database disclosed by the PMDA from April 2004 to December 2013. As a result, we recently reported the current risk of thromboembolism among COC users in Japan [26].

The aim of the present study is to estimate the risk of thromboembolism related to body mass index (BMI) and aging among users of hormonal contraceptives in Japan.

2. Methods

A case–control study of the risk of obesity and a descriptive study of the risk of age were conducted.

2.1. Subjects

For the case–control study, we used the PMDA database from April 2004 to December 2013 (http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp; http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp), and extracted thromboembolic events among adverse events from the adverse event information of COC products as our previous study [26]. The PMDA is the government organization of the MHLW in Japan that is in charge of reviewing drugs and medical devices; it deals with post-market safety and provides relief for adverse health effects. The PMDA database is only one database throughout Japan which provides us with the most reliable and validated data on thromboembolism. For the descriptive study, we use the same data from January 2009 to December 2013 because of the availability of the denominator data. The registered cases of thromboembolism in these analyses did not have any previous VTE or any family history of VTE.

For the case–control study, the tabulated open assess data of the National Health and Nutrition Survey in Japan, 2012 were used as control. The subjects of the survey are all residents in 300 randomly selected areas nationwide. For the denominator of the descriptive study, data on the annual number of each kind of COC prescribed patients from January 2009 to December 2013 throughout the country were obtained from IMS Health, JPM, a commercial agency that collects reliable data nationally and internationally on drug use and sales.

2.2. Inclusion criteria and definition of thromboembolic events

Inclusion criteria and definition of thromboembolic events were the same as our previous report [26]. Namely, the cases of thromboembolism were all COC users who experienced adverse events reported in this database during this period. The adverse events included VTE, arterial embolism and thrombosis (ATE). We defined both VTE and ATE based on the following ICD-10 codes: I26 (pulmonary embolism), I80 (venous thrombosis of the lower extremities [except I80.0, i.e. superficial thrombophlebitis]), I81 (portal vein thrombosis), I82 (other venous embolism or thrombosis), I63 (cerebral infarction), I67.6 (cerebral vein thrombosis), and I20-I25 (coronary heart diseases), I74 (arterial embolism and thrombosis). We defined it as one thromboembolic event of deep vein thrombosis (DVT) when thrombosis of the pelvic vein, inferior vena cava or the right atrium was complicated by venous thrombosis of the lower extremities as a series of venous thromboses. In addition, we defined a case of pulmonary embolism (PE) complicated with DVT as one thromboembolic event for the same reason. Moreover, we counted it as one case when VTE was complicated with another thromboembolic event of ATE, or ATE was complicated with another part of ATE at the same time. Consequently, in these cases, we counted them with one VTE event and one ATE event, or two ATE events.

These criteria are also used for the descriptive study.

2.3. Inclusion criteria of COCs

For the case–control study, hormonal contraceptives used for the case–control study include all COCs and were categorized according to estrogen content and progestin content [27]: mestranol or ethinylestradiol (EE) combined with norethisterone (the first-generation COC), EE combined with levonorgestrel or norgestrel (the second-generation COC), EE combined with desogestrel (the third-generation COC), EE combined with drospirenone (the fourth-generation COC) and progestin only (norethisterone, levonorgestrel, levonorgestrel releasing intrauterine device and dienogest). In cases with the prescription of several drugs, a suspected drug for an adverse event is defined as one given until just prior to the expression of an adverse event.

For the descriptive study, 3 therapeutic remedies for dysmenorrhea, namely, LEP (35 μg EE combined with norethisterone, 20 μg EE combined with drospirenone) and dienogest were included.

2.4. Categories of BMI for the case–control study

The BMI was categorized according to the WHO guidelines as underweight (<18.5 kg/m^2), normal range (18.5–24.9) and overweight (≥25); pre-obese (25.0–29.9), obese class 1 (30.0–34.9), obese class 2 (35.0–39.9), and obese class 3 (≥40) [28]. In this study, however, we divided BMI into three groups: underweight group (<18.5), standard group (18.5–24.9), and obesity group (≥25) by obesity criteria from the Japanese Society for the Study of Obesity [29]. The BMI was calculated using body weight and height from registered personal data.

2.5. Statistical analysis

For the case–control study, odds ratios and 95% confidence interval (CI) for thromboembolic events in obese COC users (BMI ≥ 25) and underweight users (BMI < 18.5) were calculated on the basis of a standard group to adjust confounding by age. Analyses were restricted to women aged 10–59 years and were first stratified by age in 10-year increments and combined to summarize odds ratios using the Mantel–Haenszel method.

For the descriptive study, the age-specific incidence rates of thromboembolism with 95% CI in current users of 3 therapeutic remedies for dysmenorrhea were calculated by supposing Poisson distribution.

Statistical analysis was done using SPSS version 20.

2.6. Details of ethics approval

The study was approved by the Ethics Committee of Hamamatsu University, School of Medicine (approval number E 14-266/2014). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained, but the presented data are anonymized and there is no risk of identification.

3. Results

3.1. Odds ratios according to BMI groups

Number of persons with thromboembolic events among all COC users between 2004 and 2013 and those of the control group stratified by age and BMI are shown in Table 1 and Table 2. Among a total of 581 thromboembolic events, 306 thromboembolic events for which the age and BMI became clear (VTE, 226 events; ATE, 72 events; thrombosis of unspecified sites, 8 events; one case of VTE was complicated with ATE) and 6423 controls were included in the analyses. Fig. 1. shows the odds ratios of thromboembolic events according to BMI groups. Each odds ratio was calculated compared with the standard group (BMI of 18.5–24.9) as a reference. The odds ratios (95% CI) of the underweight groups were 0.46 (0.27–0.80) for VTE, 0.76 (0.37–1.57) for ATE, and 0.51 (0.33–0.79) for overall thromboembolic events. On the other hand, the odds ratios (95% CI) of the obesity groups were 2.32 (1.71–3.15) for VTE, 1.16 (0.62–2.18) for ATE, and 1.83 (1.38–2.43) for overall thromboembolic events. As a result, overall

Table 1
Number of persons with thromboembolic events among all COC users between 2004 and 2013 stratified by age and body mass index (BMI).

Subjects	Age (years old)	Underweight (BMI < 18.5) n (%)	Standard (18.5 ≤ BMI < 25) n (%)	Obesity (BMI ≥ 25) n (%)	Overall n (%)
Overall thromboembolic events	10–19	1 (14.3)	5 (71.4)	1 (14.3)	7 (100)
	20–29	5 (10.6)	35 (74.5)	7 (14.9)	47 (100)
	30–39	10 (8.7)	75 (65.2)	30 (26.1)	115 (100)
	40–49	6 (4.9)	84 (68.9)	32 (26.2)	122 (100)
	50–59	1 (6.7)	11[a] (73.3)	3 (20.0)	15 (100)
	Overall	23 (7.5)	210 (68.6)	73 (23.9)	306 (100)
Venous thromboembolism (VTE)	10–19	1 (14.3)	5 (71.4)	1 (14.3)	7 (100)
	20–29	4 (10.8)	26 (70.3)	7 (18.9)	37 (100)
	30–39	5 (6.5)	48 (62.3)	24 (31.2)	77 (100)
	40–49	4 (4.3)	62 (66.0)	28 (29.8)	94 (100)
	50–59	1 (9.1)	7 (63.6)	3 (27.3)	11 (100)
	Subtotal	15 (6.6)	148 (65.5)	63 (27.9)	226 (100)
Arterial embolism and thrombosis (ATE)	10–19	0	0	0	0
	20–29	1 (12.5)	7 (87.5)	0 (0)	8 (100)
	30–39	5 (14.7)	23 (67.6)	6 (17.6)	34 (100)
	40–49	2 (7.7)	21 (80.8)	3 (11.5)	26 (100)
	50–59	0 (0)	4 (100)	0 (0)	4 (100)
	Subtotal	8 (11.1)	55 (76.4)	9 (12.5)	72 (100)
Thrombosis of unspecified sites	10–19	0	0	0	0
	20–29	0 (0)	2 (100)	0 (0)	2 (100)
	30–39	0 (0)	4 (100)	0 (0)	4 (100)
	40–49	0 (0)	1 (50.0)	1 (50.0)	2 (100)
	50–59	0	0	0	0
	Subtotal	0 (0)	7 (87.5)	1 (12.5)	8 (100)

Since the data are rounded off, they do not necessarily add up to 100%.
[a] One case of VTE was complicated with ATE.

thromboembolic events, particularly VTE, were significantly high-risk in the obesity group.

3.2. Incidence rates according to age distinction

Table 3 shows the age-specific estimated incidence rates of thromboembolic events per 10,000 person-years in current users of LEP and progestin only between 2009 and 2013 among Japanese. The estimated incidence rates of VTE, ATE and overall thromboembolic events per 10,000 person-years in current users of all 3 remedies for dysmenorrhea among women aged 10–59 years were 2.38 (95% CI: 2.08–2.74), 0.63 (0.48–0.82), and 3.17 (2.81–3.57), respectively; those with all LEP were 3.26 (2.83–3.74), 0.81 (0.61–1.07), and 4.28 (3.79–4.83), respectively; those with dienogest were 0.13 (0.04–0.38), 0.17 (0.07–0.44), and 0.30 (0.14–0.61), respectively. The estimated incidence rates of overall thromboembolic events increased with advanced age, i.e. those with all 3 remedies for dysmenorrhea among women aged 40–49 years were 4.61 (3.88–5.49); those with all LEP were 7.31 (6.13–8.72), respectively; those with all 3 remedies for dysmenorrhea among women aged 50–59 years were 6.49 (3.87–10.90); and those with all LEP were 13.16 (7.84–22.10), respectively. On the other hand, this tendency was not seen for dienogest for which the overall estimated incidence rates were very low.

Table 2
Number of persons of the control group stratified by age and body mass index (BMI).

Subject	Age (years old)	Underweight (BMI < 18.5) n (%)	Standard (18.5 ≤ BMI < 25) n (%)	Obesity (BMI ≥ 25) n (%)	Overall n (%)
Control group	10–19	83 (23.1)	253 (70.5)	23 (6.4)	359 (100)
	20–29	180 (22.0)	569 (69.5)	70 (8.5)	819 (100)
	30–39	272 (17.3)	1102 (70.1)	199 (12.7)	1573 (100)
	40–49	195 (11.2)	1268 (73.0)	274 (15.8)	1737 (100)
	50–59	161 (8.3)	1347 (69.6)	427 (22.1)	1935 (100)
	Subtotal	891 (13.9)	4539 (70.7)	993 (15.5)	6423 (100)

The tabulated open assess data of the National Health and Nutrition Survey in Japan, 2012 were used as control.
Since the data are rounded off, they do not necessarily add up to 100%.

4. Discussion

In this study, we clarified that the odds ratios of thromboembolic events, particularly VTE, among all COC users were significantly high in the obesity group even in Japanese. Furthermore, we clarified that the age-specific estimated incidence rates of thromboembolic events, particularly VTE, in Japanese users of all remedies for dysmenorrhea except dienogest were as high as in people in Western countries, and they were found to rise sharply after the age of 40.

