

Primary hyperparathyroidism and pregnancy

Mona A. Fouda, MBBS, MRCP(UK).

ABSTRACT

Objectives: The coexistence of primary hyperparathyroidism and pregnancy is very rare worldwide. It carries serious complications to the mother and fetus, therefore, early diagnosis and management is of paramount importance.

Methods: Over a period of 16 years from 1982-1997, 24 patients with primary hyperparathyroidism were identified from the central diagnostic index data base of King Khalid University Hospital. Out of these, only 3 women with primary hyperparathyroidism complicating pregnancy were identified.

Results: All 3 women were in the fourth decade. Two of them had coexisting vitamin D deficiency with initially normal serum calcium and were misdiagnosed as cases of osteomalacia while the third had very high serum calcium

on first presentation. A single parathyroid adenoma was identified in all 3 patients with 2 undergoing surgical removal of the adenoma. The third patient unfortunately had an abortion. The babies of the first 2 patients were born healthy with no complications.

Conclusion: Primary hyperparathyroidism, even though rare in pregnancy, carries risks to the mother and fetus and therefore early screening for asymptomatic hyperparathyroidism in all women of childbearing age and in the early antenatal period of pregnant women is recommended.

Keywords: Primary hyperparathyroidism, pregnancy.

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Primary hyperparathyroidism is a relatively common disorder with an annual incidence in the USA of 28 cases per 100,000 population.¹ It is a disease of the middle aged, seen more among women.

Primary hyperparathyroidism in pregnancy, on the other hand, is very rare with around 118 cases reported in the literature.²⁻¹² If left untreated it may lead to major maternal and fetal complications. Therefore, awareness of its occurrence and early diagnosis with the institution of appropriate management is essential for the well-being of the mother and her baby.

We describe here our experience at a teaching hospital with primary hyperparathyroidism in pregnancy over the last 16 years, and outline the current consensus on its management.

Methods. King Khalid University Hospital (KKUH) is a prestigious, tertiary healthcare centre and a prominent teaching institute in Riyadh, Saudi Arabia. From 1982 to December 1997, a total of 29 potential cases of primary hyperparathyroidism were identified from the central diagnostic index data base. Due to incomplete or missing information, 5 of those were excluded while the medical charts of the remaining 24 patients were thoroughly reviewed. Of those 24 patients, only 3 cases of primary hyperparathyroidism in pregnancy were identified.

The serum chemistry and 24 hours urinary calcium and phosphorus were determined by multi-channel autoanalyzers in the central hospital laboratory with the normal ranges being 2.12-2.60 mmol/L for serum calcium (Ca), 0.8-1.40 mmol/L for serum phosphorus, 43.0-154 U/I for serum alkaline

From the Department of Medicine, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia.

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Address correspondence and reprint request to: Dr. Mona A. Fouda, Department of Medicine, King Khalid University Hospital, PO Box 2925, Riyadh 11461, Kingdom of Saudi Arabia. Fax. 467 2558.

phosphatase (SAP), 13-42 mmol/day for urinary phosphorus and 2.5-7.5 mmol/day for urinary calcium. The serum parathormone radio-immunoassays (PTH), and 25-hydroxycholecalciferol (25-OHD₃) levels were performed in another laboratory with a normal range of 17-72 pg/ml for PTH, and 20-20 ng/ml for 25-OHD₃. Radiological investigations included one or more of the following tests; USS of the neck, parathyroid scan (Thallium Technitium subtraction study), CT scan of the neck, dual x-ray absorptiometry (DXA), bone scan, and x-ray of the hands. Normal range for bone mineral density (BMD) in Saudi women aged 20-40 years (peak bone mass) was 1.143±0.015 gm/cm² for the lumbar spine, and 0.959±0.100 gm/cm² for the femoral neck.¹³

Primary hyperparathyroidism was diagnosed on the basis of the following criteria: 1) Persistent elevation of serum calcium of more than 2.6 mmol/L in the absence of other demonstrable causes of hypercalcemia; 2) Increased circulatory immunoreactive PTH, along with pathognomonic radiological findings.

Parathyroidectomy was performed in 2 patients, one in the second trimester and the other a month after delivery with the diagnosis confirmed by histopathological examination of the excised parathyroid adenoma. The third patient had an abortion in the first trimester.

