A systematic review and narrative synthesis of antenatal interventions to improve maternal and neonatal health in Nepal

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BACKGROUND: Maternal and neonatal mortality rates remain high in many economically underdeveloped countries, including Nepal, and good quality antenatal care can reduce adverse pregnancy outcomes. However, identifying how to best improve antenatal care can be challenging.

OBJECTIVE: To identify the interventions that have been investigated in the antenatal period in Nepal for maternal or neonatal benefit. We wanted to understand their scale, location, cost, and effectiveness.

STUDY DESIGN: Online bibliographic databases (Cochrane Central, MEDLINE, Embase, CINAHL Plus, British Nursing Index, PsycInfo, Allied and Complementary Medicine) and trial registries (ClinicalTrials.gov and the World Health Organization Clinical Trials Registry Platform) were searched from their inception till May 24, 2020. We included all studies reporting any maternal or neonatal outcome after an intervention in the antenatal period. We screened the studies and extracted the data in duplicate. A meta-analysis was not possible because of the heterogeneity of the interventions and outcomes, so we performed a narrative synthesis of the included studies.

RESULTS: A total of 25 studies met our inclusion criteria. These studies showed a variety of approaches toward improving antenatal care (eg, educational programs, incentive schemes, micronutrient supplementation) in different settings (home, community, or hospital-based) and with a wide variety of outcomes. Less than a quarter of the studies were randomized controlled trials, and many were single-site or reported only short-term outcomes. All studies reported having made a positive impact on antenatal care in some way, but only 3 provided a cost-benefit analysis to support implementation. None of these studies focused on the most remote communities in Nepal.

CONCLUSION: Our systematic review found good quality evidence that micronutrient supplementation and educational interventions can bring important clinical benefits. Iron and folic acid supplementation significantly reduces neonatal mortality and maternal anemia, whereas birth preparedness classes increase the uptake of antenatal and postnatal care, compliance with micronutrient supplementation, and awareness of the danger signs in pregnancy.

Key words: antenatal care, antenatal education, birth preparedness, cash incentive, female community health volunteers, global health, maternity incentive, maternal mortality, micronutrients, neonatal mortality, participatory learning, systematic review

Introduction

The United Nations' Sustainable Development Goals (SDG) demand significant reductions in global maternal and neonatal mortality[1] by 2030, with targets of no more than 70 maternal deaths per 100,000 deliveries and no more than 12 neonatal deaths per 1000 live births. Effective antenatal care can improve both maternal and neonatal outcomes,[2,3] but its design and provision is complex.

South Asia reduced its maternal mortality ratio (MMR) by nearly 60% between 2000 and 2017, and Nepal's efforts contributed to that success with a reduction by 79% (from 901 to 186 per 100,000) between 1990 and 2017.[4]

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This study was conducted in Kathmandu, Nepal, and Bristol, United Kingdom.

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Why was this study conducted?

This study aimed to identify the antenatal interventions that have been investigated in Nepal for maternal or neonatal benefit, to help guide decision-making regarding what research avenues to pursue, and to identify the interventions that need to be implemented on priority.

Key findings

The most reported interventions involved micronutrient supplementation or education, and the majority of them showed some improvement in either uptake of care or maternal or neonatal outcomes. Only 3 studies reported cost analysis, and none were conducted in the most remote parts of Nepal.

What does this add to what is known?

Antenatal micronutrient supplementation and educational interventions have successfully improved maternal and neonatal outcomes in Nepal. Implementation research must consider the hardest-to-reach communities and must involve cost analyses to aid the translation of the results from publication to practice.

This is despite widespread poverty after the civil war (1996−2006), geographic challenges of mountainous regions, and extensive earthquake damage in 2015. However, if the SDG targets are to be met, the progress must be accelerated.

The improvements in maternal, neonatal, and child health (MNCH) in Nepal have often been attributed to the government's commitment to make maternity care accessible to all. Their safe motherhood program includes the provision of free maternity services in government hospitals and involves the "Aama" maternity incentive scheme,[5] which provides a small monetary incentive for giving birth in a facility with a skilled birth attendant (SBA) and giving attendance at 4 antenatal appointments.[6] However, several community-based trials in the antenatal period have been conducted in South Asia since 1990, showing that antenatal interventions in this region can significantly improve MNCH outcomes, and these may have contributed to the advancements seen in Nepal. For example, in Uttar Pradesh, India, a community-based behavior-change intervention led to a 54% reduction in the neonatal mortality (NMR).[7] In Pakistan, an intervention to provide outreach antenatal care through extra training for traditional birth attendants showed a 30% reduction in neonatal morbidity, although the effect on maternal mortality was less conclusive.[8] In Makwanpur, Nepal, a participatory intervention with women's groups led to a 29% reduction in the NMR and an 80% reduction in the MMR.[9] Pharmacologic treatments in the antenatal period have also been shown to improve outcomes—the provision of low-dose aspirin in pregnancy has been shown to reduce the rates of preeclampsia, preterm birth, and fetal and neonatal death.[10] Calcium supplementation has been shown to reduce the rates of preeclampsia and maternal mortality or serious morbidity.[11] To date, there has been no comprehensive overview of antenatal interventions that have already been trialed in Nepal (and to what effect).

Our aim was to identify the antenatal interventions already trialed in Nepal and understand their scale, location, cost, and effectiveness. In doing so, we aimed to establish the interventions that have the greatest potential to improve maternal and neonatal outcomes within Nepal and in other comparable settings worldwide.

Materials and Methods

Search strategy

Online bibliographic databases (Cochrane Central, MEDLINE, Embase, CINAHL Plus, British Nursing Index, PsycInfo, Allied and Complementary Medicine) and trial registries (ClinicalTrials.gov and the World Health Organization Clinical Trials Registry Platform) were searched from inception till May 24, 2020. There were no language restrictions, and both free-text and subject headings were used. The free-text search terms used included "Nepal* and Antenatal*," "Antepartum," "Prenatal," "Perinatal," and "birth preparedness." The full search strategy is available in Appendix A. The reference lists of all included articles were screened.

Study selection

We included all the studies reporting outcomes following an antenatal intervention in Nepal. The study participants were pregnant women and their partners and families. We considered studies of all designs but excluded those where only abstracts, protocols, or trial registrations were available or where the results were not published.

The protocols for included studies were covered as they provided a methodological background. We included the articles describing interventions in all settings, and no restrictions were placed on the year of study or the length of follow-up. Multicountry studies were included as long as it was possible to extract the Nepali data. The eligibility of the studies was assessed by at least 2 of the authors (K.B., M.T., M.L., N.M., A.M.), with conflicts resolved by discussion.

Data extraction

We used a data extraction form to collect the data in duplicate from the included studies. The data extracted included the intervention, outcomes, aims, study design, information about participants, location and duration of study, and any cost-effectiveness analysis. Any discrepancies were resolved by discussion.

