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**Review Article**

# The vanishing diagnosis: a comprehensive review of late-onset hypopituitarism due to Sheehan syndrome in resource-limited settings, diagnostic nosography and persistent barriers to endocrine care

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## ABSTRACT

Sheehan syndrome (SS), or postpartum pituitary necrosis, is a preventable consequence of obstetrical hemorrhage. Although its incidence has declined in high-income countries, it persists as a major cause of maternal morbidity in low-resource regions, often with diagnostic delays of decades. This review critically analyzes the epidemiological shift of SS, delineates mechanisms permitting delayed presentation, and explores factors contributing to diagnostic oversight in developing nations. We performed a narrative synthesis of literature from 2015-2025, including case series, cross-sectional studies, and reviews on hypopituitarism and neuroimaging, with emphasis on chronic glucocorticoid and thyrotrophin deficiency as clinical masqueraders. In areas with high home-delivery rates, SS prevalence may reach 3% among parous women over 20 years. Mean diagnostic delay ranges from 10-20 years, with extremes up to 50 years postpartum. Common findings include partial empty Sella on magnetic resonance imaging (MRI) and panhypopituitarism, with normocytic normochromic anemia and hyponatremia from adrenal insufficiency as predominant laboratory features. In developing nations, SS serves as a silent marker of obstetric disparities. Its nonspecific symptoms-chronic asthenia, hyponatremia, secondary hypothyroidism-are often misattributed to aging, malnutrition, or psychiatric illness. A high index of suspicion, combined with targeted hormonal assays and appropriate imaging, remains essential to reduce preventable morbidity from this overlooked endocrinopathy.

**Keywords:** Sheehan syndrome, Hypopituitarism, Postpartum hemorrhage, Developing countries, Delayed diagnosis, Empty Sella syndrome, Adrenal insufficiency

## INTRODUCTION

The physiological transformation of the female body during gestation necessitates a remarkable adaptation of the neuroendocrine axis. Specifically, the anterior pituitary gland, or adenohypophysis, undergoes significant hypertrophy and hyperplasia, primarily driven by the estrogenic milieu of pregnancy, resulting in an increase of up to one hundred thirty-six percent in its volume compared to its non-gravid state. This physiological enlargement renders the gland uniquely vulnerable to ischemic injury. When a catastrophic obstetrical event, most notably massive postpartum hemorrhage (PPH) complicated by hypovolemic shock, occurs, the delicate portal circulation supplying the anterior pituitary is compromised, leading to a cascade of cellular necrosis. First characterized by Harold Leeming Sheehan in 1937 through meticulous autopsy studies of women who succumbed to puerperal sepsis and hemorrhage, this condition, now known as SS, remains a classic cause of acquired hypopituitarism.[1,2]

In the contemporary medical landscape of high-income nations, SS is frequently relegated to the status of a rare medical curiosity, a consequence of advanced obstetrical care, routine blood transfusion protocols, and widespread institutional delivery. Epidemiologically, the incidence in these settings is low, with studies from Europe estimating a prevalence of approximately five cases per one hundred thousand women. However, this epidemiological profile does not reflect the reality of low and middle-income countries (LMICs). In regions of Sub-Saharan Africa, South Asia, and parts of Latin America, where access to emergency obstetric care remains inconsistent and home births are prevalent, SS continues to represent a significant, albeit underreported, public health challenge. A study from the Kashmir valley in the Indian subcontinent estimated the prevalence to be about three percent in women above twenty years of age, with the majority having delivered their babies at home without skilled attendance.[3-5]

The most insidious aspect of SS is not its acute manifestation, but rather its chronic, indolent evolution. While some patients may present acutely in the postpartum period with the classic triad of agalactorrhea, failure to resume menses, and hypotension, a substantial proportion of affected women experience a prolonged subclinical course. The interval between the inciting hemorrhagic event and the establishment of a definitive diagnosis frequently spans years or even decades. Retrospective analyses have documented mean diagnostic delays ranging from nine to twenty years, with extraordinary cases of diagnosis being made forty-six years after the last delivery. This latency period represents a critical failure of diagnostic recognition. The symptoms of progressive anterior pituitary insufficiency-chronic fatigue, weight loss, bradyphrenia, cold intolerance, and gastrointestinal distress-are notoriously non-specific. In the resource-constrained setting of a developing country, these manifestations are often mistakenly attributed to tuberculosis, chronic malnutrition, depression, or simply the physiological toll of multiparity.[5-8]

