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RESEARCH COMMUNICATION

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Surrogate endpoints for neonatal outcome: A rapid review

Shiraz El Adam[1] | Karissa Johnston[1] | Maanasa Venkataraman[1] | Vanessa Perez Patel[2]

[1]Broadstreet HEOR, Vancouver, British Columbia, Canada

[2]Organon, Jersey City, New Jersey, USA

Correspondence
Karissa Johnston, Vancouver, BC, V6A 1A4, Canada.
Email: kjohnston@broadstreetheor.com

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1 | INTRODUCTION

Recent research has highlighted the increasing use of surrogate endpoints in interventional trials.[1] The United States Food and Drug Administration (US FDA) defines a surrogate endpoint, or an "intermediate clinical endpoint," as: "…a marker, such as a laboratory measurement, radiographic image, physical sign, or another measure, that is not itself a direct measurement of clinical benefit, and—(A) is known to predict clinical benefit and could be used to support traditional approval of a drug or biological product; or (B) is reasonably likely to predict clinical benefit and could be used to support the accelerated approval of a drug or biological product under section 506(c)."[2] Among the "Table of Surrogate Endpoints" provided by FDA, preterm birth (PTB) is listed as a surrogate endpoint to accelerate the approval of investigational therapies for spontaneous PTB (sPTB).[3] Time to sPTB from the onset of spontaneous preterm labor (sPTL) is a surrogate endpoint that may also be reasonably likely to predict neonatal morbidity/mortality. Currently, there are no FDA-approved therapies for reducing the risk of neonatal morbidity/mortality resulting from sPTB. To understand the potential for predicting neonatal outcomes in future studies, a rapid review was conducted to synthesize the quantitative evidence on the strength of surrogacy for PTB and time to delivery from sPTL diagnosis to sPTB.

2 | METHODS

The Cochrane rapid review guidance[4] was used to identify systematic literature reviews (SLRs), randomized controlled trials (RCTs) and observational cohort studies in Ovid MEDLINE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. Searches were executed on February 16, 2023, and used predefined Population, Intervention, Comparators, Outcomes, Study design criteria (Appendix Table A1). Searches were restricted to English language and to articles published between 2002 and 2023. Searches for RCTs were restricted to those conducted in North America, while searches for SLRs were expanded to include any geographic region. Additional searches for observational studies conducted in North America or Europe and published between 2018 and 2023 were conducted. These latter search restrictions were applied to reflect studies following up on the retosiban program, now terminated.[5,6] This was the only late phase development program in the US known to have conducted observational studies published in the last 5 years, which were relevant to the research question; as such, observational studies sponsored by GlaxoSmithKline were eligible for consideration. Supplemental hand searches of reference lists, publicly available FDA documents, and the American College of Obstetricians and Gynecologists websites were conducted.

The population of interest included individuals with a singleton and uncomplicated pregnancy, with/without a history of singleton sPTB, and reported delivery at <37 weeks' gestational age, or, reported time to delivery from sPTL diagnosis to sPTB. Interventions included preventative agent(s) for the prolongation of pregnancy; or treatment of sPTL. Outcomes included short-term neonatal outcomes (defined as the time from PTB to 28 days beyond the expected due date at 40 weeks' gestational age) including morbidity and mortality (as defined by the literature). Studies were included if either one or both surrogate endpoints of interest and, simultaneously, any one or more clinically meaningful neonatal outcomes (i.e., neonatal morbidity/mortality) were reported. For this rapid review, strength of surrogacy was defined as any empirical measures of association between the surrogate endpoints of interest and clinically meaningful outcomes of interest (morbidity, mortality); empirical measures of interest included coefficients derived from correlational analyses or using regression techniques.

