MAYO CLINIC

# Endocrinology Update

Endocrinology News from Mayo Clinic

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## Inpatient Hyperglycemia: What Next?

Before 2001, hospital hyperglycemia was often neglected. This approach changed dramatically when tight glycemic control came to the forefront of hospital medicine after a single-center, randomized controlled trial (RCT) in Leuven, Belgium, of more than 1,500 patients in a surgical intensive care unit (ICU) reported a 42% reduction in mortality rate with use of intensive insulin therapy. Since then, massive efforts have been made worldwide to achieve these goals, with intensive insulin therapy becoming a benchmark in critically ill patients.

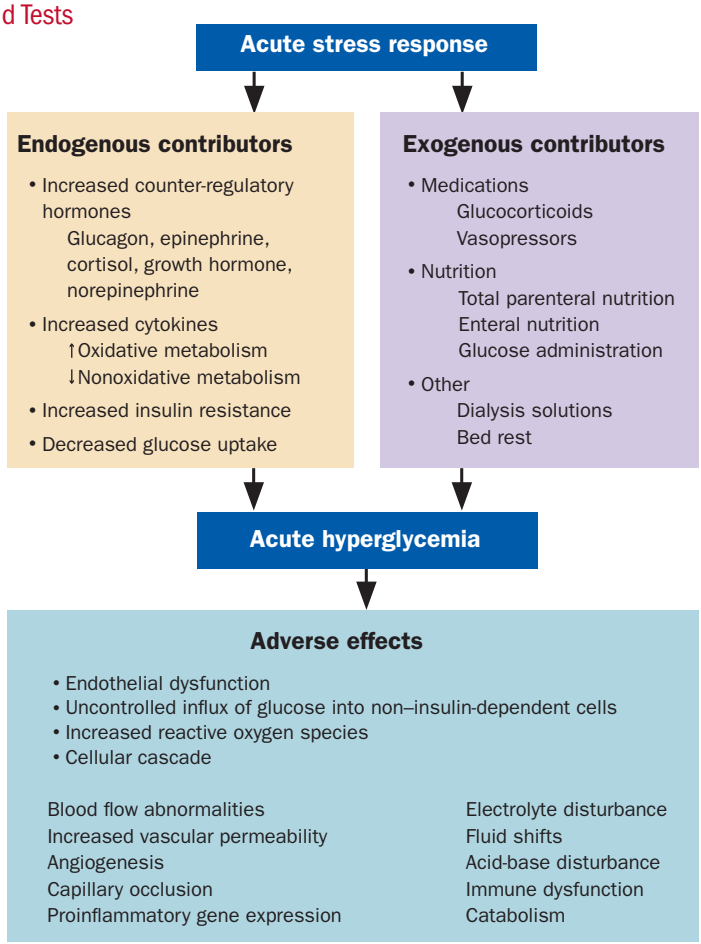


**Figure.** *Pathophysiology and adverse effects of acute hyperglycemia.*

Gunjan Y. Gandhi, MD, MSc, of the Division of Endocrinology at Mayo Clinic in Jacksonville, Florida, says: "Clinicians realized there are substantial challenges to achieving such ambitious goals in practice: multifold increased risk of hypoglycemia, increased utilization of resources, considerable revamping of infrastructure to implement glycemic management protocols, and additional personnel training and need for intense coordination among varied involved specialties. Although laudable efforts have been undertaken, from the tertiary care academic centers to small community hospitals, for the seamless implementation of insulin protocols, subsequent clinical studies in varied ICU settings did not replicate the amazing benefits reported in the study from Leuven, Belgium."

In addition, some concern started to emerge regarding possible harm. Dr Gandhi explains: "At Mayo Clinic, we conducted what still is the only RCT to assess the role of tight glycemic control (blood glucose between 80 and 100 mg/dL) intraoperatively in cardiac surgery patients. While we did not see any improvement in patient-important outcomes, we did see an increased risk of deaths and strokes in the group with tightly controlled glucose compared with the group that was treated conventionally."

