National Institute for Health and Care Excellence

Final

Hyperparathyroidism (primary): diagnosis, assessment and initial management

[J] Evidence review for pregnancy

NICE guideline NG132

Intervention evidence review

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Final

This evidence review was developed by the National Guideline Centre

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1.1 Review question: How should the management of primary hyperparathyroidism differ in pregnant women?

1.2 Introduction

This review reports on aspects of management that require consideration in pregnancy. The risks and benefits of each test or intervention need to be balanced against the risk to the unborn fetus and the mother.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Pregnant women with confirmed primary hyperparathyroidism
Interventions	• Surgery (surgery versus no surgery) • Surgical interventions (focused versus non-focused/4-gland exploration) • Surgical localisation techniques • Calcimimetics • Bisphosphonates • Monitoring • Patient information
Comparisons	All interventions compared to each other or control
Outcomes	Outcomes will follow those in the primary reviews for surgery, surgery interventions, surgical localisation, calcimimetics, bisphosphonates, monitoring and patient information. Additional outcomes: • Outcome of pregnancy – term/early/late (dichotomous outcome) • Congenital abnormalities (dichotomous outcome) • Early foetal loss (miscarriage) (dichotomous outcome) • Stillbirth (dichotomous outcome) • Admission for IV hydration (dichotomous outcome) • Complications during pregnancy (dichotomous outcome) • Eclampsia/pre-eclampsia • Complications post-partum – mother/baby – requirement for support for either (dichotomous outcome) • Apgar score baby (continuous outcome) • Calcium levels mother/baby at/around birth (continuous outcome) • Neonatal tetany or symptomatic hypocalcaemia (dichotomous outcome)
Study design	RCTs and systematic reviews of RCTs • In the absence of RCT evidence, prospective cohort studies will be included. Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified. Qualitative studies for patient information

Subgroups will follow those in the primary reviews for surgery, surgery interventions, calcimimetics, bisphosphonates, monitoring and patient information.

Pregnancy sub-groups:

- First trimester of pregnancy at the time of management
- Second trimester of pregnancy at the time of management
- Third trimester of pregnancy at the time of management

1.4 Clinical evidence

1.4.1 Included studies

A search was conducted for assessing the management of PHPT in pregnant women. This looked for studies comparing surgery (surgery versus no surgery), surgical interventions (focused versus 4-gland exploration), surgical localisation techniques, calcimimetics, bisphosphonates and monitoring in pregnant women with a confirmed diagnosis of PHPT, as specified in the review protocol. We also looked for studies on patient information in pregnant women with primary hyperparathyroidism.

No relevant randomised control trials were identified for any of the above comparisons. No qualitative studies were identified for the patient information review. Only one retrospective cohort study comparing surgery versus no surgery in pregnant women with PHPT was included in the review;[1] this is summarised in Table 3 below. Only one outcome, stillbirth before diagnosis, was reported separately for the above comparison. Evidence for this outcome is summarised in the clinical evidence summary below (Table 4).

This study also examined the rate of live births, stillbirths in pregnant women with PHPT and neonatal Apgar score. Not in line with the review protocol, these results were compared with those of a matched control group of women without PHPT. Additional outcomes reported for both the PHPT and control group that were not in the review protocol were average birth weight, caesarean section and gestational length. These outcomes have been reported so as to provide information on the potential differences in pregnancy outcomes and elevated risks between women with PHPT and women without PHPT, which could inform the differential management of pregnant women with PHPT.

Details of the surgery versus no surgery comparison are also summarised narratively.

In the study, PHPT and control groups were matched for age and gender. For each PHPT patient that fulfilled the inclusion criteria, three age- and gender- matched women without PHPT were drawn from the same central person register from the same period of time. Gestational age was adjusted for in the analysis, but there was no evidence of adjustment for any other confounding variables such as serum calcium levels. No multi-variate analysis was conducted.

No evidence was identified for the following outcomes: congenital abnormalities, admission for IV hydration, complications during pregnancy, eclampsia/pre-eclampsia, complications post-partum, calcium levels of mother/baby at/around birth, neonatal tetany or symptomatic hypocalcaemia.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Abood 2014[1] Retrospective cohort Denmark	For the PHPT group: Parathyroid surgery during observation: n=576 (54.5%) of PHPT group No parathyroid surgery: n=481 (45.5%)	PHPT: women with PHPT, n=1057; mean age (SD) 35.1 (0.2) Controls: age-and-gender matched non-exposed controls, n=3171; mean age (SD) 35.1 (0.1)	Surgery versus no surgery in PHPT: • Stillbirth before diagnosis PHPT versus controls: • Live births • Stillbirths • Average Apgar score (at 5 min) - neonates • Average birth weight • Caesarean section • Gestational length After diagnosis	Data from 1977 to 2010 The analysis was adjusted for gestational age. Serum calcium levels were obtained in 41 women with PHPT. No differences in plasma calcium levels were present.

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Surgery versus no surgery for PHPT in pregnant women

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No surgery	Risk difference with Surgery (95% CI)
Stillbirth (before diagnosis) number of cases[c]	1057[d] (1 study) unclear	VERY LOW[a,b] due to risk of bias, imprecision	RR 7.52 (0.96 to 59.11)	Moderate	
				2 per 1000	13 more per 1000 (from 0 fewer to 116 more)

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias (outcome reporting bias)
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[c] Data: episodes of stillbirth were reported before the diagnosis of PHPT was made
[d] Serum calcium levels of 41 patients were obtained and no difference was present.

See appendix F for full GRADE tables.

Additional data:

Table 4: Stillbirths, live births, Apgar score, birth weight in women with PHPT and controls aged 16–44 years at diagnosis of PHPT, reported after diagnosis

Outcomes (after the diagnosis)	PHPT (n=1057)	Control (n=3171)	*P* value
Number of women with stillbirth	1 (0.1%)	3 (0.1%)	0.74
Number of women with at least one live birth	179 (16.9%)	592 (18.7%)	0.21
Number of live born babies	262	875	-
Average Apgar score of all live born babies at 5 min (SD)	9.9 (0.03)	9.8 (0.03)	0.13
Average weight of all live born babies (SDS)	-0.41	1.06	-

Narrative data:

Women with PHPT had more live births in the year following diagnosis compared to women without PHPT, RR= 1.55, $p < 0.05$.

