A Systematic Review and Meta-Analysis of the Utility of Corticosteroids in the Treatment of Hyperemesis Gravidarum

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Supplementary Issue: Parental Nutritional Metabolism and Health and Disease of Offspring

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ABSTRACT

BACKGROUND: Corticosteroids (CCS) are effective in reducing chemotherapy-induced nausea and vomiting, but it is unknown whether CCS are effective in treating hyperemesis gravidarum (HG).

METHODS: We searched PubMed and ClinicalTrials.gov from inception to May 15, 2015, for randomized controlled trials examining the effects of CCS in HG.

RESULTS: We identified five trials ($n = 310$) examining the effects of CCS in women with HG. Meta-analysis was possible for one outcome ($n = 214$) and showed no significant effect of CCS on readmission rates (odds ratio, 0.37; 95% confidence internal: 0.1–1.35). Two small studies ($n = 104$) reported a reduction of vomiting episodes, and one ($n = 24$) found improvement of well-being, but no effect on other outcomes. None of the studies that investigated perinatal outcome ($n = 173$) found an effect of CCS and were underpowered to investigate teratogenic effects. We found evidence of publication bias.

CONCLUSION: Meta-analysis yielded no effect of CCS therapy on readmission rates. Single small studies indicated possible beneficial effects on other outcomes. Future high-quality trials are necessary and would benefit from consensus on HG definition and core outcomes of HG therapy.

KEYWORDS: corticosteroids, effectiveness, hyperemesis gravidarum, treatment

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Introduction

Over three quarters of pregnant women experience some degree of nausea or vomiting during pregnancy (NVP).[1] In 0.3–2% of pregnancies, intractable vomiting, known as hyperemesis gravidarum (HG), occurs.[1,2] Weight loss, ketonuria, dehydration, and electrolyte imbalance are the features of HG and can necessitate hospital admission. HG is the most common cause of hospital admission in the first half of pregnancy.[3] At present, none of the available options in the treatment of HG, including a range of antiemetics, is of proven efficacy.[4] Women with HG are commonly treated by intravenous rehydration, antiemetics, and electrolyte supplementation, if needed.

HG has a major detrimental effect on maternal well-being and has been associated with depression, anxiety, posttraumatic stress syndrome, and pregnancy termination.[5–7] A systematic review and meta-analysis showed that HG was associated with an increased risk of adverse perinatal outcome.[8] Therefore, any new treatment options with proven efficacy would be of great value to patients and clinicians alike. Corticosteroid (CCS) therapy is frequently employed in evidence-based strategies in the prevention or treatment of chemotherapy-induced nausea and vomiting (CINV)[9] and, therefore, presents a candidate treatment option for HG. In contrast to other antiemetic strategies, it is unclear how corticosteroids act on the reduction of nausea and vomiting symptoms. In the 1990s, the first observational evidence was published on the possible utility of CCS in the management of HG.[10–12]

Maternal systemic CCS treatment in early pregnancy has been associated with a small increase in orofacial clefts in some studies,[13,14] but not in others.[15] The continued use of CCS later in pregnancy is associated with intrauterine growth restriction and smaller neonatal head circumference.[16] Clinicians understandably remain cautious of the use of possible teratogenic medication in early pregnancy in the absence of proven efficacy.

A recent report called for the more liberal availability of CCS therapy for refractory HG[6] despite the fact that

the effectiveness of CCS therapy alone, or as an adjunct to other antiemetic strategies for the treatment of HG, has been the study of a limited number of small trials. Because meta-analysis can improve power that is often limited in single small trials, the aim of the present systematic review and meta-analysis is to summarize the available evidence on the effectiveness of CCS therapy for HG.

Methods

Study eligibility criteria. We included randomized controlled trials (RCTs) that compared the effectiveness of CCS in the treatment of HG to the effectiveness of the prevailing treatment or a placebo. Studies examining the effects of oral and parenteral administration of CCS were eligible for inclusion in this review. The participants of eligible studies were women with HG, as defined earlier, including at least information on the severity of vomiting and gestational age of participants. Studies that used outpatient and inpatient treatment regimens were eligible for inclusion. We included English language articles only. Systematic reviews, observational studies, and case reports were excluded.