The much-awaited results of the multicenter, international Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (of which Mayo Clinic in Rochester, Minnesota, was the only site in the United States) recently reported definitive and not entirely surprising evidence that there is no benefit of tightening glucose control to normal levels compared with a reasonable and achievable goal of 140 to 180 mg/dL in a heterogeneous group of critically ill patients (N>6,000). The results differ from the Leuven trial in that there was an increase in the primary end point (death at 90 days) with intensive glucose control. Severe hypoglycemia occurred in more patients

*Gunjan Y. Gandhi, MD, MSc*

in the intensive control group.

Dr Gandhi highlights: "A meta-analysis incorporated the NICE-SUGAR trial and the Leuven study among many other, smaller studies to attempt to resolve the disparate results and answer the question, Are we helping or hurting patients with tight glycemic control? The outcome of the pooled data for these 13,000 critically ill patients tells us that the truth may lie somewhere in between, and tight glycemic control may not actually have any effect on mortality rate at all. The relationship between hyperglycemia in critically ill patients (the majority of whom do not have underlying diabetes mellitus) and worse outcomes in most previous observational studies is probably not causal but a reflection of the severity of illness. Thus, attempting to reverse a normal stress response of shunting energy to critical organs may be deleterious."

## Role of Hypoglycemia

Fear of hypoglycemia is one of the key barriers for the implementation of targeted glucose control. Dr Gandhi says: "Although not shown by available data, unrecognized hypoglycemia may very well be the major culprit for the increased mortality rate, especially in critically ill patients who are sedated and connected to a mechanical ventilator. Hypoglycemia is associated with increased risk of death and prolonged hospital stay in various hospitalized patient populations. However, recent studies suggest that episodic in-hospital hypoglycemia may be a marker of greater illness severity, rather than a mediator of adverse events. Although these findings offer some reassurance to clinicians in their efforts to control glucose levels, hypoglycemic events are associated with potential for harm and should be avoided."

## Clinical Implications

Dr Gandhi suggests the following guiding principles:

- Do not neglect glycemic control in critically ill patients because studies have not tested tight vs no or poor control, but rather they have compared tight vs good control. The former question needs to be answered—but until then, summative evidence suggests that reduction of severe hyperglycemia reduces morbidity, especially from infectious complications.
- Use evidence-based glucose control protocols with a demonstrated safety record, establish hospitalwide policies that provide guidance on identification of high-risk patients, and standardize procedures for detection and treatment of hypoglycemia across nursing units. A system for tracking the frequency and severity of all hypoglycemic and hyperglycemic events allows for timely and ongoing analysis of the safety of a glycemic management program.
- There is no additional benefit in outcomes obtained through achieving normoglycemia compared with reasonable glycemic control. A moderate approach to managing critical illness–related hyperglycemia seems most prudent at this juncture (eg, goal blood glucose concentrations between 140 and 180 mg/dL). Professional organizations, such as the American Association of Clinical Endocrinologists and the American Diabetes Association, have come full circle on this issue and now recommend a more moderate approach to treating hyperglycemia in the critically ill patient. ICUs should make efforts to adjust to these goals.
- There is harm from overt and unrecognized hypoglycemia with intensive insulin therapy. Thus, strict goals cannot be achieved safely given the limitations of current technology in monitoring glucose levels. It remains to be seen whether there is benefit in tight glucose control once hypoglycemia is minimized with technological advances, such as continuous glucose monitoring systems.

## Future Directions

The underlying pathophysiologic mechanisms (Figure) behind stress hyperglycemia need to be characterized further in an attempt to prevent its adverse consequences. Dr Gandhi concludes: "Although glycemic goals have been set in a moderate range, it may be that certain subsets of patients would benefit from different glycemic goals. Further studies will need to be completed to determine whether there is a need to individualize glycemic targets depending on the patient and his or her type of critical illness. Future research should also focus on hospital-related hyperglycemia in patients on the general medical-surgical floors, where patients with blood glucose concentrations greater than 200 mg/dL are still being treated with 'sliding-scale' insulin."