Caesarean section (after diagnosis):

There were a greater number of deliveries by caesarean section (approximately double) observed in women with PHPT compared to women without PHPT in the year following the PHPT diagnosis, which remained high in the following years as well.

Gestational length (after diagnosis):

Gestational length of women with PHPT was shorter compared to women without PHPT after a diagnosis was made. The shortest gestational length observed was 260 days. It was reported that this could potentially be due to the greater number of caesarean deliveries in women with PHPT.

Subgroup comparison within PHPT women:

Surgery: n=576 (54.5%) versus no surgery: n=481 (45.5%)

Parathyroid surgery did not change the results of women with PHPT for live births, Apgar score, birth length and birth weight.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.6 Resource costs

The recommendations made by the committee based on this review are not expected to have a substantial impact on resources.

1.7 Evidence statements

1.7.1 Clinical evidence statements

Surgery versus no surgery

There was no difference between parathyroid surgery and no surgery for stillbirth in women with PHPT before the diagnosis was made (1 study, n=1057; Very Low quality).

No evidence was identified for the outcomes congenital abnormalities; admission for IV hydration; complications during pregnancy; eclampsia/pre-eclampsia; complications post-partum; calcium levels of mother/baby at/around birth; neonatal tetany or symptomatic hypocalcaemia.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The committee considered outcomes related to pregnancy such as congenital abnormalities, early fetal loss (miscarriage), stillbirth, admission for IV hydration, complications during pregnancy, eclampsia/pre-eclampsia, complications post-partum, Apgar score (baby), calcium levels of mother or baby at/around birth, neonatal tetany or symptomatic hypocalcaemia as critical outcomes for decision making. The committee also considered health-related quality of life and mortality as critical outcomes from the primary reviews for surgery, surgery interventions, surgical localisation, calcimimetics, bisphosphonates, monitoring and patient information for decision making. The important outcomes followed those in the primary reviews for surgery, surgery interventions, surgical localisation, calcimimetics, bisphosphonates, monitoring and patient information.

No evidence was available for any of the above outcomes apart from stillbirth before the diagnosis of primary hyperparathyroidism and neonatal Apgar score.

1.8.1.2 The quality of the evidence

There was evidence from one retrospective cohort study that included a comparison of parathyroid surgery with no surgery.

Stillbirth before the diagnosis of primary hyperparathyroidism was made was the only outcome reported for the comparison of women who later had or did not have surgery. The quality of the evidence was Very Low due to risk of bias and imprecision. The duration of follow up in this study was unclear and there was no clear definition of the outcome.

The study reported that apart from stillbirth before the diagnosis of primary hyperparathyroidism, no other difference was present between the two groups but results were not reported separately.

The serum calcium levels of a very small proportion of patients (41 out of 1057) were obtained. It was reported that 12 women who had experienced one or more pregnancy losses before the diagnosis had a significantly elevated mean calcium level of 1.52±0.14 mmol/litre compared to 29 women who had not experienced pregnancy loss. The committee was aware of evidence that has demonstrated the criticality of elevated maternal serum calcium levels for pregnancy complications including stillbirth. Results on serum calcium levels for the majority of patients were not available. This contributes to the high risk of bias of the study and does not allow us to reach conclusions for the outcome of stillbirth, as the low stillbirth rates reported could be associated with low corrected calcium concentrations.

The average Apgar score at 5 minutes of live born babies delivered by women with primary hyperparathyroidism after diagnosis was not reported separately for women who had surgery and women who did not have surgery to allow for a comparison. It was however reported separately for an age-matched control group of women without primary hyperparathyroidism and was found to be similar.

The analysis adjusted for gestational age; there was no evidence of adjustment for any further potentially confounding factors. The total number of births in patients and controls was not reported so as to obtain a meaningful comparison of the rate of live births occurring in each group.

No evidence was identified for the outcomes congenital abnormalities; admission for IV hydration; complications during pregnancy; eclampsia/pre-eclampsia; complications post-partum; calcium levels of mother/baby at/around birth; neonatal tetany or symptomatic hypocalcaemia.

1.8.1.3 Benefits and harms

Indications for surgery

Evidence from one retrospective cohort study comparing parathyroid surgery to no surgery suggested there was no clinically important difference in stillbirth before the diagnosis of primary hyperparathyroidism. The difference in stillbirth was reported before the diagnosis of primary hyperparathyroidism for women who later required surgery. Hence the committee considered that the outcome could potentially not be a consequence of surgery. Information about maternal serum calcium levels in the included study was not sufficient to draw conclusions about the association of this factor with pregnancy outcomes and how management of pregnant women should differ based on calcium levels. The committee acknowledged the relative paucity of data regarding the approach to undertaking parathyroidectomy in pregnancy.

The committee from their experience agreed that having surgery for hyperparathyroidism before becoming pregnant allows women to start their pregnancy with a normal serum calcium level, which reduces their risk of pregnancy-associated complications of primary hyperparathyroidism.

The committee discussed that the appropriateness of surgery will depend on a number of factors including the maternal serum calcium concentration, timing of diagnosis of primary hyperparathyroidism, localisation of the adenoma etc. and agreed that each case will need to be considered individually. The committee discussed that fetal risk including stillbirth and neonatal tetany increases with a serum calcium level above 2.85 mmol/litre and hence would benefit from multidisciplinary team (MDT) assessment. The committee from their experience noted that for a pregnant woman with primary hyperparathyroidism who is generally well and has mild hypercalcaemia the approach would be to treat conservatively (for example to drink up to 3 litres of water a day or if they are admitted for infusion of saline*)* in the first instance and may advise them to wait until after the birth before considering surgery. The committee agreed that the cut-off for serum calcium levels used as an indication for surgery in the general population would not be applicable to pregnant women.

