Do Progestin-only Oral Contraceptives Increase Cardiovascular Risk? An FPIN Help-Desk Answer

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What is an FPIN HDA?

Family Physicians Inquity Network

- Composed of HelpDesk Answers (HDAs), Clinical Inquiries(CI), and *Priority Updates from the Research Literature (*PURLS)

- HDAs are brief, structured, evidence-based answers to clinical questions written by physicians for physicians.

- answer peer-reviewed clinical questions based on the best available recent evidence including: meta-analyses, evidence-based guidelines, or original research.

- Are peer reviewed prior to publish in *Evidence-Based Practice*, a monthly journal produced by the Family Physicians Inquiries Network (FPIN).

PURLs

Priority Updates from the Research Literature

Why …?

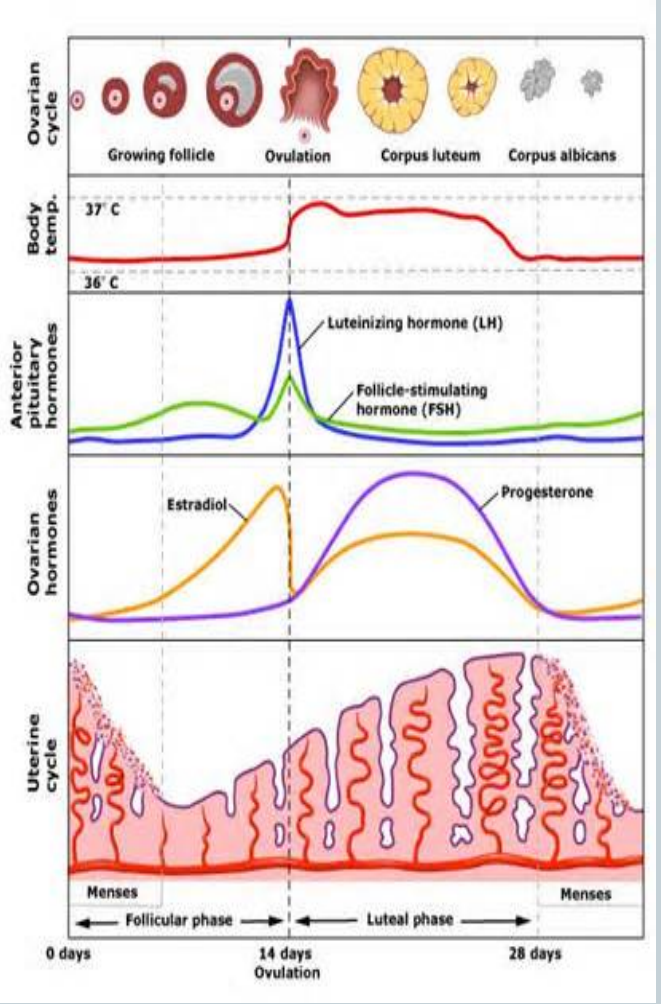
- This investigation was done to summarize the clinical findings and seeks to answer the clinical question: **Do Progestin-only Oral Contraceptives Increase Cardiovascular Risk?**

- Also…

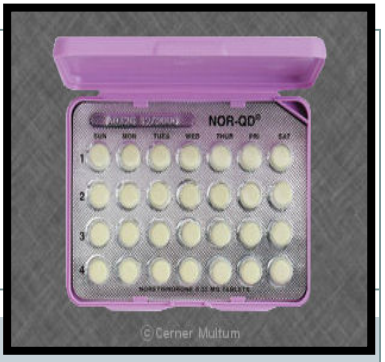
Background

-Progestin-only oral contraceptives prevent the ovaries from releasing an egg during ovulation, but mainly thicken mucus at the cervix so sperm cannot enter the uterus.

-Progestin and progesterone-only contraceptives (POC) have been used since the 1960's worldwide for birth control, menstrual regulation, etc. Over these years the dosage and side effect profiles of these medications have changed dramatically.