# Preserving Fertility in Cancer Survivors

Of the estimated 1.5 million men and women in the United States who will receive a diagnosis of cancer this year, 10% are younger than 45 years and 1% are less than 20 years of age. Overall 5-year relative survival rates for this group are excellent—nearly 80%—and ongoing improvement in cancer treatment likely will continue to increase survivorship. Jani R. Jensen, MD, of the Division of Reproductive Endocrinology and the Department of Obstetrics and Gynecology at Mayo Clinic in Rochester, Minnesota, says: "Future fertility is often a primary concern for those newly diagnosed with cancer: more than 75% of patients who are less than 35 years of age and childless at the time of their cancer diagnosis desire children in the future. Although cancer therapy can be lifesaving, treatment sequelae can be considerable and may include premature gonadal failure or infertility, thus creating an important quality-of-life issue for these individuals."

Fertility preservation refers to therapies that promote or retain fertility for patients undergoing medical treatments that otherwise could jeopardize future childbearing ability. Dr Jensen explains: "Conditions where fertility preservation may be considered include malignancies, autoimmune disorders such as lupus erythematosus, certain hematologic disorders such as vasculitis or aplastic anemia, and any other medical condition where the disease itself or its long-term management may impair fertility. Risk of permanent reproductive damage varies with the type, dose, and site of therapy rendered, as well as the patient's age at the time of treatment. In general, non–cell cycle specific types of chemotherapy, such as alkylating agents (eg, cyclophosphamide), have the highest risk of causing permanent gonadal damage. Likewise, pelvic irradiation poses a greater risk for gonadal damage than irradiation to distant sites."

Options for fertility preservation vary by age and sex. Dr Jensen continues: "Prepubertal males and females have limited options, primarily the collection and cryopreservation of gonadal tissue. The goal for later use is to autologously transplant the tissue or thaw it and perform in vitro maturation of immature gametes for use with in vitro fertilization. Both of these approaches should be considered experimental. Although there are rare case reports of births after partial or whole ovary transplantation, to date there are no reported live human births from immature gametes retrieved from cryopreserved gonadal tissue. One of the most familiar and long-standing fertility preservation strategies is sperm banking for postpubertal males. Cryopreserved sperm can be used years—even decades—after initial storage, for either insemination into a female partner or with in vitro fertilization."

*Jani R. Jensen, MD*

Postpubertal females may elect to undergo embryo or oocyte cryopreservation (Figure), processes that require 2 to 3 weeks to complete. Dr Jensen notes: "Preserving unfertilized oocytes is a relatively new technique and may be an attractive option for single women who choose not to use donor sperm to create embryos. Although the first human birth from cryopreserved oocytes was in the mid 1980s, it was not until the past decade that the technique was improved enough to make it a viable treatment option. Initial work with oocyte cryopreservation was hampered by technical difficulties, such as cytoplasmic rupture