The committee discussed that the optimal timing for parathyroid surgery would be during the second trimester of pregnancy. The committee noted the theoretical risks of congenital abnormalities during the first trimester and pre-term labour during the third trimester for surgery, but felt that surgery in the third trimester could be appropriate when the MDT considers that surgery would be beneficial to the patient.

The committee noted from their experience that although the pregnancy may develop uneventfully, severe fetal/neonatal complications have been reported even in cases of mild primary hyperparathyroidism. Hence based on their experience the committee agreed that pregnant women with a confirmed diagnosis of primary hyperparathyroidism should be referred for opinion to a specialist centre MDT, due to the high risk of associated maternal and neonatal complications. The committee considered that the MDT should include a specialist obstetrician, physician, surgeon, midwife and anaesthetist. The committee from their experience noted that surgery was successful in the majority of pregnant women with primary hyperparathyroidism.

The committee recognised that some women refuse anaesthesia during pregnancy. Parathyroid surgery could be performed under local anaesthesia if localisation has been done, but the likelihood of persistence would be higher in such cases.

Preoperative imaging

There was no evidence available on pre-operative localisation techniques for pregnant women with primary hyperparathyroidism.

The committee discussed the suitability of various imaging modalities and agreed that ultrasound could be safely considered during pregnancy. There was agreement that any type of radiation imaging should generally be avoided in pregnant women, as exposure to radiation during pregnancy could be harmful. It was noted that occasionally, low dose radiation imaging could be considered if the benefits outweigh the risks, for example when there is a chance of missing ectopic adenomas.

Based on their clinical experience, the committee agreed that sestamibi scanning should not be used in pregnant women with primary hyperparathyroidism, but could be considered appropriate by the MDT if the benefits in the use of sestamibi outweigh the risks in these patients. There was consensus that the decision to offer pre-operative imaging should be determined by a specialist MDT.

Surgical interventions

The committee discussed that in most cases of pregnant women with primary hyperparathyroidism, ultrasound would be the only localisation technique used, hence 4-gland explorations would be the default choice of surgery. However, the committee considered that the decision on the type of surgery (focused or 4-gland exploration) should be made on a case-by-case basis, by a specialist MDT.

Calcimimetics

There was no evidence available for the use of calcimimetics for primary hyperparathyroidism during pregnancy. The committee noted that in the current literature, data regarding the use of calcimimetics in pregnant women has been very limited, and it comes from case reports and is therefore insufficient to support decision making. Hence the committee agreed that calcimimetics should not be offered to women with primary hyperparathyroidism during pregnancy.

Bisphosphonates

There was no evidence regarding the use of bisphosphonates in women with primary hyperparathyroidism during pregnancy. The committee noted that there was a theoretical risk of neonatal and maternal hypocalcaemia, low birth weight, prematurity and neonatal death associated with bisphosphonates in pregnancy but acknowledged that there was insufficient clinical data to quantify this theoretical risk. Based on their clinical knowledge and in line with the BNF, the committee agreed that bisphosphonates should be avoided during pregnancy to avoid any adverse outcomes to the mother and the fetus.

Monitoring

There was no evidence in regards to monitoring pregnant women with primary hyperparathyroidism. The committee discussed that raised maternal serum calcium concentration was an important factor in determining the risk for both maternal and neonatal adverse outcomes. The committee stated that with higher serum calcium levels there was a higher risk of adverse outcomes such as stillbirth and neonatal tetany. The committee agreed that monitoring of serum calcium levels should be conducted during pregnancy in line with the advice from a specialist MDT centre. The committee from their experience stated that in current practice, maternal serum calcium levels are not measured routinely during pregnancy.

The committee considered that monitoring of pregnant women who have had parathyroid surgery should involve the measurement of parathyroid hormone and albumin-adjusted serum calcium immediately after surgery and of albumin-adjusted serum calcium every 2–4 weeks thereafter. For women who have not had parathyroid surgery or who have not been cured after surgery, the committee considered that patients should be monitored to assess symptoms and comorbidities; ultrasound of the renal tract if renal stones are suspected and measurement of albumin-adjusted serum calcium levels at least monthly. However, the committee agreed that the monitoring strategies and frequency should be tailored based on individual patient assessment and determined by advice from a specialist MDT.

The committee discussed the risk of various maternal and neonatal/fetal complications associated with primary hyperparathyroidism. Maternal complications include hypercalcaemia, thromboprophylaxis, and fetal/neonatal complications such as neonatal hypocalcaemia, neonatal tetany, prematurity and fetal loss. Hence the committee agreed that monitoring strategies in pregnant women with primary hyperparathyroidism should take these factors into consideration. The committee recognised that primary hyperparathyroidism is a risk factor for pre-eclampsia and hypertension, therefore agreed that gestational monitoring of hypertension should reflect this.

Information and support

No evidence was available for the information and support of pregnant women with primary hyperparathyroidism.

The committee acknowledged the need for reassurance of patients in regards to the possible impact of primary hyperparathyroidism on the fetus, including congenital abnormalities and adverse developments. The committee noted the absence of well-powered studies to address such associations.

The committee considered that pregnant women should be offered information on the risks and benefits of treatments including parathyroid surgery during pregnancy. The committee was not aware of evidence that women should not breastfeed although there is very little information about drugs for primary hyperparathyroidism and lactation.

1.8.2 Cost effectiveness and resource use

No economic evaluations were identified for this review.

Due to the small numbers of cases of pregnant women with primary hyperparathyroidism the committee considered it important that these people be seen in a specialist centre by a multi-disciplinary team (MDT) to ensure they are seen by clinicians with the most experience in this very specialist area of care. The committee discussed that although this would be costly due to clinician time in meeting and discussing the case, this was crucial in ensuring the most appropriate care for pregnant women and the best clinical outcomes.

When considering the economic implications of treating pregnant women it is important to consider both the costs and quality of life impact for the pregnant woman, but also the potential costs and quality of life implications to the child after birth.

