors†
No
Start therapy
Emergence of risk factors†
Yes
Hormonal contraceptive therapy
Hormonal replacement therapy
Consider methods without increased VTE risk, i.e.:
• Male partner methods if applicable
• Progestin-only pills
• LNG IUD
• Implant
If the former are of inadequate effectiveness or intolerable, recommend COC with levonorgestrel or dienogest with lowest dose estrogen possible
If still desired after risk benefit discussion, recommend transdermal estrogen at lowest effective dose and/or topical vaginal estrogen

(B)


Patients on COC/HRT who experience VTE
Start anticoagulation as able to
While on anticoagulation, can continue COC/HRT, especially to prevent rebound symptoms and menstrual bleeding (which may be worse on anticoagulation)
After 3 months of anticoagulation:
Stopping COC/HRT thereafter?
Yes
No
Continue anticoagulation while on COC/HRT
Consider stopping anticoagulation if no ongoing provoking factors† such as active malignancy, immobility after surgery etc.
Can consider stopping anticoagulation if able to switch to formulation without risk of VTE

- In general, **synthetic estrogens** present in conraceptive products **should be avoided** in those with a **personal** or **strong family history of thrombosis or thrombophilias**.

- In contrast, **natural estrogens** present in formulations for climacteric symptom management do not need to be avoided, and vaginal or transdermal formulations are preferred.

- **Transdermal estradiol** is preferred for **gender-affirming hormone therapy** and requires individualized assessment in **those at high risk of thrombosis**.

- **Progestogens** (**either synthetic progestins** or **naturally occur- ring progesterone**) can be used **safely** in nearly all patients.

- The risk of venous thrombosis can be **decreased** by **using the lowes possible dose of estrogen in combination with lower-risk progestin** (second generation) or **progesterone-only contraceptives .**

- Rings, patches, implants, and oral delivery methods of estrogen containing contraception all carry an elevated risk of venous thrombosis, as does the use of DMPA.

- **Intrauterine progestin-only devices** are the **safest choice for hormonal contraception** in patients with an increased risk of VTE including those with a history of thrombosis, certain thrombophilias, and obesity.

- Subdermal implants have a similar safety profile.

- The use of GnRH agonists for breast cancer treatment was significantly associated with a reduced risk of IHD.
- Patients who received **GnRH therapy** had a significantly decreased risk of developing IHD than those without GnRH therapy (HR = 0.18; 95% CI = 0.14–0.23).

- After adjusting for age, treatment, and comorbidity, patients who received GnRH therapy still had a **significantly lower risk of developing IHD** (AHR = 0.5, 95% CI =0.39– 0.64).

- Newer formulations of **OCPs containing natural estrogens** and **progestins with anti-mineralocorticoid effects** (i.e. drospirenone) may mitigate or even reverse the association between OCP use and BP elevations.

- The **estrogen-free contraceptive** containing **4 mg of drospirenone** in a 24/4 regimen intake provides effective contraception with a **good safety/tolerability profile** in a broad group of women, including **overweight or obese women** and is an option for most women regardless of **blood pressure, BMI or thromboembolic risks**.

- **Progestogen pills** may be indicated for obese women, smokers, hypertensive or those with risk factors for cardio- vascular disease.

- **Progestogen-only oral contraceptives** are **not associated** with a higher risk of venous thromboembolism and may even be indicated for women with a personal history of deep venous thrombosis or pulmonary embolism.

- There is **no restriction on the use of progestogen pills** by women with a history of cardiovascular disease, including myocardial infarction or stroke.

- **Progestogen pills** are not associated with **reduced bone mineral density**

- Any woman with a **personal or family history of VTE** who is contemplating starting HC, PHT, or a SERM **should be screened for a hereditary thrombophilia**

- **Aromatase inhibitors** (anastrozole, exemestane, letrozole) **are favored in women with breast cancer** who have a history of VTE because there has been **no reported increased risk of VTE with these agents.**

Cancer

- **Both oestrogens and progestogens** can regulate proliferation and it is plausible these effects may **contribute to carcinogenesis.**
- the results range from **no increase in risk to a 20%–30% elevation in risk**, and the risk seems to be temporary, limited to recent or current regular COC use.