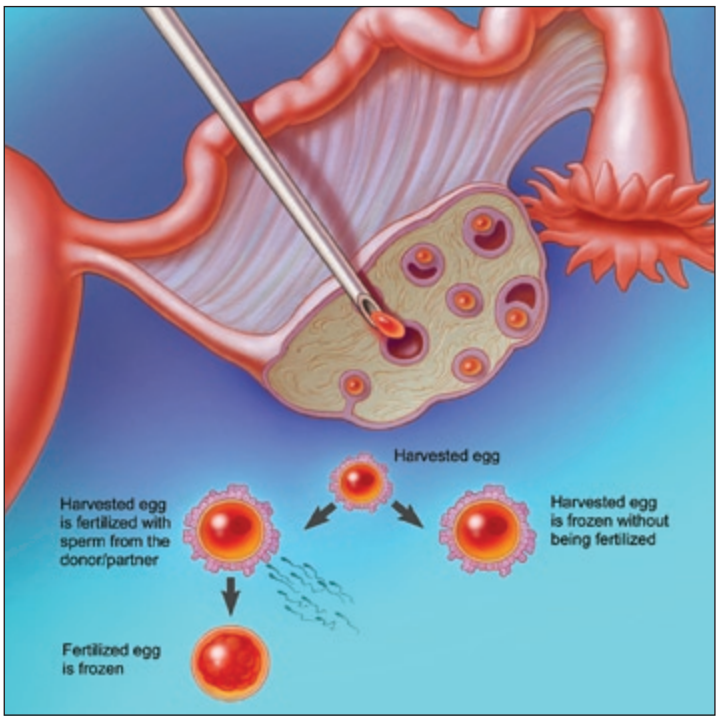


**Figure.** *Cryopreservation of oocyte or embryo. For oocyte cryopreservation, the mature eggs are cryopreserved immediately. For embryo creation, mature oocytes are combined with sperm and the embryos are cryopreserved.*

during freezing and artificial activation of the mitotic spindle, causing the oocyte to act as if it were already fertilized and thus be resistant to actual sperm fertilization. With recent technical improvements, more than 70% of oocytes can now survive the cryopreservation process, and pregnancy rates—although lower than with conventional in vitro fertilization—are reasonable."

For cryopreservation of either the oocyte or the embryo, exogenous human gonadotropins (typically, a combination of follicle-stimulating hormone and luteinizing hormone) are administered for approximately 10 to 12 days. During this time, growth of ovarian follicles is monitored with serial estradiol determinations and ultrasonography to measure follicular growth. When follicles are large enough to contain mature oocytes, human chorionic gonadotropin is given to mimic the natural preovulatory surge of luteinizing hormone, which causes the maturing oocytes to resume meiosis and prepare for ovulation. Shortly before the anticipated ovulation, the oocytes are retrieved under light anesthesia with a needle attached to a vaginal ultrasonographic probe. For oocyte cryopreservation, the mature eggs are cryopreserved immediately; for embryo creation, mature oocytes are combined with sperm. After fertilization is confirmed by the presence of 2 pronuclei (representing the genetic material of the sperm and egg), the embryos are cryopreserved. In either case, the oocytes or embryos can be used months or even years in the future.

Dr Jensen concludes: "For patients facing certain serious medical conditions, fertility preservation may provide a way to create future genetic children, a goal that may otherwise be unattainable. Patients considering fertility preservation should be counseled that time is of the essence and, where possible, fertility preservation should be initiated before receiving chemotherapy or any other fertility-jeopardizing treatment. The experimental nature of some fertility preservation strategies also should be explained to patients, and individualized risk-benefit counseling that takes patient prognosis into account should be performed before making a final decision regarding fertility preservation."

## Medical Genetics for the Endocrinologist

It is essential for the clinical endocrinologist to have a good understanding of the genetics of endocrine disease. The first challenge is to recognize that the clinical scenario may be indicative of a genetic condition. This detection requires the recognition of clinical patterns, as well as taking a good family history. Salman Kirmani, MBBS, of the Department of Medical Genetics at Mayo Clinic in Rochester, Minnesota, says: "An accurate diagnosis not only directs current management, but also allows for a personalized road map for future surveillance of patients and presymptomatic family members. With the advent of prenatal and preimplantation diagnosis of genetic disorders, couples who are at risk for having children with heritable endocrine disorders may want to use genetic information to make reproductive decisions, and they need appropriate counseling about the options available to them. Finally, with the flood of data coming in from genomewide associations studies (GWAS) and with whole-genome sequencing just around the corner, endocrinologists have to be ready for the demands of practicing individualized medicine for all of their patients."

The ideal situation would be for the endocrinologist to partner with a medical geneticist in the care of such patients. Outside of the tertiary care setting, access to a medical geneticist or a genetic counselor continues to be limited, and the endocrinologist may have to navigate through the complex issues of genetic testing and its implications until the patient can be seen by a genetics provider. Some of the common questions are highlighted below.

***What clinical situations demand consideration for a genetic syndrome?***

Dr Kirmani answers: "Pattern recognition may not be difficult for some well-known endocrine syndromes, but it is hard to expect even the best clinicians to recognize a rare genetic syndrome every time. Multiple endocrinopathies in the same patient are usually the first clue. A focused 3-generation family history often reveals a syndromic diagnosis, even when the patient has only 1 clinical finding. For example, asking a patient with a norepinephrine-secreting pheochromocytoma questions about a family history

of renal cell carcinoma or brain and retinal hemangioblastomas may uncover a diagnosis of von Hippel-Lindau (VHL) disease. Recognizing certain unusual clinical signs in association with an endocrine disorder also is essential to making a diagnosis.

