Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Acyclovir versus Valacyclovir for Herpes Virus in Children and Pregnant Women: A Review of the Clinical Evidence and Guidelines

DATE: 5 September 2014

CONTEXT AND POLICY ISSUES

Acyclovir and valacyclovir are antivirals active against Herpes Simplex Viruses (HSV) 1 and 2 and Varicella Zoster Virus.[1,2] Valacyclovir is a pro-drug of acyclovir. It is rapidly and nearly completely converted to acyclovir and L-valine (an essential amino acid) by first-pass metabolism.[2,3]

Pregnancy is listed as a warning/precaution in the Zovirax product monograph (the brand name of acyclovir). The monograph states that although post-market data does not point towards an increased risk of birth defects, acyclovir should not be used in pregnancy unless judged to be appropriate by the physician considering the potential benefits and harms.[1] Similarly, the Valrex (valacyclovir) product monograph lists pregnancy in their warnings and precautions section, stating that conclusions cannot be drawn as to the safety of valacyclovir in pregnancy because only a small number of women have been enrolled into the valacyclovir pregnancy registry.[2] Briggs' *Drugs for Pregnancy and Lactation* rates both acyclovir and valacyclovir as 'compatible' with pregnancy, noting that there is no evidence of major birth defects with either agent, and that "although the experience with valacyclovir in early pregnancy is limited, many studies have reported the use of acyclovir during all stages of pregnancy."[3] With respect to use in children, according to the product monographs, safety and effectiveness of Zovirax (acyclovir) has not been established in children less than 2 years of age,[1] whereas Valtrex (valacyclovir) safety and effectiveness has not been established in children less than 12 years of age.[2]

Both varicella (chickenpox) and herpes zoster (shingles) are caused by Varicella Zoster Virus.[4] Chickenpox is most commonly seen in early childhood, with 90% of cases occurring in children 14 and under. A Cochrane review (search date 2004) aiming to assess the efficacy of oral acyclovir in children with chickenpox did not find a statistically significant reduction in the number of days to no new lesions, however, acyclovir statistically significantly decreased the number of days to no fever and the number of lesions.[5] The authors note that the modest benefits in this mild self-limiting disease along with the impracticality of initiating antivirals within 24h of onset of rash are important limitations to the use of antivirals in otherwise healthy

children with chickenpox.[5] Complications of chickenpox in healthy children are rare and are more common in neonates, adults, and immunocompromised individuals.[4,5] Although rates of chickenpox are not higher in pregnancy than in healthy adults, with an estimated incidence of 0.7 to 3 per 1000 pregnancies, pregnant women are at higher risk of complications. A potentially severe complication of chickenpox, varicella pneumonia, occurs in an estimated 10-20% of pregnant women with chickenpox. In addition to the risk of morbidity and mortality to the pregnant mother, maternal chickenpox poses a risk of neonatal varicella if the mother acquires the infection immediately pre- or post-delivery, herpes zoster in infancy, or congenital varicella syndrome if the maternal infection occurs earlier on in the pregnancy. Herpes Zoster (shingles) in pregnancy is not associated with congenital varicella and is less contagious than chickenpox.[4]

Genital herpes can be caused by either HSV-1 or HSV -2.[6] The primary concern with genital herpes in pregnancy is possible transmission to the neonate with vaginal delivery.[6,7] The risk of neonatal transmission is much higher in women who first acquire genital herpes near the time of delivery as compared to women with a history of recurrent infections or who acquire the disease earlier in the pregnancy (30-50% vs <1%),[8] however first or primary infections near the time of delivery are rare.[6,8] A 2008 Cochrane review assessing the effectiveness of antivirals for prophylaxis of recurrent herpes in the third trimester included five randomized controlled trials (RCTs) of acyclovir and two of valacyclovir vs placebo or no treatment.[9] In a total of 1249 participants, there were no cases of symptomatic neonatal herpes. Overall, antiviral treatment decreased the risk of recurrent infection at term and subsequent cesarean section for genital herpes, with a relative risk (RR) of 0.28 (95% confidence interval [CI] 0.18 to 0.43) and 0.30 (95% CI 0.20 to 0.45), respectively. The most common manifestation of primary HSV-1 is mucocutaneous herpes. Severe manifestations of disease such as gingivomastitis and pharyngitis are more commonly seen in young children (age 1-6), and most clinical trial data assessing antiviral treatments is in this population.[10]

Although acyclovir has traditionally been seen as the drug of choice in pregnancy and pediatrics, valacyclovir has the benefit of decreased dosing frequency and potential increased compliance as a result. This report aims to review recent evidence and relevant practice guidelines on the comparative effectiveness of acyclovir and valacyclovir in children with chickenpox and in pregnant women with Herpes Simplex Virus infections, chickenpox and shingles.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes zoster infection?