Results. Table 1 shows the biochemical profile of all 3 patients. Patient 1 was a 40 year old woman, 16 weeks pregnant (Para 10 + 0, Gravida 11), and was admitted to the Obstetrics and Gynecology Ward in March 1996 as a case of hyperemesis gravidarum, with 2 months history of nausea and vomiting. She was admitted a month prior to that with similar complaints and treated conservatively with IV fluids and antacids. The patient also complained of pain in both knees and lower limbs including the pelvic area mainly after walking, with generalized weakness, easy fatigability, excessive sleep and constipation. She sometimes needed assistance to walk around. Examination showed tenderness over both iliac crests and evidence of proximal muscle weakness. Investigations showed high serum Ca level of 4.24 mmol/L, low phosphorus 0.60 mmol/L, and SAP 145 U/L. She also had low sodium of 130 mmol/L and low potassium of 3.0 mmol/L, secondary to the vomiting. She had anemia with a Hb of 82 g/L (120-160 g/L), a normal 24 hour urinary Ca of 5.06 mmol/day, and a low 24 hour urinary phosphorous of 3.05 mmol/day. She was managed initially with IV fluids but the Ca level remained above 3 mmol/L and, therefore, IV lasix was added which helped to bring the Ca level to around 2.7 mmol/L.

A neck USS showed a large, slightly hypochoic lesion, (21 x 30 mm) in the right thyroid lobe. FNA

of that mass was attempted which showed highly cellular smear with mainly follicular cells accompanied by oxyphylic cell changes which were suggestive of either a thyroid follicular neoplasm or a parathyroid adenoma.

X-ray of both hands showed cystic changes in the carpal bones with slight generalized sclerosis. USS of kidneys was normal with no renal calculi. Thyroid function test was normal. Serum PTH level was 757 pg/ml. Since the patient was in the second trimester and her condition was stable, a surgical removal of the suspected parathyroid adenoma was suggested. Surgical findings showed enlarged right superior parathyroid gland which was removed. The other 3 glands were normal. Frozen section showed a parathyroid adenoma. The Ca level came down to 2.5 mmol/L and remained normal thereafter. She was discharged and followed up during pregnancy with normal calcium level all through. She was started on calcium and vitamin D supplements to protect her bones from further demineralization during pregnancy.

The patient was seen again 5 months post delivery of a healthy baby. She delivered in another hospital so information on the newborn after delivery was lacking, however, the mother was told by the attending obstetrician that no abnormalities were found with her baby.

Patient 2 was a 38 year old woman, seen in June 1997 when she was 4 months pregnant complaining of generalized body and bony aches, especially of the lower limbs, as well as generalized weakness with polyuria and polydipsia for 3 years. She was P8 + 0 Gravida 9. Systemic examination was unremarkable and a bone profile revealed serum Ca of 2.47 mmol/L

Table 1 - Biochemical profile of patients.

Variable	Patient 1	Patient 2	Patient 3
Calcium (mmol/L) 2.12-2.60	4.2	2.5	2.4
Phosphate (mmol/L) 0.80-1.40	0.6	0.63	0.6
Alkaline phosphatase (U/L) 42-154	145	1773	1606
Urinary Ca/day (mmol/day) 2.5-7.5	5.1	3.9	5.1
Urinary Phos/day (mmol/day) 13-42	3.05	15.2	11.4
PTH (pg/mL) 17-72	757	3157*	645*
25 vit D ₃ (ng/ml) 26-120		<10	<10

*PTH levels were carried out when serum Ca levels were repeated later on and found to be high of 2.9 and 2.8 respectively for both patients

L, Phosphorus 0.63 mmol/L and SAP 1773 U/I. The patient was initially diagnosed as a case of osteomalacia and treated accordingly with calcium and vitamin D supplements. In September 1997, a repeat Ca level showed a figure of 2.87 mmol/L with phosphorus 0.58 mmol/L and SAP of 2007 U/I. Primary hyperparathyroidism was suspected and supplements were stopped. She was advised on proper hydration and to repeat the Ca level shortly. One month later, she slipped and sustained a fracture of the right femur neck. The patient was admitted to the orthopedic ward where internal fixation was performed under epidural anesthesia. Serum Ca remained high around 2.9 mmol/L, a 24 hour urinary Ca and Phosphorous was 3.9 and 15.2 mmol/day respectively. USS of the kidneys was suspicious of nephrocalcinosis. She was discharged in fair condition but 11 days later developed a swollen right leg. On the basis of a suspected deep venous thrombosis (DVT), she was again admitted and fully anticoagulated. Duplex study, however, did not confirm the DVT. Calcium level was 3.14 mmol/L, with phosphorus 0.53 mmol/L and SAP 1007 U/I. She was started on oral phosphate 500 mg every 6 hours, with calcitriol 0.25 mcg twice daily along with proper I.V hydration. She remained hypercalcemic with levels reaching above 3 mmol/L on many occasions. Intravenous lasix was started with no significant improvement. The obstetrician was of the opinion to wait until full maturity of the fetus, and therefore put her on dexamethasone until the end of pregnancy. USS of the neck showed no parathyroid adenoma.