The diagnostic challenge is further compounded by the nature of the hormonal deficiencies themselves. The somatotroph and lactotroph axes are typically the first and most severely affected due to the anatomical distribution of these cells in the lateral wings of the gland, leading to growth hormone and prolactin deficiency. However, it is the subsequent deficiency of corticotrophs (Adrenocorticotropic hormone-ACTH) and thyrotrophs (Thyroid stimulating hormone-TSH) that often precipitates medical consultation, usually in the form of an adrenal crisis or severe electrolyte disturbance. Hyponatremia, present in up to sixty-nine percent of cases, is a common harbinger, yet it is frequently treated empirically for syndrome of inappropriate antidiuretic hormone secretion (SIADH) or dehydration without investigating the central axis. Furthermore, the absence of dedicated endocrine services, the high cost of hormone assays, and the lack of access to MRI in rural areas perpetuate this cycle of neglect. Consequently, many women remain undiagnosed until they present with life-threatening complications such as hypovolemic shock or hypoglycemic coma, or until they are incidentally discovered during imaging for unrelated complaints, revealing the characteristic finding of a partially empty Sella turcica.[9-11]

This review seeks to bridge the gap between classical endocrinological knowledge and the modern reality of global health disparities. By examining the current body of literature, including recent case reports from developing countries and advances in pituitary imaging, this paper aims to underscore the necessity for a revised clinical approach. We argue that SS should not be viewed as a historical relic but rather as an ongoing sentinel event that reflects the resilience of women enduring untreated hormone deficiencies and the limitations of health systems in capturing subtle, chronic pathologies. Through this extensive analysis, we hope to provide clinicians with a robust framework for recognizing the variable facies of late-diagnosed SS, ultimately advocating for a higher index of suspicion in every woman of reproductive age presenting with unexplained endocrine or metabolic disturbances and a history of complicated childbirth.[12]

## PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS OF SS IN THE CONTEXT OF DELAYED DIAGNOSIS

The pathophysiological underpinnings of SS are intrinsically linked to the unique vascular anatomy and physiological adaptations of the anterior pituitary gland during gestation. Throughout pregnancy, the adenohypophysis undergoes substantial hyperplasia and hypertrophy, primarily driven by the estrogenic milieu, resulting in a volumetric increase of up to one hundred thirty-six percent compared to its non-gravid state. This physiological enlargement renders the gland exquisitely vulnerable to ischemic injury because the expanding parenchyma becomes compressed against the unyielding bony confines of the Sella turcica, while simultaneously experiencing increased metabolic demands that outstrip the capacity of the low-pressure portal venous system. The anterior pituitary receives its blood supply via the superior hypophyseal arteries, which form a portal plexus traversing the pituitary stalk. Unlike other organs with dual arterial supplies, the adenohypophysis lacks a direct arterial blood supply, making it uniquely susceptible to hypotension and hypovolemic shock. When a catastrophic obstetrical event, most notably massive postpartum hemorrhage complicated by hemorrhagic shock, occurs, the resultant vasospasm and systemic hypotension precipitate a cascade of cellular necrosis within the swollen gland.[10,11]