We calculated the odds ratio of the obesity group based on the obesity criteria from the Japanese Society for the Study of Obesity [29] compared with the standard group as a reference. As a result, the odds ratios of risks in VTE, ATE and overall thromboembolic events were 2.32, 1.16 and 1.83 in the obesity group, indicating that the risk of VTE in the obesity group was more than 2 times higher than in the standard group. The obesity is an apparent risk factor for VTE and COCs might strengthen this tendency among Caucasian people [2,3,18–23,24]. There are many reports that the BMI ≥ 25 is an independent risk of thromboembolism in COC users. The nested case control study conducted by Parkin et al. [18] revealed that the VTE risk with the COC use increases with a rise in BMI; when the VTE risk of COC use in women of BMI of 20–24.9 was assumed to 1.0, the odds ratios were 0.4 in women of BMI less than 20, 2.4 in women of BMI of 25–29.9, and 5.5 in women of BMI of 30 or more. The strength of the association increased with increasing BMI, indicating quantity reaction relations. The result of our study was the same as in those reports, however, we could not examine such association in BMI ≥ 30 as there were few cases. Furthermore, the risk in people of the underweight group was lower than that of the standard group as Parkin et al. reported [18]. Odds ratios were analyzed under the supposition that BMI distribution is equal in the whole Japanese people with COC users because the Health and Nutrition Survey data does not have a COC use status and some bias might occur. However, the bias may not be so large because there was no significant difference in weight increase in the women grouped according to use or non-use of COCs or the duration of COC use [30]. In addition, we could not adjust any risk factors for thrombosis besides BMI and age. However, this study revealed that obesity has a strong association with the thromboembolic events in Japanese COC users after adjusting for age. These

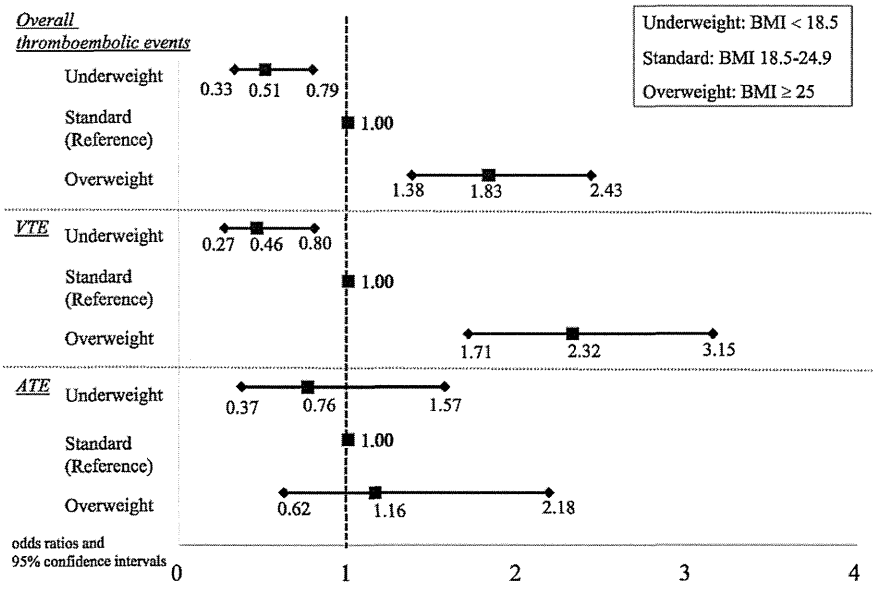

Fig. 1. Odds ratios of thromboembolic events according to BMI groups. Analyses were restricted to women aged 10–59 years and were first stratified by age in 10-year increments and combined to summarize odds ratios using the Mantel–Haenszel method. Among a total of 581 thromboembolic events, the age and BMI became clear in 306 (VTE, 226 events; ATE, 72 events; thrombosis of unspecified sites, 8 events; one case of VTE was complicated with ATE) and 6423 controls were included in the analyses. VTE, venous thromboembolism; ATE, arterial embolism and thrombosis.

results suggest that screening for obesity prior to COC prescription is important, and that careful follow-up to monitor body weight in COC users should be performed.

The incidence of thromboembolism was found to rise sharply after the age of 40. The incidence rates of overall thromboembolic events according to age difference increased over 3 fold from the age of 20–29 to over 40. Lidegaard et al. [9] reported that the relative risks of VTE were 2.91 for the age of 30–34, 4.01 for the age of 35–39, 5.29 for the age of 40–45, and 6.58 for the age of 45–49 compared with the age of 15–19 as a reference. Although the risk of thrombosis in Japanese people is lower than for Western people [26], the tendency for the risk to increase after the age of 40 is similar. Roach et al. [25] reported that the relative risk of VTE associated with COC use in women over 50 years old was 6.3 fold compared with non-hormone use. We could not compare the risk of thromboembolic events in users of LEP with those in non-hormone users in this study, however, the incidence rates per 10,000 person-years in users of LEP in women over 50 years of age were estimated to be 8.46 for VTE, 3.76 for ATE and 13.16 for overall thromboembolic events, respectively. The risks for thrombosis were found to be higher in not only VTE but also ATE in women over 50 years of age. In this study, the incidence rate of VTE among women aged 10–19 years seemed to be rather high compared with women aged 20–39 years. However, it is not necessarily high judging from each 95% CI. The reason is unclear, but VTE cases might be reported by chance though there were few prescriptions. Hormone therapies for dysmenorrhea using LEP (the same constituents of COCs) have been approved for the health insurance coverage since 2008 in Japan, and the numbers of patients taking this therapy and the incidence of the associated thrombosis are increasing [26]. Furthermore, the most risky year is the first year as we reported that the frequency of all thromboembolic events that developed within 90 days from the start of COC was 45.5% and that within 360 days was 81.2% [26]. Accordingly, it is important to sufficiently explain these risks and benefits at the time of LEP prescriptions for patients of dysmenorrhea, and physicians should prescribe LEP carefully in women under 20, over 40, and particularly at over 50 years of age.

The incidence rates for dienogest (progestin-only) were estimated to be very low in spite of advancing age. In previous studies, the risk for VTE by progestin-only pill is also not high [9,26,31,32]. On the other hand, the risks for thrombosis were found to be higher in current users of LEP, particularly at over 40 in our study. According to some epidemiologic studies [3,4,9,33,34], the VTE risk of the third- and fourth-generation COCs was higher compared to the first- and second-generation COCs. The estimated incidence rates of VTE per 10,000 person-years in current Japanese users of all LEP (the first- and fourth-generation COCs) were 3.26, slightly lower than those (3 to 9) in Western people [34]. Among LEP, the risks for thrombosis of the fourth-generation COC were estimated to be higher compared with the first-generation COC in Japanese, as in Western people, and these tendencies were marked in VTE (precise data not shown). As for the risk of ATE in our study, the difference by progestin type was as small as in a Danish historical cohort study [35], though its risk became higher at over 50 years old, and the risk of each LEP was lower than VTE. The incidence rates of VTE have increased since 2011. The fact that VTE itself has increased among young Japanese women in recent years as eating habits have become more similar to those of the West might be considered as one of the responsible reasons [36–38]. Furthermore, there might be a possibility that the incidence of thromboembolism is thought to increase with an increase in the quantity of the prescription of the fourth-generation COC after the approval for the health insurance coverage for dysmenorrhea since 2010 in Japan. Lastly, the reason for the increase in the incidence rate of the fourth-generation COC, particularly in 2013, might be that the reported cases have increased by the nationwide recognition of thromboembolism.

4.1. Study limitations

This study revealed some new evidences for thromboembolism in current users of hormonal contraceptives in Japan, however, there were several study limitations; first, the data of adverse events we used were based on a voluntary report to PMDA, and all events of COC-related thromboembolism may not be necessarily reported. Second, the denominator of incidence rates, i.e. prescription data, is not the exact person-years of COC use. However, we estimated the number of prescribed patients obtained from IMS Health, JPM. Third, we could not adjust any risk factors for thrombosis besides BMI and age. Fourth,

Table 3
Age-specific estimated incidence rates of thromboembolic events per 10,000 person-years in current users of low-dose estrogen progestin (LEP) and progestin only between 2009 and 2013 among Japanese.

Age (years old)	Remedies for dysmenorrhea	Estimated incidence rates of thromboembolic events	VTE	ATE	Thrombosis of unspecified sites	Overall thromboembolic events					
						Year					Total (5 years)
			Total (5 years)	Total (5 years)	Total (5 years)	2009	2010	2011	2012	2013	
10–59	All remedies	Events	201	53	13	13	20	50	58	126	267
		Incidence rates	2.38	0.63	0.15	1.57	1.77	2.85	2.66	4.96	3.17
		95% CI	2.08–2.74	0.48–0.82	0.09–0.26	0.92–2.69	1.15–2.74	2.16–3.76	2.06–3.44	4.17–5.91	2.81–3.57
	All LEP	Events	198	49	13	13	17	49	56	125	260
		Incidence rates	3.26	0.81	0.21	2.70	2.33	3.79	3.39	6.50	4.28
		95% CI	2.83–3.74	0.61–1.07	0.13–0.37	1.58–4.62	1.45–3.73	2.87–5.02	2.61–4.41	5.45–7.74	3.79–4.83
	Dienogest	Events	3	4	0	0	3	1	2	1	7
		Incidence rates	0.13	0.17	0.00	0.00	0.75	0.22	0.38	0.16	0.30
		95% CI	0.04–0.38	0.07–0.44	0.00–0.16	0.00–1.12	0.26–2.21	0.04–1.22	0.10–1.37	0.03–0.92	0.14–0.61
10–19	All remedies	Events	6	0	0	0	0	2	0	4	6
		Incidence rates	3.18	0.00	0.00	0.00	0.00	5.26	0.00	6.28	3.18
		95% CI	1.46–6.95	0.00–2.04	0.00–2.04	0.00–29.73	0.00–19.03	1.44–19.17	0.00–7.17	2.44–16.16	1.46–6.95
	All LEP	Events	6	0	0	0	0	2	0	4	6
		Incidence rates	3.31	0.00	0.00	0.00	0.00	5.49	0.00	6.51	3.31
		95% CI	1.52–7.22	0.00–2.12	0.00–2.12	0.00–31.13	0.00–20.03	1.51–20.03	0.00–7.38	2.53–16.74	1.52–7.22
20–29	All remedies	Events	34	5	2	1	1	5	6	28	41
		Incidence rates	1.66	0.24	0.10	0.60	0.42	1.20	1.07	4.19	2.00
		95% CI	1.19–2.32	0.10–0.57	0.03–0.36	0.11–3.43	0.07–2.40	0.51–2.82	0.49–2.34	2.90–6.06	1.48–2.72
	All LEP	Events	34	5	2	1	1	5	6	28	41
		Incidence rates	1.88	0.28	0.11	0.80	0.52	1.36	1.18	4.58	2.27
		95% CI	1.35–2.63	0.12–0.65	0.03–0.40	0.14–4.52	0.09–2.95	0.58–3.19	0.54–2.58	3.17–6.61	1.68–3.08
30–39	All remedies	Events	54	19	5	4	7	14	15	38	78
		Incidence rates	1.68	0.59	0.16	1.13	1.53	2.02	1.89	4.17	2.43
		95% CI	1.29–2.20	0.38–0.93	0.07–0.37	0.44–2.92	0.74–3.16	1.21–3.40	1.15–3.12	3.04–5.73	1.95–3.04
	All LEP	Events	52	18	5	4	6	14	14	37	75
		Incidence rates	2.27	0.79	0.22	2.03	2.09	2.76	2.33	5.31	3.28
		95% CI	1.73–2.98	0.50–1.24	0.09–0.51	0.79–5.21	0.96–4.55	1.65–4.64	1.39–3.91	3.85–7.31	2.61–4.11
40–49	All remedies	Events	98	25	5	8	11	24	36	49	128
		Incidence rates	3.53	0.90	0.18	2.91	2.84	4.21	5.00	5.96	4.61
		95% CI	2.90–4.31	0.61–1.33	0.08–0.42	1.47–5.73	1.59–5.09	2.83–6.27	3.61–6.93	4.51–7.87	3.88–5.49
	All LEP	Events	97	22	5	8	9	23	35	49	124
		Incidence rates	5.72	1.30	0.29	5.74	4.14	6.40	7.59	9.44	7.31
		95% CI	4.69–6.98	0.86–1.96	0.13–0.69	2.91–11.33	2.18–7.87	4.26–9.60	5.46–10.56	7.14–12.48	6.13–8.72
50–59	All remedies	Events	9	4	1	0	1	5	1	7	14
		Incidence rates	4.17	1.86	0.46	0.00	3.67	12.54	1.80	9.61	6.49
		95% CI	2.20–7.93	0.72–4.77	0.08–2.63	0.00–19.26	0.65–20.80	5.36–29.37	0.32–10.17	4.65–19.83	3.87–10.90
	All LEP	Events	9	4	1	0	1	5	1	7	14
		Incidence rates	8.46	3.76	0.94	0.00	7.29	22.73	3.48	20.19	13.16
		95% CI	4.45–16.08	1.46–9.67	0.17–5.33	0.00–52.99	1.29–41.27	9.71–53.21	0.61–19.72	9.78–41.68	7.84–22.10

All remedies include LEP and dienogest; LEP includes 35 μg ethinylestradiol (EE) combined with norethisterone and 20 μg EE combined with drospirenone; CI, confidence interval; VTE, venous thromboembolism; ATE, arterial embolism and thrombosis.

controls were not limited to COC users but were nationwide representative subjects under almost equal BMI distribution assumption as we mentioned because of data availability.

5. Conclusion

New evidences revealed in this study for the first time were as follows: 1) odds ratios of thromboembolic events among all COC users were significantly high in the obesity group (BMI ≥ 25) even in Japanese; 2) the risk of VTE in the obesity group was more than 2 times higher than in the standard group; 3) age-specific estimated incidence rates of thromboembolic events, particularly VTE, in Japanese users of all remedies for dysmenorrhea except dienogest were as high as in people in Western countries; 4) age-specific incidence rates were found to rise sharply after the age of 40; 5) risks for thrombosis, particularly VTE, of the fourth-generation COC were estimated to be higher compared with the first-generation COC in Japanese, as in Western people; and 6) as for the risk of ATE, the difference by progestin type was small, however, it became higher at over 50 years of age.

Disclosure

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Full Length Article

Thromboembolism as the adverse event of combined oral contraceptives in Japan

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ABSTRACT

Background: The risk of thromboembolism associated with combined oral contraceptives (COCs) in Japanese women is not clear yet. The aim of this study is to estimate the current risk of thromboembolism among COC users in Japan.
Methods: We used the Pharmaceuticals and Medical Devices Agency (PMDA) database disclosed by PMDA from April 2004 to December 2013, and extracted thromboembolic events among adverse events from the adverse event information of COC products.
Results: Of the 581 thromboembolic events, venous thromboembolism (VTE) accounted for 394 events, arterial embolism and thrombosis (ATE) were 154, and thrombosis of unspecified sites was 33. In VTE, deep vein thrombosis and pulmonary embolism were the most frequent (78.4%), followed by cerebral vein thrombosis (11.4%). In ATE, cerebral infarction was the most frequent (76.0%) and approximately 6.9-fold higher than coronary heart diseases. The annual estimated incidence per 10,000 person-years of VTE, ATE and all thromboembolisms in current users of all COCs were 1.11 (95% confidence interval: 1.00–1.24), 0.37 (0.30–0.44), and 1.56 (1.42–1.71), respectively. The frequency of all thromboembolic events that developed within 90 days from the start of COCs was 45.5%, and that within 360 days was 81.2%. Sixteen deceased cases were suspected to be associated with thromboembolism, and the estimated mortality rate between 2009 and 2013 was 0.50 (0.30–0.84) per 100,000 person-years.
Conclusions: Incidence rates of thromboembolism, particularly VTE, in Japanese current COC users became clear for the first time, being slightly lower than people in Western countries.

1. Introduction

Venous thromboembolism (VTE) associated with combined oral contraceptives (COCs; estrogen combined with progestin) was reported for the first time by Jordan in 1961 [1]. Since then, the increased risk of VTE associated with current COC use has been confirmed [2–11]. The risk of VTE in women using COCs is attributed to changes in hemostasis [12]. When attention was paid to VTE as an adverse event of COCs, the role of estrogen was pointed out. Nowadays, we know that estrogen increases gene expression as well as plasma levels of coagulation factors [13] and decreases anticoagulant factors such as protein S [14] and a tissue factor pathway inhibitor (TFPI) [15]. On the other hand, progestin stimulates the gene expression of protein S [16].

Thromboembolism is an unavoidable adverse event of COCs. However, the risk of thromboembolism associated with COCs in Japanese women is not clear yet, although Adachi et al. reported 29 cases of thromboembolism associated with COC use in Japanese women between 1992 and 2001 throughout Japan [17]. The deceased cases of VTE caused by therapeutic use of estrogen and progestin (low dose estrogen progestin; LEP) for dysmenorrhea were only reported by mass media in 2013 in Japan. The constituents of these remedies are the same as COCs. Such hormone therapies for dysmenorrhea have been approved for health insurance coverage since 2008 in Japan, and the associated thromboembolism is thought to increase with the recent increase in the quantity of those prescriptions.

Although large databases with safety information are available in Western countries, Japan does not have them, but is beginning to construct them for adverse events. In the past, the Ministry of Health, Labor and Welfare (MHLW) made it obligatory for pharmaceutical companies, hospitals, physicians, pharmacists, and others to report the adverse events with medicines. The Pharmaceuticals and Medical

Abbreviations: VTE, (venous thromboembolism); ATE, (arterial embolism and thrombosis); COCs, (combined oral contraceptives); PMDA, (Pharmaceuticals and Medical Devices Agency); TFPI, (tissue factor pathway inhibitor); LEP, (low dose estrogen progestin); MHLW, (Ministry of Health Labor and Welfare); EE, (ethinylestradiol); DVT, (deep vein thrombosis); PE, (pulmonary embolism).

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Devices Agency (PMDA) accepted the notification from companies, hospitals, physicians and others after April 2004, and established the Japanese Adverse Drug Event Report Database (PMDA database). For encouraging the utilization of adverse event information, it became available as CSV format after April 2012. Then, we could extract adverse events including thromboembolism from this database disclosed by PMDA from April 2004 to December 2013. The aim of this study is to estimate the current risk of thromboembolism among COC users in Japan.

2. Methods

2.1. Subjects

In this study, we used the PMDA database from 1 April 2004 to 31 December 2013 (see homepage, i.e., http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp; http://www.info.pmda.go.jp/fsearchnew/jsp/menu_fukusayou_base.jsp), and extracted thromboembolic events among adverse events from the adverse event information of COC products. Contraceptives were categorized according to estrogen content and progestin content [18]: mestranol or ethinylestradiol (EE) combined with norethisterone (the first-generation COCs), EE combined with levonorgestrel or norgestrel (the second-generation COCs), EE combined with desogestrel (the third-generation COCs), EE combined with drospirenone (the fourth-generation COCs) and progestin only (norethisterone, levonorgestrel, levonorgestrel releasing intrauterine device and dienogest). In cases with the prescription of several drugs, a suspected drug for an adverse event is defined as one given until just prior to the expression of an adverse event. Because a patient sometimes takes several medicines including the same components in a short period, there is a possibility that several physicians or companies report an adverse event independently. We then tried to eliminate the overlap cases based on patient registration information such as age, body weight, height, the duration of administration, the date of adverse event occurrence, and the kinds of adverse events.

2.2. Inclusion criteria and definition of thromboembolic event

The cases of thromboembolism were all COC users who experienced adverse events reported in this database during this period. The adverse events included VTE and arterial embolism and thrombosis (ATE). We defined both VTE and ATE based on the following ICD-10 codes: I26 (pulmonary embolism), I80 (venous thrombosis of the lower extremities [except I80.0, i.e. superficial thrombophlebitis]), I81 (portal vein thrombosis), I82 (other venous embolism or thrombosis), I63 (cerebral infarction), I67.6 (cerebral vein thrombosis), and I20-I25 (coronary heart diseases), I74 (arterial embolism and thrombosis). We defined it as one thromboembolic event of deep vein thrombosis (DVT) when the thrombosis of the pelvic vein, inferior vena cava or the right atrium was complicated by the venous thrombosis of the lower extremities as a series of venous thromboses. In addition, we defined a case of pulmonary embolism (PE) complicated with DVT as one thromboembolic event for the same reason. Moreover, we counted it as one case when VTE was complicated with another thromboembolic event of ATE, or ATE was complicated with another part of ATE at the same time.

2.3. Calculation of annual estimated number of COC prescribed patients

Data of the annual number of each kind of COC prescription from January 2009 to December 2013 throughout the country were obtained from IMS Health, JPM, a commercial agency that collects the reliable data nationally and internationally on drug use and sales.

The annual estimated number of prescribed patients (person-years) was estimated as follows: when each patient was supposed to take one COC tablet every day for one year, she took 13 sheets for one year. Then, the annual number of prescribed patients was estimated as the number of annually prescribed sheets nationwide divided by 13. On the other hand, in the case of dienogest, when each patient was supposed to take two tablets every day for 365 days, the annual number of prescribed patients was estimated as the number of annually prescribed tablets nationwide divided by 730 (2 times 365).

2.4. Duration of use

The duration of COC use was estimated as the period from the starting date until the end date of use or the date of the onset of the thromboembolic event.

2.5. Details of ethics approval

The study was approved by the Ethics Committee of Hamamatsu University, School of Medicine (approval number E 14-266/2014). It was performed in compliance with the Declaration of Helsinki. Consent was not obtained, but the presented data are anonymized and there is no risk of identification.

2.6. Statistical analysis

The estimated incidence rates of thromboembolism with 95% confidence interval (95% CI) in current users of different COCs were calculated by supposing Poisson distribution. Statistical analysis was done using SPSS version 20.

3. Results

3.1. Reported number of thromboembolic events

A total of 1199 adverse events, which include nausea, vomiting, irregular bleeding, anemia, and so on, associated with COC use were reported in the PMDA database between 1 April 2004 and 31 December 2013. We extracted 581 thromboembolic events from among these adverse events. Of the 581 thromboembolic events, VTE accounted for 394, ATE for 154, and thrombosis of unspecified sites was 33. Three cases of VTE (PE with DVT) were complicated with cerebral infarction and one case of ATE was complicated with another part of ATE. Therefore, overall cases of thromboembolism were 577. In 394 events of VTE, 153 (38.8%) were DVT only, 66 (16.8%) were PE only, 90 (22.8%) were PE with DVT, 45 (11.4%) were cerebral vein thromboses, and 40 (10.2%) were other venous embolisms or thromboses (7 portal veins, 6 retinal veins, 2 jugular veins, 2 subclavian veins, 2 splenic veins, 1 hepatic vein, 1 renal vein and 19 unknown parts). Thus, in VTE, the most common was DVT, PE and their combination (78.4%). It should be specially noted that cerebral vein thrombosis was as much as 11.4%. In 154 arterial thrombotic events, 117 (76.0%) were cerebral infarctions, 17 (11.0%) were coronary heart diseases, and 20 (13.0%) were other arterial embolisms and thromboses (7 mesenteric arteries, 4 renal arteries, 4 central retinal arteries, 2 peripheral arteries, 1 carotid artery, 1 spinal artery and 1 unspecified arterial thrombosis). Thus, in ATE, the most common was cerebral infarction (76.0%) which was approximately 6.9-fold higher than coronary heart diseases. Events with thrombosis of unspecified sites were 33. No case of thromboembolic events was reported in users of norethisterone, levonorgestrel and levonorgestrel releasing intrauterine device, though 9 cases of thromboembolic events (5 cases of VTE and 4 cases of ATE) were reported in the users of dienogest (Table 1).

3.2. Estimated incidence rates of thromboembolic events

The estimated incidence rates of thromboembolic events in current users of COCs with different types of progestin and progestin only were calculated by using the annual estimated number of prescribed patients from January 2009 to December 2013 (Table 2). The annual

Table 1
Number of events of overall thromboembolism in current users of different combined oral contraceptives (COCs) and progestin only between 2004 and 2013 among Japanese.

Group		Venous thromboembolism (VTE)						Arterial embolism and thrombosis (ATE)				Thrombosis of unspecified sites	Overall thromboembolism
		Deep vein thrombosis (DVT) only	Pulmonary embolism (PE) only	PE + DVT	Cerebral vein thrombosis	Other venous thromboses	Overall VTE	Cerebral infarction	Coronary heart diseases	Other arterial thromboses	Overall ATE		
Overall products of hormonal contraceptives		153	66	90	45	40	394	117	17	20	154	33	581[a]
COCs	35 μg ethinylestradiol with norethisterone (monophasic) (first-generation COC)	23	12	12	12	7	66	31	4	2	37	12	115
	30–40 μg ethinylestradiol with levonorgestrel (second-generation COC)	27	16	15	14	3	75	26	5	1	32	4	111
	30 μg ethinylestradiol with desogestrel (third-generation COC)	18	16	18	3	6	61	18	4	7	29	11	101
	20 μg ethinylestradiol with drospirenone (fourth-generation COC)	75	14	35	6	17	147	18	2	6	26	4	177
	Other COCs	8	7	8	10	7	40	20	2	4	26	2	68
Progestin only	Dienogest	2	1	2	0	0	5	4	0	0	4	0	9
	Other progestins	0	0	0	0	0	0	0	0	0	0	0	0

Other COCs include 50–100 μg mestranol with norethisterone, 50 μg ethinylestradiol with norgestrel and 35 μg ethinylestradiol with phasic norethisterone; other progestins include norethisterone, levonorgestrel and levonorgestrel releasing intrauterine device; other venous thromboses include the thrombosis of portal vein, retinal vein, jugular vein, subclavian vein, splenic vein, hepatic vein, renal vein and unknown parts; other arterial thromboses include the thrombosis of mesenteric artery, renal artery, central retinal artery, peripheral artery, carotid artery, spinal artery and unspecified artery.

[a] Three cases of VTE (PE + DVT) were complicated with 3 cases of ATE (cerebral infarction) and one case of ATE (cerebral infarction) was complicated with one case of another part of ATE. These cases are shown on a column.

estimated incidence rates per 10,000 person-years of VTE, ATE and all thromboembolisms in current users of all COCs were 1.11 (95% CI: 1.00–1.24), 0.37 (0.30–0.44), and 1.56 (1.42–1.71), respectively; those with COCs containing 35 μg EE with monophasic norethisterone were 1.75 (1.37–2.23), 0.86 (0.61–1.22), and 2.91 (2.40–3.52), respectively; those with 30–40 μg EE combined with levonorgestrel were 0.34 (0.26–0.46), 0.13 (0.08–0.21), and 0.48 (0.38–0.62), respectively; those with 30 μg EE combined with desogestrel were 0.92 (0.68–1.24), 0.46 (0.30–0.70), and 1.51 (1.19–1.91), respectively; those with 20 μg EE combined with drospirenone were 7.85 (6.68–9.22), 1.39 (0.95–2.03), and 9.45 (8.16–10.95), respectively; those with other COCs (50–100 μg mestranol with norethisterone, 50 μg EE with norgestrel, 35 μg EE with phasic norethisterone) were 0.32 (0.20–0.52), 0.16 (0.08–0.32), and 0.50 (0.34–0.74), respectively; those with progestin-only product (dienogest) were 0.30 (0.10–0.88), 0.40 (0.16–1.03), and 0.70 (0.34–1.45), respectively. Furthermore, the estimated incidence rates of all COCs have increased year by year after 2011.

3.3. Annual change of reported events of overall thromboembolism

Fig. 1. shows the annual change of reported events of overall thromboembolism between 2004 and 2013 to be 21 events in 2004; but reported events increased year by year, reaching 184 events in 2013.

3.4. Incidence according to length of use

Fig. 2. shows the incidence of overall thromboembolic events according to the length of use between 2004 and 2013. Among 581 thromboembolic events, 415 events (VTE; 299, ATE; 97, unspecified sites; 19, 2 cases of VTE were complicated with ATE and one case of ATE was complicated with another part of ATE) were clear from the length of drug use. The frequency of all thromboembolic events that developed within 90 days from the start of COCs was 45.5% (189 events), that within 180 days was 62.9% (261 events), and that within 360 days was 81.2% (337 events), reaching a plateau after 540 days in all COCs regardless of progestin type. Furthermore, 115 cases (27.7%) developed events within 30 days, and 15 (3.6%) did so within 7 days. The frequency of VTE developed within 90 days was 43.8% (131 events) of whole VTE, and that of ATE was 43.3% (42 events) of whole ATE.

3.5. Mortality

Among all adverse events 23 deceased cases were reported; 16 were suspected to be associated with thromboembolism; 13 causes of death were VTE, 1 cause was coronary heart disease, and 2 causes were sudden death. Even if cases of sudden death were included, the estimated annual mortality rate between 2009 and 2013 (14 deceased cases) was 0.50 (0.30–0.84) per 100,000 person-years.

4. Discussion

In this study, we clarified the incidence rates of thromboembolism, particularly VTE, also in current Japanese users of COCs for the first time. Almost half of the patients developed thromboembolism within 90 days after starting COCs. Furthermore, the mortality rate was estimated to be extremely low.

VTE is an unavoidable adverse event of COCs, and the FDA stated that VTE occurred in 3 to 9 per 10,000 person-years in COC users versus 1 to 5 per 10,000 person-years in non-COC users [19]. Though the risk for VTE by progestin-only pill is not high [9,20], the thrombotic risk of COCs is considered dependent on both the estrogen dose and type of progestin [10]. Estrogen dosage contained in COCs has decreased to date. It was pointed out in various countries, however, that COCs include different types of progestin which have a different VTE risk [4]. According to some epidemiologic studies [2,3,4,9,11,19,21], the VTE risk of the third- and fourth-generation COCs was higher compared to the first-

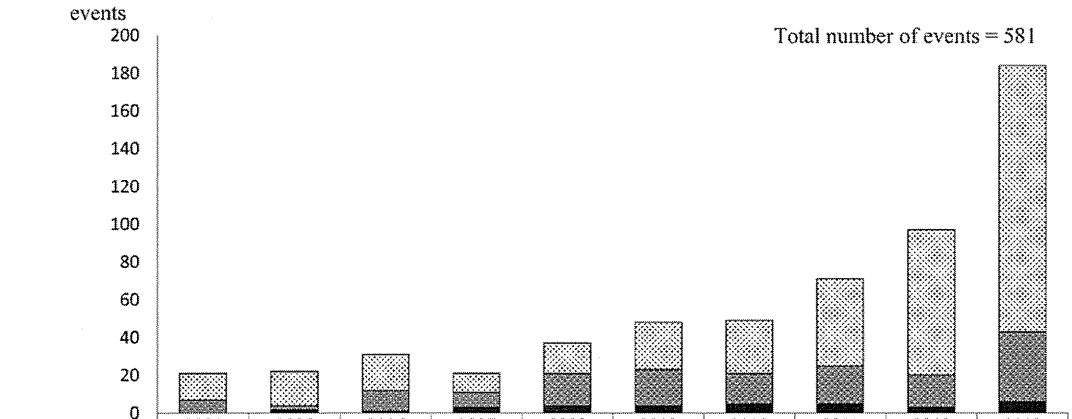
Table 2
Estimated incidence rates of thromboembolic events per 10,000 person-years in current users of different combined oral contraceptives (COCs) and progestin only between 2009 and 2013 among Japanese.

Product type of hormonal contraceptives		Estimated incidence rates of thromboembolic events	VTE	ATE	Thrombosis of unspecified sites	Overall thromboembolism					
						year					total (5 years)
			total (5 years)	total (5 years)	total (5 years)	2009	2010	2011	2012	2013	
COCs	All COCs	events	313	103	23	48	46	69	94	182	439
		10,000 person-years	281.08	281.08	281.08	48.05	50.44	57.37	61.71	63.52	281.08
		incidence rates	1.11	0.37	0.08	1.00	0.91	1.20	1.52	2.87	1.56
		95% CI	1.00–1.24	0.30–0.44	0.05–0.12	0.75–1.32	0.68–1.22	0.95–1.52	1.24–1.86	2.48–3.31	1.42–1.71
	35 μg ethinylestradiol with norethisterone (monophasic) (first-generation COC)	events	63	31	11	15	17	16	20	37	105
		10,000 person-years	36.07	36.07	36.07	4.33	6.08	7.36	8.73	9.57	36.07
		incidence rates	1.75	0.86	0.30	3.46	2.80	2.18	2.29	3.87	2.91
		95% CI	1.37–2.23	0.61–1.22	0.17–0.55	2.10–5.72	1.75–4.48	1.34–3.53	1.48–3.54	2.80–5.33	2.40–3.52
	30–40 μg ethinylestradiol with levonorgestrel (second-generation COC)	events	45	17	1	12	8	6	15	22	63
		10,000 person-years	130.91	130.91	130.91	26.14	26.96	27.14	26.02	24.66	130.91
		incidence rates	0.34	0.13	0.01	0.46	0.30	0.22	0.58	0.89	0.48
		95% CI	0.26–0.46	0.08–0.21	0.00–0.04	0.26–0.80	0.15–0.59	0.10–0.48	0.35–0.95	0.59–1.35	0.38–0.62
	30 μg ethinylestradiol with desogestrel (third-generation COC)	events	42	21	6	17	16	9	13	14	69[b]
		10,000 person-years	45.77	45.77	45.77	6.90	8.05	9.25	10.43	11.15	45.77
		incidence rates	0.92	0.46	0.13	2.46	1.99	0.97	1.25	1.26	1.51
		95% CI	0.68–1.24	0.30–0.70	0.06–0.29	1.54–3.95	1.22–3.23	0.51–1.85	0.73–2.13	0.75–2.11	1.19–1.91
	20 μg ethinylestradiol with drospirenone (fourth-generation COC)	events	147	26	4	–[a]	1	34	38	104	177[c]
		10,000 person-years	18.73	18.73	18.73	–	0.34	3.50	6.50	8.40	18.73
		incidence rates	7.85	1.39	0.21	–	2.94	9.71	5.85	12.38	9.45
		95% CI	6.68–9.22	0.95–2.03	0.08–0.55	–	0.52–16.66	6.95–13.57	4.26–8.02	10.22–15.00	8.16–10.95
	Other COCs	events	16	8	1	4	4	4	8	5	25
		10,000 person-years	49.60	49.60	49.60	10.68	9.02	10.13	10.03	9.74	49.60
		incidence rates	0.32	0.16	0.02	0.37	0.44	0.39	0.80	0.51	0.50
		95% CI	0.20–0.52	0.08–0.32	0.00–0.11	0.15–0.96	0.17–1.14	0.15–1.02	0.40–1.57	0.22–1.20	0.34–0.74
Progestin only	Dienogest	events	3	4	0	0	3	1	2	1	7
		10,000 person-years	9.98	9.98	9.98	1.23	1.61	1.87	2.40	2.87	9.98
		incidence rates	0.30	0.40	0.00	0.00	1.86	0.53	0.83	0.35	0.70
		95% CI	0.10–0.88	0.16–1.03	0.00–0.38	0.00–3.12	0.63–5.47	0.09–3.02	0.23–3.04	0.06–1.98	0.34–1.45
	Other progestins	events	0	0	0	0	0	0	0	0	0
		10,000 person-years	3.45	3.45	3.45	0.41	0.47	0.69	0.76	0.80	3.45
		incidence rates	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
		95% CI	0.00–1.11	0.00–1.11	0.00–1.11	0.00–9.31	0.00–8.22	0.00–5.56	0.00–5.07	0.00–4.81	0.00–1.11