"Use of the open-access Online Mendelian Inheritance in Man (OMIM) database (www.ncbi.nlm.nih.gov/omim) is very helpful not only for looking up the cardinal features and inheritance pattern of a particular syndrome under consideration, but also for searching to see if a combination of clinical features is part of a recognized genetic syndrome. OMIM is also linked to another useful Web site called GeneTests (www.ncbi.nlm.nih.gov/sites/GeneTests), which not only provides an up-to-date review on a number of genetic syndromes, but also provides links to commercial and research laboratories performing genetic testing."

***How would genetic testing be helpful in a particular situation?***

Genetic testing can be used to confirm a clinical diagnosis. Dr Kirmani explains: "Even when genetic testing is not essential for the diagnosis, if one is to identify presymptomatic individuals in the family who may benefit from screening, it is essential to confirm the presence of a pathogenic mutation in the proband, to ensure that accurate testing can be offered to family members at risk. In situations where the family history is not available (eg, adoption) or the clinical scenario is not characteristic, genetic testing is essential in establishing a diagnosis. Results of genetic testing also direct management, even if a clinical diagnosis is well established. A classic example is in multiple endocrine neoplasia type 2A, where the type of mutation in the *RET* proto-oncogene determines the age at onset of medullary thyroid cancer, directing the timing of prophylactic thyroidectomy in these individuals."

***How sensitive and specific is genetic testing for a particular disorder?***

Dr Kirmani highlights: "Using the example of VHL again, the testing methodology entails both sequencing and deletion/duplication analysis of the *VHL* gene. If both methodologies are used, testing is more than 99% sensitive, but if sequencing alone gives a negative result, the patient still may have a large deletion that could have been missed with sequencing alone. There also may be multiple genes responsible for a disorder, with some genes as yet undefined. Thus, limitations in both the testing methodologies and our understanding of the genetics of the disorder limit the sensitivity of most genetic tests to below 100%. Results may reveal variants of unclear significance, and a novel change in the nucleotide sequence may not necessarily be pathogenic, making interpretation of test results challenging."

*Salman Kirmani, MBBS*

***What is the role of new genetic tests that give risk profiles to patients for common disorders, such as type 2 diabetes mellitus?***

Type 2 diabetes mellitus is a multifactorial disorder, having both genetic and environmental components. Dr Kirmani says: "Even though the genetic contribution is notable, there most likely are multiple genes involved, each one contributing a small risk of disease. GWAS investigators are attempting to identify such genes, to better understand the pathophysiology of the disease. Data from such studies should be used to generate hypotheses and not to predict likelihood of disease. Unfortunately, some commercial entities are marketing these tests directly to consumers, giving them risk profiles based on the presence or absence of genetic variants. These data are not considered clinically relevant unless further prospective studies validate these concerns. Established clinical risk factors and the family history are better predictors of future onset of disease."

## Conclusion

The endocrinologist should recognize clinical situations that warrant further consideration from a genetic standpoint. Decisions on whether genetic testing is needed should be made on a case-by-case basis, ideally with a geneticist involved from the outset, since interpretation of genetic test results can be challenging.

# Endocrine Laboratory Pearls: Thyroid Tests

Physicians are comfortable ordering and interpreting familiar laboratory tests, but they might not recognize some of the tests' limitations, resulting in overutilization or in misguided confidence in the validity of the results. In addition, less-familiar laboratory tests that could improve patient care or reduce costs might be ordered too infrequently because of uncertainty about testing indications or result interpretation.