PTH level was 3157 pg/ml and 25-OHD₃ below 10 ng/ml. This confirmed the presence of primary hyperparathyroidism with co-existing osteomalacia. Later, she delivered a normal baby boy at 37 weeks who showed no evidence of hypocalcemia. Post delivery calcium was still 2.7-2.8 mmol/L but SAP came down to 481 U/I. A neck CT scan revealed a left inferior parathyroid adenoma. DXA showed severe osteopenia with lumbar spine BMD of 0.828 gm/cm² and femoral neck BMD of 0.563 gm/cm². A bone scan exhibited a super scan of metabolic bone disease. A parathyroid scan confirmed a left inferior parathyroid adenoma. She was started post delivery on clodronate 800 mg twice daily for osteoporosis and the hypercalcemia. One month later she underwent neck exploration with the removal of a left inferior parathyroid adenoma. The other 3 glands were normal. A frozen section confirmed a parathyroid adenoma. Post operatively, she developed a severe form of hungry bone syndrome with low Ca levels reaching 1.5 mmol/L in despite of continuous calcium infusion and regular calcium gluconate bolus injections, as well as oral vitamin D supplement. After a few days she corrected her metabolic abnormalities and was discharged with oral supplementation of calcium and vitamin D.

She was seen once in the outpatient clinic with

serum Ca of 2.1 mmol/L, phosphorus 0.9 mmol/L and SAP 439 U/I. She was still in a wheel-chair as the orthopedic surgeon advised her not to weight-bare for sometime. Her baby remained healthy and free of complications.

Patient 3 was a 34 year old woman (P9 + 0) presented in March 1997 with a history of bony aches for 4 years with proximal muscle weakness and difficulty in walking. She was seen before in a primary healthcare centre and diagnosed as a case of osteomalacia and treated with calcium and vitamin D supplements. She had a fracture of her left forearm recently after a minor trauma and was operated upon. Examination revealed a thin lady with marked proximal myopathy and brisk reflexes with normal gait. A bone profile before treatment revealed serum calcium level of 2.4 mmol/L, phosphorus 0.57 mmol/L and SAP 1606 U/I. She admitted being irregular on some form of supplements from another hospital. DXA showed severe osteopenia with lumbar spine BMD of 0.552 gm/cm² and femoral neck BMD of 0.416 gm/cm². Bone scan revealed a hot super scan with pseudofractures in the forearm, clavicle and pubic rami.

A parathyroid scan was carried out because of the suspicion of a coexisting adenoma which confirmed left inferior parathyroid adenoma. Later, on a repeated Ca showed a higher value of 2.7 mmol/L with persistent low phosphorus and high SAP of 1000 U/I. Twenty four hour urinary Ca was 5.04 and phosphorus was 11.4 mmol/day. Parathormone (PTH) assay initially showed a normal level of 57.5 pg/mL with low 25-OHD₃ (<10 ng/ml). Since the PTH was normal, an FNA of the parathyroid gland was attempted under CT scan guidance but specimen was unsatisfactory. During a follow up visit, she was found to be pregnant. A repeat PTH was 645 pg/ml and the Ca level of 2.8 mmol/L. Surgical exploration of the neck was postponed until she finishes the first trimester. Unfortunately, she had a threatened abortion around 6 weeks of gestation and therefore was admitted to the obstetric ward where she had a complete abortion. After that, calcium level remained around 2.7 mmol/L. The patient refused neck surgery because of some social problems and promised to come for follow-up in the clinic. Up to this date she has not shown up for her clinic visit.

Discussion. The coexistence of primary hyperparathyroidism and pregnancy is very rare. It can be easily overlooked because of the many similar complaints shared by both conditions such as, anorexia, nausea, vomiting, muscle weakness, easy fatigability, bony aches and others. The treating physician has to have a high index of suspicion if early diagnosis is to be made and appropriate treatment instituted.

The first case of primary hyperparathyroidism occurring in pregnancy was reported in 1931 by Hunter and Turnbull,¹⁴ while Friederichson in 1938

was the first to demonstrate neonatal tetany caused by maternal hyperparathyroidism.¹⁵ Now, 7 decades later, literature search, based on Medline Silver Platter (U.S. National Library of Medicine: 1966-1997)²⁻¹² has revealed a total of 121 cases including our patients. The incidence of primary hyperparathyroidism in the general population has been estimated in the USA to be 28 per 100,000 population.¹ Since primary hyperparathyroidism is seen frequently in women it would have been expected that the occurrence of primary hyperparathyroidism in pregnant women is higher than reported but it is known that the disease affects middle age women more frequently with an incidence of 68% over the age of 40 years.¹ Therefore, for a woman in a childbearing age which is commonly under the age of 40 years, to have primary hyperparathyroidism diagnosed in a pregnancy would be a very rare chance. Nevertheless, the disease, once it occurs, can lead to serious fetal and maternal complications.

