

DOI: <https://doi.org/10.53555/nvh5mt79>Publication URL: <https://nnpub.org/index.php/MHS/article/view/1939>

## OBSTETRICAL AND NEONATAL OUTCOMES AMONG PREGNANCIES COMPLICATED BY HYPERPARATHYROIDISM: SYSTEMATIC REVIEW

Samuel Halason Sihotang\*<sup>1</sup>, Prince Sianturi<sup>2</sup><sup>1</sup>Faculty of Medicine, HKBP Nommensen University, Indonesia<sup>2</sup>Faculty of Medicine, Indonesian Methodist University, Indonesia**Corresponding Author:**[drsamuelhsihotang@gmail.com](mailto:drsamuelhsihotang@gmail.com)

---

### ABSTRACT

**Background:** Primary hyperparathyroidism (PHPT) is a relatively common disorder of the parathyroid glands, causing skeletal, renal, and cardiac complications. As etiological features of PHPT, single adenoma, hyperplasia, carcinoma, and familial causes (MEN multiple endocrine neoplasia, FHH familial hypocalciuric hypercalcemia, hyperparathyroidism—jaw tumor syndrome) are presented. Primary hyperparathyroidism in pregnancy has an incidence of 1%, which is underestimated due to the plethora of undiagnosed cases.

**The aim:** This study aims to show about obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 10 articles, whereas the results of our search on SagePub brought up 60 articles. The results of the search conducted for the last year of 2013 yielded a total 2 articles for PubMed and 14 articles for SagePub. The result from title screening, a total 1 articles for PubMed and 10 articles for SagePub. In the end, we compiled a total of 7 papers. We included five research that met the criteria.

**Conclusion:** Pregnancy complicated by PHPT may lead to serious maternal and infant complications. MDT consultation ensures timely diagnosis, comprehensive treatment for the patients and better pregnancy outcomes.

**Keyword:** Hyperparathyroidism, pregnancy, obstetric, neonatal

## INTRODUCTION

Primary hyperparathyroidism (PHP) is the most common cause of hypercalcemia seen in the outpatient setting with a prevalence of 0.15% in the general population. Women are affected with PHP 3 times more commonly than men. The occurrence of PHP during pregnancy is a rare event, with less than 200 cases reported in the English literature. The incidence of PHP in pregnant reproductive age women is reported to be 8/100,000 population/year. The most common cause of primary hyperparathyroidism in pregnancy is a single adenoma, representing 85% of all cases, followed by 10% from primary parathyroid hyperplasia, 3% from multiple adenomas, and 2% from parathyroid cancer. Between 23 and 80% of patients with PHP are asymptomatic. Symptoms associated with hypercalcemia are often variable and vague in nature leading to a potential delay in the diagnosis and management of this important disorder during pregnancy.<sup>1,2</sup>

PHPT in pregnancy is associated with a number of maternal complications including hyperemesis gravidarum, nephrolithiasis and/or pancreatitis. While neonatal hypocalcemia, tetany, intrauterine growth retardation (IUGR) and fetal demise have been previously reported with PHPT in pregnancy, milder forms of PHPT being diagnosed nowadays do not seem to carry the same degree of maternal or fetal mortality or morbidity. Early recognition of PHPT has been associated with a lower rate of complications when compared to the older literature. However, medically managed PHPT still appears to be associated with an increased risk of preeclampsia and miscarriage rates. The postpartum hypercalcemic crisis has been reported in the literature as a potential complication of PHPT in pregnancy, and this likely happens when the active transplacental transfer of calcium from the mother to the fetus is lost after delivery of the placenta.<sup>3</sup>

