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The Impact of Oral Contraceptives on Cardiovascular Diseases: Risks and Considerations

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Abstract

Oral contraceptives (OCs) have revolutionised reproductive health by providing women all around the world with efficient birth control alternatives. Their effect on the risks of cardiovascular disease (CVD), however, is still a crucial topic for research. Examining the physiological impacts of sex hormones on the cardiovascular system, this review emphasises the functions of androgens and oestrogens in inflammation, lipid metabolism, and vasodilation. It looks at the possible hazards of OCs, such as diabetes, heart failure, myocardial infarction, and thromboembolism, with an emphasis on progestin-only formulations and combination oral contraceptives (COCs). The review also covers the role of OCs in treating PCOS and infertility, as well as the impact of steroid contraceptive hormones on the pathophysiology of cervical cancer. Even while OCs have a lot to offer in terms of reproduction, their cardiovascular concerns make cautious patient selection and monitoring necessary. By weighing the advantages against potential health hazards, the results highlight the necessity of customised contraceptive options.

Keywords: Oral contraceptives, Cardiovascular disease, Venous thromboembolism, infertility and PCOs, Hormonal contraception.

Introduction

Oral contraceptives (OCs) have transformed reproductive health by giving women more choice over family planning and an efficient method of birth control. Since the first oral contraceptive pill was introduced in 1960 (1), its widespread usage has had a major impact on social dynamics and public health. Notwithstanding their advantages, OCs have been connected to a few health issues, most notably their effect on the risk of cardiovascular disease (CVD) (2).

Globally, cardiovascular illnesses continue to be the largest cause of death, and risk factors such obesity, diabetes, high blood pressure, and lifestyle choices are important in how the condition develops (3). Oestrogens and progestins, the main hormonal constituents of OCs, have intricate effects on the cardiovascular system (4). Certain OC formulations have been linked to a higher risk of myocardial infarction, stroke, and venous thromboembolism (VTE), even though oestrogen has been demonstrated to have certain cardioprotective advantages, such as encouraging vasodilation and lowering oxidative stress (5).

The kind of hormonal combination, dose, length of usage, and individual patient characteristics—such as obesity, smoking status, and pre-existing metabolic conditions—all seem to have an impact on these risks. Apart from its effects on the cardiovascular system, OCs are frequently used to treat diseases including infertility and polycystic ovarian syndrome (PCOS) (6). Many women choose them as a therapy because of their ability to control menstrual cycles, reduce excess testosterone, and enhance ovarian function. Their long-term effects on glucose tolerance, metabolic health, and even cancer risk have drawn criticism, especially considering the pathophysiology of cervical cancer (7).

The objective of this study is to present a thorough examination of the advantages and possible drawbacks of OCs concerning cardiovascular health.

The use of oral contraceptives was linked to a decreased risk of coronary heart disease, heart failure, atrial fibrillation, cardiovascular disease events, and all-cause mortality; however, no significant relationships were reported for myocardial infarction, stroke, or cardiovascular disease death. It is yet unknown how using oral contraceptives (OC) affects cardiovascular disease (CVD) and all-cause mortality (8).

This article aims to provide insights into the ways in which OCs impact cardiovascular physiology, their correlation withthromboembolic illnesses, and the factors necessary for their safe usage by analysing recent research and clinical data. Healthcare professionals must be aware of these effects to prescribe hormonal contraception in a way that balances each patient's safety and effectiveness (9).

Materials and methods

The study of peer-reviewed research found in the ScienceDirect, Cochrane Database, and PubMed

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databases served as the foundation for this evaluation. We evaluated articles that were published between 1989 and 2024.

History of Oral Contraceptives:

In 1960, the first oral contraceptive was authorised by the Food and Drug Administration. The birth control pill, or "pill," as it is sometimes referred to, was used by 1.2 million American women within two years of its first distribution. The pill has been used by over 300 million women globally since it was first introduced as a straightforward, secure, and efficient way to achieve reproductive independence. As a result, many observers believe that one of the most socially significant developments in contemporary medicine is the pill (1,9).