Quality assessment

We assessed the risk of bias and the quality of studies using standardized tools. To assess the quality of included studies, we used the Consolidated Standards of Reporting Trials (CONSORT) checklist for randomized trials,[12] Strengthening the Reporting of Observational studies in Epidemiology (STROBE) for observational studies,[13]

Consolidated Criteria for Reporting Qualitative Research (COREQ) for qualitative studies,[14] and Standards of Quality Improvement Reporting Excellence (SQUIRE) for quality improvement.[15] To assess the risk of bias, we used the Newcastle-Ottawa scale[16] for nonrandomized studies and the Cochrane risk of bias tool[17] for randomized controlled trials (RCTs). We used the Weight of Evidence[18] tool for assessing the relevance of the study and to summarize the findings of our quality and the risk of bias assessments (Table 1). We developed a scoring system to enable the classification of the studies into high, medium, and low quality using the CONSORT, STROBE, and SQUIRE tools, respectively (Table 2). We developed a further scoring system to enable the classification of studies into low, medium, and high risk of bias using the Newcastle-Ottawa scale (Table 3). The numerical thresholds for each category were determined through discussion, with all the authors performing quality assessment. The studies assessed using COREQ and the Cochrane risk of bias tool were discussed and categorized on a case-by-case basis. We did not exclude any study based on the risk of bias or quality assessment results but followed the Cochrane guidance for reporting the effects of interventions and the certainty of the evidence provided.[19] Owing to the large number of different outcomes in this review, we did not specify the smallest important difference for each outcome before analysis. We assessed the importance of the effects seen based on how likely it seemed that our conclusions would hold if the true effect lay near either end of the 95% confidence interval.

Analysis

Owing to the heterogeneity in the study design and the outcomes reported, it was not possible to perform a meta-analysis. Instead, we performed a narrative synthesis using Popay methodology.[20] We tabulated the findings of the included studies and grouped the studies by the reported outcome.

Registration

The review protocol was registered with the International Prospective Register of Systematic Reviews (registration number, CRD42019128545). The review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix B, PRISMA reporting checklist).

Funding

The funding for this project was provided by the University of Bristol Global Challenges Research Fund, and 2 members of the research team were funded by the National Institute for Health Research. Neither funder played any role in the study design.

Results

The searches retrieved 4909 records, with a further 20 records identified through other sources. After deduplication, 1419 records remained, of which 1093 were removed at the abstract screening stage. A total of 326 full texts were reviewed, following which 49 papers describing 25 studies were included (Figure 1).

Of note, 6 studies were RCTs,[21–26] and 6 more were nonrandomized controlled, that is, cluster-controlled[27–30] or were before and after studies.[31,32] In addition, 9 were cohort studies,[33–41] 2 were cross-sectional,[42,43] 1 was a pure qualitative study[44], and another had cluster-controlled and qualitative elements.[45] Notably, 15 of the studies involved community-based interventions,[22,23,26–29,31,34,36–40,44,45] 9 were hospital-based,[21,24,25,30,32,33,35,42,43], and 1 contained elements of both.[41] The detailed summaries of the included studies can be found in Table 4. The types of interventions reported in the included studies are shown in Figure 2, and the study locations are shown in Figure 3.

Description of quality

More than half of all studies (14/25)[22–24,27,31–35,37,40,41,43,44] were of medium or low quality, and a similar number (13/25)[22,23,27,31–33,37,40–45] were at a medium or high risk of bias (Table 1).

Effect of interventions

Owing to the diversity of interventions, we have presented the findings according to the outcome measures.

Maternal clinical outcomes. *Iron supplementation reduces iron deficiency anemia.* Notably, 6 studies involved iron supplementation, and all showed reductions in the rates of iron deficiency anemia. The mean hemoglobin (Hb) increased following treatment with iron sucrose therapy[32,39,46] and with iron supplementation alongside vitamin A and riboflavin.[22] Greater improvements in the Hb levels were seen when an educational package was delivered alongside the supplementation, compared with supplementation alone or supplementation with pill counting, although the differences in the mean change to hemoglobin were small.[21] Another study showed that nutritional counseling accompanied by dietary assessment and menu planning leads to slightly greater increases in Hb levels than nutritional education alone.[30] The final study found that women who were not compliant with iron supplementation antenatally were 24 times more likely to be anemic (Hb<110) 1 month postpartum compared with those who were compliant.[43]

Vitamin A supplementation reduces night blindness. Both studies involving vitamin A supplementation showed a reduction in night blindness.[22,23] One showed that the symptoms of night blindness improved after 6 weeks of supplementation regardless of the source of the vitamin A; however, the biggest improvements in the plasma retinol concentrations were found in the groups receiving vitamin A from goat liver or capsule supplements.[23] The other study showed that in women reporting night blindness preintervention, bigger improvements to pupillary thresholds were seen when vitamin A supplements were accompanied by iron and riboflavin, compared with the supplements being taken alone.[22]

Influenza vaccination slightly reduces laboratory-confirmed influenza among infants but not mothers. One RCT showed that the influenza

TABLE 1
Quality, risk of bias, and relevance assessment

Study	Quality assessment	Risk of bias	Relevance
Acharya et al,[27] 2018	Medium	Medium	High
Acharya 2020	Medium	Medium	Medium
Adhikari et al,[21] 2009	High	Low	High
Bhatt et al,[42] 2018	High	Medium	Medium
Choulagai et al,[28] 2007	High	Low	High
De et al,[34] 2015	Medium	Low	Low
Devkota et al,[35] 2017	Medium	Low	Medium
Flueckiger et al,[44] 2018	Low	High	Low
Graham et al,[22] 2007	Medium	Medium	High
Haskell et al,[23] 2005	Medium	Medium	High
Hodgins et al,[36] 2010	High	Low	High
Karkee et al,[xx] 2013	Medium	Medium	Medium
Kozuki et al,[xx] 2016	High	Low	High
McPherson et al,[31] 2006	Medium	High	High
Mullany et al,[27] 2007	Medium	Low	High
Nisar et al,[46] 2014	High	Low	High
Osrin et al,[25] 2005	High	Low	High
Pokharel et al,[40] 2011	Medium	Medium	High
Saville et al,[29] 2018	High	Low	High
Sharma et al,[32] 2015	Low	High	Medium
Steinhoff et al,[26] 2017	High	Low	High
Sunuwar et al,[30] 2019	High	Low	High
Thapa et al,[41] 2016	Medium	Medium	Medium
Thapa et al,[45] 2019	High	Medium	High
Yadav et al,[43] 2019	Medium	Medium	High

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vaccination may have slightly reduced maternal influenza-like illnesses, but it made little or no difference to infant influenza-like illnesses. Meanwhile, the same vaccination slightly reduced the rate of laboratory-confirmed influenza among infants but had no important effect on the rate of laboratory-confirmed influenza among mothers.[26,47,48]

Antenatal pelvic floor muscle training is acceptable to pregnant women. One feasibility study concluded that pelvic floor muscle training (PFMT) is feasible and acceptable alongside antenatal care (ANC). Women who attended 4 PFMT sessions reported between 50% and 100% daily compliance with pelvic floor exercises. This feasibility study was not powered to identify a reduction in the symptoms of urinary incontinence or pelvic organ prolapse.[33]

Neonatal clinical outcomes. Iron–folic acid supplementation reduces neonatal mortality. Taking any iron–folic acid (IFA) supplementation during pregnancy was shown to reduce the risk of neonatal mortality by 42% in one study, but the effect was bigger (55%) when the mothers took 150 to 240 supplements of any dosage during pregnancy[39] or when mothers took >90 supplements and started these before 5 months gestation (57% reduction).[46]

Education, supplements, and food incentives all reduce rates of low birthweight babies. One study found a 25% reduction in the proportion of low birthweight babies when women took a multiple micronutrient tablet instead of a standard IFA.[25,49] Another study showed that extra training for female community health volunteers (FCHVs) and health-promoting text messages for pregnant women reduced the rates of low birthweight babies.[27,50] A final study showed that education alongside food incentives probably led to a small increase in the average birthweight, but education alone and education with cash incentives made little or no difference to the average birthweight.[29,51,52]

Pregnancy and birth knowledge. Birth preparedness classes and group antenatal care improve awareness of danger signs in pregnancy and knowledge of essential newborn practices. Attendance of birth preparedness classes (BPCs) was shown to increase the use of essential newborn practices such as breastfeeding within an hour of birth in one study,[31] whereas another showed an increase in the awareness of pregnancy-related danger signs following BPCs.[36,53,54] A further study found moderate evidence that women who attended BPCs with their husbands increased their knowledge scores slightly more than women attending alone.[24,55] This may be because of increased communication between spouses regarding health practices during or after the classes, leading to a better understanding and retention of new information. A similar finding was reported by a study looking at the impact of group ANC in comparison with individual ANC. They found that women in group ANC were better at identifying the danger signs in pregnancy and reported enjoying their ANC more.[45,56,57] There were no important differences between the 2 groups for any of the other maternal or neonatal outcomes assessed.