*Ravinder J. Singh, PhD, and Stefan K. Grebe, MD*

## Tests for Free Thyroid Hormones

Stefan K. Grebe, MD, of the Division of Clinical Biochemistry and Immunology and the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota, says: "Tests for free thyroid hormone are among the most frequently ordered laboratory tests, despite consensus that measurement of thyrotropin (TSH) should usually suffice." Dr Grebe explains that peripheral thyroid hormone testing should be limited to a few clinical scenarios:

- Confirmation of hypothyroidism or hyperthyroidism in cases with borderline abnormal serum TSH concentrations
- Assessment of severity of hyperthyroidism or hypothyroidism
- Rapidly changing thyroid hormone levels (eg, during treatment of thyrotoxicosis)
- An unreliable pituitary-thyroid feedback loop (eg, pituitary disease)
- TSH assay interferences due to TSH autoantibodies or heterophilic antibodies

Dr Grebe notes: "In many such cases, measurement of total thyroid hormones is just as informative as testing for free thyroid hormones while being analytically more reliable [Figure 1]. Moreover, free thyroid hormone assays are only marginally less susceptible to interferences from drugs or nonthyroidal illness than total thyroid hormone assays. For example, heparin (and low-molecular-weight heparin) elevates lipoprotein lipase levels, creating increased circulating concentrations of free fatty acid. These fatty acids displace thyroid hormones from binding proteins, elevating free thyroxine ($FT_4$) and free triiodothyronine ($FT_3$) levels, in some cases more than 2-fold above the upper limit of the reference ranges."

Ravinder J. Singh, PhD, in the Division of Clinical Biochemistry and Immunology and the Department of Laboratory Medicine and Pathology at Mayo Clinic in Minnesota, explains: "Even in the absence of interferences, many $FT_4$ and $FT_3$ assays give inaccurate results in some cases. Most of these assays use thyroid hormone analogues, designed to not displace thyroid hormone from binding proteins while competing with the patient's free thyroid hormone for assay antibodies. This assay design works only over a relatively narrow range of concentrations of binding proteins and thyroid hormones. Reference methodologies using physical separation of bound thyroid hormone from free thyroid hormone solve this problem, but they are only available for $FT_4$, have longer turnaround times, and continue to be susceptible to interferences related to drugs or illness."

## Measurement of Circulating Thyroid-Stimulating Immunoglobulins

Thyrotoxicosis affects about 3 million new patients in the United States each year. More

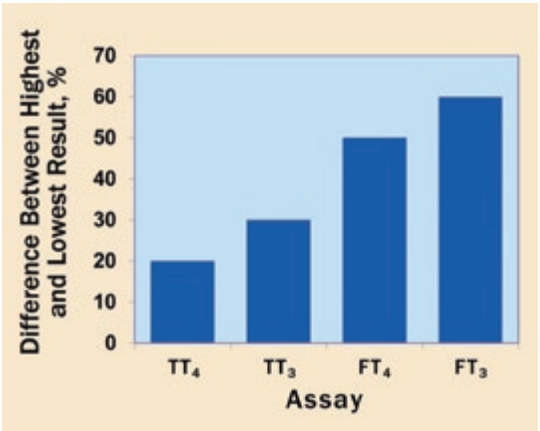


**Figure 1.** *Range of result differences of thyroid function tests on aliquots of the same sample, measured with 15 different immunoassays. These sample levels of thyroid hormones and thyroid hormone-binding proteins are within the normal reference range. In samples with abnormal concentrations of thyroid hormones or thyroid hormone-binding proteins, even larger differences are observed between the assays for free thyroxine ($FT_4$) and free triiodothyronine ($FT_3$). $TT_4$ indicates total thyroxine; $TT_3$, total triiodothyronine.*

