I. Normal Thyroid Physiology During Pregnancy
   A. Mother
      1. Increased thyroxine-binding globulin (TBG) levels after 3
         weeks (peak 12-14 weeks, plateau to term)
         a. Increased thyroxine (T₄), triiodothyronine (T₃)
            (change in T₄ greater than change in T₃)
         b. Decreased resin T₃ uptake (RT₃U)
         c. Normal free thyroxine index (FTI)
         d. Normal free T₄ (FT₄), free T₃, (FT₃) and reverse T3
            (rT₃)
      2. Normal thyroid-stimulating hormone (TSH) (but declines
         slightly as chorionic gonadotropin [hCG] rises), increased
         responsiveness to thyrotropin-releasing hormone (TRH)
      3. Normal T₄ production and turnover rates
      4. Thyroglobulin (Tg) rises throughout, especially in the last
         trimester
      5. Increased radioactive iodine uptake (contraindicated in
         pregnancy)
         a. Increased renal clearance of iodide leads to de-
            creased iodide space
         b. Increased thyroidal clearance of iodide leads to
            normal total iodide uptake
      6. Mild thyroid enlargement (goiter) in 15-85%
         a. Mainly in areas of iodine deficiency; responds to
            iodine prophylaxis
         b. Goiter is seldom seen in North America.
      7. Increased basal metabolic rate (BMR): fetus plus in-
         creased cardiac output plus respiratory and muscular
         work
      8. Increased cholesterol
   B. Fetus
      1. Thyroid
         a. Follicles recognizable by 8 weeks
         b. Iodide trapping by 10-12 weeks
         c. Hormonogenesis by 10-15 weeks
         (1) T₄
            (a) Major hormone
            (b) Reaches adult levels by 36 weeks
         (2) T₃
            (a) Minimal production until 30+ weeks
            (b) Low in amniotic fluid
         (3) Reverse T3
            (a) Major production from T4
            (b) High levels in amniotic fluid (300 ng/dL in
                first half of pregnancy; decreases to 100
                For clinical purposes of measuring free thyroxin, we have done the free
                thyroxin index and by doing this index we are able to estimate this fraction
                remarkably well. When we are interested in looking for whether there is a
                high T4, and we and to know that this represents an abnormality or is due to
                the fact that maybe there is excess TBG or more being carried because there
                is more carrier. Then we do the free thyroxin index to estimate it. The free
                thyroxin index is done by multiplying the total T4 value as well as the resin
                uptake. The resin uptake is an indirect way of estimating the amount of
                TBG. We can measure TBG directly now, but you don’t do that most times.

You can develop an index where you multiply the total T4 by the TBG that is
measured directly. Instead what we prefer to to is use resin uptake. The resin
uptake is a resin T3 uptake. That confuses everyone because it is not
measuring T3. The T3 in that particular test is put in the test tube as a marker of
the number of binding sites available on the TBG. It is measuring actually
the capacity of TBG to bind thyroxin or to bind T3 if you want to it per say.
When we multiply the total T4 by the resin uptake we get the free thyroxin
index. The way the test is constructed when the resin uptake is higher that
indicates that there are fewer binding sites available on TBG. In most cases
fewer binding sites is due to the fact that there is too much T4 circulating and
that occupies all of the binding sites. When there are a lot of open binding
sites then the resin uptake is low because your tracer is going to the open
binding sites and not to the resin. By the way that works out good. You were
able to see that the product helps us evaluate the situation so that normally in
a person with a normal amount of TBG if the resin uptake is high and the T4
is high the product is high and that points to hyperthyroidism. In the non-
pregnant normal person with normal TBG if the resin uptake is low and the
total T4 is low, the product of those two numbers is even lower and that points
to hyperthyroidism. Now let’s look and see what happens in pregnancy. One
of things that happens in pregnancy is that under the influence of the increasing
estrogen and the liver synthesizes more TBG and also the TBG is altered a
little bit chemically so that the grades is a little slower than normal. The
upshot is that TBG rises throughout pregnancy and by the end of the first
trimester it stays at high levels and at delivery it falls. Now you have excess
TBG. What is excess TBG? It suddenly gives a lot of new binding sites
available for thyroxin and alters our conventional thinking about the chemistry.
Notice the T4 rises as the TBG rises. What does that mean? There is a lot
more carrier protein and a lot more binding sites. It binds more thyroxin in
toto. However, the free fraction remains normal and is still carrying out its
work.