Search strategy and selection of studies. We searched PubMed and ClinicalTrials.gov from inception to May 2015 without methodological filters, language, or any other restrictions. We consulted ClinicalTrials.gov to find unpublished or ongoing trials. We composed a PubMed search in cooperation with a clinical librarian as follows:

> ((“Hyperemesis Gravidarum” [Mesh] OR nausea and vomiting of pregnancy[tiab] OR ((hyperemes*[tw] OR severe nausea*[tiab] OR severe vomiting[tiab] OR persistent vomiting[tiab] OR pernicious vomiting[tiab]) AND (pregnan*[tw] OR gestat*[tw] OR gravidit*[tw] OR gravidar*[tw]))) AND (“Glucocorticoids” [Pharmacological Action] OR “Adrenal Cortex Hormones”[Mesh] OR “Steroids/administration and dosage”[Mesh] OR “Steroids/drug therapy”[Mesh] OR “Steroids/therapeutic use”[Mesh] OR corticoster*[tw] OR steroid[tw] OR steroids[tw] OR glucostero*[tw] OR glucocortico*[tw] OR glycocortico*[tw] OR hydrocortison*[tw] OR dexamethason*[tw] OR methylpredn*[tw] OR triamcinolon*[tw] OR betamethason*[tw] OR prednis*[tw])) NOT (“animals”[mesh] NOT “humans” [mesh])

The studies identified by our search strategy were evaluated by two authors independently (IJG and MEV), who studied the title and abstract according to the predefined inclusion and exclusion criteria. Any disagreement was resolved through consensus or consultation with another author (RCP). The reference lists of included articles were manually screened for additional articles.

Data collection and study appraisal. We extracted data using a piloted data extraction form, about any outcome measure, indicating the following.

- The influence of CCS on nausea and vomiting severity
- The influence of CCS on the length of hospital stay or readmission to the hospital
- The influence of CCS on pregnancy outcome
- The influence of CCS on other outcome measures reported.

In order to provide a good overview of the studied effects in every trial, various definitions of nausea and vomiting severity were allowed (eg, number of vomiting episodes a day or vomiting more than five times a day). We contacted authors for supplementary data to improve the uniformity of results.

We assessed the methodological quality of each trial using the criteria formulated within the *Cochrane Handbook for Systematic Reviews of Interventions*.[17] IJG and MEV assessed the risk of bias in all the included trials, concerning random sequence generation, allocation concealment and blinding of participants, and personnel and outcome assessors. Furthermore, we assessed potential bias caused by incomplete outcome data or selective reporting. Disagreements were resolved through consensus.

We assessed publication bias by constructing a funnel plot according to the *Cochrane Handbook for Systematic Reviews of Interventions*.[17]

Data synthesis and analysis. We pooled outcome data from the studies that used different CCS regimens. We pooled the outcome data whenever the same outcome measure was available for two or more trials. We used RevMan 2014 to create forest plots. We quantified heterogeneity among trials using the I^2 statistic. We considered $I^2 > 50\%$ as an indication of substantial heterogeneity. We applied a random effects model in our meta-analysis to indentify the outcomes with substantial heterogeneity.

Results

Search results. Our PubMed search retrieved 113 articles. ClinicalTrials.gov yielded no further hits, but manual search of reference lists led to another six eligible articles. The flowchart of study screening and selection is shown in Figure 1. We deemed five trials eligible for inclusion in this review.[18–22] These trials examined the effectiveness of oral prednisolone, oral methylprednisolone, intravenous methylprednisolone, or intravenous hydrocortisone in various dosing regimens. A list of CCS and their equivalent dosing regimens is given in Table 1.

Risk of bias. In Figure 2, the risk of bias is summarized for all the studies analyzed in this review. The rationale for the risk of bias selection for all separate items is described in Supplementary Table 1. None of the studies that were assessed had a low risk of bias for all items. Because of unclear reporting of definitions, primary and secondary outcomes, selective reporting was a concern for all[18,20–22] but one study.[19] However, the study by Ziaei et al[19] was judged to have a high risk of bias, concerning the randomization procedure and blinding.