Epidemiology

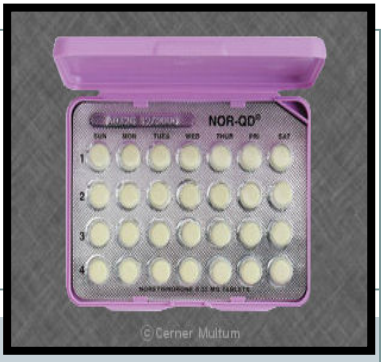


-Early data showed that combined oral contraceptives, specifically the estrogen component, could exacerbate thrombotic risk.

- Potential problems included increased cardiovascular disease (CVD) defined as venous thromboembolism (VTE), myocardial infarction (MI), and thromboembolic stroke in the earliest research papers.

- Every year 10,000 women of childbearing age suffer a venous thromboembolic disease, and this incidence is increased threefold to fivefold in women who use hormonal contraceptives

Pathogenesis



-When combined with an estrogen, the newer progestins increase activated protein C resistance more than older progestins, which may account for the observed increased incidence of venous thromboembolism.

Methods

- A literature search was performed using PubMed and Cochrane Library using keywords: “progestin,” “progesterone,” “stroke,” “venous thromboembolism,” “cardiovascular risk,” and “myocardial infarction” was done in October 2012 which yielded 3 studies.

Study #1

- In 1998, *The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception* examined the association between cardiovascular disease and use of oral, injectable progestogen-only, and combined injectable contraceptives.

-This was a hospital-based, international, multicenter, case-control trial, from 21 centers in 17 countries.

- Women aged 15-49 who had CVD (N= 3,697) and were using contraception were studied compared to controls (N= 9,997).

Study #1 Conclusion

-When compared to the control group, there was no difference in risk of all CVD combined:

- Oral POC (OR 1.1; 95% CI, 0.79–1.6)
- Injectable POC (OR 1.0; 95% CI, 0.68–1.5)

Table 4. Odds ratios (95% CI) for all CVD combined, stroke, VTE, or AMI in relation to current use of progestogen-only and injectable SHC

	Cases	Control subjects	Odds ratio (95% CI)			
			Crude		Adjusted	
CVD Combined (Stroke, VTE, and AMI)						
Nonusers	2668	8266	1.00	(ref)	1.00	(ref)†
Oral progestogens (all)	53	141	1.22	(0.86–1.72)	1.14	(0.79–1.63)
Continuous POP only	51	129	1.30	(0.91–1.86)	1.19	(0.82–1.74)
Progestogen-only injectable	37	122	0.99	(0.68–1.46)	1.02	(0.68–1.54)
Combined injectable**	13	43	0.97	(0.52–1.82)	0.95	(0.49–1.86)
All stroke*						
Nonusers	1774	5183	1.00	(ref)	1.00	(ref)‡
Oral progestogens (all)	29	70	1.26	(0.78–2.03)	1.01	(0.60–1.69)
Continuous POP only	27	60	1.33	(0.80–2.21)	1.07	(0.62–1.86)
Progestogen-only injectable	25	81	0.93	(0.58–1.48)	0.89	(0.53–1.49)
Combined injectable**	9	26	0.97	(0.45–2.10)	0.88	(0.38–2.06)‡‡
VTE						
Nonusers	635	2288	1.00	(ref)	1.00	(ref)§
Oral progestogens (all)	21	64	1.30	(0.75–2.25)	1.74	(0.76–3.99)
Continuous POP only	21	63	1.33	(0.77–2.31)	1.82	(0.79–4.22)
Progestogen-only injectable	11	34	1.27	(0.63–2.57)	2.19	(0.66–7.26)
Combined injectable**	3	10	1.21	(0.33–4.48)	1.30	(0.35–4.81)‡‡
AMI						
Nonusers	259	795	1.00	(ref)	1.00	(ref)#
Oral progestogens (all)	3	7	1.27	(0.31–5.10)	0.87	(0.15–5.01)
Continuous POP only	3	6	1.40	(0.34–5.83)	0.98	(0.16–5.97)
Progestogen-only injectable	1	7	0.52	(0.06–4.38)	0.66	(0.07–6.00)
Combined injectable**	1	7	0.50	(0.06–4.21)	0.25	(0.01–8.09)§§

