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REVIEW

Obesity and contraceptive use: impact on cardiovascular risk

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Abstract

Obesity and oestrogen containing contraceptive products are well-known independent cardiovascular risk factors. However, a significant number of obese women continue to receive prescriptions of hormonal products that contain oestrogens for their contraception. We have conducted a narrative review to discuss the latest evidence, ongoing research, and controversial issues on the synergistic effect of obesity and contraceptive use, in terms of cardiovascular risk. There is compelling evidence of an interplay between obesity and contraception in increasing cardiovascular risk. Women who present both obesity and use of combined oral contraceptives (COCs) have a greater risk (between 12 and 24 times) to develop venous thromboembolism than non-obese non-COC users. Data here discussed offer new insights to increase clinicians' awareness on the cardiovascular risk in the clinical management of obese women. The synergistic effect of obesity and COCs on deep venous thrombosis risk must be considered when prescribing hormonal contraception. Progestin-only products are a safer alternative to COCs in patients with overweight or obesity. Obese women taking contraceptives should be viewed as an 'at risk' population, and as such, they should receive advice to change their lifestyle, avoiding other cardiovascular risk factors, as a form of primary prevention. This indication should be extended to young women, as data show that COCs should be avoided in obese women of any age.

Keywords Obesity; Combined oral contraceptives; Venous thromboembolism; Cardiovascular risk; Deep venous thrombosis

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Introduction

Obesity is as a major challenge in cardiovascular patients. Indeed, adiposity exacerbates cardiac dysfunction along with hypertrophy, worsens cardiac insulin resistance, and reduces basal and insulin-stimulated glucose oxidation rates.[1]

Contraceptive use is another well-known cardiovascular risk factor, being associated with increased thrombotic risk.[2]

As such, both these conditions are conceived as potentially reversible risk factors. Their effects on cardiovascular outcomes are increasingly recognized.[3]

In this article, we will discuss the latest evidence, ongoing research, and controversial issues on the cardiovascular impact of obesity and contraceptive use, with a specific focus on clinical implications.

First, we will summarize the role of overweight/obesity as independent risk factor for thromboembolic events. Second, we will discuss the data on contraceptive use as independent risk factor for venous and arterial thromboembolic events. Third, we will summarize the available evidence on the interplay between the two factors, examining data on thromboembolic risk and contraceptive use in obese women. Finally, current clinical recommendations will be discussed.

Obesity in women of reproductive age: an independent risk factor for venous and arterial thromboembolic events

Venous thromboembolism (VTE), myocardial infarction (MI), and stroke are the most common cardiovascular diseases.

VTE is the formation of a blood clot in the vein. It mainly consists of two life-threatening conditions, deep venous thrombosis (DVT), and pulmonary embolism (PE).[4]

VTE is estimated to occur at an incidence rate of approximately 1 to 2 per 1000 person-years, with around 60% of all VTE cases presenting as DVTs-only and the other 40% giving as PEs with or without DVT. Approximately 30% of persons who experience a VTE event will experience a recurrence within the following 10 years.[5,6]

Arterial thromboembolism (ATE) is the formation of a blood clot in an artery. ATEs, such as ischaemic stroke, transient ischemic attack, or MI, are significant causes of death in developed countries. According to the World Health Organization (WHO), ischaemic heart disease and stroke were the first and second leading causes of death, responsible for approximately 16% and 11% of total deaths, respectively, in upper-middle-income countries in 2019.[7]

Multiple factors cause VTE and ATE. Some of them are invariable (age, gender, and genetic heritage). In contrast, others are subject to possible interventions, such as smoking tobacco, physical inactivity, diet habits, elevated blood pressure, type 2 diabetes, dyslipidaemia, oral contraceptive or hormone therapy use, and obesity, among others.[4,8]

Obesity/overweight are independent risk factors for VTE and ATE, and their prevalence has increased dramatically during the last decades.[9] According to the WHO, the worldwide prevalence of obesity nearly tripled between 1975 and 2016. In 2016, more than 1.9 billion (39%) adults (39% of men and 40% of women) aged 18 years and older were overweight. Of these, over 650 million adults, that is, 13% of the world's adult population (11% of men and 15% of women), were obese.[10]