The committee considered that surgery in pregnant women would be equally as effective as for the general population in providing a cure from primary hyperparathyroidism. The committee noted that there may be slightly higher costs associated with surgery compared to the general population in pregnant women.

However, as also noted in the benefits and harms section above, there is the possibility of severe maternal and fetal/neonatal complications for pregnant women with primary hyperparathyroidism. In this situation the committee considered that surgery would be even more cost effective, as surgery would help to reduce the risk of these complications, reducing costs and improving quality of life for both mother and neonate. Therefore overall the committee considered that surgery in pregnant women is likely to be cost effective.

The committee considered that the specialist MDT would be in the best position to inform care in terms of pre-operative imaging, type of surgical intervention, and monitoring on a case-by-case basis to ensure the best outcomes for pregnant women. The committee discussed that it is likely that most pregnant women would only receive ultrasound imaging for pre-operative localisation, due to the higher risks associated with radiation during pregnancy. Therefore there are lower imaging costs in this population. However, it is likely that pregnant women will require more frequent monitoring, particularly of serum calcium. However, the cost of a clinical biochemistry test is small (£1.31) and will not have a significant resource impact.

Overall, the recommendations made for pregnant women may change practice in some areas however as this is a small population these are not considered to have a substantial resource impact.

1.8.3 Other factors the committee took into account

The committee noted that the MDT would consist of an obstetrician, physician, surgeon, midwife and anaesthetist. There may also be additional members. The MDT would be responsible for a care plan.

The committee was aware of two studies with unselected cases of pregnant women with primary hyperparathyroidism [9, 20]. These studies were case series and were not included in the review as they did not meet the inclusion criteria. The committee however felt that the results of these studies could be useful to inform decision making about the management of primary hyperparathyroidism during pregnancy.

In a retrospective case series [9] of 74 pregnant women (124 pregnancies) with primary hyperparathyroidism, mild hypercalcaemia during pregnancy (serum calcium ≥ 10.5 mg/dL) was not associated with an increased risk of obstetrical complications including abortion, pre-term delivery, non-elective caesarean section, vacuum delivery, gestational hypertension, polyhydramnios and large-for-gestational-age, compared to 175 normocalcaemic pregnant women. [9] The low risk of adverse pregnancy outcomes was attributed to the considerably lower serum calcium levels of the included population compared to existing studies. Serum calcium was measured in 57 out of the total 124 pregnancies (46%) of primary hyperparathyroidism patients and was within the normal range in 8 pregnancies. A total of 43 women (58.1%) had undergone parathyroid surgery; this was successful in 38 women, in which a single adenoma was removed leading to normocalcaemia. In 5 out of 43 operated patients, surgery took place during pregnancy, resulting in normocalcaemia – this was not followed by any maternal or infant complications at either surgery or later delivery. There were no differences in abortion or any pregnancy-related complications between operated and non-operated women.

The second study was a retrospective case series of 32 women with primary hyperparathyroidism who had a total of 77 pregnancies. [20] The average serum calcium at the time of diagnosis of primary hyperparathyroidism in pregnant patients was 2.85 mmol/litre (range 2.65–3.325). Parathyroidectomy was conducted in 15 pregnant women during the 2nd trimester of pregnancy (between 13 and 23 weeks gestation). This was not associated with any maternal or fetal complications at surgery or delivery. The remaining 30 out of 62 pregnancies (48%) were complicated by fetal loss, a rate that was 3.5-fold higher than expected ($p<0.05$). Fetal loss occurred in the late first or early second trimester, with second trimester losses (30%) being six fold higher than expected ($p<0.01$) and over 4 weeks later than typical ($p<0.05$). All incidents of fetal loss occurred at elevated maternal serum calcium levels, but most (n=22, 73%) arose in cases where maternal calcium levels were above 2.85 mmol/litre. The rate of fetal loss was found to be directly correlated with maternal serum calcium levels ($R=0.972$, $p<0.01$).

The findings from the studies illustrated an association between elevated maternal serum calcium levels and adverse pregnancy outcomes, and highlighted the importance of looking at maternal serum calcium levels for the differential management of women with primary hyperparathyroidism during pregnancy based on those levels. These findings were in line with the committee's clinical experience and were taken into account in decision making about the monitoring of pregnant women with primary hyperparathyroidism.

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Appendices

Appendix A: Review protocols

Table 5: Review protocol: PHPT in pregnant women

Field	Content
Review question	How should the management of primary hyperparathyroidism differ in pregnant women?
Type of review question	Intervention reviews for all except patient information which will be a qualitative review
Objective of the review	To determine management of PHPT in pregnant women
Eligibility criteria – population	Pregnant women with confirmed primary hyperparathyroidism Exclude people: • with secondary and tertiary HPT • with multiple endocrine neoplasia • with familial hyperparathyroidism • with parathyroid carcinoma • people on medications interfering with calcium metabolism (for example, lithium). Studies including mixed populations of people with primary and secondary or tertiary hyperparathyroidism will be excluded unless subgroups are reported separately by type of hyperparathyroidism.
Eligibility criteria – intervention(s)	• Surgery (surgery versus no surgery) • Surgery interventions (focused versus non-focused/4 gland exploration) • Localisation techniques • Calcimimetics • Bisphosphonates • Monitoring • Patient Information
Eligibility criteria – comparator(s)	All interventions compared to each other or control
Outcomes and prioritisation	Outcomes will follow those in the primary reviews for surgery, surgical interventions, calcimimetics, bisphosphonates, monitoring and patient information. Additional outcomes: • Outcome of pregnancy – term/early/late (dichotomous outcome) • Congenital abnormalities (dichotomous outcome) • Early foetal loss (miscarriage) (dichotomous outcome) • Stillbirth (dichotomous outcome) • Admission for IV hydration (dichotomous outcome) • Complications during pregnancy (dichotomous outcome) • Eclampsia/pre-eclampsia • Complications post-partum – mother/baby – requirement for support for either (dichotomous outcome)

