Preeclampsia (and Subsequent Pregnancy) and Periodic Paralysis
By Richard Braun, MD
Vice President & Chief Medical Officer

One of my favorite aspects of being a Medical Director is that we are frequently presented with medical cases having conditions that are rare or unique and which, therefore, rarely pass over a medical director’s desk. Such cases allow us to research and apply the art of insurance medicine: taking the scientific research and clinical experience and applying it to a novel situation. Whenever possible, we like to share the results of this research with our colleagues in the underwriting profession.

Our case studies derive from actual cases that are forwarded to us for opinion through the facultative process, with slight modifications to protect confidentiality. And we appreciate the opportunity to quote on the unique cases presented. While the conditions we discuss may be rare or unusual, they do not necessarily represent adverse mortality outcomes. Some conditions “sound bad” but can have an excellent long-term prognosis. In addition to cases we also see a number of ECG abnormalities. To improve everyone’s ECG skills, Dr. Rooney devised the ECG Puzzler, which was so popular internally that we thought our client underwriters might enjoy them as well.

This issue presents two cases where the answer to the question “Does this condition adversely affect mortality?” may not be what one originally anticipates. The discussions highlight the basics about the conditions and the favorable or adverse factors that will help the underwriter determine the appropriate outcome.

In the first case Dr. Rooney examines an applicant with a history of preeclampsia and how this manifestation may affect the applicant’s mortality, especially given other circumstances at the time of application. Following Dr. Rooney’s discussion, I look briefly at an applicant affected by periodic paralysis. And at the end of this issue, Dr. Rooney presents his latest installment of “Underwriting Puzzlers.”

Our marketing department once asked, “Will you ever run out of cases and topics to write about?” With hundreds of thousands of medical research articles published each year, new diseases (MERS), and new molecular causes for existing disease being discovered constantly, I am confident that we will have plenty of case material. We hope that you find this issue interesting, and as always we welcome your feedback.
Our Casebook
By William Rooney, MD, FAAFP, EMBA

Dr. William (Bill) Rooney is Vice President, Medical Director at SCOR Global Life Americas. Dr. Rooney’s responsibilities include facultative case review work, researching and updating SOLEM, researching and writing articles for a variety of SCOR publications and more. He earned a Medical Degree from the University of Missouri – KC (1981) & an Executive Master’s in Business Administration from Benedictine College in Atchison, Kansas (2009). He is board certified in Family Medicine with the American Board of Family Medicine.

Case #1 – Preeclampsia and Subsequent Pregnancy

A 26 year-old female is applying for $1 million of life insurance. She is G2P1 (2 pregnancies, 1 birth) who is currently 16 weeks pregnant. Notes reflect that she had severe, early preeclampsia with her first pregnancy and had a preterm caesarian section delivery at 34 weeks. The records from the first pregnancy were not submitted. There is no history of gestational diabetes. There is no history of abnormal BP values other than with the previous pregnancy. Her current BP is normal, her urinalysis shows no proteinuria and she is being followed closely by her obstetrical team.

Questions
3 major questions arise when evaluating a case like this for mortality risk.

1. What is the risk of recurrent preeclampsia with this pregnancy?
2. What is the peripartum mortality concern when preeclampsia is present?
3. Are there any long-term mortality concerns for those with a history of preeclampsia?

Answer
First, let’s briefly review a few facts about preeclampsia.

Preeclampsia
- New onset of hypertension with either proteinuria or end-of-organ dysfunction
- Leading cause of maternal morbidity and mortality
- Incidence has increased by 25% in the US in the past 20 years

Figure 1 – Estimated Odds Ratios of Severe Obstetric Complications for Delivery Hospitalizations with Hypertensive Disorders vs. Deliveries without Hypertensive Disorders, 1998-2006

<table>
<thead>
<tr>
<th>Estimated Odds Ratio (N=36,597,061, 95% Confidence Interval)*</th>
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<tbody>
<tr>
<td>Eclampsia/Preeclampsia</td>
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ARDS: adult respiratory syndrome; PCD: perpetual cerebrovascular disorder; DICS: disseminated intravascular coagulation syndrome

*Adjusted for multiple birth, diabetes, preterm labor, chronic condition, year of study, maternal age, payer, hospital location, hospital teaching status, hospital region and mode of delivery.

**Includes eclampsia and severe preeclampsia, mild preeclampsia, chronic hypertension and gestational hypertension in hierarchical order; all groups mutually exclusive.

Preeclampsia refers to the new onset of hypertension with either proteinuria or end-of-organ dysfunction after 20 weeks of gestation in a woman previously normotensive. End-organ dysfunction can manifest itself in the following ways:

- Pulmonary edema
- Serum creatinine >1.1 mg/dl or doubling of serum creatinine in the absence of other renal disease
- Platelet count < 100,000/microliter
- > than 2 times elevation of liver transaminases
- Cerebral or visual symptoms

Preeclampsia is the leading cause of maternal morbidity and mortality. The incidence of preeclampsia has increased by 25% in the United States during the last two decades. The etiology of the condition is unclear at this time.