When we measure the binding sites available with the resin we notice that
the resin uptake falls indicating that there are more open binding sites. The
product of a high T4 and a low resin uptake gives a normal index so that in
pregnancy the free thyroxine remains entirely normal. That means that when
you see a woman who is pregnant and you begin to consider to thyroid
function, you must at least measure the T4 and measure the resin uptake as
well to get a free thyroxin index to determine is this just a reflection of the
altered TBG that occurs physiologically with pregnancy or is it a function of
an abnormal amount of thyroxin functionally.

One of the other phenomenon that occurs with pregnancy is the fact that
chorionic gonadotropin rises in the first trimester and then it begins to come
back to a lower level. It maintains that level throughout the remainder of the
pregnancy. hCG shares a similarity to TSH. They both have two protein
chains the alpha and the beta. They share the alpha chain. The beta chain is
what renders specificity. The TSH beta chain is different than the hCG beta
chain. The structure is probably even so close enough that hCG has weak
TSH like activity. In the physiologic state it has no clinical significance, but
the fact that it occurs can be shown because as hCG peaks you’ll notice that
TSH falls a little bit and still remains in the normal zone. It comes down and
then as this lowers TSH comes back up again indicating that there is some
weak TSH like activity and roughly speaking perhaps 50 units of hCG would
be equivalent in activity to perhaps one unit of TSH. This will have important
later on when we consider molar disease, trophoblastic disease which can’t
produce thyrotoxicosis because there is so much. In the physiologic state
there isn’t that much hCG, so you get only a minor effect.
I. Normal Thyroid Physiology at Term and Postpartum

A. Representative values at term

**Test** | Nonpregnant | Maternal Blood
--- | --- | ---
**Cord Blood** |
T4 | 5-12 µg/dL | 16 (9-20) |
T3 | 80-190 ng/dL | 160 (105-240) |

TSH is normal. The index is normal. The free actual measurable free hormones, T4 and T3, are within the normal range and reverse T3 is normal. What is decreased is the resin uptake and what is increased is the total T4 and T3 because of the excess being carried on TBG, which is elevated. BMI we don’t measure, but it still demonstratively elevated. Cholesterol rises for some reason. We used to think that the pregnancy per say was a stimulus maybe on the basis of the hCG or otherwise to goiter. We now believe that goiter primarily occurs in pregnancy in areas of iodide deficiency and as you know the United States no longer has any iodine deficiency so as a result if you see a pregnant woman who has developed a goiter, it is well to evaluate thyroid function. You don’t just pass it off as being due to the pregnancy. We don’t see it normally in a normal pregnancy. At about 8 to 10 weeks we watch the development of the thyroid in the fetus, so it begins a hormone recognizable by the appearance of colloid at about the 10th to 12th week. Hormone synthesis begins because as colloid is being formed and as a result it begins to be secreted by mid-term. We mentioned about how T4 is activated and becomes T3 by the action of the iodinase. The mother has three types of the iodinase. The placenta largely has type 2 and 3, and the fetus in the early parts of pregnancy as I emphasized has type 2 and 3. If that fetus does not have its own thyroid and is becoming hyperthyroid, type 2 is activated so that whatever T4 gets near the fetus can be converted to the active T3 hormone in the brain where it is important. Type 1 only appears near term, which explains why the fetus begins to produce T3 only near term. The placenta is impermeable to TSH. Note that it is permeable; however, to TRH. There has been some suggestion that an increase in thyroid function hastens the maturity of the lungs in the fetus; therefore, hastens surfactant appearance and would improve respiratory difficulties. The suggestion has been made that is they recognize a fetus that is likely to have this problem it is possible to stimulate the babies thyroid to produce thyrotoxic endogenously and improve the situation. You can’t do it by administering TSH to the mother because it doesn’t cross the placenta, but there has been some suggestion since TRH does cross it might be possible to give TRH to the mother and effect the fetus. This is obviously theoretical or experimental at this time. It is relatively impermeable to these thyroid hormones. We used to think that absolutely so, but we now realize that in the normal fetus there is relatively insignificant transfer. Those types of fetuses have a congenital problem which leads to thyroid hormone deficiency agenesis, so they know the baby is going to have this problem. When they study those they realize that perhaps 1 or 2% of these total thyroxine may cross the placenta and get into the fetus. That is the explanation why these athyrotic fetuses are born and are not full blown hypothyroid. In utero they seem to have enough hormone transfer to keep them from full blown hypothyroidism and particularly to protect the central nervous system. We now know that it is important that if we have a hyperthyroid fetus we may or may not have to treat it in utero. We have to start treatment immediately upon birth but maybe not in utero because of this minor amounts of transfer.

