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MECHANISMS IN ENDOCRINOLOGY
Epidemiology of hormonal contraceptives-related venous thromboembolism

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Abstract

For many years, it has been well documented that combined hormonal contraceptives increase the risk of venous thromboembolism (VTE). The third-generation pill use (desogestrel or gestodene (GSD)) is associated with an increased VTE risk as compared with second-generation (levonorgestrel) pill use. Other progestins such as drospirenone or cyproterone acetate combined with ethinyl-estradiol (EE) have been investigated. Most studies have reported a significant increased VTE risk among users of these combined oral contraceptives (COCs) when compared with users of second-generation pills. Non-oral combined hormonal contraception, such as the transdermal patch and the vaginal ring, is also available. Current data support that these routes of administration are more thrombogenic than second-generation pills. These results are consistent with the biological evidence of coagulation activation. Overall, the estrogenic potency of each hormonal contraceptive depending on both EE doses and progestin molecule explains the level of thrombotic risk. Some studies have shown a similar increased VTE risk among users of COCs containing norgestimate (NGM) as compared with users of second-generation pill. However, for this combination, biological data, based on quantitative assessment of sex hormone-binding globulin or haemostasis parameters, are not in agreement with these epidemiological results. Similarly, the VTE risk associated with low doses of EE and GSD is not biologically plausible. In conclusion, newer generation formulations of hormonal contraceptives as well as non-oral hormonal contraceptives seem to be more thrombogenic than second-generation hormonal contraceptives. Further studies are needed to conclude on the combinations containing NGM or low doses of EE associated with GSD.

Invited Author's profile

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Introduction

In December 2012, a young French woman sued a drug company and the head of the French drug regulatory Agency (ANSM) after she had a stroke with major sequellae when using a third-generation pill containing gestodene (GSD) and ethinyl-estradiol (EE). This case, which received extensive media coverage, has provoked alarm in France (1, 2). Subsequently, contraceptive practices have changed. This case highlighted the risks of vascular thrombo-embolic diseases associated with pills and, in particular, with the use of newer pills. The ANSM Agency has advised that later-generation pills should never be used as a first choice, and could be used if patients experienced side effects with second-generation ones.

Hormonal contraceptives are one of the most commonly proposed birth control methods, used by several million women worldwide. In several countries, hormonal contraceptives have been used by approximately more than 80% of women at some point in their reproductive life.

Formulations of combined oral contraceptives (COCs) have dramatically changed over the past 50 years. The most recent COCs contain 35–15 µg EE or estradiol (E$_2$) combined with new progestins (3). Finally, non-oral delivery methods have been recently developed for combined hormonal contraception (CHC), including the contraceptive vaginal ring and the transdermal contraceptive patch.

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism, is an uncommon disease before menopause, and its incidence strongly increases with age. Previous studies reported an estimated annual VTE incidence of about 1/10 000 persons among childbearing-aged women (4, 5). Annual VTE incidence doubles from ages 20–40 years and reaches 1/1000 persons around 45 years with a fatal outcome for around 10% of cases. Nevertheless, recent data have reported that VTE incidence among young women has steadily increased for these past 10 years to reach an annual incidence of four cases per 10 000 women (6).

Use of hormonal contraceptive explains a substantial part of the venous thrombotic events among childbearing-aged women, and VTE is the most important determinant of the benefit/risk profile of hormonal contraceptives. The VTE risk differs between the COC according to the type of progestin and the dose of EE. Recently, the most recent formulations of oral contraceptives and non-oral delivery methods have been evaluated in the context of cardio-vascular risk. Both hormones in COCs contribute to the changes in haemostatic variables. However, with the same dose of EE, the type of progestin seems to have a major impact on VTE risk. For most combinations of pills, modifications of haemostatic parameters or sex hormone-binding globulin (SHBG) are in adequation with the reported epidemiological risk. Only two associations remain controversial: norgestimate (NGM) associated with EE and GSD with low doses of EE.

This review aims to assess the association between different formulations of pills and the risk of VTE, in particular COCs containing NGM and their impact on surrogate marker of VTE risk. Indeed, all COCs are equally effective in preventing pregnancy, and their side or benefit effects are also similar. The best contraceptive strategy is thus to use the safest one with regard to venous thrombosis.