Education about medication increases compliance and reduces self-medicating. Two hospital-based interventions showed that knowledge regarding medication use improved following counseling sessions.[21,35] One of these studies showed that medication education reduced self-medication by the patients,[35] whereas the other showed a slightly improved compliance with iron supplementation when compared with pill counting only.[21] In a final,

TABLE 2
Scoring criteria for quality assessment

Quality assessment scale	Low	Medium	High
CONSORT	0–11	12–20	21–25
STROBE	0–8	9–15	16–22
SQUIRE	0–25	26–40	41–50
COREQ	Determined through case-by-case discussion		

CONSORT: Scores were awarded out of maximum of 25. Points were awarded if specific, relevant details were present in the background, methodology, analysis, and results. Points were also awarded if the trial was registered before commencing recruitment, if a protocol was publicly available, and if any sources of funding were disclosed.

STROBE: Scores were awarded out of a maximum of 22. Points were awarded if specific, relevant details were present in the background, methods, analysis, and results, and if limitations and generalisability were addressed. Points were also awarded for disclosure of sources of funding.

SQUIRE: Scores were awarded out of a maximum of 50. Points were awarded for a clear title, abstract and background; for including key aspects within the described methods and result; for discussion of strengths, limitations, and generalisability, and for providing clear conclusions including the practical usefulness of the intervention going forwards.

CONSORT, Consolidated Standards of Reporting Trials; *COREQ*, Consolidated Criteria for Reporting Qualitative Research; *STROBE*, Strengthening the Reporting of Observational studies in Epidemiology; *SQUIRE*, Standards of Quality Improvement Reporting Excellence.

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community-based study, it was found that training FCHVs to give enhanced counseling may have increased iron and folic acid supplementation compliance rates, but the certainty in the evidence is very low because of large differences in the baseline compliance rates for the participants in the intervention and control sites.[40]

Healthcare utilization. *Community birth preparedness classes may increase attendance of antenatal care.* All 3 large studies looking at BPCs (with 6285 participants collectively) showed an increase in the ANC attendance after intervention.[31,36,37,53,54,58–60] One reported a 24% increase in the number of women attending ≥2 ANC visits[31] after BPCs, whereas the other 2 showed increases in the proportion of women receiving care at least once in their pregnancy.[28,36,53,61] However, in one of these studies, the rate change in women attending 4 ANC visits was lower in the intervention group compared with the control group, which highlights the possibility of confounding factors increasing the ANC visit numbers around the time the study was taking place. This reduces the certainty with which these increases in care-seeking can be associated with the BPCs alone.[28] The uptake and awareness of the government's "Aama Programme," for example, was increasing over the period of this study (2011–2014), and it provided women throughout Nepal with a monetary incentive for attending 4 ANC appointments.[42] Women's literacy in Nepal, which has been linked with improved health awareness and outcomes in general, also increased over this period.[62]

Maternity incentive schemes increase attendance of antenatal care. In a study assessing the impact of the government-funded maternity cash incentive program, women were 6 times more likely to have attended 4 ANC visits after the implementation of the policy than before it.[42] However, rising education levels in the intervening period are also strongly associated with increasing ANC visits. Therefore, in the absence of a control group, it is again difficult to rule out the confounding factors contributing to this observed trend. The final study in this group used qualitative methods to further explore the link between incentives and ANC attendance. It found that caregivers and stakeholders saw cash incentives as a motivating factor in pregnant women's attendance of ANC visits, although the women themselves had mixed ideas about the influence of this incentive.[44]

The relationship between birth preparedness classes and uptake of skilled birth attendants is uncertain. Two studies found that BPCs led to an increase in the use of SBAs by pregnant women,[36,53] but a third study found that the use of SBAs remained low and unchanged after the introduction of BPCs.[31] A fourth study showed that women who were attending BPCs and knew any antepartum, intrapartum, or postpartum danger signs were more likely to deliver at a health facility.[37,58–60] However, this study did not test the effect of the birth preparedness intervention directly but rather tested the effect of pregnant women's levels of birth preparedness knowledge. Therefore, firm conclusions about causation cannot be made.

Birth preparedness classes increase uptake of postnatal services. The same study which found no increase in SBA use found an increase in the use of postnatal services with a birth preparedness package.[31] Another BPC study found that increases in the uptake of postnatal services were slightly

TABLE 3
Scoring criteria for risk of bias assessment

Risk of bias assessment	High	Medium	Low
Newcastle-Ottawa scale	1–4	5–6	7–9
Cochrane risk of bias	Determined through case-by-case discussion		

Newcastle-Ottawa scale: Scores awarded out of 9 based on how well the study meets the criteria related to participant selection (up to 4 points); how well the study controls for confounding factors (up to 2 points); and for the reporting of study outcomes (up to 3 points). A low score suggests the study carries a high risk of bias, and a high score suggests a low risk of bias.

