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SHEEHAN'S SYNDROME: CURRENT INSIGHTS INTO PATHOPHYSIOLOGY, CLINICAL MANIFESTATIONS, DIAGNOSTIC CHALLENGES AND MANAGEMENT STRATEGIES

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ABSTRACT

Aims: Sheehan's Syndrome (SS), also known as postpartum hypopituitarism, is a rare and potentially life-threatening endocrine disorder caused by ischemic necrosis of the pituitary gland due to massive postpartum hemorrhage and hypovolemic shock. The aim of this article is to present a comprehensive and up-to-date overview of the current understanding of Sheehan's syndrome, including its pathophysiology, epidemiology, clinical presentation, diagnostic challenges, and therapeutic approaches.
Methods: A narrative review of the literature was conducted using the PubMed, Oxford Academic, Google Scholar, and Embase databases. The analysis included original research articles, systematic reviews, and clinical guidelines published in English over recent years.
Results: Sheehan's syndrome remains an underdiagnosed condition due to its highly variable and often delayed clinical presentation. Symptoms may appear months to years after the inciting obstetric event, which hinders timely diagnosis. The most common manifestations include failure to lactate, amenorrhea, fatigue, hypotension, and features of secondary hypothyroidism or adrenal insufficiency. MRI typically reveals an empty sella or pituitary atrophy. Hormonal testing confirms multiple anterior pituitary hormone deficiencies. The condition is still most prevalent in regions with inadequate obstetric care.
Conclusions: Early recognition of Sheehan's syndrome, based on detailed obstetric history and characteristic clinical and laboratory findings, is essential to prevent severe complications and reduce diagnostic delays. Increased awareness among primary care physicians and perinatal care providers is crucial. Timely initiation of appropriate hormone replacement therapy can significantly improve patient outcomes and quality of life.

KEYWORDS

Sheehan Syndrome, Hypopituitarism, Postpartum Hemorrhage, Obstetric Labor Complications, Pituitary Gland, Hormone Replacement Therapy

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Introduction

Sheehan's syndrome, defined as postpartum hypopituitarism, is a rare and potentially life-threatening complication of severe postpartum hemorrhage, leading to ischemia and necrosis of the anterior pituitary lobe. The incidence of this condition varies depending on the economic development of a given country. Significantly lower rates of Sheehan's syndrome are reported in highly developed countries compared to those with lower levels of economic development. A study by Kristjansdottir et al. (2011) reported an incidence of 5.1 cases per 100,000 women who gave birth in the Icelandic population (24). In contrast, in India, the prevalence has been reported to reach 3.1% among women over the age of 20 (36). The marked decline in incidence in developed countries is attributed to improvements in perinatal care, early detection and management of hemorrhage, and better access to intensive care. Nevertheless, cases of this disorder are still diagnosed - sometimes many years after childbirth - due to its nonspecific, gradually progressive symptoms and the lack of clear diagnostic criteria. Furthermore, diagnosing Sheehan's syndrome remains a clinical challenge. It requires a detailed obstetric history, hormonal evaluation, and pituitary imaging (MRI). Diagnosis is often based on the combination of a characteristic medical history, the presence of panhypopituitarism, and imaging findings such as an "empty sella turcica." In light of the available scientific data, there is a need for a systematic presentation of current strategies for the diagnosis and treatment of Sheehan's syndrome.

Pathophysiology

In the third trimester of pregnancy, the volume of the pituitary gland increases due to significant hyperplasia of anterior pituitary cells - particularly lactotrophs, which produce prolactin. A retrospective study by Benson et al. (2023) indicates that the enlargement of the anterior pituitary lobe in pregnant women persists for approximately one year postpartum. The study reports an average anterior pituitary volume of 621 ± 171.6 mm^3 (705.4 ± 172.2 mm^3 for the whole pituitary) in pregnant women, compared to 522.6 ± 159.8 mm^3 (624.5 ± 163.7 mm^3 for the whole pituitary) in non-pregnant women. It also notes a reduction in the volume of the posterior pituitary lobe during pregnancy, likely due to a mass effect - compression of the posterior lobe against the dorsum sellae by the enlarging anterior lobe - which resolves after childbirth (37,4).

