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Planned delivery at 37 weeks gestation versus expectant management for non-severe chronic hypertension, a systematic review.

Jackson Njuguna

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**PLANNED DELIVERY AT 37 WEEKS GESTATION VERSUS EXPECTANT
MANAGEMENT FOR NON-SEVERE CHRONIC HYPERTENSION, A
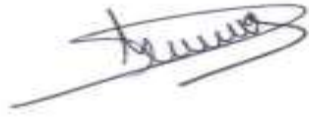SYSTEMATIC REVIEW**

By

JACKSON N. NJUGUNA

A dissertation submitted in part fulfillment of the requirements for the degree of
Master of Medicine
In Obstetrics and Gynecology

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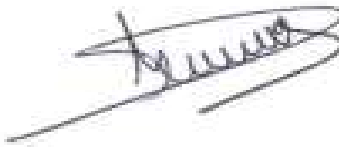Medical College, East Africa

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In Obstetrics and Gynecology

Members of the Dissertations Standard Committee appointed to vet the dissertation of

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find it satisfactory and recommend that it be submitted for evaluation by external examiners

_____

Chair, Dissertations Standard Committee

___30/05/2021___

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ABSTRACT

Background
Chronic hypertension is independently associated with an increased incidence of adverse maternal and perinatal outcomes. Delayed delivery carries maternal risks, while early delivery increases fetal risk, so appropriate timing is important. The optimal timing of delivery for women with this condition has not been adequately addressed by available literature.

Objective
To review the literature that assesses the benefits and risks of a policy of planned delivery versus expectant management in pregnant women with non-severe chronic hypertension at 37 weeks gestation. Our primary outcomes were composite maternal outcome (super-imposed pre-eclampsia, placental abruption, maternal admission to intensive care unit and composite perinatal outcome (stillbirth, admission to neonatal intensive care unit). Secondary outcomes were super-imposed pre-eclampsia, placental abruption, maternal admission to intensive care unit, stillbirth and admission to neonatal intensive care unit.

Research Design and Search Methods
A systematic review with a narrative synthesis. We carried out an electronic search of different databases including CENTRAL, MEDLINE and EMBASE. We set out to include randomized trials and cohort studies comparing planned early delivery and expectant management at 37 weeks gestation. We conducted a risk of bias assessment for each of the outcomes of interest. The quality of the evidence for the specified outcomes was assessed using the GRADE approach.

Results
We screened a total of 8830 titles and abstracts and 15 articles were selected for full text review. We found one study that was eligible for inclusion. This was a randomized controlled trial with 76 participants with similar baseline clinical characteristics. Half of them were assigned to planned delivery at 37 weeks of gestation while the other half was assigned to expectant management up to 41 weeks of gestation. There was no significant difference in the rate of super-imposed pre-eclampsia between the two groups (OR =0.9 (95% CI 0.2 to 2.3) p value 0.9). Similarly, no significant difference in the rate of placental abruption was observed between the two groups. (OR =1.0 (95% CI 0.2 to 5.2) p value 1.0). For these two outcomes, the risk of bias was high and the findings were based on a low degree of certainty of the evidence. The rate of admission to neonatal intensive care unit was higher in the planned delivery compared to the expectant management group (OR = 5.4 (95% CI 1.4 to 21.0); p value 0.01.). There were some concerns in the risk of bias for this outcome and these findings were based on a moderate degree of the certainty of the evidence.

Conclusion
In women with non-severe chronic hypertension in pregnancy, a policy of expectant management up to 41 weeks gestation was more favorable than planned delivery at 37 weeks gestation. There was no significant difference in the rates of super-imposed pre-eclampsia, placental abruption though this finding was based on a low degree of certainty of the evidence. Additionally, expectant management was associated with lower rates of admission to neonatal intensive care unit and this finding is based on a moderate level of certainty of the evidence.

LIST OF ABBREVIATIONS USED

AKUH, N	-	Aga Khan University Hospital, Nairobi
CENTRAL	-	Cochrane Controlled register of Trials
EMBASE	-	Excerpta Medica Data Base
GRADEPro	-	Grade (Evidence) Profiler
ICU	-	Intensive Care Unit
KOGS	-	Kenya Obstetricians and Gynecologists Society
MEDLINE	-	National Library of Medicine's Bibliographic Database
NICU	-	Neonatal Intensive Care Unit
RoB 2	-	Risk of Bias Assessment tool version 2
ROBINS-I	-	Risk of Bias In Non-randomized Studies of Interventions
PROSPERO	-	Prospective Register of Systematic Reviews
PRISMA	-	Preferred Reporting Items for Systematic Review and Meta-Analysis
IUGR	-	Intra-uterine growth restriction
SPE	-	Super-imposed pre-eclampsia
Mgt	-	Management
Deliv	-	Delivery

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Thank you all

DECLARATION

I declare this dissertation does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another person except where due reference have been made in the text.

(Signature of Candidate)

30 /05/ 2021

Date

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CHAPTER ONE

BACKGROUND

Hypertension is the most common medical condition in pregnancy(1). Chronic hypertension in pregnancy is defined as hypertension diagnosed or present before pregnancy or before 20 weeks of gestation(2). It affects 0.9 to 1.5% of pregnant women (3) and is associated with adverse perinatal outcomes such as growth restriction, preterm delivery and perinatal death (4). Chronic hypertension in pregnancy is also associated with an increased incidence of adverse maternal outcomes including preeclampsia, gestational diabetes and placental abruption (5).

Early delivery is associated with improved maternal outcomes and is recommended for women with mild hypertensive disease beyond 37 weeks' gestation (6). For women with pregnancy induced hypertension, preeclampsia or worsening chronic hypertension between 34-37 weeks gestation, a randomized controlled trial by Broekhuijsen et al concluded that routine delivery was associated with an increased the risk of neonatal respiratory distress syndrome and it did not decrease the risk of severe adverse maternal outcomes (7).

For chronic hypertension in pregnancy, high level evidence to guide the appropriate timing of delivery is lacking and the available evidence is conflicting. A retrospective cohort study by Harper et al concluded that expectant management beyond 39 weeks and 0 days was associated with increased risk of severe preeclampsia while increased adverse neonatal outcomes were reported with planned delivery prior to 37 weeks (8). The authors concluded that delivery at 38 or 39 weeks would offer a good balance between the risk of adverse fetal and neonatal outcomes.

In contrast, a two center randomized controlled trial done by Hamed et al showed that in women with non-severe chronic hypertension expectant management up to 41 weeks could be considered provided superimposed preeclampsia did not develop (9). The risk of developing superimposed pre-eclampsia has been reported to occur in up to half of women with preexisting hypertension and higher in those with secondary hypertension (10). A systematic review by Cluver at al looking at women with hypertensive disorders as a group found that compared to expectant management, planned early delivery after 34 weeks' gestation is more favorable for the mother (11). They however recommended that further randomized controlled trials addressing each category of hypertensive disorder in pregnancy would be required to make specific recommendations.

There has been an increase in the incidence of chronic of hypertension in pregnancy in the last decade. This has been attributed to increasing rates of obesity and delayed age at conception(12). There is also an increasing number of women who would wish to try vaginal birth after Caesarean(13). Strong evidence on the optimal timing of delivery in this population is thus necessary to ensure favorable maternal and perinatal outcomes. We conducted a systematic review to assess the benefits and risks of planned early delivery versus expectant management in pregnant women with non-severe chronic hypertension at early term (from 37 weeks onwards).

1.1 Description of condition

Hypertension in pregnancy has traditionally been defined as blood pressure of equal to or greater than 140mmHg or 90mmHg for either systolic or diastolic readings respectively or both (2).

These need to be demonstrated at least two occasions not less than four hours apart. For severe hypertension, the cut offs change to160mmHg or more for systolic or 110mmHg for diastolic blood pressures. The risk of getting superimposed preeclampsia has been shown to be higher in women with diastolic blood pressures at or above 100mmHg, and its incidence also varies based on race, body mass index, smoking status, duration of hypertension and previous history of preeclampsia (14).

A review of literature done in 2011 by Saade et al recommended different timing of delivery in preexisting hypertension based on severity. For women with chronic hypertension and not requiring treatment, the authors recommended delivery at 38 to 39 weeks. For those with chronic hypertension controlled on medications they recommended delivery at 37 to 38 weeks and 36 to 37 weeks for those with poorly controlled chronic hypertension (15). In a systematic review by Cluver et al looking at women with different hypertensive conditions in pregnancy as a group after 34 weeks, the authors concluded that planned early delivery is associated with less adverse maternal outcomes. However, they recommended that further studies are needed to look at each of the different types of hypertensive diseases and appropriate gestational age of delivery for these conditions (11).

1.2   How the intervention might work

In women with chronic hypertension in pregnancy, early delivery by planned induction of labor or caesarean section is thought to reduce adverse maternal and perinatal outcomes.

There are potential risks in conducting early delivery by induction of labor. These include adverse perinatal outcomes due to fetal distress that could result from hyper stimulation of the uterus as well as complications arising from prematurity. Several reports have indicated performing elective caesarean sections prior to 39 0/7 weeks of gestation is associated with increased rates of neonatal respiratory complications, ventilation requirement and admission to neonatal intensive care. Compared to infants delivered between 39 0/7 and 41 0/7 weeks, those delivered at 37 0/7 and 38 6/7 weeks have greater neonatal morbidity.

The present study investigated timing of delivery as the intervention. While delayed delivery increases maternal risks, early delivery is associated with increased risks to the fetus and optimal timing is important.

1.3   Why it was important to do this review

There are benefits and risks attributed to both planned early delivery and expectant management in pregnant women with non-severe chronic hypertension. The present study assessed the most appropriate timing of delivery in these women that would result in more favorable maternal and perinatal outcomes.

From the available literature, there are numerous studies done on chronic hypertension in pregnancy. The studies however, are of different study designs, looking at patients in different settings and also giving different results. There is no systematic review addressing the timing of delivery in women with non-severe chronic hypertension. For this reason, we conducted a systematic review to investigate the optimal timing in women with this condition.

1.4 Research objective

To assess the benefits and risks of a policy of planned early delivery versus a policy of expectant management in pregnant women with non-severe chronic hypertension at early term.

CHAPTER TWO

METHODS

2.1 Research design

We conducted a systematic review with a narrative synthesis as we did not find enough studies for a meta-analysis.

The study types eligible for consideration were randomized controlled trials as well as prospective and retrospective cohort studies that compared planned early delivery with expectant management for women with non-severe chronic hypertension at 37 weeks of' gestation. Cross over and quasi randomized trials were excluded as these were not appropriate for the intervention we studied.