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TABLE 4
Included studies

Study	Intervention details	Study details	Outcomes
Acharya et al,[27] 2018 Singh et al,[50] 2018	1. Capacity building of FCHVs (reinforcement training on maternal and newborn health followed by regular supervision) for the promotion of health- seeking behavior among pregnant women, including birth preparedness. 2. Periodic health promotion texts to pregnant women about maternal and child health components.	Design: Cluster RCT Setting: Community Duration: Unclear District: Dhanusha No. received intervention: 426	**Low birthweight (LBW):** Mothers in the intervention area were less likely (aOR, 0.37; 95% CI, 0.16−0.83) to have an LBW baby than mothers not in the intervention area. **Cost:** Not documented.
Acharya, et al, [33] 2020	The intervention involved questionnaires about the symptoms of urinary incontinence (UI) and pelvic organ prolapse (POP) before and after 4 sessions of pelvic floor muscle training (PFMT). The training sessions involved a video and teaching sessions with a specialized women's health physiotherapist. These 4 PFMT sessions were held alongside regular antenatal care (ANC) appointments.	Design: Cohort Setting: Hospital Duration: 11 mo District: Kavrepalanchok No. received intervention: 164	**Acceptability of intervention:** Notably, 57% of the pregnant women attended ≥4 PFMT visits and approximately 50% of these women reported 50% −100% adherence to daily PFMT. Even though most of them did not suffer from UI or POP, the women met for PFMT visits and performed PFMT at home. They reported they were motivated to prevent these conditions. **Symptoms of POP or UI:** There was no difference in the symptoms of POP or UI between the women who attended all 4 sessions of PFMT and those who attended 0−3 sessions. **Cost:** Not documented.
Adhikari et al,[21] 2009	Iron supplementation: Daily dose of 60 mg of elemental iron, alone or with pill counting (unused pills counted monthly) and/or education programme concerning iron and anemia (an initial direct counseling session and an educational brochure).	Design: RCT Setting: Hospital Duration: 3 mo District: Kathmandu No. received intervention: 320	**Hemoglobin (Hb) levels:** Education alone significantly increased Hb (difference in mean change, 0.23 g/dL; 95% CI, 0.07−0.39), as did education with pill count (difference in mean change, 0.26 g/dL; 95% CI, 0.10−0.42). Compared with the control group, pill count did not significantly increase Hb. **Anemia prevalence:** Education alone reduced anemia prevalence (OR, 0.41; 95% CI, 0.18−0.91), as did education with pill count (OR, 0.35; 95% CI, 0.16−0.78; *P*<.01). Compared with the control group, pill count did not significantly reduce anemia. **(Education groups only) knowledge about anemia and iron intake during pregnancy:** The mean knowledge scores among women in the education alone and education with pill count groups at the baseline evaluation were 9.4 and 10.7 and at the end of the study were 24.7 and 25.2, respectively. No significant difference in knowledge in education alone vs with pill count groups (*P*>.05). **(Pill count groups only) pill compliance:** Iron supplementation compliance was higher in the education with pill count group than the pill count only group (88% vs 73%, *P*<.001). **Cost:** Not reported.
Bhatt et al,[42] 2018	Government Free Delivery Care policies, notably the "Aama Programme," which provided cash incentives for women completing ≥4 ANC visits.	Design: Cross-sectional Setting: Hospital Duration: Unclear (>15 y) District: Nationwide No. received intervention: 16,837	**Attendance of 4 ANC visits:** Between 1994 and 2011, women visiting 4 ANC has increased from 9.2% to 54.3%. After adjusting for FDC policy, individual, and community level factors, women were 3 times more likely to attend 4 ANC visits than women who were pregnant when there was no incentive scheme (aOR, 3.020; *P*<.001). Similarly, women were 6 times (aOR, 6.006; *P*<.001) more likely to have attended 4 ANC visits after the implementation of "Aama." **Cost:** Not documented.
Choulagai et al,[28] 2017 Bhandari et al,[61] 2014	Intervention to increase skilled birth attendant (SBA) service utilization. The intervention elements included the following: promotion of family support to pregnant women for childbirth in a health facility and training for health facility staff in communication skills to encourage a women-friendly environment.	Design: Cluster RCT Setting: Community Duration: 19 mo District: Bajhang, Dailekh, Kanchanpur No. received intervention: 1746 intervention 2098 control	**SBA attendance:** Skilled birth care increased from 30.4% (baseline) to 56.5% (after intervention) in the intervention group. This change is 5.0% (*P*=.06) greater than the rate change in the control group. **ANC visits:** Notably, 92.4% of participants in the intervention group attended at least 1 ANC visit after intervention, compared with 83.4% at baseline. This change is 4.0% (*P*=.03) greater than the rate change in the control group. In addition, 60.9% of participants in the intervention group attended ≥4 ANC visits after intervention, compared with 46.4% at baseline. However, this change is 3.1% lower than the rate change in the control group. The mean number of ANC visits in the intervention group increased from 2.8 to 3.3, which is 0.2 greater than the change in the control group. **Cost:** Not documented.
De et al,[34] 2015 **De et al,[64] 2014**	Women were grouped into low- or high-risk categories using a simple scoring system based on obstetrical history. Changes to risk categorization were made as pregnancy progressed to take into account new information, for example, breech, APH.	Design: Cohort Setting: Community Duration: 12 mo District: Dulegauda, Tanahu No. received intervention: 187	**Neonatal complications:** The frequency of complications, for example, feeding problems, jaundice, and oral thrush was higher (27.79%) in the high-risk groups as compared with 3.6 % in the low-risk groups. **LBW:** Of 46 high-risk pregnancies, 6 (13.04%) resulted in LBW newborns. The corresponding number in the low-risk group was 5 (3.55%). **Neonatal death:** Neonatal deaths were 1 (0.7%) in the low-risk and 3 (6.52%) in the high-risk group. **Cost:** Not documented.

(continued)