The management of PHPT during pregnancy is challenging for two important reasons. One is the consequence of high calcium on maternal and fetal outcomes, although its reported effects are conflicting. Some authors have reported maternal hypertension, pre-eclampsia, miscarriages, and pre-term labour being associated with hypercalcaemia, whereas others have not. Similarly, poor fetal outcomes, including stillbirth and intrauterine growth retardation, have been reported by some, but not by others. The second reason is the potential risks of medical and surgical management of PHPT during pregnancy. Management decisions are complicated by the lack of evidence and, therefore, clarity on the best timing for medical or surgical intervention in pregnancy.<sup>4,5</sup>

## METHODS

### Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

### Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism. It is possible to accomplish this by researching or investigating of obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine of obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

### Search Strategy

We used "Obstetrical outcomes among pregnancies complicated by hyperparathyroidism"; "Neonatal outcomes among pregnancies complicated by hyperparathyroidism" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: ("Hyperparathyroidism"[MeSH Subheading] OR "Hyperparathyroidism in pregnancy"[All Fields] OR "Obstetrical outcomes by hyperparathyroidism"[All Fields]) AND ("Neonatal outcomes by hyperparathyroidism "[All Fields] OR "The effect of hyperparathyroidism in pregnancy"[All Fields]) AND ("The impact of hyperparathyroidism in pregnancy"[MeSH Terms] OR ("Incident of hyperparathyroidism"[All Fields]) OR ("Prevalence of hyperthyroidism in pregnancy"[All Fields]) AND "Complication of hyperparathyroidism in pregnancy"[All Fields])) used in searching the literature.

### Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

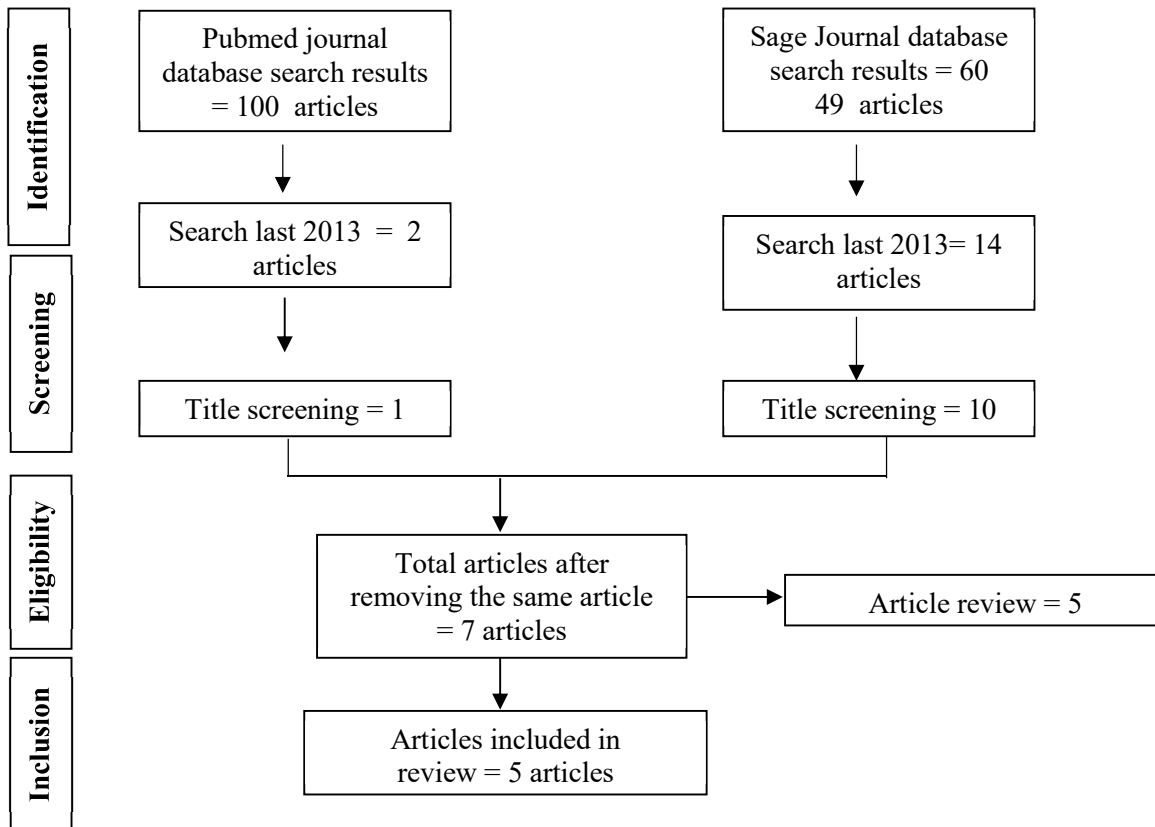


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 10 articles, whereas the results of our search on SagePub brought up 60 articles. The results of the search conducted for the last year of 2013 yielded a total 2 articles for PubMed and 14 articles for SagePub. The result from title screening, a total 1 articles for PubMed and 10 articles for SagePub. In the end, we compiled a total of 7 papers. We included five research that met the criteria.

Trahan, MJ *et al* (2023)<sup>6</sup> showed Hyperparathyroidism during pregnancy is associated with a significant increase in adverse perinatal outcomes, including preeclampsia, preterm delivery, fetal growth restriction, and congenital anomalies. As such, pregnancies among women with hyperparathyroidism should be considered high-risk, and specialized care is recommended in order to minimize maternal and neonatal morbidity.

Cassir, G *et al* (2020)<sup>7</sup> showed Rates of perinatal complications in our series are more reassuring than the ubiquitously quoted rates from small and dated studies. The diagnosis of primary hyperparathyroidism may be easily missed during pregnancy, owing to its non-specific presentation. A high index of suspicion and measurement of ionized calcium levels is encouraged, especially for patients with excessive nausea and vomiting, nephrolithiasis, atypical presentations of hypertensive disorders, or isolated polyhydramnios. Mild degrees of calcium derangement do not preclude adverse perinatal outcomes. Surgery appears to be safe, even in the third trimester. The attenuated rate of complications noted in our series may have been the result of the high proportion of surgery, though this will require verification via meta-analysis or future prospective work.

**Table 1. The literature include in this study**

<b>Author</b>	<b>Origin</b>	<b>Method</b>	<b>Sample Size</b>	<b>Result</b>
<b>Trahan, MJ et al., 2023<sup>6</sup></b>	Canada	Retrospective study	368 patient	Of 13,792,544 deliveries included over the study period, 368 were to women with hyperparathyroidism. The overall incidence of hyperparathyroidism was 2.7/100,000 births, increasing from 1.6 to 5.2/100,000 births over the study period ( $p < 0.0001$ ). Women with hyperparathyroidism were older and had more comorbidities, such as obesity, and pre-gestational hypertension and diabetes. Relative to the comparison group, women with hyperparathyroidism were more likely to deliver preterm, OR 1.69 (95% CI 1.24–2.29), to develop preeclampsia, 3.14 (2.30–4.28), and to deliver by cesarean, 1.69 (1.36–2.09). Infants born to mothers with hyperparathyroidism were more likely to be growth restricted, 1.83 (1.08–3.07), and to be diagnosed with a congenital anomaly, 4.21 (2.09–8.48).
<b>Cassir, G et al., 2020<sup>7</sup></b>	Canada	Retrospective study	23 women	From 2000 to 2017, 19 women (23 pregnancies) with primary hyperparathyroidism were identified. Most women (79%) were symptomatic at presentation, though often with non-specific manifestations. While 14% of pregnancies involved maternal/obstetric complications, fetal/neonatal complications were observed in 45%. Mild hypercalcemia was identified in 57% of women, with accompanying hypophosphatemia and hypomagnesemia in 46% and 36% of women, respectively. Surgical intervention was performed for 89% women, and no complications were encountered. Normal calcium levels achieved through treatment before conception did not fully eliminate adverse outcomes.
<b>Rigg, J et al., 2018<sup>8</sup></b>	Australia	Retrospective study	28 pregnancies	Twenty-two pregnancies were managed medically, and six patients underwent parathyroidectomy in pregnancy (five in trimester 2, and one at 32 weeks gestation). Most patients treated