2. What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with chicken pox?

3. What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes simplex virus?

4. What is the comparative clinical effectiveness of acyclovir versus valacyclovir in children with chicken pox?

5. What are the evidence-based guidelines for the use of acyclovir and valacyclovir for herpes virus or chicken pox in pregnant women and children?

KEY FINDINGS

In the last five years there has been very limited new evidence on the effectiveness of oral antivirals in children with chickenpox, pregnant women with herpes simplex virus, pregnant women with herpes zoster, or pregnant women with chickenpox.

In children with chickenpox acyclovir was shown to be effective, although clinical significance in otherwise healthy children is questionable. No evidence on the comparative effectiveness of valacyclovir in this population was identified.

There is RCT data supporting efficacy of both acyclovir and valacyclovir in pregnancy for suppression of recurrent genital herpes.

Although available data are reassuring as to the safety of valacyclovir in pregnancy, there is substantially more experience with acyclovir.

Recent practice guidelines for the treatment of both chickenpox and genital herpes in pregnancy consistently recommend acyclovir for certain clinical scenarios. Many of these guidelines also present valacyclovir as an option.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 8, 2014.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Pregnant women with: Herpes zoster infection (varicella zoster virus or shingles) Chicken pox Herpes simplex virus (types 1 & 2) in genital or mucocutaneous herpes Children with chicken pox
Intervention	Acyclovir
Comparator	Valacyclovir
Outcomes	Clinical effectiveness, safety, guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines

Exclusion Criteria

Reports not meeting selection criteria as outlined in Table 1, and reports published prior to 2009 or in languages other than English were excluded.

Critical Appraisal of Individual Studies

The quality of included studies was assessed using the Downs and Black checklist for the included non-randomized study,[11] AMSTAR for the included systematic reviews,[12] and AGREE II for practice guidelines.[13] A numeric score was not calculated for each study, instead strengths and limitations were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

The database search retrieved 371 reports, of which 8 were retrieved for full-text review after title and abstract screening. An additional 12 potentially relevant reports were identified in the grey literature search. After full-text review a total of 11 reports were included: Two reports relevant to pregnant women with chickenpox (both guidelines), seven reports relevant to pregnant women with herpes simplex virus (six guidelines and one systematic review), one report relevant to children with chickenpox (a systematic review), no reports relevant to pregnant women with shingles, and a cohort study reporting on safety of antivirals across indications in pregnant women. See Appendix 1 for a PRISMA flowchart outlining the study selection process.[14]

Summary of Study Characteristics

See Appendix 2 for a summary of characteristics of individual included studies.

What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes zoster infection?

No relevant studies or guidelines were identified, apart from a cohort study assessing safety of antivirals in pregnancy across indications (described below).

What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with chicken pox?

No relevant studies were identified, apart from a cohort study assessing safety of antivirals in pregnancy across indications. Two relevant practice guidelines were identified (described below).

What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes simplex virus?

A single relevant systematic review with a search date of January 2010 was identified.[15] An objective of this study was to answer, among other questions, "what are the effects of interventions to prevent transmission of herpes simplex virus from mother to neonate?" Eligible studies were systematic reviews as well as blinded RCTs with >20 participants and >80% follow-up.

What is the comparative clinical effectiveness of acyclovir versus valacyclovir in children with chicken pox?

A single systematic review with a search date of June 2010 was identified.[16] This study aimed to answer, among others questions, "what are the effects of treatments for chickenpox in [otherwise] healthy adults and children?" Eligible studies were systematic reviews as well as blinded RCTs with >20 participants and >80% follow-up.

Safety in pregnancy across indications.

A historical cohort study of 837,795 infants born in Denmark between January 1996 and September 2008 aimed "to investigate the risk of any major birth defects" associated with use of acyclovir, valacyclovir, or famciclovir in the first trimester of pregnancy, using nationwide registry data."[17] Infants exposed to antivirals were compared to unexposed infants. A comparison of exposure in second and third trimesters, and 4 weeks prior to conception was also performed.

What are the evidence-based guidelines for the use of acyclovir and valacyclovir for herpes virus or chicken pox in pregnant women and children?