Classification of hormonal contraceptives

Initially, COCs delivered a daily dose of 150–100 µg of EE or mestranol associated with progestin such as norethisterone acetate or norethindrone. Owing to the first results, having shown that these drugs increased the risk of cardiovascular disease, formulations of COC have drastically changed over the past 50 years. Modern COCs contain 35–15 µg of EE or E$_2$ combined with new progestins and non-oral routes of administration have been developed. Besides, progestin-only contraceptives is a contraceptive method which may be an attractive option for women with contraindication for COC. Several routes of administration are available (3).

Oral route of administration

Oral contraceptives can be classified by COC and progestin-only pills (POPs).

Combined contraceptives ▸ The first marketed COC consisted of high doses of synthetic estrogen and androgenic progestin such as norethisterone acetate or norethindrone. The current COCs now deliver 15– 50 µg of EE/day (3) and new formulations delivering natural E$_2$ have recently been marketed. A quadriphasic COC combining E$_2$ valerate and dienogest has been newly approved in Europe and USA and a second monophasic COCs that combines E$_2$ with nomegestrol acetate, a progesterone-derived progestin, is now available in several countries in Europe (7, 8, 9).

COCs are also classified into generation, according to the type of progestin associated with estrogen. The first-generation pills containing either norethisterone acetate, lynestrenol, ethynodiol acetate, or norethynodrel are no longer used. The currently available COCs are both second- and third-generation pills. The second-generation pills contain norgestrel or levonorgestrel (LNG). Since the beginning of the 1980s, the third-generation pill relies on three major new progestins (NGM, desogestrel (DSG), and GSD) (10). Drospirenone (DRSP), an aldosterone antagonist, and cyproterone acetate (CPA) are molecules presenting high-anti-androgenic effects and are classified as other generation pills (11). There is no generally accepted way to classify COC. Classification according to generations is irrespective of EE dose, and the place of NGM in the third-generation group is debated. The EMA (www.ema.europa.eu; January 2014) published a new classification, in January 2014, depending on the specific molecule of progestin and not on generation.

Progestin-only pills ▶ POPs deliver low daily doses of progestin (norethindrone, LNG, or DSG). Although the original development of oral contraceptives focussed on progestin-only products, current POPs are less used than COC because of their poorer uterine tolerance. The menstrual cycle is less well controlled, and bleeding such as spotting is common (12). Nevertheless, POPs may be an attractive contraceptive option for women with contraindications to COCs.

Non-oral route of administration

The new routes of administration of hormonal contraceptive provide continuous delivery doses of steroids. They can deliver a combination of estrogen and progestin or a progestin only.

Combined contraceptives ▶ Two non-oral routes of administration are available: a patch and a vaginal ring. The transdermal patch contains EE associated with norelgestromin (NGMN) and the vaginal ring contains EE associated with etonogestrel.

Progestin-only contraceptive ▶ Three non-oral routes of administration of POP are currently available in Europe and in the USA. The first one is an injectable 3-month contraceptive (depot medroxyprogesterone acetate), intramuscularly administered. The second type is LNG implant or more recently, etonogestrel single-rod implant that provides effective contraception for 3 years. Thirdly,

the intrauterine device delivers low doses of LNG. It is effective for 3 or 5 years according to the size of the device.

Pharmacological profile of estrogen used in hormonal contraceptives

EE is the estrogen most frequently used in COC, but some new pills now contain E_2. The Fig. 1 shows the difference in chemical structure of the two molecules.

Ethinyl-estradiol

The current COCs now contain 15–50 µg of EE/pill (3). This molecule undergoes first-pass metabolism in the gastrointestinal mucosa. Ninety percent of the EE is absorbed from the upper gastrointestinal tract, which can range from 1 to 2 h (13). It is then exposed to oxidation reaction. Following absorption, EE is metabolised during enterohepatic recirculation. EE has a strong hepatic impact related to its 17α-ethinyl group. This group prevents the inactivation of the EE and results in a slow metabolism and a long tissue retention. This probably explains why there is no difference in hepatic proteins impact between oral and non-oral EE administration (14).