A critical concept in understanding the delayed presentation of this condition is the substantial secretory reserve of the pituitary gland. More than seventy-five percent of the anterior pituitary must be destroyed before

clinically evident hypopituitarism manifests. This high threshold for symptomatic expression explains why many women survive the initial ischemic insult with minimal or no immediate postpartum symptoms, only to develop progressive hormonal deficiencies over years or decades as the necrotic tissue undergoes fibrotic involution and residual functional cells gradually succumb to chronic ischemia. The pattern of hormonal deficiency follows a predictable topographic hierarchy based on the anatomical distribution of secretory cells relative to their vascular supply. The somatotrophs and lactotrophs, which produce growth hormone and prolactin respectively, are located in the lateral wings of the gland, the most vulnerable watershed zones. Consequently, growth hormone deficiency and prolactin deficiency are the earliest and most frequently observed deficits, manifesting clinically as lactation failure and chronic fatigue. Subsequently, gonadotropin deficiency affecting luteinizing hormone and follicle-stimulating hormone secretion follows, leading to secondary amenorrhea, breast involution, and loss of axillary and pubic hair. The corticotrophs and thyrotrophs, situated in the medial and more resilient regions of the gland, are affected later in the disease course, requiring more extensive necrosis before adrenal insufficiency and central hypothyroidism become apparent.[9,10]

The clinical manifestations of SS are notoriously protean and evolve along a temporal continuum that can span decades. In the acute postpartum period, when the condition is rarely recognized in resource-limited settings, women may experience lactation failure, inability to resume menses, and episodes of unexplained hypotension. However, because these symptoms may be attributed to postpartum depression, cultural practices, or general debility following complicated delivery, they seldom prompt formal endocrine evaluation. The intermediate phase, occurring five to fifteen years after the inciting hemorrhage, often brings patients to medical attention with a constellation of vague but progressive complaints including chronic asthenia, adynamia, cold intolerance, weight loss, and gastrointestinal disturbances such as nausea, vomiting, and abdominal pain. A particularly instructive case described a woman who presented with acalculous cholecystitis, a manifestation of secondary adrenal insufficiency mimicking an acute abdomen, highlighting how cortisol deficiency can masquerade as a surgical emergency.[10,11]

The late phase, extending beyond fifteen years postpartum, represents the most challenging diagnostic scenario, particularly in developing countries where access to specialized endocrine care remains limited. During this stage, patients frequently present with life-threatening complications including severe hypoglycemia, refractory hyponatremia, hypotensive crises, and even coma. Hyponatremia represents the most common electrolyte abnormality in SS, occurring in thirty-three percent to sixty-nine percent of cases, and is primarily attributable to secondary adrenal insufficiency. The mechanism involves both cortisol deficiency-induced inappropriate antidiuretic hormone secretion and impaired free water excretion, resulting in euvolemic hyponatremia that often mimics the syndrome of inappropriate antidiuretic hormone secretion. However, unlike the latter, volume repletion with normal saline may paradoxically worsen electrolyte disturbances in adrenal insufficiency. A clinical pearl that distinguishes SS from other causes of hyponatremia is the presence of bradycardia and hypotension out of proportion to the degree of volume depletion, reflecting combined glucocorticoid and thyroid hormone deficiencies.[11,12]

The cardiovascular manifestations of long-standing SS are increasingly recognized as a source of significant morbidity. Chronic untreated hypopituitarism leads to metabolic and structural cardiac alterations, including dilated cardiomyopathy, reduced left ventricular ejection fraction, and valvular insufficiencies. A recent case report documented a patient with undiagnosed SS for an unspecified duration who developed severe mitral regurgitation and heart failure requiring percutaneous MitraClip intervention, underscoring how delayed recognition of pituitary failure can culminate in irreversible end-organ damage. The mechanisms underlying this cardiomyopathy are multifactorial, involving growth hormone deficiency-induced impairment of myocardial contractility, adrenal insufficiency-mediated electrolyte disturbances and hypotension, and hypothyroidism-related bradycardia and reduced cardiac output.[12,13]

Hematological abnormalities represent another underappreciated facet of SS's clinical spectrum. While normocytic normochromic anemia is frequently observed due to chronic illness and hormonal deficiencies, more profound alterations including pancytopenia have been reported. The mechanism involves bone marrow suppression mediated by combined thyroid hormone and cortisol deficiency, with restoration of normal cell lines following appropriate hormone replacement therapy. This finding is particularly relevant in developing countries where pancytopenia often triggers extensive and costly evaluations for hematological malignancies, tuberculosis, or nutritional deficiencies, while an underlying endocrinopathy remains overlooked.[12,13]

