ORIGINAL RESEARCH PAPER
Volume-9 | Issue-3 | March-2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# CASE STUDY OF TWO SUCCESSFUL PREGNANCIES IN SHEEHAN'S SYNDROME

Endocrinology

**Kaivan Patel** Pacific Medical College and Hospital, Udaipur, India
**Vivek Patel*** CIMS Hospital, Ahmedabad, India *Corresponding Author
**Abhijit S Pandya** Florida Atlantic University, Boca Raton, USA
**Mirjana Pavlovic** Florida Atlantic University, Boca Raton, USA

## ABSTRACT

Sheehan's syndrome (SS) is postpartum hypopituitarism which is caused by the ischemic necrosis of the anterior pituitary gland. It is usually the result of severe hypotension or shock caused by massive hemorrhage during or after delivery. Patients with this disorder have varying degrees of anterior pituitary hormone deficiency. In rare cases it may occur in posterior pituitary.
Its frequency is decreasing worldwide and it is a rare case of hypopituitarism in developed countries owing to advances in obstetric care.
However, it is still frequent in the underdeveloped and developing countries like India, especially the Northern states. As this disorder evolves slowly, it is often diagnosed late. History of postpartum hemorrhage, cessation of menses and failure to lactate are some important clues to diagnosis. Early diagnosis and appropriate treatment are important for the reduction in the mortality and morbidity of the patients. We report an unusual case of a 34-year-old female who had two normal deliveries while her underlying Sheehan syndrome remained undiagnosed. The woman presented hypothyroidism and severe headaches during her visit to our clinic and was later found to be suffering from Sheehan's syndrome. She was diagnosed as having Sheehan's syndrome by clinical manifestations, laboratory tests and MRI.
Detailed endocrinological studies were performed after patient complained of amenorrhea (failure to have normal periods). In addition to these studies, a critical review of the literature was undertaken to more clearly define the clinical and laboratory features of pregnancy in Sheehan's syndrome. We provide recommendations for diagnosis and management of the disease.

## KEYWORDS

Sheehan's syndrome, Agalactia, pituitary necrosis, postpartum hemorrhage, pregnancy

## INTRODUCTION

Sheehan's syndrome (SS) was first described by Harold Leeming Sheehan (1900-1988), a British pathologist in 1937 who found pituitary necrosis in autopsy brain specimen in females who suffered obstetric shock. The condition is most commonly observed in the poorer regions of the world where women are most likely to suffer from severe hemorrhage following childbirth, and it often occurs at home. Sheehan syndrome is a distinct manifestation, usually presents with empty or partially empty Sella syndrome (Keleştimur F (2003).) The characteristic features of SS are reduced hormonal levels in the body. The common signs of SS are growth hormone deficiency, agalactorrhea, hypothyroidism etc. Sometimes some patients may also present with loss of pubic and axillary hair cortical as well gonadotropic hormone deficiency leading to oligo menorrhea. (Shivaprasad C. (2011), Keleştimur F. (2003)) As it is a disease which manifest anterior pituitary dysfunction, it may remain for the complete lifetime.

SS was prevalent in the early centuries because of lack of proper obstetrical facilities. Now with improved obstetrical facilities, SS is rare but potentially serious postpartum complication in developed countries. Incidence in developing and low-income countries is as high as 5 per 100 000 births (Woodmansee WW (2019)). However, it is still prevalent in many developing countries.

In India due to large population obstetricians often lack necessary training which is routinely mandatory in developed countries. A recent epidemiological study from the valley of Kashmir of Indian subcontinent estimated the prevalence to be about 3% in women above 20 years of age, almost two-thirds of whom had delivered babies at home. It has been also reported that the incidence of SS in India is 2.5-4% in women above 20 years of age. (Shivaprasad C. (2011)).