1. Effect of sex hormones on Cardiovascular system:

These sex hormones' significance and their role in regulating the growth and operation of reproductive organs, the heart and circulatory system, and related illnesses are thoroughly explained. The angiogenic and antioxidant properties of estrogens, androgens, progestogens, prolactin, and oxytocin, for instance, reduce body fat, prevent inflammation, and affect the cardiovascular system. These hormones have been shown to improve anti-diabetic effects, cause vasodilation, and reduce blood pressure (10). Certain hormones, such as oxytocin, prolactin, and estrogens, offer some level of cardiovascular protection in women. However, the risk of hypertensive disorders, atherosclerosis, thromboembolic disorders, diabetes mellitus, myocardial infarction, and cardiac remodelling heart diseases is likely to rise with changes in one or more sex hormones and sex-related factors such as pregnancy, menopause, lactation, and the use of contraceptive methods. When sex hormones drastically decline, as they might after menopause or ovarian failure in women, the likelihood of certain cardiovascular issues can significantly rise (11).

OHCs are classified into two primary types:

I) Drug that contain a combination of estrogen, mostly ethinyl estradiol and progestin,

II) Drug that contains only progestin.

1.1 Mechanism of Progestogens, Estrogen, androgen, and their effects:

Progestogens. More research is necessary to clarify the precise effects of progestogens in this context, as their effects on the cardiovascular system have not been well examined. To date, progesterone has been demonstrated to enhance cardiomyocyte proliferation and β-oxidation. Additionally, it was discovered that ECs and VSMCs were stimulated to vasorelaxate by increased eNOS activity and changed calcium availability through increased expression and activity of sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) (12). Additionally, progesterone therapy appears to reduce atherogenesis by increasing HDL and decreasing LDL. It has also been discovered that progesterone raises the vascular system's NADPH oxidase activity, which raises the production of ROS (13).

Estrogens. In both male and female tissues, estrogen, including estrone 1, 17β-estradiol, estriol, and estetrol, binds to the estrogen receptors-α and -β found in the vascular endothelium, smooth muscle cells, cardiomyocytes, and cardiac fibroblasts. Because of this binding, estrogens can function as signaling agents in the cardiovascular system and other plasma membrane-based estrogen receptor-1. Contractility is decreased, vasorelaxation is encouraged, cell migration and proliferation are inhibited, atherosclerosis is avoided, antioxidant benefits are provided, and myocardial damage recovery is enhanced (14).

By decreasing the oxidation and binding of low-density lipoprotein cholesterol, decreasing platelet aggregation, and raising cyclooxygenase-2 activity, the modulatory activities of estrogen receptors provide a fast vasodilatory response and have long-term consequences (15).

Androgens. Cardiomyocyte function is improved and vasorelaxation is induced when androgens and their product, dihydrotestosterone, activate androgen receptors. By enhancing the expression of certain receptors and channels, it enhances cardiac contractile performance. It also changes how the heart handles calcium and increases contractile force (16). By boosting the production of certain enzymes, such as cyclo-oxygenase 2, xanthine oxidase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, androgens affect heart metabolism by increasing glucose absorption. Furthermore, some research suggests that androgens may have pro-inflammatory effects, while other research suggests that they have anti-inflammatory effects. For example, decreased adhesion factors suggest anti-inflammatory effects, while increased TNFα activity and the expression of vascular adhesion molecules in endothelial cells suggest pro-inflammatory effects (Figure 1.) (17).

2. Oral contraceptive result in other complications that can cause life time health issues:

2.1 Risk of diabetes after using hormonal oral contraceptives.

The influence of Oral Hormonal Contraceptives (OHC) has been studied in females with diabetes; however, the effects of progestin-and-estrogen-only interventions on lipid and carbohydrate metabolism are negligible. There has been a little alteration in lipid metabolism among OHC users, with higher levels of HDL and lower levels of triglycerides.