The diagnostic confirmation of SS relies heavily on neuroimaging, with MRI serving as the gold standard modality. The characteristic evolution of pituitary changes follows a predictable temporal sequence based on the stage of the disease. In the acute phase, which is rarely captured in delayed presentations, MRI reveals an enlarged pituitary gland with central hypointensity on T1-weighted images and hyperintensity on T2-weighted sequences, consistent with non-hemorrhagic infarction. Post-gadolinium images demonstrate peripheral enhancement of the swollen gland with an irregular, poorly enhanced central portion representing necrotic tissue. Over several weeks to months, the gland undergoes progressive involution, and by the time patients present with late-onset symptoms,

MRI typically reveals a partially empty Sella turcica, where the pituitary fossa is occupied by cerebrospinal fluid with a thin rim of residual compressed pituitary tissue lining the floor. This finding, while characteristic, requires careful interpretation as partial empty Sella can also be an incidental finding in otherwise healthy individuals; the diagnosis must therefore integrate imaging findings with a compatible clinical history and biochemical confirmation of hypopituitarism.[12,13]

A particularly instructive case from the literature described a forty-six-year-old woman with no prior medical history who presented with abdominal pain and hyponatremia, initially attributed to primary biliary cholangitis based on positive antimitochondrial antibodies. Only upon further endocrine evaluation, prompted by refractory hypotension and progressive hyponatremia, was a free T4 level less than 0.07 nanograms per deciliter and a cortisol level of 0.5 micrograms per deciliter obtained, confirming central hypothyroidism and secondary adrenal insufficiency. Subsequent MRI confirmed an empty Sella, and upon detailed obstetric history, the patient recalled a complicated childbirth twenty-three years prior requiring multiple transfusions and subsequent hysterectomy. This case illustrates two critical points for clinicians in developing countries: first, the presence of other comorbidities does not exclude SS, and second, the diagnostic latency can extend far beyond what is typically reported, with some cases escaping recognition for over four decades.[13,14]

The biochemical profile of delayed-diagnosis SS reveals distinct patterns that, when recognized, can guide appropriate testing. A low or inappropriately normal thyroid-stimulating hormone level in the setting of low free thyroxine confirms central hypothyroidism, distinguishing this condition from primary thyroid failure where thyroid-stimulating hormone would be elevated. Similarly, a low morning cortisol accompanied by a low or normal adrenocorticotropic hormone level establishes secondary adrenal insufficiency. Prolactin levels are typically low, though cases with normal prolactin have been reported due to incomplete lactotroph destruction. Gonadotropin levels are low or inappropriately normal for a woman of menopausal age, and estrogen or estradiol levels are diminished. The absence of posterior pituitary involvement in classic SS explains why diabetes insipidus, characterized by polyuria and polydipsia, is rarely observed, though subclinical defects in vasopressin secretion have been documented in some long-standing cases.[14]

Understanding the pathophysiology and recognizing the varied clinical facies of SS is particularly urgent in developing countries where the prevalence remains high and diagnostic resources are scarce. The nonspecific nature of symptoms, ranging from chronic fatigue and cold intolerance to abdominal pain and confusion, leads to misdiagnosis with tuberculosis, chronic gastritis, depression, or simply the physiological toll of multiparity. However, a carefully obtained obstetric history remains the most cost-effective diagnostic tool. Any woman of reproductive age or even postmenopausal woman with unexplained hyponatremia, refractory hypotension, bradycardia, or pancytopenia should be specifically queried about a history of postpartum hemorrhage, transfusion requirements, lactation failure, and secondary amenorrhea. In resource-limited settings where MRI and comprehensive hormone assays may be unavailable or unaffordable, the combination of a suggestive obstetric history, compatible physical findings such as loss of axillary and pubic hair, and simple laboratory findings including hyponatremia, low morning cortisol, and low free thyroxine with normal or low thyroid-stimulating hormone should prompt a therapeutic trial of glucocorticoids and thyroid hormone replacement, which can be both diagnostic and life-saving.[14,15]

