Defining the efficacy of oxytocin use on farrowing sows and stillbirth rate: a protocol for a systematic review and meta-analysis

Registration

The systematic review protocol will be registered with the University of Guelph institutional repository (Atrium). The following protocol follows the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist and the PRISMA-P Explanation and Elaboration (Moher et al., 2015).

Sarah V. Hill¹, Maria Amezcua¹, Eduardo Ribeiro², Terri O’Sullivan¹, Robert M. Friendship¹

*Corresponding author: Sarah V. Hill shill09@uoguelph.ca

¹Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, ON, Canada, N1G 2W1
²Department of Animal Bioscience, Ontario Agricultural College, University of Guelph, Guelph, ON, Canada, N1G 2W1

Author Contact:
Sarah V. Hill – shill09@uoguelph.ca; Maria Amezcua – mamezcua@uoguelph.ca; Eduardo Ribeiro – eribeiro@uoguelph.ca; Terri O’Sullivan – tosulliv@uoguelph.ca; Robert M. Friendship – rfriends@ovc.uoguelph.ca

Author Contributions:
S.V.H is the guarantor. S.V.H developed and wrote the protocol with input and revisions from all other authors. R.M.F and T.O. provided expertise in on swine health management. T.O provided expertise on statistical methodology. E.R. provided expertise on animal reproduction. S.V.H and M.A were the readers for the screening and data extraction process. R.M.F was the third reader for when there are discrepancies between the two readers. All authors read, provided feedback and approved the protocol prior to registration.

Amendments
If any amendments are made following the registration of this protocol, they will be documented and included in the final systematic review as protocol revisions.

Support
Sources
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There are no sponsors for this review.
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The sources for S.V. Hill’s PhD program are not involved in any stage of this review.

Rationale

Over the past 20 years, a lot has changed in pig farming including rapid genetic advances in selecting hyperprolific sows (Ward et al., 2020; Lukovic & Škorput, 2015; Rutherford et al., 2013). However, larger litter sizes can have ramifications which can affect the sow and the piglets during the farrowing process. For instance, larger litter sizes increase duration of farrowing, increasing the likelihood of stillbirths, dystocia and intrapartum hypoxia (Ward et al., 2020; Oliviero et al., 2019).

Oxytocin is an important hormone for sows during farrowing. The hormone is produced in the hypothalamus and released from the pituitary glands during parturition (Linneen et al., 2005). Oxytocin release has two important functions: stimulation of uterine contractions and stimulate milk let down (Linneen et al., 2005). Administration of exogenous oxytocin is a common treatment for sows experiencing prolonged farrowing and agalactia (Linneen et al., 2005). According to oxytocin labels, administration of oxytocin can also be used to induce labour, accelerate the parturition process and expel postpartum uterine debris (Oxyto-Sure, Vetoquinol; Oxy-20 NW, Rafter 8). In addition to numerous uses, its dosage range is quite wide. For the purpose of farrowing, the dose of exogenous oxytocin producers can use range between 1.5mL – 2.5mL (30 – 50 oxytocin units) (Oxyto-Sure, Vetoquinol; Oxy-20 NW, Rafter 8 Products).

Some research has shown that the misuse of oxytocin can result in complications including piglet asphyxiations and stillbirth (Linneen et al., 2005). In a survey done in the UK, researchers reported that 74% of respondents used oxytocin at least “sometimes” during farrowing and 54% of respondents used oxytocin at least “sometimes” after farrowing (Ison, Jarvis, & Rutherford, 2016). With the methodology of a systematic review and meta-analysis, the goal is to investigate the current literature on oxytocin use to define proper guidelines for oxytocin use on farrowing sows.

Objectives: The objective of this protocol is to define the methodology for a systematic review and meta-analysis. The aim of this systematic review and meta-analysis is to create a more stringent guideline for oxytocin use during farrowing which can be used by producers. The specific questions that will be addressed in the systematic review are:

1. When examining sows farrowing, were there negative side-effects to sows that received exogenous oxytocin compared to those that didn’t receive exogenous oxytocin?
2. When comparing sows that received exogenous oxytocin to sows that didn’t receive exogenous oxytocin, what was the comparative effectiveness to reducing stillbirths and improving piglet viability?
3. For questions 1 and 2, identify dosages, sow parity and reason for oxytocin administration.
Methods

Eligibility criteria:

i. **Population:** Sows either immediately before, during or immediately after farrowing stage

ii. **Intervention/Exposure:** Oxytocin given to sows either immediately before, during or immediately after farrowing stage

iii. **Comparator:** Sows either immediately before, or during, or immediately after farrowing stage not given any oxytocin or given the analogue - Carbetocin. As well as different sows given dosages and or different timing of administrations (early or late during farrowing process).

iv. **Outcomes:** Stillbirths, sow mortality, and piglet viability (such as mortality rate within the first few days, meconium staining, and rupture umbilical cords).

Publication date: Articles must have been published within the last 50 years (1970 - present).

Report characteristics: The articles must be published in English. The articles can either be published or non-published but must be available in full text.

Study design: Only articles with clinical trial study designs will be included.

