ISSN 2472-1972

Use of Cinacalcet and ^{99m}Tc-sestamibi Imaging During Pregnancy

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A case report is reviewed, in which two nontraditional interventions were used in a patient with gestational primary hyperparathyroidism: cinacalcet and technetium-99m methoxyisobutylisonitrile imaging. The rationale for these decisions is considered in view of the available data.

Freeform/Key Words: calcimimetics, hypercalcemia in pregnancy, primary hyperparathyroidism, radiation in pregnancy

The fundamental precept of *primum non nocere* (first, do no harm) carries heightened import when treating a pregnant patient. A developing baby can be profoundly affected by exposure to a drug or diagnostic imaging; however, virtually no clinical trial data exist regarding the fetal effects of most interventions. Such information is lacking because pregnant women are rarely included in studies determining the safety and efficacy of most drugs and diagnostic tests. However, withholding a treatment or a diagnostic tool from a pregnant patient is also not without potential risk. The tension between these risks, namely untreated disease vs fetal treatment exposure, complicated by a lack of evidence-based data, informs the case report of gestational primary hyperparathyroidism (PHPT) in this issue of the *Journal of the Endocrine Society* [1].

PHPT in pregnancy is uncommon. It is often associated with very mild elevations in serum calcium and can be safely monitored with no intervention. However, when associated with moderate to severe hypercalcemia, PHPT in pregnancy is known to carry substantial maternal and fetal risks [2–4]. The mother could experience hyperemesis, nephrolithiasis, recurrent urinary tract infection, and/or pancreatitis. Potential neonatal complications include low birth weight, preterm delivery, and fetal death. Moreover, neonatal hypocalcemia and tetany can ensue at birth secondary to intrauterine fetal parathyroid gland suppression. The conventional treatment of pregnant patients with symptomatic PHPT is parathyroidectomy during the second trimester, and localization is typically obtained using ultrasonography. Drug therapy and imaging with radiation are traditionally avoided. However, Horton *et al.* [1], in their case report, used two nontraditional interventions in a gravid patient: administration of cinacalcet and parathyroid localization with technetium-99m-methoxyisobutylisonitrile (^{99m}Tc-sestamibi; ^{99m}Tc-MIBI) scanning. Without evidence-based information regarding the safety and efficacy of either of these interventions in pregnancy, the rationale for these decisions merits further consideration.

Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor (CaSR) to activation by extracellular calcium, thus lowering parathyroid hormone (PTH) levels. It has been approved by the Food and Drug Administration for secondary hyperparathyroidism in patients with chronic kidney disease requiring dialysis, for

Abbreviations: 4D-CT, four-dimensional computed tomography; ^{99m}Tc, technetium-99m; CaSR, calcium-sensing receptor; CT, computed tomography; MIBI, methoxyisobutylisonitrile; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

Received 7 July 2017
Accepted 12 July 2017

hypercalcemia in patients with parathyroid carcinoma, and for severe hypercalcemia in patients with PHPT who are unable to undergo parathyroidectomy. Although the CaSR on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH synthesis and secretion, the CaSR is also expressed in multiple other tissues, including the kidneys, bone marrow, osteoclasts and osteoblasts, breast, thyroid C-cells, and gastrin-secreting cells in the stomach, intestine, and some areas of the brain [5]. It is thus plausible that cinacalcet exposure could exert effects on any of these fetal analogs. Moreover, the CaSR is present in the placenta [6]; thus, cinacalcet could theoretically inhibit physiological placental active calcium transport. The available animal data are limited. In rabbits, cinacalcet crosses the placenta, although no teratogenicity was observed at doses less than the human equivalent of 180 mg/d [7]. In rats, more reassuringly, no teratogenicity was present at higher doses (up to four times the human equivalent of 180 mg/d) [7]. The drug has been classified as pregnancy category C (*i.e.,* animal reproduction studies have shown an adverse effect on the fetus, and no adequate and well-controlled studies have been performed in humans; however, the potential benefits might warrant the use of the drug in pregnant women despite the potential risks).

Clinical reports of cinacalcet use in pregnancy are scarce [8–11]. The few available studies have reported that it has been administered at various weeks of gestation (ranging from 2 weeks during the third trimester in a parathyromatosis patient [11] to the entire duration of pregnancy in a parathyroid carcinoma patient [8]) and at various dosages (from 15 mg/d [8] to 240 mg/d [11]), with serum calcium levels during treatment ranging widely (highest serum calcium level of 14.3 mg/dL [11]). However, the drug was poorly tolerated because of nausea [8], and normalization of maternal serum calcium during pregnancy was not achieved in any of the cases.