One reviewer screened and extracted data; a second reviewer independently verified ≥ 10% of all screenings and extractions. Strength of surrogacy was determined based on a quantitative assessment of the correlation or predictive capability between each surrogate endpoint of interest and neonatal morbidity/mortality. Risk of bias was assessed using the second version of the Cochrane risk-of-bias tool for RCTs, the adapted Newcastle-Ottawa scale for observational studies, and the second version of the Assessing the Methodological Quality of Systematic Reviews tool for SLRs.

3 | RESULTS

Thirty-one articles (one observational study,[7] one pooled analysis of trial data,[8] four RCTs,[9–12] and 25 SLRs[13–37]) were included (Appendix Figure A1). Study periods within the identified RCTs ranged from 1999 through 2021; within the identified SLRs, they ranged from

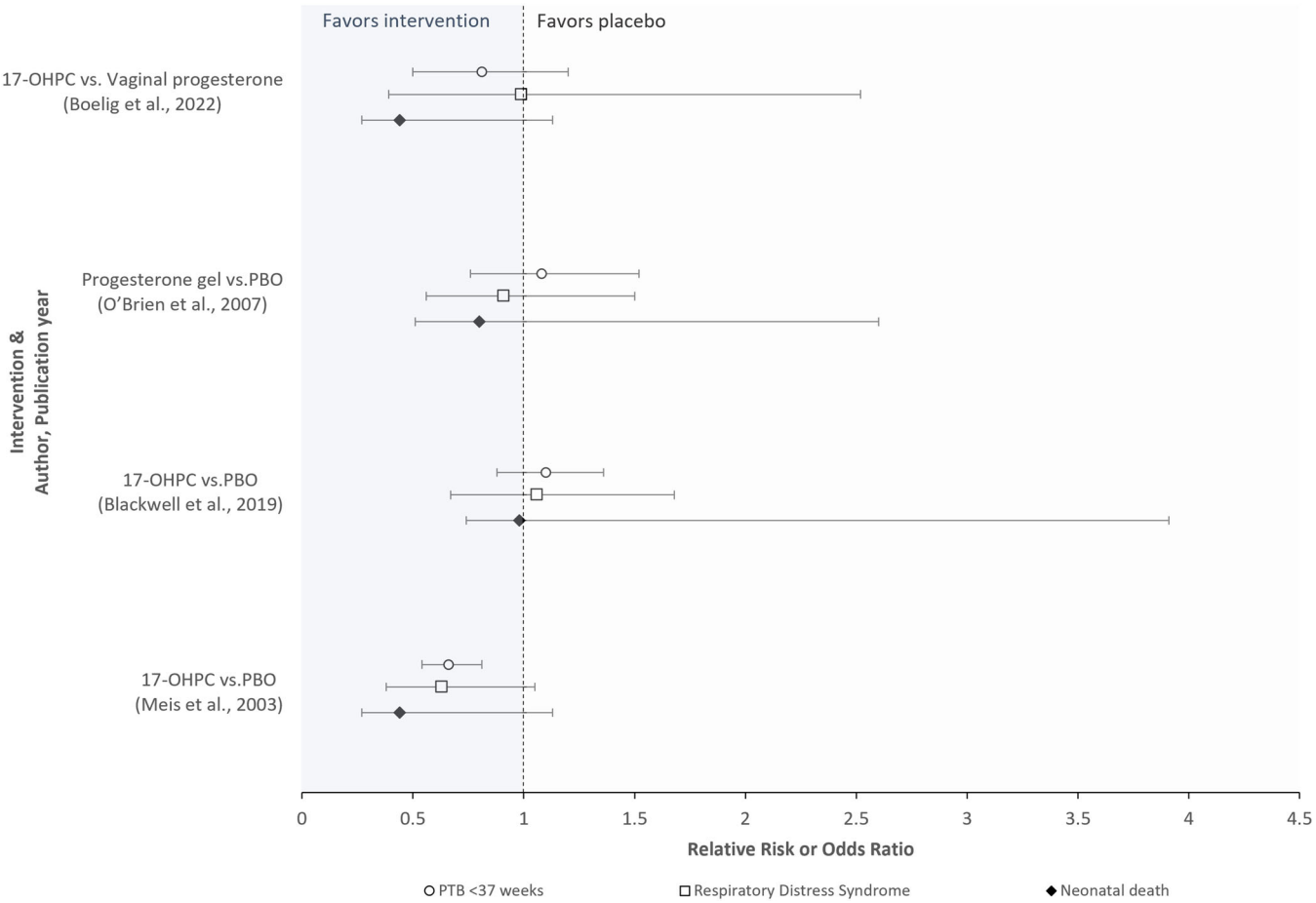

FIGURE 1 Randomized controlled trials evaluating treatment effects on the occurrence of preterm birth and, separately, neonatal morbidity/mortality outcomes ($n = 4$ studies). The O'Brien et al. study reported odds ratios; all other studies reported relative risks. Abbreviations: 17-OHPC, 17-hydroxyprogesterone caproate, PBO, Placebo, PTB, preterm birth. Interpretation: Area < 1 on the x-axis favors the intervention, while the area > 1 favors placebo. Most trials reported no statistically significant differences between study groups across surrogate and neonatal clinical endpoints; although Meis et al. reported a statistically significant reduction attributed to the intervention for the surrogate endpoint (i.e., preterm birth), significant reductions were not reported for the neonatal clinical endpoints evaluated. The strength of surrogacy was not evaluated in any study.

1957 through 2017; from 2003 to 2011 for the pooled analysis of trial data[8]; and from 2000 to 2011 for the observational study.[7]

Interventions in the four RCTs[9–12] included two trials[9,10] for 17-hydroxyprogesterone caproate (17-OHPC), one for progesterone gel,[11] and one for vaginal progesterone compared to intramuscular 17-OHPC.[12] Across the included studies, the most commonly reported neonatal morbidity outcomes were respiratory distress syndrome, necrotizing enterocolitis, bronchopulmonary dysplasia, and intraventricular hemorrhage. Neonatal mortality outcomes included perinatal loss, early infant death (defined as death after birth until 28 days of life occurring in live-born neonates delivered < $24^{0/7}$ weeks' gestation), and neonatal death (defined as death < 28 days).