				<p>medically either had a corrected serum calcium concentration &lt;2.85 mmol/L in early pregnancy or had PHPT diagnosed in trimester 3. Of viable medically managed pregnancies, 30% were complicated by preeclampsia, and preterm delivery occurred in 66% of this group. All preterm neonates required admission to the NICU for complications related to prematurity. All surgically treated patients delivered their babies at term, and there were no complications of parathyroid surgery.</p>
<p><b>Jiao, H et aal., 2021<sup>9</sup></b></p>	<p>China</p>	<p>Retrospective study</p>	<p>11 women</p>	<p>The median onset age of the patients was 32 (25 ~ 38) years. PHPT was diagnosed in two cases before pregnancy, in six cases during pregnancy and in one case postpartum. The main clinical manifestations were nausea, vomiting, and other nonspecific symptoms, with anemia as the most common maternal complication. Hypercalcemia crisis was developed in one case. The median levels of preoperative serum calcium and parathyroid hormone (PTH) were 3.08 (2.77 ~ 4.21) mmol/L and 300.40 (108.80 ~ 2603.60) pg/ml, respectively. The parathyroid ultrasonography tests were positive in eight cases and negative in one patient who had an ectopic lesion localized by 99mTc-MIBI. Parathyroidectomy was conducted in 7 cases during the 2nd trimester, including 2 patients diagnosed before pregnancy who refused surgery, 1 patient during the 1st trimester, and 1 patient postpartum, with a significant reduction in serum concentrations of calcium and PTH. A management algorithm was developed.</p>
<p><b>Hirsch, D et al., 2015<sup>10</sup></b></p>	<p>Denmark</p>	<p>Retrospective cohort study</p>	<p>4228 participants</p>	<p>A total of 1057 women with PHPT and 3171 controls were identified. The number of women giving birth and experiencing abortions did not differ between the two groups (live births, P=0.21 and abortions, P=0.12). Also birth weight, length, Apgar score, and gestation length at abortion</p>

				did not differ. Within the first year after the diagnosis was made, gestation length was lower in women with PHPT than that in controls. However, this was linked to more deliveries by caesarian sections.
--	--	--	--	---

Rigg, J *et al* (2018)<sup>8</sup> showed Maternofetal outcomes have improved relative to that reported in early medical literature in patients treated medically and surgically, but the rates of preeclampsia and preterm delivery were higher in medically treated patients. The study was limited by its retrospective design and small sample sizes.

Jiao, H *et al* (2021)<sup>9</sup> showed that pregnant women with PHPT should be managed by MDT according to the algorithm. If PHPT is confirmed in fertile women before pregnancy, parathyroidectomy should be strongly suggested and performed. If PHPT is diagnosed during pregnancy, even in its mild form, surgical treatment, optimally during the 2nd trimester, is effective and safe for pregnancy and neonatal outcome.

Hirsch, D *et al* (2015)<sup>10</sup> showed A diagnosis of PHPT did not seem to increase the rate of abortions in our study. Reducing the abortion risk may therefore not be an indication for parathyroidectomy during pregnancy in patients with mild PHPT. The PHPT diagnosis does not seem to affect birth weight, length and Apgar score. The higher number of deliveries by cesarean section after the diagnosis was made may be associated with lower gestation age. The strategy for delivery should be carefully considered in pregnant women with PHPT.