Saravanan S. et al (2011) report that traditional birth assistants (TBAs) attend 37 percent of deliveries that are performed at home. They do regularly visit patients once the pregnancy is detected and provide necessary follow-ups. Thus, it may or may not lead to any complications during pregnancy. However, most of them lack extensive training with regards to complications that arise during child birth according to the authors. This could often result in delay in detection of rare diseases such as SS. Some degrees of hypopituitarism occur in nearly 1/3rd of patients with severe postpartum hemorrhage. Although symptomatic posterior pituitary function is uncommon, many patients have impaired neurohypophysis function tests. It is still frequent in both underdeveloped and developing countries. These factors account for the fact that in India the incidence of SS is 2.5%-4% higher in women population with age is over 20 as reported by Shivaprasad C. (2011).

### Pregnancy During SS

In early 70's Martin J E et al (1970) reported a case successful pregnancy of a patient who had suffered a massive post-partum hemorrhage attended by coma. During the 16 years after, the patient had only occasional menses but went through three uneventful pregnancies. In her fourth pregnancy, there were both clinical and laboratory features of decreased thyroidal and adrenal function during the fourth month. The authors report that these functions improved on hormonal replacement therapy. Tests for ACTH, TSH and GH done three months after delivery revealed significant decrease in pituitary secretory capacity.

Grimes HG, Brooks MH (1980) report the case of a 38-year-old woman who had eight spontaneous pregnancies after the onset of hypopituitarism secondary to massive postpartum hemorrhage. Hormonal replacement therapy was not provided before that. Earlier seven pregnancies had terminated in spontaneous abortions. Normal premature infant at 32 weeks gestation was delivered after Hormone replacement therapy during the eighth pregnancy. Detailed endocrinological studies were performed after the onset of eight pregnancy. Studies of pituitary function during and after the eighth pregnancy demonstrated that the patient had measurable amounts of GH, FSH, LH, TSH, ACTH, and prolactin in her plasma under basal conditions. However, these hormones did not increase approximately in response to pregnancy, stress, and specific stimuli. The authors report that the evaluation of placental function was performed at 26 weeks gestation. This evaluation consisted of measurement of estradiol, progesterone, human placental lactogen, and chorionic gonadotropin. However, no abnormality was revealed.

Soussou M. et al (2018) report a case of a 38-year-old woman who delivered her first child in 2007 with considerable bleeding during delivery. She didn't have any lactation failure and was able to resume menstrual cycles. In her second pregnancy in 2010 she had a cesarean delivery which was complicated by bleeding as well. She had to be transfused and was kept for 10 days in intensive care. Central hypothyroidism and cortisol deficiency were revealed during post-delivery investigations. She had also developed spaniomenorrhea. As

a result, hydrocortisone and Levothyroxine were prescribed. In 2015, the patient was again pregnant and was able to give birth without any complications. The authors report that the MRI had objectified an empty sellar.

## CASE DESCRIPTION:

Our case is of 34-year-old female with no menses in last 6 months, she had a history of severe irregular cycles which ranged from 3-4 months since last 15 years. She is a mother of three children of which two are male and one female, youngest child being 12-years-old. Her obstetric history consists of excessive bleeding during her 1st pregnancy which was managed by massive blood transfusion. She gave birth to a female child; agalactorrhea was present during the first months of lactation. The female child expired after 9 months which was unrelated to the mother's complicated pregnancy. Our patient was diagnosed with hypothyroidism with lab values of TSH – 7.01 MICROUI/ml, serum T4 – 3.8 ug/dl, serum T3- 0.6 and for that she was given thyroxine 10 mg along with amitriptyline for her severe headache. The patient presented with other complaints like visual problem, postural dizziness, polyuria. Two deliveries occurred after the first pregnancy which was associated with complications and were completely normal and uneventful. However she had experienced lactation failure (agalactorrhea) during both successful pregnancies. SS is characterized by lactation failure in the postpartum period, but this is observed in some cases only. Both of her children are still alive.