The placenta is permeable to anti-thyroid drugs, immunoglobulin’s, and the course in hyperthyroidism in Graves disease the immunoglobulin inhibit. In other words, antibodies TSH receptor on the thyroid follicular cell these cross the placenta. These might be affecting fetal thyroid function. Notice that the anti-thyroid drugs and iodides cross the placenta as do beta-blockers. This is very important when we treat a woman with thyrotoxicosis who is pregnant because we have to take into account the effect of our anti-thyroid drugs on fetal thyroid function. In Graves disease the hyperthyroidism is normal but in excessive amounts. At the time somebody had the bright idea why not give the mother a heck of a lot of anti-thyroid drugs and block her thyroid out and then we will give her normal thyroxin to keep her euthyroid. It soon appeared that there one could not do that because of the fetus. Because what happens is the anti-thyroid drug crossed the placenta so you produced hyperthyroidism in the fetus. When you fed the mother thyroxin you brought her up to euthyroidism but not enough crossed the placenta to keep the fetus from becoming hyperthyroid. That becomes a very important consideration and when we manage a patient with hyperthyroidism; we will take this phenomenon into account as we are managing it.

Let’s look and see what happens then in a woman as she comes to term. Physiologically what has changed? The T4 has risen because there is excess TBG binding it and maybe the T4 has not gone up that much, but it is towards
(15-85)

<table>
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<tr>
<th>Test</th>
<th>Range</th>
<th>Value</th>
<th>Notes</th>
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<tr>
<td>TSH</td>
<td>0.3-5.0 µU/mL</td>
<td>3.0</td>
<td>(0.5-5)</td>
</tr>
<tr>
<td>FTI</td>
<td>1.2-4.3</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.3-5.0 µU/mL</td>
<td>3.0</td>
<td>(0.5-5)</td>
</tr>
</tbody>
</table>

B. Changes in neonate (“neonatal T3-toxicosis”)
1. TSH surge due to cooling and other factors
   a. 10 µU/mL at birth
   b. 100-200 µU/mL at 30 minutes
   c. 13/µU/mL at 48 hours
2. T3 and FT3 increase 800-900% by 24 hours; normal in 14 days
3. T4 increases by 50%, FT4 by 300% by 24 hours; normal in 14 days
4. rT3 stable for 24 hours; normal by 5 days
5. Thyroglobulin (Tg) increases at 6 hours; remains elevated for several months
6. Transient hypothyroxinemia with normal TSH is common in premature infants
   (<2,000 g)—may be associated with later neurologic or mental developmental problems

C. Changes in mother
1. Gradual decline in TBG
2. T4 and T3 normal by 6 weeks

H. Hyperthyroidism During Pregnancy
A. Etiologies
   1. Graves’ disease (90-95 %)
   2. Trophoblastic disease (hCG in excess of 100,000 mIU/mL)
   3. Silent thyroiditis
   4. Toxic adenoma
   5. Factitial or medicamentosa
B. Incidence
   1. Reduced fertility in uncontrolled thyrotoxicosis
   2. Most have antecedent hyperthyroidism
   3. Occurs in 0.02-3.7% (generally about 0.2%) of all preg-
the high side. The mother has increases in T3, but the fetus doesn’t produce very much T3 as we indicated, so it tends to have a much lower value in its blood. Reverse T3 the mother tends to keep within the normal zone, but the fetus producing a lot of reverse T3, therefore, at term in its blood there is circulating T3. TBG is elevated because of the estrogen phenomenon and even some that spills over. The fetus isn’t that high, but it does have a little bit of excess. The resin uptake has fallen remarkably as we’ve indicated. The fetus is normal. The index remains normal in both instances. The TSH is normal, although the fetus tends to have a relatively high TSH value when compared to its T4 value making one think that there is a little resistance to T4 activity in the fetus. That is not a hard fact phenomenon. Nevertheless, the fetus does tend to have a slightly higher TSH value. There is a sudden TSH surge at birth. It is starts dropping again within a few hours and by the end of the first day it is pretty much back to the normal zone. As a result of this TSH surge there is a sudden outpouring of both T4 and T3 in the fetus circulation.