Ludwing's review in (1962)¹⁶ showed a 50% incidence of fetal morbidity and mortality including still births, abortion, neonatal tetany and neonatal deaths. Francis L Delmonico and co-workers reported an 80% incidence of fetal complications.¹⁷ In 1980, Deutsch et al, reported a similar complication rate of 80% in unoperated cases.¹⁸

The reason for the neonatal hypocalcemia that occurs secondary to maternal hypercalcemia is that calcium ions cross the placenta freely to the fetus but parathyroid hormone does not.^{17,19,20} This leads to fetal hypercalcemia and suppression of parathyroid gland function with subsequent neonatal hypoparathyroidism and hypocalcemia leading to tetany. The hypercalcemia itself may be toxic to the fetus through an unknown mechanism²⁰ leading to abortion and still birth. Some authors^{21,22} have postulated a higher perinatal death in mothers with bone disease. All of our 3 patients had evidence of active bone lesions but the first 2 were operated successfully once the diagnosis was made and had healthy normal babies. The third patient unfortunately had an abortion before definite management could be implemented.

Hyperparathyroidism doesn't impair fertility²² but causes increased maternal morbidity in the form of increased maternal risk of hypertension and urinary tract infections, which are probably attributable to a decline in renal function.^{2,17}

Due to the high incidence of maternal and fetal morbidity and mortality, the ideal approach would be the surgical removal of the diseased parathyroid gland(s). The first successful parathyroidectomy during pregnancy was reported by Petit and Clark (1947)²³ and since then many similar cases have been published.^{2-6,8-12,17-20} Before 1970, surgical removal of the parathyroid adenoma, which constitutes 80-90% of the causes of primary hyperparathyroidism, used

to be postponed until after delivery because of the fear of surgery and anesthesia on the pregnant mother and the fetus. Kristofferson and his group³ reported that mothers who were allowed to remain hypercalcemic till the end of pregnancy had a higher percentage of complicated births (53%) as compared to those who underwent parathyroidectomy during pregnancy (24%). Kelly in a later review in 1991,⁵ reported a 53% neonatal complication in medically treated pregnant women compared to only 12.5% in those who underwent parathyroidectomy during pregnancy.

It is advisable to defer surgery until 16 weeks of gestation when the fetal organs have fully developed. The risk from anesthesia is not much different from other types of surgery performed during pregnancy.²⁴ Moreover, the risk of anesthesia induced abortion is also minimal.²⁵ However, the hazards of premature labor in the third trimester is high and, therefore, the ideal time for a parathyroidectomy is the second trimester.^{3,17} Medical management of the hypercalcemia is indicated before surgery. In the post-operative period transient hypocalcemia, either because of the suppressed function of the other parathyroid glands and the presence of a hungry bone syndrome or both, can be effectively managed with calcium and vitamin D supplements.

There is evidence in the literature to suggest decreased rate of neonatal deaths and complications of hyperparathyroidism during pregnancy^{2,5} which is probably attributed to increased awareness of the condition with early diagnosis and appropriate management. Nevertheless, only 54% of deliveries from 1976 through 1990 resulted in term births without tetany⁵ indicating the seriousness of the condition. After delivery the baby should be monitored carefully for anticipated complications and treated accordingly.

Two of the patients came to our attention because of hyperparathyroid bone disease coexisting with osteomalacia. This is not uncommon in our population (unpublished data), but it has been reported in Western countries that nephrolithiasis is a prominent feature of maternal hyperparathyroidism.²⁶

In conclusion, primary hyperparathyroidism in pregnancy even though rare has potentially serious complications which could be avoided by implementing early screening for asymptomatic hyperparathyroidism in all women of child bearing age and as early as possible in the first trimester so as to tailor the treatment to the individual need. Surgical excision of the diseased gland is the definitive preferred method of treatment but should be deferred until the second trimester to minimize the risk of abortion or early delivery. Surgery should not be contraindicated because of the pregnancy itself. Medical control of the hypercalcemia is indicated prior to surgery. Patients with advanced hypercalcemia especially in the form of bone disease

carry worse prognosis and should be monitored more closely.

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