OHC contraceptives have fewer side effects, lower glycaemic control throughout pregnancy, and increase long-term survival. When using OHC, some ladies have seen slight increases in insulin and glucose tolerance. WHO advises people with diabetes or at risk for developing the disease to consider all kinds of OHCs and choose the one that is best for their health, just as it is for women who are obese (18).

2.2 Risk of heart failure using hormonal oral contraceptives.

Progesterone and estrogen are among the OHC that have already been linked to an elevated risk of ischemic heart disease. The use of progesterone-only contraception and fertility treatments, however, did not appear to be associated with an increased risk of cardiovascular disorders (19).

Because estrogen inhibits NADPH activity, activates thioredoxin reductase, and lowers oxidative stress and

apoptosis in the heart, it increases cardiac contractility and avoids increasing cardiac hypertrophy. Comparing female OHD users to those who had never used OHD in their lives, it was proposed that there is no higher risk of heart failure, myocardial infarction, or stroke. However, OHC usage has been linked to improvements in ventricular mass and stroke volume; this might be because of the growth-promoting and fluid-retaining properties of estrogens (20).

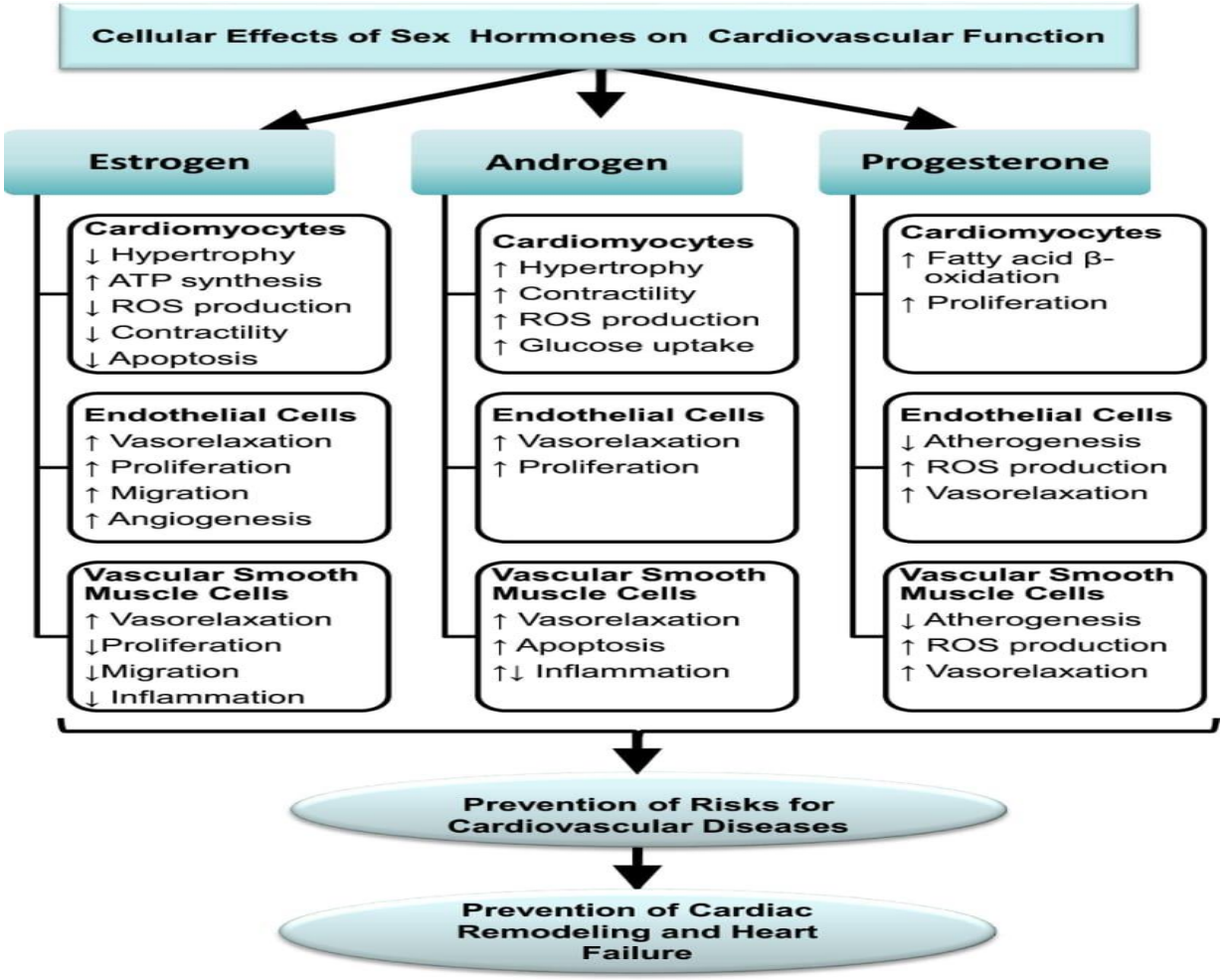

Figure. 1. Effect of sex hormones on cardiovascular function (20).
https://doi.org/10.1139/cjpp-2024-0041

2.3 Risk of thromboembolism associated with use of combined oral contraceptives(COC).

Combination oral contraceptives (COCs) increase the relative risks of venous thromboembolic events by more than four times and arterial thromboembolic events by nearly twice, respectively. The risk of venous thromboembolism decreases to 2.76 above baseline risk after four years of therapy, with the highest risk occurring during the first year of use (OR: 4.17). The risk of myocardial infarction disappears when therapy is discontinued and is unaffected by the length of treatment. The benefits of this birth control method outweigh the hazards, and most women who take COCs have little absolute cardiovascular risks (21).However, due to disproportionately high cardiovascular risks, COCs may occasionally be unsuitable. The risk of