This is a physiologic phenomenon, and we have to take that into account, and I’ll mention that a little bit down the road when we are talking about the complications.

Now let’s look at what are the abnormal condition? Probably one of the most common ones you are going to encounter of the thyroid condition is hyperthyroidism. It is mostly due to Graves disease and trophoblastic disease because of the excessive hCG. You can get enough TSH like activity to produce hyperthyroidism. We may see it as a phenomenon of auto-immune thyroiditis, but this largely occurs in the postpartum period. You can have an autonomous adenoma of the thyroid which independently secretes excess thyroxin. Let’s not forget the fact that it is always possible for the patient to be had been placed on T4 and take excessive amounts or to in fact take it, and we would have factitial hyperthyroidism. If a woman has Graves disease it is usually she has that first and then the pregnancy ensues. A woman who is an uncontrolled hyperthyroid there is very much reduced fertility, so she is very much less likely to get pregnant than normal. The incidence of hyperthyroidism in pregnancy has been estimated to be well under 1%. It is not a common phenomenon but on the other hand all of you QB see a lot of pregnancies, so you may very well encounter such a situation. It produces the usual signs and symptoms: tremor, nervousness, anxiety, jitters, doesn’t gain weight as you would expect in pregnancy and so forth. One of the things we have to rule out is that in patient who develop hyperemesis that there is a euthyroid hyperthyroxinemia. In other words, you measure the patient, she is vomiting and you are concerned about her general activity. You happen to get a free thyroxin index total T4 and low and behold you find out that the thyroxin is inappropriate high for that stage of pregnancy. It turns out that most of these are not truly hyperthyroid. How do we distinguish it? it may be very difficult and in doubt if you don’t have a clear cut evidence of it being a euthyroid hyperthyroxin, it is not inappropriate to begin treatment with an anti-thyroid drug and see how the patient goes until the hyperemesis disappears and then see what you are left with. It is either a true hyperthyroid or the other state. As I mentioned in the hyperemesis it is largely a biochemical event, and the patient does not have the clinical signs of the euthyroid hyperthyroxin. She does not have the clinical signs of Graves disease. she doesn’t have the goiter. She doesn’t have the tremor. There is usually no prior history. I think in general we can think of this as euthyroid hyperthyroxinemia.

It has been called gestational thyrotoxicosis. It is thought that if it is this condition and due to the hyperemesis that the zinc levels in the red cells are normal. If it is truly hyperthyroidism Graves type of disease that the zinc levels are low. There has been no absolute chemical way to be certain, and you have to look at the patient in to and follow the patient. When in doubt its worthwhile treating with anti-thyroid drugs. Graves disease being an autoimmune disease may be aggravated in the early parts of pregnancy but typically as immune suppression occurs with the pregnancy Graves disease improves. Postpartum the patient may remain in a permanent remission or in fact may rebound and get toxic all over again. What are the function tests you expect in a toxic patient? The T4 will be elevated but even more levated. T3 is usually way over 250. The resin uptake is inappropriately high for that stage of pregnancy. The index is in the abnormal range. TSH is suppressed. If left untreated, and it should not be left untreated, it is possible to have
Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Hyperthyroid</th>
<th>Euthyroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>&gt;20</td>
<td>9-20 µg/dL</td>
</tr>
<tr>
<td>T3</td>
<td>&gt;250</td>
<td>105-240 ng/dL</td>
</tr>
<tr>
<td>RT₃U</td>
<td>&gt;25</td>
<td>18-25 %</td>
</tr>
<tr>
<td>FTI</td>
<td>&gt;4.3</td>
<td>1.2-4.3</td>
</tr>
<tr>
<td>TSH</td>
<td>&lt;0.5</td>
<td>0.5-5 µU/mL</td>
</tr>
</tbody>
</table>

