Supplementary Appendix. Grading of Recommendations Assessment, Development and Evaluation (GRADE) tables for recommendations reviewed, *U.S. Medical Eligibility Criteria for Contraceptive Use, 2024*. (Nguyen AT, Curtis KM, Tepper NK, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2024. MMWR Recomm Rep 2024;73[No. RR-4]:1–126. https://www.cdc.gov/mmwr/volumes/73/rr/rr7304a1.htm)

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1. **Risk of thrombosis among those using progestin-only contraception.**
   Systematic review question: Among those using progestin-only contraception, is there an increased risk of arterial thrombosis or venous thromboembolism compared to no, non-hormonal, or other contraception? This table is based on Tepper NK, Nguyen AT, Curtis KM, Whiteman MK. Progestin-only contraception and thrombosis: An updated systematic review. Contraception 2024: in preparation.

Outcome	Number of Studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed or cases	Number of patients: unexposed or controls	Effect	Certainty
LNG-IUD										
LNG-IUD use vs. non-use among women in general population										
VTE	3[1-3]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	496,341 WY	18,047,154 WY	RR range 0.6-0.9, not statistically significant	Very low
VTE	3[4-6]	Case control	Serious[a]	Not serious	Serious[c]	Not serious	21,608	106,764	OR range 0.3-0.7, not statistically significant	Very low
Stroke	1[7]	Cohort	Serious[a]	Not serious	Serious[c]	Not serious	184, 875 WY	9,336,662 WY	RR 0.7, not statistically significant	Very low
AMI	1[7]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	184, 875 WY	9,336,662 WY	RR 1.0, not statistically significant	Very low
LNG-IUD use vs. non-use among women with history of VTE										
VTE	2[8, 9]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	19[e]	1,450	Incidence: 5.3% (LNG-IUD) vs 13.5% (non-use) 0 (LNG-IUD) vs 4.7% (non-use)	Very low
Implant										
Implant use vs. non-use among women in general population										
VTE	1[3]	Cohort	Serious[f]	Not serious	Very serious[b]	Not serious	29,497 WY	5,892,182 WY	RR 1.4, not statistically significant	Very low
VTE	2[5, 6]	Case control	Serious[a,f]	Not serious	Very serious[b]	Not serious	21,110	105,303	OR range 0.9-1.1, not statistically significant	Very low
Stroke	1[7]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24,957 WY	9,336,662 WY	RR 0.9, not statistically significant	Very low

Stroke	1[10]	Case control	Serious[a,g]	Not serious	Very serious[b]	Not serious	518	1,547	OR 1.0, not statistically significant	Very low
AMI	1[7]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24,957 WY	9,336,662 WY	RR 2.1, not statistically significant	Very low
AMI	1[10]	Case control	Serious[a,g]	Not serious	Very serious[b]	Not serious	307	1,049	OR 3.5, not statistically significant	Very low
Implant use vs. non-use among women with history of VTE										
VTE	1[8]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	3	37	Incidence: 33.3% (implant) vs. 13.5% (non-use)	Very low
Implant use vs. non-use among postpartum women										
VTE	1[11]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	8,369	3,378,751	OR 1.8, not statistically significant	Very low
Implant use vs. not-use among women with diabetes										
VTE or ATE	1[12]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	124	2,730	Incidence/1000 WY: 0 (implant) vs. 3.4 (non-use)	Very low
DMPA										
DMPA use vs. non-use among women in general population										
VTE	4[4-6, 13]	Case control	Serious[a,f]	Serious[h]	Serious[c]	Not serious	22,535	109,210	OR range 2.2-3.0, 3 studies statistically significant	Very low
Stroke	1[13]	Case control	Serious[a,f]	Not serious	Very serious[b]	Not serious	1,799	5,264	OR 0.9, not statistically significant	Very low
AMI	1[13]	Case control	Serious[a,f]	Not serious	Very serious[b]	Not serious	260	802	OR 0.7, not statistically significant	Very low
DMPA use among smokers vs. non-use among non-smokers										
VTE	1[13]	Case control	Serious[a,f]	Not serious	Very serious[b]	Serious[i]	354	1,315	OR 7.0, not statistically significant	Very low
DMPA use vs. non-use among women with history of VTE										
VTE	1[8]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	5	37	Incidence: 0% (DMPA) vs. 13.5% (non-use)	Very low
DMPA use vs. non-use among postpartum women										

VTE	1[14]	Cohort	Serious[a]	Not serious	Not serious	Not serious	11,159	3,102,011	RR 1.9, statistically significant	Low
DMPA use vs. non-use among women with diabetes										
VTE or ATE	1[12]	Cohort	Serious[a]	Not serious	Not serious	Not serious	2,266	2,730	RR 4.7, statistically significant	Low
DMPA use vs. non-use among women with lupus										
PE	1[15]	Cohort	Very serious[d,j,k]	Not serious	Very serious[b]	Not serious	10	18	Incidence: 0% (DMPA) vs 5.6% (non-use)	Very low
AMI	1[15]	Cohort	Very serious[d,j,k]	Not serious	Very serious[b]	Not serious	10	18	Incidence: 10% (DMPA) vs 0% (non-use)	Very low
POPs										
POP use vs. non-use among women in general population										
VTE	2[1, 2]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	148,219 WY	24,309,944 WY	RR range 0.6-1.1, not statistically significant	Very low
VTE	7[5, 6, 13, 16-19]	Case control	Very serious[j]	Serious[h]	Serious[c]	Not serious	23,148	117,649	OR range 0.6-2.6, not statistically significant	Very low
Stroke	1[7]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	257,622 WY	28,009,986 WY	RR (by POP type) range 0.4-1.4, not statistically significant	Very low
Stroke	5[13, 18, 20-22]	Case control	Very serious[j,k]	Not serious	Very serious[b]	Not serious	2,398	8,768	OR range 0.9-1.6, not statistically significant	Very low
AMI	1[7]	Cohort	Serious[a]	Not serious	Very serious[b]	Not serious	123,619 WY	28,009,986 WY	RR (by POP type) range 0.8-1.5, not statistically significant Incidence/100,000 WY: 0 (POP) vs. 13.2 (non-use)	Very low
AMI	4[13, 18, 23, 24]	Case control	Very serious[d,k]	Not serious	Very serious[b]	Not serious	861	2,949	OR range 0.9-1.5, not statistically significant 20% (POP) vs. 31.6% (non-use)	Very low
POP use vs. non-use among women with thrombophilia or history of VTE										

VTE	3[8, 25, 26]	Cohort	Very serious[d,k]	Not serious	Very serious[b]	Not serious	154	265	RR range 0.8-1.3, not statistically significant Incidence: 5.6% (POP) vs. 13.5% (non-use)	Very low
POP use among women with HTN vs. non-use among women without HTN										
VTE	2[13, 18]	Case control	Serious[a,f]	Not serious	Very serious[b]	Serious[i]	595	2,933	OR range 1.2-2.3, not statistically significant	Very low
Stroke	2[13, 18]	Case control	Serious[a,f]	Very serious[l]	Serious[c]	Serious[i]	1,267	5,272	OR 10.9, statistically significant No strokes in POP users	Very low
AMI	2[13, 18]	Case control	Serious[a,f]	Not serious	Very serious[b]	Serious[i]	256	1,164	OR range 0.8-1.9, not statistically significant	Very low
POP use vs. non-use among smokers										
AMI	1[27]	Case control	Very serious[d]	Not serious	Very serious[b]	Not serious	592	2,711	Incidence: 50% (POP) vs. 17.9% (non-use)	Very low
POP use among smokers vs. non-use among non-smokers										
VTE	2[13, 18]	Case control	Serious[a,f]	Not serious	Very serious[b]	Serious[i]	439	2,171	OR range 0.95-2.4, not statistically significant	Very low
Stroke	2[13, 18]	Case control	Serious[a,f]	Serious[h]	Very serious[b]	Serious[i]	1,358	4,386	OR 2.5, not statistically significant Incidence: 50% (POP) vs. 27% (non-use)	Very low
AMI	2[13, 18]	Case control	Serious[a,f]	Serious[h]	Very serious[b]	Serious[i]	140	872	OR range 7.2-10.4, 1 study statistically significant	Very low
POP use vs. non-use among women with diabetes										
VTE or ATE	1[12]	Cohort	Serious[a,g]	Not serious	Not serious	Not serious	3,306	2,730	RR 3.69, statistically significant	Low
POP use vs. non-use among women with lupus										

PE	1[15]	Cohort	Very serious[d,j,k]	Not serious	Very serious[b]	Not serious	15	18	Incidence 6.7% (POP) vs 5.6% (non-use)	Very low
AMI	1[15]	Cohort	Very serious[d,j,k]	Not serious	Very serious[b]	Not serious	15	18	0 AMI in POP users	Very low
POC (combined, unspecified, or non-contraceptive formulations)										
POC use vs. non-use among women in general population										
VTE	3[28-30]	Case control	Very serious[j]	Not serious	Very serious[b]	Not serious	63,113	315,720	OR range 0.98-1.3, not statistically significant	Very low
POC use among women with FVL mutation vs. non-use among women without FVL mutation										
VTE	1[5]	Case control	Very serious[j]	Not serious	Not serious	Serious[i]	413	534	OR 5.4, statistically significant	Very low
POC use among women with PT gene mutation vs. non-use among women without PT gene mutation										
VTE	1[5]	Case control	Very serious[j]	Not serious	Very serious[b]	Serious[i]	465	566	OR 0.7, not statistically significant	Very low
POC use vs. non-use among women with history of VTE										
VTE	3[9, 31, 32]	Cohort	Very serious[j]	Not serious	Very serious[b]	Serious	392	1,749	RR range 0.6-3.6, not statistically significant Incidence density/yr: 3.8% (POC) vs. 4.7% (non-use)	Very low
POC use vs. non-use among women with diabetes										
VTE or ATE	1[12]	Cohort	Very serious[j]	Not serious	Serious[c]	Not serious	8,250	139,358	Women <35 RR 2.02, statistically significant Women ≥35 RR 1.33 (not statistically significant)	Low

AMI, acute myocardial infarction; ATE, arterial thromboembolism; DMPA, depot medroxyprogesterone acetate; FVL, Factor V Leiden; HTN, hypertension; IUD, intrauterine device; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; POPs, progestin-only pills; PT, prothrombin gene mutation; RR, relative risk; VTE, venous thromboembolism; WY, women-years.

Footnotes

[a]Risk of bias considered serious because of concern for information bias.

[b]Imprecision considered very serious because of very wide confidence intervals.

[c]Imprecision considered serious because of wide confidence intervals.

[d]Risk of bias considered very serious because of concern for confounding.

[e]Number not reported in 1 study [9].

[f]Risk of bias considered serious because of concern for selection bias.

[g]Risk of bias considered serious because of concern for confounding.

[h]Inconsistency considered serious because of varying results between studies.

[i]Indirectness considered serious because analyses compared users with thrombogenic conditions to non-users without thrombogenic conditions.

[j]Risk of bias considered very serious because of concern for information bias.

[k]Risk of bias considered very serious because of concern for selection bias.

[l]Inconsistency considered very serious because of major differences in results between studies.