venous thromboembolism appears to be 2.5 times greater for current COC users and 10 times higher for users under 35 than for those who do not use COCs. For COC users who currently smoke, the risk of myocardial infarction is 10 times greater, while the risk of stroke is nearly three times higher. When uncontrolled hypertension is present, the risk of myocardial infarction and ischemic stroke is approximately three times greater, while the risk of haemorrhagic stroke is fifteen times higher (22).

2.4 Role of steroid contraceptive hormone in the pathogenesis of invasive cervical cancer.

Invasive cervical cancer continues to be a leading cause of disease and mortality, especially among women from underdeveloped nations where screening is either non-existent or insufficient. The primary cause of this illness appears to be high-risk human papillomavirus (HPV) out of all the contributing variables. However, not all HPV-positive women will develop cervical cancer (Figure 2).

According to the WHO research on steroid contraceptives and neoplasia, those who take the long-acting contraceptive depo-medroxyprogesterone acetate had a 1.2 relative chance of developing invasivecancer (23).

In the transcriptional regulatory areas of the HPV DNA, steroids attach to certain DNA sequences to either promote or inhibit the transcription of different genes. Since there was no evidence of an elevated risk of cervical cancer and studies have demonstrated a causal relationship, particularly among long-term users, some previous findings were comforting. Finding hormone receptors in cervical tissue expanded the role of steroids. Prior research on oral contraceptive steroids did not find any elevated risk, even after adjusting for other risk factors including smoking and the number of partners (24).

Cervical cancer is one of the most preventable, early detectable, and curable as well.One of the most common malignancies among women in underdeveloped areas, it is projected that 570,000 new cases occurred in 2018 (or 84% of all cases globally). Over 85% of the nearly 311,000 women who lost their lives to cervical cancer in 2018 did so in low- and middle-income nations(25).
Research indicates that using OCs for five or more years may raise your chance of developing cervical cancer (26).