- Data show that the **ongoing** and **prolonged use of COCs** may provide **diminished risk for endometrial, colorectal** and **ovarian cancers.**

- The relationship between COC use and liver malignancy risk assessments has provided conflicting findings.
- Some studies have suggested that hormonal contraceptives may increase the risk of not only hepatocellular carcinoma but also intrahepatic cholangiocarcinoma.

Breast cancer:

- Oestrogens and progestogens are among the modifiable factors that may increase the risk of breast cancer (BC) and this has been confirmed, for instance, in hormone replacement treatment **(HRT) in the post-menopausal population**.

- Researches of **BC risk among women who use COCs** show conflicting results: from no increase in risk to a 20%–30% elevation in risk.
- There was little evidence that **DMPA exposure** may **increase the overall risk for breast cancer.**
- **Long-term use did not result in any risk increase.**

- There were indications that the incidence of breast cancer was possibly increased in current and recent users, especially in women younger than 35 years.

- Women **with breast cancer** who were **ever-users of OC**, as compared to **never-users of OC,** did not experience a higher all-cause or breast cancer specific mortality, after the adjustment of risk factors.

- Although studies **do not clearly support increased risk with COC use in high-risk groups**, such as women with family history of cancer or BRCA carriers, local and international guidelines are available for clinical decision-making.

- Oral contraception leads to a risk reduction of ovarian cancer also in BRCA mutation carriers.

  An increase in breast cancer risk due to OC cannot be excluded.

  Women with **BRCA mutation** who **consider OC use** have to be informed about **possible increase in breast cancer risk** and alternative contraceptive methods.

  OC should not be used for the prevention of ovarian cancer in this population.

- The levels of risks varied between **types of HRT**, with **higher risks for combined treatments and for longer duration of use**

- **Synthetic progestogens (progestins)** have been linked to **increased breast cancer risk**; however, the role of **endogenous progesterone in breast physiology and carcinogenesis is less clearly defined.**

- **BRCA1/2 carriers:**
- Women who possess the BRCA1 and BRCA2 genes compose a **high-risk population** and correspond to **10–15% of all BC cases.**

- In the study outlined above, there was no indication of a significantly elevated BC risk in **COC users in general**, **for ongoing users** or **in the first decade after discontinuance of use.**

- A new meta-analysis reported the **elevated risk for breast cancer among long-term users (>5 years),** while a protective effect for ovarian cancer was observed regardless of COC use

Ovarian cancer:

- **COCs** show a likely promising initial **preventive measure for ovarian cancer**.
- Researches have consistently demonstrated that **continued use of COCs lowers the risk of ovarian cancer.**
- Various broad pooled studies advocate that COCs provide a protective effect on ovarian malignancy risk, with a risk decrease of **up to 50%** with **longer periods of COC use**
- COC use seems to be correlated with a **reduced risk of fallopian tube malignancy** in the common population .
- COCs have a strong and long-lasting suppressive effect on endometrial, ovarian and colorectal cancers.

- **Endometrial cancer:**
- The use of COCs provides **prevention against endometrial neoplasia**.
- The use of COCs reduced the risk of endometrial cancer **by 30%–40%** in broad epidemiologic studies, and the risk decrease persevered for years after cessation.
- **Progestin-only** contraceptives seem to grant even **stronger protection** versus carcinogenesis of endometrium in epidemiologic studies .
- Moreover, it has also been shown that in women receiving perimenopausal HRT, the addition of **progestins** to the regime decreases the oestrogenic side effect on endometrial carcinogenesis

- **Cervical cancer:**
- Cervical malignancy risk increased with continuation of use and waned after discontinuation

- **COC** use might, for instance, enhance the cervical vulnerability to HPV transmission and resultant infection or it might alter persistence or disposition of virus or the advancement or reversion of malign and premalign lesions.