Laboratory tests were performed and the results were: -

| Test | Result (Before treatment) | Result (After treatment) | Reference Range |
|---|---|---|---|
| Luteinizing H. | 1.89 miU/ml | 3.5 miU/ml | 2.39-6.6 - Follicular phase |
| Follicular Stimulating H. | 2.1 miU/ml | 4.1 miU/ml | 2.5-10.2 – Follicular phase |
| Cortisol | 4.05 ug/dl-8:00 AM | 5.7 ug/dl | 4.3-22.4 ug/dl |
| T3 | 7.9 ug/ml | 9.8 ug/ml | 8.46-20.2 ug/ml |
| T4 | 4.58 ug/dl | 6.9 ug/ml | 5.13-14.06 ug/dl |
| TSH | 7.4ulU/ml | 3.9 ulU/ml | 0.27-4.2 ulU/ml |
| Sodium | 144.3mmol/L | 144 mmol/L | 136-145 mmol/L |
| Potassium | 4.3mmol/L | 4.2 mmol/L | 3.5-5.1mmol/L |

Endocrinologist suggested MRI-BRAIN in which partially empty Sella with thinned out anterior pituitary was seen which was suggestive of SS. The MRI is shown below (Figs. 1 and 2). Along with those symptoms like polyuria, severe headache, lactation failure and reports of cervical erosion and mild hyponatremia helped in making the diagnosis of SS. Cortisol deficiency is life-threatening and was treated with glucocorticoids before giving thyroid hormone replacement. The patient was started on hormonal replacement therapy (HRT) to treat gonadotropin (FSH/LH) deficiency. The basis of treatment is lifelong replacement of deficient hormones. Anterior pituitary hormones are generally affected in the following order after necrosis; growth hormone, prolactin, follicle stimulating hormone, luteinizing hormone, adrenocorticotropic hormone and then thyroid stimulating hormone (Woodmansee WW (2019)).

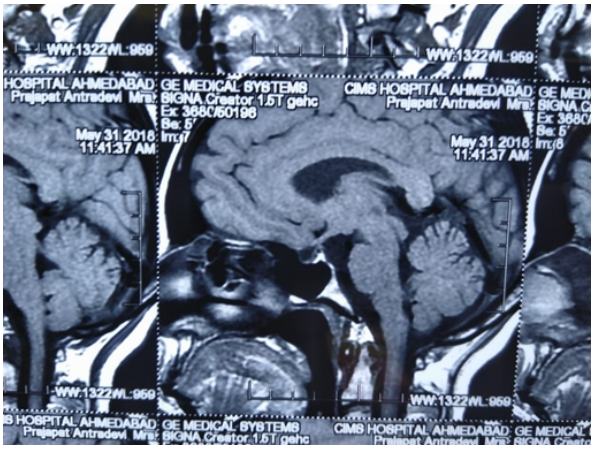


**Fig. 1 Lateral MRI scan of the brain**

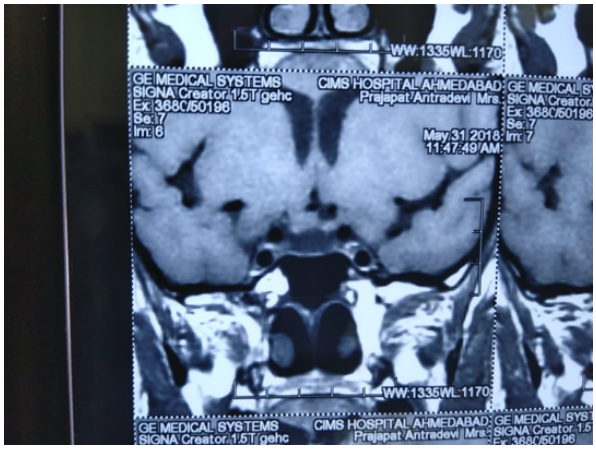


**Fig 2 MRI scan of the brain**

After two months the patient was asked to return for a follow up. The clinical features of SS are highly variable and depend on the degree of failure of secretion of pituitary hormones. The following tests were conducted during the visit:

The patient was specifically asked if she suffered frequent headaches and whether she had any complaints related to eyesight. Headaches can result due to optic nerve chiasm which in turn results from onset of SS. This is often associated with visual field loss. The answer was no. Severe lowering of blood sodium levels or hyponatremia is often seen in SS patients so those levels were checked and were found to be normal. Due to pituitary failure SS patients may also experience an acute setting of extreme hypovolemia which can result in hyponatremia (diabetes insipidus). Diabetes insipidus or passage of excessive quantities of dilute urine occurs due to the lack of anti-diuretic hormone from the posterior pituitary. Tests were conducted to make sure that was not the case here. Psychosis can occur in some cases due to SS so both patient and family members were asked necessary questions in order to determine that patient had no issues related to psychosis.

