Cohort Study
Potential PURL Review Form
PURL Jam Version
Version #12 Sept 20, 2010

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

1. Citation	Weill A, Dalichampt M, Raguideau F, Ricordeau P, Blotière PO, Rudant J, Alla F, Zureik M. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ. 2016 May 10;353:i2002. doi: 10.1136/bmj.i2002.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/?term=27164970
3. First date published study available to readers	5/10/2016
4. PubMed ID	27164970
5. Nominated By	Other Other: Stephen A. Wilson
6. Institutional Affiliation of Nominator	Other Other: UPMC
7. Date Nominated	8/5/2016
8. Identified Through	Other Other: BMJ
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	8/17/2016
11. Potential PURL Review Form (PPRF) Type	Cohort Study
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Anne Mounsey
14. Reviewer Affiliation	Other Other: UNC
15. Date Review Due	10/12/2016

16. Abstract

OBJECTIVE:
To assess the risk of pulmonary embolism, ischaemic stroke, and myocardial infarction associated with combined oral contraceptives according to dose of oestrogen (ethinylestradiol) and progestogen.
DESIGN:
Observational cohort study.
SETTING:
Data from the French national health insurance database linked with data from the French national hospital discharge database.
PARTICIPANTS:
4 945 088 women aged 15-49 years, living in France, with at least one reimbursement for oral contraceptives and no previous hospital admission for cancer, pulmonary embolism,

ischaemic stroke, or myocardial infarction, between July 2010 and September 2012.
MAIN OUTCOME MEASURES:
Relative and absolute risks of first pulmonary embolism, ischaemic stroke, and myocardial infarction.
RESULTS:
The cohort generated 5 443 916 women years of oral contraceptive use, and 3253 events were observed: 1800 pulmonary embolisms (33 per 100 000 women years), 1046 ischaemic strokes (19 per 100 000 women years), and 407 myocardial infarctions (7 per 100 000 women years). After adjustment for progestogen and risk factors, the relative risks for women using low dose oestrogen (20 µg v 30-40 µg) were 0.75 (95% confidence interval 0.67 to 0.85) for pulmonary embolism, 0.82 (0.70 to 0.96) for ischaemic stroke, and 0.56 (0.39 to 0.79) for myocardial infarction. After adjustment for oestrogen dose and risk factors, desogestrel and gestodene were associated with statistically significantly higher relative risks for pulmonary embolism (2.16, 1.93 to 2.41 and 1.63, 1.34 to 1.97, respectively) compared with levonorgestrel. Levonorgestrel combined with 20 µg oestrogen was associated with a statistically significantly lower risk than levonorgestrel with 30-40 µg oestrogen for each of the three serious adverse events.
CONCLUSIONS:
For the same dose of oestrogen, desogestrel and gestodene were associated with statistically significantly higher risks of pulmonary embolism but not arterial thromboembolism compared with levonorgestrel. For the same type of progestogen, an oestrogen dose of 20 µg versus 30-40 µg was associated with lower risks of pulmonary embolism, ischaemic stroke, and myocardial infarction.

17. Pending PURL Review Date: 10/12/2016

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

1 The study addresses an appropriate and clearly focused question.

☒ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments:

2 The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.

☐ Well covered ☐ Not addressed
☒ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments:

3 The study indicates how many of the people asked to take part did so, in each of the groups being studied

☐ Well covered ☐ Not addressed
☐ Adequately addressed ☐ Not reported
☐ Poorly addressed ☒ Not applicable
Comments: observational cohort study

4 The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.

☐ Well covered ☐ Not addressed
☒ Adequately addressed ☐ Not reported
☐ Poorly addressed ☐ Not applicable
Comments:

5 What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?

not applicable as this was an observational cohort study

6 Comparison is made between full participants and those lost to follow up, by exposure status.	☐ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments: observational cohort study	☐ Not addressed ☐ Not reported ☒ Not applicable
7 The outcomes are clearly defined.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable
8 The assessment of outcome is made blind to exposure status	☐ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments: observatinal cohort study	☐ Not addressed ☐ Not reported ☒ Not applicable
9 Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	☐ Well covered ☒ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable

10 What are the key findings of the study?	OCPs with low dose estrogen (20 microgram) in combination with any progesterone were less likely to cause pulmonary embolism and arterial thromboembolic events. Of all progesterones, levonorgestrel resulted in overall lowest risk for pulmonary embolism and arterial thormbembolism
11 How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests?	Funded by the French National Health Insurance Fund and the French National Agency for Medicins and Health Products Safety. The authors are employed by these agencies. No conflicts of interest declared or suspected.