The participants in the studies as pre-specified in our protocol were women with non-severe chronic hypertension from 37 weeks 0 days gestation or beyond up to 42 weeks 0 days of gestation. Non severe chronic hypertension was defined as blood pressure at or above 140mmHg systolic and/or 90mmHg or above for diastolic but not exceeding 159mmHg and/or 109mmHg respectively at the time of recruitment into the study or prior to twenty weeks gestation whichever was earlier. This was regardless of absence or presence of baseline proteinuria but with no other signs of end organ compromise. We did not exclude women who were on antihypertensive medication at the time of recruitment if they had non-severe chronic hypertension.

The intervention we studied was timing of delivery.

The primary outcomes we set out to assess were;

1. Composite maternal outcome (including pre-eclampsia, placental abruption, admission to ICU)

2. Composite perinatal outcome (including stillbirth, NICU admission)

The secondary maternal outcomes were pre-eclampsia, placental abruption and admission to ICU. The secondary perinatal outcomes were stillbirth and admission to NICU)

2.2 Data collection procedures

2.2.1 Search methods for identification of studies

We carried out an electronic search of three different databases namely CENTRAL, MEDLINE and EMBASE, based on a comprehensive search strategy addressing the research question. We did not apply any date or language restrictions and all the databases were searched from inception to the date of the search. The actual search strategy used on MEDLINE is provided below in Table 1 and the ones used for CENTRAL and EMBASE search are provided as appendix 2 and 3 respectively.

Table 1: MEDLINE search strategy as at 28/12/2020

Search Number	Search Terms	Results
#1	Search: chronic hypertension Sort by: Most Recent	82,750
#2	Search: "chronic hypertension"	3,251
#3	Search: hypertension	549,529
#4	Search: hypertens*	561,642
#5	Search: blood pressure	624,622
#6	Search: "blood pressure"	452,607
#7	Search: high blood pressure	637,648
#8	Search: elevated blood pressure	549,900
#9	Search: "elevated blood pressure"	6,699
#10	Search: "increased blood pressure"	3,781
#11	Search: increased blood pressure	634,659
#12	Search: "Hypertension" [Mesh] Sort by: Most Recent	291,027
#13	Search: "Blood Pressure" [Mesh] Sort by: Most Recent	293,019
#14	Search: "high blood pressure" Sort by: Most Recent	15,647
#15	Search:(((((((((((((C(" high blood pressure") OR ("Blood Pressure"[Mesh])) OR ("Hypertension" [Mesh])) OR (increased blood pressure))OR ("increased blood pressure")) OR ("elevated blood pressure")) OR(elevated blood pressure)) OR (high blood pressure)) OR ("bloodpressure')) OR (blood pressure)) OR (hypertens*)) OR(hypertension)) OR ("chronic hypertension")) OR (chronichypertension)	990,706
#16	Search: "timing of delivery"	652
#17	Search: timing of delivery	11,888
#18	Search: "timely delivery'	415
#19	Search: timely delivery	11,888
20	Search: planned delivery	41,179
21	Search: "planned delivery"	216
#22	Search: "Delivery, Obstetric" [Mesh] Sort by: Most Recent	81,386
#23	Search: obstetric deliver*	97,543
#24	Search: deliver*	822,234
#25	Search: Caesarean deliver*	41,679
#26	Search: Cesarean deliver*	41,679
#27	Search: "Parturition" [Mesh] Sort by: Most Recent	17,709
#28	Search: Parturition	123,448
#29	Search: birth*	394,158
#30	Search: childbirth*	27,390
#31	Search: child birth*	133,671
#32	Search: Caesarean section*	67,678

Search Number	Search Terms	Results
#33	Search: Cesarean section*	67,678
#34	Search: Normal deliver*	60,992
#35	Search: Vaginal deliver*	28,228
#36	Search: pregnan*	1,041,122
#37	Search: gestation*	258,524
#38	Search: pregnancy[MeSH Terms]	921,030
#39	Search: ((pregnan*) OR (gestation*)) OR (pregnancy[MeSH Terms)	1,125,424
#40	Search: ((((((((((((((((((((((Vaginal deliver*) OR (Normal deliver*)) OR (Cesarean section*)) OR (Caesarean section*)) OR (child birth*)) OR (childbirth*)) OR (birth*)) OR (Parturition)) OR ("Parturition"[Mesh])) OR (Cesarean deliver*)) OR (Caesarean deliver*)) OR (deliver*)) OR (obstetric deliver*)) OR ("Delivery, Obstetric" [Mesh])) OR ("planned delivery")) OR (planned delivery)) OR (timely delivery)) OR ("timely delivery")) OR ("timing of delivery")) OR (timing of delivery)) AND ("Delivery, Obstetric" [Mesh])) AND ((("Pregnancy"[Mesh]) OR (gestation*)) OR (pregnan*)) AND ((((((((((((("'high blood pressure') OR ("Blood Pressure" [Mesh])) OR ("Hypertension"[Mesh])) OR (increased blood pressure)) OR ("increased blood pressure")) OR ("elevated blood pressure")) OR (elevated blood pressure)) OR (high blood pressure)) OR ("blood pressure")) OR (blood pressure)) OR (hypertens*)) OR (hypertension)) OR ("chronic hypertension")) OR (chronic hypertension))	4,567
#41	Search: "Randomized Controlled Trial" [Publication Type] Sort by:	520,802
#42	Search: controlled clinical trial Sort by: Most Recent	754,121
#43	Search: controlled clinical trial (pt)	2,510
#44	Search: "Random Allocation" [Mesh] Sort by: Most Recent	104,260
#45	Search: "Observational Study" [Publication Type] Sort by: Most Recent	90,343
#46	Search: "Observational Studies as Topic" [Mesh] Sort by: Most Recent	5,748
#47	Search: "Clinical Studies as Topic" [Mesh] Sort by: Most Recent	354,818
#48	Search: "Clinical Trial" [Publication Type] Sort by: Most Recent	878,581
#49	Search: cohort stud*	2,309,089
#50	Search: randomized controlled trial	687,793
#51	Search: observational stud*	226,805

Search Number	Search Terms	Results
#52	Search: (((((((((((observational stud*) OR (randomized controlled trial)) OR (cohort stud*)) OR ("Clinical Trial" [Publication Type])) OR ("Clinical Studies as Topic" [Mesh])) OR ("Observational Studies as Topic" [Mesh])) OR ("Observational Study" [Publication Type])) OR ("Random Allocation" [Mesh])) OR (controlled clinical trial (pt))) OR (controlled clinical trial)) OR ("Randomized Controlled Trial" [Publication Type])) OR ("Randomized Controlled Trials as Topic" [Mesh])	3,398,760
#53	Search: (((((((((((observational stud*) OR (randomized controlled trial)) OR (cohort stud*)) OR ("Clinical Trial" [Publication Type])) OR ("Clinical Studies as Topic" [Mesh])) OR ("Observational Studies as Topic" [Mesh])) OR ("Observational Study" [Publication Type])) OR ("Random Allocation" [Mesh])) OR (controlled clinical trial (pt))) OR (controlled clinical trial)) OR ("Randomized Controlled Trial" [Publication Type])) OR ("Randomized Controlled Trials as Topic" [Mesh])) AND (((((((((((((((((((Vaginal deliver*) OR (Normal deliver*)) OR (Cesarean section*)) OR (Caesarean section*)) OR (child birth*)) OR (childbirth*)) OR (birth*)) OR (Parturition)) OR (""Parturition" [Mesh])) OR (Cesarean deliver*)) OR (Caesarean deliver*)) OR (deliver*)) OR (obstetric deliver*)) OR ("Delivery, Obstetric" [Mesh])) OR ("planned delivery")) OR (planned delivery)) OR (timely delivery)) OR ("timely delivery")) OR ("timing of delivery")) OR (timing of delivery)) AND (Delivery, Obstetric" [Mesh])) AND ((("Pregnancy" [Mesh]) OR (gestation*)) OR (pregnan*))) AND ((((((((((((" high blood pressure") OR ("Blood Pressure" [Mesh])) OR ("Hypertension" [Mesh])) OR (increased blood pressure)) OR ("increased blood pressure")) OR ("elevated blood pressure™")) OR (elevated blood pressure)) OR (high blood pressure)) OR ("blood pressure")) OR (blood pressure)) OR (hypertens*)) OR (hypertension)) OR ("chronic hypertension")) OR (chronic hypertension)))	1,975

2.2.2 Searching other resources

We did not do hand searching or search for gray literature. All studies that warranted full article review were in English and they were all included in the PRISMA flow diagram. We also searched the reference list of the included study. None of the referenced studies was eligible for inclusion.

2.3 Data collection and analysis

All potential studies obtained from the search strategy were assessed by two review authors independently. We designed a title and abstract screening tool for this process and piloted it on 30 articles with no discrepancies arising. The tool was thus approved for use. Study titles and

abstracts were screened for eligibility by two independent review authors. We pooled all articles identified by electronic searches together and removed duplicates by matching author names and study titles. We resolved any disagreements arising from the title and abstract screening via consensus between the involved review authors.

Full text reviews were also done by two independent review authors. This was done for articles deemed eligible for selection and those requiring further interrogation to determine eligibility. Disagreements were resolved by consensus. We used the Covidence web application software approved by the Cochrane Collaboration (16) to facilitate the review steps. We displayed the process of study selection in a flow diagram and did a detailed descriptive analysis.

2.4 Data extraction and management

We used the Cochrane collaboration data extraction template (17) to design a data extraction tool which we customized to fit our review. This was piloted on one study with minor discrepancies and appropriate modifications to fit the objectives of this review. The form was used by two review authors to collect data independently. Disagreements arising from the data collection were resolved by consensus. Extracted data included the study title, first author, year of publication, journal of publication, study design, setting, gestational age range at delivery, parity, smoking status, history of pre-eclampsia, duration of hypertension modes of delivery, as well as the main maternal and perinatal outcomes. We also captured data on the results for the different outcomes and the risk of bias assessment for the same. The data was then input into the risk Excel worksheet of the risk of bias tool version 2 (18) and checked for accuracy. Any discrepancies were resolved by consensus.

2.5 Assessment of the risk of bias

Two reviewers independently assessed the included study, a randomized controlled trial, for the risk of bias based on the criteria in the Cochrane Handbook for systematic Reviews (19) for Interventions as outlined in the Risk of Bias tool version 2 (Rob 2.0). We assessed the included study for bias in the domains of the randomization process, deviation from intended interventions, missing outcome data, measurement of the outcome and selection of the reported results. This was done for each outcome reported in the study and overall judgement on the risk of bias made per outcome. The risk of bias for each outcome was classified as 'high risk', 'low risk' or 'some concerns'. If multiple studies would have been eligible for inclusion, we would have done a sensitivity analysis for studies with high-risk of bias to interrogate their impact on the overall treatment effect. Graphic representations of potential bias was done using the RoB2 Microsoft Excel worksheet (18) approved by the Cochrane collaboration and any discrepancies resolved via consensus.