WHO. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception. 1998. Table 4, page 5

Study #2

- In 1999, the *Transnational study on Oral Contraceptives and the Health of Young Women* examined the association between cardiovascular disease and use of oral POC with a diagnosed cardiovascular event (N= 394), and compared them to a control group (N= 2,366)

- This study was a multicenter, case-control study of European women, aged 16-44, from 16 centers in 5 countries.

Study #2 Conclusions

- There was no increase in overall CVD risk with oral POC use when compared to the non-user group.
  - OR 0.84; 95% CI, 0.45-1.6

- There was no increased risk for:
  - Myocardial infarction (OR 0.94; 95% CI, 0.31-2.9)
  - Thromboembolic CVA (OR 1.6; 95% CI, 0.24-10.72)
  - VTE (OR 0.68; 95% CI, 0.28-1.66)

Study #3

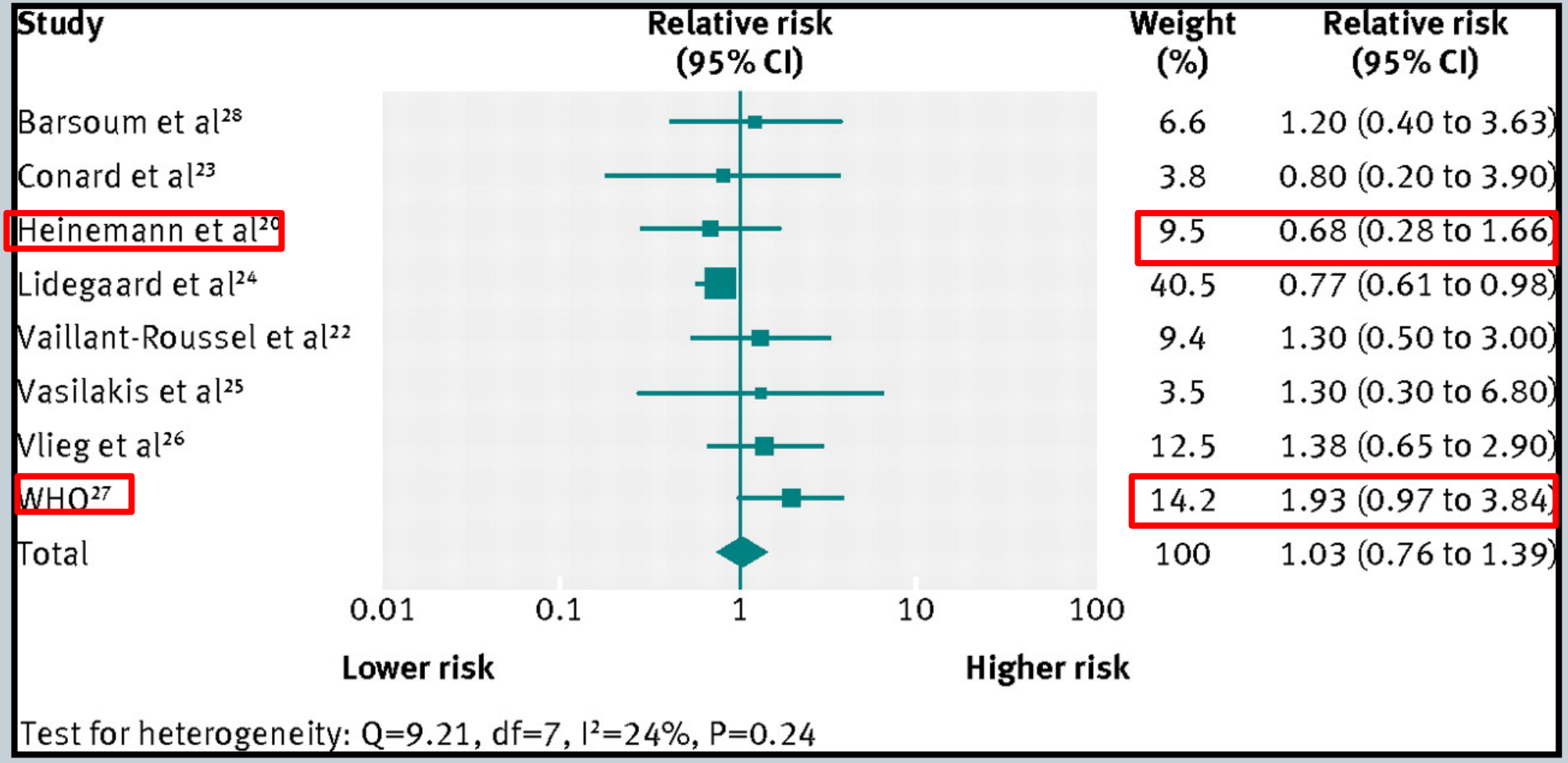
- A meta-analysis of 8 observational studies evaluated for increased risk of VTE among women <50 years old with and without a documented VTE (N=147 and 346 respectively) who were using oral, injectable, or intrauterine POCs.

- 8 trials; N= 493.

Study #3 Conclusions

-There was no increased risk for VTE in women using progestin-only pills or intrauterine devices.

- POC - RR 1.0 (95% CI, 0.76-1.4;
- Intrauterine devices - RR 0.61; 95% CI, 0.24-1.5)


Study
Relative risk (95% CI)
Weight (%)
Relative risk (95% CI)
Barsoum et al[28] 6.6 1.20 (0.40 to 3.63)
Conard et al[23] 3.8 0.80 (0.20 to 3.90)
Heinemann et al[20] 9.5 0.68 (0.28 to 1.66)
Lidegaard et al[24] 40.5 0.77 (0.61 to 0.98)
Vaillant-Roussel et al[22] 9.4 1.30 (0.50 to 3.00)
Vasilakis et al[25] 3.5 1.30 (0.30 to 6.80)
Vlieg et al[26] 12.5 1.38 (0.65 to 2.90)
WHO[27] 14.2 1.93 (0.97 to 3.84)
Total 100 1.03 (0.76 to 1.39)
0.01
0.1
1
10
100
Lower risk
Higher risk
Test for heterogeneity: Q=9.21, df=7, I²=24%, P=0.24

But…

- However, in a subgroup analysis, there was a significant increased risk of VTE among injectable progestin users (2 trials, N=38; RR 2.7, 95%CI, 1.3-5.5).

- This suggests that injectable POC use in patients at higher risk of developing VTE (i.e. thrombophilic patients) should be limited; but further studies are indicated to make this conclusion.

Limitations

- Study #1- potential for false-negative findings due to wide confidence intervals resulting from the small numbers of cases and control subjects.
using the SHC under investigation
- Study #2 – small number of cases exposed to POC
- Study #3 – the small number of studies, potential biases, and lack of adjustment for confounders since it depends on the quality of each individual primary study.

Future Studies…

- - Is there any change in CV risk with other thrombophilic disorders such as Factor V Leiden, MTHFR, lupus, or thrombophilia?

- - Any changes to CV risk with anticoagulation therapy?

The Bottom Line...

- There does not appear to be an increased risk of progestogen/ progestin-only contraceptive (POC) use and cardiovascular disease (CVD), venous thromboembolism (VTE), thromboembolic stroke, or acute MI.

- There may be a risk of VTE among injectable POC users, although more studies are needed (SOR: B, meta-analysis of observational trials, case control trials).

The Bottom Line...

The World Health Organization and US Centers for Disease Control and Prevention guidelines on “Medical eligibility criteria for contraceptive use”:

- All modes of progestin-only contraception are advocated, even for higher risk women such as those with hereditary thrombophilia, history of estrogen induced venous thromboembolism, or history of recurrent venous thromboembolism.

WHO criteria:

Table 6
Eligibility criteria of the WHO in relation to VTE.

Condition	COC/ P/R	CIC	POP	DMPA	Implants	Cu-IUD	LNG IUD
Deep venous thrombosis (DVT)/ Pulmonary embolism (PE)							
a) History of DVT/PE	4	4	2	2	2	1	2
b) Acute DVT/PE	4	4	3	3	3	1	3
c) DVT/PE and established on anticoagulant therapy	4	4	2	2	2	1	2
d) Family history	2	2	1	1	1	1	1
e) Major surgery with prolonged immobilization	4	4	2	2	2	1	2
Known thrombogenic mutations	4	4	2	2	2	1	2
Superficial venous thrombosis							
a) Varicose veins	1	1	1	1	1	1	1
b) Superficial thrombophlebitis	2	2	1	1	1	1	1

*COC: Low dose combined oral contraceptives; P: Combined patch; R: Combined vaginal ring; CIC: Combined injectable contraceptives; POP: Progestin-only pills; DMPA: depot medroxyprogesterone acetate, Cu-IUD: Copper-bearing intrauterine devices; LNG IUD: Levonorgestrel-releasing intrauterine devices.

References

.1. WHO. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. Contraception. 1998 May;57(5):315-2. [LOE: 3b]

.2. Heinemann LA, et al. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Eur Journal of Contraception & Reprod. Health Care. 1999 Jun;4(2):67-73. [LOE: 3b]

.3. Mantha S, et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ 2012 Aug 7;345:e4944. doi: 10.1136/bmj.e4944. [LOE: 2a]

Questions:

Table 1. Steroid hormonal contraceptives

	Brand names	Cases	Control subjects
Oral progestogens			
Continuous			
d-Norgestrel 0.03 mg	Levonorgestrel, Microlut, Microval, Norgeston	7	6
dl-Norgestrel 0.075 mg	Neogest, Ovrette	34	94
Ethynodiol diacetate 0.5 mg	Continuin, Femulen	2	8
Lynestrenol 0.5 mg	Exluton	1	1
Norethisterone 0.35 mg	Dianor, Micronor, Micronovum, Noriday	7	20
Postcoital and "visiting pills":†			
d-Norgestrel 0.75 mg	Postinor	2	3
Anorethidrate dipropionate 7.5 mg	Visiting pill 53	0	5
dl-Norgestrel 3.0 mg	Norgestrel visiting pill	0	2
Norethisterone 5.0 mg	Visiting pill	0	2
Injectable preparations			
Progestogen-only:			
Medroxyprogesterone acetate 150 mg	Depo-Provera (DMPA), Lady Safe	37	114
Norethisterone oenanthate 200 mg	Noristerat (Noretidrone)	0	4
Not known*		0	4
Combined			
Alfasona acetofenide 120 mg + estradiol enanthate 10 mg	Unalmes	2	10
Dihydroxyprogesterone acetophenide 150 mg + estradiol enanthate 10 mg	Agurin, Perlutal, Perlutan	11	33
Hydroxyprogesterone caproate 250 mg + estradiol valerate 5 mg	Injectable No. 1	0	1
Megestrol acetate 25 mg + estradiol 3.5 mg	Injectable No. 2	0	1

*One control subject from Kenya and three control subjects from Indonesia who reported use of an injectable contraceptive of unknown type included here, as only progestogen-only injectables were available in these countries.

†Progestogens available in China taken on days of intercourse or daily for short periods (maximum 15 days).

WHO. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception. 1998. Table 1, page 3

Eligibility criteria according to WHO.

Category	Definition
1	A condition for which there is no restriction for the use of the contraceptive method
2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method
4	A condition which represents an unacceptable health risk if the contraceptive method is used