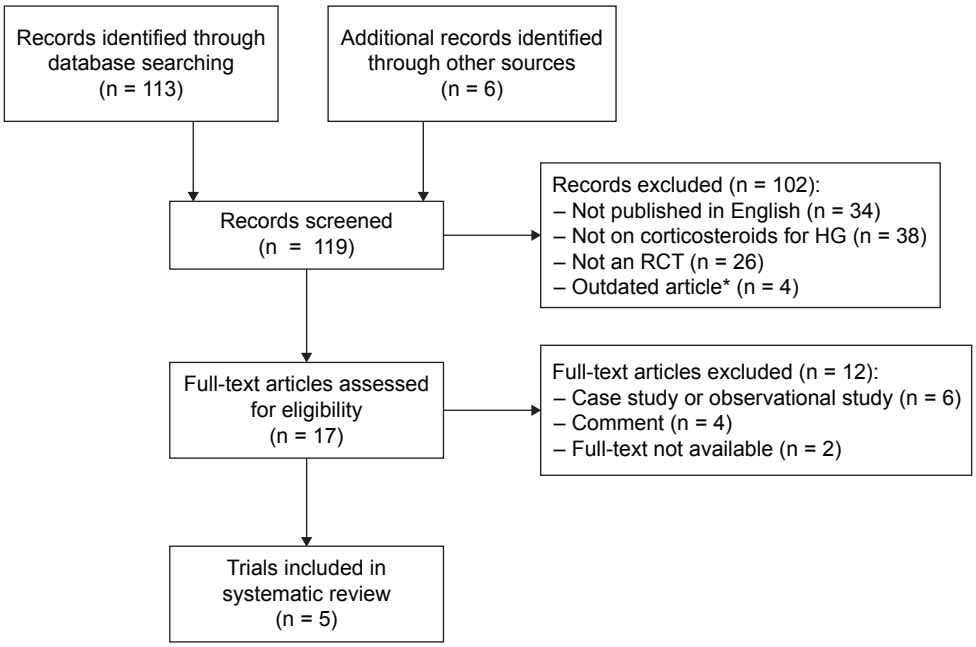

Figure 1. Flowchart of study selection.
Note: *An updated version of the article was available.

The study by Nelson-Piercy et al was terminated preterm, which may have introduced bias.[18] Remarkably, the authors stated that the early termination of their study was due to the conviction among caregivers that randomization between prednisolone and placebo was unethical because prednisolone was clearly effective. Bias might also be introduced in the study by Safari et al[20] due to significant baseline inequality of HG duration between both treatment groups. Although coincidence might have caused this difference, the authors do not state how they have addressed this in their analyses.

Prednisolone and HG. Two small trials ($n = 104$) studied the effectiveness of prednisolone in reducing HG symptoms. Nelson-Piercy et al[18] randomized between oral prednisolone and placebo, while Ziaei et al[19] randomized between oral prednisolone and promethazine. In the study by Nelson-Piercy et al,[18] treatment was converted to intravenous medication if participants were still vomiting and dependent on intravenous rehydration after 72 hours. The inclusion criteria and dosage regimens are listed in Table 2.

Baseline characteristics. In the study by Nelson-Piercy et al,[18] 12 participants were treated with oral prednisolone, and 12 with placebo. Only 1 of the 12 women randomized to

Table 1. Corticosteroids and their equivalent dosage.[28]

CORTICOSTEROID	EQUIVALENT DOSAGE (mg)
Prednis(ol)one	5
Methylprednisolone	4
Hydrocortisone	20

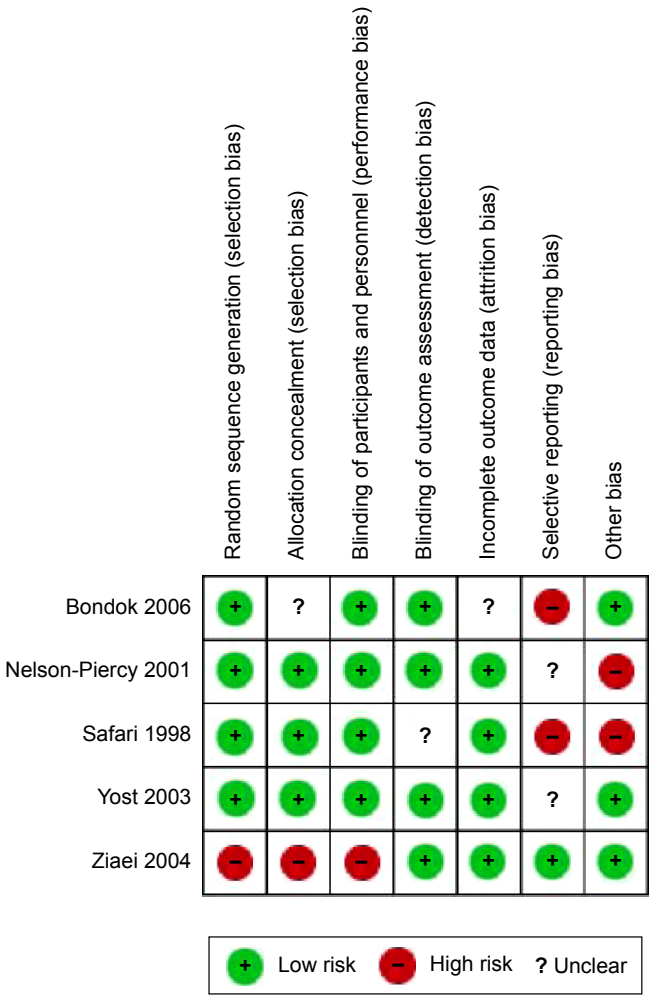

Figure 2. Summary risk of bias.

Table 2. Study characteristics of included trials.