Hyperplasia increases the metabolic and nutritional demands of the pituitary gland. However, despite the enlargement of the anterior lobe, there is no corresponding increase in its blood supply. This region is supplied by the superior hypophyseal artery (SHA), which forms primary capillary plexuses around the hypothalamus. Blood then flows through portal veins into secondary capillary networks within the anterior pituitary. This capillary system operates under relatively low pressure, and when combined with the increased gland volume, the anterior pituitary becomes more vulnerable to impaired perfusion under conditions of hypotension.

In contrast, the posterior pituitary is directly supplied by the inferior hypophyseal artery (IHA), which makes it more resistant to ischemic injury (6). A sudden drop in blood pressure leads to pituitary ischemia and subsequent necrosis of pituitary cells, which underlies the disruption of endocrine function and gives rise to the clinical manifestations of Sheehan's syndrome.

Factors Contributing to the Development of Postpartum Hypopituitarism

The primary cause of the sudden drop in blood pressure leading to Sheehan's syndrome is massive postpartum hemorrhage, which results in acute hypoperfusion of the low-pressure vascular system supplying the anterior pituitary, ultimately causing ischemic necrosis of the gland (23). Additionally, hemorrhagic shock and the ensuing hypotension provoke a reflex vasoconstriction, further exacerbating the ischemia. It has also been suggested that the enlarging pituitary may compress the pituitary arteries (particularly the superior hypophyseal artery, SHA), limiting blood flow, and that a smaller sella turcica may contribute to this compression. However, most patients diagnosed with Sheehan's syndrome have a normally sized sella turcica on imaging, suggesting that a reduced sella size likely plays only a secondary role in the pathogenesis of selected cases (23,7).

Coagulopathies may also contribute to the development of Sheehan's syndrome. Conditions such as von Willebrand disease may increase postpartum bleeding, intensifying the degree of shock and pituitary necrosis (16). On the other hand, disseminated intravascular coagulation (DIC) may lead to the formation of microthrombi that impair microcirculation (7, 29).

In a study by Gokalp et al., the prevalence of specific gene mutations and their potential influence on the development of Sheehan's syndrome was investigated in a cohort of 40 women with SS and 45 healthy controls. The authors suggested that mutations in genes such as FV-Leiden, FII G20210A, MTHFR C677T, MTHFR A1298C, and PAI-1 4G/5G may increase the risk of developing the syndrome. Elevated plasma homocysteine levels were also identified as a possible risk factor (14). Furthermore, mutations in genes involved in the proper development of the pituitary gland and cranial bones during embryogenesis may increase susceptibility to Sheehan's syndrome. This was supported by a study by Diri et al. (2016), which included 44 women with SS and 43 healthy controls. The study found that the mean expression levels of the genes HESX1, TLE1, TLE3, and MSX2 were significantly different in women with SS compared to healthy individuals, suggesting their potential role in the disease's pathogenesis. However, further studies are needed to confirm these findings (8).

Autoimmune mechanisms may also play a role in the development of hypopituitarism following postpartum hemorrhage. Necrosis of the pituitary gland may expose previously sequestered antigens, triggering the formation of autoantibodies and contributing to long-term pituitary dysfunction. A study by Goswami et al. (2002) found anti-pituitary antibodies (PitAb) in 63.1% of women with Sheehan's syndrome, compared to 14.2% in the control group, suggesting an autoimmune component (15). Another study by De Bellis et al. (2008), conducted in 20 women with SS (median disease duration: 25.5 years), detected anti-pituitary antibodies in 35% of patients and anti-hypothalamic antibodies in 40%. The authors proposed that an autoimmune process involving both the hypothalamus and the pituitary might contribute to the delayed onset of pituitary dysfunction in SS patients (15).

Although extremely rare, pituitary ischemia may also result from hemorrhage unrelated to childbirth, such as splenic artery rupture, gastrointestinal bleeding, or gunshot wounds in pregnant women. Postpartum hypopituitarism may also occur in women who did not experience massive obstetric hemorrhage but developed other acute critical conditions such as fulminant hepatic failure or anaphylactic shock (7).