No observational studies were eligible for inclusion in this review. If any such studies had been included, their risk of bias would have been assessed by two reviewers independently using the ROBINS-I tool (20) and any discrepancies resolved by consensus.

The GRADE Pro software Guideline Development Tool (21) was used to input data from data extraction and risk of bias assessment tools in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the outcome of interest, was obtained using the GRADE approach. This was based on five parameters namely; study

limitations, consistency of effect, imprecision, indirectness and publication bias. Based on this, the evidence was downgraded from high quality by one or two levels if found to have serious or very serious limitations respectively. The quality of evidence was then classified as high, moderate or low for each outcome of interest.

2.6 Measures of treatment effect

We aimed to conduct both a narrative and a quantitative synthesis of the study data. For dichotomous data, we set out to use pooled summary risk ratio to present results at a 95% confidence interval. In our review, only one study was eligible for inclusion and thus we could not assess a pooled summary affect. We therefore presented the risk ratio for the outcomes of interest based on the results of the included study. If continuous data was present, we would have used the mean difference if outcomes were measured in the same way between studies and standardized mean difference for studies that measured similar outcomes via different methods.

2.7 Dealing with missing data

We carried out our analysis of the outcomes based on an intention to treat effect as a way of dealing with possible attrition. In the included study, no participants were lost to follow up and all were analyzed as initially randomized.

2.8 Assessment of heterogeneity

We only included one study hence did not conduct an assessment of heterogeneity.

If we had found enough studies to include for a meta-analysis, we would have evaluated them for clinical heterogeneity by examining the variability of participants' baseline characteristics, medical history among trials, and by examining the variability of studies' characteristics. These would have included randomization, allocation concealment, blinding or losses to follow-up.

We would have assessed statistical heterogeneity in each meta-analysis using the I2 statistic with a value of greater than 30% being regarded as an indicator of significant heterogeneity.

2.9 Assessment of reporting bias

If we had conducted a meta-analysis with over 10 studies, funnel plots would have been used to assess for the risk of publication bias. If asymmetry was detected on visual assessment, we would have done exploration for possible bias.

2.10   Data synthesis

For data that could be reasonably assumed to be estimating the same underlying treatment effect, the fixed effects model would have been used to combine the data. We would have used the random effects model if we found sufficient heterogeneity, in order to produce an overall summary if an average treatment effect across the studies was considered clinically meaningful. A quantitative synthesis would not have been done if I^2 was equal to or greater than 50%. Instead, a narrative qualitative synthesis would have been done. If I^2 was above 30%, we would

have used the fixed-effect model and if it fell between 30% and 50%, the random-effects model would have been used.

2.11   Subgroup analysis and investigation of heterogeneity

Had we found significant heterogeneity, we would have used subgroup analysis and sensitivity analysis to investigate it. Subgroup analysis would have been based on participants' characteristics including age, ethnicity, parity, body mass index, smoking status, history of pre-eclampsia, use of antihypertensive medication, gestational ages at delivery (between 37+0 and 37+6 weeks, between 38+0 and 38+6, between 39+0 and 39+6 and between 40+0 and 40+6 weeks), duration of the hypertension, presence or absence of baseline proteinuria and each gestational week. Primary outcomes in subgroup analysis would have been composite maternal and composite perinatal outcomes.

2.12   Sensitivity analysis

This would have been performed if the studies showed significant heterogeneity by excluding studies with high risk or some concerns in the risk of bias according to study design.

2.13   Ethical considerations

This review was exempted from the Aga Khan University Ethics Review Committee (Ref: 2020/IERC-155(vl)) as it was a retrospective review analysis of clinical data without any identifiable information about patients. Protocol registration for this review was done in PROSPERO under the registration number CRD42021245696.

2.14   Expected application of results

This information will be useful to clinicians in Obstetrics who are now seeing an increasing number of women with chronic hypertension in pregnancy and are weighing the benefits and risks of expectant management compared to early delivery for chronic hypertension from 37 weeks of gestation. We plan to disseminate the study findings through presentation in relevant professional body meetings such as the Kenya Obstetrics and Gynecology Society (KOGS) conferences. In addition, we are aiming to publish the findings in a peer reviewed journal to reach more potential users and guide clinical practice at a wider level.

CHAPTER THREE

RESULTS

Based on the search strategy, the electronic search of bibliographic databases produced a total of 8830 articles that were then exported to the Covidence web application for the initial screening. A total of 749 duplicates were removed and 8081 articles went through title and abstract screening. Title and abstract screening was done based on a pre-specified form. The form was piloted on 30 titles and abstracts by two independent reviewers and no discrepancies arose at this stage.

Following title and abstract screening, a total of 8084 articles were deemed irrelevant for the review and 15 articles were eligible for the full text review. At the title and abstract screening stage, a total of 13 conflicts arose. These disagreements were resolved by consensus and 15 articles were eventually considered to be eligible for full text review. We measured the degree of agreement at the title and abstract screening using the kappa statistic and got a score of 0.68 which indicates a good level of agreement.

We obtained the full text manuscripts for all the 15 selected studies for full text review. Two independent review authors reviewed the full texts for each of the selected articles. Out of the 15 articles two independent reviewers agreed on one article for inclusion. We extracted the data and conducted a risk of bias assessment for the included study. Two review authors discussed any discrepancies that arose in this process and resolved them by consensus. Of the excluded studies, based on our pre-specified eligibility criteria, 9 were studying the wrong population and 3 used the wrong study design. For the remaining 2 studies, one was studying the wrong intervention while the other used the wrong indication for the intervention. The degree of agreement was also measured using the kappa statistic yielding a score of 0.634 indicating a good level of agreement. We also searched the reference list of the included study. None of the referenced studies was eligible for inclusion.

The summary of bibliographic database search results is displayed on table 2.

The process of study selection has been displayed in a PRISMA flow diagram as shown on figure 1.

Table 2: Summary of bibliographic database search results

Database	Date of last search	Articles found
MEDLINE	28/12/2020	1,975
CENTRAL	12/01/2021	4,046
EMBASE	28/3/2021	2,809
Total		8,830