TABLE 4
Included studies *(continued)*

Study	Intervention details	Study details	Outcomes
Devkota et al,[35] 2017	Antenatal counseling regarding medication use.	Design: Cohort Setting: Hospital Duration: 4 mo District: Fulbari, Kaski No. received intervention: 275	**Knowledge:** The mean knowledge scores increased from 8.8±3.6 to 12.86±1.27 of 20. This encompassed knowledge about their complications, their medicine name and uses, and medicine safety. **Attitude:** The mean attitude scores increased from 15.2±1.9 to 17.81±1.55 of 20. **Medicine practice:** The mean practice scores increased from 11.8±2.6 to 15.96±2.05 of 20. The percentage of respondents taking medicines without consultation reduced from 64.2% to 2.2%. **Cost:** Not documented.
Flueckiger et al,[44] 2018	Monetary incentives for attending 4 ANC visits and delivering in a healthcare facility.	Design: Qualitative Setting: Community Duration: Unclear (<12 mo) District: Sahare No. received intervention: 37	**Motivation for attending 4 ANC visits:** All mothers and caregivers expressed that the primary motivation for ANC attendance and institutional delivery is concern for the health of the mother and baby. Mothers were divided on whether the monetary incentive was motivating for them to attend ANC visits. All caregivers noted the monetary incentive as a motivating factor. The majority of the stakeholders expressed that the monetary incentive plays a motivating role in ANC attendance and that attendance has increased. **Cost:** Not documented.
Graham et al,[22] 2007	Vitamin A (and iron and riboflavin) supplementation: Nightblind pregnant women were randomly assigned to receive (6 d/wk under supervision for 6 wk) a vitamin A–fortified rice curry dish providing 850 μg retinal activity equivalents/d with either a 30-mg Fe and 6-mg riboflavin (FeR+VA) capsule or a placebo control (VA only) capsule.	Design: RCT Setting: Community Duration: 22 mo District: Saptari No. received intervention: 55 intervention 51 control	Women who were iron deficient at baseline (n=38) had significantly greater improvement in PT score with iron and riboflavin supplementation than without (P=.05). Iron and riboflavin supplements significantly reduced the prevalences of riboflavin deficiency (from 60% to 6%; P<.0001), iron deficiency anemia (from 35% to 15%; P<.007), and abnormal PT (from 87% to 30%; P<.05) from baseline. Mean increases in erythrocyte riboflavin (P<.0001) and plasma ferritin (P=.01) were greater in the FeR+VA group than in the VA only group. **Cost:** Not reported.
Haskell et al,[23] 2005	Vitamin A (and iron and riboflavin) supplementation: women received (6 d/wk for 6 wk) a meal supplemented with 850 μg vitamin A equivalents as retinyl palmitate, vitamin A–fortified rice, goat liver, amaranth leaves, carrots, or 2000 μg vitamin A as retinyl palmitate.	Design: RCT Setting: Community Duration: 22 mo District: Saptari No. received intervention: 397 (divided into the 6 intervention groups)	**Symptoms of night blindness:** Dark adaptation improved on average in all groups of night blind women who received small daily doses of vitamin A for 6 wk, regardless of the source of vitamin A. At the end of the study, only 2 women (0.6%) reported that they still had symptoms of night blindness. **Pupillary threshold:** Among women who initially reported night blindness, the initial and final mean PTs were −0.71±0.04 and −1.42±0.02 log cd/m^2 (P<.0001), respectively, which indicates improvement in dark adaptation after 6 wk of supplementation. Mean PTs decreased significantly (P<.0001) in all treatment groups during the 6-wk intervention. **Change in plasma retinol concentrations:** Among the women who initially reported night blindness, the initial and final mean plasma retinol concentrations were 0.96+0.05 μmol/L and 1.07+0.05 μmol/L, respectively (P<.0001). The final mean plasma retinol concentration in the goat liver group was significantly (P<.05) higher than that in the groups that received the same prescribed amount of vitamin but not significantly different from the final mean concentration in the high-dose capsule group. **Change in plasma carotenoid, ferritin, zinc, and Hb concentrations:** The final mean plasma concentrations of carotenoids and α-tocopherol differed significantly by treatment group in response to supplementation. **Cost:** Not reported.
Hodgins et al,[36] 2010 VRG 2007 McPherson et al,[54] 2010	A community level birth preparedness package, incorporating home-based antenatal counseling, postnatal home visits, and prescriptions of iron/folate in pregnancy and iron and vitamin A postnatally.	Design: Cohort Setting: Community Duration: 2 y District: Banke, Jhapa, Kanchanpur No. received intervention: VRG: 2640 women 859 husbands 814 mothers-in-law Hodgins et al,[36] 2010: 1740 women	*From Valley Research Group (VGR) report:* **Knowledge:** Awareness by recently delivered women of at least 3 pregnancy-related danger signs also increased significantly (26%–54% in Jhapa, 46%–87% in Banke, and 17%–67% in Kanchanpur). **Service utilization:** The percentage of recently delivered women (RDW) who received prenatal care at least once from appropriate ANC providers increased (from 74% at baseline to 88% at follow-up in Jhapa, 77%–91% in Banke and 81%–88% in Kanchanpur). Use of skilled birth attendants increased. Overall, at follow-up 45% of the RDW in Jhapa (vs 36% at baseline), 17% in Banke (vs 11% at baseline) and 24% in Kanchanpur (vs 17% at baseline) reported delivering their last child with the assistance of skilled providers (doctor, staff nurse, or auxiliary nurse midwife [ANM]). **Care-seeking during emergencies:** The percentage of RDW who sought care from a health facility for danger signs during labor increased in Banke (25%–31%) and in Kanchanpur (30%–46%) but remained essentially unchanged in Jhapa (54% at baseline; 55% at follow-up) **Cost:** The booklet cost $0.60 to produce. Other cost details not reported.
Karkee et al,[37] 2013b Karkee et al,[58] 2013a Karkee et al,[59] 2014a Karkee et al,[60] 2014b	The Birth Preparedness and Complication Readiness (BP/CR) program, initiated in 2002 by the government. More details are indicated in the study by McPherson et al,[31] 2006.	Design: Cohort Setting: Community Duration: 11 mo District: Kaski No. received intervention: 701	**Association between obstetrical knowledge and place of delivery:** Women who acknowledged that unexpected problems could occur during pregnancy and childbirth were more likely (OR, 5.83; 95% CI, 2.95–11.52) to deliver at a health facility than others unaware of the possible consequences. Women who knew any antepartum danger sign (OR, 2.16; 95% CI, 1.17–3.98), any intrapartum danger sign (OR, 3.8; 95% CI, 2.07–6.96) and any postpartum danger sign (OR, 3.47; 95% CI, 1.93–6.25), tended to deliver at a health facility. **Cost:** Not documented.
Kozuki et al,[38] 2016a Kozuki et al,[63] 2016b	Training of ANM to perform ultrasound. ANMs were then sent on home visits to screen pregnant women for the 3 risk factors—fetal	Design: Cohort Setting: Community Duration: 13 mo	**Accuracy of noncephalic presentations:** The positive predictive value ranged from 92.6% to 100%, and the negative predictive values were all nearly 100%. **Accuracy of placenta praevia:** There was 100% agreement between ANMs and reviewers about 2 partial or complete placenta previa cases.

(continued)

TABLE 4
Included studies *(continued)*

Study	Intervention details	Study details	Outcomes
	presentation, multiple gestation, and placental position.	District: Sarlahi No. received intervention: 815 women	**Accuracy of multiple gestations:** For multiple gestation, the ANM and the reviewer readings agreed 100% of the time, but sensitivity had wide confidence intervals as a result of the small number of cases. Facility delivery rate (Kozuki et al,[xx] 2015): We saw no statistically significant difference in the facility delivery rate between the ultrasound and comparison group. **Cost:** The estimated cost of the ultrasound machine, gel, personnel and training over 5 y was $10,355 for 15,000 births. Estimated that 160 perinatal deaths may be averted with early diagnosis; a cost of $65 per life saved.
McPherson et al,[31] 2006	The birth preparedness package (BPP) implemented through the government health system in Siraha, Nepal, during 2003–2004. The package includes interpersonal communications with clients, a flip-chart for use by community health workers, and key chains with key messages for pregnant women.	Design: Before and after study Setting: Community Duration: 2 y District: Siraha No. received intervention: 162	**Changes in essential newborn care:** The endpoint estimates for essential newborn practices promoted through the BPP increased by 20%–30% compared with the baseline. **The birth preparedness index (BPI):** The BPI increased from 33% at baseline to 54% at endpoint. **Use of antenatal and postnatal care:** Attendance at ≥2 ANC visits increased from 49% to 73% (P=.001). The use of postnatal care services within 1 wk of delivery increased from 11% to 25% (P=.01), whereas the use within 6 wk of delivery doubled from 17% to 34% (P=.02). **Skilled birth attendance:** The use of SBAs at endpoint remained unchanged from baseline at 17%. **Care-seeking during emergencies:** Of women who reported emergencies, the percentage who received treatment at a health facility remained constant at baseline and endpoint. **Cost:** Not reported.
Mullany et al,[27] 2007 Mullany et al,[55] 2009	Two 35-min health education sessions, received by pregnant woman with or without her partner. First session received at enrollment; second session received 4–6 wk later. In addition, women received a health education flier.	Design: RCT Setting: Hospital Duration: 5 mo District: Kathmandu No. received intervention: 145—with husbands 148—woman alone 149—control	Mullany et al,[27] 2007 **Birth preparedness:** Women in the couples group were nearly twice as likely as control group women to report making >3 birth preparations (21.8% vs 10.9%). None of the birth preparedness outcomes was different between women in the couples group vs women in the woman-alone group. **Healthcare utilization:** Women assigned to the couples group were more likely to attend the postpartum visit than participants assigned either to the control group (61% vs 47%, RR, 1.29; 95% CI, 1.04–1.60) or to the woman-alone group (61% vs 49%, RR, 1.25; 95% CI, 1.01–1.54). Mullany et al,[55] 2009 **Maternal and reproductive health knowledge levels of pregnant women:** Women educated with husbands increased their knowledge scores by an average of 67.7% from baseline to follow-up, compared with 61.6% and 54.7% in the women-alone and control groups respectively. **Cost:** Not reported.
Nisar and Dibley,[46] 2014 Nisar et al,[39] 2015	Any antenatal iron–folic acid supplements taken for at least a day during pregnancy.	Design: Retrospective cohort Setting: Community Duration: 15 y District: Nationwide No. received intervention: 2001–4700 2006–4140 2011–4051 Total: 12,891	Nisar et al,[39] 2015 **Early neonatal mortality (deaths <8 d of age):** With any use of IFA supplements, the risk of early neonatal mortality was reduced by 45% (aHR, 0.55; 95% CI, 0.38–0.79; P=.002) **Neonatal mortality (deaths <31 d of age):** With any use of IFA supplements, the risk of neonatal mortality was reduced by 42% (aHR, 0.58; 95% CI, 0.39–0.85; P=.005) for neonatal mortality. Approximately 55% reduction in the risk of neonatal mortality in infants whose mothers consumed 150–240 supplements in their pregnancy. Protective effect of an early start of IFA supplements (first 2 mo) in pregnancy on the risk of neonatal mortality (53%, P=.023) Nisar et al,[46] 2014 **Early neonatal mortality:** The risk of early neonatal death was significantly reduced by 51% (aHR, 0.49; 95% CI, 0.32–0.75) in with any use of IFA compared with none. **Early initiation of IFA:** When supplementation started at or before 20 wk, the adjusted risk of early neonatal mortality was reduced by 53% in Nepal compared with no IFA. **Greater use:** When >90 IFA supplements were used and started at or before 20 wk, the adjusted risk of early neonatal deaths was reduced by 57%. A total of 4600 early neonatal deaths could be prevented annually if all pregnant women used >90 IFA supplements and started at or before the fifth month of pregnancy. **Cost:** Not reported.
Osrin et al,[25] 2005 Hindle et al,[49] 2006	Dietary supplement, UNIMMAP, taken daily from the 12th wk of gestation—at minimum—until delivery, compared with a daily supplement of iron (60 mg) and folic acid (400 μg) recommended by the government. The UNIMMAP contains vitamin A 800 μg, vitamin E 10 mg, vitamin D5 μg, vitamin B1 1.4 mg, vitamin B2 1.4 mg, niacin 18 mg, vitamin B6 1.9 mg, vitamin B12 2.6 μg, folic acid 400 μg, vitamin C 70 mg, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 μg and iodine 150 μg.	Design: RCT Setting: Hospital Duration: 2 y District: Janakpur, Dhanusha No. received intervention: 1200	Osrin et al,[25] 2005 **Birthweight:** Mean birthweight was 2733 g (SD, 422) in the control group and 2810 g (SD, 453) in the intervention group, representing a mean difference of 77 g (95% CI, 24–130; P=.004) and a relative fall in the proportion of LBW by 25%. **Gestational duration:** No difference was recorded in the duration of gestation (0.2 wk [−0.1 to 0.4]; P=.12), infant length (0.3 cm [−0.1 to 0.6]; P=.16), or head circumference (0.2 cm [−0.1 to 0.4]; P=.18). Hindle et al,[49] 2006 **Inflammatory markers:** Blood eosinophils; plasma concentrations of the acute phase reactants C-reactive protein, alpha-1-acid glycoprotein (AGP), neopterin, and ferritin; milk Na:K; and the production of interleukin (IL) 10, IL-4, interferon gamma, and tumor necrosis factor alpha in whole blood did not differ significantly between the supplemented and control groups. **Cost:** Not reported.

(continued)

TABLE 4
Included studies *(continued)*

Study	Intervention details	Study details	Outcomes
Pokharel et al,[40] 2011 The Nielson Company Report, 2011	Training FCHVs to give enhanced counseling to pregnant women regarding the importance of iron supplementation. FCHVs also trained to encourage women to attend antenatal appointments.	Design: Cohort study Setting: Community Duration: 6 y Districts: 70 districts throughout Nepal No. received intervention: not known	Of note, in 2009 the DHS data were used to give outcomes for women in 3 sets of districts; those where the intervention had been in place for at least 12 mo, those where the intervention had not yet been implemented, and those with no plans of implementing the intervention. **Attendance at ANC:** Approximately 92% of respondents in intervention districts attended ANC clinics, significantly higher than in preintervention districts (66%) or nonintervention districts (86%). **Coverage among pregnant women with any IFA:** Approximately 90% in intervention districts, significantly higher than in districts that were preintervention (65%), but not significantly higher than in districts in where no intervention was planned (86%). **Compliance with IFA supplementation:** Higher among pregnant women in intervention districts and nonintervention districts (68% and 66%) than among those from districts before intervention implementation (44%). **Coverage of deworming tablets:** Higher in intervention districts and nonintervention districts than in districts before intervention (69% and 73%, respectively, vs 52%). **Cost:** Not documented.
Saville et al,[29] 2018 Saville et al,[52] 2016 Harris-Fry et al,[51] 2018	Participatory Learning and Action (PLA) comprises women's groups that discuss and form strategies about nutrition in pregnancy, LBW, and hygiene. One of the 4 groups received standard care (the control group), one group received PLA only, one group received PLA plus cash transfer, and the final group received PLA plus food transfer.	Design: Cluster RCT Setting: Community Duration: 12.5 mo District: Dhanusha, Mahottari No. received intervention: Control: 5310 PLA only: 5626 PLA+cash: 7272 PLA+food: 6884 Total: 25,092	Primary outcomes: **Birthweight measured within 72 h:** Birthweight measured within 72 h appeared to be incrementally higher in PLA (28.9 g; 95% CI, 37.7−95.4; n=488), PLA+cash (50.5 g; 95% CI, 15.0−116.1; n=509), and PLA+food (78.0 g; 95% CI, 13.9−142.0; n=629) arms, but the only significant difference was between control and PLA plus food. **Secondary outcomes:** No significant differences in most secondary outcomes measured. **Institutional deliveries:** Significantly more institutional deliveries (OR, 1.46; 95% CI, 1.03−2.06; n=2651) and lower rates of colostrum discarding (OR, 0.71; 95% CI, 0.54−0.93; n=2548) were observed in the PLA+food arm compared with control (institutional delivery, n=2251; colostrum, n=2087). **Cost:** Cash transfer amount and some staff costs documented, but overall costs of intervention/implementation not documented
Sharma and Tiwari[32] 2015	Iron sucrose infusion: Iron sucrose was administered as 200 mg elemental iron in 100 mL of 9% normal saline infusion over 1 h everyday up to total calculated dose.	Design: Before and after study Setting: Hospital Duration: 12 mo District: Kathmandu No. received intervention: 37 (but only 7 of these antenatal women)	**Hb level:** Before iron sucrose therapy, the mean Hb level was 7.5 gm/dL. After therapy, the mean Hb level was 10.3 gm/dL. **Ferritin level:** Before iron sucrose therapy, the serum ferritin was 12.8 mg/mL. After therapy, the mean serum ferritin level was 300mg/dL. **Total iron:** Before therapy, total iron was 40 mg/dL. After, it was 85 mg/dL. **Cost:** Not reported.
Steinhoff et al,[26] 2017 Tielsch et al,[48] 2015 Katz et al,[47] 2018	Flu vaccination: seasonally recommended trivalent inactivated influenza vaccine	Design: RCT Setting: Community Duration: 2 y (12 mo × 2) District: Sarlahi No. received intervention: 3693	**Maternal influenza-like illness:** A reduction of 19% (95% CI, 1−34) in all influenza-like illnesses combining cohort 1 and 2 (RR, 0.81 [0.66−0.9] *P*=.041). Cohort 1 was not significantly different; Cohort 2 was statistically different. **Laboratory-confirmed influenza in infants:** A reduction of 30% in laboratory-confirmed influenza in infants combining cohort 1 and 2, but not statistically significant (RR, 0.7 (0.52−0.95) *P*=.020). **Maternal laboratory-confirmed influenza, influenza-like illness in infants, preterm birth (RR, 0.91 [0.77−1.08]), small for gestational age births:** No difference. **Birthweight:** Maternal immunization reduced the rates of LBW by 15% (95% CI, 3−25) in both cohorts combined. **Adverse effects:** Similar between both the groups. **Cost:** Not reported.
Sunuwar et al,[30] 2019	The intervention group received nutritional counseling and individualized dietary assessment and menu planning, the control group received the counseling only.	Design: Nonrandomized controlled study Setting: Hospital Duration: 5 mo District: Kathmandu No. received intervention: 53	**Maternal nutritional knowledge:** Maternal nutritional knowledge scores increased by more in the intervention group (score change 8.26 cf 1.05; *P*<.001) **Anemia:** A bigger increase in Hb level was seen in the intervention group compared with the control group (change in Hb +0.56 cf +0.16; *P*=.002). **Anthropomorphic data:** There was no difference between the 2 groups with respect to changes in weight or BMI and no significant difference in heights between the 2 groups. **Dietary changes:** Women in the intervention group increased their intake of red meat, liver, and fish (*P*<.001), vitamin C rich fruits (*P*=.006), dairy products (*P*=.013), eggs (*P*=.016), and dark green leafy vegetables (*P*=.006) more than women in the control group. **Cost:** Not documented.
Thapa et al,[41] 2016a Thapa et al,[65] 2016b Feldhaus et al,[66] 2016	Calcium supplementation: Provided calcium supplementation (daily dose of 1 g of elemental calcium beginning at 4 mo gestation) through government ANC services to pregnant women. ANC providers distributed and counseled women regarding calcium use and FCHVs reinforced calcium-related messages.	Design: Cohort Setting: Hospital and community Duration: 14 mo District: Dailekh No. received intervention: 9246	**Coverage of ANC and delivery services:** Approximately 94.6% of women interviewed attended at least 1 ANC visit and received calcium. **Calcium coverage:** The full course of calcium (1 gm daily for 150 d) was provided to 82.3%. **Compliance with calcium intake instructions:** Full compliance was 67.3% of calcium recipients. **Discontinuation:** Significant predictors of completing a full course were gestational age at first ANC visit and number of ANC visits during their most recent pregnancy (*P*<.01). **Knowledge about calcium and acceptability:** Notably, 99.2% reported that they took it as instructed with respect to dose, timing, and frequency. **Feasibility of the intervention:** Over 97% would recommend calcium to others and would use it during a subsequent pregnancy.

(continued)

TABLE 4
Included studies *(continued)*

Study	Intervention details	Study details	Outcomes
			Costs: The costs to start-up calcium introduction in addition to $MgSO_4$ were as follows: total fixed program cost (not including variable costs per individual), $117,656.29 (start-up costs, $44,804.09; ongoing program implementation costs, $72,852.19); $0.44 total program costs per individual. Initially $0.01/tablet (Nepali Rupees, 0.65/tablet), then US$ 0.016/tablet (Nepali Rupees (NR), 1.35/tablet).
Thapa et al,[45] 2019 Maru et al,[57] 2018 Harsha Bangura et al,[56] 2020	A trial of ANC in groups of 12 instead of individual antenatal appointments.	Design: Cluster-controlled and qualitative Setting: Community Duration: 21 mo Districts: Achham No. received intervention: 457	**Institutional birth rate or attendance of 4 ANC visits:** No significant difference between intervention and control groups in institutional birth rate, attendance of 4 ANC visits, postpartum contraceptive use, stillbirth rate, perinatal mortality rate, or infant mortality rate. Women in the intervention group were better at identifying key danger signs in pregnancy (P=.01) and were more likely to report that their antenatal appointments were "very enjoyable" (84% vs 60%). **Cost:** Annual per capita cost $0.5, or per woman cost of NR 4000 ($37).
Yadav et al,[43] 2019	The study was evaluating the efficacy of the daily iron–folic acid supplementation program, available for all pregnant women in Nepal from the second trimester onward, as advised by the WHO and funded by the Government of Nepal.	Design: Cross-sectional Setting: Hospital Duration: 7 mo District: Mechi, Koshi, Sagarmatha, Sunsari and Siraha districts. No. received intervention: 328	**IFA compliance:** Women who were not compliant with taking their IFA as recommended were 24 times as likely (aOR, 24.16 [10.0–58.3]) to be anemic at 1 mo postpartum. **Heme iron intake:** Women who reported not having heme iron in their diet were 3.3 times as likely to be anemic (aOR, 3.35 [1.4–8.1]). **Ethnicity:** Women from Terai castes were 2.7 times as likely to be anemic as those from mountain and hill castes (aOR, 2.725 [1.294–5.736]). **Cost:** Not documented.

Please note: Some studies were reported across several journal articles, for example where protocol and results were published separately. Where this was the case, we grouped all articles associated with a given study under the first author of the article reporting the majority of the results. All articles associated with each study are listed in Table 1 Column 1, with the study name highlighted in bold.

aOR, adjusted odds ratio; *aHR*, adjusted hazard ratio; *APH*, antepartum haemorrhage; *BMI*, body mass index; *cf*, compare; *CI*, confidence interval; *DHS*, Demographic Health Survey; *FCHV*, female community health volunteer; *FDC*, free delivery care; *No.*, number; *PT*, pupillary threshold; *RCT*, randomized control trial; *WHO*, World Health Organization.

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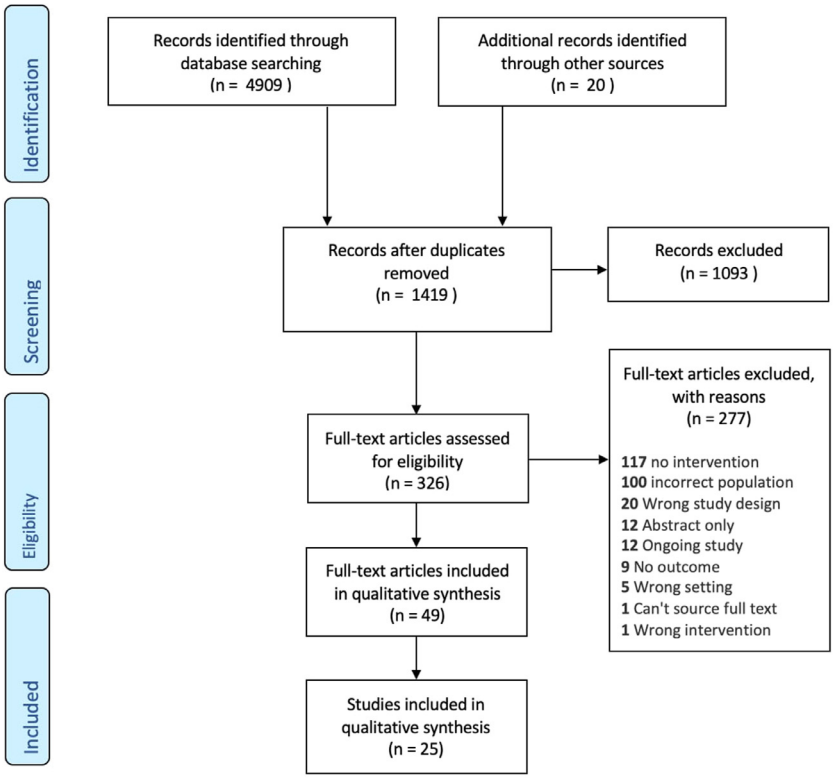
more marked when women were educated alongside their husbands, compared with when they received no education or were educated alone,[24,55] which may be because of a male dominance in the household decision-making.