Symptoms of Sheehan's Syndrome

The symptoms of Sheehan's syndrome are typically divided based on the time of onset after childbirth into early symptoms, which manifest within the first few weeks postpartum, and late symptoms, which may not appear until many years later.

Often, the first sign of the disease is failure of lactation. Damage to lactotroph cells leads to impaired prolactin secretion, which directly results in cessation of lactation (3).

Due to adrenocorticotropic hormone (ACTH) deficiency, secondary adrenal insufficiency develops, leading to inadequate cortisol production. Cortisol plays a key role in fluid and electrolyte balance; its deficiency leads to impaired suppression of vasopressin (ADH) secretion. This causes excessive water retention by the kidneys and, consequently, hypotonic hyponatremia. Thus, a low sodium level is often one of the earliest indicators of Sheehan's syndrome. Patients may present with weakness, nausea, dizziness, or even altered mental status. The deficiency of ACTH also contributes to decreased aldosterone secretion, which results in sodium loss and potassium retention, further exacerbating the hyponatremia (34).

Because cortisol is essential for maintaining normal blood glucose levels - through stimulating gluconeogenesis and inhibiting peripheral glucose uptake - its deficiency leads to impaired glucose production and carbohydrate metabolism, manifesting as hypoglycemia. This is particularly prominent in the acute phase of Sheehan's syndrome, when the ACTH and cortisol deficiencies are most severe. Symptoms of hypoglycemia include fatigue, dizziness, confusion, and even loss of consciousness (43, 33).

Deficiency of pituitary gonadotropins (FSH, LH) leads to delayed resumption or absence of menstruation postpartum (oligomenorrhea, amenorrhea). However, this symptom may be overlooked due to the frequent use of hysterectomy in cases of postpartum hemorrhage or the early resumption of hormonal contraception after childbirth, which can mask menstrual irregularities (37, 13).

The deficiency in gonadotropins also disrupts sex hormone production (estrogens, progestogens, testosterone) in the ovaries and adrenal glands. This can lead to decreased libido, vaginal dryness, and atrophy of female secondary sexual characteristics. A study by Mandal et al. (2021) found that 93% of sexually active women with Sheehan's syndrome experienced sexual dysfunction (26, 27).

As a result of reduced TSH secretion, thyroid hormone synthesis is impaired, leading to symptoms of hypothyroidism. Patients may experience fatigue, bradycardia, hypotension, dry skin, cold intolerance, weight gain, and constipation. Hair loss and impaired concentration may also occur (37). Similar symptoms, including fatigue, weight gain, and dry skin, are caused by growth hormone (GH) deficiency (5). GH deficiency is also associated with increased body weight and total fat mass, especially abdominal fat, along with abnormal lipid profiles - elevated total cholesterol, LDL, and triglycerides, and decreased HDL levels. This contributes to an increased risk of metabolic syndrome, atherosclerosis, and cardiovascular complications (21).

Rare symptoms may include seizures or even coma (40). Sheehan's syndrome has also been linked to transient psychotic episodes, which tend to resolve with appropriate hormone replacement therapy (40). The condition may also be associated with depression, although its exact pathophysiology in the context of SS remains unclear (35).

Although much less common, posterior pituitary damage can also occur in Sheehan's syndrome. This can impair the secretion of hypothalamic hormones stored in the posterior pituitary, such as oxytocin and vasopressin. When this part of the gland is affected, a typical manifestation is diabetes insipidus (vasopressin deficiency), presenting as polyuria and increased thirst (30).

Over time, the damaged portion of the pituitary may atrophy. Imaging studies may show a partially or completely empty sella (empty sella syndrome) in some patients (32).

Diagnosis of Sheehan's Syndrome

The foundation of diagnosing Sheehan's syndrome (SS) lies in obtaining a thorough medical history. The primary causative factor to consider is postpartum hemorrhage leading to hypovolemic shock, which results in hypoxia and necrosis of the pituitary gland, subsequently causing classic signs of pituitary hormone deficiency (e.g., menstrual irregularities, agalactia, excessive fatigue, dry skin). Basic laboratory tests including complete blood count, serum sodium, and blood glucose - should also be performed as part of the initial evaluation.