D. Maternal complications of untreated thyrotoxic pregnancy

1. Pregnancy-induced hypertension
2. Congestive heart failure
3. Thyroid storm with labor
4. Increased abortion rate (30-50 %)
5. Premature labor
6. Stillbirth or neonatal death
7. Low birth weight (LBW) baby
8. Slight increase in frequency of fetal abnormalities

E. Management of uncomplicated hyperthyroid pregnancy

1. Thioamide drugs
   a. PTU drug of choice (methimazole may increase risk of aplasia cutis; placental transfer of PTU only 25 % of that of methimazole)
   b. Concomitant T₄ or T₃ treatment does not prevent fetal complications of excess thioamide dosage (goiter, subclinical or overt hypothyroidism)

hypertension, premature labor, increased abortion, and thyroid storm especially with labor may occur.

How do we treat the patient? The drug of choice is PTU. Tapazole or methimazole has been considered. It has been advised not to use Tapazole because there was some concern that it caused fetal scalp defects. If you overdose do tend to get a fetal goiter and hyperthyroidism. Start with a good dose to bring the mother under control and then as fast as possible after you pretty well controlled her then start tapering back so that you bring the mother to term with the lowest anti-thyroid drug dose that is possible. Typically most women with Graves disease can come to term with doses of past 150 mg a day. At that dose, you are not likely to have any problems with the fetus nor with the mother.

Beta-blockers are relatively contraindicated but not absolutely so that in the early stages of bringing this woman under control it is perfectly okay to give some Popranolol. I like to use Popranolol because it is short acting, so you can manipulate it up and down. If you use the longer acting ones you may want to back off it. If you bring the woman to term without any Popranolol in the situation, then you don’t have any problems with the fetus. Even if it is necessary it is possible to bring the woman to term on Popranolol and not have a significant fetal problem. You have to watch them closely. They may tend to have lower Apgar scores. We tend to avoid iodide. Some infants are quite sensitive to iodide, and they can really quickly produce a goiter.

Surgery as a form of treatment is undesirable. First of all, you are not going to operate on anyone who is in control. You have to control the hyperthyroidism. When you encounter the woman in the first trimester, and she is toxic it is going to take a couple of months to bring under good type control and get the dose properly adjusted. By that time you are pretty late in pregnancy, and I don’t see any advantage to operating in a woman. It is perfectly proper to carry the woman to term on anti-thyroid drugs. It can be done. it has been done. But I prefer to avoid thyroid surgery. Radioiodine is an absolute contraindication because even before the fetal thyroid is formed you are going to be radiated the developing fetus and secondly after 12 weeks the iodide you give the mother will get to the fetus, and you’ll have a hyperthyroid fetus.

Titrade the PTU to lowest dose. Maintain the index to within the normal limits and maintain the TSH within the normal range. It is probably worthwhile to follow the TSH levels at least once after you think you’ve reached euthyroidism to be sure that you are in the appropriate zone. Ideally you can even do it twice every couple of months to be sure that you are staying within the normal zone. In a patient who you are treating for Graves disease it is worth while at 30 weeks to check for the levels of these thyroid receptor antibodies. If the stimulating antibodies are very high it is possible that the fetus is going to have neonatal hyperthyroidism. If the blocking antibodies, thyroxin binding inhibitory, the blocking antibodies are very high it is possible that may cross the placenta, and you will get neonatal hypothyroidism. You want to look at that. A patient who has previously had Graves disease you think she is cured and now she gets pregnant, I think it is worthwhile to repeat this course at 30 weeks, but it probably worthwhile to check thyroid function earlier at 12 weeks to make sure that she doesn’t have signs of having relapse with her pregnancy. If there is a recurrence you want to restart you anti-thyroid drugs. If the woman seems hyperthyroid you are going to start thyroxin, then you get the antibodies as I indicated. If the stimulating antibodies are extremely high you can anticipate one the pediatrician about neonatal hyperthyroidism, but if it is very high some people have advised starting the mother on PTU deliberately to get the fetus treated with PTU so that the fetus does not have neonatal hyperthyroidism. If the blocking antibodies are very high, you may want to consider that the fetus is hypothyroid and start treatment.