Figure 1: PRISMA flow diagram

```
┌──────────────────────────────────┐           ┌──────────────────────────────────┐
│ 8,830 Studies imported for        │  ──────▶  │   749 duplicates removed          │
│ screening                         │           │                                   │
└──────────────────────────────────┘           └──────────────────────────────────┘
                │
                ▼
┌──────────────────────────────────┐           ┌──────────────────────────────────┐
│ 8,081 Studies screened            │  ──────▶  │   8,066 studies irrelevant        │
└──────────────────────────────────┘           └──────────────────────────────────┘
                │
                ▼
┌──────────────────────────────────┐           ┌──────────────────────────────────┐
│ 15 full-text studies assessed for │  ──────▶  │      14 studies excluded          │
│ eligibility                       │           │                                   │
│                                   │           │  10 Wrong patient information     │
│                                   │           │   3 wrong study designs           │
│                                   │           │   1 wrong intervention            │
└──────────────────────────────────┘           └──────────────────────────────────┘
                │
                │                                ┌──────────────────────────────────┐
                │                                │      0 studies ongoing            │
                │                                │  0 studies awaiting classification│
                │                                └──────────────────────────────────┘
                ▼
┌──────────────────────────────────┐
│ 1 Study included                  │
└──────────────────────────────────┘
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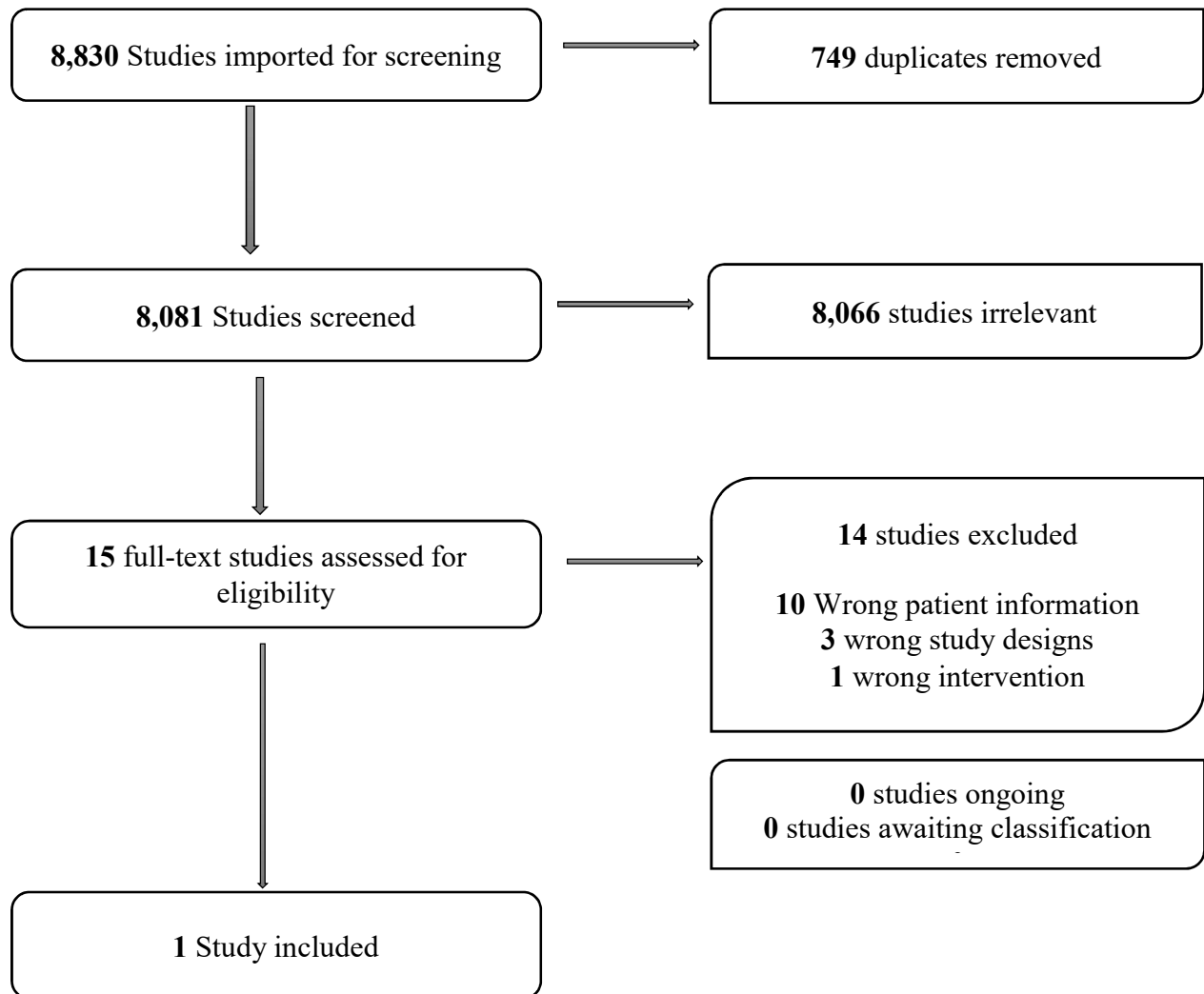
3.1 Characteristics of the included study

The included study was a two arm two center randomized controlled trial conducted between April 1, 2012 and October 31, 2013. It was carried out at Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt.

3.2 Participants

The study participants were pregnant women who presented to the clinics at Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. The participants included in this study were women with a singleton pregnancy with mild to moderate chronic hypertension and no proteinuria. They were recruited starting from 24 to 36 weeks gestation. A diastolic blood pressure between 90 and 110 mmHg and/or systolic pressure between 140 and 160 mmHg on 2 occasions at least 6 hours apart was used to define mild to

moderate chronic hypertension. This needed to have been present prior to 20 weeks gestation or if the woman was known to have chronic hypertension before pregnancy.

Women with severe chronic hypertension (blood pressure ≥ 160/110 mmHg) and pregnancy induced hypertension were excluded from this study. Those found to have new onset pre-eclampsia and were previously normotensive were also excluded. The study authors also excluded women with secondary hypertension. This was done by examination and relevant tests including renal function tests, urine analysis, abdominal ultrasound, renal artery Doppler, urinary catecholamine, and autoimmune serologic profile. They also excluded women with target organ damage by funduscopic, renal and cardiac evaluation. Other criteria for exclusion were non cephalic fetal presentation at recruitment, low lying placenta, scarred uterine, fetal anomalies, or pre-existing diabetes mellitus.

A total of 102 women were assessed for eligibility of whom 26 were excluded, where 4 declined to participate while 22 did not meet the inclusion criteria. Seventy six women were then randomized individually to the two intervention groups. The participants' ages ranged from 18 to 40 years with average age being 28.4 years for the intervention group and 29.2 years for the comparator group. Parity ranged from 0 to above 5 in both groups and the duration of chronic hypertension was from 1 to 7 years. A total of 43 women were on antihypertensive medication and 16 had gestational diabetes mellitus. 12 women had a prior history of pre-eclampsia. The gestational age at recruitment ranged from 24 to 36 weeks while the gestational age at delivery was from 28 to 41 weeks. None of the participants had baseline proteinuria.

The authors did not indicate the racial distribution of the participants or smoking or other substance use status. From the information available, there were no significant differences in the baseline characteristics between the two groups.

The flow of participants through the study has been displayed on figure 2 and a summary of the participants' baseline characteristics is shown on table 3.

Figure 2: Participants flow diagram

Patients assessed for eligibility
(n=102)

Enrollment

Total excluded (n=26):
Refused to participate
(n=4)
Did not meet inclusion
criteria (n=22)

Randomization via computer – generated table
(n=76)

Group A (n=38)

Allocated to planned
delivery at 37 weeks

Allocation

Group B (n=38)

Allocated to expectant
management to 41 weeks

Lost to follow-up (n=0)

Follow-up

Lost to follow-up (n=0)

Final analysis for primary
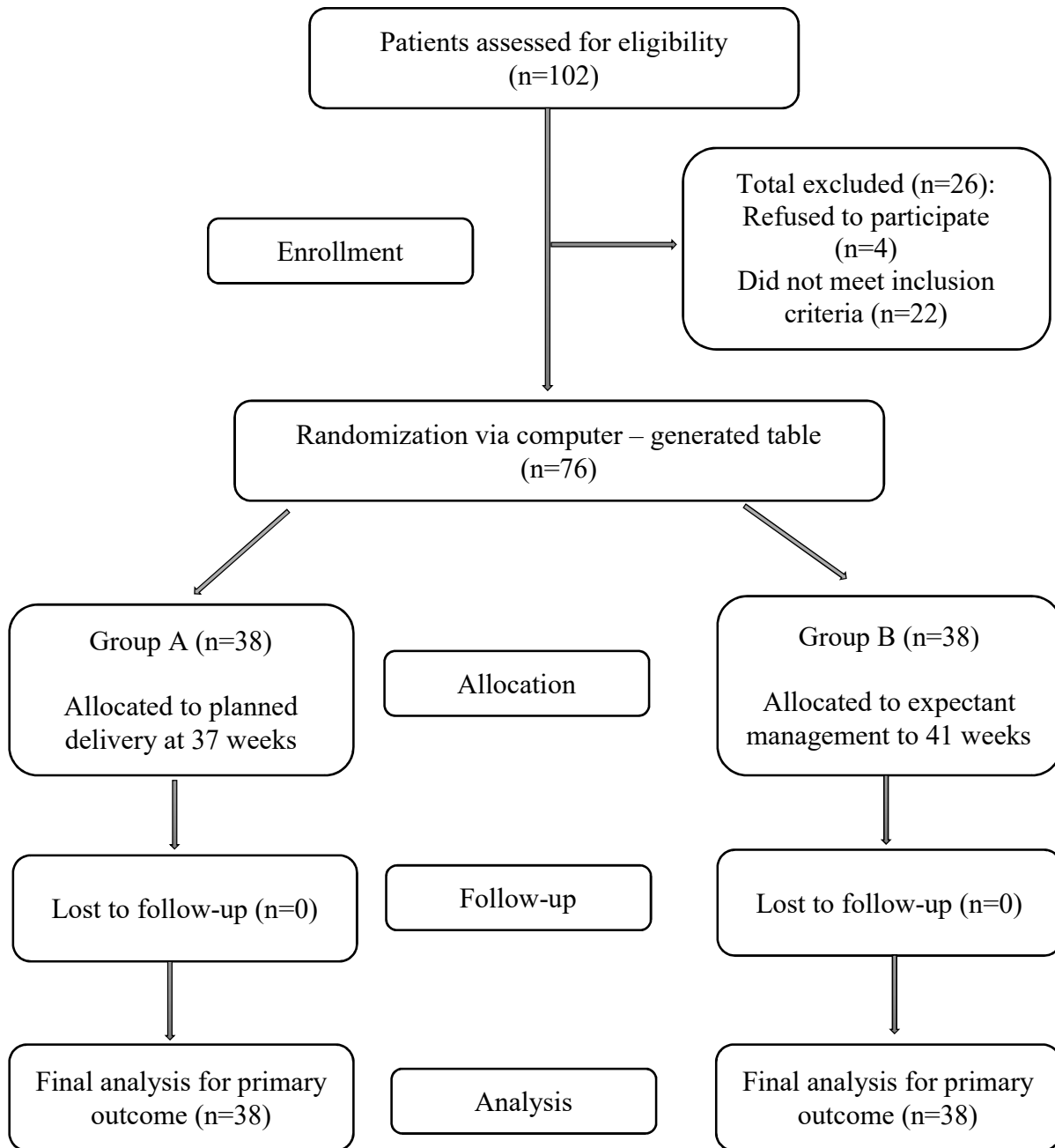outcome (n=38)

Analysis

Final analysis for primary
outcome (n=38)

Table 3: Participants baseline characteristics

Variable	Planned delivery (n = 38)	Expectant management (n = 38)	P value
Maternal age, y	28.4 ± 5.7 (18-39)	29.2 ± 6.6 (19-40)	0.5
Age group, y			0.8
<20	3 (7.9)	2 (5.3	
20-34	24 (63.2)	23 (60.5)	
≥35	11 (28.9)	13 (34.2)	
Parity			0.3
0-1	2 (5.3)	5 (13.2)	
2-4.	22 (57.9)	23 (60.5)	
≥5	14 (36.8)	10 (26.3)	
Past history of pre-eclampsia	5 (13.2)	7 (18.4)	0.7
Duration of chronic hypertension, y	2.8 ± 1.06 (1-6)	3.3 ± 1.4(1-7)	0.1
Gestational age at recruitment, wk	31.2 ± 3.6 (24-36)	31.3 ± 3.9 (24-36)	0.9
Systolic BP at admission, mm Hg	153.2 ± 6.4 (140-160)	154.8 ± 52 (140-160)	0.3
Diastolic BP at admission, mm Hg	97.3 ± 5.1 (90-105)	98.4 ± 4.5 (90-105)	0.3
Associated diabetes mellitus	7 (18.4)	9 (23.7)	0.7
Antihypertensive treatment			0.9
None	17 (44.7)	16 (42.1)	
a-Methyldopa	13 (34.2)	13 (34.2)	
Nifedipine	2 (5.3)	4 (10.5)	
Labetalol	2 (5.3)	2 (5.3)	
Combinations	4 (10.5)	3 (7.9)	

y – years, wk- weeks

3.3 Intervention

Following randomization of the 76 eligible participants, 38 were allocated to the experimental intervention of planned delivery at 37 weeks gestation while the other 38 were allocated to the comparator intervention of expectant management up to 41 weeks gestation.

For the experimental intervention group delivery was conducted at 37 completed weeks, if there were no maternal or fetal complications that would have necessitated preterm delivery. Cervical assessment was done to determine the approach to induction of labor. Oxytocin infusion and amniotomy were used if the Bishop's score was > 8, while vaginal misoprostol at a dose of 50 µg every 6 hours up to a maximum of 200 µg, was used if the Bishop's score was 8 and below. This was followed by oxytocin infusion and amniotomy. For women who were already on antihypertensive medication before recruitment, this was continued and with appropriate monitoring of the dose to achieve optimal blood pressure control.

In the comparator intervention group, participants were managed expectantly until labor set in spontaneously or up to 41 gestational weeks, whichever came earlier. Monitoring was done on an outpatient basis. This involved measurement of blood pressure and proteinuria screening 2 to 3

times in a week. They were admitted for the initial evaluation and if any fetal or maternal complications occurred. For women who were already on antihypertensive medication before recruitment, this was continued and with appropriate monitoring of the dose to achieve optimal blood pressure control.

3.4 Outcomes

The primary outcome in the included study was superimposed pre-eclampsia. Secondary outcomes investigated were severe chronic hypertension, placental abruption, oligohydramnios, intrauterine growth restriction, preterm delivery, birth weight, cesarean delivery, admission to NICU, and perinatal mortality. An amniotic fluid index of less than 5 cm was used as the criteria for diagnosing oligohydramnios. Perinatal mortality was death occurring to the fetus after 24 weeks gestation or death of a neonate in their first seven days of life. Fetal growth restriction was diagnosed if the estimated fetal weight fell under the 10th percentile using population-based growth curves and presence of associated abnormal Doppler flow indices.

Our review set out to assess the composite maternal outcome (super-imposed pre-eclampsia, admission to ICU, placental abruption) and composite perinatal outcome (stillbirth, admission to NICU) as the primary outcomes. The secondary maternal outcomes were super-imposed pre-eclampsia, maternal admission to ICU, and placental abruption. The secondary perinatal outcomes were stillbirth and admission to NICU. The included study did not assess maternal admission to ICU as an outcome. Though the study describes perinatal mortality as an outcome, it did not specifically assess stillbirth. We therefore describe the three outcomes that were pre-specified in our protocol.

As regards superimposed pre-eclampsia, the study authors described the outcome as new onset of proteinuria based on a 24 hour urine collection (300 mg/24 h) regardless of the severity of the hypertension, or a low platelet count (platelets below 100 000/mL). The outcome was assessed from the time of intervention which was at 37 weeks gestation to 41 weeks gestation. There was no significant difference in the rate of super-imposed pre-eclampsia in the two groups. Twelve cases of superimposed pre-eclampsia occurred in the planned delivery group while 13 occurred in the expectant management group with an OR of 0.9 (95% CI 0.2 to 2.3, p value 0.9).

The authors calculated a sample size based aiming to detect any statistical difference in the development of superimposed pre-eclampsia between the two groups. The assumed risk of superimposed pre-eclampsia from the mid trimester of pregnancy was 20%–40% (mean, 30%). They hypothesized that planned delivery at 37 weeks might result in a 30%–50% reduction in this risk with considerable clinical significance. Seventy four study participants would be required to demonstrate this difference with 80% power and a type 1 error probability of 5%