Estradiol

The natural estrogen E_2 used in two oral contraceptives is combined with either nomegestrol acetate or dienogest.
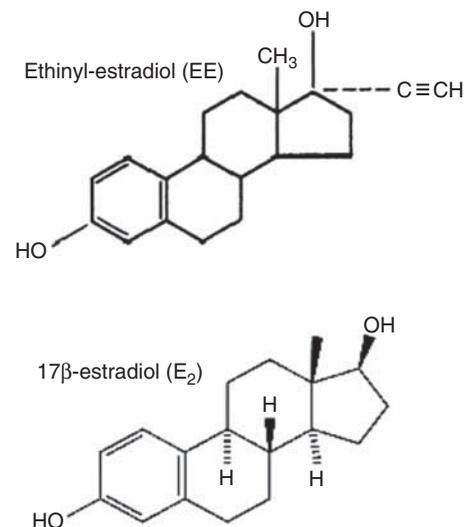

Figure 1

Structure of ethinyl-estradiol and 17β-estradiol used in contraception.

In contrast to EE, the E_2 has a short half-life and an action on hepatic proteins, depending on the method of administration. Indeed, E_2 is 200–20 000 times less potent than EE on marker of estrogenicity, such as SHBG. Given orally, E_2 has a lesser stimulatory effect on hepatic proteins. Given transdermally, E_2 has no impact on hepatic coagulation parameters (13).

Pharmacological profile of progestins used in hormonal contraceptives

The first generation of progestins, primarily designed for use in contraceptives, was derived from testosterone and consisted of norethisterone and its derivatives. However, due to their adverse effects on vascular risk attributed to their androgenicity, new progestins were synthesized in the last two decades. Newer generation progestins now result in a stronger progestogenic activity coupled with a strong anti-gonadotropic effect and with decreased androgenic effects.

The progestins are characterised by non-selectivity for the various steroid receptors. In addition to their interaction with the progesterone receptor, they can also bind to the androgen receptor, the estrogen receptor by metabolisation, the glucocorticoid receptor or the mineralocorticoid receptor. Table 1 gives these different impacts. Some of the progestins, such as NGM, are prodrugs that undergo metabolism to become active. Most of the

progestins are well absorbed when administered orally and undergo first-pass metabolism (13).

Progestins belong to norsteroids (estranes or gonanes), pregnanes, 19-norpregnanes, or spironolactone derivative's group. The group of estranes is structurally related to testosterone. In addition, it can exert estrogenic effects. Dienogest, a new non-ethyl progestin, is also an estrane derivative, but differs from norethisterone by having anti-androgenic and anti-mineralocorticoid properties and no estrogenic or glucocorticoid activity. The group of gonanes includes LNG, norgestrel, NGM, DSG, and GSD. NGM shows highly selective progestational activity and minimal androgenicity. While norethisterone and LNG are included in first- and second-generation COCs, respectively, DSG and GSD are included in third-generation COCs (15). Regarding NGM, its belonging to second- or third-generation is debated. The rationale for classifying NGM-containing formulations as second-generation COCs is that NGM is at least partially converted to LNG. NGMN and LNG are the main active metabolites of NGM. Nevertheless, the pharmacological effects of LNG derived from NGM–COC are minimised. NGMN must contribute significantly to the biological activity of NGM in target tissues. NGM–COC provides a pharmacological profile which is probably different from that of LNG–COC (16).

The pregnanes (17hydroxy-progesterone) are structurally related to progesterone. Whereas medroxyprogesterone acetate has strong androgenic and glucocorticoid activities,

Table 1 Hormonal effect of the different progestins used in contraception.