The reason why I suggested you always treat your hyperthyroid pregnant women and get them under control is the risk that at term you can precipitate a thyroid storm. It is more likely to occur the more uncontrolled the hyperthyroidism is. What we do is give supportive therapy, but the specific therapy is to give high amounts of beta-blockers to cut many of the peripheral
c. Typical PTU doses
   (1) Start: 300 mg/day
   (2) At term: 50-150 mg/day
d. Use lowest dose possible; keep maternal thyroid function indices near top of normal range

2. Propranolol and other β-blockers
   a. Avoid entirely or use only until T₄ levels normalized
   b. Fetal complications of drugs
      (1) Lower Apgar scores
      (2) Intrauterine growth retardation (IUGR)
      (3) Postnatal bradycardia and hypoglycemia
      (4) Possibly teratogenic (3-4 cases in literature)

3. Iodides: relative contraindication because of fetal goiter and hypothyroidism
4. Radioiodine: absolute contraindication
5. Surgery: undesirable, but feasible

F. Management of pregnancy in treated, prior hyperthyroidism
   1. Obtain RT₃, U, T₄, FTI, and TSH in third and seventh months
   2. Mother should be euthyroid at term
      a. If recurrent hyperthyroidism, treat with PTU
      b. If post-therapeutic hypothyroidism, treat with thyroxine (titrate dose vs TSH level)
   3. Obtain TSI and TBH in seventh month
      a. Alert pediatrician to neonatal hyperthyroidism if TSI greater than 130%
      b. Consider prophylactic, low-dose PTU during last trimester if TSI unusually high (greater than 500%)
      c. Alert pediatrician to neonatal hypothyroidism if TBH greater than 10%

G. Management of threatened or overt thyroid storm
   1. Prevent by early recognition and adequate treatment of hyperthyroidism
   2. Occurs rarely; highest risk at delivery
   3. High fetal wastage
   4. Steroids, iodides, and sympatholytic drugs

H. Fetal and neonatal problems in maternal hyperthyroidism
   1. Prematurity and IUGR
   2. Goiter due to iodide or thioamide treatment (iodide goiters larger than thioamide goiters): may be detectable by ultrasound and treated by intra-amniotic injection of T₄ (250 ug once a week x 3 weeks or 500 µg/q 2 weeks to term)
   3. Fetal hyperthyroidism
      a. Pulmonary hypertension

In the nursing mother, PTU has relatively limited transfer to milk, so it is probably safe to keep it up if it is absolutely necessary. Tapazol has a higher degree of transfer. Radioiodine is obviously contraindicated. There is a high degree of transfer into the milk and on top of it when the mother is nursing the baby she is going to be radiating him. Wait until the mother no longer is nursing the baby to give her definitive therapy with radioiodine. Before that, if the woman is not nursing, it is perfectly okay to give PTU or Tapazol and beta-blockers and keep her under control until she is no longer handling the baby regularly at which time you can give her definitive therapy.

Trophoblastic hyperthyroidism. It occurs mainly with carcinoma. It is due to the enormous levels of hCG. The patient may have overt thyroid toxicosis or relatively few clinical signs. The thyroid function tests including the radioactive iodine test are quite high because the thyroid is being stimulated. The therapy is to treat the mole but also to step in with anti-thyroid drugs. I have treated a patient very successfully with radioiodine. The gynecologist was treating the trophoblastic tumor we were bringing the patient under control. One of the problems that we see in the range of 5-9% of all pregnancies with some geographic problems. We see more of this in the Great Lakes area than we do in the East. There is more of it in Asia then there is in the United States. Some countries you see it very rarely. That is the problem of postpartum thyroiditis. It seems to be due to the fact that during pregnancy there is an immunosuppression when the woman delivers she gets a rebound. These patients with these conditions tend to show high perimeters of anti-microsomal antibodies. They may follow certain HLA serotypes, but it is of interest that a fair number may recur with the next pregnancy.