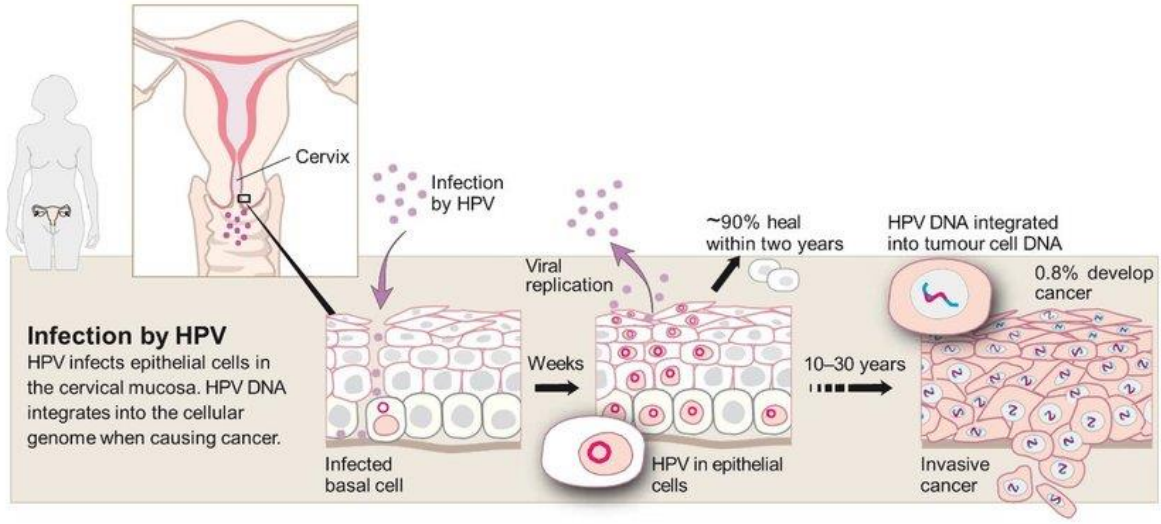

Figure 2. Pathogenesis of Cervical cancer (27).
https://www.researchgate.net/figure/Pathogenesis-of-HPV-in-cervical-cancer-copyright-C-The-Nobel-Committee-for-Physiology_fig3_324478085

3. Drospirenone-containing contraceptive exerts positive effects on cardiac uric acid PAI-1 but not GSK-3.

Combination oral contraceptives (COC) have been linked to an increased risk of cardiac problems. And These issues are associated with elevated levels of glycogen synthase kinase-3 (GSK-3) and cardiac and circulation plasminogen activator inhibitor-1 (PAI-1). Cardiovascular PAI-1 and GSK-3 levels may not be impacted by or may even benefit from contraceptives containing drospirenone, a progestin that works against androgens. It is currently unclear from research how drospirenone oral contraceptives stack up against other androgenic ones (28).
After evaluating the impact on myocardial uric acid (UA), PAI-1, GSK-3, and some haematological parameters of a contraceptive comprising ethinyl estradiol and drospirenone (DSP) against one containing ethinyl estradiol and levonorgestrel (LVG). The findings indicated that LVG therapy, rather than DSP treatment, increased the granulocyte-lymphocyte ratio (GLR), platelet-lymphocyte ratio (PLR), plasma and cardiac tissue UA, and plasma and cardiac PAI-1. Nevertheless, the circulating GSK-3 was impacted by the DSP therapy. When combined, the results demonstrated that cardiac UA and PAI-1 were impacted by LVG rather than DSP.
Based on these findings, COC-containing drospirenone may be a safer and more effective method of birth control than androgenic contraceptives because it seems to have beneficial effects on cardiac UA and PAI-1 levels but has no effect on GSK-3(29).