Pharmacological class	Molecules	Progestogenic activity	Estrogenic activity	Androgenic activity	Anti-androgenic activity	Glucocorticoid activity	Anti-mineralocorticoid activity
Micronised progesterone	Micronised progesterone	+	−	−	±	±	+
Pregnanes	Chlormadinone acetate	+ +	−	−	+	+	−
	Cyproterone acetate	+ +	−	−	+ + +	+	−
	Medroxyprogesterone acetate	+	−	+	−	+ +	−
Norpregnanes	Nomegestrol acetate	+	−	−	−	−	−
19-Nortestosterone ethinylated							
Estranes	Norethisterone acetate	+ +	+	+	−	−	−
Gonanes	Levonorgestrel	+ +	−	+	−	±	−
	Gestodene	+ +	−	+	−	±	−
	Norgestimate	+ +	−	±	−	−	−
	Desogestrel	+ +	−	+	−	−	−
19-Nortestosterone non-ethinylated	Dienogest	+ +	−	−	+	−	+
Spironolactone derivatives	Drospirenone	+	−	−	+	−	+ +

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other pregnane derivatives, such as CPA, have potent anti-androgenic activity. DRSP is a progestin derived from spironolactone with an anti-mineralocorticoid action and a slightly anti-androgenic action (13).

Hormonal contraceptives and risk of VTE

For many years, it has been shown that use of COC was positively associated with VTE risk. This increase in VTE risk is highest during the first year of use. It may vary according to the different characteristics of COCs, such as estrogen dose, molecule, and type of progestins. More recently, the new formulations of oral contraceptives and non-oral routes of administration have been evaluated in the context of VTE risk. Several meta-analyses or quantitative assessments have been performed for evaluating the association between different type of COC and VTE risk (17, 18, 19, 20, 21). Quantitative assessments on surrogate markers have also been published.

Table 2 presents the risk of VTE among those who use 30–35 μg of EE within different types of progestins as compared with COC containing LNG, as well as from the Stegeman's network meta-analysis (17) and from our epidemiological update (19). In 2013, Stegeman et al. published a network meta-analysis of 26 studies. The use of COC increased the risk of VTE as compared with non-use (relative risk 3.5 (95% CI 2.9–4.3)). The risk estimate of VTE for 30 μg EE-LNG users as compared with non-users was 2.4 (95% CI 1.8–3.2). With the same doses of EE (30–35 μg), the COC containing DRSP, CPA, DSG, or GSD had a similar increased risk of VTE as compared with COC containing LNG. The use of non-oral routes of combined contraceptives, patch, or vaginal ring was also associated with a higher VTE risk as compared with second-generation pills (19). These increases of risks are biologically plausible and include more deleterious changes in haemostasis among users of these new progestins than among LNG users. In combination with EE, these new progestins appear to induce a resistance to activated protein C (APC), a surrogate marker of VTE risks significantly more pronounced than biological changes observed with use of second-generation pill (22, 23). Moreover, the effect on APC resistance of the different molecules of progestin associated with the same EE dose has been clearly investigated in randomised controlled trials (24, 25, 26). These studies confirm that third-generation progestin induced a higher APC resistance than did LNG (24, 25). Several investigators have postulated that acquired APC resistance (measured as the effect of APC on thrombin generation) may explain the thrombotic effect of hormonal contraceptives.

SHBG, which has been recently positively correlated with APC resistance among pill users, is another useful pharmacological marker to indirectly predict the venous thrombotic safety of a combined contraception (27, 28, 29). SHBG is a carrier protein synthesized by the liver. Its transcription has been shown to be highly estrogen sensitive. The relationship between the effects on acquired resistance to APC in users of different types of COC parallels the effects on SHBG in users of those COCs (27). As APC-resistant SHBG appears to be higher among users of DSG, DRSP, and CPA containing pills than among users of LNG pills (27, 28).

Discrepancies between epidemiological results and biological data

So far, the classical classification of COC into generations is inappropriate concerning third generation. Indeed, the place of NGM in the third-generation group is debated. The EMA has published a new classification in January 2014, depending on type of progestins and not on generation. The EMA concluded that COC containing NGM had a VTE risk similar to that reported for COC

Table 2 VTE risk and combined contraception according to the types of hormonal contraceptives.

	Combined contraceptive OR (95% CI)						
	Gestodene (+30 μg EE)	Desogestrel (+30 μg EE)	Norgestimate (+35 μg EE)	Drospirenone (+30 μg EE)	Cyproterone acetate (+35 μg EE)	Vaginal ring	Transdermal system[d]
(19)[a]			1.2 (0.9–1.5)[b]	1.7 (1.4–2.2)	1.8 (1.4–2.3)	1.7 (1.3–2.3)	1.5 (1.2–1.8)
(17)[c]	1.5 (1.2–2.0)	1.8 (1.4–2.2)	1.0 (0.7–1.3)	1.6 (1.2–2.1)	1.6 (1.1–2.2)		

LNG, levonorgestrel; EE, ethinyl-estradiol; OR, odds ratio.
[a]Compared with COC containing LNG.
[b]Result from Table 3.
[c]Compared with COC containing 30 μg EE+LNG.
[d]Compared with norgestimate pill.