VTE, venous thromboembolism; ATE, arterial embolism and thrombosis; CI, confidence interval; other COCs include 50–100 μg mestranol with norethisterone, 50 μg ethinylestradiol with norgestrel and 35 μg ethinylestradiol with phasic norethisterone; other progestins include norethisterone, levonorgestrel and levonorgestrel releasing intrauterine device.
[a] Not sold in Japan.
[b] One case of ATE was complicated with one case of ATE.
[c] One case of VTE was complicated with one case of ATE. These cases are shown on both columns.

and second-generation COCs, though a prospective, controlled, noninterventional cohort study revealed that the risk of VTE of fourth-generation COCs was similar to another generation of COCs during routine clinical use [22]. Recently, a nested case–control study in the United Kingdom between 2001 and 2013 confirmed that current exposure to any COCs was associated with an increased risk of VTE compared with no exposure in the previous year, and corresponding risks associated with current exposure to the third- and fourth-generation COCs were significantly higher than those for the first- and second-generation COCs [11]. As for VTE in our study, the fourth-generation COCs showed the most reported cases, followed by the second-generation COCs, the first -generation COCs, and lastly the third-generation COCs. Then, we estimated the incidence rates per 10,000 person-years of thromboembolism in current users of COCs. As a result, the fourth-generation COCs was the highest, followed by the first-generation COCs, the third-generation COCs, and lastly the second-generation COCs. On the other hand, the risk of the progestin-only pill was low in our study as well as those in Western countries. From our results, the incidence rates of VTE in Japanese COC users are estimated to be lower compared to those of the Western world, and VTE was frequent in the fourth-generation COCs and subsequently was high in the first-generation COCs, not the third-generation COCs, like Western countries. In our study, there were different VTE risks according to types of progestin in Japanese as in people in Western countries. However, we could not obtain a definite conclusion about the risk according to the progestin type now because the number of reported cases of adverse events might vary according to the progestin type. In the section on study limitations, we described more precise reasons in detail.

The 15-year Danish historical cohort study [23] revealed that 2.1 per 10,000 person-years of thrombotic strokes and 1.0 per 10,000 person-years of myocardial infarction occurred. Although the absolute risks of thrombotic strokes and myocardial infarction associated with the use of hormonal contraception were low, the risk was increased by a factor of estrogen dose, with relatively small differences in risk according to progestin type. As for ATE in our study, the first-generation COCs showed the most reported cases, followed by the second-generation



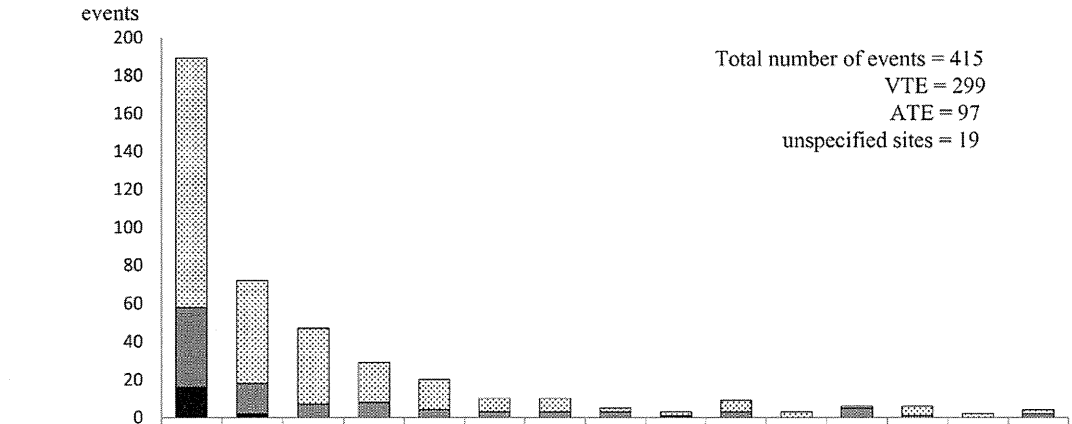
year	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
VTE	14	18	19	10	16	25	28	46	77	141
ATE	7	2	11 *	8	17*	19	16 †	20	17	37*
unspecified sites	0	2	1	3	4	4	5	5	3	6

Fig. 1. Annual change of reported events of overall thromboembolism between 2004 and 2013. Number of thromboembolic events of venous thromboembolism (VTE), arterial embolism and thrombosis (ATE), and thrombosis of unspecified sites are shown in gray bars, dark bars, and black bars, respectively. * One case of cerebral infarction was complicated with one case of pulmonary embolism with deep vein thrombosis; † One case of cerebral infarction was complicated with one case of another part of ATE.

COCs, the third-generation COCs, and lastly the fourth-generation COCs, the difference of which was small. As for the annual estimated incidence rates of ATE, however, the results were just the same as for VTE. The difference by progestin type was as small as the Danish historical cohort study, and the incidence rates of ATE among all COCs were much lower than that of VTE. The risk of VTE in women using COCs is attributed to changes in coagulability. The etiology of ATE is different from that of VTE, therefore, the risk of ATE might be lower than that of VTE.

The frequency of all thromboembolic events that developed within 90 days from the start of COCs was 45.5% in all COCs regardless of progestin type. The Western reports [2,4,8,9] revealed that the frequency of thromboembolism that developed within 3 months was the highest, quite similar to our data on Japanese women. This tendency was approximately similar in both VTE and ATE. Furthermore, 27.7% of all thromboembolic events developed within 30 days, and 3.6% did so within 7 days. These results suggest that physicians should guide patients to be careful about the possible onset of thromboembolism within the first 90 days in particular from the start of COCs. In contrast, there were few cases whose thromboembolism developed five years after the start of COCs, suggesting that the risk of thromboembolism considerably decreases after several years passing from the start of COCs in Japanese people, unlike in Western people. Therefore, it is not necessary to change types of progestin where the QOL of users has been maintained in drug use over 90 days from the start of initial COCs.

In this study, we could extract 581 thromboembolic events reported by December 2013 after April 2004 when the information of adverse events was available. This number increases remarkably in comparison with 29 cases of thromboembolism associated with COC use in Japanese women between 1992 and 2001 throughout Japan as reported by Adachi et al. [17]. VTE involved 394 events, about 2.5 times that of ATE



Dates from the start of COCs	~90	91~180	181~270	271~360	361~450	451~540	541~630	631~720	721~810	811~900	901~990	991~1080	1081~1440	1441~1800	1801~
VTE	131*	54*	40	21	16	7	7	2	2	6	3	1	5	2	2
ATE	42	16†	7	8	4	3	3	3	0	3	0	5	1	0	2
unspecified sites	16	2	0	0	0	0	0	0	1	0	0	0	0	0	0

Fig. 2. The incidence of overall thromboembolic events according to the length of use between 2004 and 2013. Number of thromboembolic events of venous thromboembolism (VTE), arterial embolism and thrombosis (ATE), and thrombosis of unspecified sites are shown in gray bars, dark bars, and black bars, respectively. Among 581 thromboembolic events, 415 cases (VTE; 299, ATE; 97, unspecified sites; 19) were clear from the length of drug use. The frequency of all thromboembolic events that developed within 90 days from the start of COCs was 45.5%, that within 180 days was 62.9%, and that within 360 days was 81.2%, reaching a plateau after 540 days in all COCs regardless of progestin type. * One case of pulmonary embolism with deep vein thrombosis was complicated with one case of cerebral infarction; † One case of cerebral infarction was complicated with one case of another part of ATE.

events. It was approximately 20–30 reported events per year from 2004 through 2008, but reached 184 reported events in 2013. Thus, our study clearly showed that COC use is one of the risks for thromboembolism also in Japan, and the reported events of thromboembolism is recently increasing among Japanese women taking COCs. The increase in VTE after 2011 in particular was remarkable for the following reasons; 1) VTE itself has increased among Japanese young women in the recent decade [24–28]. 2) Hormone therapies for dysmenorrhea using the same COC constituents (LEP) have been approved for health insurance coverage since 2008 in Japan, and the numbers of patients taking this therapy and the incidence of the associated VTE are increasing. 3) The numbers of reported events in PMDA have also increased, and the knowledge and the diagnostic skills for COC-associated thromboembolism have also improved. Therefore, it is important to explain sufficiently the benefits and the thromboembolic risk when prescribing COCs.

4.1. Study limitations

This study revealed many new evidences for thromboembolism in current users of hormonal contraceptives for the first time throughout Japan. However, there were several study limitations; First, the data of adverse events we used were based on a voluntary report to PMDA, and all events of COCs-related thromboembolism may not be necessarily reported. Second, the denominator of incidence rates, i.e. prescription data, is not the exact person-years of COC use. However, we estimated the number of prescribed patients obtained from IMS Health, JPM.

5. Conclusion

We clarified the incidence rates of thromboembolism in current Japanese users of COCs for the first time. Of the 581 thromboembolic events, VTE accounted for 394 events, about 2.5 times that of ATE events, increasing after 2011 in particular. New evidences revealed in this study for the first time were as follows: 1) Incidence rates of thromboembolism, particularly VTE, in Japanese current COC users became clear, being slightly lower than people in Western countries. 2) There are different VTE risks according to types of progestin in Japanese, as in Western people. 3) The frequency of all thromboembolic events that developed within 90 days from the start of COCs was highest, as in Western people. 4) We could not obtain a definite conclusion about the risk according to progestin type at present. However, it is not necessary to change types of progestin where the QOL of users has been maintained in drug use over 90 days from the start of initial COCs. 5) Lastly, the mortality rate was estimated to be extremely low.

Disclosure

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－ 第25回日本産婦人科・新生児血液学会特別講演 －

女性ホルモン剤と血栓症

Thromboembolism associated with combined oral contraceptives

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要　旨

海外では経口避妊薬（OC）として使用されている女性ホルモン剤が、2008年以降、日本では月経困難症の治療薬（LEP）として保険適用され、その服用者は増加している。こうした中、血栓症による死亡例が報告されたことから、現在は患者携帯カードが義務付けられている。OC/LEPに含まれるエストロゲンには血液凝固因子産生亢進や抗凝固系に働くプロテインS産生を抑制する働きがあり、その服用により易血栓性になる（活性化プロテインC抵抗性）。海外の疫学調査ではOC服用者の静脈血栓塞栓症リスクは、年間１万人あたり３～９人で、妊娠中や分娩後に比べて低いとされている。今回我々は、日本での発症リスクは欧米より低いもののプロゲスチンの種類によっては発症率に殆ど差はないことや、約半数が服用開始後90日以内に発症することなどを明らかにした。OC/LEP服用中に血栓症に起因すると思われる症候がみられた場合は、ただちに服用を中止し、処方元の医療機関に連絡していただきたい。何事も早期診断・早期治療が大切である。

Key words; 女性ホルモン剤、血栓症、エストロゲン、プロゲスチン、活性化プロテインC抵抗性

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はじめに

海外では経口避妊薬（OC：oral contraceptives、低用量ピル）として使用されている女性ホルモン剤が、2008年以降、日本では月経困難症の治療薬（LEP：low dose estrogen progestin）として保険適用され、その服用者は増加の一途を辿っている。これらはOCと共に広く処方され、避妊のみならず月経調整、月経痛や月経過多の改善、月経前症候群の症状改善などの目的で、多数の女性に使用されている。こうした中、日本ではあまり知られていなかった血栓症による死亡例が報告されたことから、厚生労働省は医療関係者などに注意喚起するように製薬会社に指示し、現在はOC/LEP共に患者携帯カードが義務付けられるまでになった[1-3]。

本総説では、女性ホルモン剤と血栓症の歴史、欧米とわが国の現況、血栓症の発症機序、さらには安全な処方等に焦点を絞って解説する。

1．OCに含まれる性ホルモン

現在OCには2種類ある。すなわち、混合型OCといわれる合成エストロゲンと合成プロゲステロン様物質（プロゲスチン）が含まれているもの、もう一つはミニピルといわれるプロゲスチンだけが含まれているものである。OCに含まれる合成エストロゲンとしてはエチニルエストラジオール（EE：ethinylestradiol）が最も一般的である。古くからの製剤の中にはメストラノールという合成エストロゲンを含むものもあるが、体内でEEに変換されてから効果を発揮するので、本質的には同じものである。EEと天然型エストラジオール17β（E2）に関しては、子宮内膜に対する作用としてはE2の方が強いが、肝臓におけるタンパク合成誘導に関してはEEの方が強い。プロゲステロンに関しては、天然型はプロゲステロン、合成されたプロゲステロン様物質はプロゲスチン、天然型と合成物を合わせた場合にはプロゲストーゲンと呼ばれ、用語上区別されている。プロゲスチンは、エストロゲンに比較すると多くの種類が存在し、1950年代以降、第1世代といわれるノルエチステロン、ノルエチノドレルを皮切りに、第4世代といわれる最新のドロスピレノンまで10種類以上を数える。現在の混合型OCは、合成エストロゲンであるEEと第1世代から第4世代までのいずれかのプロゲスチンを含んでいる。プロゲスチンのうち第1世代、第2世代（レボノルゲストレル等）、第3世代（デソゲストレル等）に属するものは、アンドロゲン（19-ノルテストステロン）に由来するため、プロゲステロン的性格とアンドロゲン的性格を有し、いずれの性格が相対的に強く出るかは側鎖によって変わる。例えば、米国ではOC服用により性欲低下が認められる場合、アンドロゲン活性を有する第2世代プロゲスチン含有のOC（以下、第2世代OCと略。すべての世代において同様に略）が良く、ニキビの女性にはアンドロゲン活性の弱い第3世代OCが良いともいわれている。エストロゲンの働きにより肝臓で性ホルモン結合グロブリン（SHBG：sex hormone binding globulin）の合成が誘導され、生理的には血中のE2とテストステロンを結合し、これらのホルモンが遊離型状態で過剰に存在しないように調節する役割を担っている[4]。

しかし、合成エストロゲンであるEEはSHBGと結合しないため、天然型E2に比し、肝臓におけるタンパク合成誘導が強く働くことが、OCの重大な副作用である血栓症と深く関係している。なお、第4世代のドロスピレノンは、プロゲステロン活性が高く、アンドロゲン作用が全くないため、海外ではニキビや月経前の浮腫対策としても有用といわれている。

2．OCの効果と副作用

OCの最も重要な効用は避妊効果であるが、いくつもの副効用が報告されている。すなわち、子宮内膜症、月経困難症、過多月経、貧血、卵巣癌、子宮体癌、大腸癌、骨粗鬆症、ニキビ、良性卵巣疾患等に対するメリットである。OC自体は自由診療であるが、2008年以降、日本ではLEP（OCと本質的には同じ）が月経困難症（子宮内膜症）の治療薬として保険適用されていることはすでに述べた通りである。しかし、その一方で最も頻度の多い嘔気・嘔吐をはじめ、多くの副作用も報告されているが、その中でも生命に係わる副作用は循環器系障害、とくに肺塞栓症（pulmonary embolism: PE）/深部静脈血栓症（deep vein thrombosis: DVT）等の静脈血栓塞栓症（VTE：venous thromboembolism）、心筋梗塞、虚血性脳梗塞あるいは出血性脳梗塞等の血栓

症に関するものである[5]。

3．OCが原因とされる世界初の肺塞栓症報告例

子宮内膜症に関連する症状への女性ホルモン剤治療の最初の試みは、おおよそ70年以上前に始められ進展してきた。1957年にFDA（food and drug administration：米国食品医薬品局）で、Enavid（Enovid®）が不妊症と月経異常の治療薬として認可を受け、1960年に避妊薬として認可された。その後現在に至るまで女性ホルモン剤は広く世界で使用されているが、たびたび血栓症の問題に悩まされてきた。

PEは、ひらめ筋静脈など下腿の深部静脈にできた小さな血栓が膝窩静脈や大腿静脈に進展し、その血栓の一部、とくにフリーフロート血栓が遊離して血流に乗り、肺動脈に塞栓を来す病態である。静脈血栓の形成にはVirchowの3徴として、血液凝固能の亢進、血流のうっ滞、血管壁の損傷の3つの因子が関与しているが、女性ホルモン剤は、このうちの血液凝固能の亢進に関連する血栓形成のリスク因子とされている。

さて、OCとPEに関しては、1961年にJordan WMがLancet誌にPEに関する記載をしたのが世界最初の報告である[6]。症例は40歳の未婚の女性看護師で、子宮内膜症の開腹手術の既往を持つ。偽妊娠療法としてEnavid10mg（Enovid®：ノルエチノドレル9.85mg/メストラノール0.15 mg）の治療が行われていたが、強い嘔気と嘔吐のため投薬は中止された。しかし、中止10日後にPEを発症したという。彼女はPEを起こすまでは下肢および骨盤内に全く血栓症の症状を示さず、またベッド上臥床等の不動状態もみられなかった。多分Enavidが原因の嘔吐と脱水による二次性のPEであったものと思われる（Figure 1[3,6]）。

その後毎年OCと循環器系障害の副作用が報告されていくが、発売前はむしろ乳癌や子宮頚癌等のがんの副作用が懸念されていたので、循環器系障害については驚き以外の何物でもなかった。この結果、エストロゲン含量の高いOCでは循環器系障害のリスクが高まるという結論が下され、以後エストロゲン含量が高用量のOCから、中用量OC、低用量OC、そして超低用量OCへと世界の潮流は変遷して現在に至っている。なお、プロゲスチンの世代に拘わらず、OCに含まれるエストロゲン量が50μg以上のOCを高用量OC、50μgのOCを中用量OC、50μg未満のOCを低用量OC、30μg未満のOCを超低用量OCと呼ぶことになっている。

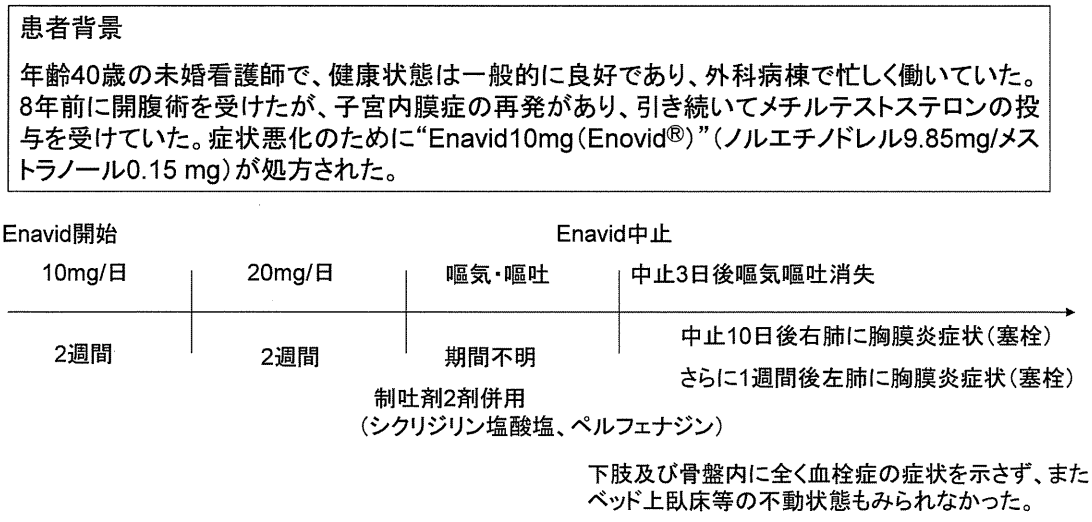

Figure 1. 経口避妊薬による肺塞栓症の世界で最初の報告

（文献3, 6より引用して作成）

4．OCと静脈血栓塞栓症に関する歴史的論争

OCは1960年代、英米を中心に第1世代OCがVTEを誘発することが注目され、前述したようにエストロゲンの含有量に関連があると指摘されたため、エストロゲン量の低用量化が進められた（第1次VTE問題）。しかし、1980～90年代になって第3世代OC（デソゲストレルおよびゲストデン）が第1世代OC（ノルエチンドロン系）および第2世代OC（レボノルゲストレル、ノルゲストレル）と比べVTEの発症率が高いことが英国のCSM（Committee on Safety of Medicines：医薬品安全性委員会）およびWHOによって続けて報告され[7,8]、使用を控えるべきであるという声明が出されたが、これに対しては反論も多く大論争に発展した。この論争では、第3世代OCのVTEリスクは高くても、心臓血管障害および脳血管障害に関するリスクは低く、一方、第2世代OCはVTEのリスクは低くても、心臓血管障害および脳血管障害のリスクが相対的に高く、全体的には両者のリスクは同程度であり、そしてこれらの疾患は生殖年代では極めて稀れであるため、いずれも安全性は高いという結論に落ち着いた。なお、第3世代OCと第2世代OCのリスク差を前提とし、OC処方時にはこのリスク差を女性に説明すべきであると勧告されている（第2次VTE問題）。さらに、1990年代には抗アンドロゲン作用を特徴とする第3世代ではない酢酸シプロテロン含有OCのVTEリスクについても主にドイツで問題視され、第2世代OC（レボノルゲストレル）に比し4倍の発症率と推定されたが[9]、結果的には第3世代OCと同等かやや上回るリスクという結論が得られた（第3次VTE問題）。そして2000年代になると第4世代OC（ドロスピレノン）のVTEリスクについて米国で問題が提起され、FDAによって2012年に第4世代OCの血栓形成のリスクに関する現時点での結論が公表されるに至った（第4次VTE問題）。すなわち、疫学的調査によれば、ドロスピレノンは第2世代OC（レボノルゲストレル）や他のプロゲスチンより3倍ほどリスクを上げると報告されているものの、リスクに差はないとする論文もあり、はっきりとした見解は明らかになっていない。したがって、医師は服用者に対してリスクとベネフィットをきちんと説明し、使用するかどうか選択させるべきである（Figure 2[3,4,7-11]）。例えば、海外の疫学調査では、非妊婦やOC非服用者のVTE発症リスクは、年間1万人あ