4. Oral contraceptive in infertile patients.

The primary objective of treatment for anovulatory individuals with PCOS is to induce mono-ovulatory periods. Gonadotropins remain essential even thougha few treatment approaches have been put forth. A higher ovarian response associated with gonadotropin treatment, particularly in women with polycystic ovaries, raises the likelihood of multiple pregnanciesor ovarian hyperstimulation syndrome (OHSS).Patients with PCOS are often treated with oral estroprogestinformulations for contraceptive usage. Regularizing menstrual periods, enhancing clinical and biochemical hyperandrogenism, and improving the ultrasonographic image of polycystic ovaries are all benefits of oral contraceptives (OCs) (30).
OCs were utilized to prevent the development of functional ovarian cysts following the administration of GnRH agonists and to enhance reproductive results in both high-responder and poor-responder individuals. GnRH antagonists are utilized in IVF protocols to avoid an early LH peak, while OCs have been employed in these procedures more recently.
The experimental group consisted of 40 consecutive PCOS patients, whereas the control group consisted of 40 PCOS patients who were matched for body mass index and age. For 14 days, gonadotropin was administered intramuscularly (IM) at a dosage of 75 IU each day. The daily dosage was raised by 37.5 IU each week until

active follicular development was seen during ultrasound examination if no ovarian response (at least one follicle with a primary diameter of ≥10 mm) was seen. Up to a daily limit of 225 IU, any additional adjustments were made in weekly increments of 37.5 IU. If a dominant follicle appeared, the u-FSH dosage was continued until the follicle's diameter was at least 17mm.

Human chorionic gonadotropin (hCG) (10,000 IU, IM) was administered 24 hours following the last gonadotropin injection if no more than three leading follicles measuring ≥17 mm were seen. Cycle abandonment (cancelled cycles) was indicated by the existence of more than three dominant follicles with a diameter of ≥14 mm or by the lack of follicular response following 35 days of therapy. Each subject had timed sexual activity 34–36 hours after receiving an hCG injection. No medication was given repeatedly to support the luteal phase. Each stimulation cycle's length, u-FSH units, peak E2 levels, and the number of dominant follicles on the day after hCG delivery were noted (Figure 3.).

The number of cancelled cycles, ovulations, pregnancies, and abortions in each group were assessed at the conclusion of the trial. In both groups, OHSS, the rate and frequency of multiple pregnancies, and monofollicular cycles were also noted. An ovulatory cycle with just one dominant follicle (≥17 mm) was referred to as a mono-ovulatory cycle. On the eighth day following hCG injection, a plasma P assay of >10 ng/mL (32 nmol/L) and the observation of a reduction in follicular dimensions and liquid in the cul-de-sac were used to retrospectively diagnose the ovulation(31).