If SS is suspected, a comprehensive endocrine workup is essential. A critical component is assessing the hypothalamic - pituitary - adrenal (HPA) axis, typically through measuring morning cortisol and ACTH levels. Decreased concentrations of both hormones indicate secondary adrenal insufficiency. To confirm the diagnosis, the cosyntropin stimulation test is often recommended (44).

Next, the pituitary - thyroid axis should be evaluated. This generally includes measurements of TSH and free T4 (FT4), and less commonly free T3 (FT3). In SS-related secondary hypothyroidism, the hormonal profile typically shows low or inappropriately normal TSH levels (due to impaired pituitary response to low thyroid hormone levels) and reduced FT4, while FT3 is less frequently decreased. A TRH stimulation test can also be used. Absence of TSH rise after TRH administration suggests pituitary dysfunction (17).

SS can also impair the gonadotropin axis. Evaluation includes measuring FSH and LH levels. Low FSH and LH in the presence of secondary amenorrhea suggest central hypogonadism. Importantly, in postmenopausal women, FSH and LH should be physiologically elevated; inappropriately low levels are indicative of pituitary damage (44).

Given that lactation failure is one of the earliest manifestations of SS, particular diagnostic emphasis should be placed on measuring prolactin levels. Low or undetectable levels of prolactin postpartum suggest pituitary injury. In addition, a TRH stimulation test may be used: in healthy individuals, TRH stimulates prolactin secretion. In cases of lactotroph damage, prolactin fails to rise adequately (9, 44).

The growth hormone (GH), insulin-like growth factor 1 (IGF-1) axis may also be affected. Reduced GH secretion leads to low IGF-1 levels, which serves as a diagnostic marker for SS. If IGF-1 levels are within the normal range, GH stimulation tests (e.g., using insulin or glucagon) can be performed to confirm or exclude the diagnosis (21).

A study by Diri et al. (2014) involving 114 women with SS (with an average diagnostic delay of 19.7 years) found that 55.3% had panhypopituitarism and 44.7% had partial pituitary insufficiency. The study also showed that the number of hormone deficiencies increased over time, highlighting the importance of evaluating multiple hormonal axes in the diagnostic process (9).

The gold standard for diagnosing Sheehan's syndrome is MRI of the pituitary gland. The imaging findings depend on the time elapsed since the ischemic event. In the acute phase (up to several weeks postpartum), the pituitary may appear enlarged with central hypointense areas on T1-weighted images and hyperintense signals on T2, consistent with ischemic changes. A "rim enhancement" pattern may be seen after gadolinium administration, indicating peripheral contrast uptake (22).

In the subacute and chronic phases (several months later), the pituitary gland gradually atrophies. MRI may reveal glandular atrophy, often leading to a partial or complete "empty sella" appearance. The sella turcica may be filled with cerebrospinal fluid, and the flattened pituitary gland may lie along the floor of the sella (37, 22, 31).

Treatment of Sheehan's Syndrome

In the acute phase, immediate priorities include achieving hemodynamic stabilization, correcting electrolyte imbalances - particularly hyponatremia and hypoglycemia and initiating glucocorticoid therapy to prevent adrenal crisis during this critical period (34).

The next step involves hormone replacement therapy. After the introduction of glucocorticoids, levothyroxine therapy is initiated, with dosage tailored according to FT4 levels, not TSH. This order of treatment minimizes the risk of precipitating an adrenal crisis and ensures effective hormone replacement (20).

Subsequently, premenopausal women are treated with estrogen therapy (combined with progestin if the ovaries are preserved), which improves bone metabolism, lipid profiles, and overall well-being (12). A study by Agarwal et al. (2018) found that women with SS had significantly reduced bone mineral density (BMD) compared to controls. It also demonstrated that estrogen therapy combined with calcium and vitamin D3 supplementation led to improved lumbar spine BMD (2). For women planning pregnancy, pulsatile GnRH therapy or gonadotropin administration may be used to induce ovulation (18).