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]

Citation Instructions

For UpTo Date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS as editor & current year as publication year.

EXAMPLE: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert dated modified if given.} Accessed February 12, 2009. {whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at: http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert dated modified if given.} Accessed June 5, 2009.{search date}

1. DynaMed excerpts

2. DynaMed citation/access date

Title. Author. In: DynaMed [database online]. Available at: www.DynamicMedical.com Last updated: . Accessed

3. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

4. UpToDate excerpts

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: . Accessed

6. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

7. PEPID PCP excerpts
www.pepidonline.com
username: fpinauthor
pw: pepidpcp

8. PEPID citation/access data

Author. Title. In: PEPID [database online]. Available at: http://www.pepidonline.com. Last updated: . Accessed

9. PEPID content updating

1. Do you recommend that PEPID get updated on this topic?
☐ Yes, there is important evidence or recommendations that are missing
☐ No, this topic is current, accurate and up to date.
If yes, which PEPID Topic, Title(s):

2. Is there an EBM Inquiry (HelpDesk Answers and Clinical Inquiries) as indicated by the EB icon (EB) that should be updated on the basis of the review?
☐ Yes, there is important evidence or recommendations that are missing
☐ No, this topic is current, accurate and up to date.
If yes, which Evidence Based Inquiry(HelpDesk Answer or Clinical Inquiry), Title(s):

10. Other excerpts (USPSTF; other guidelines; etc.)

11. Citations for other excerpts

12. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer; Revised by the Pending PURL Reviewer as needed]

1. Validity: How well does the study minimize sources of internal bias and maximize internal validity?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☐1 ☒2 ☐3 ☐4 ☐5 ☐6 ☐7

2. If 4.1 was coded as 4, 5, 6, or 7, please describe the potential bias and how it could affect the study

results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

3. Relevance: Are the results of this study generalizable to and relevant to the health care needs of patients cared for by "full scope" family physicians?

Give one number on a scale of 1 to 7
(1=extremely well; 4=neutral; 7=extremely poorly)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

4. If 4.3 was coded as 4, 5, 6, or 7, lease provide an explanation.

5. Practice changing potential: If the findings of the study are both valid and relevant, does the practice that would be based on these findings represent a change from current practice?

Give one number on a scale of 1 to 7
(1=definitely a change from current practice; 4=uncertain; 7=definitely not a change from current practice)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

6. If 4.5 was coded as 1, 2, 3, or 4, please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

7. Applicability to a Family Medical Care Setting:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, educating or counseling a patient; or creating a system for implementing an intervention?

Give one number on a scale of 1 to 7
(1=definitely could be done in a medical care setting; 4=uncertain; 7=definitely could not be done in a medical care setting)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

8. If you coded 4.7 as a 4, 5, 6 or 7, please explain. .

9. Immediacy of Implementation: Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug or other essentials available on the market?

Give one number on a scale of 1 to 7
(1=definitely could be immediately applied; 4=uncertain; 7=definitely could not be immediately applied)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

10. If you coded 4.9 as 4, 5, 6, or 7, please explain why.

11. Clinical meaningful outcomes or patient oriented outcomes: Are the outcomes measured in the study clinically meaningful or patient

Give one number on a scale of 1 to 7
(1=definitely clinically meaningful or patient oriented; 4=uncertain; 7=definitely not clinically meaningful or patient oriented)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

oriented?