Eclampsia refers to the development of grand mal seizures in a woman with preeclampsia, when no other neurological condition could account for the seizure. Besides eclampsia, preeclampsia is associated with increased incidence of acute renal failure, cerebral hemorrhage, hepatic failure, placental abruption, disseminated intravascular coagulation and pulmonary edema.

Preeclampsia is typically classified as either mild or severe as recommended by the American College of Obstetricians and Gynecologists.

Preeclampsia is considered severe if any of the following findings are present:

- Systolic BP 160 mm Hg or higher, or Diastolic BP 110 mm Hg or higher on two occasions while on bed rest for at least 4 hours
- Platelet count < 100,000/microliter
- Pulmonary edema
- Impaired liver function manifested by either of the following:
  a. Abnormally elevated liver function tests (LFTs) to 2x normal
  b. Severe persistent Right Upper Quadrant or epigastric abdominal pain not explained by an alternative diagnosis
- New-onset cerebral or visual disturbances

Preeclampsia is felt to be present in about 7.5 percent of the pregnancies in the United States. It is believed to account for 1 maternal death per 100,000 live births and 6.4 deaths per 10,000 cases of preeclampsia. The following table shows the mortality and morbidity concerns in one large study published by the American College of Obstetricians and Gynecologists in 2009 (Figure 1).

**Treatment**

Treatment of preeclampsia depends on the manifestations of the disorder, the severity of the findings, the stability of the fetal and maternal condition and the fetal viability. Delivery of the baby is the definitive treatment, particularly for those pregnancies at $\geq$ 37 weeks of gestation. In pregnancies with less than 37 weeks of gestation, delivery is still performed frequently if there is evidence of serious maternal end-organ dysfunction or non-reassuring tests of fetal viability. Frequently utilized treatments include: anti-hypertensives for severe hypertension, careful monitoring of fluid administration and seizure prophylaxis – typically in the form of magnesium sulfate.

Risk of preeclampsia increases in women who have had a previous pregnancy complicated by preeclampsia, as in the case presented. This is particularly true if the condition was previously severe and of early onset. The risk of recurrence is felt to be about 5-7 percent of women with a history of non-severe preeclampsia but the incidence rises to 25-65 percent for those with early onset, severe preeclampsia. Recurrence is also more common following a preeclamptic singleton pregnancy versus a preeclamptic twin pregnancy. Figure 2 illustrates the risk.
In addition, there are significant long term mortality concerns for those women who have suffered with preeclampsia. These include cardiovascular, end-stage renal and diabetes mellitus disorder related complications.

The risk of later life cardiovascular (CV) disease is significant. In 2011, the American Heart Association added preeclampsia to its list of risk factors for CV disease. Many feel that if there is a history of recurrent preeclampsia, preterm birth from preeclampsia, or there was fetal growth restriction with a previous preeclamptic pregnancy, the CV risk is approximately equal to the CV risk from obesity or smoking. These women are at increased risk of hypertension and CV disease including myocardial infarction, stroke and congestive heart failure. The risk increases with the severity of the preeclampsia as documented in Figure 3.

The risk for end-stage renal disease (ESRD) later in life is also significant in women with preeclampsia. One large study found that there was a four-fold increase in the development of ESRD in those women who had preeclampsia with their first pregnancy (Vikse, BE, et al. “Preeclampsia and the risk of end-stage renal disease.” NEJM. 2008; 359 (8):800).

There was a two-fold increase in the risk of developing diabetes mellitus for those women having preeclampsia in the absence of gestational diabetes mellitus in a study involving over one million women followed for 16.5 years (Feig, DS et al. “Preeclampsia as a risk factor for diabetes: a population-based cohort study.” PLOS Collections. 2013 April 16; 10.1371/journal.pmed. 1001425.). This is exemplified in Figure 4, from that article.

Returning to the Case
In this particular case, the history of severe, early preeclampsia resulting in a preterm delivery presumes an increased risk of developing preeclampsia again in this current pregnancy. The preeclampsia would carry some increased risk for mortality during this pregnancy. In addition, there are some long term mortality concerns as well. These increased mortality concerns relate to cardiovascular disease, end-stage renal disease as well as development of diabetes mellitus with its associated morbidity and mortality.
Case 2 – Periodic Paralysis

By Richard Braun, MD

Dr. Braun is Vice President & Chief Medical Officer for SCOR Global Life Americas. He received a Bachelor of Science Degree from the Towson State University (1975) and earned his Medical Degree from the University of Maryland (1979). Dr. Braun is board certified in Internal Medicine, Insurance Medicine and is a past President of the American Academy of Insurance Medicine.