References

1. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. Bmj 2009;339:b2890. https://doi.org/10.1136/bmj.b2890
2. Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. Bmj 2011;343:d6423. https://doi.org/10.1136/bmj.d6423
3. Lidegaard O, Nielsen LH, Skovlund CW, Løkkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. Bmj 2012;344:e2990. https://doi.org/10.1136/bmj.e2990
4. van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol 2010;30:2297-300. https://doi.org/10.1161/atvbaha.110.211482
5. Bergendal A, Persson I, Odeberg J, Sundström A, Holmström M, Schulman S, et al. Association of venous thromboembolism with hormonal contraception and thrombophilic genotypes. Obstet Gynecol 2014;124:600-9. https://doi.org/10.1097/aog.0000000000000411
6. Cockrum RH, Soo J, Ham SA, Cohen KS, Snow SG. Association of Progestogens and Venous Thromboembolism Among Women of Reproductive Age. Obstet Gynecol 2022;140:477-87. https://doi.org/10.1097/aog.0000000000004896
7. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366:2257-66. https://doi.org/10.1056/NEJMoa1111840

8. Maher KN, Quint EH, Weyand AC. Management of Contraception in Adolescent Females With Hormone-Related Venous Thromboembolism. J Adolesc Health 2022;71:127-31. https://doi.org/10.1016/j.jadohealth.2022.02.009
9. Martinelli I, Lensing AW, Middeldorp S, Levi M, Beyer-Westendorf J, van Bellen B, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood 2016;127:1417-25. https://doi.org/10.1182/blood-2015-08-665927
10. Petitti DB, Siscovick DS, Sidney S, Schwartz SM, Quesenberry CP, Psaty BM, et al. Norplant implants and cardiovascular disease. Contraception 1998;57:361-2. https://doi.org/10.1016/s0010-7824(98)00036-5
11. Floyd JL, Beasley AD, Swaim LS, Turrentine MA, Nijjar JB. Association of Immediate Postpartum Etonogestrel Implant Insertion and Venous Thromboembolism. Obstet Gynecol 2020;135:1275-80. https://doi.org/10.1097/aog.0000000000003760
12. O'Brien SH, Koch T, Vesely SK, Schwarz EB. Hormonal Contraception and Risk of Thromboembolism in Women With Diabetes. Diabetes Care 2017;40:233-8. https://doi.org/10.2337/dc16-1534
13. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Contraception 1998;57:315-24.
14. Tepper NK, Jeng G, Curtis KM, Boutot ME, Boulet SL, Whiteman MK. Venous Thromboembolism Among Women Initiating Depot Medroxyprogesterone Acetate Immediately Postpartum. Obstet Gynecol 2019;133:533-40. https://doi.org/10.1097/aog.0000000000003135
15. Mintz G, Gutiérrez G, Delezé M, Rodríguez E. Contraception with progestagens in systemic lupus erythematosus. Contraception 1984;30:29-38. https://doi.org/10.1016/0010-7824(84)90076-3
16. Lidegaard O, Edström B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. Contraception 1998;57:291-301. https://doi.org/10.1016/s0010-7824(98)00033-x
17. Lidegaard Ø, Edström B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. Contraception 2002;65:187-96. https://doi.org/10.1016/s0010-7824(01)00307-9
18. Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Eur J Contracept Reprod Health Care 1999;4:67-73. https://doi.org/10.3109/13625189909064007
19. Heikinheimo O, Toffol E, Partonen T, But A, Latvala A, Haukka J. Systemic hormonal contraception and risk of venous thromboembolism. Acta Obstet Gynecol Scand 2022;101:846-55. https://doi.org/10.1111/aogs.14384
20. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. Bmj 1993;306:956-63. https://doi.org/10.1136/bmj.306.6883.956
21. Tzourio C, Tehindrazanarivelo A, Iglésias S, Alpérovitch A, Chedru F, d'Anglejan-Chatillon J, Bousser MG. Case-control study of migraine and risk of ischaemic stroke in young women. Bmj 1995;310:830-3. https://doi.org/10.1136/bmj.310.6983.830
22. Lidegaard Ø, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. Contraception 2002;65:197-205. https://doi.org/10.1016/s0010-7824(01)00306-7
23. Thorogood M, Mann J, Murphy M, Vessey M. Is oral contraceptive use still associated with an increased risk of fatal myocardial infarction? Report of a case-control study. Br J Obstet Gynaecol 1991;98:1245-53. https://doi.org/10.1111/j.1471-0528.1991.tb15397.x
24. Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. Bmj 1999;318:1579-83. https://doi.org/10.1136/bmj.318.7198.1579
25. Conard J, Plu-Bureau G, Bahi N, Horellou MH, Pelissier C, Thalabard JC. Progestogen-only contraception in women at high risk of venous thromboembolism. Contraception 2004;70:437-41. https://doi.org/10.1016/j.contraception.2004.07.009

26. Vaillant-Roussel H, Ouchchane L, Dauphin C, Philippe P, Ruivard M. Risk factors for recurrence of venous thromboembolism associated with the use of oral contraceptives. Contraception 2011;84:e23-30. https://doi.org/10.1016/j.contraception.2011.06.008
27. Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med 2001;161:1065-70. https://doi.org/10.1001/archinte.161.8.1065
28. Barsoum MK, Heit JA, Ashrani AA, Leibson CL, Petterson TM, Bailey KR. Is progestin an independent risk factor for incident venous thromboembolism? A population-based case-control study. Thromb Res 2010;126:373-8. https://doi.org/10.1016/j.thromres.2010.08.010
29. Bergendal A, Bremme K, Hedenmalm K, Lärfars G, Odeberg J, Persson I, et al. Risk factors for venous thromboembolism in pre-and postmenopausal women. Thromb Res 2012;130:596-601. https://doi.org/10.1016/j.thromres.2012.05.024
30. Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. Lancet 1999;354:1610-1. https://doi.org/10.1016/s0140-6736(99)04394-9
31. Christiansen SC, Lijfering WM, Helmerhorst FM, Rosendaal FR, Cannegieter SC. Sex difference in risk of recurrent venous thrombosis and the risk profile for a second event. J Thromb Haemost 2010;8:2159-68. https://doi.org/10.1111/j.1538-7836.2010.03994.x
32. Le Moigne E, Tromeur C, Delluc A, Gouillou M, Alavi Z, Lacut K, et al. Risk of recurrent venous thromboembolism on progestin-only contraception: a cohort study. Haematologica 2016;101:e12-4. https://doi.org/10.3324/haematol.2015.134882

2. **Risk of thrombosis among those with obesity using combined hormonal contraception.**
Systematic review question: Among those with obesity using combined hormonal contraception, is there an increased risk of arterial thrombosis or venous thromboembolism compared to no, non-hormonal, or other contraception? This table is based on Snyder EM, Curtis KM, Nguyen AT, Belay B, Kortsmit K, Folger S, Whiteman, MK. Combined hormonal contraceptive use and risk for thrombosis among women with obesity: A systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed or cases	Number of patients: comparison or controls	Effect	Certainty
Acute myocardial infarction										
AMI	2[1, 2]	Case-control	Serious[a]	Serious[b]	Serious[c]	Not serious	516	1,916	Increased risk with COC and high BMI (1 study); no difference (1 study)	Low
Stroke										
Ischemic stroke	2[3, 4]	Case-control	Serious[a]	Serious[b]	Serious[c]	Not serious	374	2,116	Increased risk with COC and high BMI (1 study); no difference (1 study)	Low
Hemorrhagic stroke	1[3]	Case-control	Serious[a]	Not serious	Serious[c]	Not serious	193	1,191	No increased risk with COC and high BMI	Low
Cerebral venous thrombosis										
CVT	1[5]	Case-control	Very serious[d]	Not serious	Serious[c]	Not serious	129	3,148	Increased risk with COC and high BMI	Very low
Venous thromboembolism										
BMI	9[6-13]	Case-control	Serious[e]	Not serious	Serious[c]	Not serious	3,626	6,054	Increased risk with COC and high BMI	Low
BMI	1[14]	Cohort	Serious[f]	Not serious	Serious[c]	Not serious	NR	NR	Increased risk with COC and high BMI	Low
Obesity (ICD-10 code)	1[15]	Case-control	Very serious[g]	Not serious	Serious[c]	Not serious	1,166	11,660	Increased risk with COC and high BMI	Very low
Obesity (ICD-10 code)	1[16]	Cohort	Very serious[g]	Not serious	Serious[c]	Not serious	16,304	47,861	Increased risk with COC and high BMI	Very low

AMI, acute myocardial infarction; BMI, body mass index; COC, combined oral contraception; CVT, cerebral venous thrombosis; NR, not reported.

Footnotes

[a]Risk of bias is considered serious due to the BMI being self-reported with height and weight.

[b]Inconsistency is considered serious due differing direction of findings between studies.

[c]Imprecision is considered serious due to the small number of events and wide confidence intervals.

[d]Risk of bias is considered very serious due to BMI being self-reported with 37% missing data and unclear measurement of COC use.

[e]Risk of bias is considered serious due to BMI being self-reported, lack of validation of COC use, and missing data.

[f]Risk of bias is considered serious due to lack of validation of exposure measurement and self-report of covariates.

[g]Risk of bias is considered very serious due to measurement of obesity through ICD-10 codes.

References

1. Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98:1058-63. https://doi.org/10.1161/01.cir.98.11.1058
2. Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345:1787-93. https://doi.org/10.1056/NEJMoa003216
3. Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT, Jr., Sidney S, Raghunathan TE, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke 1998;29:2277-84. https://doi.org/10.1161/01.str.29.11.2277
4. Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke 2002;33:1202-8. https://doi.org/10.1161/01.str.0000015345.61324.3f
5. Zuurbier SM, Arnold M, Middeldorp S, Broeg-Morvay A, Silvis SM, Heldner MR, et al. Risk of Cerebral Venous Thrombosis in Obese Women. JAMA Neurol 2016;73:579-84. https://doi.org/10.1001/jamaneurol.2016.0001
6. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1995;346:1575-82.
7. Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD, Farmer RD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. Eur J Contracept Reprod Health Care 2000;5:265-74. https://doi.org/10.1080/13625180008500402
8. Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost 2003;89:493-8.
9. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP, Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception 2004;70:3-10. https://doi.org/10.1016/j.contraception.2004.02.010
10. Pomp ER, le Cessie S, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. Br J Haematol 2007;139:289-96. https://doi.org/10.1111/j.1365-2141.2007.06780.x
11. Suchon P, Al Frouh F, Henneuse A, Ibrahim M, Brunet D, Barthet MC, et al. Risk factors for venous thromboembolism in women under combined oral contraceptive. The PILl Genetic RIsk Monitoring (PILGRIM) Study. Thromb Haemost 2016;115:135-42. https://doi.org/10.1160/th15-01-0045
12. Parkin L, Sweetland S, Balkwill A, Green J, Reeves G, Beral V. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. Circulation 2012;125:1897-904. https://doi.org/10.1161/circulationaha.111.063354
13. Todd J, Lawrenson R, Farmer RD, Williams TJ, Leydon GM. Venous thromboembolic disease and combined oral contraceptives: A re-analysis of the MediPlus database. Hum Reprod 1999;14:1500-5. https://doi.org/10.1093/humrep/14.6.1500

14. Klovaite J, Benn M, Nordestgaard BG. Obesity as a causal risk factor for deep venous thrombosis: a Mendelian randomization study. J Intern Med 2015;277:573-84. https://doi.org/10.1111/joim.12299
15. Schink T, Princk C, Braitmaier M, Haug U. Use of combined oral contraceptives and risk of venous thromboembolism in young women: a nested case-control analysis using German claims data. Bjog 2022;129:2107-16. https://doi.org/10.1111/1471-0528.17268
16. Traven SA, Farley KX, Gottschalk MB, Goodloe JB, Woolf SK, Xerogeanes JW, Slone HS. Combined Oral Contraceptive Use Increases the Risk of Venous Thromboembolism After Knee Arthroscopy and Anterior Cruciate Ligament Reconstruction: An Analysis of 64,165 Patients in the Truven Database. Arthroscopy 2021;37:924-31. https://doi.org/10.1016/j.arthro.2020.10.025

3. **Risk of thrombosis, bleeding complications, and drug-drug interactions among those on anticoagulant therapy and using hormonal contraception. Systematic review question: Among those on anticoagulant therapy and using contraception, is there an increased risk of arterial thrombosis or venous thromboembolism, bleeding complications, or drug-drug interactions compared to no, non-hormonal, or other contraception?** This table is based on Nguyen AT, Tepper NK, Gold H, Ramer S, Curtis KM, Whiteman MK. Safety of contraception among people using anticoagulant therapy: an updated systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed or cases	Number of patients: unexposed or controls	Effect	Certainty
Cu-IUD vs. no method										
Hemoglobin	1[1]	Cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	34	25	18 mos 11.4 (Cu-IUD) vs. 12.5 (comparison), p>0.05	Very low
Heavy bleeding	2[1, 2]	Cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	43	123	18 mos 58.8% (Cu-IUD) vs 38.4% (comparison) 3 mos 11.1% (Cu-IUD) vs 0 (comparison)	Very low
Cu-IUD vs. LNG-IUD										
Heavy bleeding	1[3]	Cohort	Very serious[c]	Not serious	Not serious	Not serious	27	176	30 days 25.9% (Cu-IUD) vs. 11.4% (LNG-IUD), p=0.04	Very low
LNG-IUD vs. non-hormonal use/no method										
Recurrent VTE	1[4]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	NR	1,413	Incidence density %/year 0 (0.0-24.0) (LNG-IUD) vs. 4.7 (3.3-6.4) (comparison)	Very low
Heavy bleeding	1[4]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	NR	1,413	Incidence density %/year 14.3 (1.7-51.5) (LNG-IUD) vs 21.4 (18-25.1) (comparison)	Very low
Hemoglobin	1[5]	RCT	Serious[e]	Not serious	Not serious	Not serious	20	20	Baseline, 6 mos LNG-IUD: 10.3±0.8, 12.1±0.7, p<0.05; Comparison: 10.1±0.9, 10.0±0.8, p>0.05	Moderate
Mean bleeding days/month	1[5]	RCT	Serious[e]	Not serious	Not serious	Not serious	20	20	Baseline, 6 mos LNG-IUD: 6.8±1.2, 2.0±0.7, p<0.05; comparison: 6.9±1.0, 6.9±1.0, p>0.05	Moderate
Implant vs. no method										

Heavy bleeding	1[2]	Cohort	Very serious[f]	Not serious	Very serious[b]	Not serious	17	98	3 mos 11.7% (Cu-IUD) vs. 0% (comparison)	Very low
DMPA vs. no method										
Heavy bleeding	1[2]	Cohort	Very serious[f]	Not serious	Very serious[b]	Not serious	23	98	3 mos 0 in both groups	Very low
POC (combined or unspecified) vs. non-hormonal										
Recurrent VTE	2[4, 6]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	220	1,418	Incidence density %/year 3.8 (0.8-11.23) (POC) vs. 4.7 (3.3-6.4) (comparison) No recurrent VTE in either group	Very low
Heavy bleeding	1[4]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	217	1,413	Incidence density %/year 13.3 (6.1-25.1) (POC) vs. 21.4 (18.1-25.1) (comparison)	Very low
COC vs. non-hormonal										
Recurrent VTE	1[6]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	3	5	No recurrent VTE in either group	Very low
Prothrombin time ratio	1[7]	Cross-over	Very serious[g]	Not serious	Not serious	Serious[h]	12	12	1.7±0.1 (COC) vs. 1.5±0.1 (comparison), p<0.01	Very low
Heparin concentration	1[8]	Cohort	Serious[i]	Not serious	Very serious[b]	Serious[h]	9	9	0.209 (COC) vs. 0.216 (comparison), not significant	Very low
Estrogen-containing (combined or unspecified) vs. non-hormonal										
Recurrent VTE	1[4]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	306	1,413	Incidence density %/year 4.0 (1.1-10.2) (estrogen) vs. 4.7 (3.3-6.4) (comparison)	Very low
Heavy bleeding	1[4]	Cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	306	1,413	Incidence density %/year 31.3 (20.7-45.0) (estrogen) vs. 21.4 (18.1-25.1) (comparison)	Very low

COC, combined oral contraception; Cu, copper; DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; LNG, levonorgestrel; NR, not reported; OR, odds ratio; POC, progestin-only contraception; POP, progestin-only pill; RCT, randomized clinical trial; SD, standard deviation; VTE, venous thromboembolism.

Footnotes:

[a]Risk of bias considered very serious due to selection bias, information bias, and confounding.

[b]Imprecision considered very serious due to small numbers, no power calculations, or wide confidence intervals with no statistically significant results.

[c]Risk of bias considered very serious due to information bias.

[d]Risk of bias considered very serious due to confounding.

[e]Risk of bias considered serious due to selection bias.

[f]Risk of bias considered very serious due to information bias and confounding.

[g]Risk of bias considered very serious due to intersubjective variability.

[h]Indirectness considered serious due to reporting of laboratory markers without clinical outcomes.

[i]Risk of bias considered serious due to concerns about design, sample size, exposure, intersubjective variability, population, and steady state of perpetrator drug.

References:

1. Abdalla MY, el Din Mostafa E. Contraception after heart surgery. Contraception 1992;45:73-80. https://doi.org/10.1016/0010-7824(92)90143-h
2. Bernard C, Pekny C, Omukagah CO, Bernard CO, Manji I, Pastakia SD, Christoffersen-Deb A. Integration of contraceptive services into anticoagulation management services improves access to long-acting reversible contraception. Contraception 2018;98:486-91. https://doi.org/10.1016/j.contraception.2018.07.139
3. O'Laughlin DJ, Bartlett MA, Fischer KM, Marshall AL, Pruthi RK, Casey PM. Bleeding Complications Associated With Intrauterine Contraception in Women Receiving Anticoagulation Therapy. Mayo Clin Proc Innov Qual Outcomes 2022;6:98-105. https://doi.org/10.1016/j.mayocpiqo.2021.12.005
4. Martinelli I, Lensing AW, Middeldorp S, Levi M, Beyer-Westendorf J, van Bellen B, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood 2016;127:1417-25. https://doi.org/10.1182/blood-2015-08-665927
5. Kilic S, Yuksel B, Doganay M, Bardakci H, Akinsu F, Uzunlar O, Mollamahutoglu L. The effect of levonorgestrel-releasing intrauterine device on menorrhagia in women taking anticoagulant medication after cardiac valve replacement. Contraception 2009;80:152-7. https://doi.org/10.1016/j.contraception.2009.02.007
6. Maher KN, Quint EH, Weyand AC. Management of Contraception in Adolescent Females With Hormone-Related Venous Thromboembolism. J Adolesc Health 2022;71:127-31. https://doi.org/10.1016/j.jadohealth.2022.02.009
7. de Teresa E, Vera A, Ortigosa J, Pulpon LA, Arus AP, de Artaza M. Interaction between anticoagulants and contraceptives: an unsuspected finding. Br Med J 1979;2:1260-1. https://doi.org/10.1136/bmj.2.6200.1260
8. Ence TJ, Wilson DE, Flowers CM, Chen AL, Glad BW, Hershgold EJ. Heparin metabolism and heparin-release lipase activity during long-term estrogen-progestin treatment. Metabolism 1976;25:139-45. https://doi.org/10.1016/0026-0495(76)90044-5

4. **Risk of thrombosis among those with thrombophilia using hormonal contraception.**
Systematic review question: Among those with thrombophilia using hormonal contraception, is there an increased risk of arterial thrombosis or venous thromboembolism compared to no or non-hormonal contraception? This table is based on Tepper NK, Nguyen A, Curtis KM, Baumhart C, Schieve L, Whiteman MK. Safety of hormonal contraception among women with thrombophilia: An updated systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed or cases	Number of patients: unexposed or controls	Effect	Certainty
Factor V Leiden mutation										
OC (presumed mostly COC) use (with mutation) vs. non-use (with mutation)										
VTE	2[1, 2]	Case control	Very serious[a]	Serious[b]	Very serious[c]	Not serious	52	43	OR range 5.0-6.5, 1 study statistically significant; Incidence: 28.5% vs. 5.7%	Very low
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	10[1, 3-11]	Case control	Very serious[d]	Not serious	Very serious[c]	Serious[e]	1,239[f]	2,320[f]	OR range 10.2-64.7, all statistically significant	Very low
Stroke	2[12, 13]	Case control	Very serious[g]	Not serious	Very serious[c]	Serious[e]	95[h]	479[h]	OR range 11.2-12.9, all statistically significant	Very low
POC (with mutation) vs. non-use (without mutation)										
VTE	1[4]	Case control	Serious[i]	Not serious	Serious[j]	Serious[e]	413	534	OR 5.4, statistically significant	Very low
Prothrombin gene mutation										
OC (presumed mostly COC) use (with mutation) vs. non-use (with mutation)										
VTE or ATE	1[14]	Case control	Very serious[d]	Not serious	Very serious[c]	Not serious	32	108	OR 4.7, statistically significant	Very low
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	9[4-6, 8-11, 15, 16]	Case control	Very serious[d]	Not serious	Very serious[c]	Serious[e]	1,076[k]	2,214[k]	OR range 5.1-149.3, 8 studies statistically significant	Very low
Stroke	1[12]	Case control	Very serious[g]	Not serious	Very serious[c]	Serious[e]	NR	NR	OR 3.1, not statistically significant	Very low
POC (with mutation) vs. non-use (without mutation)										
VTE	1[4]	Case control	Serious[i]	Not serious	Serious[j]	Serious[e]	465	566	OR 0.7, not statistically significant	Very low

Antithrombin deficiency										
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	2[17, 18]	Cohort	Very serious[d]	Not serious	Very serious[c]	Serious[e]	26	37	Incidence: (per pt year) 27.5% vs. 3.4%; 5.14% vs. 1.77%	Very low
Protein C deficiency										
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	2[17, 18]	Cohort	Very serious[d]	Not serious	Very serious[c]	Serious[e]	40	30	Incidence: (per pt year) 11.95% vs. 6.9%; 7.06% vs. 2.23%	Very low
Protein S deficiency										
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	2[17, 18]	Cohort	Very serious[d]	Serious[b]	Very serious[c]	Serious[e]	38	26	Incidence: (per pt year) 6.5% vs. 8.6%; 2.42% vs. 0.46%	Very low
Factor V Leiden and prothrombin gene mutations										
CHC (mostly COC or OC type unspecified) use (with mutation) vs. non-use (without mutation)										
VTE	2[5, 8]	Case control	Very serious[d]	Not serious	Very serious[c]	Serious[e]	125[l]	445[l]	OR range 16.97-86.5, all statistically significant	Very low

ATE, arterial thromboembolism; CHC, combined hormonal contraception; COC, combined oral contraception; MI, myocardial infarction; NR, not reported; OC, oral contraception; OR, odds ratio; POC, progestin-only contraception; VTE, venous thromboembolism.

Footnotes

[a]Risk of bias considered very serious due to selection and information biases.

[b]Inconsistency considered serious due to varying results among studies.

[c]Imprecision considered very serious due to small numbers and no power calculations.

[d]Risk of bias considered very serious due to selection bias, information bias, and confounding.

[e]Indirectness considered serious because analyses compared users with thrombophilia to non-users without thrombophilia.

[f]Number of patients not reported in 4 studies [1, 5, 7, 9].

[g]Risk of bias considered very serious due to information bias.

[h]Number of patients not reported in 1 study [12].

[i]Risk of bias considered serious due to information bias.

[j]Imprecision considered serious due to lack of power calculations.

[k]Number of patients not reported in 3 studies [5, 9, 16].

[l]Number of patients not reported in 1 study [5].

References

1. Spannagl M, Heinemann LA, Schramm W. Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? Eur J Contracept Reprod Health Care 2000;5:105-12. https://doi.org/10.1080/13625180008500383
2. Vandenbroucke JP, Koster T, Briët E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344:1453-7. https://doi.org/10.1016/s0140-6736(94)90286-0
3. Andersen BS, Olsen J, Nielsen GL, Steffensen FH, Sørensen HT, Baech J, Gregersen H. Third generation oral contraceptives and heritable thrombophilia as risk factors of non-fatal venous thromboembolism. Thromb Haemost 1998;79:28-31.
4. Bergendal A, Persson I, Odeberg J, Sundström A, Holmström M, Schulman S, et al. Association of venous thromboembolism with hormonal contraception and thrombophilic genotypes. Obstet Gynecol 2014;124:600-9. https://doi.org/10.1097/aog.0000000000000411
5. Emmerich J, Rosendaal FR, Cattaneo M, Margaglione M, De Stefano V, Cumming T, et al. Combined effect of factor V Leiden and prothrombin 20210A on the risk of venous thromboembolism--pooled analysis of 8 case-control studies including 2310 cases and 3204 controls. Study Group for Pooled-Analysis in Venous Thromboembolism. Thromb Haemost 2001;86:809-16.
6. Khialani D, le Cessie S, Lijfering WM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The joint effect of genetic risk factors and different types of combined oral contraceptives on venous thrombosis risk. Br J Haematol 2020;191:90-7. https://doi.org/10.1111/bjh.16666
7. Kuipers S, Cannegieter SC, Doggen CJ, Rosendaal FR. Effect of elevated levels of coagulation factors on the risk of venous thrombosis in long-distance travelers. Blood 2009;113:2064-9. https://doi.org/10.1182/blood-2008-06-160135
8. Legnani C, Palareti G, Guazzaloca G, Cosmi B, Lunghi B, Bernardi F, Coccheri S. Venous thromboembolism in young women; role of thrombophilic mutations and oral contraceptive use. Eur Heart J 2002;23:984-90. https://doi.org/10.1053/euhj.2001.3082
9. Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003;102:1363-6. https://doi.org/10.1182/blood-2003-02-0443
10. Martinelli I, Taioli E, Bucciarelli P, Akhavan S, Mannucci PM. Interaction between the G20210A mutation of the prothrombin gene and oral contraceptive use in deep vein thrombosis. Arterioscler Thromb Vasc Biol 1999;19:700-3. https://doi.org/10.1161/01.atv.19.3.700
11. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP, Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception 2004;70:3-10. https://doi.org/10.1016/j.contraception.2004.02.010
12. Martinelli I, Battaglioli T, Burgo I, Di Domenico S, Mannucci PM. Oral contraceptive use, thrombophilia and their interaction in young women with ischemic stroke. Haematologica 2006;91:844-7.
13. Slooter AJ, Rosendaal FR, Tanis BC, Kemmeren JM, van der Graaf Y, Algra A. Prothrombotic conditions, oral contraceptives, and the risk of ischemic stroke. J Thromb Haemost 2005;3:1213-7. https://doi.org/10.1111/j.1538-7836.2005.01442.x
14. Momot AP, Nikolaeva MG, Yasafova NN, Zainulina MS, Momot KA, Taranenko IA. Clinical and laboratory manifestations of the prothrombin gene mutation in women of reproductive age. J Blood Med 2019;10:255-63. https://doi.org/10.2147/jbm.S212759

15. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998;338:1793-7. https://doi.org/10.1056/nejm199806183382502
16. Tufano A, Guida A, Coppola A, Nardo A, Di Capua M, Quintavalle G, et al. Risk factors and recurrent thrombotic episodes in patients with cerebral venous thrombosis. Blood Transfus 2014;12 Suppl 1:s337-42. https://doi.org/10.2450/2013.0196-12
17. Pabinger I, Schneider B. Thrombotic risk of women with hereditary antithrombin III-, protein C- and protein S-deficiency taking oral contraceptive medication. The GTH Study Group on Natural Inhibitors. Thromb Haemost 1994;71:548-52.
18. van Vlijmen EF, Brouwer JL, Veeger NJ, Eskes TK, de Graeff PA, van der Meer J. Oral contraceptives and the absolute risk of venous thromboembolism in women with single or multiple thrombophilic defects: results from a retrospective family cohort study. Arch Intern Med 2007;167:282-9. https://doi.org/10.1001/archinte.167.3.282

5. **Risk of worsening kidney disease, hypertension, thrombosis, adverse events, or reduced contraceptive effectiveness among those with chronic kidney disease using contraception.**
Systematic review question: Among those with chronic kidney disease using contraception, is there a risk of worsening kidney disease, hypertension, thrombosis, adverse events, or reduced contraceptive effectiveness compared to no, non-hormonal, or other contraception? This table is based on Kortsmit K, Nguyen AT, Curtis KM, Burgner A, Folger S, Whiteman MK. Safety and effectiveness of contraception among women with chronic kidney disease: A systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: treatment	Number of patients: comparison	Effect	Certainty
OC use vs. none										
Development of HTN with PKD1	1[1]	Cohort	Very serious[a]	Not serious	Very serious[b]	Serious[c]	33	21	RR (95% CI): 1.2 (0.5 to 3.0)	Very Low
Development of HTN with PKD2	1[1]	Cohort	Very serious[a]	Not serious	Very serious[b]	Serious[c]	7	13	RR (95% CI): 1.3 (0.4 to 4.0)	Very Low
Development of ESRD with PKD1	1[1]	Cohort	Very serious[a]	Not serious	Very serious[b]	Serious[c]	33	21	RR (95% CI): 1.05 (0.31 to 3.62)	Very Low
Peritoneal dialysis vs. healthy participants										
Blood pressure changes with COC use	1[2]	Non-comparative cohort	Very serious[d]	Not serious	Very serious[e]	Not serious	5	NA	No significant differences	Very Low
EE levels	1[2]	NRCT	Serious[f]	Not serious	Very serious[g]	Very serious[h]	5	5	Higher concentrations in peritoneal dialysis group compared with healthy population	Very Low
Norethindrone levels	1[2]	NRCT	Serious[f]	Not serious	Very serious[g]	Very serious[h]	5	5	No significant differences	Very Low
Drospirenone use by renal function (normal, mild impairment, moderate impairment)										

Serum potassium levels	1[3]	NRCT	Very serious[i]	Not serious	Very serious[g]	Very serious[h]	10 mild renal impairment; 7 moderate renal impairment	11 normal renal function	Normal renal function mean difference ± SD: -0.10 ± 0.22; Mild renal impairment mean difference ± SD: -0.20 ± 0.23; Moderate renal impairment mean difference ± SD: -0.10 ± 0.32	Very Low
Drospirenone levels	1[3]	NRCT	Serious[i]	Not serious	Very serious[g]	Very serious[h]	10 mild renal impairment; 7 moderate renal impairment	11 normal renal function	AUC_{0-24} ng*h/mL) Normal function: 549 Mild impairment: 573 Moderate impairment: 751	Very low

CI, confidence interval; COC, combined oral contraception; EE, ethinyl estradiol; ESRD, end stage renal disease; HTN, hypertension; NA, not applicable; NRCT, non-randomized clinical trial; OC, oral contraception; PKD, polycystic kidney disease; RR, risk ratio; SD, standard deviation.

Footnotes

[a]Risk of bias is considered very serious due to <80% response rate, serious differences between those who participated and those lost to follow-up; not reported how data on oral contraceptive pills was collected; unclear how covariate data was collected and was not accounted for in analyses; variability in age at entry into study.

[b]Imprecision is considered very serious due to the small sample size and wide CI.

[c]Indirectness is considered serious due to the study population having unknown kidney function.

[d]Risk of bias is considered very serious due to <80% response rate; unclear how covariate data was collected and was not accounted for in analyses; variability in disease state requiring peritoneal dialysis.

[e]Imprecision is considered very serious due to the small sample size and lack of comparison group.

[f]Risk of bias is considered serious due to the study design (due to use of a parallel rather than cross-over design), large intersubject variability, and concerns about the study population (due to a wide age range or variability of disease severity).

[g]Imprecision is considered very serious due to the small sample size and large standard deviation or coefficient of variation.

[h]Indirectness is considered very serious due to the use of pharmacokinetic outcomes as proxy measures of potential clinical outcomes.

[i]Risk of bias is considered very serious due to <80% response rate, serious differences between those who participated and those who did not; did control for covariates in analyses; large degree of variability in age; postmenopausal status was assessed; short follow-up; crude estimates of confounding variables.

[j]Risk of bias is considered serious due to the study design (due to use of a parallel rather than cross-over design), large intersubject variability, and concerns about the study population (due to a wide age range or variability of disease severity).

References

1. Dicks E, Ravani P, Langman D, Davidson WS, Pei Y, Parfrey PS. Incident renal events and risk factors in autosomal dominant polycystic kidney disease: a population and family-based cohort followed for 22 years. Clin J Am Soc Nephrol 2006;1:710-7. https://doi.org/10.2215/cjn.01581105
2. Price TM, Dupuis RE, Carr BR, Stanczyk FZ, Lobo RA, Droegemueller W. Single- and multiple-dose pharmacokinetics of a low-dose oral contraceptive in women with chronic renal failure undergoing peritoneal dialysis. Am J Obstet Gynecol 1993;168:1400-6. https://doi.org/10.1016/s0002-9378(11)90772-8
3. Schürmann R, Blode H, Benda N, Cronin M, Küfner A. Effect of drospirenone on serum potassium and drospirenone pharmacokinetics in women with normal or impaired renal function. J Clin Pharmacol 2006;46:867-75. https://doi.org/10.1177/0091270006289973

6. **Risk of worsening viral hepatitis or cirrhosis* among those with liver disease using hormonal contraception.**
Systematic review question: Among those with liver disease using hormonal contraception, is there a risk of worsening liver disease compared to no, non-hormonal, or other contraception? This table is based on Kapp N, Tepper NK, Nguyen AT, Garbarino S, Kortsmit K, Curtis KM, Whiteman MK. Safety of hormonal contraception among women with liver disease: A systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed	Number of patients: comparison	Effect	Certainty
COC users with chronic hepatitis										
Changes in serum transaminase	1[1]	Non-comparative cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	10	NA	All participants after 4 weeks had normal transaminase levels; few mild elevations prior to end of first month of use	Very low
Hepatitis: COC use vs. non-use**										
Changes in AST/ALT	2[2, 3]	Non-randomized trial	Very serious[c]	Not serious	Very serious[b]	Not serious	112	115	No differences between groups in either study (p>0.05)	Very low
Hospitalization	1[2]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	34	34	Hospitalization days: 12.2 for COC group vs. 12.4 for non-COC group (p=0.92)	Very low
Necro-inflammatory activity	1[4]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	105	52	Grade of necroinflammatory activity: 1.18 vs. 1.18 (not significant, p-value NR)	Very low
Mean fibrosis score	1[4]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	105	52	Mean fibrosis score: 1.38 vs. 1.80 (p=0.02)	Very low
Rate of hepatic fibrosis	1[4]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	105	52	Rate of hepatic fibrosis: 108 vs. 115 (not significant, p-value NR)	Very low

ALT, alanine aminotransferase; AST/, aspartate aminotransferase; COC, combined oral contraception; NA, not applicable; NR, not reported; OC, oral contraception (type not specified).

*No studies were identified on patients with cirrhosis using contraception.

**Most studies assessed COCs, but one study (Schweitzer et al., 1975) assessed oral contraceptives of unknown type and we assume that most of these were COCs; another study (Di Martino et al., 2004) included mostly COC users but 6% were POP users.

Footnotes

[a]Risk of bias is considered very serious due to selection and information biases.

[b]Imprecision is considered very serious due to the small sample size, lack of power calculations, and lack of statistically significant results.

[c]Risk of bias is considered very serious due to selection bias, information bias, and use of crude estimates.

References

1. Eisalo A, Konttinen A, Hietala O. Oral contraceptives after liver disease. Br Med J 1971;3:561-2. https://doi.org/10.1136/bmj.3.5774.561
2. Schweitzer IL, Weiner JM, McPeak CM, Thursby MW. Oral contraceptives in acute viral hepatitis. Jama 1975;233:979-80.
3. Wang P, Lai Z, Tang J, Xu W, Mi X, Ma F. Safety of hormonal steroid contraceptive use for hepatitis B virus carrier women. Pharmacoepidemiol Drug Saf 2000;9:245-6. https://doi.org/10.1002/1099-1557(200005/06)9:3<245::Aid-pds500>3.0.Co;2-7
4. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F, et al. Progression of liver fibrosis in women infected with hepatitis C: long-term benefit of estrogen exposure. Hepatology 2004;40:1426-33. https://doi.org/10.1002/hep.20463

7. **Risk of worsening liver tumors among those with liver disease using hormonal contraception.**
Systematic review question: Among those with liver disease using hormonal contraception, is there a risk of worsening liver disease compared to no, non-hormonal, or other contraception? This table is based on Kapp N, Tepper NK, Nguyen AT, Garbarino S, Kortsmit K, Curtis KM, Whiteman MK. Safety of hormonal contraception among women with liver disease: A systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed	Number of patients: comparison	Effect	Certainty
Focal nodular hyperplasia (FNH)										
COC continued use vs. discontinued use										
Change in FNH lesion number or size	2[1-3]	Comparative cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	28	110	Continued use: 1 increased lesion size, 2 decreased or resolved, 25 stable Discontinued use: 4 increased lesion size, 9 decreased, 97 stable Statistical testing NR	Very low
COC use vs. non-use										
Change in FNH lesion number or size	1[1, 2]	Comparative cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	26	14	COCs: 1 lesion resolution; Non-use: no changes Statistical testing NR	Very low
POP use vs. non-use										
Change in FNH lesion number or size	1[1, 2]	Comparative cohort	Very serious[a]	Not serious	Very serious[b]	Not serious	7	14	No changes in either group Statistical testing NR	Very low
OC use (type not specified) vs. non-use										
Proportion with OC use among those with lesion growth vs. no growth	1[4]	Case-control	Very serious[c]	Not serious	Very serious[b]	Not serious	17 (cases, lesion growth)	78 (controls, no growth)	Lesion growth: 5/17 (29%) used OCs; no growth: 25/78 (32%) used OCs (p=0.83)	Very low
Hepatocellular adenoma (HCA)										
COC continued use vs. discontinued use										

Change in HCA lesion size	1[5]	Non-comparative cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	78	NA	4/78 (5%) with complete response, 29/78 (37%) with partial response, 44/78 (56%) stable, 1/78 (1%) progression	Very low
Malignant transform-ation	1[5]	Non-comparative cohort	Very serious[d]	Not serious	Very serious[b]	Not serious	78	NA	No malignant transformation	Very low
OC (type not specified) continued use vs. discontinued use										
Change in HCA lesion size	1[6]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	27	36	Continued use: 52% stable, 15% regression, 33% progression; Discontinued use: 78% stable, 19% regression, 3% progression (p=0.06, 0.74, 0.001)	Very low
Malignant transform-ation	1[6]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	27	36	One malignancy, not stated whether OC user or discontinuer	Very low
Estrogen use vs. no hormonal exposure										
Change in HCA lesion size	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	7	19	Estrogen: 29.4% median change in sum of diameters; No hormones: -7.4%; p-value NR	Very low
Malignant transform-ation	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	7	19	No malignant transformation	Very low
Progestin use vs. no hormonal exposure										
Change in HCA lesion size	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	8	19	Progestin: -15% median change in sum of diameters; No hormones: -7.4% (p=0.52)	Very low
Change in HCA lesion size	1[8]	Non-comparative cohort	Not serious	Not serious	Very serious[b]	Not serious	13	NA	1/13 progression, 10/13 stable, 2/13 regression	Very low
Malignant transform-ation	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	8	19	No malignant transformation	Very low
Malignant transform-ation	1[8]	Non-comparative cohort	Not serious	Not serious	Very serious[b]	Not serious	13	NA	No malignant transformation	Very low

Progestin use vs. estrogen use										
Change in HCA lesion size	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	8	7	Progestin: -15% median change in sum of diameters; Estrogen: 29.4% (p=0.04)	Very low
Malignant transform-ation	1[7]	Comparative cohort	Very serious[e]	Not serious	Very serious[b]	Not serious	8	7	No malignant transformation	Very low
OC use (type not specified) vs. non-use										
Change in HCA lesion size	1[9]	Non-comparative	Very serious[f]	Not serious	Very serious[b]	Not serious	96	NA	76/96 (79%) with regression	Very low

COC, combined oral contraception; FNH, focal nodular hyperplasia; HCA, hepatocellular adenoma; NA, not applicable; NR, not reported; OC, oral contraception; POP, progestin-only pill.