Among the RCTs included (Figure 1)[9–12] results were inconsistent and no strength of surrogacy assessment was conducted; three RCTs[9–11] had low risk of bias and one RCT[12] had a high risk of bias. The pooled analysis study[8] compared vaginal progesterone to other procedural interventions such as cervical pessary and cerclage in three separate trials, each evaluating different treatment protocols. This study[8] reported no significant differences in sPTB at <37 weeks' gestational age, neonatal morbidity, or perinatal loss; magnitudes of association were inconsistent, and considerable variability was evident for the neonatal outcomes reported. One observational study,[7] rated "good quality," illustrated lower frequency of neonatal morbidity/mortality events as weeks' gestational age at birth increased; a strength of surrogacy assessment was not conducted.

Among the 25 SLRs[13–37] included (Figure 2), 21 were systematic reviews of RCTs, two[28,34] included RCTs and observational studies, and two[23,27] included only observational cohort studies[23] or case-control studies.[27] Most SLRs assessed progesterone-based interventions, but some summarized the evidence on the use of other treatments or procedures such as tocolytic drugs,[20,34–36] cervical pessary,[27,38] cervical cerclage,[28,37] corticosteroids,[23] hormones,[13] and others (e.g., omega 3 fatty acids,[14] probiotics,[24] and ethanol[25]). Among the 25 SLRs[13–37] included, most SLRs assessed progesterone-based interventions,[16–19,26,29–33,37] followed by treatments or procedures such as tocolytic drugs, cervical pessary, cervical cerclage, corticosteroids, hormones, and other agents (e.g., omega 3 fatty acids, probiotics etc.). Like the results from the RCTs in this review, the conclusions of the SLRs were inconsistent and absent any strength of surrogacy assessment; 80% of the SLRs included had low or critically low quality (Figure 2).

4 | DISCUSSION

The absence of a direct quantitative assessment, defined as any empirical measure of association between the surrogate endpoints of interest and neonatal morbidity/mortality, among the studies in this rapid literature review, which spanned the last 20 years, precludes the ability to draw conclusions on the strength of surrogacy. Such information, if available, would facilitate a deeper understanding by

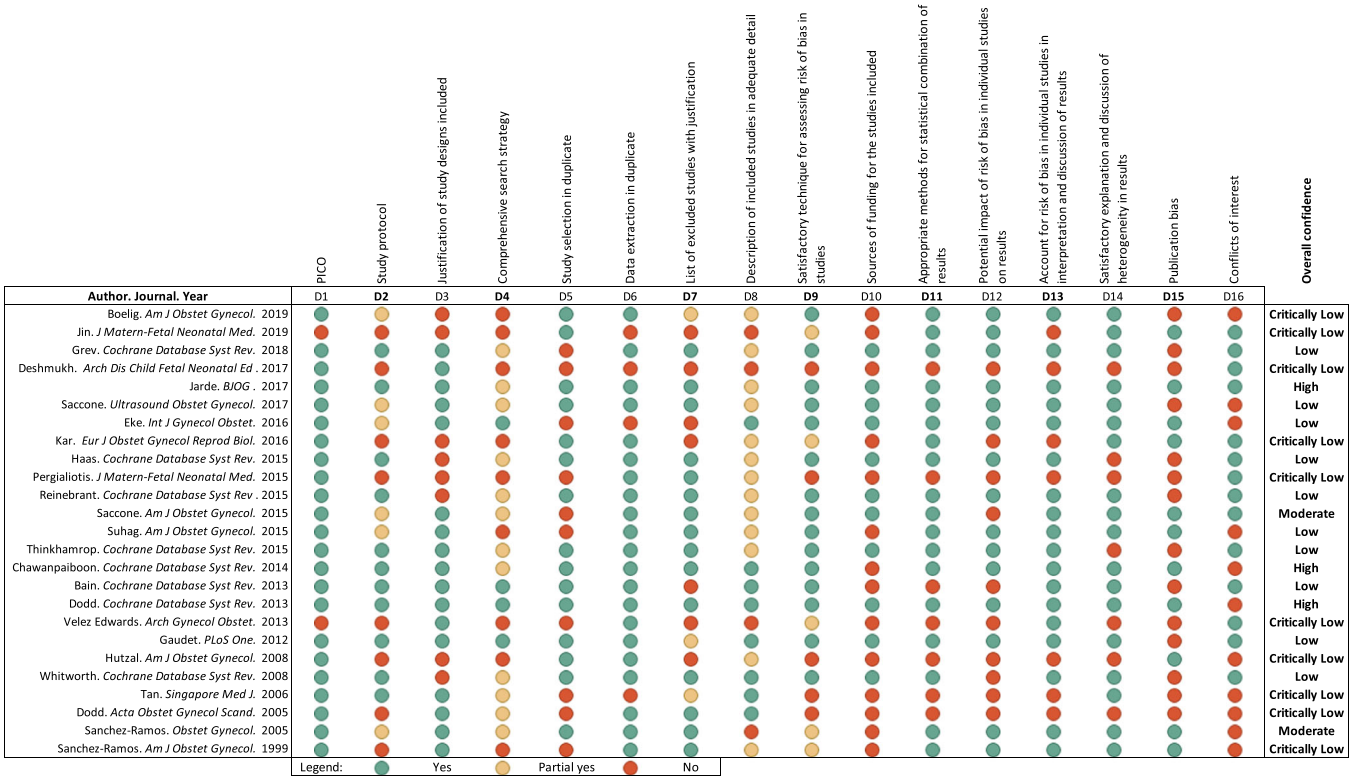

FIGURE 2 AMSTAR-2 quality assessment of systematic literature reviews (n = 25 studies). Interpretation: Overall confidence rating: High, no or one noncritical weakness; Moderate, more than one noncritical weakness; Low, one critical flaw with or without noncritical weaknesses; Critically Low, more than one critical flaw with or without noncritical weaknesses. Abbreviations: AMSTAR, Assessing the Methodological Quality of Systematic Reviews; PICO, Population Intervention Comparator Outcomes.