A 29 year-old man applied for life insurance. 2.5 years prior to the application he reported an episode of lower extremity weakness and inability to walk which resolved over a period of several days. He lost 40 pounds, and did well until 10 months prior to application. At that time he again developed weakness and was taken to the emergency room. His serum potassium was found to be 2.1 (3.5-5.5 mEq/L). He was given potassium supplements and discharged. Two months later he had another episode of weakness and “collapse” and was diagnosed with thyrotoxicosis and periodic paralysis. His serum potassium level was normal at that time. He had another episode of “shakes, palpitations, fatigue and heat intolerance” about a month later. The last records from two months prior to application showed he was prescribed a potassium supplement and had a normal serum potassium, a TSH of .01 (0.4-4.5 mIU/L) and a T4 of 0.8 (0.8-1.8 mg/dl).

What are the mortality implications of the diagnosis?

Periodic paralyses (PP) are a heterogeneous group of disorders, of which thyrotoxic periodic paralysis is a specific entity. Typically, they present as irregular episodes of flaccid muscle weakness, and most are associated with alterations in serum potassium levels. Many are inherited either as an autosomal dominant pattern with variable penetrance or as a sporadic point mutation. They can also be categorized as hypokalemic, hyperkalemic and paramyotonic forms. In general, these genetic alterations affect the ion channels in the cell membranes of muscle cells. The ion channels move potassium and other ions into or out of cells, and the defective channels cause the muscle cells to become depolarized and unable to contract. Cranial musculature and respiratory muscles are often spared. One form of periodic paralysis, Anderson-Tawil Syndrome, is also associated with prolonged QT syndrome and significant arrhythmias of the heart, fainting and sudden death.

Thyrotoxic periodic paralysis (TPP) is the most common type of secondary, hypokalemic PP. 85 percent of cases occur in males. TPP occurs most often in males of Chinese, Japanese, Vietnamese, Filipino, Korean or Thai descent, although it has been reported in 0.1-0.2% of those with hyperthyroidism in the US. The typical age at onset is between 20 & 40. Triggering factors such as salt or carbohydrate loading, exercise, fatigue and hyperinsulinemia have been reported. An episode often begins with cramping, stiffness and muscle pain. The weakness is usually proximal and symmetric and typically starts in the legs and moves to the arms. A flaccid paralysis and hypoactive reflexes are seen during attacks. The attacks last from hours to days and often resolve spontaneously. Often, low serum potassium is observed during episodes of weakness. Typically, strength returns to normal between episodes, but fixed muscle weakness may develop over time. Changes of hypokalemia (QT prolongation, QRS widening, U waves and flattened T waves) can be seen on the electrocardiogram. Physical signs
of thyrotoxicosis may also be observed: rapid pulse, perspiration, enlarged or tender thyroid, exophthalmos, etc. The combination of low serum potassium during an attack and low Thyroid Stimulating Hormone (TSH) combined with elevated thyroid hormone levels is sufficient to make the diagnosis of TPP.

Treatment of TPP consists of potassium supplementation during an episode (with caution as the total body potassium may be normal, and rebound hyperkalemia may occur as potassium moves out of cells). The symptoms of thyrotoxicosis can be controlled with beta-blockers. And this can be followed by definitive treatment of the hyperthyroidism with antithyroid drugs, surgery or radioactive iodine.

The treatment of the thyroid disease almost always results in the resolution of the episodes of paralysis.

Returning to the Case
Given the information above, there is slight mortality risk associated with TPP during the episode due to potential paralysis of respiratory muscles or arrhythmias related to hypokalemia. There was no indication in the current case that the thyroid disease was being treated. But after the thyroid disease is treated and stability is established, the extra mortality risk should be minimal.

References


Underwriting Puzzler...
By William Rooney, MD, FAAFP, EMBA

In February’s issue we presented a case involving a 31-year-old male applying for life insurance. The applicant had disclosed undergoing a “Mustard Procedure” as a child. The ECG for the applicant is reposted below.
The ECG reveals RVH, which could have serious mortality impacts. For a full discussion of this ECG and the Mustard Procedure, please visit http://www.scorgloballifeamericas.com/Publications/Pages/Housecalls.aspx and click on Underwriting Puzzler Answer 2/15/14.

**Now for this Installment of the Puzzler**

For this issue, we present an ECG recently received by a direct writer. What abnormalities, if any, are present? And how would you assess this applicant’s risk?

Feel free to try your hand at assessing this ECG. Once you have your determinations visit http://www.scorgloballifeamericas.com/Publications/Pages/Housecalls.aspx and click on Underwriting Puzzler Answer 6/25/14 to compare your answer to our assessment.

If you have any questions please feel free to contact me at brooney@scor.com.
## Medical and Underwriting Contacts

Have a question for our underwriters or medical directors? Below are key contacts in our medical and underwriting departments.

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