Six practice guidelines addressing treatment of genital herpes in pregnancy[8,18-22] and two addressing treatment of chickenpox in pregnancy[23,24] were identified. All of the included guidelines were published in 2012 or earlier. The Public Health Agency of Canada (PHAC) guidelines for the management of sexually transmitted infections, which address antiviral treatment of genital herpes in pregnancy, are published in an online "Evergreen edition": a 2010 document is being updated with new content posted as it becomes available.[25] The American College of Obstetricians and Gynecologists (ACOG) guidelines for the Management of Herpes in Pregnancy were published in 2007,[22] however the ACOG reaffirmed the currency of the guidelines in 2012 after an updated literature search and review by the guideline committee.[26] Five of the included guidelines provided grading of recommendations and/or levels of evidence.[18,20,22,23,25] (see Appendix 3).

Summary of Critical Appraisal

See Appendix 4 for a summary of strengths and limitations of included reports.

The two included systematic reviews[15,16] were of poor quality. They both performed a GRADE evaluation of evidence for each intervention, however they both had several limitations: results of quality assessment of individual studies was not reported, criteria for selection of studies was unclear, characteristics of included studies were not provided, a detailed search strategy was not provided, and study selection was not performed independently by at least two reviewers (an information specialist pre-selected studies for potentially eligibility after screening abstracts retrieved by the literature search, and a single reviewer determined eligibility).

Although it was not randomized, the cohort study assessing the risk of major birth defects with antivirals was of good quality. There was complete one-year follow-up, and a number of potential confounding variables were adjusted for, including birth year, measures of socioeconomic status, maternal smoking status, ethnicity, and use of other medications.[17] The study was large, with over 800,000 births total, however the number of women exposed to valacyclovir was low at only 229, versus 1561 for acyclovir. This is reflected by the wider confidence intervals for the odds ratio estimate for major birth defects with valacyclovir. Exposure was determined by a prescription drug register, so there is potential bias related to misclassification of exposure status; it was not known whether the drugs were taken as prescribed.

Of the seven practice guidelines for which the AGREE II criteria was able to be applied, three (all concerning pregnant women with genital herpes) were of fair quality,[8,22,25] while four were of poor or very poor quality.[18,21,23,24] The AGREE II criteria was not applied to the Alberta guidelines for sexually transmitted infections[20] since they were adapted from the included PHAC guidelines.[19] With the exception of the CDC practice guidelines for the management of sexually transmitted infections,[8] descriptions of guideline development were consistently poor according to the AGREE II criteria. This domain includes: the use of systematic methods to search for evidence; the clear description of criteria for selection of evidence; strengths and limitations of the body of evidence; methods for formulating recommendations; consideration of benefits, side

effects and risks; explicitly linking recommendations and evidence; external review by experts; and, having a procedure in place for updating the guidelines.[13] Specifically, although New Zealand's guidelines for the management of genital herpes[21], the South Australian chickenpox guidelines[24] and PHAC's sexually transmitted infection guidelines[25] state that their recommendations are based on evidence, there is no description of the retrieval or selection of evidence for use in the guidelines. The SOGC guidelines for the treatment of chickenpox[23] and European guidelines for the treatment of genital herpes[18] each state that a literature search was performed but a description of the search is not provided and the process of selection of evidence is not described. The CDC[8] and ACOG[22] guidelines for the management of genital herpes each provided a description of the literature search, but only the CDC guidelines described a process of selection of evidence for inclusion in the guidelines. The methods used to formulate recommendations are not described in any of the included guidelines with the exception of the CDC guidelines.[8]

Summary of Findings

> *What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes zoster infection?*

No relevant studies or guidelines were identified, apart from a cohort study assessing safety of antivirals in pregnancy across indications (described below).

> *What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with chicken pox?*

No relevant studies were identified, apart from a cohort study assessing safety of antivirals in pregnancy across indications and two practice guidelines (described below).