	• Apgar score baby (continuous outcome) • Calcium levels mother/baby at/around birth (continuous outcome) • Neonatal tetany or symptomatic hypocalcaemia (dichotomous outcome)
Eligibility criteria – study design	RCTs and systematic reviews of RCTs • In the absence of RCT evidence, prospective cohort studies will be included. Retrospective cohort studies will be included only if insufficient prospective cohort studies are identified. Qualitative studies for patient information
Other inclusion exclusion criteria	• Non-English language articles • Conference abstracts
Proposed sensitivity / subgroup analysis, or meta-regression	Subgroups will follow those in the primary reviews for surgery, surgical interventions, calcimimetics, bisphosphonates, monitoring and patient information. Pregnancy sub-groups: • First trimester of pregnancy at the time of management • Second trimester of pregnancy at the time of management • Third trimester of pregnancy at the time of management
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote for bibliography, citations, sifting and reference management Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical search databases to be used: Medline, Embase, Cochrane Library, CINAHL, PsycINFO Date: all years Health economics search databases to be used: Medline, Embase, NHSEED, HTA Date: Medline, Embase from 2002 NHSEED, HTA – all years Language: Restrict to English only Supplementary search techniques: backward citation searching Key papers: Not known
Identify if an update	N/A
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10051
Highlight if amendment to	N/A

previous protocol	
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Jonathan Mant in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration	Not registered

number	

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations (recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered). • Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[19] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

Review question	All questions – health economic evidence
	Setting: • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 06 August 2018	Exclusions
Embase (OVID)	1974 – 06 August 2018	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2018 Issue 8 of 12 CENTRAL to 2018 Issue 7 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 06 August 2018	Exclusions
PsycINFO (ProQuest)	Inception – 06 August 2018	Exclusions

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14

16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hyperparathyroidism] explode all trees
#2.	MeSH descriptor: [Hyperparathyroidism, Primary] explode all trees
#3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) near/6 (HPT or hyperparathyroidis*)):ti,ab
#4.	PHPT:ti,ab
#5.	MeSH descriptor: [Parathyroid Neoplasms] explode all trees

#6.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)):ti,ab
#7.	(or #1-#6)

CINAHL (EBSCO) search terms

S1.	(MH "Hyperparathyroidism")
S2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 HPT) OR ((primary or asymptomatic or symptomatic or mild or familial or maternal) n6 hyperparathyroidis*)
S3.	PHPT
S4.	(MH "Parathyroid Neoplasms")
S5.	(parathyroid* n3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcemi* or hypercalcaemi*))
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT “questions and answers” or PT response or PT software or PT teaching materials or PT website
S8.	S6 NOT S7

PsycINFO (ProQuest) search terms

1.	su.Exact("parathyroid neoplasms" OR "hyperparathyroidism" OR "hyperparathyroidism, primary")
2.	PHPT
3.	((primary or asymptomatic or symptomatic or mild or familial or maternal) Near/6 (HPT or hyperparathyroidis*))
4.	(parathyroid* near/3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumor* or tumour* or cancer* or metasta* or hypercalcaemi* or hypercalcemi*))
5.	1 or 2 or 3 or 4
6.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))
7.	(s1 or s2 or s3 or s4) NOT (su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females"))) or ti(rat or rats or mouse or mice))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the primary hyperparathyroidism population in the NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. The NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics papers published since 2002.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2002 – 06 August 2018	Exclusions Health economics studies
Embase	2002 – 06 August 2018	Exclusions Health economics studies

Database	Dates searched	Search filter used
Centre for Research and Dissemination (CRD)	HTA - Inception – 06 August 2018 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	hyperparathyroidism/ or hyperparathyroidism, primary/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	Parathyroid Neoplasms/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.

38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	26 and 43

Embase (Ovid) search terms

1.	hyperparathyroidism/ or primary hyperparathyroidism/
2.	((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)).ti,ab.
3.	PHPT.ti,ab.
4.	parathyroid tumor/ or parathyroid adenoma/ or parathyroid carcinoma/
5.	(parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	Case report/ or Case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	Nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental animal/
19.	Animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.

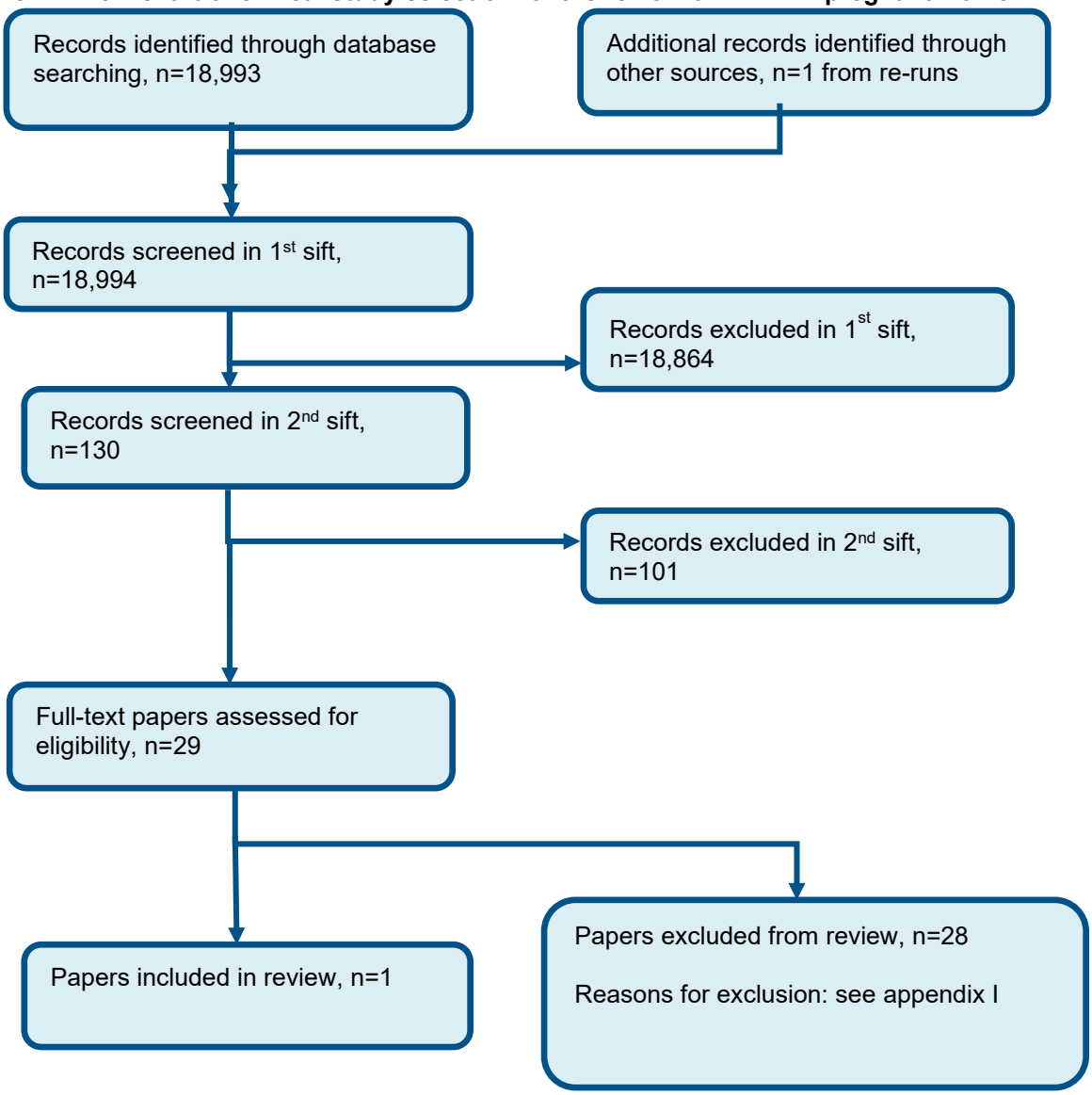
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	24 and 38