Information Sources: The search will include a range of relevant databases to identify peer-reviewed literature. Table 1 represents the databases used.

Table 1: Databases used to search for relevant literature

<table>
<thead>
<tr>
<th>Database</th>
<th>Interface</th>
<th>Query Box</th>
<th>Wildcards</th>
</tr>
</thead>
</table>
| PubMed                                           | National Center for Biotechnology Information (NCBI) | All fields                              | * - any group of characters
Note: wildcard can only be used if word is 4 or more characters |
| CAB Direct                                       | CAB Interface (CABI)               | All fields                              | ? - 0 to 1 character
* - any group of characters |
| Web of Science Core Collection                   | Web of Knowledge                   | Topic (title, abstract, author keywords and Keyword Plus ®) | $ - 0 to 1 character
* - any group of characters |
| ProQuest dissertations and theses global (1988 - present) | ProQuest                          | Anywhere except full text               | ? - 0 to 1 character
* - any group of characters |

In addition, a manual search in the table of contents for the following relevant conferences and reports in the American Association of Swine Veterinarian database including:
• AASV Annual Meeting (1999-2020)
• AASV Pre-Conference Seminars (2007-2019)
• Allen D. Leman Swine Conference (1998-2019)
• George A. Young Swine Health and Management Conference (1999-2012)
• ISU Swine Disease Conference for Swine Practitioners (1999-2019)
• Journal of Swine Health and Production (1993-2020)

**Search strategy:** The search strategy used for this review was developed using key concept terms and words. Population, Intervention and Outcome terms will be connected using Boolean operators ‘AND’ and ‘OR’. Table 4 represents an example of the search string that will be used for this review. The method used to develop the search string has been illustrated below (Table 2, 3 & 4). To acquire more data from abstracts with no full-text and conference proceedings, S.V.H will contact the corresponding author. The two readers will do a final check for all relevant articles by reviewing the references of all articles which passed the two screening stages.

Table 2: Results of initial search string to identify articles investigating oxytocin use at farrowing and stillbirth rates, published between 1970 - present using Web of Science core collection database as of July 23/2020.

<table>
<thead>
<tr>
<th>#</th>
<th>Search Terms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(swine OR sow$ OR porcine OR pig$ OR gilt$)</td>
<td>440, 312</td>
</tr>
<tr>
<td>2</td>
<td>(oxytocin OR carbetocin)</td>
<td>27, 205</td>
</tr>
<tr>
<td>3</td>
<td>(stillbirth OR dystocia OR farrow* OR “fetal expulsion” OR intrapartum OR parturition OR stillborn OR birth OR meconium OR mortality OR hypoxia)</td>
<td>1,467,554</td>
</tr>
<tr>
<td>4</td>
<td>1 AND 2</td>
<td>973</td>
</tr>
<tr>
<td>5</td>
<td>3 AND 4</td>
<td>282</td>
</tr>
</tbody>
</table>

To ensure all keywords have been selected appropriately, a quick search on controlled vocabulary terms were done on MeSH 2020 browser and CAB thesaurus (Table 3). New terms were added to the search string (Table 4).

Table 3: Controlled vocabulary terms for PICO keywords

<table>
<thead>
<tr>
<th>Key Term</th>
<th>MeSH 2020 browser:</th>
<th>CAB thesaurus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population:</strong> Pigs</td>
<td>Sus scrofa</td>
<td>Sus domesticus Sus scrofa domesticus</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Oxytocin*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Carbetocin* | N/A | N/A
---|---|---

**Outcome:**
- Stillbirth
  - Fetal death
- Dystocia
  - Uterine inertia
- Hypoxia
  - Anoxia
  - Anoxemia
  - Hypoxemia
- Mortality
  - Fetal Mortality
  - Neonatal mortality
  - Perinatal mortality

* Oxytocin and carbetocin names are specified for animal use - no synonyms necessary
**Web of science has no controlled vocabulary or assignment of subject terms
*** Proquest uses MeSH 2020 thesaurus

Table 4: Results of search string with addition of controlled vocabulary, published between 1970 - present using Web of Science core collection database as of July 23/2020

<table>
<thead>
<tr>
<th>#</th>
<th>Search Terms</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(swine OR sow$ OR porcine OR pig$ OR gilt$ OR ”sus scrofa” OR “sus domesticus” OR “sus scrofa domesticus”)</td>
<td>442,036</td>
</tr>
<tr>
<td>2</td>
<td>(oxytocin OR carbetocin)</td>
<td>27,205</td>
</tr>
<tr>
<td>3</td>
<td>(stillbirth OR dystocia OR farrow* OR “fetal expulsion” OR intrapartum OR parturition OR stillborn OR birth OR meconium OR mortality OR hypoxia OR “fetal death” OR “uterine inertia” OR “parturition complications” OR anoxia OR anoxemia OR hypoxemia OR “fetal mortality” OR “neonatal mortality” OR “perinatal mortality”)</td>
<td>1,491,102</td>
</tr>
<tr>
<td>4</td>
<td>1 AND 2</td>
<td>973</td>
</tr>
<tr>
<td>5</td>
<td>3 AND 4</td>
<td>284</td>
</tr>
</tbody>
</table>

**Data Management:** The resulting articles from the search string will be downloaded into a bibliographic software program (EndNoteWeb, Clarivate Analytics) or (Mendeley Ltd, Elsevier).
Then all citations will be loaded onto DistillerSR where the following screening and data collection will be done. Prior to screening, all duplicates will be removed in Distiller SR.

**Selection Process:** The protocol for this review will have two stages of screening. The first stage will screen papers which were the result of the search string by assessing the relevance of the title and abstract.

1) “Is the title and abstract available in English?”
2) “Does the title and/or abstract mention exogenous oxytocin or Carbetocin use on sows?”
3) “Does the title and/or abstract mention infectious causes of stillbirths?”

The response to these questions will include YES, NO and UNCLEAR. A reference will be excluded if the reader identifies a NO to questions 1-3. A reference will be excluded if the reader identifies a YES to question 3. If there are any discrepancies between the two readers, a third reader will evaluate the title/abstract. If a reader responds with UNCLEAR for any of the questions, a third reader will evaluate the title/abstract.

The second stage of screening will determine the relevance of each article by assessing the full-text.

1) “Is the full text available in English?”
2) “Is the text more than 500 words
3) “Does the article discuss the use of exogenous oxytocin for farrowing purposes?”
4) “Does the full-text focus on infectious causes of stillbirths?”
5) “Is there a comparator group (either Carbetocin or no oxytocin)?”
6) “Is the study design a trial”

The response to these questions will include YES, NO and UNCLEAR. A reference will be excluded if reader identifies a NO to questions 1-3, 5 and 6. A reference will be excluded if reader identifies a YES to question 4. If there are any discrepancies between the two readers, a third reader will evaluate the full-text.

**Data collection process:** The eligible studies will be further processed for data collection. The two readers will use a standardized form through DistillerSR to ensure consistency in data extraction.

**Data items:** The following information will be collected:
*Study information:* year of Publication, year (or range) study was conducted, month(s) study was conducted, and country.
*Population information:* research or commercial herd, breed of sows, number of sows and parity of sows.
*Intervention and comparator information:* Name of exogenous oxytocin used, reason for oxytocin use, perform manual assistance, supervision during farrowing, dosage, number of administrations per sow and combine oxytocin with pain medication.
Outcomes and prioritisation:
Outcome data to be extracted:
- Stillbirth rate
  a) Total piglets born, piglets born alive and dead
  b) Farrowing order
- Mean interval time between piglets in minutes
- Mean duration time of farrowing in minutes
- Meconium staining of piglet (degree of staining)
  a) Mild, medium, severe
- Umbilical cord appearance?
  a) Adhered or ruptured
- Sow behaviour
  a) Nesting behaviour, eating and drinking, position in crate
- Sow mortality

Risk of bias individual studies
The Cochrane tool for Risk of Bias in Randomized studies of interventions (RoB 2.0) will be used for assessing the risk of bias for each study (Sterne et al., 2019). Assessing the risk of bias for individual studies will be done at the outcome level. The assessment will be performed independently by two readers. Using the RoB assessment tool, there are a fixed set of domains being used to assess the overall risk of bias. The following set of domains of bias include: confounding (bias due to either unmeasured or uncontrolled variable which predicts whether individual receives intervention of interest), selection (bias due to selection of participants into study and/or bias due to missing data), information (measurement error in outcome status or measurement error in exposure status) and reporting bias (selection of outcome measure, type of analysis and/or selective reporting (Sterne et al., 2019). The RoB assessment tool consists of a series of signalling questions. Based on the responses to the questions, an overall risk of bias will be determined: ‘Low’, Moderate’, ‘Some Concerns’ (Sterne et al., 2019).

Data synthesis
Prior to conducting a meta-analysis, the readers will confirm that the studies are homogenous in terms of study design and comparators. If meta-analysis is deemed inappropriate due to study heterogeneity, a qualitative narrative summary will be done instead. This would entail descriptive text and tables summarizing study characteristics and findings. Each meta-analysis will be visualized using a forest plot. For the meta-analysis, data synthesis will be done for each outcome separately. The goal is to assess the direction of effect for each outcome, the sized of effect and whether the effect is consistent across studies (Deeks et al., 2011). Finally, readers will assess the strength of evidence for effect by assessing study design and risk of bias (Deeks et al., 2011). Dichotomous data will be analyzed using a risk ratio (with 95% confidence interval) of an event occurring. Continuous data will be analyzed using the mean difference approach. Possible sources of heterogeneity include parity of the sow, oxytocin combined with pain medication, supervision and manual assistance. Subgroup analysis will be performed on these possible sources of heterogeneity.

Meta-bias(es)
To reduce reporting bias, a funnel plot will be assessed for each outcome synthesized with 10 or more studies.

Confidence in cumulative evidence
The strength of evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (Guyatt et al., 2008). This system assesses the risk of bias, publication bias, precision, directness and consistency for each outcome (Guyatt et al., 2008).
Reference