> *What is the comparative clinical effectiveness of acyclovir versus valacyclovir in pregnant women with herpes simplex virus?*

The single relevant systematic review[15] included one study, which was a Cochrane review with a 2007 search date.[9] The systematic review reported the results of the Cochrane review: The Cochrane review included 7 RCTs with a total of 1249 pregnant women with a history of genital herpes at 36 weeks gestation. There were no cases of neonatal herpes in any of the RCTs. Antiviral prophylaxis with both acyclovir (in five RCTs with 799 women, RR 0.25 95% CI 0.15 to 0.43 vs placebo) and valacyclovir (two RCTs with 450 women, RR 0.34 95% CI 0.17 to 0.68 vs placebo) effectively decreased the risk of recurrence of genital herpes at delivery. The risk of caesarean delivery was also reduced with antiviral prophylaxis by both acyclovir (RR 0.27 95% CI 0.16 to 0.46) and valacyclovir (RR 0.35 95% CI 0.17 to 0.70).[9] This systematic review concluded, based on the Cochrane review, that there is high-quality evidence that acyclovir and valacyclovir reduce the risk of recurrence of infection and resulting caesarian section at term, and there is insufficient evidence to form conclusions regarding the possible transmission of herpes from mother to neonate owing to the rarity of neonatal herpes. The included Cochrane review did not pool data on adverse effects. The two RCTs reporting on neonatal adverse events were underpowered to detect rare neonatal or maternal adverse events. One of the included RCTs reported higher levels of aspartate aminotransferase in placebo group infants than in those receiving valacyclovir, however another RCT reported no difference between groups for this outcome. No evidence of differences in maternal renal function between groups

was noted in one included RCT, and a lack of hematological and biological toxicity was noted in another included RCT.[15]

What is the comparative clinical effectiveness of acyclovir versus valacyclovir in children with chicken pox?

This identified systematic review[16] included one study relevant to this research question, which was a Cochrane review with a 2004 search date assessing acyclovir vs placebo in healthy children.[5] The Cochrane review included three RCTs of acyclovir within 24 hours of rash onset vs placebo in a total of 979 children and adolescents. The Cochrane review found a statistically significant weighted mean difference of -1.1 days (95% CI -1.3 to -0.9) for duration of fever, but the reduction in the primary outcome of time to new lesions (-0.8 days, 95% CI -1.6 to 0.02) was not statistically significant. There were no statistically significant differences in adverse effects.[5] This systematic review concluded, based on the included Cochrane review, that there is high quality evidence for the efficacy of acyclovir for the reduction in duration of fever, and that acyclovir is no more effective than placebo for the decreasing the time to no new lesions in children with chickenpox. This systematic review found no eligible studies assessing valacyclovir for chickenpox in healthy or immunocompromised adults or children.[16]

Safety in pregnancy across indications.

A nationwide Danish cohort study found that 2.4% babies of unexposed mothers were diagnosed with a major birth defect by age one, as compared to 2.2% of the 1804 pregnancies exposed to any of the antivirals (adjusted odds ratio 0.89, 95% CI 0.65 to 1.22).[17] Individually, exposure to acyclovir (n=1561) and valacyclovir (n=229) in the first trimester were not statistically significantly associated with major birth defects, with an adjusted odds ratio of 0.82 (95% CI 0.57 to 1.17) for acyclovir and 1.21 (95% CI 0.56 to 2.62) for valacyclovir. It is worth noting that the sample size for valacyclovir was much smaller, resulting in a wider confidence interval. Results for second and third trimester exposure were similar. Although the data is reassuring, moreso for acyclovir than valacyclovir, a potentially clinically significantly increased risk of major birth defects cannot be ruled out on the basis of this study.

What are the evidence-based guidelines for the use of acyclovir and valacyclovir for herpes virus or chicken pox in pregnant women and children?

Two guidelines address management of chickenpox in pregnancy. The SOGC guidelines recommend oral antivirals for “significant” varicella infection in pregnancy and give acyclovir as an example with no mention of valacyclovir,[23] whereas the South Australian guidelines recommend oral antivirals, either acyclovir or valacyclovir, within 24h of onset of rash.[24].

Six guidelines address the management of genital herpes in pregnancy. All of the included guidelines suggest suppressive oral antivirals late in pregnancy (i.e. from 36 weeks to term) for certain indications, including women with a history of recurrent genital herpes or genital herpes acquired earlier in the pregnancy. Three of the guidelines recommend acyclovir specifically,[8,18,21] two do not give preference to a particular antiviral,[19,22] and one recommends acyclovir with a higher grading of recommendation than valacylcovir.[20] Six of the included guidelines also

address treatment of first episode or recurrent episodes of genital herpes in pregnancy: four specifically recommend acyclovir,[8,18,19,21] and two do not preferentially recommend either oral antiviral.[20,22]

Also see Appendix 5 for relevant recommendations from the included guidelines.

Limitations

Valacyclovir and acyclovir have not been directly compared in randomized trials addressing any of the research questions, therefore no conclusions can be drawn as to their comparative effectiveness.