**DISCUSSION**

The parathyroid glands, first reported by Sir Richard Owen during a rhinoceros necropsy in 1862 and studied in detail by Swedish anatomist Ivar Sandstrom in 1880, were one of the last organs to be discovered in the body, and insufficient knowledge about their location and blood supply was the source of inadvertent postoperative tetany in the early 20th century. Early parathyroidectomies for primary parathyroid disease ranged from successful adenoma excision by Felix Mandl in 1927, to multiple reoperations for persistent hyperparathyroidism in Charles Martell, until eventually his mediastinal parathyroid gland was discovered and removed. The parathyroid glands continue to pose challenges as we learn more about their often nuanced pathophysiology and clinical manifestations.<sup>11</sup>

The vast majority of pathology associated with the parathyroid glands, which control calcium homeostasis through the secretion of parathyroid hormone (PTH), is from primary hyperparathyroidism (PHPT), which will be the focus of this review. There have been enormous developments in our understanding of this disease and its more subtle variants. Traditional treatment of the hypercalcemic state with hydration and loop diuretics has given way to bisphosphonates. Moreover, changes in criteria for surgical management, along with advances in preoperative and intra-operative localization modalities and minimally invasive methods have changed the surgical landscape. The purpose of this review is to highlight these advances and provide clinicians with the most up-to-date information on treatment of the hypercalcemic state due to excess PTH secretion.<sup>11</sup>

PTH levels fall early in pregnancy and remain low, before rising late in gestation to reach prepregnancy levels postpartum. A decrease in serum calcium likely reflects the hemodilution associated with pregnancy. Although the majority of fetal calcium is accrued in the final trimester, maternal calcium absorptive capacity increases markedly early in pregnancy and remains high throughout. To facilitate fetal mineral demands an increase in bone resorption and formation occurs in pregnancy, leading to a transitory reduction in BMD. Special consideration should be given to pregnancy in adolescence, a period associated with active bone accretion, in which additional maternal skeletal adaptation may be required.<sup>12</sup>

Fetal calcium homeostasis differs considerably from that of the mother, uniquely adapted to facilitate skeletal mineralization. Calcium and phosphorous are actively transferred through the placenta but this does not determine fetal levels, which are maintained at higher concentrations than in maternal circulation. 1,25(OH)2D circulates at low levels in the fetus, likely due to suppression of 1a-hydroxylase by the high levels of calcium and phosphorous. Although fetal PTH concentrations are relatively low, PTH-related protein (PTHrP), the origins of which remain unclear, is present at high concentrations.<sup>12,13</sup>

The majority of primary hyperparathyroidism cases (~90%) occur sporadically, usually due to parathyroid adenomas. The remaining ~10% of cases occur as hereditary disorders, which include multiple endocrine neoplasias (MEN1, MEN2A, MEN4), familial hypocalciuric hypercalcaemia (FHH), hyperparathyroidism jaw tumour (HPT-JT) and familial isolated primary hyperparathyroidism (FIPH). Genetic testing in pregnant women with primary hyperparathyroidism should be considered as familial parathyroid disorders are often associated with an earlier age of onset compared to sporadic disease. Furthermore, genetic testing can guide the management of primary hyperparathyroidism. As demonstrated in case 1, genetic testing diagnosed MEN1, which informed both the surgical approach of subtotal parathyroidectomy and the need



for bilateral neck exploration due to the higher risk of multiple parathyroid gland disease in MEN1. This genetic diagnosis also allowed the patient to receive counselling on her increased risk of pancreatic and pituitary tumours, and enabled cascade family screening.<sup>14</sup>

The main symptomatology may mimic this of pregnancy, although severe maternal and fetal complications occur in untreated hypercalcemia. Mild hyperparathyroidism could be treated conservatively, but in cases of severe or symptomatic hypercalcemia, parathyroidectomy is the treatment of choice.<sup>15</sup>

## CONCLUSION

Pregnancy complicated by PHPT may lead to serious maternal and infant complications. MDT consultation ensures timely diagnosis, comprehensive treatment for the patients and better pregnancy outcomes.