The postpartum thyroid toxicosis occurs in the first three months postpartum. Typical signs and symptoms are goiter and the whole works. They have high functional levels, but the TSH is suppressed. Notice this that the radioiodine uptake is suppressed. In Graves disease you have a patient who has thyroid hyperfunction but if you do a radioiodine uptake it is difficult because the antibodies are stimulating thyroid uptake. In this type of disease this is due to the dumping of thyroxin stores from the thyroid. It is an inflammatory process which causes a thyroxin leak from the thyroid. As a result the patient becomes toxic. As a result of that, that shuts off TSH. There is no abnormal stimulating antibody to cause uptake so as a result the radioiodine uptake falls to zero. If you see a patient who doesn’t have eye signs and she is postpartum she may be getting Graves disease as a new one. The way to distinguish it is to measure her 24 hour radioiodine uptake. In a new Graves disease appearing for the first time postpartum she will have a high uptake. In this postpartum thyroid toxicosis syndrome she will have a suppressed uptake because the thyroid has dumped it. it is a self limited disease. There is no point in treating it. There is no point in treating it with radioiodine. There is no point in treating it with PTU because she has already dumped the stores. What you do is treat her with sympathetic therapy by using the beta-blockers to control manifestations until the self-limited process burns itself off. It may recur with subsequent pregnancies, and it may be followed with hypothyroidism. The typical signs of hypothyroidism are high TSH and other types of antibodies. You put the patient on a thyroxine to keep them eumetabolic. At about three or four months after you’ve begun therapy it is wise to back off on your thyroxine replacement therapy to see if the disease has regressed on its own. If it hasn’t and the patient doesn’t become symptomatic, stop the thyroxine and watch what happens. If when you cut back your thyroxine the patients gets hypothyroid symptoms again, then you know that she has a permanent hypothyroidism, so bring the dose back up to where you need to. There are some patients with hypothyroidism who can get pregnant. On occasion it will be posttherapeutic. Sometimes it will be congenital. When these patients become hyperthyroid they have very much a reduced fertility.
b. Visceromegaly
c. Thyromegaly
d. Advanced bone age
e. Craniosynostosis
f. All detectable by ultrasound

4. Neonatal hyperthyroidism
   a. Typically associated with Graves’ disease only (one out of 70)
   b. Due to transplacental passage of TSI
c. Self-limited, disappears along with maternal IgG
d. LBW, accelerated maturity, 25-50% mortality
e. Onset: day 1-10 (masking by PTU)
f. Treat with antithyroid drugs
g. Differential diagnosis: congenital TBG excess (X-linked inheritance), very rarely genetic mutation with activation of TSH receptor

5. Intrauterine and neonatal hypothyroidism
   a. Iodide, PTU, inadvertent RAI; transplacental TBH in 1/180,000 births; Spontaneous: 1/4,000
   b. Prenatal diagnosis: low amniotic rT3, high amniotic TSH; low fetal T4 and high TSH by umbilical vein sampling (cordocentesis)
c. Cord blood: T4 less than 11, TSH greater than 50; confirm by heel-stick filter paper spot for T4 at 2-5 days; if suspicious, measure TSH (maternal factor may interfere with assay)
d. Clinical signs unapparent at birth: normal size and brain function at birth (transplacental passage of low doses T4, plus enhanced conversion of T4 to T3 in brain by 5’deiodinase ID)
e. Increased respiratory distress syndrome; retarded skeletal and CNS development; intra-amniotic T4 treatment increases lung maturity
f. T4 in milk may mask signs, but not adequate for treatment
g. Early postnatal treatment prevents overt mental retardation in term babies (recommended dose: 10-15/mcg/kg/day), but not in premature <30 wks gestational age

I. Postpartum management of hyperthyroid mother
   1. Nursing is contraindicated if mother is taking methimazole; nursing is allowable if taking PTU since it has only limited transfer to milk (10% of serum level)
   2. RAI therapy results in significant radiation at neck for 1-2 weeks (up to 28% of dose into milk in first 48 hours)
3. Iodides contraindicated in nursing mothers (neonatal hypothyroidism)