which these surrogate endpoints can reasonably predict neonatal morbidity/mortality. Reporting guidelines for surrogate endpoints are under development, which could improve transparency in the reporting of such endpoints, especially for clinical trials, thus facilitating the interpretation of future trial results.[39,40] Although a rapid review approach was undertaken which may have resulted in some studies or other relevant data being missed by design, this review highlights the need for empirical evidence to better support the use of these surrogate measures particularly given their role as key efficacy endpoints in investigational studies assessing therapeutic intervention for the prevention of sPTB.

AUTHOR CONTRIBUTIONS

Shiraz El Adam: Writing—original draft; methodology; validation; visualization; writing—review and editing; project administration; supervision. **Karissa Johnston**: Methodology; writing—review and editing; supervision. **Maanasa Venkataraman**: Methodology; validation; visualization; writing—review and editing. **Vanessa Perez Patel**: Conceptualization; investigation; methodology; writing—review & editing; supervision.

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CONFLICTS OF INTEREST STATEMENT

Shiraz El Adam, Karissa Johnston, and Maanasa Venkataraman are employees of Broadstreet HEOR and received consultancy fees from Organon. Vanessa Perez Patel is an employee of Organon.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

TRANSPARENCY DECLARATION

The authors had full access to all studies included in this rapid review. VPP affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study have been explained. As only previously published data was included in this study, ethics approval was not required.

ORCID

Shiraz El Adam http://orcid.org/0000-0002-8036-2495

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APPENDIX A

TABLE A1 Population, intervention, comparators, outcomes, and study design (PICOS) criteria.

Population	Individuals with a singleton and uncomplicated pregnancy, with/without a history of singleton sPTB, and: o Reported delivery at <37 weeks' gestational age Or o Reported time to delivery from sPTL diagnosis to sPTB Note: individuals with complicated pregnancies and neonates with congenital or chromosomal conditions were excluded.
Intervention/comparator	A. Preventative agent(s) for the prolongation of pregnancy; or B. Treatment of sPTL; or C. No intervention No exclusions were planned based on intervention or comparator.
Outcomes	Short-term neonatal outcome (short-term defined as the time from PTB to 28 days beyond the expected due date at 40 weeks' gestational age): o Presence of morbidity (defined by the literature) o Severity of morbidity (defined by the literature) o Neonatal death
Study design	A. Phase 2 and/or Phase 3 clinical trials o Databases: MEDLINE and CENTRAL o Publication dates: 2002-2023 o Region: North America (US, Canada) B. Observational cohort studies (prospective or retrospective) o Databases: MEDLINE o Publication dates: 2018-2023 o Region: North America (US, Canada), Europe C. Reviews (systematic, scoping, and rapid reviews), and meta-analyses o Databases: MEDLINE and CDSR o Publication dates: *unrestricted* o Region: *unrestricted* o Languages included: English

Note: The retosiban program, now terminated, was the only late phase development program in the US which was known to have conducted observational studies published in the last 5 years (from the time of search execution) which were relevant to the research question; as such, observational studies sponsored by GlaxoSmithKline were eligible for consideration.

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; MEDLINE, Medical Literature Analysis and Retrieval System Online; PICOS, Population, Intervention, Comparator, Outcomes, Study design; PTB, preterm birth; PTL, preterm labor; sPTB, spontaneous preterm birth; sPTL, spontaneous preterm labor; US, United States.