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Hyperparathyroidism EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Hyperparathyroidism, Primary EXPLODE ALL TREES
#3.	(((primary or asymptomatic or symptomatic or mild or familial or maternal) adj6 (HPT or hyperparathyroidis*)))
#4.	(PHPT)
#5.	MeSH DESCRIPTOR Parathyroid Neoplasms EXPLODE ALL TREES
#6.	((parathyroid* adj3 (adenoma* or carcinoma* or hyperplasia* or neoplas* or tumo?r* or cancer* or metasta* or hypercalc?emi*)))
#7.	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8.	* IN NHSEED
#9.	* IN HTA
#10.	#7 AND #8
#11.	#7 AND #9

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of PHPT in pregnant women



Appendix D: Clinical evidence tables

Study	Abood 2014[1]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n=1057 women with PHPT + n=3171 controls)
Countries and setting	Conducted in Denmark; Setting: national patient registry hospital
Line of therapy	Not applicable overall; first-time surgery for women with PHPT
Duration of study	Data collected from 1st January 1977 to 31st December 2010
Method of assessment of guideline condition	Method of assessment/diagnosis: based on registry codes: hyperparathyroidismus primarius and adenoma, hyperparathyroidismus primarius and hyperplasia, crisis hyperparathyroidismi, osteitis fibrosa cystica generalisata, nephrocalcinosis e hyperparathyroidismi, nephrocalcinosis e hyperparathyroidismi, hyperparathyroidismus alia, hyperparathyroidismus and PHPT and hyperparathyroidism without specification.
Stratum	Overall
Subgroup analysis within study	PHPT patients who underwent parathyroid surgery during observation (n=576, 54.5%)
Inclusion criteria	Women between 16 and 44 years with a diagnosis of PHPT; age-and-gender matched women without PHPT.
Exclusion criteria	Not specified; all women with a PHPT diagnosis, pregnancy and pregnancy outcomes were included
Recruitment/selection of patients	All patients registered in the National Hospital Discharge Register with a PHPT diagnosis from 1st January 1977 to 31st December 2010; for each patient, three-age and gender-matched women without PHPT from the central person register
Age, gender and ethnicity	Age - Mean (SD): PHPT group: 35.1(0.2); Control group: 35.1(0.1), Gender: Females. Ethnicity: not specified
Further population details	Age: 16-44 2. Gender: Female All patients with a PHPT diagnosis were initially considered. Among those, women aged 16–44 were identified and pregnancy and outcomes of pregnancy were studied. For each of these patients, three women without PHPT matched by age and gender were selected.
Extra comments	The Abortion register was subject to uncertainty during the first years, and the Birth Register included the first 6 months of 2010. Based on these parameters, a head-to-head comparison between patients and controls was made. Comparisons were made using t-test for two samples, x2 test, log-rank test, odds ratio

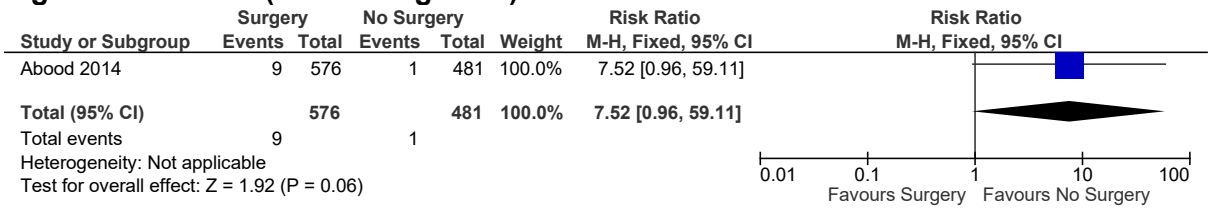
Study	Abood 2014[1]
	(OR), relative risk (RR) and 95% CI. To adjust for gestational age, an adjusted SDS for gestational age and gender was calculated. Primary outcomes included live births, stillbirth and abortions. Secondary outcomes included birth weight, Apgar score at 5 min. Outcome definition: Abortion was defined as termination of pregnancy by the removal or expulsion from the uterus of a foetus or embryo before the stage of viability. It can occur spontaneously, in which case it is called a miscarriage or may be induced for other reasons (for example medical reasons). No other outcome definitions were provided.
Indirectness of population	No indirectness
Interventions	PHPT group: (n=576) Intervention 1: Parathyroid surgery during observation period. Concurrent medication/care: not specified. Indirectness: No indirectness (n=481) Intervention 2: No parathyroid surgery during observation period. Concurrent medication/care: not specified. Indirectness: No indirectness
Funding	No specific grant from public, commercial or non-profit sector.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Parathyroid surgery versus No parathyroid surgery Protocol outcome 1: Stillbirth - Actual outcome for PHPT: Episodes of stillbirth before the diagnosis was made; Group 1: 9/576, Group 2: 1/481 Risk of bias: All domain - High, Selection – High/Low, Blinding – low, Incomplete outcome data - Low, Outcome reporting - High, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness Narrative data: For 1057 women with PHPT and 3171 control women without PHPT	