## REFERENCES

- [1] Malekar-Raikar S, Sinnott BP. Primary Hyperparathyroidism in Pregnancy—A Rare Cause of Life-Threatening Hypercalcemia: Case Report and Literature Review. *Case Rep Endocrinol*. 2011;2011:1–6.
- [2] Kattar N, Migneron M, Debakey MS, Haidari M, Pou AM, McCoul ED. Advanced Computed Tomographic Localization Techniques for Primary Hyperparathyroidism: A Systematic Review and Meta-analysis. *JAMA Otolaryngol - Head Neck Surg*. 2022;148(5):448–56.
- [3] Ali DS, Dandurand K, Khan AA. Primary hyperparathyroidism in pregnancy: Literature review of the diagnosis and management. *J Clin Med*. 2021;10(13).
- [4] Arshad MF, Arambewela MH, Bennet WM, Sterrenburg M, Balasubramanian SP. Primary hyperparathyroidism in pregnancy: experience of a tertiary centre. *Surg Today [Internet]*. 2023;53(4):470–5. Available from: <https://doi.org/10.1007/s00595-022-02583-8>
- [5] Ye Z, Silverberg SJ, Sreekanta A, Tong K, Wang Y, Chang Y, et al. The Efficacy and Safety of Medical and Surgical Therapy in Patients With Primary Hyperparathyroidism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Bone Miner Res*. 2022;37(11):2351–72.
- [6] Trahan MJ, Antinora C, Czuzoj-Shulman N, Benjamin A, Abenhaim HA. Obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism. *J Matern Neonatal Med [Internet]*. 2023;36(1). Available from: <https://doi.org/10.1080/14767058.2023.2170748>
- [7] Cassir G, Sermer C, Malinowski AK. Impact of Perinatal Primary Hyperparathyroidism on Maternal and Fetal and Neonatal Outcomes: Retrospective Case Series. *J Obstet Gynaecol Canada [Internet]*. 2020 Jun;42(6):750–6. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1701216320300487>
- [8] Rigg J, Gilbertson E, Barrett HL, Britten FL, Lust K. Primary Hyperparathyroidism in Pregnancy: Maternofetal Outcomes at a Quaternary Referral Obstetric Hospital, 2000 Through 2015. *J Clin Endocrinol Metab*. 2018;104(3):721–9.
- [9] Jiao H ning, Sun L hao, Liu Y, Zhou J qiao, Chen X, Liu J min, et al. Multidisciplinary team efforts to improve the pregnancy outcome of pregnancy complicated with primary hyperparathyroidism: case series from a single hospital. *BMC Pregnancy Childbirth*. 2021;21(1):1–9.
- [10] Hirsch D, Kopel V, Nadler V, Levy S, Toledano Y, Tsvetov G. Pregnancy outcomes in women with primary hyperparathyroidism. *J Clin Endocrinol Metab*. 2015;100(5):2115–22.
- [10] Islam AK. Advances in the diagnosis and the management of primary hyperparathyroidism. *Ther Adv Chronic Dis*. 2021;12:1–20.
- [11] Kiely M, Hemmingway A, O’Callaghan KM. Vitamin D in pregnancy: current perspectives and future directions. *Ther Adv Musculoskelet Dis*. 2017;9(6):145–54.
- [12] Waterhouse M, Sanguinetti E, Baxter C, Duarte Romero B, McLeod DSA, English DR, et al. Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-Health Trial. *J Cachexia Sarcopenia Muscle*. 2021;12(6):1428–39.
- [13] McCarthy A, Howarth S, Khoo S, Hale J, Oddy S, Halsall D, et al. Management of primary hyperparathyroidism in pregnancy: A case series. *Endocrinol Diabetes Metab Case Reports*. 2019;2019(1).
- [14] Pliakos I, Chorti A, Moysidis M, Kotsovolis G, Kaltsas T, Pana A, et al. Parathyroid adenoma in pregnancy: A case report and systematic review of the literature. *Front Endocrinol (Lausanne)*. 2022;13(October):1–12.