Randomized controlled trials are typically of insufficient size and duration to adequately assess safety in pregnancy. Although the recent cohort study included in this review was of good quality, lack of randomization leads to potential residual confounding and the number of women exposed to valacyclovir was small (n=229).

All of the included practice guidelines were weak in several AGREE II instrument domains. It is reassuring, however, that recommendations were fairly consistent across guidelines.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Available RCT data supports the efficacy of both acyclovir and valacyclovir for suppression of recurrent genital herpes at term compared to placebo, however no RCTs directly comparing acyclovir and valacylcovir were identified. No studies assessing the efficacy of oral antivirals for chickenpox or shingles in pregnancy were identified. Although available evidence suggests that valacyclovir is safe in pregnancy, there is substantially more data and experience with acyclovir. It is likely that many clinicians and patients would prefer acyclovir over valacyclo{ir in pregnancy for this reason, and this is reflected in many recent practice guidelines.

There is a lack of data concerning the use of valacyclovir in children, whereas RCT data supports the efficacy of acyclovir for symptomatic treatment of chickenpox in children.

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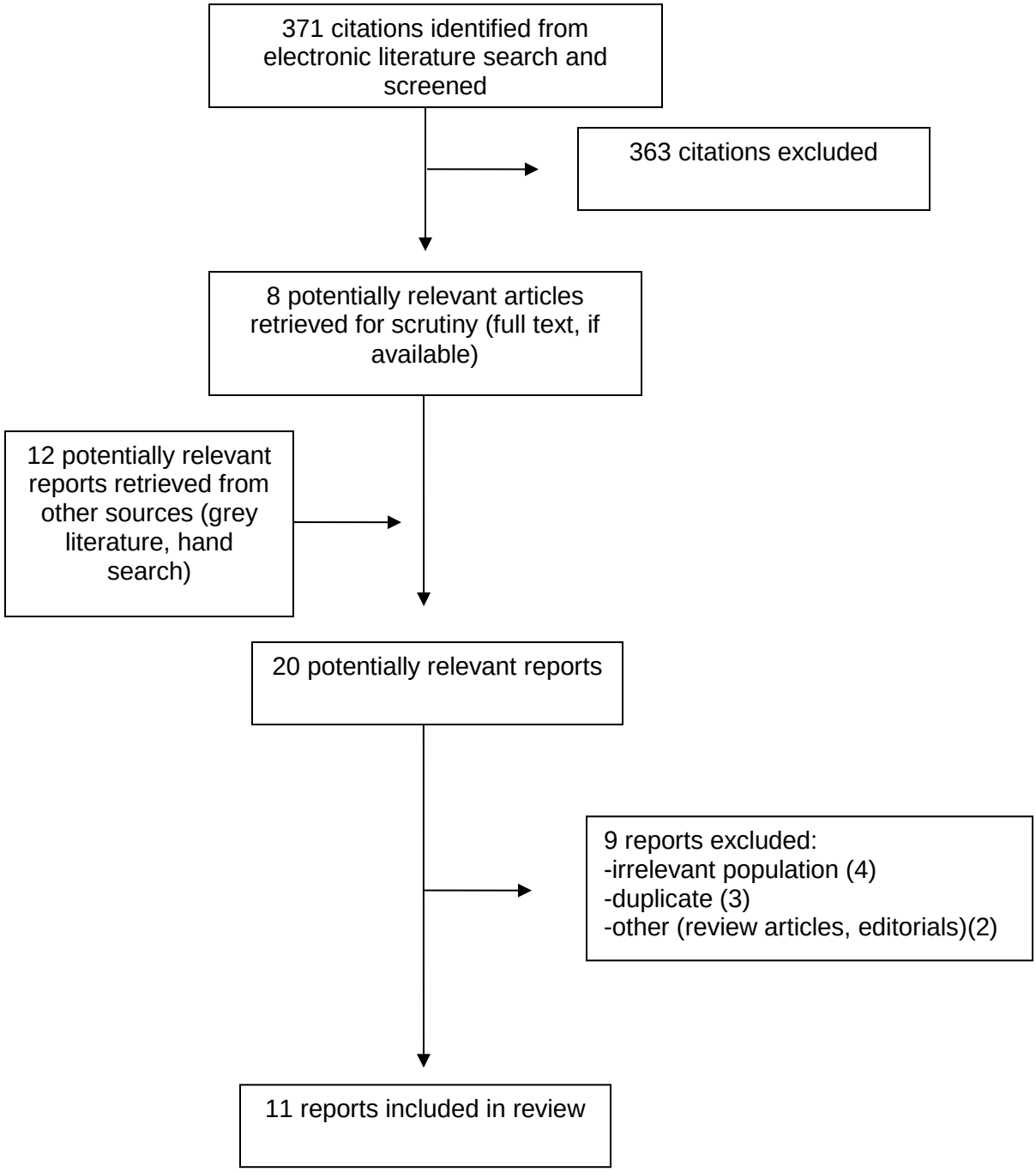
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics

Characteristics of included studies					
First author, Publication year	**Study Design**	**Population**	**Intervention**	**Comparator**	**Outcome Measures**
Holler, 2011[15]	Systematic Review	Pregnant women >36 weeks with a history of genital herpes	Antivirals (acyclovir, valacyclovir)	Placebo	Rates of neonatal herpes, rate of recurrent genital herpes at term, rate of caesarean delivery for genital herpes, adverse effects
Breuer, 2011[16]	Systematic Review	Healthy children with chickenpox	Acyclovir, valacyclovir	Placebo	Duration of illness, mortality, rate of chickenpox, complications of chickenpox, disease severity, adverse effects
Pasternak, 2010[17]	Cohort Study	All infants born alive in Denmark January 1st 1998 to September 30th 2008	Acyclovir, valacyclovir, famciclovir	Infants of mothers who received none of these antivirals	Major birth defects

APPENDIX 3: Guidelines' Grading of Recommendations and Levels of Evidence

Grading of recommendations and levels of evidence in included guidelines		
Guideline, society or institute, year	**Grading of recommendations**	**Level of evidence**
Society of Obstetricians and Gynaecologists of Canada (SOGC), Shrim 2012[23]	A . There is good evidence to recommend the clinical preventive action B . There is fair evidence to recommend the clinical preventive action C . The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D . There is fair evidence to recommend against the clinical preventive action E . There is good evidence to recommend against the clinical preventive action L . There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making	I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well–designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
South Australian Maternal & Neonatal Clinical Network, 2013[24]	None	None
International Union Against Sexually Transmitted Infections, Patel 2010[18]	A. Evidence at level Ia or Ib B. Evidence at level IIa, IIb or III C. Evidence at level IV	Ia: Meta-analysis of randomized controlled trials Ib: At least one randomized controlled trial IIa: At least one well designed controlled study without randomization IIb: At least one other type of well-designed quasi-experimental study III: Well-designed non-experimental descriptive studies IV: Expert committee reports or opinions of respected authorities
Public Health Agency of Canada (PHAC), 2010[25]	A. Strongly recommends that clinicians routinely provide the treatment to eligible patients. Good evidence that the treatment improves important health outcomes and concludes that benefits substantially outweigh harms B. Recommends that clinicians routinely provide the treatment to	I: Evidence from at least one properly randomized, controlled trial II: Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies or from

Grading of recommendations and levels of evidence in included guidelines		
Guideline, society or institute, year	**Grading of recommendations**	**Level of evidence**
	eligible patients. At least fair evidence that the treatment improves important health outcomes and concludes that benefits outweigh harms C. No recommendation for or against routine provision of the treatment. At least fair evidence that the treatment can improve health outcomes but concludes that the balance of the benefits and harms is too close to justify a general recommendation D. Recommends against routinely providing the treatment to asymptomatic patients. At least fair evidence that the treatment is ineffective or that harms outweigh benefits L. Evidence is insufficient to recommend for or against routinely providing the treatment. Evidence that the treatment is effective is lacking, of poor quality or conflicting, and the balance of benefits and harms cannot be determined	dramatic results in uncontrolled experiments III: Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
Alberta, 2012[20]	As above. These guidelines were adapted from PHAC guidelines.[25]	
Centers for Disease Control and Prevention (CDC), 2010[8]	None	None
New Zealand Herpes Foundation, 2012[21]	None	Grade A: Very strong evidence. Based on well-designed prospective randomized controlled clinical trials. Grade B: Fairly strong evidence. Based on evidence from case-control or cohort studies, or clinical trials lacking one or more of the above features. Grade C: Weak evidence or firmly held opinion. Based on published case reports, well-written reviews or consensus.
American College of Obstetricians and	Level A. Recommendations are based on good and consistent scientific evidence. Level B. Recommendations are based on limited or inconsistent scientific	I: Evidence obtained from at least one properly designed RCT. II-1: Evidence obtained from well-designed controlled trials without randomization.