Table 3 VTE risk associated with oral contraceptive combined norgestimate and 35 µg ethinyl-estradiol.

References	Study type	Number of cases/controls	OR (95% CI) compared with 30 LNG	OR (95% CI) compared with non-user
(30)	Case–control	19/31	1.9 (0.95–3.6)	
(31)	Nested case–control	15/40 440 WY	1.1 (0.6–2.0)	
(32)	Case–control	18/118		1.7 (1.0–3.2)
(33)	Nested case–control	124/511	1.1 (0.8–1.5)	
(34)	Case–control	9/4		5.9 (1.7–21)
(6)[a]	Cohort	165/267 664 WY		3.5 (2.9–4.3)
		Pooled OR	1.2 (0.9–1.5)	3.3 (2.7–3.9)

30 LNG, 30 µg ethinyl-estradiol+levonorgestrel; WY, women-years; OR, odds ratio.
[a]Confirmed events.

containing LNG. These recommendations were based on epidemiological data (6, 17). All studies (6, 30, 31, 32, 33, 34) (Table 3) reported an increased VTE risk of NGM-containing COC as compared with non-users. The pooled OR showed a significantly increased VTE risk among users of 35 µg of EE combined with NGM, as compared with non-users (pooled OR=3.3 (95% CI 2.7–3.9)), and a similar risk as compared with LNG–COC (pooled OR=1.2 (95% CI 0.9–1.5)). Lidegaard *et al.* (6) have published results about the risk of VTE in the case of confirmed diagnosis of VTE or not. Unlike Stegeman *et al.* we used relative risk of confirmed diagnosis to calculate the pooled OR (Table 3). This could explain the difference between the pooled OR that we calculated and the one from Stegeman *et al.* (17). According to data on SHBG and APC-resistance, similar VTE risks between 35 µg EE-NGM and 30 µg EE-LNG are not biologically plausible. Studies on haemostasis markers show more deleterious changes in haemostasis among users of 35 µg EE-NGM compared with 30 µg EE-LNG. In the study by Johnson *et al.* (35), transdermal (EE+NGMN) and oral contraceptives (EE+ NGM) have similar impacts on biomarkers of vascular disease risk, notably with a substantial increase in the APC resistance. In the Oral Contraceptive and Hemostasis Study Group's randomised multicenter study, all oral combined contraceptives were associated with an increase in coagulation and fibrinolytic activity (26). The percentage change in APC resistance from baseline (no COC use) until cycle 6 (with COC use) was 73.6% (95% CI 40.8–121.5) for COC containing 30 µg EE+150 mg of LNG, and 147.9% (95% CI 103.0–204.3) for COC containing

35 µg EE+250 NGM (26). This last increase was similar for COC containing DSG or GSD and the same doses of EE.

Concerning SHBG and NGM, the use of 250 µg NGM associated with 35 µg EE resulted in a significantly higher SHBG level when compared with COC containing 150 µg LNG associated with 30 µg EE (151 vs 92 nmol/l respectively, $P=0.002$). The difference can be, however, due to different doses in EE (15). Zimmerman *et al.* (36) reviewed the impacts of COC on testosterone and SHBG level in healthy non-polycystic ovary syndrome women. This meta-analysis was carried out to evaluate the concentrations of SHBG depending on the dose of EE and generation of progestins (36). Table 4, adapted from Zimmerman *et al.*, presents the effect of COC on mean difference of SHBG concentrations (COC use compared with no COC), depending on EE dose and type of progestins. The mean concentration for the group 35 µg EE+NGM users is 123.07 (95% CI 72.62–173.51) (37, 38, 39, 40, 41) and for the group 30 µg EE+LNG users is 22.08 (95% CI 15.60–28.55) (42, 43, 44, 45, 46, 47). Taking into account these biological data, it is thus really unexpected that a similar VTE risk between these two combined pills can be observed.