Footnotes

[a]Risk of bias is considered very serious due to selection bias, information bias, and use of crude estimates.

[b]Imprecision is considered very serious due to the small sample size and lack of power calculations.

[c]Risk of bias is considered very serious due to information bias and use of crude estimates.

[d]Risk of bias is considered very serious due to information bias.

[e]Risk of bias is considered very serious due to the use of crude estimates and differences in baseline characteristics.

[f]Risk of bias is considered very serious due to selection bias and use of crude estimates.

References

1. Mathieu D, Kobeiter H, Cherqui D, Rahmouni A, Dhumeaux D. Oral contraceptive intake in women with focal nodular hyperplasia of the liver. Lancet 1998;352:1679-80. https://doi.org/10.1016/s0140-6736(05)61451-1
2. Mathieu D, Kobeiter H, Maison P, Rahmouni A, Cherqui D, Zafrani ES, Dhumeaux D. Oral contraceptive use and focal nodular hyperplasia of the liver. Gastroenterology 2000;118:560-4. https://doi.org/10.1016/s0016-5085(00)70262-9
3. D'Halluin V, Vilgrain V, Pelletier G, Rocher L, Belghiti J, Erlinger S, Buffet C. [Natural history of focal nodular hyperplasia. A retrospective study of 44 cases]. Gastroenterol Clin Biol 2001;25:1008-10.
4. Halankar JA, Kim TK, Jang HJ, Khalili K, Masoom HA. Understanding the natural history of focal nodular hyperplasia in the liver with MRI. Indian J Radiol Imaging 2012;22:116-20. https://doi.org/10.4103/0971-3026.101084
5. Haring MPD, Gouw ASH, de Haas RJ, Cuperus FJC, de Jong KP, de Meijer VE. The effect of oral contraceptive pill cessation on hepatocellular adenoma diameter: A retrospective cohort study. Liver Int 2019;39:905-13. https://doi.org/10.1111/liv.14074

6. Silva TS, Sung M, Nelson DW, DiFronzo AL, O'Connor VV. A Multicenter, 10-Year Experience With Hepatocellular Adenoma: Risk Factors and Disease Course. Am Surg 2022;88:2345-50. https://doi.org/10.1177/00031348211011084
7. Qureshy Z, Lokken RP, Kakar S, Grab J, Mehta N, Sarkar M. Influence of progestin-only hormonal use on hepatocellular adenomas: A retrospective cohort study. Contraception 2023;119:109915. https://doi.org/10.1016/j.contraception.2022.11.006
8. Demory A, Péron JM, Calderaro J, Selves J, Mokrane FZ, Amaddeo G, et al. Body weight changes and duration of estrogen exposure modulate the evolution of hepatocellular adenomas after contraception discontinuation. Hepatology 2023;77:430-42. https://doi.org/10.1002/hep.32734
9. van Aalten SM, Witjes CD, de Man RA, Ijzermans JN, Terkivatan T. Can a decision-making model be justified in the management of hepatocellular adenoma? Liver Int 2012;32:28-37. https://doi.org/10.1111/j.1478-3231.2011.02667.x

8. **Risk of thrombosis, pain, or osteopenia/osteoporosis among those with sickle cell disease using hormonal contraception.**
Systematic review question: Among those with sickle cell disease using hormonal contraception, is there a risk of arterial thrombosis, venous thromboembolism, pain, or osteopenia/osteoporosis compared to no, non-hormonal, or other contraception? This table is based on Nguyen AT, Roe AH, Curtis KM, Pecker LH, Naik RP, Warner L, Whiteman MK. Safety of hormonal contraception use among those with sickle cell disease: a systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed	Number of patients: comparison	Effect	Certainty
Sickle Cell Disease										
HC use vs. non-use										
Pain crises (days of acute VOC during menses)	1[1]	Cross-sectional	Very serious[a]	Not serious	Very serious[b]	Not serious	36	17	HC use not associated with days of VOC pain vs. no HC use (mean days NR; p=0.49)	Very low
BMD	1[2]	Cohort	Very serious[c]	Not serious	Very serious[b]	Not serious	9	16	BMD z-scores, median (range): baseline HC -0.7 (-3.0, 0.4) vs. no HC -1.4 (-5.2, 1.0) (p=0.44); 6 months: HC -1.30 (-3.1, 0.3) vs. no HC -1.35 (-4.4, 1.1) (p=0.57)	Very low
CHC use vs. non-use										
Pain crises	2[3, 4]	NRCT; cross-sectional	Very serious[d]	Not serious	Very serious[b]	Not serious	49	89	Pain crises at 3 months: CHC (72.7%) vs. sterilization (92%); 12 months: CHC (45.5%) vs. sterilization (50%); p-value NR ≥ 4 pain episodes/year: CHCs (60%) vs. no HC (50.7%), p=0.072	Very low
Pain crises	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	67	NA	5.9% with increased pain crises during COC use	Very Low
Any stroke	1[6]	Cohort	Serious[f]	Not serious	Very serious[b]	Not serious	178*	1,079	HR (95% CI): 1.9 (0.6-5.9) for CHC group vs. comparison group (reference)	Very low

Ischemic stroke	1[6]	Cohort	Serious[f]	Not serious	Very serious[b]	Not serious	178[*]	1,079	HR (95% CI): 3.6 (0.8-16.5) for CHC group vs. comparison group (reference)	Very low
Hemorr-hagic stroke	1[6]	Cohort	Serious[f]	Not serious	Very serious[b]	Not serious	178[*]	1,079	HR (95% CI): 1.2 (0.5-5.7) for CHC group vs. comparison group (reference)	Very low
DVT	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	67	NA	2.9% with deep vein thrombosis during COC use	Very Low
POC use vs. non-use										
Pain crises	1[4]	Cross-sectional	Very serious[d]	Not serious	Very serious[b]	Not serious	6	73	≥ 4 pain episodes/year: POC use (16.6%) vs. no HC (50.7%), p=0.118	Very low
Implant use (nomegestrel acetate) vs. non-use										
Pain crises	1[7]	Cohort	Very serious[g]	Not serious	Very serious[b]	Not serious	20	10	1, 3, 6, 9, 12 months: 0, 0, 20%, 40%, 10% for implant group vs. 50%, 30%, 10%, 35%, 10% for comparison group	Very low
DMPA use vs. non-use										
Pain crises	1[8]	RCT	Very serious[h]	Not serious	Very serious[b]	Not serious	23	23	Episodes of pain crises: DMPA phase 29 episodes among 14 (61%) participants vs placebo phase 58 episodes among 20 (87%) participants, p=0.05	Very low
Pain crises	1[3]	NRCT	Very serious[d]	Not serious	Very serious[b]	Not serious	13	16	Pain crises at 3 months: DMPA (50%) vs. sterilization (92%); 12 months: DMPA (30%) vs. sterilization (50%); statistically significant (p-value NR)	Very low
Pain crises	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	26	NA	0% with increased pain crises during DMPA use	Very Low
VTE	1[9]	Non-comparative cohort	Serious[i]	Not serious	Very serious[b]	Not serious	12	NA	0 VTEs during study period	Very low

DVT	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	26	NA	0% with deep vein thrombosis during DMPA use	Very Low
Osteopenia	1[9]	Non-comparative cohort	Serious[i]	Not serious	Very serious[b]	Not serious	12	NA	0 cases osteopenia during study period	Very low
POP use vs. non-use										
Pain crises	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	30	NA	0% with increased pain crises during POP use	Very Low
DVT	1[5]	Non-comparative cross-sectional	Very serious[e]	Not serious	Very serious[b]	Not serious	30	NA	0% with deep vein thrombosis during POP use	Very Low

BMD, bone mineral density; CI, confidence interval; CHC, combined hormonal contraception; COC, combined oral contraception; DMPA, depot medroxyprogesterone acetate; DVT, deep venous thrombosis; HC, hormonal contraception; HR, hazard ratio; NA, not applicable; NR, not reported; NRCT, non-randomized clinical trial; OC, oral contraception; OR, odds ratio; POC, progestin-only contraception; POP, progestin-only pills; RCT, randomized clinical trial; SCD, sickle cell disease; VOC, vaso-occlusive crisis; VTE, venous thromboembolism.

Footnotes

*OC, presumed mostly COC

[a]Risk of bias is considered very serious due to measurement for recent contraceptive use, the unclear description of the comparison group (non-hormonal or no contraceptive use), and the use of crude estimates only.

[b]Imprecision is considered very serious due to the small sample size, lack of power calculations, and wide/no variance reported.

[c]Risk of bias is considered very serious due to the major differences between those who did and did not respond/participate, inadequate follow-up time, and the use of crude estimates only.

[d]Risk of bias is considered very serious due to lack of information on recruitment or response rate, self-reported exposure, and the use of crude estimates only.

[e]Risk of bias is considered very serious due to lack of response rate, unclear timing of contraceptive use, poor description of outcome assessment, and lack of description of the follow-up time.

[f]Risk of bias is considered serious due to self-report of exposure and the unclear description of the comparison group (non-hormonal or no contraceptive use).

[g]Risk of bias is considered very serious due to lack of information on selection of participants, lack of reporting of response rate and follow-up, and use of crude estimates only.

[h]Risk of bias is considered very serious due to the lack of information on blinding, allocation sequence, and baseline characteristics.

[i]Risk of bias is considered serious due to use of administrative data with no validation of exposure or outcomes.

References

1. Day ME, Stimpson SJ, Rodeghier M, Ghafuri D, Callaghan M, Zaidi AU, et al. Contraceptive Methods and the Impact of Menstruation on Daily Functioning in Women with Sickle Cell Disease. South Med J 2019;112:174-9. https://doi.org/10.14423/smj.0000000000000949
2. Harrell KJ, Stanek J, Bonny AE, Christian-Rancy M, Creary SE, Desai P, O'Brien SH. A pilot study of hormonal contraceptive use and bone mineral density in young women with sickle cell disease. Pediatr Blood Cancer 2018;65:e27398. https://doi.org/10.1002/pbc.27398
3. de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. Contraception 1997;56:313-6. https://doi.org/10.1016/s0010-7824(97)00156-x
4. Carvalho FA, Souza AI, Ferreira A, Neto SDS, Oliveira A, Gomes M, Costa MFH. Profile of Reproductive Issues Associated with Different Sickle Cell Disease Genotypes. Rev Bras Ginecol Obstet 2017;39:397-402. https://doi.org/10.1055/s-0037-1604179
5. Howard RJ, Lillis C, Tuck SM. Contraceptives, counselling, and pregnancy in women with sickle cell disease. Bmj 1993;306:1735-7. https://doi.org/10.1136/bmj.306.6894.1735
6. Qureshi AI, Malik AA, Adil MM, Suri MF. Oral contraceptive use and incident stroke in women with sickle cell disease. Thromb Res 2015;136:315-8. https://doi.org/10.1016/j.thromres.2015.04.013
7. Nascimento Mde L, Ladipo OA, Coutinho EM. Nomegestrol acetate contraceptive implant use by women with sickle cell disease. Clin Pharmacol Ther 1998;64:433-8. https://doi.org/10.1016/s0009-9236(98)90074-1
8. De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle-cell disease. Lancet 1982;2:229-31. https://doi.org/10.1016/s0140-6736(82)90320-8
9. O'Brien SH, Klima J, Reed S, Chisolm D, Schwarz EB, Kelleher KJ. Hormonal contraception use and pregnancy in adolescents with sickle cell disease: analysis of Michigan Medicaid claims. Contraception 2011;83:134-7. https://doi.org/10.1016/j.contraception.2010.06.017

9. **Risk of complications or reduced contraceptive effectiveness among those with solid organ transplant using contraception.**
Systematic review question: Among those with solid organ transplant using contraception, is there a risk of complications (thrombosis, hypertension, fracture/bone loss, infection, organ rejection) or reduced contraceptive effectiveness compared to no, non-hormonal, or other contraception? This table is based on Baker CC, Suresh T, Nguyen AT, Curtis KM, Whiteman MK. Safety and effectiveness of contraception among women with solid organ transplant: A systematic review. Contraception 2024: in preparation.