Grading of recommendations and levels of evidence in included guidelines		
Guideline, society or institute, year	**Grading of recommendations**	**Level of evidence**
Gynecologists (ACOG), 2007[22]	evidence. Level C. Recommendations are based primarily on consensus and expert opinion.	II-2: Evidence obtained from well-designed cohort of case-control analytic studies, preferably from more than one center or research group. II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

APPENDIX 4: Summary of Critical Appraisal of Included Reports

Summary of strengths and limitations of included studies and guidelines		
First author, Publication year, Study Design	**Strengths**	**Limitations**
Hollier, 2011[15] **Sytematic Review**	-GRADE evaluation of quality of evidence was performed for each intervention	-Unclear methods for determination of study eligibility (included one systematic review) -Study selection was not performed in duplicate -Quality assessment of individual studies was not provided -No summary of characteristics of included studies was provided
Breuer, 2011[16] **Systematic Review**	-GRADE evaluation of quality of evidence was performed for each intervention	-Unclear methods for determination of study eligibility (included one systematic review) -Study selection was not performed in duplicate -Quality assessment of individual studies was not provided -No summary of characteristics of included studies was provided
Pasternak, 2010[17] **Cohort study**	-Complete follow-up -Large sample size for acyclovir -Description of adjustment for potential confounding variables	-Non-randomized (cohort study) -Prescription data was used to determine drug exposure -Lack of blinded endpoint evaluation -Small sample size for valacyclovir
Shrim, 2012[23] **Practice Guideline**	-Key recommendations are clearly identified -Grading of recommendations and level of evidence was provided	-Non-specific recommendations -No description of how recommendations were developed and minimal description of the literature search -Limitations of available evidence were not discussed
South Australian Maternal & Neonatal Clinical Network, 2013[24] **Practice Guideline**	-Developed recently with a planned update in 2016	- No description of literature search, selection of evidence, or guideline development -No review of available evidence -No grading of recommendations
Patel, 2010[18] **Practice Guideline**	-Provided grading of recommendations and level of evidence	No description of the process of guideline development -Evidence not presented -No description of process for selection of evidence

Summary of strengths and limitations of included studies and guidelines		
First author, Publication year, Study Design	**Strengths**	**Limitations**
		-Recommendations are not easily identifiable and are unclear
Public Health Agency of Canada, 2010[25] **Practice Guideline**	-Provided grading of recommendations with level of evidence; supplemental resources provided; information is easily navigated online; externally reviewed	- No description of literature search, selection of evidence, or guideline development
Alberta, 2012[20] **Practice Guideline**	Did not assess. These guidelines are adapted from PHAC 2010 [25] (see above)	
Centers for Disease Control and Prevention (CDC), 2010[8] **Practice Guideline**	-Systematic literature review described -Brief discussion of evidence within each section with more detail presented in separate publications	-No grading of recommendations or level of evidence -Key recommendations not clearly identifiable
New Zealand Herpes Foundation, 2012[21] **Practice Guideline**	-Incorporation of patient input is evident	-No description of literature search, selection of evidence, or guideline development -No list of authors, contributors or reviewers or information re: potential conflicts of interest
American College of Obstetricians and Gynecologists, 2007,reaffirmed 2012[22] **Practice Guideline**	-Objectives clearly described -Level of evidence and grading of recommendations provided	-Method for formulating recommendations not described -Non-specific recommendations -No list of authors, contributors or reviewers or information re: potential conflicts of interest