While it has been well demonstrated that reducing daily dose of EE from 100 to 50 µg and from 50 to 30 µg was associated with a decrease in thrombotic risk, comparison of the VTE risk among users of 30 and 20 µg daily doses of EE remained inconclusive. Two large studies have recently suggested that reducing the daily dose of EE from 30 to 20 µg could be associated with a decrease in the thrombotic risk (6, 34). Nevertheless, further data are needed to confirm this result.

Concerning EE doses, Stegeman *et al.* (17) have shown that the VTE risk for COC containing DSG

Table 4 Effect of combined oral contraceptives (COCs), depending on ethinyl-estradiol (EE) dose and type of progestins, on mean difference of sex hormone-binding globulin (SHBG) concentrations (nmol/l) (COC compared with no COC). Adapted from Zimmerman *et al.*

Dose of EE	Molecule of progestins	Mean difference of SHBG (nmol/l) (95% CI)
20–25 µg	Levonorgestrel	21.6 (11.6–31.7)
	Desogestrel	112.7 (84.1–141.3)
	Gestodene	121.0 (84.2–157.8)
	Norgestimate	196.9 (154.2–239.6)
30–35 µg	Levonorgestrel	22.2 (15.6–28.7)
	Desogestrel	155.2 (128.9–181.5)
	Gestodene	129.7 (83.1–176.4)
	Norgestimate	123.1 (72.6–173.5)

Table 5 VTE risk among gestodene-containing combined oral contraceptive users according to doses of ethinyl-estradiol (EE).

| References	20 μg EE vs non-user		30 μg EE vs non-user		20 vs 30 μg EE
	Number of cases/controls[a]	OR (95% CI)	Number of cases/controls[a]	OR (95% CI)	OR (95% CI)
(48)	–	–	21/71	–	–
(49)	–	–	5/4	5.2 (1.3–20.6)	–
(31)	–	–	63/143 581 WY	–	–
(32)	6/30	2.0 (0.7–5.7)	206/486	3.5 (2.8–4.5)	0.5 (0.2–1.6)
(34)	14/32	–	119/67	5.6 (3.7–8.4)	0.3 (0.2–0.7)
(6)[b]	240/472 118 WY	5.07 (4.37–5.88)	575/668 355 WY	6.2 (5.6–6.9)	–
Pooled OR		3.7 (1.6–8.8)		5.0 (3.4–7.3)	0.3 (0.2–0.5)

WY, women-years; –, no data; 20 GSD = 20 μg EE + gestodene; 30 GSD, 30 μg EE + gestodene; OR, odds ratio.
[a]Number of controls except for WY data (total number).
[b]Confirmed events.

was higher compared with the COC containing LNG regardless of EE dose (20 μg EE or 30 μg EE). For DRSP, we do not have any data about COC containing 20 μg EE. By contrast, 20 μg EE + GSD users have a similar VTE risk to 20 μg EE + LNG or 30 μg EE + LNG users as compared with non-users, with a relative risk of 2.2 (95% CI 1.4–3.2), 2.2 (95% CI 1.3–3.6), and 2.4 (95% CI 1.8–3.2) respectively. Thus, the users of these three combinations have the lowest thrombosis risk (17, 18). Table 5 presents the VTE risk among users of COC containing GSD as a non-users reference group (6, 31, 32, 34, 48, 49). The users of 20 μg EE + GSD or 30 μg EE + GSD have an increased thrombotic risk when compared with non-users (respectively pooled OR = 3.7 (95% CI 1.6–8.8) and 5.0 (95% CI 3.4–7.3)). The VTE risk among users of 20 μg EE + GSD seems to be lower than with 30 μg EE + GSD (pooled OR 0.32 (95% CI 0.23–0.47)). Nevertheless, further data are needed to confirm this