## DIAGNOSTIC APPROACHES IN RESOURCE-LIMITED SETTINGS

The diagnostic journey for a woman with late-diagnosed SS in a developing country is fraught with obstacles that begin with the nonspecific nature of her presenting complaints and extend to the limited availability of confirmatory testing. The clinical suspicion for SS must remain elevated in any parous woman who reports a history of severe postpartum hemorrhage, even when that event occurred decades prior to her current presentation. The cornerstone of diagnosis remains a meticulously obtained obstetric history, a tool that costs nothing yet yields invaluable diagnostic direction when clinicians take the time to inquire about lactation failure, secondary amenorrhea, and the need for blood transfusions following delivery.[15,16]

When a patient presents with the characteristic constellation of symptoms-chronic fatigue, generalized weakness, pallor, cold intolerance, weight loss, and gastrointestinal disturbances-the initial laboratory evaluation should include serum electrolytes, blood glucose, complete blood count, and baseline hormonal assessments. Hyponatremia represents one of the most common and diagnostically useful findings in SS, occurring in approximately sixty percent of cases, and its presence should immediately raise suspicion for secondary adrenal insufficiency rather than more common causes such as syndrome of inappropriate antidiuretic hormone secretion or dehydration. The mechanism underlying this electrolyte disturbance involves cortisol deficiency-induced inappropriate vasopressin secretion coupled with impaired free water excretion, creating a euvolemic hyponatremic state that can be life-threatening if not recognized promptly.[15,16]

The biochemical confirmation of hypopituitarism requires a systematic evaluation of the anterior pituitary axes. Central hypothyroidism is established by demonstrating a low free thyroxine level accompanied by a thyroid-stimulating hormone concentration that is inappropriately

low or normal, distinguishing this condition from primary thyroid failure where thyroid-stimulating hormone would be elevated. Secondary adrenal insufficiency is confirmed by a low morning serum cortisol level, typically below three micrograms per deciliter, with a concomitantly low or inappropriately normal adrenocorticotropic hormone concentration. In cases where baseline cortisol levels are indeterminate, a cosyntropin stimulation test can be performed, though this requires access to synthetic adrenocorticotropic hormone which may not be available in all resource-limited settings. The gonadotropin axis evaluation reveals low or inappropriately normal luteinizing hormone and follicle-stimulating hormone concentrations in the setting of diminished estradiol levels, confirming hypogonadotropic hypogonadism. Prolactin levels are typically low, reflecting the vulnerability of lactotrophs to ischemic injury, though normal prolactin values do not exclude the diagnosis as partial preservation of lactotroph function can occur.[16]

Pituitary imaging plays a crucial role in confirming the diagnosis and excluding other Sellar pathologies. MRI remains the gold standard modality, and in chronic SS, the characteristic finding is a partially or completely empty Sella turcica, where the pituitary fossa is occupied by cerebrospinal fluid with a thin rim of compressed residual pituitary tissue lining the Sellar floor. One study reported that seventy-four-point two percent of patients demonstrated a completely empty Sella on MRI, while twenty-three-point three percent showed a partially empty Sella. However, it bears emphasis that an empty Sella can also be an incidental radiographic finding in up to thirty-five percent of the general population, so this finding must be interpreted within the appropriate clinical and biochemical context. In settings where MRI is unavailable or unaffordable, computed tomography may demonstrate the empty Sella phenomenon, though with less resolution of the pituitary stalk and surrounding structures.[17]

The pancytopenia that occasionally accompanies SS represents a particularly insidious manifestation that can lead to extensive and costly hematological evaluations if the underlying endocrinopathy is not recognized. Normocytic normochromic anemia is the most common hematological abnormality, but cases of complete bone marrow suppression with leukopenia and thrombocytopenia have been documented. The mechanism involves bone marrow hypofunction mediated by combined thyroid hormone and cortisol deficiency, and the pancytopenia typically resolves completely within several months of initiating appropriate hormone replacement therapy, a finding that can serve as both a diagnostic confirmation and a therapeutic triumph. Hematologists working in resource-limited settings should therefore include hypopituitarism in their differential diagnosis when evaluating women of reproductive age with unexplained pancytopenia, particularly when there is a history of complicated childbirth.[16,17]