Appendix 5:Summary of Relevant Recommendations From Included Guidelines

Relevant recommendations from included guidelines	
Chickenpox in pregnancy	**Society of Obstetricians and Gynecologists of Canada (SOGC) Clinical Practice Guidelines for Management of Chickenpox in Pregnancy, 2012:[23]** -"Women with significant (e.g. pneumonia) varicella infection in pregnancy should be treated with oral antiviral agents (e.g. acyclovir 800mg 5 times daily)(IIIC)".(page 288) These guidelines note that "data…do not indicate increased adverse events related to [acyclovir] use in pregnancy." There is no mention of valacyclovir or its safety in pregnancy. These guidelines do not address shingles in pregnancy, as it "is not associated with viremia and does not appear to cause fetal sequelae."[23](page 290) **South Australian perinatal practice guideline – varicella zoster (chicken pox) in pregnancy, 2013[24]** -For management of varicella zoster in pregnancy, if it has been less than 24h since the appearance of rash: oral acyclovir 800 mg 5 times a day for 7 days OR oral valacyclovir 1 g three times a day for 7 days; no antivirals if >24 hours since appearance of rash.[24](page 4)
Genital herpes in pregnancy	**European guidelines for the management of genital herpes, 2010**[18] -For first and second trimester acquisition of genital herpes "suppressive acyclovir 400mg three times daily from 36 weeks gestation may prevent HSV lesions at term (Ib, B)." The same recommendation for third trimester acquisition has an evidence rating of (IV, C) and a rating of (Ia, A) for women with a history of recurrent genital herpes. -For management of recurrent infection in early pregnancy, "newer antivirals should be avoided and the dose of [acyclovir] titrated down to the minimum effective level" if antivirals are used.[18] **Canadian guidelines on sexually transmitted infections from the Public Health Agency of Canada (PHAC), 2010**[19,25] -Acyclovir 200mg four times daily, acyclovir 400mg three times daily, or valacyclovir 500mg twice daily starting at 36 weeks gestation until delivery for women who have had an outbreak within the previous year.[A-1] -Acyclovir 200mg orally five times per day for 5-10 days for treatment of primary infection during pregnancy.*[A-I]*[19] **Alberta treatment guidelines for sexually transmitted infections (STI) in adolescents and adults, 2012[20]** -Suppressive therapy with acyclovir 400 mg orally three times daily initiated at 36 weeks until parturition [A-I] or valacyclovir 500 mg orally twice daily initiated at 36 weeks until parturition [B-I] to reduce possible transmission to neonate. -Antiviral therapy may be initiated earlier in pregnancy in patients experiencing symptomatic outbreaks.[20]

Relevant recommendations from included guidelines	
	Note: Although these guidelines were adapted from PHAC's guidelines (above), their grading of recommendation for valacyclovir suppressive therapy differ from that of PHAC, with a rating of B-1 instead of A-1. **Sexually transmitted diseases treatment guidelines, Centers for Disease Control and Prevention (CDC), 2010** [8] -Oral acyclovir can be used for first episode or severe recurrent episodes of genital herpes, and as suppressive therapy in late pregnancy to decrease the risk of recurrence and consequent C-section at term (dose not specified in pregnancy section).[8] These guidelines note that the safety of systemic valacyclovir, acyclovir and famciclovir in pregnancy "has not been definitively established.", but that data for acyclovir are reassuring while there is limited data for valacyclovir and famciclovir.(page 24) **Guidelines for the management of genital herpes in New Zealand, 2012**[21] -"In the absence of definitive data it is recommended that prophylactic acyclovir from 36 weeks should be used selectively, rather than routinely offered, for women with a history of recurrent genital herpes, e.g. to those women who have had an episode in the current pregnancy, and that women should be given the same advice on postnatal surveillance of their babies as those who have not had suppressive therapy."(Grade B; page 25) -"Management of pregnant women with first episode genital herpes, first and second trimester acquisition: Management of the woman should be in keeping with her clinical condition, using acyclovir in standard doses as indicated."(Grade C; page 26) -Consider acyclovir for third trimester acquisition if vaginal delivery is unavoidable, and request and refer to a pediatrician experienced in HSV infection.(Grade C; page 26) These guidelines also note that acyclovir may theoretically "suppress the production of neutralizing antibodies to the immunogen, glycoprotein D, thus having an effect on passive immunity to the fetus, and may suppress rather than treat newborn infections, thus leading to a delay in presentation of neonatal disease."(page 25) Although all of their relevant recommendations are for acyclovir, they also state: "Data collected via the Acyclovir Pregnancy Register (1984-99) found the observed rates and types of birth defects for 1234 pregnancies exposed to acyclovir did not differ significantly from those in the general population. Some studies on the use of valacyclovir (an acyclovir pro-drug) from 36 weeks gestation have addressed toxicity issues and identified no safety concerns in mothers, fetuses or neonates."(page 30)

Relevant recommendations from included guidelines	
	American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin: Management of herpes in pregnancy, 2007. Currency was reaffirmed in 2012.[22] -"Women with active recurrent genital herpes should be offered suppressive viral therapy at or beyond 36 weeks of gestation".(grade B; page 7)[22] The document includes dosing recommendations (adapted from CDC guidelines) for both acyclovir and valacyclovir for suppressive therapy, primary or first episode infection, and symptomatic recurrent infection in pregnancy. It is not specified if any particular antiviral is preferred.