TRIAL	METHODS	PARTICIPANTS (n)		INCLUSION CRITERIA	THERAPY		OUTCOMES
		INTERVENTION	CONTROL		INTERVENTION	CONTROL	
Nelson-Piercy[18] (2001)	RCT Double-blind Multi-centre Inpatient	12	12	<12 weeks gestation Hospital (re)admission for HG, necessitating IV rehydration (≥1 week in case of first admission, ≥24 hrs in case of subsequent admission) and treatment with ≥1 antiemetic and thiamine Ketonuria on admission	Oral prednisolone 20 mg 2 dd for 1 week. Conversion to IV hydrocortisone 100 mg 2 dd in case of persistent vomiting and dependence on IV rehydration after 72 hrs	Placebo according to CCS regimen	Daily vomiting frequency Nausea severity (VAS-score) Wellbeing (VAS-score) Dependence on IV rehydration Drinking and eating ability Weight gain Hospital readmission during pregnancy Neonatal outcome
Ziaei[19] (2004)	RCT Single-blind Single-centre Outpatient	40	40	6–12 weeks gestation Vomiting >3 times per day during last 72 hrs or; Ketonuria not responding to dietary manipulation and weight loss	Oral prednisolone 5 mg 1 dd for 10 days. 72 hrs prior to study medication no antiemetic treatment	Oral promethazine 25 mg 3 dd for 10 days. 72 hrs prior to study medication no antiemetic treatment	Daily vomiting frequency Nausea severity (VAS-score) Sickness
Safari[20] (1998)	RCT Double-blind Single-centre Inpatient	20	20	≤16 weeks gestation Persistent vomiting after IV hydration or readmission for HG Ketonuria Weight loss <20 weeks pregnant Persistent vomiting after outpatient management with promethazine 25 mg 4 dd ≥3+ ketonuria	Oral methylprednisolone 16 mg 3 dd for 3 days, followed by tapering regimen halving the dose every 3 days	Oral promethazine 25 mg 3 dd for 2 weeks	Symptom improvement ≤2 days of treatment Hospital readmission for HG during study period
Yost[21] (2003)	RCT Double-blind Single-centre Inpatient	56	54	<20 weeks pregnant Persistent vomiting after outpatient management with promethazine 25 mg 4 dd ≥3+ ketonuria	IV methylprednisolone 125 mg 1 dd for 1 day, followed by tapering regimen with oral prednisolone (1 day 40 mg, 3 days 20 mg, 3 days 10 mg, 7 days 5 mg). In case of persistent vomiting after 2 days, single dose IV methylprednisolone 80 mg IV hydrocortisone 300 mg 1 dd for 3 days, followed by tapering regimen (2 days 200 mg, 2 days 100 mg). Additional placebo (saline IV) 2 dd	Placebo according to CCS regimen	ER visits Total length of hospital stay Hospital readmission during pregnancy Pregnancy outcome Neonatal outcome
Bondok[22] (2006)	RCT Double-blind Single-centre Inpatient	20	20	≤16 weeks gestation Persistent vomiting necessitating ICU admission Ketonuria >5% pre pregnancy weight loss	IV hydrocortisone 300 mg 1 dd for 3 days, followed by tapering regimen (2 days 200 mg, 2 days 100 mg). Additional placebo (saline IV) 2 dd	IV metoclopramide 10 mg 3 dd for 1 week	Daily vomiting frequency Serum albumine ICU readmission within 2 weeks after study completion

Abbreviations: RCT, randomized controlled trial; HG, hyperemesis gravidarum; IV, intravenous; CCS, corticosteroid; VAS, visual analog scale; ER, emergency room; ICU, intensive care unit.

prednisolone entered the study during the first HG hospital admission compared to 5 of the 12 women randomized to placebo ($P < 0.01$). Mean gestational age was 10.6 ± 2.1 weeks for women randomized to prednisolone compared to 8.3 ± 1.9 weeks for women randomized to placebo. In the study by Ziaei et al,[19] 40 women were randomized to oral prednisolone and 40 women were randomized to oral promethazine. Baseline characteristics were similar for both randomization groups. Participants had a mean gestational age of 11 weeks and three vomiting episodes per day.

Effects of prednisolone on disease severity. After one week of treatment, Nelson-Piercy et al[18] did not find significant differences between prednisolone and placebo in terms of nausea improvement (self-reported using a visual analog scale (VAS), $P = 0.10$), still vomiting (self-reported; relative risk (RR), 1.4; 95% confidence interval (CI): 0.6–3.2), or vomiting more than five times per day (self-reported; RR, 2.5; 95% CI: 0.6–10.5), nor was there an effect on dependence on intravenous fluids (RR, 1.0; 95% CI: 0.2–4.0) or conversions to intravenous medication in case of insufficient improvement on oral therapy as stated in the protocol (RR, 2.0; 95% CI: 0.6–6.2). However, oral prednisolone significantly improved well-being when compared to placebo (median VAS improvement, 6.5 vs. 3.5 points; $P = 0.02$). In addition, food intake (self-reported; 0–7 scale ranging from no to normal intake) and weight gain increased significantly in women randomized to prednisolone when compared to placebo (median increase, 2.0 vs. 1.5 points; $P = 0.04$ and 1.25 kg vs. −0.10 kg; $P = 0.03$, respectively). In the study by Ziaei et al,[19] women randomized to prednisolone had less reduction in nausea severity (VAS) and number of self-reported vomiting episodes and less improved sickness (self-reported; defined as no improvement/becoming worse vs. any improvement) after 48 hours of treatment compared to women randomized to promethazine (no or mild nausea: odds ratio (OR), 0.33; 95% CI: 0.13–0.86; less than three vomiting episodes per day: OR, 0.22; 95% CI: 0.08–0.61; sickness improved: OR, 0.33; 95% CI: 0.13–0.86). However, the two treatment strategies were equally effective between day 3 and day 10 for all the three measures, which was also true for day 17, a week after treatment had stopped. Ziaei et al[19] also reported on side effects of treatment. None of the women randomized to prednisolone experienced drowsiness, where 6 of the 40 women randomized to promethazine experienced drowsiness (0% vs. 15%; $P = 0.03$).

Effects of prednisolone on the length of hospital stay and readmission rates. Nelson-Piercy et al[18] did not find significant differences in the length of hospital stay according to the treatment allocation (median, seven days for both prednisolone and placebo), but readmission rates were reduced in women randomized to prednisolone compared to placebo (RR, 0.6; 95% CI: 0.3–1.4). Ziaei et al[19] treated participants on an outpatient basis. Hospital (re)admissions were not included as an outcome measure.

Effects of prednisolone on perinatal outcome. In the study by Nelson-Piercy et al,[18] follow-up was available for 11 participants in both randomization groups. There were no differences in gestational age at birth and birth weight. There was one neonatal death in the prednisolone group and two in the placebo group, all due to prematurity. Ziaei et al[19] did not examine pregnancy or neonatal outcomes.

Methylprednisolone and HG. Safari et al[20] and Yost et al[21] studied the effectiveness of methylprednisolone in the treatment of HG ($n = 166$). Safari et al[20] randomized between oral methylprednisolone and oral promethazine, while Yost et al[21] randomized between intravenous methylprednisolone and placebo. Both studies applied a tapering regimen for methylprednisolone. Total study duration was two weeks. In the study by Yost et al,[21] study medication was prescribed in addition to usual care, including antiemetic treatment with 25 mg promethazine and 10 mg metoclopramide intravenously every six hours for one day and thereafter administered orally if needed (Table 2).

Baseline characteristics. Safari et al[20] randomized 20 participants in each treatment group. Compared to oral methylprednisolone, participants randomized to promethazine had significantly longer duration of HG symptoms at study entry (14 vs. 28 days; $P = 0.03$). Otherwise baseline characteristics were similar, with a mean gestational age of 9.8 ± 2.1 weeks for methylprednisolone and 9.5 ± 2.7 weeks for promethazine. In the study by Yost et al, 56 participants were randomized to intravenous methylprednisolone and 54 participants were randomized to placebo. There were no differences in baseline characteristics, with a mean gestational age of 11.0 ± 2.7 and 10.8 ± 2.7 weeks, respectively.

Effects of methylprednisolone on disease severity. Safari et al[20] reported on therapy failure within two days of treatment (defined as persistent vomiting more than five times per day, inability to drink, and the participant's self-reported impression of improvement). Three participants in the methylprednisolone group and two participants in the promethazine group experienced therapy failure. Yost et al[21] did not report any measures of disease severity.

Effects of methylprednisolone on the length of hospital stay and readmission rates. In the study of Safari et al,[20] the length of hospital stay was not reported, but readmission rates were significantly lower among women randomized to methylprednisolone (0 of 17 vs. 5 of 15 readmissions; $P < 0.001$). Yost et al[21] found that the total length of hospital stay did not differ significantly between methylprednisolone and placebo (7.6 ± 18.0 vs. 4.3 ± 4.3 days; $P = 0.18$). Hospital readmission rates were similar for both treatment groups (19 of 56 vs. 19 of 54 readmissions; $P = 0.89$).

Effects of methylprednisolone on perinatal outcome. Safari et al[20] reported pregnancy outcomes for 12 participants in the methylprednisolone group and 11 participants in the promethazine group. There were no differences in birth weight and Apgar scores. One participant randomized to methylprednisolone delivered a child with a metabolic disorder, which resulted in neonatal death. In the study by Yost et al,[21]

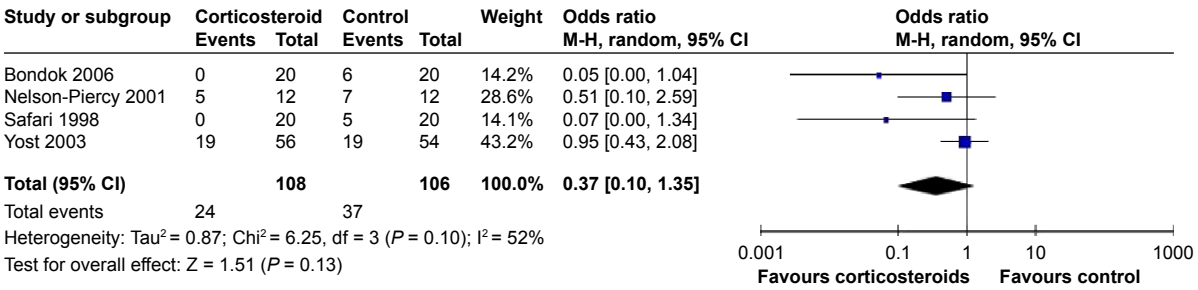

Figure 3. Forest plot of hospital readmissions for HG after treatment with corticosteroids compared to placebo or alternative therapy.

there were no differences in pregnancy complications and neonatal outcomes. There was one stillborn fetus in the methylprednisolone group and one major anomaly in the placebo group. There were no neonatal deaths.

Hydrocortisone and HG. Bondok et al[22] compared the effectiveness of intravenous hydrocortisone to intravenous metoclopramide in patients suffering from HG necessitating intensive care unit (ICU) admission. An intravenous tapering regimen was applied (Table 2).

Baseline characteristics. In each study group, 20 participants were randomized. Baseline characteristics were similar, with a mean gestational age of 10 ± 2.7 and 11 ± 2.4 weeks for participants randomized to hydrocortisone and metoclopramide, respectively.

Effects of hydrocortisone on disease severity. After one week of treatment, the mean number of vomiting episodes was significantly reduced in participants randomized to hydrocortisone when compared to metoclopramide (95.8 vs. 76.6% reduction; $P < 0.001$). A sharp decline in the number of vomiting episodes during the first three days was found in participants randomized to hydrocortisone, which was not observed in those randomized to metoclopramide ($P < 0.001$). Participants randomized to hydrocortisone had significantly higher serum albumin levels at day 7 (3.67 ± 0.29 g/dL) compared to participants randomized to metoclopramide (2.93 ± 0.31 g/dL; $P < 0.001$).

Effects of hydrocortisone on the length of hospital stay and readmission rates. The length of hospital stay was not reported. None of the 20 participants randomized to hydrocortisone were readmitted to the ICU, whereas 6 of 20 participants randomized to metoclopramide were readmitted to the ICU ($P < 0.001$).

Effects of hydrocortisone on perinatal outcome. The effects of intravenous hydrocortisone and metoclopramide on pregnancy or neonatal outcomes were not reported.

Meta-analysis. Due to the heterogeneity of studied outcomes, it was only possible to pool data for hospital readmissions.

Hospital readmission. Hospital readmission was reported in four studies[18,20–22] with a total of 214 participants, of whom 108 were treated with CCS and 106 received placebo or an alternative treatment. Hospital readmission was necessary for 24 participants treated with CCS (22%) compared to 37 participants in the control group (35%). Meta-analysis showed no significant effect of CCS on readmission rates (OR, 0.37; 95% CI: 0.10–1.35; $P = 0.13$). The results are summarized in a forest plot (see Fig. 3).

Publication bias. A funnel plot was created to visualize possible publication bias (see Fig. 4). Three small studies[18,20,22] reported a positive effect of CCS on hospital readmission rates,[18,20,22] while the largest study did not.[21]

Discussion

Our systematic search retrieved five randomized trials, with 310 participants, which studied the effects of CCS therapy on HG. Due to differential reporting of outcome measures, meta-analysis was possible only for one outcome. Our meta-analysis revealed no significant effect on readmission rates. Two small trials reported reduction of vomiting episodes and improvement of well-being among participants allocated to CCS, but no effect on the other outcomes. The trials were underpowered to investigate clinically relevant differences in perinatal outcomes.

Interpretation. The five trials each used different dosages of CCS. The best investigated CCS strategy to combat CINV is 8–20 mg of dexamethasone per day, in adjunct to

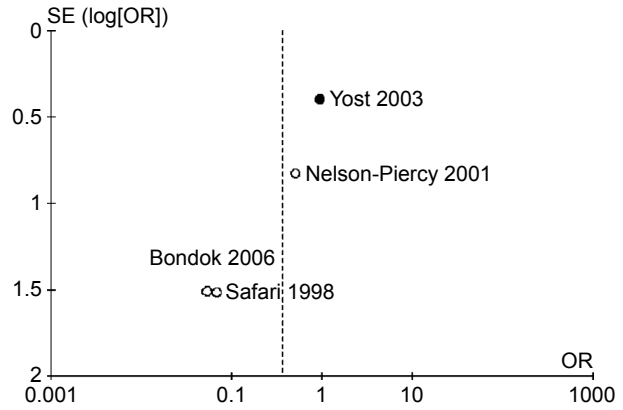

Figure 4. Funnel plot illustrating possible publication bias for studies reporting on hospital readmissions for HG after treatment with corticosteroids.

antiemetic medication.[9] Dexamethasone is generally avoided in pregnancy due to its higher biopotency and its ability to bypass the placental 11-P-hydroxysteroid-dehydrogenase-2 and exert effects on the developing fetus. The trial reported by Ziaei et al[19] employed a lower CCS equivalent dose (5 mg prednisolone ≈0.8 mg dexamethasone) than the standard CINV treatment; the other included studies employed similar[18,20,22] or higher doses.[21] We found no evidence for the hypothesis that a lack of effect on outcomes could be due to suboptimal CCS dosage strength: the largest trial retrieved by our systematic search[21] also employed the highest dose of CCS. This study found no improvement of any outcomes in comparison to placebo, making a dose–response effect of CCS on HG symptoms unlikely.

The mechanism of action by which CCS therapy is able to reduce nausea and vomiting is unknown. In the prevention and treatment of CINV, CCS are employed in combination with antiemetics[9] and have limited efficacy when used as monotherapy. Our study found no evidence that CCS therapy was efficacious only when employed in combination with antiemetics. The only study to report the continued use of CCS in combination with antiemetic therapy[21] found no effect on any of the outcomes. One study[18] reported increased well-being after CCS therapy, which might be a reflection of the fact that short-term CCS use has the potential to elevate mood.[23]

It is conceivable that CCS therapy may be more effective in more severe HG in comparison to NVP. The patients included in our systematic search results ranged from outpatient care to ward admission to ICU admission. Indeed, the study among outpatients found no evidence of effect,[19] whereas the study of patients admitted to the ICU did find an effect on reduction of vomiting episodes and lower rates of readmission when compared to metoclopramide.[22]

Due to small study sizes and lack of reporting congenital anomalies and long-term offspring health, our systematic review was unable to reach any conclusions regarding the possible harms of CCS administration in early pregnancy. Moreover, our study was not specifically designed to identify articles assessing adverse perinatal outcomes after the use of CCS, whether or not used for HG treatment. A meta-analysis of observational studies on CCS for NVP revealed no increase in the risk of major malformations. However, a subanalysis of only case–control studies revealed a small but significant increase in the risk of oral clefts after CCS exposure in the first trimester.[24]

An accumulating body of experimental evidence indicates that exposure to CSS could have programing effects on long-term health, including cognitive function, anxiety, and hypothalamic pituitary adrenal function.[16] Future studies of CCS administration in early pregnancy should include information on congenital anomalies and measures of long-term health.

Limitations. The majority of studies retrieved by our search were small, including between 12 and 20 patients per treatment strategy. Interestingly, the largest study we found reported negative findings, whereas the three smallest studies reported effects on some of the outcomes. The overrepresentation of small studies with positive findings raises the likelihood of publication bias. The studies included in our review were all published before registration of clinical trials became mandatory for funding agencies and for publication in the major journals.[25] A search in ClinicalTrials.gov did not yield any additional trials. We did not include conference abstracts in our search strategy and were, therefore, unable to further investigate the issue of publication bias.

The fact that each of the included trials applied a different definition of HG and studied a different combination of outcomes, hampered our ability to produce aggregated conclusions. Our efforts to retrieve supplementary data from the study authors to enable further meta-analysis were only partly successful. Consensus on a set of core outcomes would have improved our ability to reach firm conclusions, which has been the topic of recent publications.[26,27] Consensus on HG definition and core outcome sets for HG and NVP research should be prioritized by the HG research community to facilitate the interpretation of future trials.

Conclusion

Currently, there is insufficient evidence to support CCS in the treatment of HG. The available evidence is hampered by small study size, inconsistent diagnosis definition, publication bias, low study quality, and lack of consensus on both short- and long-term outcomes. Although, in severe HG cases, CCS treatment might still be considered as a treatment of last resort, there is an urgent need for an adequately powered placebo-controlled RCT, which investigates the utility of CCS in combination with antiemetics in patients with refractory HG. This trial should study the effectiveness and safety of CCS therapy for both mothers and offspring, when prescribed in combination with antiemetics.

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Author Contributions

Conceived and designed the experiments: IJG and RCP. Analyzed the data: IJG and MEV. Wrote the first draft of the manuscript: MEV and RCP. Contributed to the writing of the manuscript: IJG and RCP. Agreed with manuscript results and conclusions: IJG, MEV, TJR, and RCP. Jointly developed the structure and arguments for the paper: IJG, MEV, and RCP. Made critical revisions and approved the final version: IJG, TJR, and RCP. Edited the manuscript's English: RCP. All the authors reviewed and approved the final manuscript.

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Supplementary Material

Supplementary Table 1. Extended table on the risk of bias of included trials.

BIAS	AUTHOR'S JUDGMENT	SUPPORT FOR JUDGMENT
Nelson-Piercy[18]		
Random sequence generation	Low risk	Randomization was performed by computer generated allocation
Allocation concealment	Low risk	Study medication was pharmacy-controlled (the code was held and medication was dispensed by pharmacies of participating hospitals)
Blinding of participants, personnel and outcome assessors	Low risk	The trial was double-blinded. Tablets provided to both randomization groups were identical in appearance
Incomplete outcome data	Low risk	Information on participant attrition was provided. Only one participant withdrew from the study
Selective reporting	Unclear risk	Outcomes were pre specified, but some outcomes have been reported in not pre specified ways
Other sources of bias	High risk	Inclusion of participants stopped prematurely for several reasons, including departure of key staff members and the erroneous belief among involved caregivers that because one of the treatment strategies under study was clearly effective and therefore randomization was unethical
Ziaei[19]		
Random sequence generation	High risk	Non-random components were used (gestational age, gravidity, maternal age and severity of symptoms)
Allocation concealment	High risk	A list of random numbers was used
Blinding of participants, personnel and outcome assessors	High risk	The main investigator was blinded to study medication, but due to unequal medication regimens for both randomization groups, patients could not have been blinded, while outcome measures were self-reported
Incomplete outcome data	Low risk	Participant attrition was addressed
Selective reporting	Low risk	All outcome measures were reported
Other sources of bias	Low risk	None
Safari[20]		
Random sequence generation	Low risk	Randomization was performed by computerized random number generator
Allocation concealment	Low risk	Sequentially numbered envelopes were used. They were prepared by a third part not involved in the study
Blinding of participants, personnel and outcome assessors	Unclear risk	It was stated that the primary investigators, attending physicians and patients were blinded to study medication but that nurses dispensing medication could observe a difference in shape. It was not described whether the number of pills prescribed per day was unaffected by the tapering regimen of the intervention treatment. Therefore blinding of participants was not clear, while self-reported outcome measures were used
Incomplete outcome data	Low risk	Information on participant attrition was provided. The number of participants lost to follow-up was equal for both randomization groups
Selective reporting	High risk	A composite outcome of response to treatment was defined (primary outcome), but only certain aspects have been reported without statistical testing
Other sources of bias	High risk	There was a significant inequality at baseline of disease duration, which is a marker of disease severity and thus has a high risk of affecting study outcomes. Authors do not state that they have adjusted their analyses for disease duration at study entry. Furthermore, the chosen strategy by the researchers to end study participation when symptoms did not improve within two days is questionable
Yost[21]		
Random sequence generation	Low risk	Randomization was performed by computer-generated blocks of 20
Allocation concealment	Low risk	Study medication was pharmacy-controlled (dispensed by the investigational drug service of the trial hospital)
Blinding of participants, personnel and outcome assessors	Low risk	The trial was double-blinded. Tablets provided to both randomization groups were identical in appearance
Incomplete outcome data	Low risk	Information on participant attrition was provided. Baseline characteristics of participants lost to follow-up were not different from those who completed the study

(*Continued*)

Supplementary Table 1. (*Continued*)

BIAS	AUTHOR'S JUDGMENT	SUPPORT FOR JUDGMENT
Selective reporting	Unclear risk	Primary and secondary outcome measures were not defined sufficiently
Other sources of bias	Low risk	None
Bondok[22]		
Random sequence generation	Low risk	Randomization was performed by computer randomization list
Allocation concealment	Unclear risk	Randomization code was held, but insufficient information on method of concealment was given (i.e. sequentially numbered drug containers)
Blinding of participants, personnel and outcome assessors	Low risk	The main investigator, clinicians, nurses and patients were blinded to study medication. Drug containers were identical in appearance and medication regimen was equal for both randomization groups
Incomplete outcome data	Unclear risk	No information on participant attrition was provided
Selective reporting	High risk	A composite outcome of response to treatment was defined (primary outcome), but only certain aspects have been reported
Other sources of bias	Low risk	None