Even fewer data are available with regard to the fetal effects of cinacalcet. The drug could conceivably suppress fetal PTH secretion, although whether the suppression would exceed that already present owing to maternal hypercalcemia from PHPT is unknown. Acute neonatal hypocalcemia was reported in three of the gestational cinacalcet cases [9–11], with the longest need for postpartum treatment being 1 month [9]. The neonatal sequelae of cinacalcet can also be extrapolated from reports of infants with an activating mutation in the CaSR (*e.g.,* autosomal dominant hypocalcemia), because constitutive genetic CaSR activation should elicit a similar physiological effect as cinacalcet. Although patients with autosomal dominant hypocalcemia can be asymptomatic, neonatal hypocalcemic seizures have been reported [12], supporting a potential neonatal adverse effect from cinacalcet. With regard to long-term developmental sequelae of *in utero* cinacalcet exposure, with the exception of a 4-year-old "normal" child [9], these are unknown.

The case report by Horton *et al.* [1] also described the use of four-dimensional computed tomography (4D-CT), with and without contrast, and nuclear medicine imaging with ^{99m}Tc-sestamibi (^{99m}Tc-MIBI) in their patient. With a pregnant patient, it is well-established that fetal irradiation should be avoided [13]. *In utero* radiation exposure raises concerns about an increased risk of fetal anomalies, intellectual disability, growth restriction, pregnancy loss, or subsequent cancer from the ionizing radiation [13]. The effective radiation dose with 4D-CT imaging is 10.4 mSv [14]. It is perhaps reassuring that the fetal risk of anomalies, growth restriction, or abortion have not been reported with radiation exposures less than a higher cutoff of 50 mGy [15]. Moreover, iodinated contrast media with CT imaging has not led to teratogenic effects in animals [16, 17], although its use is nevertheless troubling because it can cross the placenta and enter the fetal circulation or amniotic fluid [16].

^{99m}Tc-MIBI is a γ-emitting radionuclide widely used with single photon emission tomography for parathyroid localization in nonpregnant patients with PHPT [18]. It has been shown to cross the placenta in animals [19] and, the same as cinacalcet, has been classified as pregnancy category C. However, the very limited clinical information regarding ^{99m}Tc scintigraphy in pregnancy could be cautiously interpreted as reassuring. A prospective registry study of 122 women exposed to ^{99m}Tc scintigraphy in the first trimester at doses <5 mGy showed no association with increased birth defects or adverse pregnancy outcomes [20]. Although the study did not specifically include ^{99m}Tc-MIBI, it did include ^{99m}Tc-pertechnetate,

which is more radiotoxic than ^{99m}Tc-MIBI [21]. Recent guidelines from the American College of Obstetricians and Gynecologists are consistent with these data. They have stated that a ^{99m}Tc-MIBI scan that results in fetal exposure of <5 mGy is much lower than the exposure associated with fetal harm [15]. Thus, a parathyroid localizing scan that does not exceed this level of exposure perhaps would not be unsafe during pregnancy. In one report of two pregnant patients in which ^{99m}Tc-MIBI parathyroid localization was performed, along with CT scans of the neck and chest, the ^{99m}Tc-MIBI dose was reduced from the standard 20-mCi dose by 50%, leading to fetal exposure of <5 mGy, with acceptable maternal imaging [22]. No birth defects or adverse pregnancy outcomes were reported [22]. Because fetal exposure also results from proximity to radionuclides excreted into the maternal bladder, maternal hydration and frequent voiding have been recommended to reduce this type of exposure [15].

The case of the patient described by Horton *et al.* [1] posed difficult management issues. After presenting with marked hypercalcemia in her first trimester, she was ultimately found to have a parathyroid adenoma in an ectopic location. From the very scant data available, it appears that cinacalcet use in pregnancy might not effectively reduce serum calcium, perhaps owing to poor tolerance, and it appears to carry a risk of neonatal hypocalcemia. In contrast, 4D-CT and ^{99m}Tc-MIBI scanning in pregnancy might be of less concern if the fetal exposure is less than a threshold such as 5 mGy. Questions regarding cinacalcet and imaging for parathyroid localization in pregnancy will most likely remain without definitive answers. Many Food and Drug Administration-approved medications and diagnostic imaging tests will probably continue to lack information about adverse fetal effects [13, 15]; thus, fetal drug and radiation exposure should be avoided when possible. Ultimately, the physician must weigh the risks of drug exposure and diagnostic testing against the risks of nontreatment and nondiagnosis to protect the welfare of both the mother and the fetus in a careful balance.

Acknowledgments

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The present study was supported by National Institutes of Health Grant K24-DK074457.

Disclosure Summary: The authors have nothing to disclose.

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