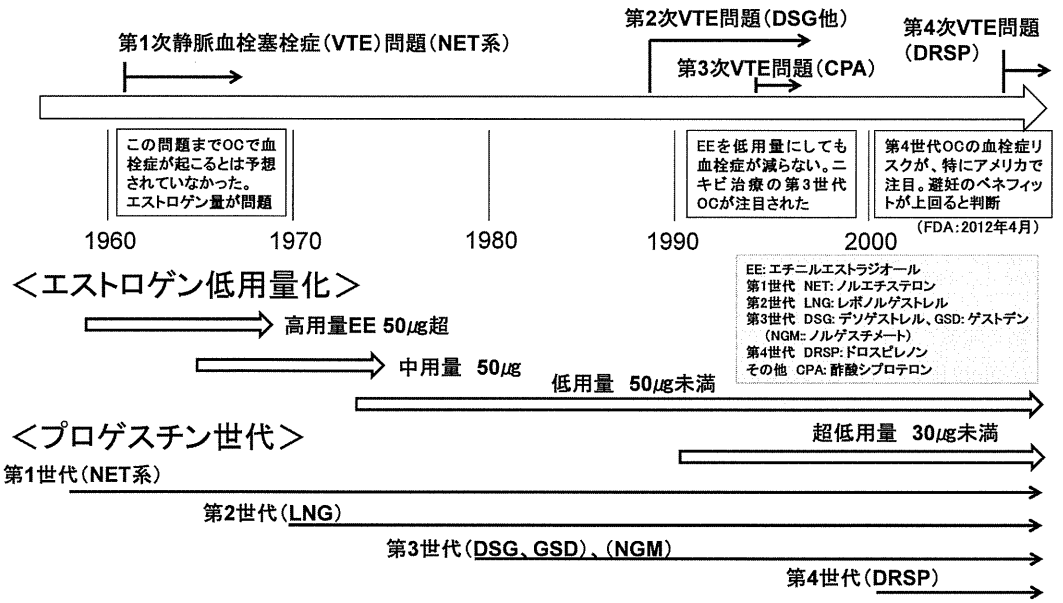

Figure 2. エストロゲンの低用量化とプロゲスチンの歴史

VTE: venous thromboembolism; OC: oral contraceptives; FDA: food and drug administration

（文献3, 4, 7 - 11より引用して作成）

たり1～5人、OC服用者で同3～9人、妊婦は同5～20人、分娩後12週間では同40～65人であるため（Figure 3 [3, 11]）、OC服用者は妊産婦に比べてまだまだ低く、ベネフィットがリスクを上回るであろうという見解である。

デンマークのコホート研究によれば、第1世代OCのノルエチステロンの血栓症リスクは、第2世代OCのレボノルゲストレルより若干低い（いずれもOC非服用者の1.5～2倍）が、第3世代OCのデソゲストレルや第4世代OCのドロスピレノンはリスクがさらに2倍と高い（P＝0.001 vs レボノルゲストレル)とされる（Figure 4 [3, 10]）。また、Lidegaard Øは従来の報告をまとめた総説の中で、第3世代OCのデソゲストレルおよびゲストデン、

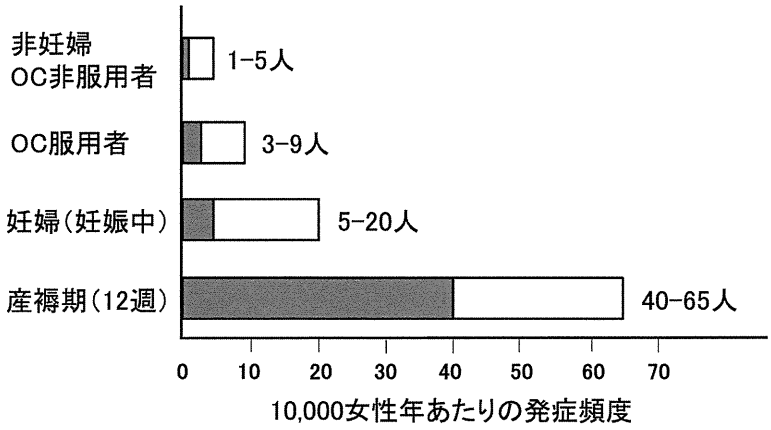

Figure 3. OC服用者における静脈血栓塞栓症リスク

OC: oral contraceptives　　（文献3, 11より引用して作成）

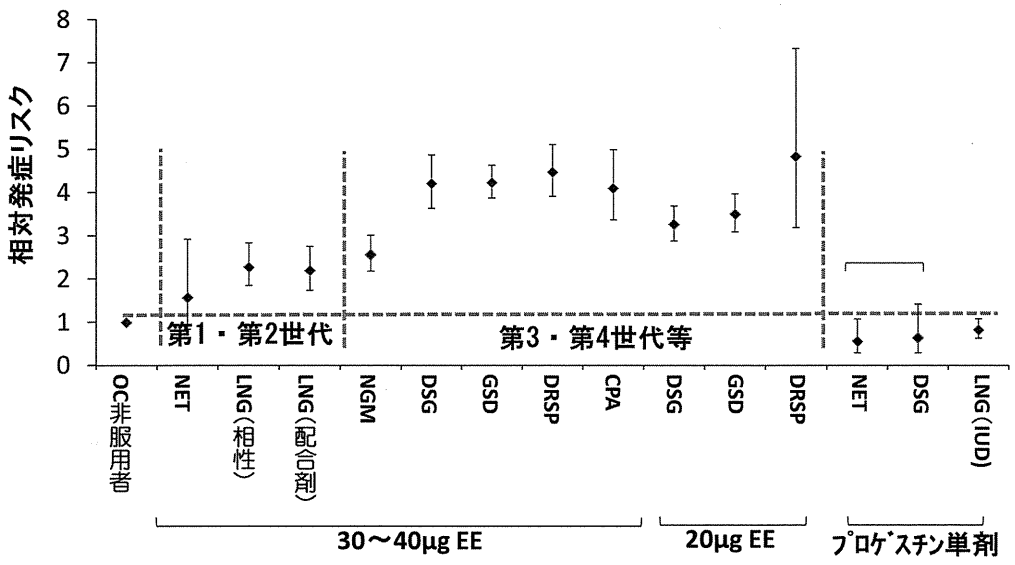

Figure 4. 薬剤別の静脈血栓塞栓症発症リスク

OC: oral contraceptives; NET: ノルエチステロン; LNG: レボノルゲストレル;
NGM: ノルゲスチメート; DSG: デソゲストレル; GSD: ゲストデン; DRSP: ドロスピレノン;
CPA: 酢酸シプロテロン; IUD: intrauterine device; EE: エチニルエストラジオール

（文献3, 10より引用して作成）

第4世代OCのドロスピレノン、そして酢酸シプロテロン含有OCを高リスクOCと位置付け、VTEの発症リスクは、OC非服用者に対し6倍、低リスクOCと位置付けた第1世代OCのノルエチステロン、第2世代OCのレボノルゲストレル、そしてノルゲスチメート含有OC服用者に対し約2倍としている。一方、虚血性脳卒中や心筋梗塞などの動脈血栓症（ATE）リスクは、プロゲスチンの種類に関係なく差はわずかで約50-100%の増加に留まり、さらにプロゲスチン単剤では、発症リスクが約2倍のデポー製剤を除き、VTEもATEもリスクは増加しないと結論している[12]。これに対して、FDAと欧州医薬品庁からの要求を受け、ドロスピレノン含有OCの短期および長期使用における心血管と全般的安全性を評価するために計画された、大西洋横断大規模前向き比較アクティブサーベイランス観察研究の結果が2014年に報告され、ドロスピレノン含有OCはVTEもATEも他のOCとは有意差が認められなかったとされた[13]。ところが、最近発表されたイギリスの15歳～49歳における2001年～2013年までの大規模なコホート内症例対象研究によれば、過去に指摘されている後方視的研究における様々な問題点を調整した結果、VTE10,562症例の検討において、いかなるOCであっても現在使用中の場合は非使用者に比し、調整オッズ比は2.97（以下95%信頼区間：2.78-3.17）とVTE発症リスクを増加させると報告された。さらに、プロゲスチン種類別では、第1世代OCのノルエチステロンが2.56（2.15-3.06）、第2世代OCのレボノルゲストレルが2.38（2.18-2.59）であるのに対し、第3世代OCのデソゲストレルが4.28（3.66-5.01）、第4世代OCであるドロスピレノンが4.12（3.43-4.96）と有意に高かった。そして10,000女性年あたりのVTE発生数は第2世代OCのレボノルゲストレルが6人と最も少なく、第3世代OCのデソゲストレルが14人と最も多く、やはりプロゲスチンの種類でVTE発症リスクに差があることが証明されたという[14]（日本で発売されているプロゲスチンのみ紹介した）。

一方、OCとは異なり、プロゲスチン単剤のVTE発症リスクはOC非服用者と同等であるとされているのは前述した通りである[10, 12]。Mantha Sらは、8つの調査研究のメタアナリシスの結果より、プロゲスチン単剤のVTE相対リスクは全体として1.03（0.76-1.39）、サブ解析としてプロゲスチン単剤のピルでは0.90 (0.57-1.45)、プロゲスチンIUD（intrauterine device：子宮内避妊用具）では0.61 (0.24-1.53)と低かったが、プロゲスチン注射剤では2.67 (1.29-5.53)とやや高いので、今後の調査が必要と報告している[15]。そして、2014年になって日本ではじめてレボノルゲストレル含有IUDが保険適用され、血栓症高リスクの患者に対する使用が今後期待される。

5．生体内の血液凝固制御系

1）主な血液凝固制御系

健常人の生体内での凝固制御系は、主として3制御系がある。それは、①TFPI（tissue factor pathway inhibitor: 組織因子経路抑制因子）凝固制御系、②AT（antithrombin: アンチトロンビン）凝固制御系、③APC（activated protein C: 活性化プロテインC）凝固制御系、である（Figure 5 [2, 3, 16]）。TFPI凝固制御系とAT凝固制御系は、それぞれに強力な凝固制御活性があり、TFPI凝固制御系は“組織因子の阻害”で、AT凝固制御系は“トロンビンおよびFXaをはじめとする活性化凝固因子の阻害”を通して凝固を制御する。とくにATはトロンビンに対するもっとも強い凝固制御系である。一方APC凝固制御系は、凝固系が活性化されトロンビンが形成されて初めて動き始める凝固制御系で、その活性は凝固系の活性に比例して調節される。すなわち、トロンビンは凝固系の活性が亢進しすぎると自らネガティブフィードバックをかけて凝固系を制御し、凝固活性と凝固制御活性のバランスの調整を行っていると考えられる。したがって、凝固系とAPC凝固制御系との間で適切なバランスが崩れると異常な血栓形成が起こることが推測される。

2）APC凝固制御系の機序[17, 18]

まず、健常人の場合のAPC凝固制御系の機序について説明する。プロテインC（protein C: PC）はセリンプロテアーゼの前駆体であり、凝固系の最終産物であるトロンビン・トロンボモジュリン複合体でPC分子の一部分が切断され、その結果できたAPCがセリンプロテアーゼ活性を発揮できるよう

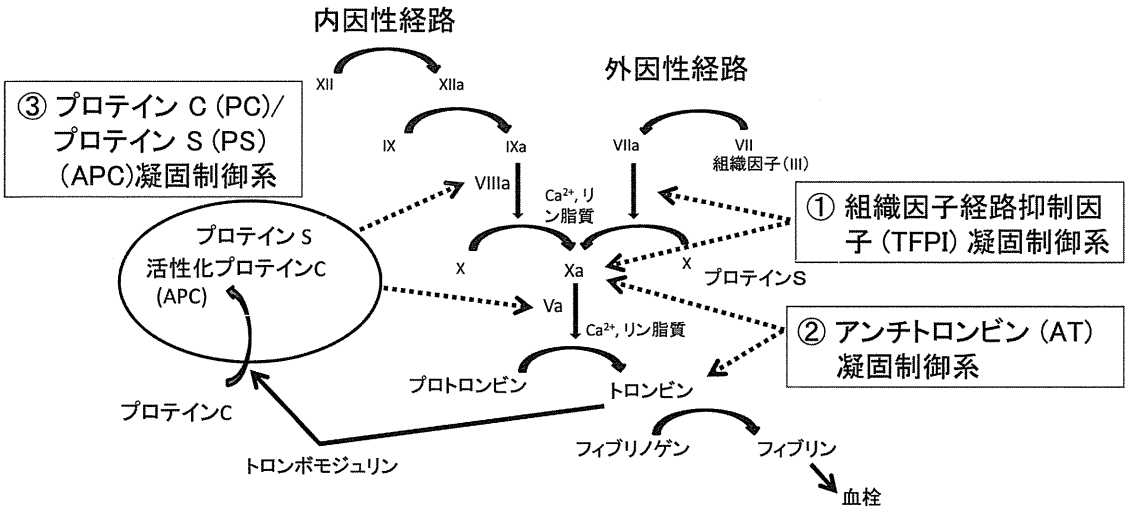

Figure 5. 主な血液凝固制御経路

TFPI: tissue factor pathway inhibitor; AT: antithrombin; APC: activated protein C; PC: protein C; PS: protein S; Va, VIIIa等のa は、活性化血液凝固因子を意味する。

(文献 2, 3, 16より引用して作成)

になる。しかし、APC分子はそれだけでは十分なプロテアーゼ活性を示すことはできず、プロテインS (protein S: PS) と結合したAPC/PS複合体を形成してはじめて十分なセリンプロテアーゼ活性 (= APC凝固制御系) を発揮する。APC/PS複合体は、活性化血液凝固第V因子 (FVa : aは活性化血液凝固因子を意味する。以下、同様) の506番目のアルギニンをまず切断、次に306番目のアルギニンを切断し、FVaを不活性化して凝固活性を抑制する。すなわち、PSはAPC凝固制御活性を左右する重要な因子である。

一方欧米白人の血栓性素因であるFactor V Leiden (FVL) 変異では、第V因子の506番目のアルギニンがグルタミンに変異しているために、APC凝固制御系では切断されなくなり、FVaの不活性化が健常人の場合よりも遅れることになる。APC凝固制御系は、FVL変異でも第V因子の306番目のアルギニン部分は切断可能であるので、FVaはそのうちに切断・不活性化されるが、健常人に比較して凝固制御が遅れる。その結果、FVL変異保因者では、凝固活性がAPC凝固制御活性より相対的に強くなって過剰な血栓形成が起こり、血栓症が発症しやすくなると考えられる。

そしてPS活性低下 (PS変異) に代表されるアジア人、とくに日本人の血栓性素因では、PS活性自体が低下しているためにAPC凝固制御系活性全体が低下し、凝固制御がかかり難くなる。この場合も凝固活性がAPC凝固制御活性よりも相対的に強くなって血栓形成傾向が起こり、血栓症を発症しやすくなると考えられる。

以上のことより、欧米白人のFVL変異保因者であっても、日本人のPS変異保因者であっても、“凝固活性がAPC凝固制御活性よりも相対的に強くなった状態”になっていることが血栓症発症機序といえる。このような状態をAPC抵抗性という。すなわち、APC凝固制御系と凝固系活性とのバランスが、生体内での血栓形成調節に重要な役割を果たしていることを示している。

3) プロテインS欠乏症

先天性PS欠乏症は、わが国での発症頻度はATやPCとは異なり欧米人より高いため、アジア人、とくに日本人特有の先天性血栓性素因といえる。先天性欠乏症は、抗原量・活性値ともに減少するタイプ

Ⅰ、抗原量が正常で活性値のみ減少するタイプⅡのほかに、遊離型PSのみ低下するタイプⅢに分けられる。通常常染色体優性遺伝である[16]。なお、ホモ接合体では、新生児劇症紫斑病がみられ、予後不良である（PCも同様）。

PSはビタミンK依存性蛋白で、肝で合成される（PCも同様）。血漿中半減期は42時間で、遊離型が40%、C4bBp（Complement 4b-binding protein）とのタンパク結合型が60%で循環している[19]。遊離型PSのみがAPCに対するco-factorとしての生物作用を発揮するため、逆にC4bBpを増加させるような状況である妊娠、炎症、手術のストレスなどはPS活性を減少させる。とくに妊娠経過とともにPS活性は減少し、正常妊娠でも30%前後に低下することがある。この現象はOC/LEP服用中も同様で、PS活性は減少する。Suzuki Aらはこの機序として、エストロゲンそのものがPSのmRNA発現を抑制することを報告した[20]。すなわち、エストロゲン刺激は、ヒストンの脱アセチル化によりPS遺伝子のヒストン蛋白への結合を強固にし、その転写を抑制していること、すなわち、PS遺伝子のdown-regulationが示唆されたのである。その強さはエストロゲンの種類によって異なると考えられるが、この現象によってC4bBpの増加に関係なく、妊娠初期もしくはOC/LEP服用直後からPS活性が低下することが説明できる。

前述したようにPSは補酵素としてAPCがリン脂質と結合するのを強め、APCのFVa、FⅧaに対する凝固阻害作用を促進する。また、PSはTFPIによるFXa阻害活性をも促進する。

PS遺伝子にはたくさんの遺伝子変異や多型が見られ、これらのPS活性の多くは減少するが、血栓症を来す可能性はこれらの間でかなり異なる。近年、日本人のPS徳島変異（K196E）は非常に多く、DVT患者における発症頻度が欧米人の約5-10倍で、日本人DVT患者の31%がこの変異を持っていたこと[21]、および日本人におけるPS徳島変異は欧米人の約10倍で、日本人DVT患者のOdds比は5.58であり、日本人における血栓性素因として欧米人のFVL変異に匹敵するものであることが明らかになった[22]。PS徳島変異は、1993年に徳島大学と名古屋大学でほぼ同時に血栓症患者で見出されたPS異常分子である[23, 24]。血中に分泌されたPS分子の196番目のリジン（K）がグルタミン酸（E）に変異しており、PS活性が低下している。発見当初はK155Eと呼ばれていたが、K196Eと同じもので、アミノ酸番号の付け方で残基番号が違っているだけである。健常日本人の55名に1名の高頻度でヘテロ接合体として見出されている。PS徳島分子をホモ接合体として保因しているDVT患者が見つかっているが、その患者の血中PS活性は35%（蛋白量は94%）であり、PS徳島の分子活性（＝比活性）は約40%弱に低下している。今後さらなる詳細な検討が必要ではあるが、PS徳島変異とVTEの因果関係に関しては、①日本人では、PS徳島分子をヘテロ接合体で保因する健常人が2%弱の頻度で存在すること、②その割合がDVT患者で上昇し、オッズ比が5.9-9.3になることなどから、PS徳島変異は日本人における有力な血栓性素因の一つであると考えて良い[3, 17, 21-24]。

4）APC抵抗性とAPC感受性比（APC sensitivity ratio：APC-sr）

FVL変異では第V因子に先天異常があるためAPCによるFVaの分解が遅れ、一方日本人ではPSの変異によりやはり第V因子（FVa）の分解が遅れるので、どちらの場合にもAPC抵抗性が起ることになる。APC抵抗性はこれら先天性血栓性素因以外にOC/LEP服用や妊娠、抗リン脂質抗体症候群、悪性疾患などによっても後天的に起こることが報告されている（Figure 6 [3, 25-27]）。

APC抵抗性は、内因性トロンビン産生能（endogenous thrombin potential：ETP）に基づくAPC-srを測定することによって把握できる。ETPとは、合成基質（S-2238）を用いて血漿中のトロンビン産生を経時的に測定する方法で、現在では合成基質に代り蛍光基質（ZGGR-AMC）を用いた測定法となっている。すなわち、クエン酸加血漿にリン脂質、ヒトリコンビナント組織因子を添加し37℃加温の後、蛍光基質及びCaCl2を添加し外因系凝固反応を惹起する。生成されたトロンビンは蛍光基質の発色基を切断し、その後ATにより中和され、反応が終結する。一部トロンビンはα2マクログロブリンとも結合し、蛍光基質との反応を続けるため、コンピュータ解析によりその影響を除外する。このような蛍光

基質の水解反応を一次微分した曲線がトロンビン産生曲線であり、そのarea under the curve（AUC）をETPとして算出する。本測定系にAPCを添加・反応させることでETPを抑制することができるため、患者血漿と正常男性コントロール血漿にそれぞれ8.7nMのAPCを添加した際のETPの抑制率を比で表したものをAPC-srとして算出する（Figure 7 [3, 25]）。

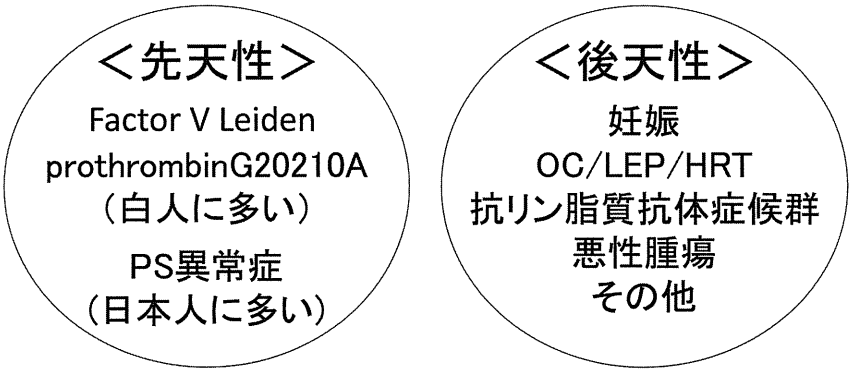

Figure 6. 活性化プロテインC（APC）抵抗性
(activated protein C resistance)

PS: protein S; OC: oral contraceptives; LEP: low dose estrogen progestin; HRT: hormone replacement therapy

（文献 3, 25-27より引用して作成）

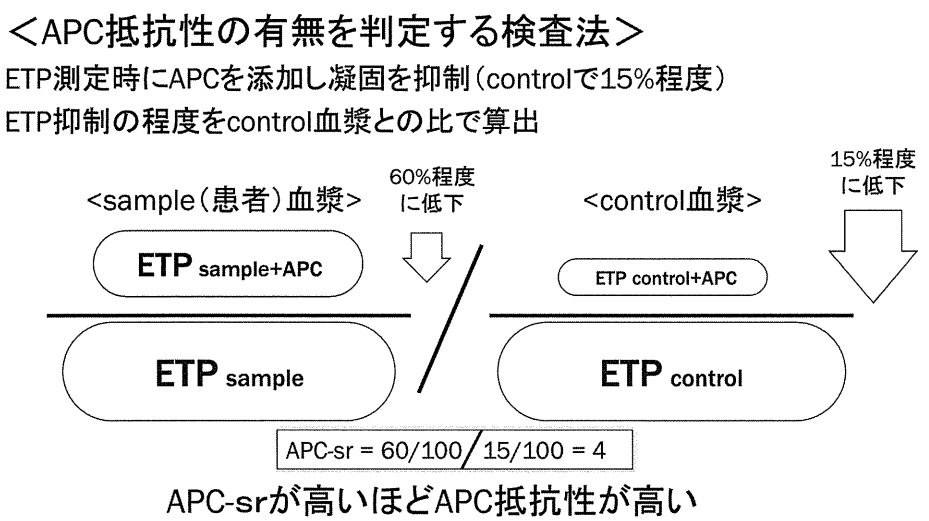

Figure 7. 活性化プロテインC感受性比（APC sensitivity ratio：APC-sr）の測定

＊ETP：endogenous thrombin potential

（文献 3, 25より引用）