SS patients are known to suffer from amenorrhea (failure to have normal periods), loss of axillary and pubic hair, appearance of wrinkles around the eyes and lips, early aging, weakness and loss of weight, dryness of the skin, and loss of pigmentation. Hence the exam addressed those issues. It is also recommended that the exam must check for following less common, but more severe symptoms:

Circulatory collapse, Severe lowering of blood sodium levels, or hyponatremia; Diabetes insipidus or passage of excessive quantities of dilute urine due to the lack of anti-diuretic hormone from the posterior pituitary; Hypoglycemia; Congestive heart failure; Severe mental changes.

Laboratory tests on follow up showed all the hormones in normal concentration in the body. Fluid and electrolyte level were balanced. The patient felt fine and healthier than before. The patient was still unable to tolerate oral contraceptives. It was inferred that due to ongoing Hormone replacement therapy the patient was unable to tolerate oral contraceptive pill due to opposing actions. The hormone replacement was started and continued in the same manner. Patient showed positive compliance towards the drug regimen. Thyroid and cortisol were introduced first. Later estrogen was started to bring back the normal menstrual cycle. Returning of the required estrogen concentration in the body, the patient's menstrual cycle came back to normal with adequate bleeding which was absent earlier.

## DISCUSSION:

The most common hormone deficiency in SS is of LH and FSH which leads to irregular cycles. The deficiency of LH and FSH can occur gradually. SS may have developed in the patient after 1st pregnancy as it was the only complicated pregnancy she had. The SS remained undiagnosed and only hypothyroidism was taken into account for which she was prescribed thyroxine tablets. Two unplanned pregnancies have occurred after the first pregnancy. During those two pregnancies no complications were recorded. However, there is a possibility that the progressive and more intense damage could have

happened during those two normal deliveries. Parikh R et al (2016) discuss a case where there was a delay of 15 years in diagnosis of SS. As suggested by the authors, the avascularization due to blockade of hypophyseal arteries could have stimulated further pituitary damage leading to FSH and LH deficiency after the two normal deliveries in this case. Moreover, as mentioned by Parikh R. et al (2016) enlargement of the pituitary gland, small Sella size, disseminated intravascular coagulation, and/or autoimmunity may have played a role in the pathogenesis of hypopituitarism in this woman.

Radiographic images of brain are also helpful in diagnosis/confirmation of SS. MRI scan can often help in detecting the onset of SS at an early state due to the presence of enlarged pituitary, with low T1, high T2 homogenous signal. Ring enhancement may be observed. Later stages of SS can be determined by the presence of empty Sella of normal size. In developing countries MRI scans are often very expensive and a CT scan of the brain may suffice since SS can be confirmed by the presence of ring enhancement surrounding a low attenuation empty Sella.

Management should be focused on identifying missing or deficient hormones and replacing them, to ensure that patients with hypopituitarism do not succumb to circulatory collapse. Growth hormone deficiency should also be corrected.

Indeed, it has been reported that inadequate hormone concentration in the body can cause a miscarriage. Progesterone is critical in embryo implantation. Elzaan C et al (2013). Subclinical hypothyroidism is also associated with an increased risk of miscarriage and pre-term delivery and decreased IQ (Intelligent quotient) in offspring as reported by Stagnaro-Green and Pearce (2012).

Hence it is critical that the patient receives information about the safety of her pregnancy and regular follow-ups are recommended. Hypopituitarism during pregnancy should be followed strictly, and normal hormone levels should be achieved before any pregnancy. In many cases it is possible that some of the anterior pituitary functions like gonadotrophic and corticotropic secretions may be preserved. In cases where patient's gonadal function is preserved, contraceptive use should be recommended.

