

Dear Dr. Fang-Fang Ji and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Twin pregnancy with triple parathyroid adenoma: a case report and literature review" (Name of Journal: World Journal of Clinical Cases; Manuscript NO: 40351; Manuscript Type: CASE REPORT). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the point-by-point responds to the reviewer's comments are detailed as following.

**Responds to the EDITORIAL CORRECTIONS:**

1. For manuscripts submitted by non-native speakers of English, please provided language certificate by professional English language editing companies.

**Responses:** We have already handed it over to professional English language editing company ( AJE ) , and the language certificate is attached.

2. A short running title of less than 6 words should be provided.

**Responses:** We thank editorial for pointing out this point. We have added this in our manuscript according to the editorial's request. (line 7-8, Page 1)

3. Please offer the grant approval.

**Responses:** The grant approval can be seen in the attachment.

4. Please offer the audio core tip, the requiriment are as follows: In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications: Acceptable file formats: .mp3, .wav, or .aiff. Maximum file size: 10 MB. To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate

should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

**Responses:** Thanks for the suggestion. We have offered the audio core tip in attachment following this criteria.

5. Please write the comments. Writing requirements for each subsection: (1) Case characteristics: Please summarize main symptoms in one sentence. (2) Clinical diagnosis: Please summarize main clinical findings in one sentence. (3) Differential diagnosis: Please summarize thoughts and methods for differential diagnosis in one sentence. (4) Laboratory diagnosis: Please summarize laboratory testing methods and major findings in one sentence. (5) Imaging diagnosis, Please summarize imaging methods and major findings in one sentence. (6) Pathological diagnosis: Please summarize pathological methods and major findings in one sentence. (7) Treatment: Please summarize treatments and drugs used in one sentence. (8) Related reports: Please provide other contents related to the case report to help readers better understand the present case. (9) Term explanation: Please explain uncommon terms present in the case report. (10) Experiences and lessons: Please summarize experiences and lessons learnt from the case in one sentence.

**Responses:** We have added this in our manuscript according to the request (line 21-29, Page 12; line 1-26, Page 13; line 1-3, Page 14).

#### **Responds to the reviewer's comments:**

##### **Reviewer 1#:**

Thanks for your carefully review and great comments, we have revised our manuscript according to your comments:

1. The indications and time selection for parathyroid gland resection in this clinical scenario should be delineated if the conservative approach doesn't take effect in controlling the symptom including severe vomit, hypercalcemia crisis, fracture etc. The benefit /risk ratio of peripartum surgery in this type of patients should be closely assessed preoperatively. Are there any clinical data

supporting conservative medical support for this patient till labour before the parathyroid adenoma surgery is considered to be performed? In addition, disregarding which anesthetic approach is selected in surgery, the impact of drug and noxious surgical stimulus might have adverse effect on fetus, how is the perioperative fetus protection management implicated in this case (magnesium sulfate infusion etc)?

**Responses:** Thanks for your comment and good question. According to the low prevalence of PHPT during pregnancy, and currently there is no guideline include any official recommendations for PHPT during pregnancy. Therefore, it can only be consulted through literature review and combined with its own experience. According to Norman, foetal loss was seen at all levels of elevated maternal calcium but most were above 11.4 mg/dl (2.85 mmol/l). The rate of foetal loss increased directly with increasing maternal serum calcium levels ([Norman J, Politz D, Politz L. Clinical Endocrinology. 2010; 71\(1\):104-109](#)). Current evidence supports parathyroidectomy as the main treatment, performed preferably during the second trimester, when the serum calcium is above 11 mg/dL (2.75 mmol/L). In the patients with mild forms of PHPT, which are nowadays the most frequent, a conservative management is generally preferred. ([Dochez V, Ducarme G. Archives of Gynecology & Obstetrics. 2015; 291\(2\):259-263](#)). We think the timing of surgical management of PHPT in pregnancy also should think over acute maternal presentation, fetal status, maternal medical and surgical history, and the patient's response to medical management. Surgical treatment may also have some adverse effects on patients and fetuses, but literature reported that the prognosis of surgery is better than conservative treatment in most circumstances. ([Kelly T R. Surgery. 1991; 110\(6\):1033-1034](#)). In this case, after 2 weeks of rehydration, diuresis, and expansion, combined with Calcitonin treatment, the minimum value of blood calcium level was 2.95 mmol/L, and the decrease was significantly reduced or even appeared the trend of increase in the following week. Then combined with patient's inadequate response to medical therapy and the wishes of patients and her families, we finally chose surgery in the second trimester. (line 26-32, Page 9)

At present, the conservative treatment methods for PTPH mainly include

rehydration, Calcitonin, Bisphosphonates and Cinacalcet. The use of rehydration and Calcitonin is relatively mature, and no adverse effects of the fetus have been reported in the literature. Bisphosphonates and Cinacalcet can cross the placenta and are embryotoxic at high doses (Djokanovic N, Kliegergrossmann C, Koren G. *J Obstet Gynaecol Can.* 2008; 30(12):1146-1148). Although these have been used in few cases with good results, but more evidence of safety is required (Edling K L, Korenman S G, Janzen C, et al. *Endocrine Practice Official Journal of the American College of Endocrinology & the American Association of Clinical Endocrinologists.* 2014; 20(2):14-17). This patient is currently in the middle and late pregnancy. If conservative treatment is continued, the best operation period may be missed, and there would have likely been an escape phenomenon, which can lead to severe consequences, such as refractory hypercalcemia, possibly a high calcium crisis, hematuria, coma, and death. After communicating with the patient and her families, they chose surgery, so we did not continue to try Bisphosphonate and Cinacalcet. In theory, it is possible for this patient to continue conservative treatment, but the patient is unwilling to bear the risk of Bisphosphonate and Cinacalcet, then surgery was performed during the second trimester. I hope that there will be more trial results in the future, and provide more choices and basis for the treatment of such patients. (line 15-20, Page 9)