For placental abruption, the study authors did not describe the method used for assessing the outcome. This outcome was assessed from the time of intervention at 37 weeks of gestation up to 41 weeks of gestation. No significant difference in the rate of placental abruption was observed between the two groups. Each arm had 3 participants developing placental abruption giving an OR of 1.0 (95% CI 0.2 to 5.2) p value 1.0.

The rate of admission to NICU was higher in the planned delivery compared to the expectant management group occurring in 12 and 3 participants respectively with an OR = 5.4 (95% CI 1.4 to 21.0) p value 0.01.

A summary of the outcomes in the included study is displayed on table 4.

Table 4: Participants outcome data

Clinical outcome	Planned delivery [n= 38]	Expectant management [n= 38]	Odds ratio (95%CI)	P value
Gestational age at delivery, wk	35.7 ± 1.2 (28-37)	38.1 ± 2.7 (31-41)	-	0.001
Superimposed Pre-eclampsia	12 (31.6)	13 (34.2)	0.9 (0.3-2.3)	0.9
Severe chronic hypertension	5 (13.2)	3 (7.9)	1.7 (0.3-7.9)	0.7
Total preterm birth	10 (26.3)	12 (31.3)	0.9 (0.3-2.4)	0.8
Placental abruption	3 (7.9)	3 (7.9)	1.0 (0.2-5.2)	1.0
Oligohydramnios	8 (21.1)	5 (13.2)	1.7 (0.5-5.9)	0.5
Intrauterine growth restriction	6 (15.9)	4 (10.5)	1.2 (0.4 - 4.3)	0.8
Birth weight, kg	2.8 ± 0.6 (1.6-4.0)	3.2 ± 0.6 (1.9-4.1)	-	0.01
NICU admission	12 (31.6)	3 (7.9)	5.4 (1.4-21.0)	0.01
Perinatal mortality	2 (5.3)	1 (2.6)	2.0 (0.1-23.6)	1.0

wk – weeks, kg - kilogram

3.5 Excluded studies

Of the 14 excluded studies, based on our pre-specified eligibility criteria, 10 were studying the wrong population and 3 used the wrong study design. For the remaining 2 studies, one was studying the wrong intervention. A summary of the excluded studies and the reasons for their exclusion is provided on table 5 below.

Table 5: Characteristics of excluded studies

Study ID	Study Title	Study Design	Aim of the Study	Reason For Exclusion
Lydakis 1998	Obstetric and neonatal outcome following chronic hypertension in pregnancy among different ethnic groups	Retrospective cohort study	To investigate differences in prevalence of pre-eclampsia, gestational age at delivery, birth weight, ponderal index and perinatal mortality in women with chronic hypertension from a multiracial population.	Wrong study design

Study ID	Study Title	Study Design	Aim of the Study	Reason For Exclusion
Laura 2018	When to Induce Labour to Limit risk in pregnancy hypertension) - a multicentre, randomized controlled trial	Trial Protocol for a randomized controlled trial.	To assess whether planned early term delivery at 38+0 to 38+3 weeks (compared with expectant care until at least 40+0 weeks) will reduce a composite of 'poor maternal outcome' without increasing neonatal care unit admission in women with chronic hypertension or gestational hypertension	Wrong patient population
Browne 2015	Perinatal outcomes after hypertensive disorders in pregnancy in a low resource setting	Prospective cohort study	To evaluate perinatal outcomes of pregnancies complicated by hypertensive disorders in pregnancy in an urban sub-Saharan African setting	Wrong patient population
Thangaratinam 2015	Immediate delivery in women with non-severe hypertensive disorders at 34-37 weeks' gestation does not reduce maternal complications, and increases neonatal risks more than under expectant management	Commentary on a randomized controlled trial	To investigate the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in women with hypertensive disorders in late preterm pregnancies	Wrong study design
Bernardes 2019	Delivery or expectant management for prevention of adverse maternal and neonatal outcomes in hypertensive disorders of pregnancy: an individual participant data meta-analysis	Individual participant data meta-analysis	To compare immediate delivery with expectant management for prevention of adverse maternal and neonatal outcomes in women with gestational hypertension or pre-eclampsia without severe features from 34 weeks of gestation	Wrong study design

Study ID	Study Title	Study Design	Aim of the Study	Reason For Exclusion
Broekhuijsen 2015	Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT II trial)	Randomized controlled trial	To investigate the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in women with hypertensive disorders in late preterm pregnancies	Wrong patient population
Zwertbroek 2020	Neonatal developmental and behavioral outcomes of immediate delivery versus expectant monitoring in mild hypertensive disorders of pregnancy: 5-year outcomes of the HYPITAT II trial	Follow up of randomized controlled trial	To compare effects of immediate delivery vs expectant monitoring on neurodevelopmental and behavioral outcomes at 5 years of age in offspring of women with mild late preterm hypertensive disorders	Wrong patient population
Harper 2016	Gestational Age of Delivery in Pregnancies Complicated by Chronic Hypertension	Retrospective cohort study	To identify the gestational age of planned delivery in pregnancies complicated by chronic hypertension that minimizes the risk of perinatal death and severe adverse events	Wrong patient population. The study authors did not distinguish between severe and non-severe chronic hypertension.
Parazzini 1998	Nifedipine versus expectant management in mild to moderate hypertension in pregnancy.	Randomized controlled trial	To compare the effect of routine treatment with the calcium channel blocker nifedipine in mild to moderate hypertension in pregnancy	Wrong intervention

Study ID	Study Title	Study Design	Aim of the Study	Reason For Exclusion
Hutcheon 2011	Optimal timing of delivery in pregnancies with pre-existing hypertension.	Population based cohort study	To determine the optimal timing of delivery in pregnancies with chronic hypertension by quantifying the gestational age-specific risks of stillbirth associated with ongoing pregnancy and the gestational age-specific risks of neonatal mortality or serious neonatal morbidity following the induction of labour	Wrong patient population. Chronic hypertension in this study included both pre-existing hypertension with and without super-imposed pre-eclampsia. Non-severe chronic hypertension was not defined.
Ram 2018	Timing of Delivery in Women With Chronic Hypertension	Retrospective population-based study	To assess whether routine induction of labor at 38 or 39 weeks in women with chronic hypertension is associated with the risk of superimposed preeclampsia or cesarean delivery	Wrong patient population
Broekhuijsen 2015	Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II)	Randomized controlled trial	To investigate the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in women with hypertensive disorders in late preterm pregnancies	Wrong patient population
Broekhuijsen 2014	Delivery versus expectant monitoring for late preterm hypertensive	Randomized controlled trial	To assess the effectiveness of immediate delivery for women with hypertensive disorders in late preterm pregnancy in women with hypertensive disorders	Wrong patient population

Study ID	Study Title	Study Design	Aim of the Study	Reason For Exclusion
	disorders of pregnancy.			
Langenveld 2011	Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia between 34 and 37 weeks' gestation (HYPITAT-II): a multicentre, open-label randomized controlled trial.	Study protocol for a randomized controlled trial	To investigate the effect of immediate delivery versus expectant monitoring on maternal and neonatal outcomes in women with hypertensive disorders in late preterm pregnancies	Wrong patient population and wrong study design

3.6 Risk of bias in the included study

We assessed the risk of bias for each of the three outcomes outlined in our protocol as described in the study, using the risk of bias assessment tool version 2 and also assessed the overall risk of bias for the study. These have been presented graphically in figures 3 and 4 respectively.

3.6.1   Randomization process

For sequence generation, the study randomized participants based on a computer generated table that assigned them to the two interventions at a ratio of 1:1. The overall judgement for the risk of bias in this domain was low. This was the same for all the outcomes. There was no information on whether allocation concealment was done in this study for all the three outcomes. It is possible that lack of allocation concealment might have had an effect on treatment decisions. As such, the overall judgement for all the outcomes was 'some concerns'.

3.6.2   Deviations from intended interventions

Blinding of participants and personnel for all the three outcomes was not done in the included studies and this applied to all the three outcomes.

On blinding outcome assessors for all outcomes, the study authors did not give information on whether this was done. This may have affected treatment or assessment decisions especially for super-imposed pre-eclampsia and placental abruption. Regarding admission to NICU, it is also not clear whether outcome assessors were blinded but it was unlikely that this would have affected treatment or assessment outcomes.

Overall, we considered the risk of bias to be 'high' for superimposed pre-eclampsia and 'some concerns' for admission to NICU.

3.6.3 Missing outcome data

All participants recruited to the study were followed up to completion of the study and no attrition was reported. Data on all the study outcomes was available for all the participants as initially assigned to the two interventions. The participants were also analyzed based on intention to treat basis.

The risk of bias in this domain was low for all the three outcomes.

3.6.4 Measurement of the outcome

The authors described the method used to assess for super-imposed pre-eclampsia based on laboratory investigations (proteinuria or thrombocytopenia). There was no information on how placental abruption was assessed and the criteria for admission to NICU was not indicated.

It is likely that patients in the experimental intervention group who were admitted for delivery, had closer monitoring compared to the expectant management group that was monitored as outpatients. This might have affected outcome assessment with the likelihood of favoring more events in the experimental group. For admission to NICU, though the criteria for admission was not indicated, it was unlikely to affect to affect the overall result.

Overall, we found the risk of bias in this domain to be 'high' for the outcomes of super-imposed pre-eclampsia and 'low' for admission to NICU.

3.6.5 Selective reporting

The study authors did not make any reference to a study of protocol or trial registration. For this reason it was not possible to ascertain whether all pre-specified outcomes were assessed or not. As a result, we ranked the overall risk of bias in this domain as 'some concerns' for all the outcomes.