## THERAPEUTIC STRATEGIES FOR DELAYED PRESENTATIONS

The treatment of SS is predicated on lifelong hormone replacement therapy targeting each deficient endocrine axis, with the overarching goal of restoring physiological function, alleviating symptoms, and preventing the life-threatening complications associated with untreated hypopituitarism. The fundamental principle governing the initiation of replacement therapy is the prioritization of glucocorticoid administration before the introduction of thyroid hormone, a sequence that cannot be overemphasized in clinical practice. When thyroid hormone is administered to a patient with unrecognized or untreated adrenal insufficiency, the accelerated metabolism and clearance of cortisol can precipitate an acute adrenal crisis, a potentially fatal event characterized by profound hypotension, hypoglycemia, and cardiovascular collapse. The case report by Ourdi and colleagues documented that all seven patients in their Moroccan series received appropriate hormone substitution therapy once the diagnosis was established, though the mean diagnostic delay of thirty-one years had already allowed substantial morbidity to accrue.[17]

Glucocorticoid replacement is typically achieved with hydrocortisone administered at a total daily dose of fifteen to twenty-five milligrams, divided into two or three doses to approximate the physiological circadian rhythm of cortisol secretion. A common regimen involves ten milligrams upon awakening, five milligrams at midday, and five milligrams in the early evening, though the exact dosing must be individualized based on clinical response and avoidance of overtreatment signs such as weight gain, glucose intolerance, and osteoporosis. In the acute setting of an adrenal crisis, which remains a frequent presentation of undiagnosed SS in developing countries, intravenous hydrocortisone at a dose of fifty to one hundred milligrams every six to eight hours is administered until hemodynamic stability is achieved, followed by transition to oral maintenance therapy. Patients and their families require thorough education regarding stress-dose steroid coverage during intercurrent illnesses, surgical procedures, or traumatic injuries, as the inability to mount an endogenous cortisol response can prove fatal if supplemental glucocorticoids are not administered.[18,19]

Thyroid hormone replacement is initiated only after adequate glucocorticoid replacement has been established, typically twenty-four to forty-eight hours after starting hydrocortisone therapy. Levothyroxine is the preferred preparation, with a typical starting dose of twenty-five to fifty micrograms daily for older adults or those with cardiovascular concerns, while younger patients may be started directly on full replacement doses calculated at approximately one point six micrograms per kilogram of body weight daily. The dose is titrated gradually based on clinical response and serial measurements of free thyroxine, with the goal of achieving levels in the mid-to-upper reference range. Unlike primary hypothyroidism

where thyroid-stimulating hormone serves as the primary monitoring tool, in central hypothyroidism, thyroid-stimulating hormone levels are uninformative and may remain low or normal despite inadequate replacement, so free thyroxine becomes the parameter of choice for dose adjustment. The case of myxedema coma complicating SS reported by Singh and colleagues illustrates the catastrophic consequences of delayed thyroid hormone replacement, as their patient required a five hundred microgram loading dose of levothyroxine via nasogastric tube after her sensorium deteriorated despite initial hydrocortisone therapy.[18,19]

The management of hypogonadotropic hypogonadism in women with SS requires an individualized approach based on the patient's age, fertility desires, and long-term bone health considerations. For premenopausal women who do not wish to conceive, estrogen-progesterone replacement therapy is indicated to prevent the osteoporosis, genitourinary atrophy, and cardiovascular consequences of prolonged estrogen deficiency. Combined oral contraceptive pills offer a convenient option, though transdermal preparations may be preferred in some settings. For women seeking fertility, ovulation induction with exogenous gonadotropins represents a highly effective intervention, though the cost and required monitoring may be prohibitive in resource-limited settings. Spontaneous pregnancies in untreated SS are exceedingly rare, but successful conception and delivery have been reported following appropriate gonadotropin therapy. The case report by Raizada and colleagues highlighted that osteopenia and osteoporosis affect up to fifty-seven-point two percent and thirty-five-point four percent of patients with SS respectively, underscoring the importance of addressing hypogonadism for long-term skeletal health.[18,19]

Growth hormone deficiency is nearly universal in SS due to the topographic vulnerability of somatotrophs, yet growth hormone replacement therapy remains inaccessible to the vast majority of patients in developing countries due to its high cost and parenteral route of administration. The consequences of untreated growth hormone deficiency include persistent fatigue, reduced quality of life, adverse lipid profiles characterized by elevated total cholesterol and triglycerides, increased visceral adiposity, and accelerated atherosclerosis.