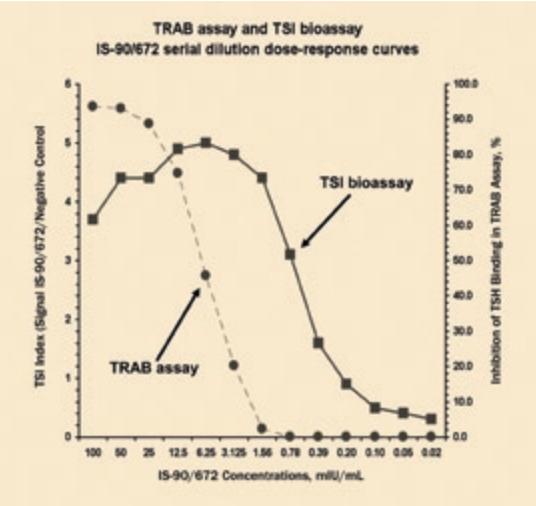


**Figure 2.** *Serial dilution curves of international standard material (IS-90/672) of thyroid-stimulating immunoglobulins (TSIs). The 2 curves are parallel to each other along their linear portions, indicating that the 2 tests have similar responses to IS-90/672. The TSI bioassay curve is shifted to the right, suggesting better detection sensitivity than the thyrotropin receptor autoantibody–binding (TRAB) assay. At very high TSI concentrations, the TSI bioassay might be less accurate than the TRAB assay because of a high-dose hook effect. The reference range for the TSI bioassay is a TSI index of <1.3; the reference range for the TRAB assay is <16% thyrotropin (TSH)-binding inhibition.*

than 60% of cases are caused by Graves' disease, a disorder characterized by production of autoantibodies (thyroid-stimulating immunoglobulins [TSIs]) that stimulate the TSH receptor. Since TSIs are disease specific and are detectable in more than 90% of patients with Graves' disease, they reliably distinguish Graves' disease from other causes of thyrotoxicosis.

Dr Singh says: "There are 2 different types of clinical assays for TSI detection: TSH receptor autoantibody–binding (TRAB) assays and TSI bioassays. In TRAB assays, labeled TSH competes with TSI in patient serum for binding to assay TSH receptors. TSI bioassays use cell lines that express the TSH receptor and a cyclic adenosine monophosphate (cAMP)-controlled luciferase gene. When these cells are exposed to TSIs, cAMP is produced and thus drives luciferase production, which in turn leads to light production upon cell lysis and substrate addition."

Dr Grebe explains: "TRAB assays and TSI bioassays show about 90% agreement in detecting TSIs, with the latter being somewhat more sensitive at low TSI concentrations and the former possibly giving more accurate results at high TSI concentrations [Figure 2]. Either assay is more accurate (and cheaper) than a radioactive iodine uptake and scan, which are traditionally used to differentiate Graves' disease from other causes of thyrotoxicosis. TRAB assays and TSI bioassays are also particularly useful in distinguishing hyperemesis gravidarum–related thyrotoxicosis from a first-trimester presentation of Graves' disease."

He continues: "Another key application during pregnancy is risk assessment for fetal/neonatal Graves' disease. This disorder can occur in pregnant women who had previous thyroid-ablative treatment for Graves' disease. These women have normal thyroid function test results, but they might still be producing TSIs, which can pass through the placenta to the infant and cause fetal thyrotoxicosis. Results of maternal TRAB assay or TSI bioassay that are more than 2 or 3 times the upper limit of the reference ranges are correlated with fetal thyrotoxicosis, indicating a need for high-risk obstetric care and serial TRAB assays or TSI bioassays."

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# Resources

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- Clinical trials
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# Upcoming Education Opportunities

### Mayo Clinic Nutrition in Health and Disease

September 15-16, 2011. Seattle, Washington

This course—designed for physicians, nurse practitioners, physician assistants, dietitians, and health and wellness staff—will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory setting. An additional course objective is to discuss wellness programs that include nutrition, physical activity, and other lifestyle behaviors. The course will be held at the Hyatt at Olive 8. For more information about this course, please call 800-323-2688 or visit http://www.mayo.edu/cme/endocrinology.

### 15th Mayo Clinic Endocrine Course

April 16-21, 2012. Palma, Mallorca, Spain

This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The course will span the full spectrum of endocrinology. For more information about this course, please visit http://www.mayo.edu/cme/endocrinology.

# 2011 Graduating Endocrine Surgery Fellow

Bianca J. Vazquez, MD, and her program director, Clive S. Grant, MD. Dr Vazquez's new appointment is at Presbyterian Healthcare Services, Albuquerque, New Mexico.

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