Study	Abood 2014[1]
Protocol outcome 2: Stillbirth -Actual outcome: Stillbirth (after diagnosis): Number of women with stillbirth after diagnosis: PHPT group: 1 (0.1%), Control group: 3 (0.1%) Protocol outcome 3: Apgar score-baby -Actual outcome: Average Apgar score (SD) at 5 min of live born babies (after diagnosis): PHPT group: 9.9 (0.03), Control group: 9.8 (0.03) Number of women with at least one live birth (after diagnosis): PHPT group: 179 (16.9%), Control group: 592 (18.7%) Number of live born babies (after diagnosis): PHPT group: 262, Control group: 875 Average birth weight of live born babies SDS (after diagnosis): PHPT group: -0.41, Control group: 1.06 Cesarean section: There was a greater number (approximately double) of deliveries by cesarean section in women with PHPT than women without PHPT the year following diagnosis, which remained in subsequent years. Gestational length: Gestational length was shorter in the PHPT group compared to the control group after diagnosis. Gestational length was never below 260 days. Subgroup comparison within PHPT women: Parathyroid surgery did not change the results of women with PHPT in regards to live births, Apgar score, birth length and birth weight. The only significant difference between women with PHPT who underwent surgery and those who did not was noted in episodes of stillbirth (before the diagnosis).	
Protocol outcomes not reported by the study	Health related Quality of life; Mortality; preservation of end organ function (bone mineral density, fractures, renal stones and renal function), deterioration in renal function/renal replacement; persistent hypercalcaemia; BMD of the distal radius or the lumbar spine; cardiovascular events; adverse events (including voice change, hypoparathyroidism, bleeding, severe hypocalcaemia, hypercalcaemia, vocal cord paralysis/ laryngeal nerve injury, haematoma, infection); length of hospital stay; reoperation; unnecessary neck exploration; cancer incidence; congenital abnormalities; early foetal loss (miscarriage); admission for IV hydration; Complications during pregnancy; Eclampsia/pre-eclampsia; Complications post-partum-mother/baby-requirement for support for either; Calcium levels mother/baby at/around birth; Neonatal tetany or symptomatic hypocalcaemia.

Appendix E: Forest plots

E.1 Surgery versus no surgery in pregnant women with PHPT

Figure 2: Stillbirth (before diagnosis)



Appendix F: GRADE tables

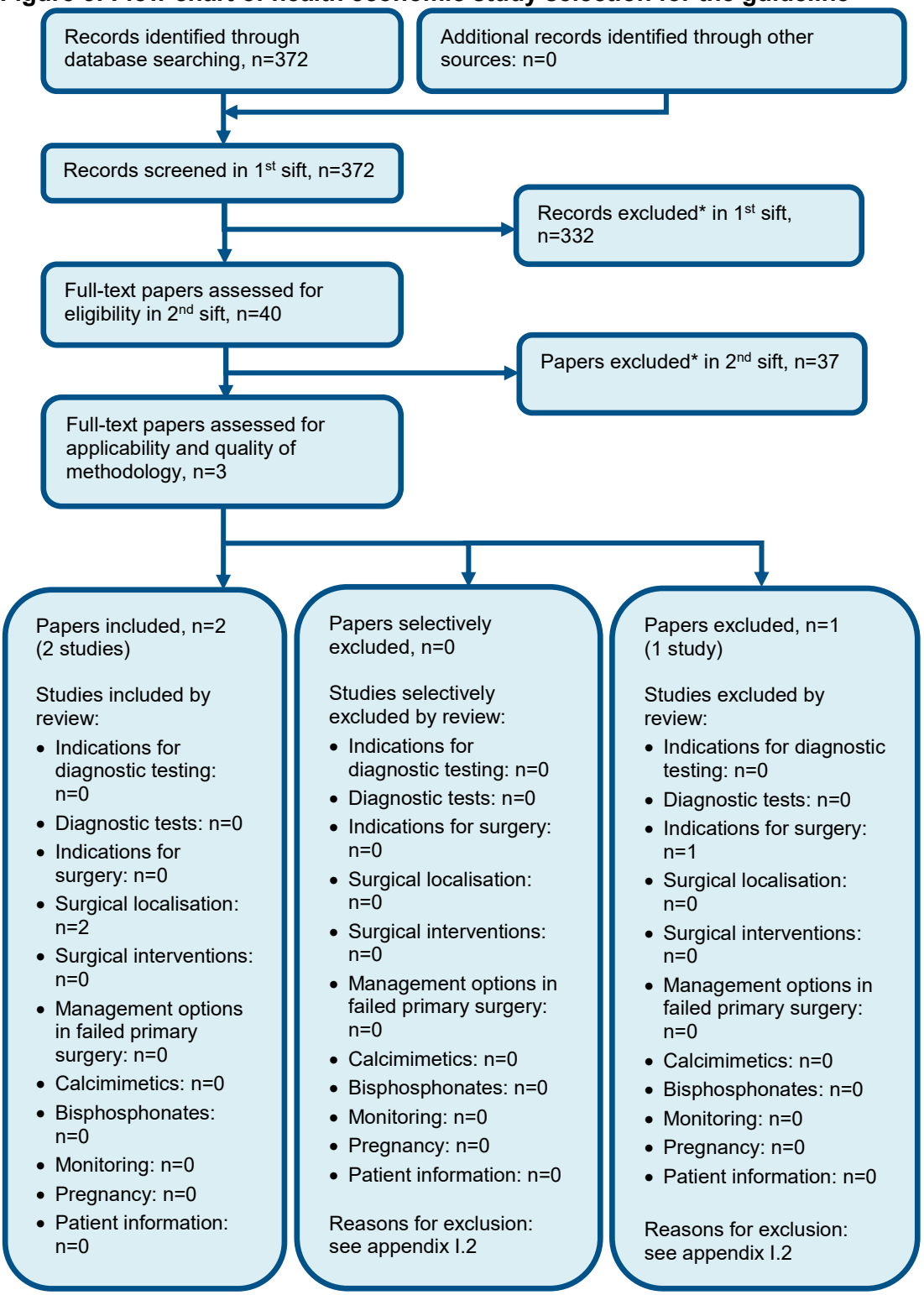
Table 9: Clinical evidence profile: Surgery versus no surgery for PHPT in pregnant women