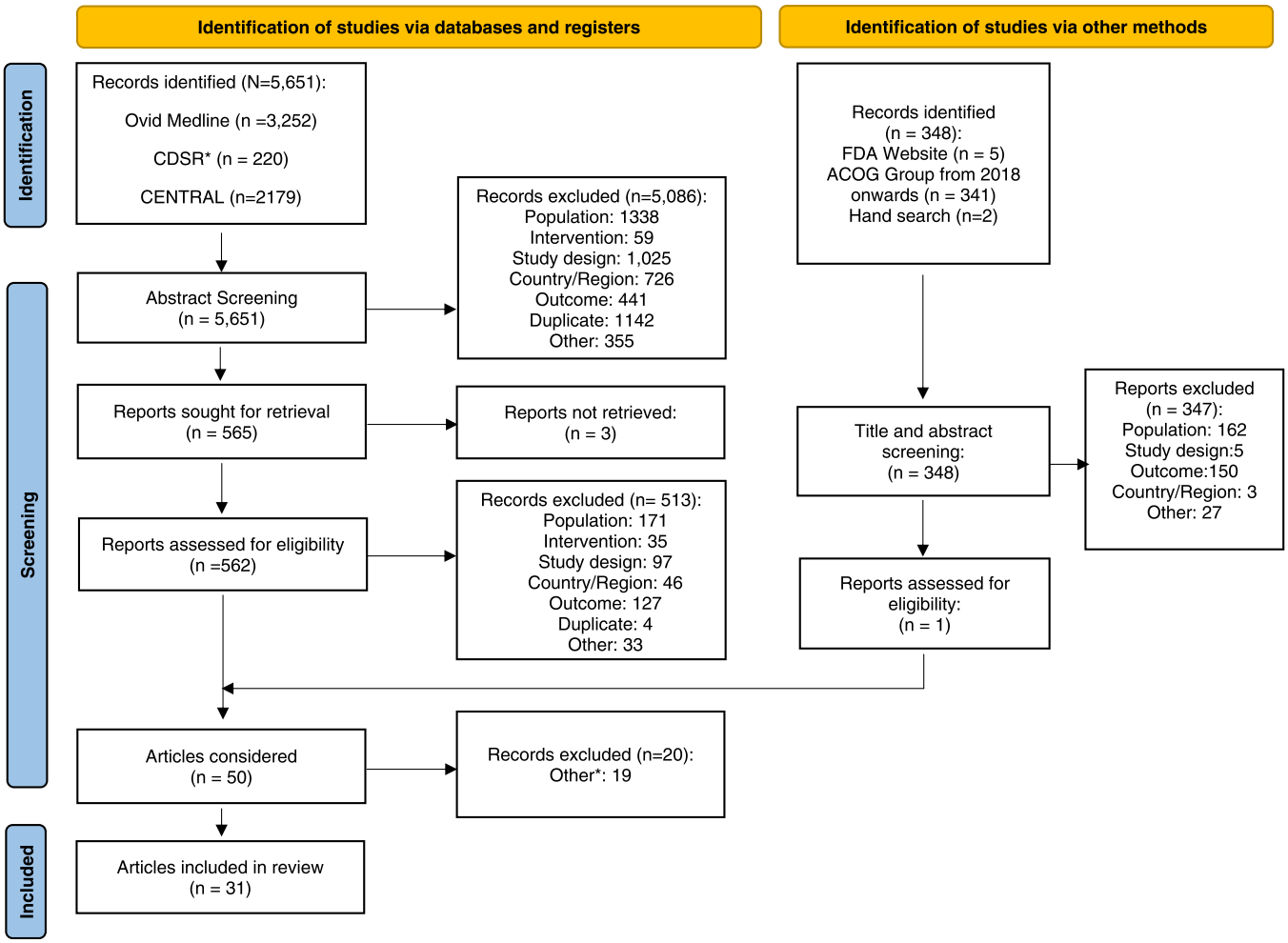

FIGURE A1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram. From: Page MJ, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. Notes: *Articles did not report treatment effect simultaneously in surrogate endpoint(s) and morbidity/mortality outcomes.