Metaanalysis – Systematic Review
Potential PURL Review Form
PURL Jam Version
Version #12 Sept 21, 2010

Another good reason to recommend low-dose aspirin
***J Fam Pract*. 2015;64:301-303.**

PURLs Surveillance System
Family Physicians Inquiries Network

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

1. Citation	Henderson JT, Whitlock EP, O'Conner E, Senger CA, Thompson JH, Rowland MG. Low-Dose Aspirin for the Prevention of Morbidity and Mortality From Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2014 Apr. PMID: 24783270.
2. Hypertext link to PDF of full article	http://www.ncbi.nlm.nih.gov/pubmed/24783270
3. First date published study available to readers	4/1/14
4. PubMed ID	24783270
5. Nominated By	Jim Stevermer Other:
6. Institutional Affiliation of Nominator	University of Missouri Other:
7. Date Nominated	6/28/14
8. Identified Through	InfoPOEMs Other:
9. PURLS Editor Reviewing Nominated Potential PURL	Kate Rowland
10. Nomination Decision Date	7/3/14
11. Potential PURL Review Form (PPRF) Type	Metaanalysis
12. Other comments, materials or discussion	
13. Assigned Potential PURL Reviewer	Liz Nuygen, MD
14. Reviewer Affiliation	University of Chicago Other:
15. Date Review Due	8/28/14
16. Abstract	OBJECTIVE: We conducted a systematic review of the evidence on the use of low-dose aspirin for the prevention of morbidity and mortality from preeclampsia to support the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendation. Prior reviews have established that benefits of aspirin prophylaxis are not obtained in populations of healthy or unselected pregnant women not at high risk of preeclampsia. In this review we considered the evidence on benefits and harms of low-dose aspirin for women at elevated risk of developing preeclampsia and consequent maternal and fetal health outcomes. Three key questions (KQs) were systematically reviewed:

1) Is there evidence that aspirin reduces adverse maternal or fetal health outcomes? 2) Is there evidence that aspirin reduces incidence of preeclampsia? and 3) What are the harms of low-dose aspirin use during pregnancy?
DATA SOURCES:
We identified nine existing relevant systematic reviews and performed a search of MEDLINE, the Database of Abstracts of Reviews of Effects, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published from January 2006 through 2013. We supplemented searches by examining bibliographies from previous systematic reviews and retrieved articles, previous USPSTF reviews, and consulting outside experts. We searched Federal agency trial registries for ongoing and/or unpublished trials.
STUDY SELECTION:
We conducted dual independent review of 544 abstracts against a priori inclusion and exclusion criteria. The 75 potentially relevant articles identified were then independently evaluated by two reviewers against the same inclusion/exclusion criteria and critically appraised for quality/risk of bias using USPSTF criteria. Discrepancies were resolved in discussion with a third reviewer. A single investigator extracted study characteristics and outcomes for all fair- to good-quality studies into tables and a second reviewer checked accuracy.
DATA ANALYSIS:
Evidence for all KQs was qualitatively synthesized. Quantitative synthesis of outcomes where there was sufficient data used random-effects meta-analysis models as the primary analysis. Analyses were stratified by the timing of aspirin administration and dosage, with statistical tests of strata differences conducted. Funnel plots and tests for small-study effects were conducted.
RESULTS:
One large U.S. study (n=2,539), one large international study based in the United Kingdom (n=9,364), and 13 smaller trials were included for evaluation of benefits of aspirin. Additionally, six randomized, controlled trials (RCTs) of women not at increased risk for preeclampsia contributed to the analysis of harms. Five of these studies were prophylaxis RCTs among women with low or average preeclampsia risk: a good-quality multisite study in the United States (n=3,135) and a smaller U.S. study (n=606), a good-quality multisite study in France and Belgium (n=3,294), a good-quality hospital-based study in Barbados (n=3,647), and a fair-quality U.K.-based study (n =122). The sixth study was a good-quality Australia-based RCT of fetal growth restriction treatment (n=51). Two observational studies were also included for the review of harms: a good-quality cohort study following 47,400 women enrolled during pregnancy and a good-quality case-control study based on data from a large prospective cohort study (n=3,129). Based on pooled results, low-dose aspirin administered after the first trimester of pregnancy to women at elevated risk of preeclampsia reduced the risk of preeclampsia by at least 10 percent (and perhaps 24%), with beneficial effects on

perinatal health outcomes; intrauterine growth restriction (IUGR) was reduced 20 percent and preterm birth an estimated14 percent, although the actual effect for these two outcomes may be more modest, given the possible bias due to small-study effects. Consistent with findings of lower rates of preterm birth and IUGR, birth weight averaged 130 g more in infants whose mothers took low-dose aspirin. We did not find evidence of serious harms from aspirin use (i.e., no effect on perinatal mortality), although power was limited for such a rare event. Individual trials were inconsistent, with nonstatistically significant findings in the direction of both modest benefit and modest harm; pooling of perinatal mortality findings suggested a tendency toward a reduced (rather than increased) risk of perinatal mortality (relative risk [RR], 0.92 [95% CI, 0.76 to 1.96]), particularly when analyses were limited to only women at increased risk of preeclampsia (RR, 0.81 [95% CI, 0.65 to 1.01]). Similarly, available evidence on intracranial fetal bleeding suggested no effect with low-dose aspirin (RR, 0.84 [95% CI, 0.61 to 1.16]). Although there was no overall effect of low-dose aspirin on several maternal harms (i.e., postpartum hemorrhage, Cesarean delivery), we could not eliminate the possibility of an increased risk of abruption because of power limitations and heterogeneity of risk for preeclampsia. Pooling limited to trials enrolling higher-risk pregnant women (the target for aspirin intervention) somewhat attenuated the potential for harm from abruption, but results remained heterogeneous. Two observational studies on aspirin use during pregnancy had null findings for the potentially harmful outcomes considered (miscarriage and cryptorchidism).