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery	No surgery	Relative (95% CI)	Absolute		
Stillbirth (before diagnosis) (follow-up from years 1977 to 2010 ; assessed with: number of cases)												
1	observational studies	Serious[a]	no serious inconsistency	no serious indirectness	Serious[b]	None	12/576 (2.1%)	0.2%	RR 7.52 (0.96 to 59.11)	13 more per 1000 (from 0 fewer to 116 more)	⊕OOO VERY LOW	IMPORTANT

[a] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias (outcome reporting bias)
[b] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 3: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Anast 1976[2]	Non-systematic review; screened for references
Deutsch 1980[3]	Inappropriate study design: case reports
Dochez 2015[4]	Systematic review; screened for references
Fouda 2000[5]	Inappropriate study design: case report (n= 3). Incorrect interventions.
Gaeke 1977[6]	Inappropriate study design: case report
Gelister 1989[7]	Inappropriate study design: case series (n=15)
Gokkaya 2016[8]	Inappropriate study design: case series (n=4)
Hirsch 2015[9]	Inappropriate study design: case series
Hui 2010[10]	Inappropriate study design: case report (of 3 women)
Hultin 2009[11]	Inappropriate comparison: no comparison
Kamenicky 2016[12]	Non-systematic review; screened for references
Kandil 2009[13]	Inappropriate study design: case report
Kelly 1991[14]	Inappropriate study design: case series (n=12)
Komarowska 2017[15]	Non-systematic review; screened for references
Kristoffersson 1985[16]	Inappropriate study design: review of individual cases
Ludwig 1962[17]	Inappropriate study design: two case observation, single case with confirmed hyperparathyroidism.
McMullen 2010[18]	Inappropriate design: case series (n=7)
Norman 2009[20]	Inappropriate design: case series (n=32)
Pellegrino 1977[21]	Inappropriate study design: case report
Pothiwala 2009[22]	Incorrect interventions. Inappropriate study design: case report (n=2).
Rostom 2018[23]	Inappropriate study design: case report
Rubin 1968[24]	Not review population. Case report. Inadequately confirmed diagnosis.
Rutkowska 2015[25]	Inappropriate comparison. Incorrect intervention: single case report.
Schnatz 2002[26]	Literature review; screened for references
Schnatz 2005[27]	Review of case reports. Screened for references.
Stringer 2017[28]	Inappropriate study design (case series, n=8)
Ullah 2017[29]	Not review population. Observational study of single case without confirmed PHPT.
Walker 2014[30]	Inappropriate study design: case series (n=5)

I.2 Excluded health economic studies

None.

Appendix J: Research recommendations

J.1 Managing primary hyperparathyroidism during pregnancy

Research question: What are the optimal management strategies for primary hyperparathyroidism during pregnancy?

Why this is important:

This purpose of this research recommendation is to highlight aspects of management that require consideration in pregnancy. The risks and benefits of each test or intervention need to be balanced against the risk to the unborn fetus and the mother.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Women of childbearing age and pregnant women with primary hyperparathyroidism Intervention(s): All management strategies for primary hyperparathyroidism – surgery (with or without surgical localisation), calcimimetics and conservative management/monitoring. Comparison: All interventions compared to each other Outcome(s): • Mortality • Health-related quality of life • Deterioration in renal function • Fractures • Occurrence of kidney stones • Persistent hypercalcaemia • Bone mineral density (lumbar spine and/or distal radius) • Cardiovascular events • Adverse events • Outcome of pregnancy – term/early/late • Congenital abnormalities • Early foetal loss (miscarriage) • Stillbirth • Admission for IV hydration • Complications during pregnancy • Eclampsia/pre-eclampsia • Complications post-partum – mother/baby – requirement for support for either • Apgar score baby • Calcium levels mother/baby at/around birth • Neonatal tetany or symptomatic hypocalcaemia
Importance to patients or the population	A registry would inform what management strategies lead to better maternal and fetal outcomes.
Relevance to NICE guidance	Publications based on the registry would inform an update of the guideline. Currently there is very limited evidence to inform the recommendations.
Relevance to the NHS	The evidence could support the case for specialised services to support women who are pregnant with primary hyperparathyroidism.
National priorities	None
Current evidence	Very limited evidence was reported for the systematic review on ‘How should the management of primary hyperparathyroidism differ in pregnant

base	women?' Only one retrospective cohort study comparing surgery versus no surgery in pregnant women with PHPT was identified in the review and only one outcome, stillbirth before diagnosis, was reported separately for the above comparison. No evidence was available for other management strategies such as calcimimetics, bisphosphonates and monitoring.
Equality	No equality issues anticipated
Study design	UK registry
Feasibility	The registry data would need to be inputted by a designated person at each centre.
Other comments	None
Importance	• High: the research is essential to inform future updates of key recommendations in the guideline.