J. Hyperthyroidism due to trophoblastic disease
1. Etiology
   a. Mole: 90-92%
   b. Choriocarcinoma: 8-10%
2. Pathogenesis: very high titers hCG (usually > 100,000U) stimulate thyroid (only certain isoforms may activate TSH receptor)
3. Findings
   a. Minimal to overt clinical toxicosis
   b. Significant sized goiter
   c. Lab diagnostic: very high T4 T3; high RAI
4. Treatment
   a. Evacuate mole: response rapid
   b. Chemotherapy for choriocarcinoma
   c. And thyroid treatment, including RAI if necessary
   d. Storm precautions

IV. Postpartum Thyroiditis (PPT) Syndromes
A. Etiology
   1. Probably autoimmune
   2. Rebound of antithyroid antibodies (following suppression during pregnancy by cytokines elaborated by fetal suppressor T cells)
B. Incidence: approximately 5% of pregnancies, but 25% of type 1 diabetes pregnancies
C. Pathology: goiter with lymphocytic thyroiditis
D. Postpartum thyrotoxicosis
   1. Onset: 4-6 weeks postpartum
   2. Self-limited in weeks to 3 months
   3. Typical clinical symptoms and signs
   4. Painless goiter
   5. High T₄, T₃, but suppressed RAIU and TSH; often high antimicrosomal antibody (TMAb) and antithyroglobulin antibody (TgAb)
   6. Symptomatic treatment only (B-blockers)
   7. Followed by hypothyroid phase, then return to euthyroidism
   8. May recur one or more times with subsequent pregnancies
   9. Geographic clustering: Great Lakes region, Japan
E. Postpartum hypothyroidism
   1. Onset between 3-6 months postpartum, lasts 3-6 months
   2. May follow transient thyrotoxic phase (above) or occur separately
3. Typical symptoms and signs of hypothyroidism

4. Low $T_4$, $T_3$, RAI uptake; high TSH; often high TMAb, TgAb

5. Spontaneous clinical remission, with regression of lymphocytic infiltrate

6. Treat with levo-thyroxine as long as necessary; permanent hypothyroidism in 25%, some after an interval of euthyroidism

V. Hypothyroidism and Pregnancy

A. Etiologies
   1. Chronic lymphocytic thyroiditis (Hashimoto)
   2. Idiopathic primary hypothyroidism
   3. Post-therapeutic (RAI or re section)
   4. Goitrous

B. Incidence of pregnant hypothyroids
   1. Extremely low
   2. Most have antecedent disease
   3. Markedly reduced fertility in untreated hypothyroidism

C. Maternal manifestations
   1. Usual clinical symptoms and signs
   2. Laboratory
      a. Low RT3U in first trimester
      b. Inappropriately low $T_4$ and $T_3$ for stage of pregnancy
      c. High TSH, low FTI
   3. Increased abortion and stillbirth rate
   4. Hashimoto's may have spontaneous remission during pregnancy, with recurrence postpartum

D. Treatment: levo-thyroxine
   1. Requirement for replacement $T_4$ in women with treated antecedent hypothyroidism usually increases 25-50% during pregnancy for unknown reasons (recognized by increasing TSH levels)
   2. Maintain $T_4$ levels typical for pregnancy
   3. Titrate dose against TSH level; assess level each trimester
   4. Ferrous sulfate interferes with thyroxine absorption. Separate by two or more hours

E. Fetal problems
   1. Increased incidence of congenital anomalies
   2. No increase in incidence of cretinism
   3. No problems related to thyroid hormone economy

VI. Other thyroid problems in pregnancy

A. Benign nodules
   1. Unusual to rare in pregnancy
   2. Usual pathology: follicular, colloid adenoma, etc
3. Normal thyroid function for pregnancy
4. Do not scan with radioactive isotopes
5. Fine needle aspiration cytology desirable
6. Ultrasound to assess solid vs cystic, size changes
7. Levo-thyroxine for suppression until term
8. If nursing infant, maintain normal T4 levels in mother
9. Definitive treatment when not pregnant, not nursing

B. Thyroid carcinoma
1. Very rare with pregnancy
2. Most patients elect to be aborted
3. Normal thyroid function in most throughout pregnancy
4. Levo-thyroxine for suppression until term
5. Definitive treatment when aborted or delivered
6. No special fetal problems
7. Pregnancy subsequent to diagnosis does not affect course of malignancy