LIMITATIONS:

Very little new evidence has accrued since the completion of a number of large studies conducted in the 1990s. Since then there have been multiple systematic reviews, including one individual-level meta-analysis, and a few smaller trials (n<1,000). The serious health outcomes that are the aim of aspirin prophylaxis are rare and there is insufficient power, even in pooled analyses, to detect effects that could be clinically important. There is evidence of small-study bias in the evidence we reviewed, based on funnel plots, formal statistical tests, and observation of forest plots sorted by sample size, showing a clear decrease in effect size with increasing sample size. Given that the large studies are from multiple sites, they likely share some of the features of small studies in terms of study operations. Those studies combined in the large multisite trials, however, are necessarily reported in the literature regardless of results, whereas null findings of small independent trials may be less likely to publish null results. Trial characteristics cannot always be disentangled from study size due to the presence of small-study effects. The ability to draw conclusions related to dosage from the available trial evidence is limited by the fact that the two largest studies used 60 mg of aspirin, although they differed on other important characteristics. Thus, stratification by dosage is potentially confounded; the apparent benefit of a dose

greater than 75 mg found in other systematic reviews could be due either to the small sample effect, a true dose effect, or a combination of these factors.
CONCLUSIONS:
For women at elevated risk of preeclampsia, prophylaxis with low-dose aspirin (60 to 150 mg) beginning after the first trimester of pregnancy reduced risk of preeclampsia and important adverse perinatal health outcomes. Specifically, modestly reduced risks of preterm birth, IUGR, and possibly perinatal mortality were supported by the evidence. Consistent with lower risk of preterm birth and IUGR, a significant difference in birth weight was also present. Statistical significance was not attained for the estimated 19 percent reduction in risk of perinatal mortality, although power to detect this difference was under 50 percent; there is a risk of incorrectly accepting a null result for perinatal mortality based on currently available data. The effects on perinatal mortality observed in the two largest trials were consistent with a benefit, although more modest. The pooled results finding reduced risk of preeclampsia with low-dose aspirin supports the causal pathway leading to the observed direct health outcomes. The pooled results may have overestimated the benefit, however, given the evidence of small-study effects and more modest results in the two largest trials. However, given the consistency of the effect size in the large trials and the results of pooled analysis, at least a 10 percent reduction in preeclampsia was supported by the evidence. This reduction in preeclampsia incidence likely underlies the observed perinatal health benefits. There was limited evidence of harms associated with low-dose aspirin use during pregnancy. A potential increased risk of abruption could not be ruled out, but evidence of harm from other bleeding-related complications, such as postpartum hemorrhage, maternal blood loss, and neonatal intracranial or intraventricular bleeding was not found. The evidence on longer-term outcomes for offspring from in utero aspirin exposure (low-dose) is very limited, but followup data from one large randomized, controlled trial is reassuring.

17. Pending PURL Review Date

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

1. What types of studies are included in this review?

RCT Other: also were reviewed were large observational studies but these were not included in the pooled analyses

2. What is the key question addressed by this review? Summarize the main conclusions and any strengths or weaknesses.

3 key quesitons were being addressed: Does low dose aspirin reduce adverse maternal and fetal health outcomes among women at high risk for pre-emclampsia? Does low dose aspirin prevent preeclampsia? Does low does aspirin use during pregnancy cause harm to the mother and fetus/

3. Study addresses an appropriate and clearly focused question - ***select one***

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

Comments:

4. A description of the methodology used is included.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable
5. The literature search is sufficiently rigorous to identify all the relevant studies.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable
6. Study quality is assessed and taken into account.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable
7. There are enough similarities between selected studies to make combining them reasonable.	☒ Well covered ☐ Adequately addressed ☐ Poorly addressed Comments:	☐ Not addressed ☐ Not reported ☐ Not applicable
8. Are patient oriented outcomes included? If yes, what are they?	Yes, preeclampsia, hemorrhage, placental abruption, maternal and fetal death, low birthweight, preterm birth, IUGR	
9. Are adverse effects addressed? If so, how would they affect recommendations?	Yes, had aspirin was shown to cause harm, the recommendation would be to avoid aspirin in pregnancy	
10. Is funding a potential source of bias? If yes, what measures (if any) were taken to insure scientific integrity?	No	
11. To which patients might the findings apply? Include patients in the meta-analysis and other patients to whom the findings may be generalized.	Pregnant women at high risk for preeclampsia	
12. In what care settings might the findings apply, or not apply?	In any practice setting providing prenatal care for a high-risk population	
13. To which clinicians or policy makers might the findings be relevant?	Family medicine physicians doing high-risk ob, OB-Gyne physicians	

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: Feb 2014. Accessed October 2014

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

Give low dose aspirin at < _16 weeks in pregnant women at high risk for preeclampsia

4. UpToDate excerpts

5. UpToDate citation/access date

Always use Basow DS as editor & current year as publication year.
Title. Preeclampsia: Prevention Author. Phyllis August In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: September 19, 2014. AccessedOctober 23, 2014

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

Give low dose aspirin to pregnanst women with moderate to high risk of preeclamsia as it reduces the risk of preeclamsia along with adverse pregnancy outcomes like preterm delivery and IUGR.

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]
[to be 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.

The recommendation would be for family medicine physicians caring for women at high risk for preeclampsia to start low dose aspirin at 16 weeks gestation until delivery.

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 oriented?

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

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

Validity is the weakest issue in this study given the high heterogeniety and the potential bias from smaller, lower quality studies.