12. If you coded 4.11 as a 4, 5, 6, or 7, please explain why.

13. In your opinion, is this a Pending PURL?
Criteria for a Pending PURL:

- Valid: Strong internal scientific validity; the findings appears to be true.
- Relevant: Relevant to the practice of family medicine
- Practice changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.
- Applicability in medical setting:
- Immediacy of implementation

Give one number on a scale of 1 to 7
(1=definitely a Pending PURL; 4=uncertain; 7=definitely not a Pending PURL)
☒1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

14. Comments on your response in 4.13

In our group faculty discussion majority agreed this is practice changing given clear benefits in a large cohort study to minimizing estrogen dosage and preferring levnorgestrel when possible to minimize risk of PE, MI and ischemic stroke

SECTION 4.1: Diving for PURLs
[optional for the potential PURL reviewer -if you wish to be the author on the summary]

1. Study Summary- Please summarize the study in 5-7 sentences

This study is an observational cohort study with 4,945,088 participants using combination oral contraceptives in a real life setting. Outcomes measured include relative risk of pulmonary embolism, myocardial infarction and ischemic stroke when comparing different combinations of estrogen dose with the same progesterone, and comparing across various progesterones. This study concludes that for the same progesterone, low dose estrogen (20 micrograms) results in lowest risk of adverse event (PE, MI, CVA). The study also concludes that of all progesterones studied, levonorgestrel resulted in lowest risk of adverse events (PE, MI, CVA).

2. Criteria- note yes or no for those which this study meets

RELEVENT - yes
VALID - yes
CHANGE IN PRACTICE- yes
MEDICAL CARE SETTING - yes
IMMEDIATELY APPLICABLE - yes
CLINICALLY MEANINGFUL - yes

3. Bottom Line- one –two sentences noting the bottom line recommendation

Recommendation: To reduce risk of PE, MI, CVA, prescribe combination oral contraceptives with low dose estrogen (20 micrograms) in combination with levonorgestrel.

4. Title Proposal

SECTION 5: Editorial Decisions
[to be completed by the FPIN PURLs Editor or Deputy Editor]

1. FPIN PURLs editorial decision (select one)

☐1 Pending PURL Review—Schedule for Review
☐ 2 Drop

☐ 3 Pending PURL

3. Follow up issues for Pending PURL Reviewer

3. FPIN PURLS Editor making decision

☐1 Bernard Ewigman
☐2 John Hickner
☐3 Sarah-Anne Schumann
☐4 Kate Rowland

4. Date of decision

5. Brief summary of decision

SECTION 6: Survey Questions for SERMO, PURLs Instant Polls and Other Surveys
[To be completed by the PURLs Survey Coordinator and PURLs Editor]

1. Current Practice Question for Surveys

2. Barriers to Implementation Question for Surveys

3. Likelihood of Change Question for Surveys

4. Other Questions for Surveys

SECTION 7: Variables for Secondary Database Analyses

1. Population: Age, gender, race, ethnicity

2. Diagnoses

3. Drugs or procedures

SECTION 8: Pending PURL Review Assignment
[to be completed by PURLs Project Manager

1. Person Assigned for Pending PURL Review

2. Date Pending PURL Review is due

SECTION 9: Pending PURL Review
[to be completed by the Pending PURL Reviewer]

1. Did you address the follow up issues identified at the PURL Jam (Section 5.2). Add comments as needed.

☐ Yes
☐ No
☒ Not applicable
Comments:

2. Did you review the Sermo poll & Instant Poll results (if available)? Add comments as needed.

- ☐ Yes
- ☐ No
- ☒ Not applicable

Comments:

3. Did you modify Sections 2, 3, or 4? Add comments as needed.

- ☐ Yes
- ☐ No
- ☐ Not applicable

Comments:

SECTION 10: PURL Authoring Template
[to be completed by the assigned PURL Author]

Author Citation Information (Name, Degrees, Affiliation)

1. Practice Changer

2. Illustrative Case

3. Background/
Clinical Context/Introduction/Current Practice/

4. Study Summary

5. What's New

6. Caveats

7. Challenges to Implementation

8. Acknowledgment Sentence

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center For Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources or the National Institutes of Health.

If using UHC data:
We acknowledge Sofia Medvedev of University HealthSystem Consortium (UHC) in Oak Brook, IL for analysis of the National Ambulatory Medical Care Survey data.

9. References