For most patients, growth hormone (GH) replacement should also be considered. GH therapy is initiated only after the adrenal and thyroid axes have been stabilized. GH doses are adjusted gradually based on IGF-1 levels and the patient's clinical response. In a study by Tanriverdi et al. (2005) involving 14 women with SS, GH supplementation was associated with reduced total and LDL cholesterol, increased HDL, as well as decreased waist circumference and waist-to-hip ratio (42). Similarly, a study by Vieira Soares et al. (2006) demonstrated improvements in lipid profiles, reduction of carotid intima-media thickness, and decrease in visceral fat in 10 SS patients treated with GH. However, the study also noted the development of impaired glucose tolerance, likely due to increased insulin resistance, despite favorable changes in body composition (41).

Given the high prevalence of sexual dysfunction in women with SS, dehydroepiandrosterone (DHEA) supplementation is an important aspect of treatment. A study by Mandal et al. (2022) involving 28 women with SS showed that those who received 25 mg of DHEA twice daily for three months had a significant improvement in the Female Sexual Function Index (FSFI) compared to those receiving placebo. After the treatment crossover, women who initially received DHEA and then placebo experienced a decline in FSFI scores, although these remained within the range of acceptable sexual function. The study also reported a significant increase in serum DHEA levels post-treatment. The authors concluded that DHEA therapy is effective and safe for women with SS and sexual dysfunction (28).

If posterior pituitary insufficiency is present, vasopressin or its analog desmopressin is used for replacement therapy (39).

Monitoring and Challenges in Access to Treatment in Developing Countries

Patients with Sheehan's syndrome require long-term follow-up. Optimal care involves a multidisciplinary team, including an endocrinologist, gynecologist, internist, and dietitian, as well as regular monitoring with hormonal testing, imaging studies (particularly bone densitometry, due to the risk of decreased bone density in SS patients), and metabolic evaluations, especially lipid and glucose profiles - mainly because of the risk of developing metabolic syndrome. In the long term, hypopituitarism either stabilizes or progresses. A progressive course over time has been observed in approximately half of all patients, necessitating periodic adjustments and increases in hormone doses (13, 38, 25).

A study by Das et al. (2022) showed that among SS patients under long-term observation (mean duration 9.8 ± 6.8 years), 63% developed non-alcoholic fatty liver disease (NAFLD), and 51% presented with severe NAFLD. GH deficiency and higher BMI were identified as predictive factors for NAFLD. Additionally, the frequency of mild systolic dysfunction was increased in SS patients (18.8%) compared to the control group (7.7%). Monitoring included periodic echocardiography and FibroScan to assess liver health and cardiac function (10).

Sheehan's syndrome also significantly impacts patients' quality of life due to chronic fatigue, mood disorders, and sexual dysfunction, which together impair social functioning. Infertility is another important issue in SS, often requiring ovulation induction therapy (19).

In developing countries, the diagnosis of SS is typically delayed by about 20 years, compared to a delay of approximately 9 years in developed countries. This is attributed to low awareness, limited perinatal care and medical infrastructure, and a higher prevalence of home deliveries compared to developed nations (1).

Conclusions

Sheehan's syndrome is an underdiagnosed disorder, often recognized many years after symptom onset, and still predominantly affects women in developing countries. Its symptoms result from deficiencies of specific pituitary hormones, mainly ACTH, TSH, GH, PRL, and also LH/FSH. Clinical manifestations include agalactia, amenorrhea, loss of secondary sexual characteristics, hyponatremia, hypoglycemia, as well as fatigue, weight gain, cardiovascular disturbances, and occasionally depression. MRI of the pituitary plays a key role in diagnosis, alongside hormonal testing. Treatment is based on hormone replacement therapy. Due to its frequently nonspecific presentation, the disease often goes undiagnosed. Therefore, increased vigilance in perinatal care is essential to recognize this condition early. Management requires a multidisciplinary approach, involving endocrinologists, gynecologists, internists, and dietitians. Due to the rarity of the condition, large prospective studies are lacking. There is an urgent need to implement better diagnostic tools in regions with limited access to healthcare.

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