Studies have demonstrated that growth hormone replacement can significantly improve these metabolic parameters and reduce carotid intimal medial thickness, but until generic formulations or government subsidy programs become available in low-resource settings, most patients will remain without this beneficial therapy. The editorial by Raizada and Madhu emphasized that Indian patients with SS likely experience cardiovascular morbidity and mortality far exceeding that seen in developed countries, partly attributable to the lack of growth hormone replacement access.[18,19]

## COMPREHENSIVE MONITORING AND LONG-TERM FOLLOW-UP

The management of SS extends far beyond the initial hormone replacement prescription, encompassing lifelong monitoring for treatment adequacy, medication adherence, and the development of long-term complications. Regular clinical assessments should evaluate symptom control, including energy levels, cognitive function, body weight, blood pressure, and overall well-being. Biochemical monitoring includes periodic measurement of free thyroxine to guide levothyroxine dosing, morning cortisol levels to assess glucocorticoid replacement adequacy, and estradiol levels in premenopausal women receiving estrogen therapy. Patients require ongoing education about the importance of medication adherence, as the consequences of treatment interruption can be severe, particularly during periods of physiological stress.[18,19]

The cardiovascular system deserves particular attention in long-term follow-up, as untreated or inadequately treated hypopituitarism is associated with increased risk of hypertension, dyslipidemia, insulin resistance, and premature coronary artery disease. Studies have documented elevated inflammatory markers including high-sensitivity C-reactive protein and interleukin-6 in patients with SS, along with increased coronary artery calcification scores compared to controls. The lipid profile in SS is characterized by elevated total cholesterol, triglycerides, and low-density lipoprotein cholesterol accompanied by reduced high-density lipoprotein cholesterol, abnormalities that improve but do not always normalize with adequate hormone replacement. Regular screening for metabolic syndrome, diabetes mellitus, and cardiovascular risk factors is therefore essential, with aggressive management of any identified abnormalities.[18,19]

Bone health monitoring represents another critical component of long-term care for women with SS, given the profound impact of prolonged hypogonadism on skeletal integrity. Dual-energy X-ray absorptiometry scanning should be performed at baseline and every two to five years thereafter to assess bone mineral density, with particular attention to the lumbar spine and femoral neck. Patients with osteopenia or osteoporosis require optimization of calcium and vitamin D status, consideration of bisphosphonate therapy if indicated, and reassurance that estrogen replacement alone can significantly improve bone density over time. The study by Agrawal and colleagues found that bone texture imaging parameters were altered in SS patients, indicating disruption of the normal trabecular pattern even when bone mineral density remained within reference ranges.[18,19]

The mental health and quality of life of women living with SS represent frequently overlooked but critically important domains of care. The chronic fatigue, cognitive impairment, and physical limitations imposed by untreated hypopituitarism can lead to social isolation, loss of

economic productivity, and significant psychological distress. Patients with SS have been shown to perform worse than controls in both physical and psychological health domains of standardized quality-of-life instruments, yet these improvements often lag behind biochemical normalization even after hormone replacement is initiated. The delayed diagnosis of SS, often spanning decades, means that many women have endured debilitating symptoms throughout their most productive years, a tragedy that could be prevented through increased physician awareness and improved access to diagnostic services.[18,19]

