

A primer on pituitary injury for the reproductive endocrinologist: a proper differential diagnosis can be developed and the resultant mechanism diagnosed

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Sheehan's Syndrome

Sheehan's syndrome was first described in 1937 [1]. Owing to the hormonal requirements of pregnancy and the post partum state the pituitary gland undergoes hypertrophy and is more susceptible to injury. The pituitary gland is supplied with blood from the circle of Willis; a vascular anastomosis caused by the confluence of the end-vessels of the right and left anterior middle and posterior cerebral arteries. This gland is also supplied internally by the superior and inferior hypophyseal arteries which are branches off the internal carotid. When a massive peri partum or post partum haemorrhage occurs, flow to these vessels is severely diminished and may lead to partial or complete infarction of the pituitary gland. Since the end vessels are supplying the circle of Willis this region is most at risk from the resultant hypotension. The damage of the gland may be further aggravated by a compensatory vasospasm or resultant thrombosis of these arteries [2, 3]. However, thrombosis seems less likely due to the many vessels supplying the circle of Willis. Other causes of pituitary failure in pregnancy include severe head injury, subarachnoid haemorrhage, heart diseases, and massive stroke [3], all inducing severe hypotension. Non obstetrical causes of hypotension can also lead to a Sheehan's like presentation including, severe non-obstetric bleeding, liver disease and acute haemorrhagic fever [4-8]. In the developed world, the prevalence of Sheehan's syndrome has decreased significantly due to blood, volume expander and crystalloid transfusions. However, in developing countries where hospital care may be rarer and people have a tendency to deliver at home, Sheehan's seems to remain a persistent problem. In Kashmir, India, where most women deliver at home. a study found that 3.1 % of all women had Sheehan's syndrome [9]. A Turkish study suggested that among 338 women studied with hypo pituitarism 28% had Sheehan's syndrome. This study found Sheehan's syndrome to be the second most common cause of pituitary dysfunction among women evaluated [10]. The diagnosis of Sheehan's syndrome is often missed with one study from the developed world finding that the average delay of diagnosis was slightly more than 9 years [11]. Sheehan's syndrome can have a variable presentation. Injury to the pituitary gland can result in pan hypopituitarism or may be partial, and very much depends on the quantity and location

of the glandular injury. Occasionally the patient presents with diabetes insipidus within a few days of the haemorrhage, and the important diagnostic symptoms are polyuria and polydipsia. In the case of pan hypopituitarism the immediate life threatening condition is hypocortisolism, with severe hypothyroidism being a delayed issue. In adults lack of growth hormone production fails to present with symptoms. Hypo prolactinemia will present with an inability to breast feed due to lack of lactation. Hypo gonadotropic hypogonadism will present with prolonged amenorrhea. Common symptoms include post-partum marked sensitivity to cold, mental apathy, physical weakness, somnolence, nausea, anorexia, and anaemia [12]. Sheehan's syndrome may present with rare signs and symptoms, such as hypoglycemia, hypernatremia, anaemia, pancytopenia, bradychardia, diabetes insipidus, headache, and loss of consciousness [12].

Simmond's disease

Simmond's disease is caused by pituitary injury due to severe haemorrhage in a non pregnancy state. Simmonds disease is rarer than Sheehan's syndrome, which is most likely due to a smaller pituitary gland when women are not pregnant so that it is not so susceptible to blood flow variations. This smaller gland has less hormonal requirements because of its non-pregnancy state and, as a result, it has increased tolerance to temporarily impaired blood flow. A recent study of people with severe traumas including head injury found that the prevalence of major

anterior pituitary failure was 57% [13]. While in this series the occurrence of growth hormone deficiency was 40%, making it the most common hormone to be affected in Simmond's disease [13]. FSH and LH deficiency was 23%, TSH deficiency was 17% and ACTH deficiency occurred in 10% of subjects [13]. It has often been felt that Simmond's disease may be overlooked because growth hormone seems to be the most common hormone affected and it will have little clinical implications in adults. Therefore, due to its lack of symptoms, diagnosis often is missed. Never the less, failure of menstrual cyclicity after a non obstetrical trauma with blood loss should lead to an investigation for hypogonadotropism or other pituitary insufficiencies.

Dahan's Syndrome

Dahan's syndrome is pituitary injury due to severe vasospasm, without significant haemorrhage [14]. The initial case presented in a woman with severe pre-eclampsia who was given bromocriptin to arrest lactation due to an intra uterine foetal demise [14]. The women had minimal blood loss, and did not have a pituitary adenoma. Both pre-eclampsia and bromocriptin have been noted to induce vasospasm and whether the syndrome was due to one of these causes or a combination of both remains unknown. Although felt not to occur due to the protective effect of multiple arteries supplying blood to the pituitary gland, it makes intuitive sense that since the end arteries provide flow to this gland and severe hypotension can induce pituitary injury, it stands to reason that severe vasospasm may also injure the gland. In this case the patient presented with dysfunction in FSH, LH, prolactin, growth hormone and ACTH release. TSH release was normal [14]. The prevalence of this syndrome remains unknown since up until recently it was felt not to occur and may have been previously overlooked. It also remains unknown as to whether Dahan's syndrome occur in non pre-partum states when the gland is less at risk to injury.

Pituitary Apoplexy

Pituitary apoplexy is infarction of a pituitary adenoma and intra-mass haemorrhage with result injury to hormone production by the gland. Recognized mechanisms of induction include overgrowth of the masses blood supply and spontaneous necrosis causing haemorrhage and infarction, or rupture of an intra-adenoma aneurism [15, 16]. It has been postulated that pituitary

macro adenomas have a high metabolic rate, poor blood flow and are susceptible to hypoglycemia which predisposed them to spontaneous infarction [16]. The intra-mass haemorrhage results in enlargement of the mass which compresses adjacent structures. Pituitary apoplexy typically presents as an acute episode of head ache, visual disturbance, cranial nerve palsies, and mental status changes. The resultant damage to the gland usually causes hormonal dysfunction. Although, likely under diagnosed since in many cases the pituitary adenoma is unknown the incidence of pituitary apoplexy is between 0.6 and 7% of pituitary masses [17-20]. The most common pituitary adenomas which resulted in apoplexy are non-functioning, growth hormone secreting, and prolactinomas, in that order [21]. Since pituitary injury has been noted in micro adenomas which lack the metabolic aggressiveness of macro adenomas the role of vasospasm in their development has yet to be determined. Hypopituitarism can be partial or complete at initial presentation. Endocrine dysfunction is very common at initial presentation, which is consistent with the fact that many of these patients had initially a macroadenoma which would affect hormone levels [22]. Posterior pituitary involvement is rare in pituitary apoplexy and therefore, diabetes insipidus is reported in only 3% of cases. Anterior pituitary hormone dysfunction however is present in about 80% of patients at initial presentation. ACTH deficiency occurs in about 70% of cases, and remains the most urgent life threatening event. TSH deficiency occurs in 50% of subjects while 75% of patients lack FSH and LH, respectively [23-29]. Prolactin can be raised due to stalk compression or from an underlying prolactinoma [30]. It should be noted that low levels of prolactin at presentation are likely to predict residual hypopituitarism after definitive decompression [31].

Conclusion

These four clinical scenarios represent mechanism of pituitary injury which would interfere with reproduction particularly by preventing FSH and LH release. They are commonly overlooked, depending on hormones impacted can be life threatening and should be known to clinicians involved in reproduction. As more is known the relationship between these three syndromes, pituitary apoplexy and there pathophysiology will become better understood.

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