Outcome	Number of studies	Study design	Risk of bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposure	Number of patients: comparison	Effect	Certainty
Solid organ transplant recipients: Implant use vs. non-hormonal use										
Post-transplantation infection	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	50.0% vs. 54.2% (p=1.0)	Very low
Changes in immuno-suppressant therapy	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	79.2% vs. 87.5% (p=0.7)	Very low
Graft failure	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	4.2% vs. 0% (p=1.0)	Very low
Graft rejection	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	33.3% vs. 33.3% (p=1.0)	Very low
Repeat transplant surgery	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	8.3% vs. 0% (p=0.49)	Very low
Effectiveness (pregnancy)	1[1]	Comparative cohort	Serious[a]	Not serious	Very serious[b]	Not serious	24	24	1 pregnancy in implant group (after discontinuation); 1 pregnancy in comparison group	Very low
LNG-IUD users: Solid organ transplant recipients vs. healthy patients										
Effectiveness (inflammatory markers)	1[2]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Very serious[d]	5	11	Some significant differences in serum cytokines (range p=0.01 to 0.46); no significant differences in serum soluble receptor levels (p>0.05)	Very low
Effectiveness (cytokine levels from uterine lavage)	1[2]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Very serious[d]	5	11	No significant difference in lavage cytokine levels (p>0.05)	Very low

Effectiveness (endometrial macrophage activity)	1[2]	Comparative cohort	Very serious[c]	Not serious	Very serious[b]	Very serious[d]	5	11	No significant difference in endometrial macrophage activity (p>0.05)	Very low
LNG-IUD use among solid organ transplant recipients (non-comparative)										
Effectiveness (pregnancy)	4[3-6]	Non-compar-ative	Serious[a]	Not serious	Very serious[b]	Not serious	47	NA	No pregnancies reported; follow-up time ranged from 1-84 months	Very low
Safety (pelvic infection)	3[3, 4, 6]	Non-compar-ative	Serious[a]	Not serious	Very serious[b]	Not serious	35	NA	No pelvic infections reported; follow-up time ranged from 1-84 months	Very low
CHC use among solid organ transplant (non-comparative)										
Effectiveness (pregnancy)	4[7-10]	Non-compar-ative	Serious[e]	Not serious	Very serious[b]	Not serious	76	NA	No pregnancies reported; follow-up time ranged from 12-70 months	Very low
Safety (graft dysfunction/ rejection/ change in immuno-suppressant therapy)	4[7-10]	Non-compar-ative	Serious[e]	Not serious	Very serious[b]	Not serious	76	NA	1 symptoms of graft rejection; follow-up time ranged from 12-70 months	Very low

CHC, combined hormonal contraception; IUD, intrauterine device; LNG, levonorgestrel; NA, not applicable.

Footnotes

[a]Risk of bias is considered serious due to safety and effectiveness outcomes being identified through chart review with no active follow-up or validation.

[b]Imprecision is considered very serious due to the small sample size and no power calculations.

[c]Risk of bias is considered very serious due to lack of information on the population source and recruitment flow and the reporting of only crude measures with unknown influence of confounding variables.

[d]Indirectness is considered very serious due to the use of changes in the uterine environment as a proxy measure for contraceptive effectiveness.

[e]Risk of bias is considered serious due to lack of information on the population source and recruitment flow and self-reported outcomes.

References

1. Lew J, Sheeder J, Lazorwitz A. Etonogestrel contraceptive implant uptake and safety among solid organ transplant recipients. Contraception 2021;104:556-60. https://doi.org/10.1016/j.contraception.2021.06.007

2. Kim CR, Martinez-Maza O, Magpantay L, Magyar C, Gornbein J, Rible R, Sullivan P. Immunologic evaluation of the endometrium with a levonorgestrel intrauterine device in solid organ transplant women and healthy controls. Contraception 2016;94:534-40. https://doi.org/10.1016/j.contraception.2016.06.021
3. Juliato CRT, Stahlschmidt P, Fernandes A, Monteiro I, Bahamondes L. A case series on the use of levonorgestrel 52 mg intrauterine system after organ transplant. Contraception 2018;98:252-4. https://doi.org/10.1016/j.contraception.2018.04.017
4. Ramhendar T, Byrne P. Contraception for renal transplant recipients in the Republic of Ireland : a review. Ir J Med Sci 2013;182:315-7. https://doi.org/10.1007/s11845-012-0889-3
5. Bahamondes MV, Hidalgo MM, Bahamondes L, Monteiro I. Ease of insertion and clinical performance of the levonorgestrel-releasing intrauterine system in nulligravidas. Contraception 2011;84:e11-6. https://doi.org/10.1016/j.contraception.2011.05.012
6. Huguelet PS, Sheehan C, Spitzer RF, Scott S. Use of the levonorgestrel 52-mg intrauterine system in adolescent and young adult solid organ transplant recipients: a case series. Contraception 2017;95:378-81. https://doi.org/10.1016/j.contraception.2016.11.008
7. Paternoster DM, Riboni F, Bertolino M, Garofalo G, Lazzarich E, Surico N, Stratta P. The contraceptive vaginal ring in women with renal and liver transplantation: analysis of preliminary results. Transplant Proc 2010;42:1162-5. https://doi.org/10.1016/j.transproceed.2010.03.132
8. Jabiry-Zieniewicz Z, Bobrowska K, Kaminski P, Wielgos M, Zieniewicz K, Krawczyk M. Low-dose hormonal contraception after liver transplantation. Transplant Proc 2007;39:1530-2. https://doi.org/10.1016/j.transproceed.2007.02.063
9. Pietrzak B, Bobrowska K, Jabiry-Zieniewicz Z, Kaminski P, Wielgos M, Pazik J, Durlik M. Oral and transdermal hormonal contraception in women after kidney transplantation. Transplant Proc 2007;39:2759-62. https://doi.org/10.1016/j.transproceed.2007.09.014
10. Bader Y, Helmy S, Promberger R, Marschalek J, Jirecek S, Jaksch P, Ott J. Hormonal contraception in female lung transplant recipients: a case series. J Fam Plann Reprod Health Care 2014;40:294-6. https://doi.org/10.1136/jfprhc-2013-100783

10. Risk of intrauterine device expulsion after postpartum placement by timing of placement

Systematic review question: What is the risk of intrauterine device expulsion after postpartum placement by timing of placement?

This table is based on Nguyen AT, Wright S, Jeng G, Averbach S, Jatlaoui T, Ermias Y, Curtis KM, Tepper NK, Whiteman MK. Intrauterine device expulsion after postpartum placement by timing of placement: a systematic review and meta-analysis. Contraception 2024: in preparation.

Outcome	Number of studies	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients with IUDs placed	Complete IUD expulsion rate, % (range among studies)	Certainty
Pooled complete IUD expulsion rates								
IUD placement timing								
Immediate (≤10 min of placental delivery)	65[1-65]	Serious[a]	Not serious	Serious[b]	Not serious	12,225	8.6% (0.0-31.9%)	Very low
Early (>10 min to <4 wks postpartum)	15[3, 13, 21, 41, 46, 66-74]	Serious[a]	Not serious	Serious[b]	Not serious	19,452	4.5% (0.0-46.7%)	Very low
Early inpatient (>10 min to <72 hrs)	11[3, 13, 21, 41, 46, 59, 69-72, 75]	Serious[a]	Not serious	Serious[b]	Not serious	2,044	25.1% (3.5-46.7%)	Very low
Early outpatient (72 hrs to <4 wks)	4[66-68, 74]	Serious[a]	Not serious	Not serious	Not serious	17,408	2.0% (0.0-2.1%)	Low
Within 72 hours (≤72 hrs)	12[50, 66, 76-85]	Serious[a]	Not serious	Serious[b]	Not serious	8,702	7.7% (1.4-29.8%)	Very low
Interval (≥4 wks)	21[2, 6, 8, 13, 19, 21, 29, 33, 49, 57, 61, 66, 67, 69, 70, 72, 74, 83, 86-88]	Serious[a]	Not serious	Not serious	Not serious	70,722	1.6% (0.0-4.8%)	Low

IUD, intrauterine device.

Footnotes

[a]Risk of bias is considered serious due to selection bias with the response and follow-up rate, the non-standard definition and diagnosis of expulsion, and the differential lengths of follow-up.

[b]Imprecision is considered serious due to wide range of complete IUD expulsion rates among studies.

References

1. Gueye M, Gaye YF, Diouf AA, Mbaye M, Niang MM, Gueye SM, et al. [Trancesarean intra-uterine device. Pilot study performed at Dakar teaching hospital]. Journal de gynecologie, obstetrique et biologie de la reproduction 2013;42:585-90. https://doi.org/10.1016/j.jgyn.2013.06.003
2. Lester F, Kakaire O, Byamugisha J, Averbach S, Fortin J, Maurer R, Goldberg A. Intracesarean insertion of the Copper T380A versus 6 weeks postcesarean: a randomized clinical trial. Contraception 2015;91:198-203. https://doi.org/10.1016/j.contraception.2014.12.002
3. Morrison C, Waszak C, Katz K, Diabate F, Mate EM. Clinical outcomes of two early postpartum IUD insertion programs in Africa. Contraception 1996;53:17-21.

4. Okoye NP, Onwusulu DN, Nnamani CP. Clinical Outcomes of Trans-caesarean and Vaginal Post-placental CuT380A IUCD Insertions: a Comparative Study. International journal of tropical disease & health 2021;42:46-57. https://doi.org/10.9734/ijtdh/2021/v42i630471
5. Puzey M. Mirena at caesarean section. Eur J Contracept Reprod Health Care 2005;10:164-7. https://doi.org/10.1080/13625180500233851
6. Abdel-Ghany A, Khalifa E, El-Din MZ, Ibrahim E, Abdallah A, Abdel-Aziz M, et al. Intrapartum versus postpartum insertion of intrauterine device in women delivering by cesarean section. BMC Pregnancy Childbirth 2022;22:365. https://doi.org/10.1186/s12884-022-04681-4
7. Afzal M, Zaman S, Ismat S, Hayat T. Examine the efficacy and safety of immediate postpartum intrauterine contraceptive devices in C-Section and vaginal deliveries. Pakistan Journal of Medical and Health Sciences 2020;14:859-61.
8. Bayoumi YA, Dakhly DMR, Bassiouny YA, Gouda HM, Hassan MA, Hassan AA. Post-placental intrauterine device insertion vs puerperal insertion in women undergoing caesarean delivery in Egypt: a 1 year randomised controlled trial. Eur J Contracept Reprod Health Care 2020;25:439-44. https://doi.org/10.1080/13625187.2020.1823366
9. Celen S, Sucak A, Yildiz Y, Danisman N. Immediate postplacental insertion of an intrauterine contraceptive device during cesarean section. Contraception 2011;84:240-3. https://doi.org/10.1016/j.contraception.2011.01.006
10. Elsedeek MS. Puerperal and menstrual bleeding patterns with different types of contraceptive device fitted during elective cesarean delivery. Int J Gynaecol Obstet 2012;116:31-4. https://doi.org/10.1016/j.ijgo.2011.07.036
11. Elsedeek MS. Five-year follow-up of two types of contraceptive device fitted during elective cesarean delivery. Int J Gynaecol Obstet 2015;130:179-82. https://doi.org/10.1016/j.ijgo.2015.02.031
12. Elshamy E, Nofal A, Ibrrahim D. Postplacental Insertion of Levonorgestrel Intrauterine System Versus Copper Intrauterine Device: A Prospective Study. J Obstet Gynaecol India 2021;71:150-5. https://doi.org/10.1007/s13224-020-01409-2
13. Eroglu K, Akkuzu G, Vural G, Dilbaz B, Akin A, Taskin L, Haberal A. Comparison of efficacy and complications of IUD insertion in immediate postplacental/early postpartum period with interval period: 1 year follow-up. Contraception 2006;74:376-81. https://doi.org/10.1016/j.contraception.2006.07.003
14. Khan FS, Nazeer S, Afridi N, Amina N, Kanwal S, Khan S. Acceptance, Follow-up and Outcome of Postpartum Intrauterine Contraceptive Device in C section and Normal delivery. Pakistan Journal of Medical and Health Sciences 2020;14:1177-9.
15. Ragab A, Hamed HO, Alsammani MA, Shalaby H, Nabeil H, Barakat R, Fetih AN. Expulsion of Nova-T380, Multiload 375, and Copper-T380A contraceptive devices inserted during cesarean delivery. Int J Gynaecol Obstet 2015;130:174-8. https://doi.org/10.1016/j.ijgo.2015.03.025
16. Sucak A, Ozcan S, Celen S, Caglar T, Goksu G, Danisman N. Immediate postplacental insertion of a copper intrauterine device: a pilot study to evaluate expulsion rate by mode of delivery. BMC Pregnancy Childbirth 2015;15:202. https://doi.org/10.1186/s12884-015-0637-6
17. Heller R, Johnstone A, Cameron ST. Routine provision of intrauterine contraception at elective cesarean section in a national public health service: a service evaluation. Acta Obstet Gynecol Scand 2017;96:1144-51. https://doi.org/10.1111/aogs.13178
18. Newton J, Harper M, Chan KK. Immediate post-placental insertion of intrauterine contraceptive devices. Lancet 1977;2:272-4.
19. Chen BA, Reeves MF, Hayes JL, Hohmann HL, Perriera LK, Creinin MD. Postplacental or delayed insertion of the levonorgestrel intrauterine device after vaginal delivery: a randomized controlled trial. Obstet Gynecol 2010;116:1079-87. https://doi.org/10.1097/AOG.0b013e3181f73fac
20. Cohen R, Sheeder J, Arango N, Teal SB, Tocce K. Twelve-month contraceptive continuation and repeat pregnancy among young mothers choosing postdelivery contraceptive implants or postplacental intrauterine devices. Contraception 2016;93:178-83. https://doi.org/10.1016/j.contraception.2015.10.001
21. Dahlke JD, Terpstra ER, Ramseyer AM, Busch JM, Rieg T, Magann EF. Postpartum insertion of levonorgestrel--intrauterine system at three time periods: a prospective randomized pilot study. Contraception 2011;84:244-8. https://doi.org/10.1016/j.contraception.2011.01.007

22. Eggebroten JL, Sanders JN, Turok DK. Immediate postpartum intrauterine device and implant program outcomes: a prospective analysis. Am J Obstet Gynecol 2017;217:51.e1-.e7. https://doi.org/10.1016/j.ajog.2017.03.015
23. Goldthwaite LM, Sheeder J, Hyer J, Tocce K, Teal SB. Postplacental intrauterine device expulsion by 12 weeks: a prospective cohort study. Am J Obstet Gynecol 2017. https://doi.org/10.1016/j.ajog.2017.08.001
24. Gonzalez J, Stimmel S, Rana R, Diggs AI, Pan S, Overbey J, et al. Ultrasound location of intrauterine devices placed at cesarean section over the first year postpartum. Contraception 2020;101:399-404. https://doi.org/10.1016/j.contraception.2020.03.003
25. Gurney EP, McAllister A, Lang B, Schreiber CA, Sonalkar S. Ultrasound assessment of postplacental copper intrauterine device position 6 months after placement during cesarean delivery. Contracept X 2020;2:100040. https://doi.org/10.1016/j.conx.2020.100040
26. Hayes JL, Cwiak C, Goedken P, Zieman M. A pilot clinical trial of ultrasound-guided postplacental insertion of a levonorgestrel intrauterine device. Contraception 2007;76:292-6. https://doi.org/10.1016/j.contraception.2007.06.003
27. Jatlaoui TC, Marcus M, Jamieson DJ, Goedken P, Cwiak C. Postplacental intrauterine device insertion at a teaching hospital. Contraception 2014;89:528-33. https://doi.org/10.1016/j.contraception.2013.10.008
28. Levi E, Cantillo E, Ades V, Banks E, Murthy A. Immediate postplacental IUD insertion at cesarean delivery: a prospective cohort study. Contraception 2012;86:102-5. https://doi.org/10.1016/j.contraception.2011.11.019
29. Levi E.E. SGS, Zerden M.L., Garrett J.M., and Bryant A.G. Intrauterine Device Placement During Cesarean Delivery and Continued Use 6 Months Postpartum. Obstet Gynecol 2015;126:5-11.
30. Martinez OP, Wilder L, Seal P. Ultrasound-Guided Compared With Non-Ultrasound-Guided Placement of Immediate Postpartum Intrauterine Contraceptive Devices. Obstet Gynecol 2022;140:91-3. https://doi.org/10.1097/aog.0000000000004828
31. Nelson AL, Chen S, Eden R. Intraoperative placement of the Copper T-380 intrauterine devices in women undergoing elective cesarean delivery: a pilot study. Contraception 2009;80:81-3. https://doi.org/10.1016/j.contraception.2009.01.014
32. Sinkey RG, Blanchard CT, Maier J, Novara A, Mazzoni SE, Goepfert AR, et al. The effects of offering immediate postpartum placement of IUDs and implants to pregnant patients with heart disease. Contraception 2022;105:55-60. https://doi.org/10.1016/j.contraception.2021.09.005
33. Whitaker AK, Endres LK, Mistretta SQ, Gilliam ML. Postplacental insertion of the levonorgestrel intrauterine device after cesarean delivery vs. delayed insertion: a randomized controlled trial. Contraception 2014;89:534-9. https://doi.org/10.1016/j.contraception.2013.12.007
34. Woo I, Seifert S, Hendricks D, Jamshidi RM, Burke AE, Fox MC. Six-month and 1-year continuation rates following postpartum insertion of implants and intrauterine devices. Contraception 2015;92:532-5. https://doi.org/10.1016/j.contraception.2015.09.007
35. da Silva Nóbrega AB, Pitangui ACR, Vieira CS. Factors associated with missing strings and expulsion after postplacental insertion of copper T380A intrauterine devices. Int J Gynaecol Obstet 2022;157:67-75. https://doi.org/10.1002/ijgo.13806
36. Giovanelli SA, Torloni MR, Guazzelli CAF. Post-Placental Intrauterine Device Insertion in Brazilian Adolescents: Clinical Outcomes at 12 Months. J Pediatr Adolesc Gynecol 2021. https://doi.org/10.1016/j.jpag.2021.10.009
37. Laporte M, Marangoni M, Jr., Surita F, Juliato CT, Miadaira M, Bahamondes L. Postplacental placement of intrauterine devices: A randomized clinical trial. Contraception 2020;101:153-8. https://doi.org/10.1016/j.contraception.2019.12.006
38. Letti Muller AL, Lopes Ramos JG, Martins-Costa SH, Palma Dias RS, Valerio EG, Hammes LS, et al. Transvaginal ultrasonographic assessment of the expulsion rate of intrauterine devices inserted in the immediate postpartum period: a pilot study. Contraception 2005;72:192-5. https://doi.org/10.1016/j.contraception.2005.03.014
39. Marangoni M, Jr., Laporte M, Surita F, Kraft MB, Bahamondes L, Juliato CRT. One-year follow up on post-placental IUD insertion: A randomized clinical trial. Acta Obstet Gynecol Scand 2021;100:596-603. https://doi.org/10.1111/aogs.14081

40. Zaconeta AM, Oliveira AC, Estrela FS, Vasconcelos TM, França PS, Wanderley MDS, Amato AA. Intrauterine Device Insertion during Cesarean Section in Women without Prenatal Contraception Counseling: Lessons from a Country with High Cesarean Rates. Rev Bras Ginecol Obstet 2019;41:485-92. https://doi.org/10.1055/s-0039-1693677
41. Bhat S, Damle H, Darawade S, Junnare K, Ashturkar M. To study the acceptance of postpartum intrauterine contraceptive device, CU T 380 A, in a tertiary care hospital in India. Journal of Reproductive Health and Medicine 2016;2:93-8. https://doi.org/https://doi.org/10.1016/j.jrhm.2016.05.002
42. Dias T, Abeykoon S, Kumarasiri S, Gunawardena C, Padeniya T, D'Antonio F. Use of ultrasound in predicting the success of intrauterine contraceptive device (Copper T) insertion immediately after delivery. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 2014. https://doi.org/10.1002/uog.14733
43. Gupta S, Malik S, Sinha R, Shyamsunder S, Mittal MK. Association of the Position of the Copper T 380A as Determined by the Ultrasonography Following its Insertion in the Immediate Postpartum Period with the Subsequent Complications: An Observational Study. J Obstet Gynaecol India 2014;64:349-53. https://doi.org/10.1007/s13224-014-0532-5
44. Hooda R, Mann S, Nanda S, Gupta A, More H, Bhutani J. Immediate Postpartum Intrauterine Contraceptive Device Insertions in Caesarean and Vaginal Deliveries: A Comparative Study of Follow-Up Outcomes. International journal of reproductive medicine 2016;2016:7695847. https://doi.org/10.1155/2016/7695847
45. Jakhar R, Singhal G. Safety and Efficacy of Intra-caesarean IUCD: A Prospective Study at a Tertiary Care Centre. J Obstet Gynaecol India 2019;69:325-9. https://doi.org/10.1007/s13224-019-01242-2
46. Lerma K, Bhamrah R, Singh S, Blumenthal PD. Importance of the delivery-to-insertion interval in immediate postpartum intrauterine device insertion: A secondary analysis. Int J Gynaecol Obstet 2020;149:154-9. https://doi.org/10.1002/ijgo.13115
47. Mishra S. Tale of the Tails, the Missing Postpartum IUCD Strings. J Obstet Gynaecol India 2017;67:202-7. https://doi.org/10.1007/s13224-016-0940-9
48. Singal S, Bharti R, Dewan R, Divya, Dabral A, Batra A, et al. Clinical Outcome of Postplacental Copper T 380A Insertion in Women Delivering by Caesarean Section. Journal of clinical and diagnostic research : JCDR 2014;8:OC01-4. https://doi.org/10.7860/jcdr/2014/10274.4786
49. Braniff K, Gomez E, Muller R. A randomised clinical trial to assess satisfaction with the levonorgestrel- releasing intrauterine system inserted at caesarean section compared to postpartum placement. Aust N Z J Obstet Gynaecol 2015;55:279-83. https://doi.org/10.1111/ajo.12335
50. Wojcik N, Watkins L, Nugent R. Patient acceptability, continuation and complication rates with immediate postpartum levonorgestrel intrauterine device insertion at caesarean section and vaginal birth. Aust N Z J Obstet Gynaecol 2022. https://doi.org/10.1111/ajo.13535
51. Xu J, Yang X, Gu X, Xu S, Zhou X, Chen Y, et al. Comparison between two techniques used in immediate postplacental insertion of TCu 380A intrauterine device: 36-month follow-up. Reproduction and contraception 1999;10:156-62.
52. Dewan R, Dewan A, Singal S, Bharti R, Kaim M. Non-visualisation of strings after postplacental insertion of Copper-T 380A intrauterine device. J Fam Plann Reprod Health Care 2017;43:186-94. https://doi.org/10.1136/jfprhc-2015-101200
53. Unal C, Eser A, Tozkir E, Wildemeersch D. Comparison of expulsions following intracesarean placement of an innovative frameless copper-releasing IUD (Gyn-CS®) versus the TCu380A: A randomized trial. Contraception 2018. https://doi.org/10.1016/j.contraception.2018.03.034
54. Colwill AC, Schreiber CA, Sammel MD, Sonalkar S. Six-week retention after postplacental copper intrauterine device placement. Contraception 2018;97:215-8. https://doi.org/10.1016/j.contraception.2017.10.012
55. Gurney EP, Sonalkar S, McAllister A, Sammel MD, Schreiber CA. Six-month expulsion of postplacental copper intrauterine devices placed after vaginal delivery. Am J Obstet Gynecol 2018;219:183.e1-.e9. https://doi.org/10.1016/j.ajog.2018.05.032
56. Hinz EK, Murthy A, Wang B, Ryan N, Ades V. A prospective cohort study comparing expulsion after postplacental insertion: the levonorgestrel versus the copper intrauterine device. Contraception 2019;100:101-5. https://doi.org/10.1016/j.contraception.2019.04.011

57. Soon R, McGuire K, Salcedo J, Kaneshiro B. Immediate Versus Delayed Insertion of the Levonorgestrel Intrauterine Device in Postpartum Adolescents: A Randomized Pilot Study. Hawaii J Med Public Health 2018;77:60-5.
58. Agarwal K, Dewan R, Mittal P, Aggarwal A. Visibility of Strings After Postplacental Intracesarean Insertion of CuT380A and Cu375 Intrauterine Contraceptive Device: A Randomized Comparative Study. J Obstet Gynaecol India 2017;67:324-9. https://doi.org/10.1007/s13224-017-0965-8
59. Kumar S, Srivastava A, Sharma S, Yadav V, Mittal A, Kim YM, et al. One-year continuation of postpartum intrauterine contraceptive device: findings from a retrospective cohort study in India. Contraception 2019;99:212-6. https://doi.org/10.1016/j.contraception.2018.12.003
60. Cole M, Thomas S, Mercer BM, Arora KS. Impact of training level on postplacental levonorgestrel 52 mg intrauterine device expulsion. Contraception 2019;99:94-7. https://doi.org/10.1016/j.contraception.2018.11.003
61. Turok DK, Leeman L, Sanders JN, Thaxton L, Eggebroten JL, Yonke N, et al. Immediate postpartum levonorgestrel IUD insertion & breastfeeding outcomes: A noninferiority randomized controlled trial. Am J Obstet Gynecol 2017. https://doi.org/10.1016/j.ajog.2017.08.003
62. Shukla M, Qureshi S. Post-placental intrauterine device insertion--a five year experience at a tertiary care centre in north India. The Indian journal of medical research 2012;136:432-5.
63. Mishra S. Evaluation of Safety, Efficacy, and Expulsion of Post-Placental and Intra-Cesarean Insertion of Intrauterine Contraceptive Devices (PPIUCD). J Obstet Gynaecol India 2014;64:337-43. https://doi.org/10.1007/s13224-014-0550-3
64. Blumenthal PD, Chakraborty NM, Prager S, Gupta P, Lerma K, Vwalika B. Programmatic experience of post-partum IUD use in Zambia: an observational study on continuation and satisfaction. Eur J Contracept Reprod Health Care 2016;21:356-60. https://doi.org/10.1080/13625187.2016.1201655
65. Vishwakarma S, Verma V, Singh M, Mittal N. Experience on Safety, Expulsion, and Complication of Intracesarean Post-Partum Intrauterine Copper Device. Cureus 2020;12:e10647. https://doi.org/10.7759/cureus.10647
66. Armstrong MA, Raine-Bennett T, Reed SD, Gatz J, Getahun D, Schoendorf J, et al. Association of the Timing of Postpartum Intrauterine Device Insertion and Breastfeeding With Risks of Intrauterine Device Expulsion. JAMA Netw Open 2022;5:e2148474. https://doi.org/10.1001/jamanetworkopen.2021.48474
67. Chen MJ, Hou MY, Hsia JK, Cansino CD, Melo J, Creinin MD. Long-Acting Reversible Contraception Initiation With a 2- to 3-Week Compared With a 6-Week Postpartum Visit. Obstet Gynecol 2017;130:788-94. https://doi.org/10.1097/aog.0000000000002246
68. Zerden ML, Stuart GS, Charm S, Bryant A, Garrett J, Morse J. Two-week postpartum intrauterine contraception insertion: a study of feasibility, patient acceptability and short-term outcomes. Contraception 2017;95:65-70. https://doi.org/10.1016/j.contraception.2016.08.005
69. Bryant AG, Kamanga G, Stuart GS, Haddad LB, Meguid T, Mhango C. Immediate postpartum versus 6-week postpartum intrauterine device insertion: a feasibility study of a randomized controlled trial. African journal of reproductive health 2013;17:72-9.
70. Lichtenstein Liljeblad K, Kopp Kallner H, Brynhildsen J. Effectiveness, safety and overall satisfaction of early postpartum placement of hormonal IUD compared with standard procedure: An open-label, randomized, multicenter study. Acta Obstet Gynecol Scand 2022;101:424-30. https://doi.org/10.1111/aogs.14331
71. Stuart GS, Bryant AG, O'Neill E, Doherty IA. Feasibility of postpartum placement of the levonorgestrel intrauterine system more than 6 h after vaginal birth. Contraception 2012;85:359-62. https://doi.org/10.1016/j.contraception.2011.08.005
72. Stuart GS, Lesko CR, Stuebe AM, Bryant AG, Levi EE, Danvers AI. A randomized trial of levonorgestrel intrauterine system insertion 6 to 48h compared to 6weeks after vaginal delivery; lessons learned. Contraception 2015;91:284-8. https://doi.org/10.1016/j.contraception.2014.12.009
73. Lavin P, Waszak C, Bravo C. Preliminary report on a postpartum CuT 200 study, Santiago, Chile. Int J Gynaecol Obstet 1983;21:71-5.
74. Baldwin MK, Edelman AB, Lim JY, Nichols MD, Bednarek PH, Jensen JT. Intrauterine device placement at 3 versus 6weeks postpartum: a randomized trial. Contraception 2016;93:356-63. https://doi.org/10.1016/j.contraception.2015.12.006
75. Lavin P, Bravo C, Waszak C. Comparison of T Cu 200 and Progestasert IUDs. Contraceptive delivery systems 1983;4:143-7.

76. Muhumuza J, Migisha R, Ngonzi J, Kayondo M, Mugyenyi G. Risk factors for postpartum intrauterine device expulsion among women delivering at a tertiary Hospital in Uganda: a prospective cohort study. Contracept Reprod Med 2021;6:7. https://doi.org/10.1186/s40834-021-00153-w
77. Rwegoshora FJ, Muganyizi PS, Kimario GF, Paul PP, Makins A. A one-year cohort study of complications, continuation, and failure rates of postpartum TCu380A in Tanzania. Reprod Health 2020;17:150. https://doi.org/10.1186/s12978-020-00999-4
78. Fatima S, Rehman A, Ahmed Z, Sajid MM, Habiba U, Rehman A. Postpartum Insertion Of Intrauterine Contraceptive Device: A Safe And Effective Contraception. J Ayub Med Coll Abbottabad 2022;34(Suppl 1):S671-s7. https://doi.org/10.55519/jamc-03-s1-10029
79. Iftikhar PM, Shaheen N, Arora E. Efficacy and Satisfaction Rate in Postpartum Intrauterine Contraceptive Device Insertion: A Prospective Study. Cureus 2019;11:e5646. https://doi.org/10.7759/cureus.5646
80. Cooper M, McGeechan K, Glasier A, Coutts S, McGuire F, Harden J, et al. Provision of immediate postpartum intrauterine contraception after vaginal birth within a public maternity setting: Health services research evaluation. Acta Obstet Gynecol Scand 2020;99:598-607. https://doi.org/10.1111/aogs.13787
81. Kumar S, Sethi R, Balasubramaniam S, Charurat E, Lalchandani K, Semba R, Sood B. Women's experience with postpartum intrauterine contraceptive device use in India. Reprod Health 2014;11:32. https://doi.org/10.1186/1742-4755-11-32
82. Puri MC, Guo M, Shah IH, Stone L, Maharjan D, Canning D. Provider and Women Characteristics as Risk Factors for Postpartum Copper IUD Expulsion and Discontinuation in Nepal. Int Perspect Sex Reprod Health 2020;46:235-45. https://doi.org/10.1363/46e1220
83. Bonilla Rosales F, Aguilar Zamudio ME, Cazares Montero Mde L, Hernandez Ortiz ME, Luna Ruiz MA. [Factors for expulsion of intrauterine device Tcu380A applied immediately postpartum and after a delayed period]. Revista medica del Instituto Mexicano del Seguro Social 2005;43:5-10.
84. El Beltagy N, Darwish E, Kasem M, Hefila N. Comparison between Cupper T380 IUD and Multiload 375 IUD in early postpartum insertion. Middle Eastern Fertility Society Journal 2011;16:143-8. https://doi.org/http://dx.doi.org/10.1016/j.mefs.2010.12.006
85. Blumenthal PD, Goldthwaite LM. Intrauterine Device Insertion During Cesarean Delivery: The Rising Tide of the Postdelivery Intrauterine Device. Obstet Gynecol 2015;126:1-2. https://doi.org/10.1097/AOG.0000000000000944
86. Laes E, Lehtovirta P, Weintraub D, Pyorala T, Luukkainen T. Early puerperal insertions of copper-T-200. Contraception 1975;11:289-95.
87. Ramos-Rivera M, Averbach S, Selvaduray P, Gibson A, Ngo LL. Complications after interval postpartum intrauterine device insertion. Am J Obstet Gynecol 2022;226:95.e1-.e8. https://doi.org/10.1016/j.ajog.2021.08.028
88. Roy M, Hazra A, Merkatz R, Plagianos M, Alami M, Gaur LN, et al. Progesterone vaginal ring as a new contraceptive option for lactating mothers: Evidence from a multicenter non-randomized comparative clinical trial in India. Contraception 2020;102:159-67. https://doi.org/10.1016/j.contraception.2020.04.016

11. Risk of reduced medication abortion effectiveness among those systemic hormonal contraception.

Systematic review question: Among those who underwent medication abortion, is there a risk of reduced medication abortion effectiveness (surgery to complete abortion, ongoing pregnancy) with immediate versus delayed initiation of systemic hormonal contraception?

This table is based on Kim C, Nguyen AT, Berry-Bibee E, Ermias Y, Gaffield ME, Kapp N. Systemic hormonal contraception initiation after abortion: A systematic review and meta-analysis. Contraception. 2021 May;103(5):291-304. Doi: 10.1016/j.contraception.2021.01.017. Epub 2021 Feb 3. PMID: 33548267; PMCID: PMC8040936.

Outcome	Number of studies	Study design	Risk of Bias	Inconsistency	Imprecision	Indirectness	Number of patients: exposed	Number of patients: comparison	Effect	Certainty of evidence
Medication abortion effectiveness										
ENG implant use: immediate vs. delayed initiation										
Surgery to complete abortion	2[1, 2]	RCT	Serious[a]	Not serious	Very serious[b]	Not serious	506	495	Immediate 3.9% vs. delayed 3.9%; difference (90% CI): 0.08% (-3.06-3.25%) Immediate 5.7% vs. delayed 3.8%; difference (95% CI): 1.3% (-0.9-4.1%)	Low
Surgery to complete abortion	1[3]	Cohort	Very serious[c]	Not serious	Serious[d]	Not serious	57	62	Immediate 96.5% vs. delayed 98.4% (p=0.47)	Very low
Ongoing pregnancy	1[1]	RCT	Serious[a]	Not serious	Very serious[b]	Not serious	229	234	Immediate 0.9% vs. delayed 0.9%; difference (90% CI): 0.02% (-1.8-1.85%)	Low
COC use: immediate vs. delayed initiation										
Surgery to complete abortion	1[4]	RCT	Very serious[e]	Not serious	Very serious[d]	Not serious	19	19	Immediate 0% vs. delayed 0%	Very low
DMPA use: immediate vs. delayed initiation										
Surgery to complete abortion	1[5]	RCT	Serious[a]	Not serious	Very serious[b]	Not serious	220	226	Immediate 6.4% vs. delayed 5.3%; difference (90% CI): 1.1% (-2.8-4.9%)	Low
Ongoing pregnancy	1[5]	RCT	Serious[a]	Not serious	Serious[f]	Not serious	220	226	Immediate 3.6% vs. delayed 0.9%; difference (90% CI): 2.7% (0.4-5.6%)	Moderate

CI, confidence interval; COC, combined oral contraception; DMPA, depot medroxyprogesterone acetate; ENG, etonogestrel; RCT, randomized clinical trial.

Footnotes

[a]Risk of bias is considered serious due to the timing in delayed group not being described and ultrasound assessment not reported as blinded.

[b]Imprecision is considered very serious due to the 90% CI that includes both appreciable benefit and harm.

[c]Risk of bias is considered very serious due to no confounding assessment and few participants in delayed implant group had implant placed.

[d]Imprecision is considered serious due to the small sample size and no information given about power calculation.

[e]Risk of bias is considered very serious due to limited or no details on allocation concealment, participant rates, outcome assessment (blinding and criteria used), and COC adherence.

[f]Imprecision is considered serious due to the wide CI that does not include zero.

References

1. Raymond EG, Weaver MA, Tan YL, Louie KS, Bousiéguez M, Lugo-Hernández EM, et al. Effect of Immediate Compared With Delayed Insertion of Etonogestrel Implants on Medical Abortion Efficacy and Repeat Pregnancy: A Randomized Controlled Trial. Obstet Gynecol 2016;127:306-12. https://doi.org/10.1097/aog.0000000000001274
2. Hognert H, Kopp Kallner H, Cameron S, Nyrelli C, Jawad I, Heller R, et al. Immediate versus delayed insertion of an etonogestrel releasing implant at medical abortion-a randomized controlled equivalence trial. Hum Reprod 2016;31:2484-90. https://doi.org/10.1093/humrep/dew238
3. Barros Pereira I, Carvalho RM, Graça LM. Intra-abortion contraception with etonogestrel subdermal implant. Eur J Obstet Gynecol Reprod Biol 2015;185:33-5. https://doi.org/10.1016/j.ejogrb.2014.11.025
4. Martin CW, Brown AH, Baird DT. A pilot study of the effect of methotrexate or combined oral contraceptive on bleeding patterns after induction of abortion with mifepristone and a prostaglandin pessary. Contraception 1998;58:99-103. https://doi.org/10.1016/s0010-7824(98)00072-9
5. Raymond EG, Weaver MA, Louie KS, Tan YL, Bousiéguez M, Aranguré-Peraza AG, et al. Effects of Depot Medroxyprogesterone Acetate Injection Timing on Medical Abortion Efficacy and Repeat Pregnancy: A Randomized Controlled Trial. Obstet Gynecol 2016;128:739-45. https://doi.org/10.1097/aog.0000000000001627