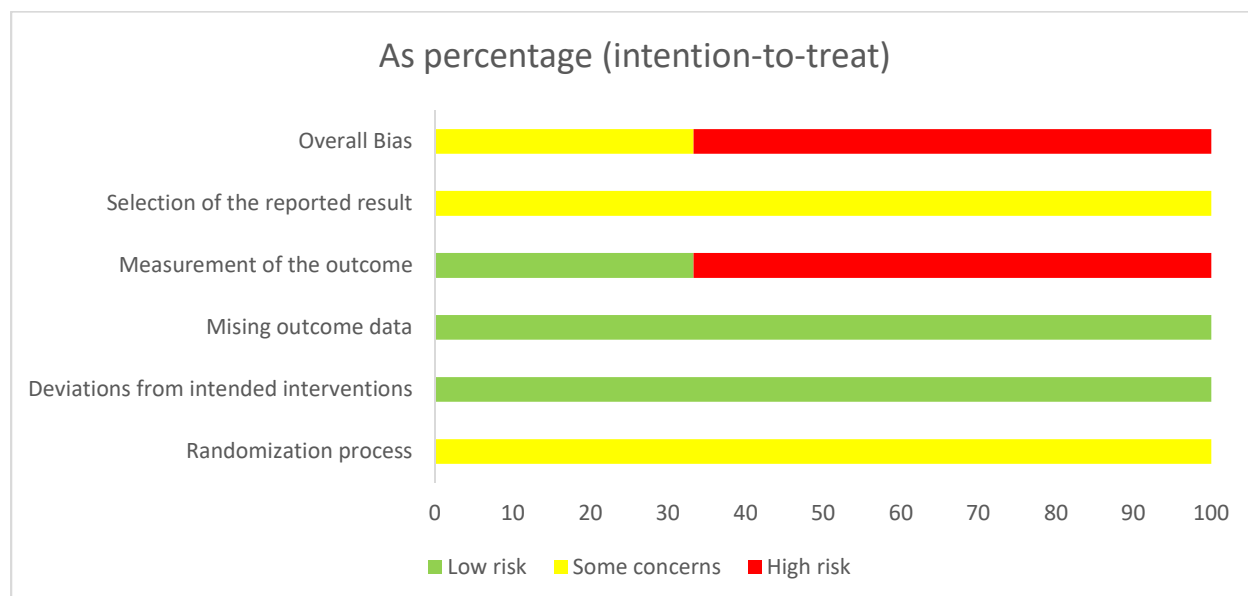**Figure 3: Overall risk of bias for the included study**

As percentage (intention-to-treat)

| | Low risk | Some concerns | High risk |

Figure 4: Risk of bias for specific outcomes

Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall			
Hamed 2014	Planned deliv	Expectant Mgt	SPE	1	?	+	+	−	?	−		+	Low risk
Hamed 2014	Planned deliv	Expectant Mgt	Abruption	1	?	+	+	−	?	−		?	Some concerns
Hamed 2014	Planned deliv	Expectant Mgt	NICU adm	1	?	+	+	+	?	!		−	High risk

3.7 Summary of findings

Using the GRADE Pro software Guideline Development Tool (21) input data from the data extraction and risk of bias assessment tools in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the outcome of interest, was obtained using the GRADE approach. This was based on five parameters namely; study limitations, consistency of effect, imprecision, indirectness and publication bias. Based on this, the evidence was downgraded from high quality by one or two levels if found to have serious or very serious limitations respectively. The quality of evidence was then classified as high, moderate or low for each outcome of interest. Table 6 displays this summary of findings.

Table 6: Summary of findings

Summary of findings table

Planned delivery at 37 weeks gestation compared to Expectant Management up to 41 weeks for Non-severe chronic hypertension

Patient or population: Non-severe chronic hypertension
Setting: Saudi Arabia and Egypt. Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. April 2012 - October 2013
Intervention: Planned delivery at 37 weeks gestation
Comparison: Expectant Management up to 41 weeks

Outcomes	Anticipated absolute effects[*] (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Expectant Management up to 41 weeks	Risk with Planned delivery at 37 weeks gestation				
Super-imposed Pre-eclampsia (SPE) assessed with: Proteinuria and Thrombocytopenia	342 per 1,000	**319 per 1,000** (135 to 545)	**OR 0.9** (0.3 to 2.3)	76 (1 RCT)	⊕⊕◯◯ LOW [a]	Planned delivery at 37 weeks gestation probably results in little to no difference in super-imposed Pre-eclampsia.

Summary of findings table

Planned delivery at 37 weeks gestation compared to Expectant Management up to 41 weeks for Non-severe chronic hypertension

Patient or population: Non-severe chronic hypertension
Setting: Saudi Arabia and Egypt. Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. April 2012 - October 2013
Intervention: Planned delivery at 37 weeks gestation
Comparison: Expectant Management up to 41 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Expectant Management up to 41 weeks	**Risk with Planned delivery at 37 weeks gestation**				
Placental Abruption (Abruptio) assessed with: Not indicated	79 per 1,000	**0 per 1,000** (17 to 308)	**OR --** (0.2 to 5.2)	76 (1 RCT)	⊕⊕○○ LOW [b]	The evidence suggests that planned delivery at 37 weeks gestation results in little to no difference in placental Abruption.
Admission to NICU (NICU admission) assessed with: Number of admissions	79 per 1,000	**316 per 1,000** (107 to 643)	**OR 5.4** (1.4 to 21.0)	76 (1 RCT)	⊕⊕⊕○ MODERATE [c]	Planned delivery at 37 weeks gestation likely results in a large increase in admission to NICU.

Summary of findings table

Planned delivery at 37 weeks gestation compared to Expectant Management up to 41 weeks for Non-severe chronic hypertension

Patient or population: Non-severe chronic hypertension
Setting: Saudi Arabia and Egypt. Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. April 2012 - October 2013
Intervention: Planned delivery at 37 weeks gestation
Comparison: Expectant Management up to 41 weeks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Expectant Management up to 41 weeks	**Risk with Planned delivery at 37 weeks gestation**				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Blinding of participants was not done. It is unclear whether outcome assessors were blinded. Inpatient monitoring for the intervention group could have led to more cases being reported due to the likelihood of more frequent monitoring than in the comparator group monitored as outpatients.

b. Blinding of participants was not done. It is unclear whether outcome assessors were blinded. The standard of measurement for placental abruption was not indicated hence objectivity could not be assessed. It is also not clear whether the same standard was applied for both groups.

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Inpatient monitoring for the intervention group could have led to more cases being reported than in the comparator group monitored as outpatients.

c. Blinding of participants was not done. It is unclear whether outcome assessors were blinded. The criteria used for admission to NICU was not indicated hence objectivity could not be assessed. However, this was presumably done by the neonatologists hence their treatment decisions were unlikely to have been affected by lack of blinding.

CHAPTER FOUR

DISCUSSION

4.1 Summary of main results

This review indicated that in women with non-severe chronic hypertension in pregnancy, a policy of expectant management up to 41 weeks gestation was more favorable than planned delivery at 37 weeks gestation. This is because there is no significant difference in the rates of super-imposed pre-eclampsia, placental abruption or perinatal mortality between the two interventions. Additionally, expectant management was associated with lower rates of admission to NICU.

4.2 Overall completeness and applicability of evidence

We aimed to be as broad and inclusive as possible in the search strategy and did not apply any date or language restrictions in our primary search. In our search, both randomized controlled trials and cohort studies were included. After assessment of selected studies, one randomized controlled trial was deemed eligible for the final review. We also searched the reference list of the included study. None of the referenced studies was eligible for inclusion.

We registered the review protocol with PROSPERO under registration number CRD42021245696 prior to starting the formal screening of results based on eligibility criteria. We conducted our review based on the steps outlined in the protocol.

As such, we could not conduct a meta-analysis as earlier intended in our protocol. We therefore did a narrative synthesis as earlier pre-specified. The included study did not assess admission to ICU as an outcome as this was not set out in the trial protocol.

4.3 Quality of the evidence

The results of this review were based on one randomized controlled trial as no other articles from the search were deemed eligible for inclusion. The study looked at patients seen at Maternity-Children Hospital, Al-Qassim region, Saudi Arabia and Women's Health Center, Assiut University, Egypt. Since the study authors did not describe the racial distribution and the study was conducted in two settings, the findings cannot be extrapolated to the general population.

The study had varying risks of bias for the three outcomes of interest ranging from 'high risk' to 'some concerns'. The level of evidence was then determined using the GRADE approach. Regarding the risk of super-imposed pre-eclampsia, the study findings indicated that planned delivery at 37 weeks gestation probably results in little to no difference in the rate of this outcome. This conclusion is based on moderate level of certainty of the evidence. The evidence also suggested that planned delivery at 37 weeks gestation results in little to no difference in placental abruption though is based on a low level of certainty of the evidence.

The study findings also demonstrated that planned delivery at 37 weeks gestation likely results in a large increase in admission to NICU compared to expectant management and this was based on a moderate level of certainty of the evidence.

4.4 Potential biases in the review process

Assessing the risk of bias involves review authors making subjective judgements. We minimized this potential limitation in our review was by adhering to the procedures outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (19) .This was achieved by having two review authors independently assess the studies at every step of the review with any discrepancies being resolved any by consensus, and if necessary involving a third reviewer in the decision. Measurement of the level of agreement using the kappa statistic at the initial screening of articles and at the level of full text review indicated an acceptable level of agreement for systematic review.

Our search was limited to three major electronic bibliographic databases. We did not search for unpublished trials or gray literature and no correspondence was made to experts in the area of study. As a result, publication bias could have arisen which could have affected the direction of the results in an unpredictable manner.

4.5 Conclusion

4.5.1 Implications for practice

In the setting of non-severe chronic hypertension in pregnancy, the evidence shows that expectant management up to 41 weeks gestation could be chosen over planned delivery at 37 weeks gestation as this was associated with significantly lower rates of admission to NICU. There was no significant difference in rates of developing super-imposed pre-eclampsia, placental abruption or perinatal mortality.

4.5.2 Implications for research

The question on optimal timing of delivery for women with non-severe chronic hypertension at term is critical but not adequately addressed by currently available literature. There is need for high quality studies that are sufficiently powered to address the review question taking into consideration the need for allocation concealment, blinding of outcome assessors and clearly outlined methods of assessing the outcomes of interest. These studies should also include other outcomes like maternal admission to ICU. Randomized controlled trials that include participants in different settings would improve the generalizability of the findings. This will enable combining of data from different studies to assess pooled effects in a meta-analysis. Consequently, this will enable recommendations to be made with a higher level of certainty.

REFERENCES

1. Alessia Mammaro,Sabina Carrara,Alessandro Cavaliere,Santina Ermito,Angela Dinatale,Elisa Maria Pappalardo,Mariapia Militello RP. Hypertensive Disorders in Pregnancy. J Prenat Med [Internet]. 2009 [cited 2021 May 30];3(1):1–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3279097/pdf/prenatal-03-0001.pdf

2. ACOG Practice Bulletin No. 203: Chronic Hypertension in Pregnancy. Obstet Gynecol [Internet]. 2019 Jan 1 [cited 2021 May 30];133(1):e26–50. Available from: https://journals.lww.com/greenjournal/Fulltext/2019/01000/ACOG_Practice_Bulletin_No__203__Chronic.50.aspx