Clinical audit. Two of the studies with "capacity-building" interventions audited the results of their interventions. One found a high diagnostic accuracy for a home-based ultrasound performed by auxiliary nurse midwives (ANMs) and done for identifying noncephalic presentations, placenta previa, and multiple gestations.[38,63] Another study triaged women into different risk categories and compared neonatal outcomes between the high-risk and low-risk groups, finding a higher rate of neonatal complications in the high-risk group than in the low-risk group.[34,64] The data for both these studies are of limited value in demonstrating the effectiveness of the interventions because of the lack of a control group.

Cost-effectiveness. Only 3 studies reported any cost-effectiveness analysis. In one, the authors carried out an in-depth cost-effectiveness analysis of a calcium supplementation program and found a total fixed program cost of $0.44 per individual. This represents a cost per disability-adjusted life year averted of $25.33 when compared with standard magnesium treatment and is therefore favored above a willingness-to-pay threshold of around $30.[41,65,66] The second carried out a cost-effectiveness analysis of an ultrasound program for diagnosing pregnancy complications and found a cost of $65 per life saved.[38,63] In the third study, the authors found that the introduction of group ANC cost approximately $0.5 per capita extra, compared with routine care, but that women enjoyed their ANC more and were better at identifying the danger signs in pregnancy.[45,56,57] This study did not look at whether this improved the maternal or neonatal outcomes locally.

FIGURE 1
PRISMA diagram



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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Discussion

Principal findings

We found 25 studies with diverse approaches to improving ANC in Nepal, and we identified the following 2 intervention types that accounted for a large proportion of studies conducted: interventions involving micronutrients and educational interventions. Other interventions involved cash and food incentives, staff training, and service development.

Nearly all interventions reported an improvement in the outcomes for mothers, neonates, or health system utilization. However, not all of the studies were of high quality. Some were not comparative,[34,38,41,42,60] making it hard to ascertain their true impact; several of the observational studies did not adequately consider confounding factors. Some studies used short-term, surrogate outcome measures rather than longer-term assessments.[24,35,36,55] Finally, only a few studies involve multiple sites, and all the studies conducted in hospitals were single-center studies.[21,25,35,41,42]

Implications for future research

We found little research assessing the impact of the Government of Nepal's "Aama Programme." This scheme is 10 years old and yet we identified only 2 articles investigating the effectiveness of cash incentives for women attending 4 ANC visits.[42,44] Several other papers not included in this review explore the effectiveness of the incentives for transportation and health facility delivery,[67,68] suggesting that the ANC element has been less well-evaluated.

A further gap is seen in interventions involving mobile technology. Only 1 article in our review involves an mHealth intervention component,[27] despite the proliferation of mHealth interventions for maternal health in other low- and middle-income countries over the recent years.[69,70] It is unclear whether this omission is owing

FIGURE 2
Types of antenatal interventions in included studies

This bubble diagram illustrates the types of antenatal intervention reported in included studies, with the size of the bubbles proportional to the number of studies. The biggest category of intervention was dietary supplementation, with 9 studies focusing on micronutrient supplementation or other dietary changes.

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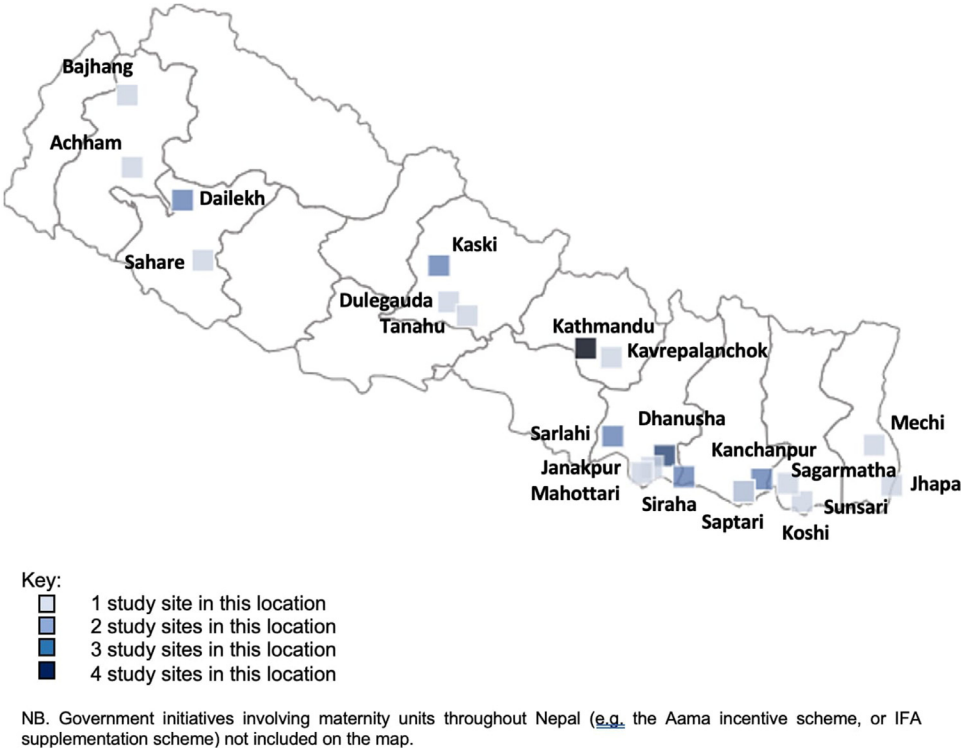
to a lack of interventions or a lack of research into this area.

There was a lack of reporting about the cost-effectiveness of interventions, with only 3 studies performing comprehensive cost-effectiveness analysis.[41,45,56,57,65,66] Cost-effectiveness information is important for ensuring effective resource allocation by the government and donors.[71] In future research, it is vital that this is considered.

There were clear regional concentrations of study sites, with most studies being conducted in the lowland Terai region and none in the most mountainous, difficult-to-access areas. The limited infrastructure within the Himalayas understandably makes research more difficult, but without including these communities in the trials of antenatal interventions, it will be very difficult to improve outcomes for the hardest-to-

FIGURE 3
A map illustrating the sites of studies involving antenatal interventions in Nepal



NB. Government initiatives involving maternity units throughout Nepal (e.g. the Aama incentive scheme, or IFA supplementation scheme) not included on the map.

This map illustrates the sites within Nepal where studies involving antenatal interventions have taken place. The color of the square on the map corresponds to the number of studies that have taken place in that location.

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reach groups. Finally, there were a few multisite, high-quality RCTs.

Strengths and limitations

A key strength of this review is its broad inclusion criteria and exclusive focus on Nepal; we are aware of only one other systematic review in maternity care that focuses on Nepal.[72] The broad inclusion criteria may also contribute to one of the study's weaknesses: the heterogeneity in its results. The huge breadth in interventions and outcomes we identified makes meta-analysis impossible and limits meaningful judgement about the relative effect of one intervention compared with another.

We only included studies with interventions specifically targeting pregnant women or ANC services and therefore excluded the interventions targeting all women of reproductive age or the wider community. This meant excluding some high-quality studies with interventions that report maternal and neonatal outcomes.[73–75] However, broadening the focus beyond ANC was outside the scope of this review.

Conclusion

Our systematic review found good quality evidence that micronutrient supplementation and educational interventions can bring important clinical benefits. IFA supplementation significantly reduces neonatal mortality and maternal anemia, whereas BPCs increase the uptake of antenatal and postnatal care, compliance with micronutrient supplementation, and awareness of danger signs in pregnancy. Where there is strong evidence that an intervention may bring clinical benefit implementation studies, including participants from the hardest-to-reach communities and incorporating cost-effectiveness analyses would be beneficial in highlighting the potential barriers to uptake. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2021.100019.

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