result. This similar VTE risk between 20 μg EE + GSD, 20 μg EE + LNG or 30 μg EE + LNG is not biologically plausible. Studies on haemostasis markers show more deleterious changes in haemostasis among users of GSD than among users of LNG containing COC. Higher ETP-based APC sensitivity ratios are found in users of COC containing DSG, GSD, and NGM compared with those using LNG-containing COC (26). The increase in SHBG levels is significantly lower after the use of COC containing 20–25 μg EE compared with COC containing 30–35 μg EE ($P = 0.05$). COCs containing LNG result in the minimal increase in SHBG (Table 4). The concentration of the mean difference of SHBG for the group 20 μg EE + GSD users is 121.0 (95% CI 84.2–157.8) (50), for the group 30 μg EE + LNG users is 22.2 (95% CI 15.6–28.7) (42, 43, 44, 45, 46, 47) and for 20 μg EE + LNG users is 21.6 (95% CI 11.6–31.7) (46, 51, 52, 53, 54).
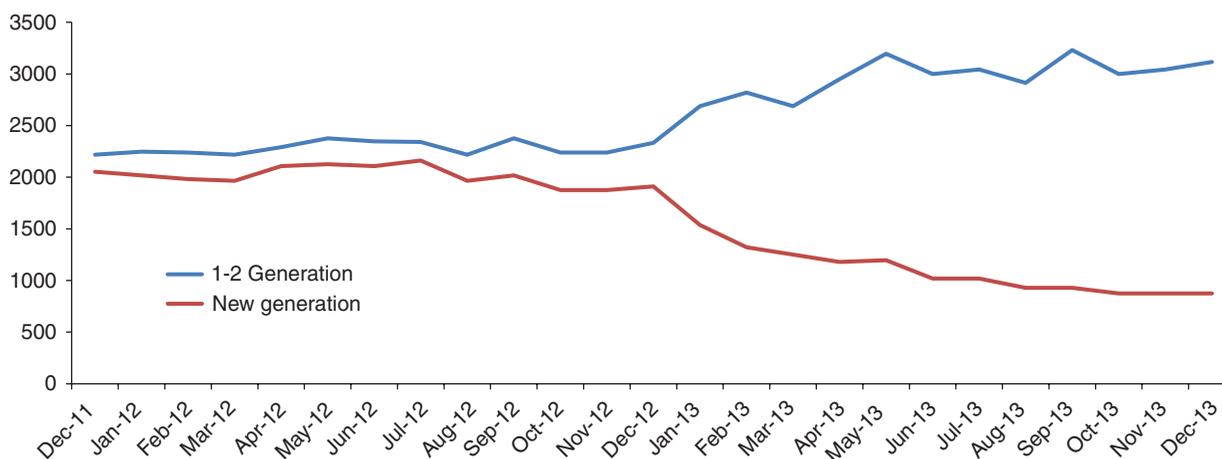
Figure 2
Evolution of combined oral contraceptives used in France between 2012 and 2013 (adapted from ANSM).

Evolution of COC use in France between 2012 and 2013

In 2013, the French Drug Regulatory Agency (ANSM) advised that later-generation pills should never be used as a first choice and can be used only if women had side effects with second generation. The later-generation pills stopped being reimbursed by the social security system. This media hype resulted in decreased use of later-generation pills in France between 2012 and 2013 (http://ansm.sante.fr/September 2013), with 45% reduction in later-generation COC use and an increase by 30% of first- and second-generation pills (Fig. 2). Many women, fearful of hormonal therapy, stopped using their contraceptive pills.

Conclusion

For many years it has been shown that use of COCs was positively associated with VTE risk. These risks may vary according to different characteristics of COCs, such as estrogen dose, molecule and type of progestins. Classification according to generations was irrespective of specific molecule of progestins, and the place of NGM in the third-generation group is debated. The EMA has published a new classification in January 2014, depending on molecule of progestins and not on their generation.

The EMA concluded that COC containing NGM have the same risk of VTE as that of COC containing LNG. These recommendations are based on epidemiological data. According to their impact on SHBG and APC resistance, similar VTE risks between 35 µg EE-NGM and 30 µg EE-LNG are not biologically plausible. Whether low doses of EE associated with GSD carry similar risk as 20 µg EE+LNG or 30 µg EE+LNG remains to be confirmed. Studies on haemostasis markers show more deleterious changes in haemostasis among users of GSD than among users of LNG-containing COC. Nevertheless, further data are needed to evaluate these discordances between epidemiological results and biological parameters.

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