The differential diagnosis of SS is a non-functioning adenoma. However, patients with Sheehan's are likely to be still young when the clinical features become obvious; furthermore, they have reduced levels of insulin-like growth factor 1 (IGF-1) levels, and growth hormone levels are low, needing to be replaced for optimum restoration of the normal health, lipid profile and quality of life. Cortisol deficiency is life-threatening and should always be treated with glucocorticoids before giving thyroid hormone replacement. Hormone replacement therapy (HRT) is required to treat gonadotropin (FSH/LH) deficiency. Fertility treatment is required for those who want to conceive. In addition, diabetes insipidus should be treated by replacing ADH with the synthetic analog 1-desamino-8-d-arginine vasopressin (desmopressin, DDAVP).

## CONCLUSION

SS itself is a rare syndrome in recent times, and successful pregnancies occur rarely in cases where it is not managed with proper treatment and regular follow-ups. This woman achieved two successful and normal pregnancies while only maintaining her thyroid hormones makes it a distinct case of SS. It occurs as a result of ischemic pituitary necrosis secondary to brutal and extended shock due to obstetric hemorrhage. Vasospasm, thrombosis, and vascular compression of the hypophyseal arteries have also been described as possible causes of the syndrome. Enlargement of the pituitary gland, small Sella size, disseminated intravascular coagulation and autoimmunity have been suggested to play a role in its pathogenesis according to the National Organization of Rare Diseases (NORD). As this disorder evolves slowly, it is often diagnosed late. The symptoms of hypopituitarism appear months to years after the episode of hemorrhage, with an average lag period of about 13 years. It has been reported by NORD that approximately 75% loss of pituitary tissue occurs by the time the manifestations are observed.

History of postpartum hemorrhage, cessation of menses and failure to lactate are some important clues to diagnosis. SS is diagnosed by the finding of an empty or partially empty Sella, in about 70% and 30% of patients, respectively. Diabetes insipidus may occur as a rare manifestation of SS Woodmansee WW (2019). Early diagnosis and appropriate treatment are important for the reduction in the mortality and morbidity of the patients.

## REFERENCES


1. Soussou M. et al (2018) Maryam Soussou, Ghizlane El Mghari and Nawal El Ansari, “Sheehan's syndrome: Pregnancy is still possible”, Endocrine Abstracts (2018) 56, p738
2. Parikh R. et al (2016) Rohan Parikh, Varun Buch, Mitesh Makwana & Harit N. Buch, “The Price of a 15-Year Delay in Diagnosis of Sheehan's Syndrome”, Baylor University Medical Centre Proceedings, 29:2, pp. 212-213, 2016
3. Saravanan, S., (2011). Saravanan, S., Turrell, G., Johnson, H., Fraser, J., & Patterson, C. “Traditional birth attendant training and local birthing practices in India. Evaluation and Program Planning”, 34(3), pp 254-265. 2011
4. Shivaprasad C (2011). Shivaprasad C. “Sheehan's syndrome: Newer advances.” Indian J Endocrinology Metab. 15(Suppl3): pp S203–S207. 2011
5. Keleştimur F.(2003). Keleştimur F, “Sheehan's syndrome”, Pituitary, 6(4): pp181-188. 2003
6. Woodmansee WW (2019). Woodmansee WW. Pituitary Disorders in Pregnancy. Neurologic clinics. 37 (1): pp 63-83, 2019.
7. Grimes HG, Brooks MH (1980). Grimes HG, Brooks MH, “Pregnancy in Sheehan's syndrome. Report of a case and review”, Obstet Gynecol Surv. Aug; 35(8):481-488, 1980.
8. Martin J E et al (1970). Joseph E Martin, Paul C. MacDonald, and Norman M. Kaplan, “Successful Pregnancy in a Patient with Sheehan's Syndrome, N Engl J Med; 282: pp 425-427, 1970.
9. Elzaan C et al (2013); Elzaan C van Niekerk, Igno Siebert, Theunis Frans Kruger, “An evidence-based approach to recurrent pregnancy loss”, South African Journal of Obstetrics and Gynecology 19(3):pp. 61-65.2013.
10. Stagnaro-Green & Pearce (2012), Stagnaro-Green, A. and Pearce E. “Thyroid disorders in pregnancy”, E. Nature. Rev. Endocrinol. 8 (11),pp. 650-658, 2012