- While using COCs among women with persistent human papillomavirus (HPV) infection and CINs, patients should be reminded that longer (>5 years) durations of use may increase the risk of carcinoma in situ and invasive carcinoma

- **For cervical cancer**, COCs seem **to enhance the risk with more than 5 years of use**, and in many studies, **this enhanced risk diminishes after discontinuation and restores to those of never-users within 10 years**

- Although the **carcinogenic effects reported on breast and cervical cancer are reversibl**e, the overall risk can further be reduced by methods such as lifestyle changes(e.g., lactation, smoking, exercise and weight control) or HPV vaccines.

- **Colorectal cancer:**
- The use of COCs may decrease the risk of colorectal cancer.
- In a cohort of 1.3 million women, which was followed up for 13 years, **ever-use of COCs** was found to be associated with an elevation in risk of **anal cancer** (OR = 1.51, 95% CI: This may be associated with HPV-related pathways as in cervical cancer.
- Several mechanisms, direct and indirect, were suggested for how **COCs modify the risk for CRC.**
- These tumour suppressive receptors are demonstrated to be diminished with age in **colon tissue** through methylation of the receptor gene and this gene may be upregulated by circulating oestrogen.

- **Liver cancer:**
- There is some evidence regarding the probable biochemical pathways through which hormones may **promote carcinogenesis in liver**.
- Hepatocytes carry oestrogen receptors, which are found **to be upregulated in HCC**, probably because of their proliferative and mutagenic effects.
- The proliferation of cholangiocytes in the **intrahepatic bile duct** is upregulated by oestrogens.
- Laboratory findings propose that **oestrogens** are **cofactors for cholangiocarcinogenesis**
- Interestingly, in the study, hysterectomy was associated with nearly **two fold risk of ICC** but not oophorectomy; this may be due to prevalently seen **cofactors** in this group, such as adiposity, diabetes, HRT use or misclassification of the surgical procedures in cohorts

- **Endometriosis** can increase the risk of endometrial cancer and breast cancer, and women with endometriosis are recommended to receive routine screening in long-term management

Migrane:

- Migraine is a major neurological disorder affecting **one in nine adults worldwide** with a significant impact on health care and socioeconomic systems.
- Combined hormonal contraceptives (CHCs) may be used in the majority of women with headach and migraine.

- They carry a small, but **significant vascular risk**, especially in **migraine with aura (MA)** and, eventually in **migraine without aura (MO)** with additional risk factors for stroke (smoking, hypertension, diabetes hyperlipidemia and thrombophilia, age over 35 years).

- **Guidelines** recommend **progestogen-only contraception** a an alternative safer option because it does not seem to be associated with an increased risk of venous thromboembolism (VTE) and ischemic stroke.

Effects of oestrogen and progesterone on mood :

- Estrogen and progesterone influence neurochemistry, brain function and the activity of **neurotransmitters gamma-aminobutyric acid**, **serotonin** and **dopamine.**
- There is evidence to suggest that **oestrogen** is **neuroprotective in the hypothalamus**, **hippocampus, amygdala and brainstem**, protecting the brain from neurodegenerative disease, cognitive decline and affective disorders.
- Functional brain imaging studies have indicated that oestrogen regulates the activation of brain regions implicated in emotional and cognitive processing such as the amygdala
- The use of **OCs**, particularly during the first 2 years, **increases the risk of depression**.
- **OC** use **during adolescence might increase the risk of depression later in life.**

- An **increased risk for first use** of an **antidepressant** and first diagnosis of depression among users of different types of oral contraceptive pills, with the highest rates among adolescents.

- Users of **medroxyprogesterone acetate**, an **injectable progestogen contraceptive**, reportedly have **greater depressive symptoms** than those in non-users.

- Oral contraceptive pills may provide relief from depressive symptoms in women with **premenstrual dysphoric disorder** by **stabilising the fluctuations in hypothalamic–pituitary–gonadal** steroid production.

- In this disorder, the regular use of an active oral contraceptive pill (without seven days of placebo pills) has an antidepressant effect.

Liver Function:

- The use of **hormonal contraceptives** induced changes in liver function test.
- The activity of **liver serum enzymes** and the **mean value of total and direct bilirubin** were higher among hormonal contraceptive users than respective controls.
- The mean **levels of total protein** and **albumin** were not different among the two groups.
- This change has been observed to be associated with the class of hormonal contraceptives and the duration of HC use.

- **Hepatocellular adenomas(HCA)** are rare, hormone-driven, benign liver tumours. HCA >50 mm are associated with haemorrhage and malignant transformation.
- Guidelines recommend cessation of oral contraceptive pills (OCP) for size reduction;
- **Large HCA** showed faster regression than small HCA, but this required a longer time than the currently advised 6-month period.

- No HCA-induced complications were observed during follow-up.

- A conservative approach could lead to HCA regression **below 50 mm** and thereby potentially prevent unnecessary hepatic surgery in a majority of patients

Hepatic adenomas:

- There are associated complications such as intralesional bleeding, malignant transformation, pregnancy, and liver adenomatosis.
- The number of lesions does not seem to have an association with risk of hemorrhage, whereas, size of the lesion does .
- In addition to increased risk of complications secondary to size of tumor, other risk factors include exophytic growth of the tumor and location in the left hepatic lobe.
- A female patient on OCPs with adenoma(s) may be advised to discontinue birth control putting her at increased risk of pregnancy.
- On the other hand, pregnancy increases the patient's exposure to hormones which is a known risk factor for increased growth of HCA.

- Treatment are dependent on a multitude of factors such as presenting symptoms, size of the lesion, sex of patient, and imaging results

- During discrete periods of **progestin-only use**, **HCA growth overall declined**, similar to declining growth during periods without exogenous hormonal exposure.

- In summary, we found no increased risk of HCA growth in female patients taking progestin-only agents for contraceptive purposes, with median HCA size decreasing in the progestin-only and no hormone exposure groups, and increasing in the estrogen exposure group.

FNH:

- **Focal nodular hyperplasia (FNH)** of the liver is a rare benign nodular lesion that arises in women of reproductive age.

- Discontinuation of OC use might have reduced the size of the FNH.

Chronic kidney disease:

- In the **early CKD stages** (stages 1–2–3a), in patients **without hypertension** or **proteinuria** (except in SLE + aPL), virtually all options are available.

- The contraceptive pill should be avoided in every CKD stage in hypertensive patients and in patients in stages 3b–5, as well as in patients with procoagulatory status, including systemic diseases such as SLE, or nephrotic proteinuria.

- The options in these cases include progestin-only contraceptives, which can, however, cause **spotting** (sometimes increased by heparin use in dialysis patients), intrauterine devices, barrier methods and surgical sterilization.

- Data on intrauterine devices suggest that the risk of pelvic infection is slightly higher after insertion

- **Dialysis patients** are not good candidates for the pill, and alternative solutions should be sought
- **In kidney transplant patients** the use of the pill should be limited to the few patients with normal kidney function, normo-tension and no proteinuria, while alternative solutions need to be sought in all the other cases
- No contraindications, except for spotting, exist for **progestin-only birth control agents**; however, due to potential pharmacologic interactions, the level of antirejection drugs should be carefully monitored.
- While no formal contraindications exist for emergency progestin use, this treatment should not be routinely used in patients with occasional intercourse, and the risk of pharmacologic interactions should be borne in mind (in particular with calcineurin inhibitors).

Take Home Massage:

- Meticulous history-taking and clinical examination are important components of contraceptive counseling that enable the **identification of all potential risk factors**.
- In situations of increased risk, decisions must be taken individually.
- Depending on the nature of the patient's underlying illness, **interdisciplinary collaboration** may be advisable.
- Even in situations of increased risk, an appropriated **risk-benefit analysis** should make it possible to find a suitable contraceptive method for any woman who needs one