## CONCLUSION

SS, first described by Harold Leeming Sheehan in 1937, persists as a significant cause of maternal morbidity and preventable hypopituitarism in developing countries, where it serves as a silent marker of obstetric disparities and healthcare system limitations. The pathophysiology of this condition is rooted in the unique vulnerability of the enlarged pregnant pituitary gland to ischemic necrosis following postpartum hemorrhage, yet the clinical manifestations typically unfold over years or decades, creating a protracted diagnostic odyssey for affected women. The average diagnostic delay in resource-limited settings ranges from eight to thirty-one years, with some patients remaining undiagnosed for nearly five decades after their incipient hemorrhagic event. This latency period represents a critical failure of diagnostic recognition, during which women endure progressive hormonal deficiencies that masquerade as common conditions such as chronic fatigue syndrome, depression, tuberculosis, or simply the physiological toll of multiparity.

The clinical presentation of late-diagnosed SS is characterized by the gradual emergence of anterior pituitary hormone deficiencies in a predictable sequence, beginning with growth hormone and prolactin deficiency manifesting as lactation failure and chronic asthenia, followed by gonadotropin deficiency causing secondary amenorrhea and loss of axillary and pubic hair, and culminating in corticotroph and thyrotroph deficiencies that produce the life-threatening complications of adrenal insufficiency and central hypothyroidism. Hyponatremia emerges as the most common electrolyte abnormality, present in up to sixty-nine percent of cases, and should prompt immediate consideration of secondary adrenal insufficiency in any woman with a history of complicated childbirth. The hematological manifestations of SS, including normocytic anemia and, in rare cases, pancytopenia, can be fully reversed with appropriate hormone replacement, yet they often trigger extensive and costly evaluations for primary bone marrow disorders when the underlying endocrinopathy remains unrecognized.

The diagnostic confirmation of SS requires a high index of clinical suspicion, a meticulously obtained obstetric history, biochemical confirmation of hypopituitarism, and neuroimaging demonstrating the characteristic finding of a partially or completely empty Sella turcica. However, in many resource-limited settings, access to MRI and comprehensive hormone assays remains severely constrained, forcing clinicians to rely on clinical judgment and therapeutic trials of hormone replacement. The treatment of SS involves lifelong hormone replacement with glucocorticoids, thyroid hormone, and sex steroids, administered in a carefully sequenced manner that prioritizes cortisol repletion before thyroid hormone introduction to prevent adrenal crisis. Growth hormone replacement, while beneficial for quality of life and cardiovascular risk reduction, remains inaccessible to the majority of patients in developing countries due to cost barriers.

The long-term management of SS extends beyond hormone replacement to encompass comprehensive monitoring for cardiovascular disease, metabolic syndrome, osteoporosis, and psychological morbidity, all of which occur at increased frequency in this population. The editorial by Raizada and Madhu emphasized that patients with SS demonstrate elevated inflammatory markers, increased coronary artery calcification, and adverse lipid profiles that predispose them to premature cardiovascular events, yet these abnormalities can be mitigated with aggressive risk factor modification and, when available, growth hormone replacement. The persistence of SS in developing countries reflects not a failure of medical knowledge but a failure of healthcare infrastructure, physician education, and access to basic obstetric and endocrine services. The solution requires a multipronged approach encompassing improved obstetric care to prevent postpartum hemorrhage, enhanced training of primary care clinicians to recognize the protean manifestations of hypopituitarism, expanded access to diagnostic imaging and hormone assays, and public health campaigns to educate women about the symptoms of pituitary failure following complicated childbirth.

SS must no longer be relegated to the status of a historical curiosity or a rare endocrinological oddity. In the contexts of sub-Saharan Africa, South Asia, Latin America, and other resource-limited regions, it remains a present and preventable cause of maternal morbidity that claims the vitality, productivity, and quality of life of countless women who survive their initial obstetric hemorrhage only to succumb to the insidious progression of untreated hypopituitarism. Every woman who presents with unexplained fatigue, hyponatremia, hypoglycemia, hypotension, or pancytopenia deserves a thoughtful inquiry into her obstetric history, and every clinician who cares for women of reproductive age must remain vigilant for the possibility of SS, for in that vigilance lies the opportunity to transform decades of suffering into a future of restored health and dignity.

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