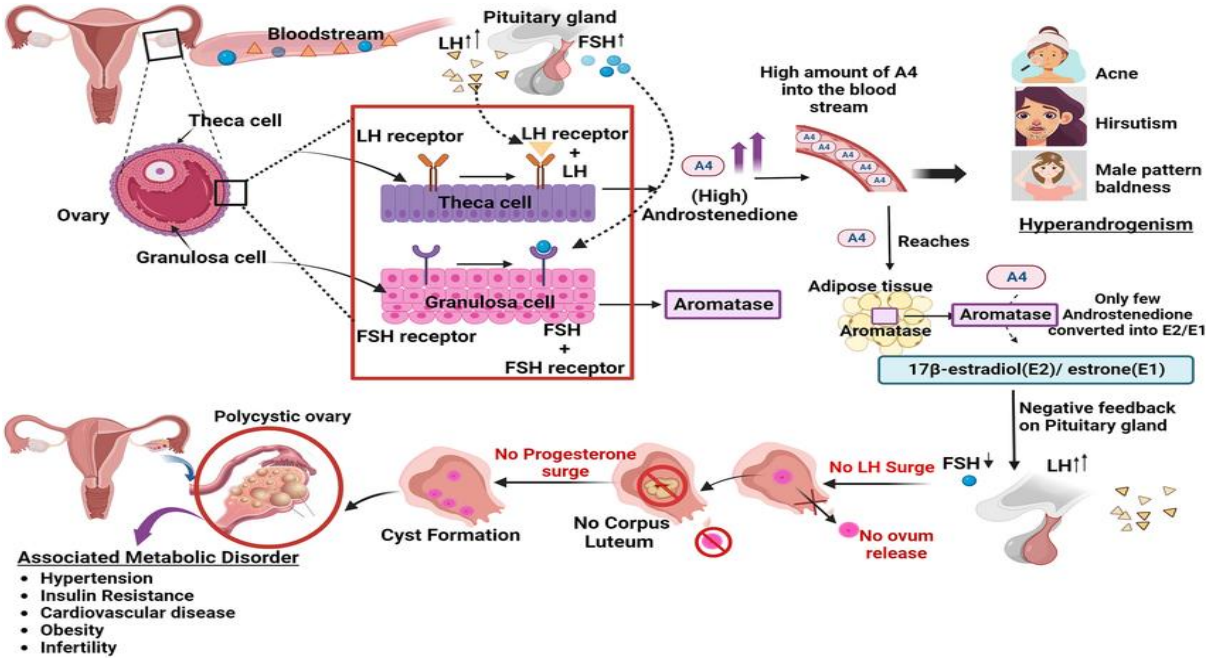

Figure 3. Mechanism of PCOs.
https://images.app.goo.gl/ivKkDjHtB3E3Vhvv5

Conclusion

The usage of infertility therapies, such as ovulation-inducing medications that raise ovarian hormone levels, has grown as women's ages at first pregnancy have increased. Notwithstanding their efficacy, these medications have hazards such ovarian hyperstimulation syndrome and unfavourable pregnancy outcomes (32). The most common histologic subtype of ovarian cancer, which is the deadliest gynecologic cancer in the developed world, is serous ovarian cancer, which typically has a poor prognosis. Ovarian serous borderline tumors (SBTs) are non-invasive tumors that are suspected of being a precursor to some types of serous ovarian cancer. Although they are non-invasive, they can spread outside the ovaries as implants, which can be either non-invasive or invasive. Unlike serous ovarian cancer, an SBT is typically diagnosed in women who are 10 to 15 years younger and have a much better prognosis. Although the literature is conflicting, prior research indicates that ovarian borderline and invasive tumors, including SBTs and serous ovarian cancer, may have a similar risk factor profile (33).

Two known preventive factors against serous ovarian cancer are parity and the use of oral contraceptives (OC). Similarly, while the preventive effect of OC use in relation to SBTs has not been consistent in the research that is currently accessible, some studies have revealed a potential protective effect of parity on the formation of an SBT. Infertility and hormone replacement treatment (HRT) use have been demonstrated to raise the incidence of serous ovarian cancer, in contrast to parity and OC use. However, not enough research has been done on the relationship between infertility or HRT use and the emergence of an SBT (34).

Numerous earlier researchhas either analyzed ovarian borderline tumors as a single group or ovarian cancer and borderline tumors together, without considering the distinct histologic subtypes. Furthermore, most studies

have included cases that did not undergo centralized pathologic review, and the relatively small number of studies that have looked at the risk of developing an SBT linked to factors like parity, infertility, and use of OCs or HRT have been based on a small number of cases (n = 42–110). The latter may be significant because prior research has shown that 9–21% of SBTs are misclassified, with most of these misclassified tumors being of genuinely benign origin. Therefore, the current study's goal was to investigate the risk of developing an SBT linked to parity, infertility, and the use of OC and HRT in a large nationwide case-control study that included age-matched female controls and all SBT cases in Denmark from 1978 to 2002 that were confirmed by a centralized expert pathology review (35).

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