3. Bateman BT, Bansil P, Hernandez-Diaz S, Mhyre JM, Callaghan WM, Kuklina E V. Prevalence, trends, and outcomes of chronic hypertension: A nationwide sample of delivery admissions. Am J Obstet Gynecol [Internet]. 2012;206(2):134.e1-134.e8. Available from: http://dx.doi.org/10.1016/j.ajog.2011.10.878

4. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, Chappell LC. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014 Apr;348:g2301.

5. Zetterström K, Lindeberg SN, Haglund B, Hanson U. Maternal complications in women with chronic hypertension: A population-based cohort study. Acta Obstet Gynecol Scand. 2005;84(5):419–24.

6. Koopmans CM, Bijlenga D, Groen H, Vijgen SMC, Aarnoudse JG, Bekedam DJ, et al. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks ' gestation (HYPITAT): a multicentre , open-label randomised controlled trial. 36:979–88.

7. Broekhuijsen K, Van Baaren GJ, Van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, et al. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): An open-label, randomised controlled trial. Lancet [Internet]. 2015;385(9986):2492–501. Available from: http://dx.doi.org/10.1016/S0140-6736(14)61998-X

8. Harper LM, Biggio JR, Anderson S, Tita ATN. Gestational Age of Delivery in Pregnancies Complicated by Chronic Hypertension. Obstet Gynecol. 2016 Jun;127(6):1101–9.

9. Hamed HO, Alsheeha MA, Abu-Elhasan AM, Abd Elmoniem AE, Kamal MM. Pregnancy outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery. Int J Gynaecol Obstet. 2014 Oct;127(1):15–20.

10. Chappell LC, Enye S, Seed P, Briley AL, Poston L, Shennan AH. Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study. Hypertens (Dallas, Tex 1979). 2008 Apr;51(4):1002–9.

11. Cluver C, Novikova N, Koopmans CM, West HM. Planned early delivery versus

expectant management for hypertensive disorders from 34 weeks gestation to term. Cochrane database Syst Rev. 2017 Jan;1:CD009273.

12. Harper LM, Biggio JR, Anderson S, Tita ATN. Gestational age of delivery in pregnancies complicated by chronic hypertension. Obstet Gynecol. 2016;127(6):1101–9.

13. Attanasio LB, Kozhimannil KB, Kjerulff KH, Professor MA. Women's preference for vaginal birth after a first delivery by cesarean.

14. Group S, Criteria D. risk factors for adverse neonatal outcomes in women with chronic hypertension. 1998;667–71.

15. Saade G. NIH Public Access. 2012;118:323–33.

16. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia [Internet]. [cited 2021 May 30]. Available from: https://support.covidence.org/help/how-can-i-cite-covidence

17. Data extraction forms | Cochrane Developmental, Psychosocial and Learning Problems [Internet]. [cited 2021 May 30]. Available from: https://dplp.cochrane.org/data-extraction-forms

18. Risk of bias tools - Current version of RoB 2 [Internet]. [cited 2021 May 30]. Available from: https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2

19. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training [Internet]. [cited 2021 May 30]. Available from: https://training.cochrane.org/handbook

20. Risk of bias tools [Internet]. [cited 2021 May 30]. Available from: https://www.riskofbias.info/

21. GRADEpro [Internet]. [cited 2021 May 30]. Available from: https://gradepro.org/

APPENDICES

Appendix 1: Title and abstract screening form

Citation, Title, and Abstract Screening
1. Does the **title or abstract** NOT indicate that a chronic hypertension in pregnancy systematic review or meta-analysis was conducted?
      a. Yes: continue screening
      b. No: stop screening

Abstract Screening
2. Does the **abstract** indicate that chronic hypertension in pregnancy at 37 weeks gestation was studied?
      a. Yes or Unsure/Unclear: continue screening
      b. No: stop screening
            -For example: the study only samples other hypertensive disorders in pregnancy such as pre-eclampsia, pregnancy induced hypertension or eclampsia

3. Does the **abstract** indicate that this study was either randomized or cohort study?
      a. Yes or Unsure/Unclear: continue screening
            -Key words: randomized controlled trial, retrospective cohort, prospective cohort, longitudinal, population based.
      b. No: stop screening
            -For example: the study only used cross-sectional, prevalence, rate, incidence, or all data collected at the same time, quasi randomized trial, case-control

4. Does the **abstract** indicate that timing of delivery was studied?
      a. Yes or Unsure/Unclear: continue screening
            -Key words: timing of delivery, planned delivery, elective delivery, child birth, parturition, expectant management, delayed delivery
      b. No: stop screening
            -Other constructs, in the absence of timing of delivery above, **not** eligible: treatment of chronic hypertension, choice of medication for chronic hypertension

5. Does the **abstract** indicate that the study uses a quantitative design?
      a. Yes or Unsure/Unclear: continue screening
            -Key words: regression, covariate, modeling, structural equation modeling, mean, standard deviation, correlation, variance
      b. No: stop screening
            -For example: qualitative only: ethnography, action research, social observation, focus groups, case study research

Decision: **Should this article be included?**
      a. **Yes**, all 6 screening questions answered Yes or Unclear
      b. **No**, at least one answers definitely "No"

Appendix 2: CENTRAL Search Strategy as at 12/01/2021

Search Number	Search Terms	Results
#1	Chronic hypertension	8,746
#2	"chronic hypertension"	389
#3	hypertens*	69,044
#4	blood pressure	107,419
#5	"blood pressure"	93,314
#6	high blood pressure	26,022
#7	"high blood pressure"	2,854
#8	elevated blood pressure	5,470
#9	"elevated blood pressure"	1,184
#10	increased blood pressure	28,095
#11	"increased blood pressure"	517
#12	MeSH descriptor: [Hypertension] explode all trees	18,055
#13	MeSH descriptor: [Essential Hypertension) this term only	169
#14	#1 0R #2 0R #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	141,976
#15	pregnan*	68,159
#16	"pregnancy"	59,442
#17	gestation*	26,028
#18	"gestation"	12,559
#19	MeSH descriptor: [Pregnancy] explode all trees	22,051
#20	#15 OR #16 OR #17 OR #18 OR #19	77,643
#21	timing of delivery	2,290
#22	"timing of delivery"	134
#23	timely delivery	661
#24	"timely delivery"	44
#25	planned delivery	4,046
#26	"planned delivery"	49
#27	deliver*	86,102
#28	Caesarean section	13,655
#29	Caesarean delivery	7,484
#30	birth	34,350
#31	child birth*	13,092
#32	childbirth*	4,339
#33	vaginal deliver*	5,809
#34	Normal deliver*	9,347
#35	MeSH descriptor: [Parturition] explode all trees	445
#36	#21 0R #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34	115,626

Search Number	Search Terms	Results
#37	#14 AND #20 AND #36	4,046
	in Trials	

Appendix 3: EMBASE Search Strategy as at 28/03/2021

Search Number	Search Terms	Results
#1	exp hypertension/	824,914
#2	exp maternal hypertension/	20,470
#3	hypertens*.mp.	1,054,170
#4	exp blood pressure/	663,190
#5	blood pressure.mp.	695,143
#6	high blood pressure.mp.	24,892
#7	exp elevated blood pressure/	828,845
#8	elevated blood pressure.mp.	15,000
#9	increased blood pressure.mp.	5,670
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR#8 OR #9).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	19,435,840
#11	exp pregnancy/	831,344
#12	pregnan*.mp.	1,139,645
#13	exp gestation period/	15,203
#14	gestation*.mp.	364,843
#15	(#11 OR #12 OR #13 OR #14).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4,546,672
#16	exp delivery/	173,239
#17	timing of delivery.mp.	1,314
#18	timely delivery.mp.	692
#19	cesarean section/	111,041
#20	deliver*.mp.	1,210,736
#21	obstetric delivery/	13,758
#22	obstetric deliver*.mp.	14,052
#23	planned delivery.mp.	368
#24	C?esarean section.mp.	121,545
#25	c?esarean deliver*.mp.	23,350
#26	exp birth/	31,974
#27	parturition.mp.	19,764
#28	birth*.mp.	545,176
#29	exp childbirth/	67,727
#30	childbirth/	22,973
#31	childbirth* .mp.	40,007
#32	child birth*.mp.	1,653
#33	normal deliver*.mp.	3,155

Search Number	Search Terms	Results
#34	vaginal deliver*.mp.	42,626
#35	c?esarean section*.mp.	122,613
#36	(#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR ##33 OR#34 OR #35).mp. [(mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	6,599,875
#37	"randomized controlled trial (topic)"/	203,809
#38	randomized controlled trial.mp.	878,836
#39	controlled clinical trial/	464,364
#40	randomization/	91,061
#41	observational study/	234,321
#42	clinical trial/	1,025,636
#43	exp Cohort Studies/	711,088
#44	observational study/	234,321
#45	observational stud*.mp.	289,940
#46	cohort stud*.mp.	352,568
#47	prospective study/	689,669
#48	prospective stud*.mp.	783,874
#49	retrospective study/	1,085,686
#50	retrospective stud*.mp.	1,133,607
#51	(#37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50).mp. [mp=title, abstract, heading word, drug trade name. original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3,698,771
#52	(#10 AND #15 AND #36 AND #51).mp. (mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, Keyword, floating subheading word, candidate term word]	2,809

Appendix 4: Data collection form

Intervention review – RCTs and non-RCT

Review title or ID	
Study ID (surname of first author and year first full report of study was published e.g. Smith 2001)	
Report ID	
Report ID of other reports of this study	
Notes	

General Information

Date form completed (dd/mm/yyyy)	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type (e.g. full report, abstract, letter)	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria (Randomized controlled trial, retrospective or prospective cohort study, Non-severe chronic hypertension, Timing of delivery from 37 weeks gestation)	Eligibility criteria met? Yes No Unclear	Location in text or source (pg & ¶/fig/table/other)
Type of study	Randomized Controlled Trial		
	Cohort Study		
Participants			
Types of intervention			
Types of comparison			
Types of outcome measures			
INCLUDE ☐ EXCLUDE ☐			

Reason for exclusion	NA	
Notes:		

Characteristics of included studies
Methods

	Descriptions as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Aim of study (e.g. efficacy, equivalence, pragmatic)		
Design(e.g. parallel, crossover, non-RCT)		
Unit of allocation (by individuals, cluster/ groups or body parts)		
Start date		
End date		
Duration of participation (from recruitment to last follow-up)		
Ethical approval needed/ obtained for study	☐ Ye ☐ No ☐ Unclear	
Notes:		

Participants

	Description	Location in text or source (pg & ¶/fig/table/other)