During the perioperative period, we did the following measures to protect the fetus: (1) We did not have the patient perform a radiological examination (except ultrasound). (2) During the whole process, we used safer treatment (hydration, calcitonin), and did not use potentially dangerous drugs such as bisphosphonate. (3) We also hang magnesium sulfate to inhibit contractions and reduce the possibility of premature birth. (4) We take local infiltration rather than general anesthesia to minimize the impact on the fetus. (5) In the operation, we use a bipolar electrocautery for surgery.

2. There are some spelling mistakes in this article, and the language needs to be further embellished.

**Responses:** We apologize for the spelling mistakes. We have handed it over to professional English language editing company ( AJE ) and corrected it. Revised portion are marked in red in the paper.

**Reviewer 2#:**

Thanks for your high valued evaluation, we have revised our manuscript according to your comments:

1. The authors had mentioned several times that “radiological examinations” is a contraindication of pregnancy. The expressing is quite misleading and inappropriate. “Radiological examination” is a very broad entity, including not only CT but ultrasound and MRI etc. If the authors were trying to say examinations based on X-ray were not suit for pregnancy, please be more specific. In addition, CT is not mandatory for the diagnosis of parathyroid adenoma, for me, it won’t even be considered in such a case. So there is no need to mention what the authors have done for “continue the pregnancy”.

**Responses:** Thanks very much for pointing us out our mistakes. After further reviewing the literature, we strongly agree with your point of view. The “radiological examinations” we are talking about mainly refers to the <sup>99m</sup>Tc-sestamibi scintigraphy. And we have made changes in the corresponding sections of the article. Revised portion are marked in red in the paper. (line 5 and 20, Page 4; line 19-20, Page 6; line 14-15, Page 8).

2. Please discuss if there were any connection of pregnancy and parathyroid adenoma. Were there any possible that pregnancy stimulate the growth of parathyroid adenoma?

**Responses:** Thanks for your good question and kind advice. In the past, it was thought that the calcium level in pregnancy falls. Thereby stimulating parathyroid hyperplasia and even lesions, leading to an increase in PTH hormone levels, promoting 1,25-dihydroxyvitamin D production and increasing blood calcium. Thus, there is a “physiological hyperparathyroidism” which acts to preserve maternal calcium homeostasis in the presence of increasing extracellular fluid volume. However, some scholars have found that PTH levels during pregnancy are basically normal or

even low (Cross N A, Hillman L S, Allen S H, et al. *American Journal of Clinical Nutrition*. 1995; 61(3):514-523). The result is contrary to the theory that low calcium stimulates elevated PTH during pregnancy. Therefore, some scholars believe that the increase of 1,25-dihydroxyvitamin D induced by pregnancy and the increase of calcium absorption in the intestine are the main regulators of calcium metabolism, and have no obvious relationship with the level of PTH. At the same time, there is a dilution of blood, hypoalbuminemia and increased glomerular filtration rate. These may lead to the fact that the blood calcium level in pregnancy is basically within the normal range or even lower in the third trimester (Dahlman T, Sjöberg H E, Bucht E. *Acta Obstetricia Et Gynecologica Scandinavica*. 1994; 73(5):393). The current findings are not yet a good indication of the relationship between pregnancy and parathyroid adenoma, and the relationship between the two still needs further research. In combination with this case report, because the patient did not check the neck ultrasound and blood calcium levels before pregnancy, it is impossible to know whether these lesions appear after pregnancy. However, high calcium appeared in the 18th week of pregnancy, and the 22-week ultrasound showed that the lesions had a maximum diameter of about 2.5 cm. It is difficult to explain such a large lesion with only the stimulation of low calcium levels in the early pregnancy. Therefore, the author believes that these lesions should not occur after pregnancy. However, whether the growth of parathyroid adenoma is stimulated by pregnancy is theoretically possible. Because of the low incidence and difficulty in early detection, there is no relevant literature. And this is a very good research content, further research is needed to confirm this conjecture.

3. Why the other two adenomas were not preoperatively diagnosed? The bigger one is 2.5cm × 1.5cm × 1.0cm.

**Responses:** Thanks for your good question. First of all, this case is quite special: the other two lesions do not show atypical, and it is difficult to distinguish from the intrathyroid lesions. In the operation, we found the other two lesions are mostly embedded in the thyroid gland really. In addition, 90% of parathyroid adenomas are single-shot, and multiple cases are rare. And the

patient's PTH is only 187 pg/ml, the clinical symptoms are not obvious, so we think the possibility of multiple parathyroid adenoma is relatively small. Second, the experience and diagnostic level of us needs to be further improved.

Sincerely yours,

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