Body mass index (BMI), calculated as the ratio of an individual's weight (in kg) to his or her squared height (in meter), is one of the most popular measures of body mass.[9] For adults, WHO define overweight as a BMI $\geq$ 25 kg/m^2 and obesity as a BMI $\geq$ of 30 kg/m^2.[10]

A positive association has been found between VTE risk and overweight and obesity risk measures, such as body weight, BMI, waist circumference, hip circumference, and total body fat mass.[11] Thus, comparing obese with non-obese patients, Stein *et al*.[12] found that the relative risk (RR) of both VTE and PE is more than doubled, 2.5 [95% confidence interval (CI) 2.49–2.51] and 2.21 (95% CI 2.20–2.23), respectively, in obese subjects (*Table 1*) of all ages. However, obesity was shown to have a greater impact on DVT and PE risks in women aged 40 years or less[12] before age becomes another independent risk factor. In men and women of 40 years or less, the RR for PE is 5.19, and the RR for DVT is 5.20 with

Table 1 Relative risks of venous thromboembolism in patients with acquired risk factors of obesity and hormonal contraceptive use (data from references shown in table)

Acquired risk factors of VTE	RR (95% CI) of (confirmed) VTE		Reference
Obese vs. non-obese patients			
	DVT	**PE**	
All ages	2.50 (2.49–2.51)	2.21 (95% CI 2.20–2.23)	Stein *et al*. (2005)[12]
<40 years	5.20 (5.15–5.25)	5.19 (5.11–5.28)	
COC users vs. non-users			
Levonorgestrel-EE 150–30 mcg	2.92 (2.23–3.81)		*Lidegaard *et al*.* (2011)[13]
Desogestrel-EE 150–30 mcg	6.61 (5.60–7.80)		
Gestodene-EE 75–30 mcg	6.24 (5.61–6.95)		
Drospirenone-EE 3 mg-30 mcg	6.37 (5.43–7.47)		
Levonorgestrel-EE 150–30 mcg	2.95 (2.61–3.33)		**Vinogradova *et al*.* (2015)[14]
Desogestrel-EE 150–30 mcg (1)	6.23 (5.03–7.72)		
Gestodene-EE 75–30 mcg (1)	6.47 (4.98–8.39)		
Drospirenone-EE 3 mg-30 mcg	6.09 (4.73–7.83)		
Combined non-oral contraceptives users vs. non-users			
Norelgestromin-EE patch	7.90 (3.54–17.65)		Lidegaard *et al*. (2012)[15]
Vaginal ring of etonorgestrel-EE	6.48 (4.69–8.94)		
POP users vs. non-users			
Implant of Etonorgestrel	1.40 (0.6–3.4)		Lidegaard *et al*. (2012b)[15]
Levonorgestrel IUD	0.72 (0.49–1.06)		Lidegaard *et al*. (2011)[13]
Norethisterone pill	0.68 (0.30–1.51)		
Desogestrel pill	0.61 (0.20–1.90)		

(1) Desogestrel and Gestodene were prescribed in combinations having different doses of oestrogen (20 and 30 mcg), but no associations between VTE risk and oestrogen dose were found.
CI, confident interval; COC, combined oral contraceptives; DVT, deep venous thrombosis; EE, ethinylestradiol; IUD, intrauterine device; PE, pulmonary embolism; RR, relative risk; VTE, venous thromboembolism.
*Relative risk with 95% confidence intervals, adjusted for age, calendar year, and level of education.
**Odds ratios with 95% confidence intervals, adjusted for body mass index, smoking status, alcohol consumption, ethnic group, chronic and acute conditions, and use of other hormonal contraceptives.

the subgroup of women being exposed to an even higher RR of 6.10 for DVT (*Table 1*). The increased risk of VTE in younger obese women aged 40 years or less is relevant because this population usually seeks contraception, an additional independent risk factor for VTE and PE.

There are no other published data, to the best of our knowledge, that differentiates obese women according to their age with regard to their increased risk of VTE or PE.

For women who are overweight without being obese, Severinsen *et al*.[11] found out that the OR of spontaneous VTE was 1.45, 1.81, and 2.82 among women with BMIs of 23.7–26.3, 26.4–29.9, and >29.9 showing a growing impact of weight on VTE risk.

As for the pathophysiological underpinnings reasoning why VTE are more altered than ATE in obese patients, impairment of fibrinolytic activity, increased prothrombotic factors, pro-inflammatory state, and predisposition to venous stasis have been postulated as possible mechanisms for increased VTE risk.[16] Conversely, the loss of body weight has been shown to reduce the concentrations of coagulation factors and plasminogen activator inhibitor-1 towards the normal range.[16]

Severely obese patients (BMI 41.7 ± 4.6 kg/m^2), who underwent bariatric surgery, improved their coagulation profiles after experimenting an appropriate weight loss (usually 1 year after surgery), with a clear reduction in the hypercoagulable state, without any effect on the fibrinolytic function, thus decreasing thromboembolic risk.[17] For these reasons, contraceptive counselling should be given to women after bariatric surgery.[18]

In addition, it has been postulated that low-grade inflammation in obesity may be a shared pathway between MI and VTE risks. Horvei *et al*.[1] found that high levels of C-reactive protein (CRP ≥ 3 mg/L vs. <1 mg/L) were associated with increased risks of MI and VTE in women and that the incidence rates of VTE increased with combined higher BMI and CRP. The same study suggests that the inflammation marker 'CRP' partly mediates the association between obesity and MI and VTE.

Finally, it should be noted that pregnancy and puerperium are well-established risk factors for VTE in both obese and non-obese women, as discussed in the following.

In summary, overweight/obesity is an independent risk factor for thromboembolic events. In women aged 40 years or less, the risk of DVT increases 6.1 times compared with non-obese women of the same age group.

Contraceptive use: a well-known risk factor for venous and arterial thromboembolic events

Drug-induced thrombosis can be a transient or persistent cardiovascular risk factor depending on the duration of the drug therapy. Combined hormonal contraception products are among the most relevant causes of continuous increased thrombotic risk in young women.

A good number of studies have evaluated the risk of VTE and ATE depending on the type of contraceptive used. Lidegaard *et al*.,[13] in a cohort study using national historical registries from Denmark, assessed the risk of VTE from the use of combined oral contraceptives (COCs) according to progestogen type and oestrogen dose. These authors concluded that compared with non-users of COCs, current users of oral contraceptives with levonorgestrel had a three-fold increased risk of VTE (confirmed cases by anticoagulation prescriptions), and those using oral contraceptives with desogestrel, gestodene, drospirenone, or cyproterone had a six-fold to seven-fold increased risk (*Table 1*). Similar results for VTE risk (confirmed cases by anticoagulation prescriptions) were obtained by Vinogradova *et al*.[14] using data based on national population and prescribing practices in the UK (*Table 1*). Regarding the RR of VTE in current users of combined non-oral hormonal contraception, Lidegaard *et al*.[15] found that compared with non-users, the RR of confirmed VTE in users of transdermal combined contraceptive patches was 7.9 (95% CI 3.5 to 17.7) and of the vaginal ring was 6.5 (4.7 to 8.9) (*Table 1*).

Progestin-only products (POPs), such as low dose norethisterone pills, desogestrel only pills, or hormone-releasing intrauterine devices (IUD), are not associated to an increased risk of VTE[13] (*Table 1*). With the levonorgestrel-containing IUD's use, an increased VTE risk was not found either by van Hylckama Vlieg and Middeldorp's studies.[19]

The use of COCs also increases the risk of ATE. Lidegaard *et al*.,[20] in a 15 year Danish historical cohort study, evaluated the risks of thrombotic stroke and MI associated with the use of various types of hormonal contraception, according to oestrogen dose, progestin type, and route of administration. The estimated RRs of thrombotic stroke and MI among users of COCs containing ethinylestradiol at 30 to 40 μg did not differ significantly according to the type of progestin, ranging from 1.40 to 2.20 for stroke and from 1.33 to 2.28 for MI. For women who used a reduced dose of ethinylestradiol (20 μg), as compared with non-users, the RRs of thrombotic stroke and MI with desogestrel were 1.53 and 1.55, respectively. For women using drospirenone with ethinylestradiol at a dose of 20 μg, the RR of thrombotic stroke was lower than 1.00, with no MI. Authors concluded that, although the absolute risks of thrombotic stroke and MI associated with the use of COCs were low, the risk increased by a factor of 0.9 to 1.7 with COCs including ethinylestradiol at a dose of 20 μg and by a factor of 1.3 to 2.3 with those including ethinylestradiol at an amount of 30 to 40 μg, with relatively small differences in risk according to progestin type.[20]

Concerning POPs, neither the levonorgestrel-releasing IUD nor the subcutaneous implants significantly increased the risk of thrombotic stroke or MI in the study performed by

Lidegaard *et al*.[20] In a systematic review and meta-analysis conducted by Glisic *et al*.[21] to determine the impact of POPs use on cardiometabolic outcomes, including VTE, myocardial infarction, stroke, hypertension, and diabetes, it was found that the adjusted RRs for VTE, MI, and stroke for oral POPs users versus non-users were 1.06, 0.98, and 1.02, respectively. Stratified analysis by route of administration showed that injectable POP depot medroxyprogesterone (DMPA) had an increased risk of VTE of 2.62, while no risk was associated with oral POPs: 1.06. These results suggest that oral POPs use is not associated with an increased risk of developing cardiometabolic outcomes.[21]

A new progestin-only pill containing drospirenone at a dosage of 4 mg in a regimen 24/4 has been recently approved by the US FDA and all European regulatory agencies. During its clinical development programme, no cases of VTE or ATE were reported, although among the 2500 patients studied, 41.9% in a US study and 16.6% in European studies had at least one risk factor for VTE or ATE.[22] These results support the evidence that oral POPs are not associated with an increased risk of ATE and VTE.

Several hypotheses have been considered concerning mechanisms underlying the increased risk of thromboembolic events in young women using COCs. Elevated oxidative stress (blood hydroperoxides) was found in 77.0% of COC users vs. 1.6% only in non-COC users. High CRP levels (≥2.0 mg/L, considered risky for cardiovascular diseases) were found in 41.0% of COC users vs. 9.5% only in non-COC users.[23] These results add to the evidence that COC use alters oxidative homeostasis and modifies the low-grade inflammatory status in young women.[23] In addition, the use of COCs is associated with changes in the levels of coagulation factor, leading to a predisposition to venous thrombosis. In this regard, patients taking COCs have higher levels of fibrinogen, factor VII, and factor X, in addition to increased resistance to the natural anticoagulant activity of activated protein C (APC).[19,24]

On the contrary, publications do not suggest an increase in risk for VTE and ATE for POPs users with a possible exception for injectable DMPA.[2,19]

Finally, it should be noted that, regarding estradiol valerate (E2V) and dienogest, few studies measured the increased risk of COCs that use E2V instead of ethinylestradiol in the general population (obese and non-obese). The International Active Surveillance study 'Safety of Contraceptives: Role of Estrogens' (INAS-SCORE)[25] concluded that the combination of E2V with dienogest was associated with similar or even lower cardiovascular risk compared with other COC and levonorgestrel containing COCs. An Italian study[26] showed E2V/dienogest and ethinylestradiol/levonorgestrel contraceptives to induce a similar VTE risk, that is, 3 times higher than non-users of hormonal contraception. Thus, E2V may continue to negatively impact on the risk of VTE, and this should be taken into account at the time of prescription.

To our knowledge, there are no published data to evaluate if natural estradiol in COCs exposes obese patients to a different risk than non-obese patients or to ethinylestradiol in COC in obese patients. Data so far available suggest that natural estradiol combination OC exposes patients to similar vascular risks as levonorgestrel combined to ethinylestradiol.

Regarding ethinylestradiol dose and VTE, there are no data so far available on the distinctive impact of ethinylestradiol dose on DVT in obese and non-obese women. A study[13] showed a trend to lower DVT risks with lower EE doses in the general population. Specifically, this study found that the oral contraceptives with desogestrel or gestodene and 20 μg ethinylestradiol implied a relative risk of venous thromboembolism that were 23% and 17% lower than the same progestogens with 30 μg ethinylestradiol.

In summary, COCs use increases the risk of VTE and ATE as compared with non-use. The procoagulant state induced by COCs, oxidative stress, and a pro-inflammatory state contribute to the COCs-mediated predisposition to VTE and ATE. POPs do not increase VTE and ATE risks, with some remaining doubts with injectable DMPA.

Contraceptive use in obese women potentiates thromboembolic risk

The combination of COCs use and overweight/obesity increases the risk of thromboembolic events in women of reproductive age.

Nightingale *et al*.[27] conducted a meta-analysis to evaluate the effects of age, BMI, smoking, and general health on VTE risk in COCs users. The incidence rate of idiopathic VTE among COC users was 39.4 per 100 000 exposed woman-years. Apart from age, smoking, or general ill health, a relevant factor identified as being significantly associated with idiopathic VTE in women using COCs was BMI of ≥25 kg/m^2 that showed an odds ratio (OR) of 1.4 (*Table 2*). Interestingly, in this study, the increase in the OR is associated to increases in BMI. Thus, COC users with a BMI of (30 < 34.9) had an OR of 1.8 and those with a BMI ≥ 35 kg/m^2 had an OR of 3.1, when compared with COC users with a BMI of 20–24.9 (*Table 2*). This study supports the hypothesis that obesity is a causal factor of VTE in COC users.[27]

An increased risk for VTE was also found by Abdollahi *et al*.[28] in women presenting both risks, obesity and COCs use. The evaluation of the combined effect of obesity and COCs among women aged 15–45 revealed that COCs further increased the impact of obesity on the risk of VTE, leading to a 10-fold increased risk among women with a BMI greater than 25 kg/m^2 who used oral contraceptives (*Table 2*).[28]

Similar results were obtained by Pomp *et al*.[29] in a large population-based case–control study. The authors confirmed that overweight (25 ≤ BMI < 30) and obesity

Table 2 Synergistic effect of body mass index and oral contraceptive use on the risk of venous thrombosis (data from references shown in table)

BMI (kg/m^2)	OR (95% CI) of (confirmed) VTE	Reference
Oral contraceptive users who were overweight/obese vs. non-users of oral contraceptives of normal weight (BMI <25 kg/m^2)		
25 to ≤30	1.4 (1.0–2.0)	Nightingale *et al*. (2000)[27]
30 to <35	1.8 (1.1–2.9)	
>35	3.1 (1.6–5.8)	
>25 to <30	10.2 (3.8–27.3)	Abdollahi *et al*. (2003)[28]
>30	9.8 (3.0–31.8)	
>25 to <30	11.63 (7.46–18.14)	Pomp *et al*. (2007)[29]
>30	23.78 (13.35–42.34)	

BMI, body mass index; CI, confident interval; OR, odds ratio; VTE, venous thromboembolism.

($30 \leq$ BMI < 40) increase the risk of VTE 1.7-fold (OR adjusted by age and sex) and 2.4-fold, respectively. However, when overweight and obesity are associated with COC use, the authors found that in women using COCs with overweight ($25 \leq$ BMI < 30), the VTE risk increased 12-fold (OR 11.63) and if COCs use associates with obesity ($30 \leq$ BMI < 40) the VTE risk increased 24-fold (OR 23.78) if compared with non-overweight, non-COCs users (*Table 2*).

The risk of ATE, such as MI and stroke, has also been assessed in obese women using COCs. In a review by Horton *et al*.,[30] the authors found limited evidence concerning the increased risk of MI and stroke in obese women using COCs. Data were non-conclusive as compared with normal-weight non-COCs users. On the contrary, for VTE, obese COC users consistently had a risk of 5 to 8 times that of obese non-users and approximately 10 times that of non-obese non-users.[30]

Regarding mechanisms involved in the increased risk of VTE in obese women using COCs, the inflammation marker CRP was associated with BMI and COC use, among others.[3] For example, in young women, a one standard deviation increase in BMI was associated with a 0.37 standard deviation increase in log (CRP), provided other variables are held constant. COC use is associated with a 0.23 standard deviation increase in log (CRP), whereas POP use is associated with a 0.04 decrease in log (CRP).[3] The combination of obesity and COCs use appears to potentiate the pro-inflammatory state in young women and trigger the cardiovascular risk increase. In contrast, POPs use does not add cardiovascular risk to obese women.

In summary, in women who combine both obesity and COCs use, data from the literature indicate that cardiovascular risks, mainly VTE risks, increase between 12 and 24 times compared with non-obese non-COC users. The synergistic effect of obesity and COCs on DVT risk must be considered when prescribing hormonal contraception. POPs are a safer alternative to COCs in patients with overweight or with obesity.

Conclusions and recommendations

The risk of VTE and PE increases progressively with BMI, and in obese women, it is more than double that of non-obese subjects. Overweight/obesity has the most substantial impact on women under 40 years when RR is 5 times higher than non-obese subjects. Hypercoagulability, hypofibrinolysis, and a pro-inflammatory state seem to be underlying mechanisms involved in the increased risk of thromboembolic events in obese women.[1,9,16]

Reproductive-aged women who underwent bariatric surgery should avoid pregnancy for 12–24 months because of their weight loss.[18] A possibly decreased efficacy of contraceptive products due to surgical procedures has been postulated in this group. However, the United Kingdom Medical Eligibility Criteria (UKMEC) provides grade 1 (a condition for which there is no restriction for the use of the method) to POPs in women with history of bariatric surgery with BMI ≥ 35 kg/m^2, while CHCs are not recommended.[31]

The RR of VTE comparing COCs users with non-users are between 3 and 7 times higher in users vs non COCs users.[13,14] On the contrary, POPs, such as low dose norethisterone pills, desogestrel only pills, or hormone-releasing IUD are not associated with an increased risk of VTE,[13,19] while the drospirenone only pill did not report any case of VTE or ATE along with its clinical development programme.[22] There is limited evidence that injectable DMPA might increase the risk of VTE.[2,19]

Also, thrombophilic states may have an impact on the embolic events in obese women under contraception although no data on this specific population are available to our knowledge. Family history of VTE, thrombophilia, age, and obesity must be taken into consideration at the time of prescribing hormonal contraception.

Of note, the absolute risks of thrombotic stroke and MI associated with the use of COCs are low, although they seem to be ethinylestradiol dose-dependent.[20]

In the case of COCs use in obese women, the thromboembolic risk, mainly of VTE, is potentiated, ranging between 12 and 24 times if compared with the risk in non-obese, non-users of COCs.[24,25]

Given that VTE risks tend to associate in the same subject and that overweight/obesity can be associated with cigarette smoking, arterial hypertension, and age, it is crucial to assess the consolidated thrombotic risk resulting from the presence of each VTE risk if present in the same subject.

The recommendation is to exercise caution with the use of COCs in patients with overweight and obesity, choosing the safest alternatives when prescribing hormonal contraception due to the rising global prevalence of obesity.

Currently, obesity in combination with a sedentary lifestyle deserves special consideration when prescribing hormonal contraception due to excessive VTE risk.[27]

Recommendations from the WHO, the Center for Disease Control (CDC), and the United Kingdom Medical Eligibility Criteria (UKMEC) provide grade 1 (a condition for which there is no restriction for the use of the method) to all POPs, including pills, IUDs, or implants for women with BMI $\geq$ 30 kg/m^2.[31–33] In addition, the WHO, CDC, and the UKMEC provide grade 2 recommendations for progestogen-only pills and progestogen-only implants when multiple risk factors for cardiovascular diseases, such as smoking, diabetes, hypertension, obesity, and dyslipidaemias coexist.[31–33]

POPs should be considered a safer alternative than COCs in obese women and in women combining several thromboembolic risks who are seeking hormonal contraception.

Conflict of interest

Giuseppe M. C. Rosano, Maria Angeles Rodriguez-Martinez, Ilaria Spoletini, and Pedro Antonio Regidor declare that they have no conflict of interest.

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