Population description (from which study participants are drawn)		

Setting (including location and social context)			
Inclusion criteria			
Exclusion criteria			
Method of recruitment of participants (e.g. phone, mail, clinic patients)			
Informed consent obtained	☐ Yes ☐ No ☐ Unclear		
Total no. randomized (or total pop. at start of study for NRCTs)			
Clusters (if applicable, no., type, no. people per cluster)			
Baseline imbalances			
Withdrawals and exclusions (if not provided below by outcome)			
Age			
Sex			
Parity			
Race/Ethnicity			
Duration of hypertension			
On medication for hypertension			
Co-morbidities			
Smoking status			
Baseline Proteinuria			
Gestational age at delivery			
Mode of delivery			
Subgroups measure			
Subgroups reported			
Notes:			

Intervention groups
Intervention Group 1

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Theoretical basis (include key references)		
Description (include sufficient detail for replication, e.g. content, dose, components)		
Duration of treatment period		
Timing (e.g. frequency, duration of each episode)		
Delivery (e.g. mechanism, medium, intensity, fidelity)		
Providers (e.g. no., profession, training, ethnicity etc. if relevant)		
Co-interventions		
Economic information (i.e. intervention cost, changes in other costs as result of intervention)		
Resource requirements (e.g. staff numbers, cold chain, equipment)		
Integrity of delivery		
Compliance		
Notes:		

Outcomes

Outcome 1 (SUPERIMPOSED PRE-ECLAMPSIA)

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Outcome name		

Time points measured (specify whether from start or end of intervention)		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/ reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear	Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power (e.g. power & sample size calculation, level of power achieved)		
Notes:		

Outcome 2 (PLACENTAL ABRUPTION)

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Outcome name		
Time points measured (specify whether from start or end of intervention)		
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		

Person measuring/ reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		
Is outcome/tool validated?	☐ ☐ ☐ Yes No Unclear	
Imputation of missing data (e.g. assumptions made for ITT analysis)		
Assumed risk estimate (e.g. baseline or population risk noted in Background)		
Power (e.g. power & sample size calculation, level of power achieved)		
Notes:		

Outcome 3 (ADMISSION TO NICU)

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Outcome name		
Time points measured (specify whether from start or end of intervention)	From the start of the intervention	pg16 par 8
Time points reported		
Outcome definition (with diagnostic criteria if relevant)		
Person measuring/ reporting		
Unit of measurement (if relevant)		
Scales: upper and lower limits (indicate whether high or low score is good)		

Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear		
Imputation of missing data (e.g. assumptions made for ITT analysis)			
Assumed risk estimate (e.g. baseline or population risk noted in Background)			
Power (e.g. power & sample size calculation, level of power achieved)			
Notes:			

Other

Study funding sources (including role of funders)		
Possible conflicts of interest (for study authors)		
Notes:		

Risk of Bias assessment

Domain	Risk of bias Low High Unclear	Support for judgement (include direct quotes where available with explanatory comments)	Location in text or source (pg & ¶/fig/table/other)
Random sequence generation (selection bias)	☐ ☐ ☐		
Allocation concealment (selection bias)	☐ ☐ ☐		
Blinding of participants and personnel (performance bias)	☐ ☐ ☐		
(if separate judgement by outcome(s) required)	☐ ☐ ☐		

Blinding of outcome assessment (detection bias)	☐ ☐ ☐		
(if separate judgement by outcome(s) required)	☐ ☐ ☐		
Incomplete outcome data (attrition bias)	☐ ☐ ☐		
(if separate judgement by outcome(s) required)	☐ ☐ ☐		
Selective outcome reporting? (reporting bias)	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Data and analysis

For RCT/CCT
Dichotomous outcome (Super imposed pre-eclampsia)

	Description as stated in report/paper				Location in text or source (pg & ¶/fig/table/other)
Comparison					
Outcome					
Subgroup					
Time point (specify from start or end of intervention)					
Results	Intervention		Comparison		
	No. with event	Total in group	No. with event	Total in group	
Any other results reported (e.g. odds ratio, risk difference, CI or P value)					
No. missing participants					

Reasons missing			
No. participants moved from other group			
Reasons moved			
Unit of analysis (by individuals, cluster/groups or body parts)			
Statistical methods used and appropriateness of these (e.g. adjustment for correlation)			
Reanalysis required? (specify, e.g. correlation adjustment)	☐ Yes ☐ No ☐ Unclear		
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear		
Reanalysed results			
Notes:			

Outcome 2 (Placental Abruption)

	Description as stated in report/paper		Location in text or source (pg & ¶/fig/table/other)
Comparison			
Outcome			
Subgroup			
Time point (specify from start or end of intervention)			
Results	Intervention	Comparison	
	No. with event	Total in group	No. with event	Total in group	
Any other results reported (e.g. odds ratio, risk difference, CI or P value)			
No. missing participants			
Reasons missing			
No. participants moved from other group			
Reasons moved			

Unit of analysis (by individuals, cluster/groups or body parts)		
Statistical methods used and appropriateness of these (e.g. adjustment for correlation)		
Reanalysis required? (specify, e.g. correlation adjustment)	☐ Yes ☐ No ☐ Unclear	
Reanalysis possible?	☐ Yes ☐ No ☐ Unclear	
Reanalysed results		
Notes:		

Outcome 3 (Admission to NICU)

	Description as stated in report/paper					Location in text or source (pg & ¶/fig/table/other)
Comparison						
Outcome						
Subgroup						
Time point (specify from start or end of intervention)						
Results	Intervention		Comparison			
	No. with event	Total in group	No. with event	Total in group		
Any other results reported (e.g. odds ratio, risk difference, CI or P value)						
No. missing participants						
Reasons missing						
No. participants moved from other group						
Reasons moved						

Unit of analysis (by individuals, cluster/groups or body parts)				
Statistical methods used and appropriateness of these (e.g. adjustment for correlation)				
Reanalysis required? (specify, e.g. correlation adjustment)	☐ Yes	☐ No	☐ Unclear	
Reanalysis possible?	☐ Yes	☐ No	☐ Unclear	
Reanalysed results				
Notes:				

Other information

	Description as stated in report/paper	Location in text or source (pg & ¶/fig/table/other)
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information (from whom, what and when)	None.	
Notes:		

Appendix 5: Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Study details

Reference	

Study design
- X   Individually-randomized parallel-group trial
- ☐   Cluster-randomized parallel-group trial
- ☐   Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as
Experimental: [   ] Comparator: [   ]

Specify which outcome is being assessed for risk of bias [   ]

Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Is the review team's aim for this result…?
- ☐   to assess the effect of assignment to intervention (the 'intention-to-treat' effect)
- ☐   to assess the effect of adhering to intervention (the 'per-protocol' effect)

If the aim is to assess the effect of adhering to intervention, select the deviations from intended intervention that should be addressed (at least one must be checked):
- ☐   occurrence of non-protocol interventions
- ☐   failures in implementing the intervention that could have affected the outcome
- ☐   non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)
- ☐   Journal article(s) with results of the trial
- ☐   Trial protocol
- ☐   Statistical analysis plan (SAP)
- ☐   Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐   Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐   "Grey literature" (e.g. unpublished thesis)
- ☐   Conference abstract(s) about the trial
- ☐   Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐   Research ethics application

☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research) ☐ Personal communication with trialist ☐ Personal communication with the sponsor		

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions		Comments	Response options
1.1 Was the allocation sequence random?			Y / PY / PN / N / NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?			Y / PY / PN / N / NI
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?			Y / PY / PN / N / NI
Risk-of-bias judgement			Low / High / Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?			NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI

Signalling questions	Comments	Response options
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA / Y / PY / PN / N / NI
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA / Y / PY / PN / N / NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y / PY / PN / N / NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?		Y / PY / PN / N / NI
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y / PY / PN / N / NI
2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA / Y / PY / PN / N / NI
2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA / Y / PY / PN / N / NI
2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA / Y / PY / PN / N / NI
2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA / Y / PY / PN / N / NI

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y / PY / PN / N / NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA / Y / PY / PN / N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA / Y / PY / PN / N / NI
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA / Y / PY / PN / N / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		Y / PY / PN / N / NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		Y / PY / PN / N / NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		NA / Y / PY / PN / N / NI

	Comments	
4.4 <u>If Y/PY/NI to 4.3</u>: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA / Y / PY / <u>PN / N</u> / NI
4.5 <u>If Y/PY/NI to 4.4</u>: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA / Y / PY / <u>PN / N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		Y / PY / PN / N / NI (<u>Y / PY</u>)
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		Y / PY / <u>PN / N</u> / NI
5.3 ... multiple eligible analyses of the data?		Y / PY / <u>PN / N</u> / NI
Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low / High / Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable