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CASE REPORT OPEN ACCESS

# Hydrocortisone as a Potential Treatment of Savage Ovary Syndrome: A Rare Case from Syria

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**Abstract**

A 32-year old woman with a secondary amenorrhea for 5 years presented to my clinic (April 2019), previously had been treated as a premature ovarian failure patient and put on HRT. With further investigation, FSH Levels were high at the menopausal range, whereas the AMH levels and antral follicles count were within normal ranges and found to be age-compatible, These findings, as well as the failure of ovaries to respond to exogenous gonadotropins, helped to set the diagnosis of Savage Ovary Syndrome, which is also known as Insensitive Ovary Syndrome (IOS). Written informed consent was obtained from the patient for publication of this case report and accompanying images" Patient was convinced to be treated empirically with a high dose of Hydrocortisone and the result was the patient well responded as a normal spontaneous menstruation happened. The analysis of FSH and estradiol induces normal values and the return of the functional activity of the ovary to the formation of multiple ovarian bilateral follicle and give an echo feature similar to the ovarian hyper stimulatory syndrome with an increase the thickness of the endometrium. This case shows the importance of further studying patients with secondary amenorrhea and high levels of gonadotropins and not to treat them all as premature ovary insufficiency patients, just like our patient was firstly treated for a long time. Furthermore, the case highlights the potential benefit of the treatment of Savage Ovary Syndrome patients with Hydrocortisone.

Key words: Resistant ovarian syndrome, Insensitive ovary, Antral follicles, Gonadotropin, Secondary amenorrhea, Infertility.

## BACKGROUND

Gonadotropin Resistant Ovary Syndrome or Insensitive Ovary Syndrome or Savage Syndrome was described as a separate syndrome in 1969 by Jones de Moraes-Ruehsen.[1] It is characterized by hypergonadotropic amenorrhea, but with normal follicular apparatus appearance on transvaginal ultrasonography study (ovaries contain primordial follicles and normal antral follicle count). However, the human gonadotropins fail to enhance the primordial follicles to grow. Possible etiologies behind this syndrome include antibodies against FSH receptor or mutations in FSH receptor gene.[2] We present a case of Savage syndrome that was diagnosed in a 32-year old patient complaining of secondary amenorrhea and infertility. She had spontaneous menstruation after treatment with a daily dose of 200 mg of hydrocortisone. This report aims to provide evidence of the importance of furthermore studying the possible immunologic etiologies behind Savage syndrome as the immunosuppressor treatment resulted in spontaneous menstruation.

## Case presentation

A 32-year old G2P2A0 woman presented to our clinic with a complaint of secondary amenorrhea for 5 years. She had normal regular (8/28) menstrual cycles from menarche at the age of 15-year old until 27 years of age. She got married at the age of 24 and had two children from two completed non-complicated pregnancies, both of which ended with a C-section indicated because of CPD (Cephalopelvic disproportion). Last C-section was 6 years and 8 months prior to her presentation to our clinic. She breastfed her younger baby for 20 months and experienced menstruating irregularity among these months. And during lactation she was taking progestin-only OCPs for contraception. Amenorrhea started just after she ablactate her second boy. She consulted her former OBS/GYN for amenorrhea and she was put on hormone therapy, which helped her to get menses but only when taking the medication. Suggested diagnosis was Idiopathic premature ovarian failure. When presented to our clinic, she had no hirsutism or any other hyper androgenism signs and no abnormalities were found on pelvic examination. Patient history ruled out hypothalamic diseases, such as anorexia, excessive weight loss, heavy exercise. As well as pituitary diseases such as Shyhan Syndrome and uterus causes of secondary amenorrhea. And MRI was clean ruling out pituitary tumors as a cause of amenorrhea and infertility. Transvaginal ultrasonography showed a regular shaped uterus of normal size and a flat endometrium (Figure 5). As well as normal size ovaries

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with a normal number of antral primordial follicles, whereas we couldn't do an ovarian biopsy as the patient refused undergoing such a penetrating procedure.

Laboratory investigations, including complete blood count, blood chemistry and urine analysis revealed normal results. Brain MRI normal and Simple X-Ray of the skull showed normal sella turcica. However, the hormonal investigations showed normal pituitary function and visual examination revealed no abnormalities in the visual field.

ACTH, TSH, Prolactin, FT4, Inhibin B, Testosterone, Androstenedione, Dehydro-epiandrosterone sulphate and cortisol levels were normal. However, Plasma Follicle-Stimulating Hormone (FSH) and Luteinizing hormone (LH) were elevated to the menopausal range at 26.7 U/mL (normal 2-15 U/mL) and 50.8 U/mL (normal 2-8 mIU/mL) respectively. Whereas repeated measurements of Estradiol levels were all low. AMH concentration was 6.92 ng/mL and this is within normal limits for the patient's age.

Autoimmune disorders (lupus erythematosus, polyglandular insufficiency, diabetes and myasthenia gravis) were excluded by blood test. The failure to respond to exogenous nor endogenous gonadotropin made the diagnosis of Savage syndrome highly suspected as the patient met most of the criteria of gonadotropin resistant ovary syndrome. Patient was convinced to be treated empirically with a daily dose of Hydrocortisone (50 x 4 mg per day) and the result was that and the patient responded as a normal spontaneous menstruation happened. Return of analyzes of FSH, estradiol and AMH to normal values (FSH 5.9) (Estradiol 91.8), (AMH 7.15) and the return of functional activity of the ovary in the form of multiple ovarian follicle giving a similar echo appearance of ovarian hyper stimulatory syndrome as shown in Figures 1, 2, 3 and 4.

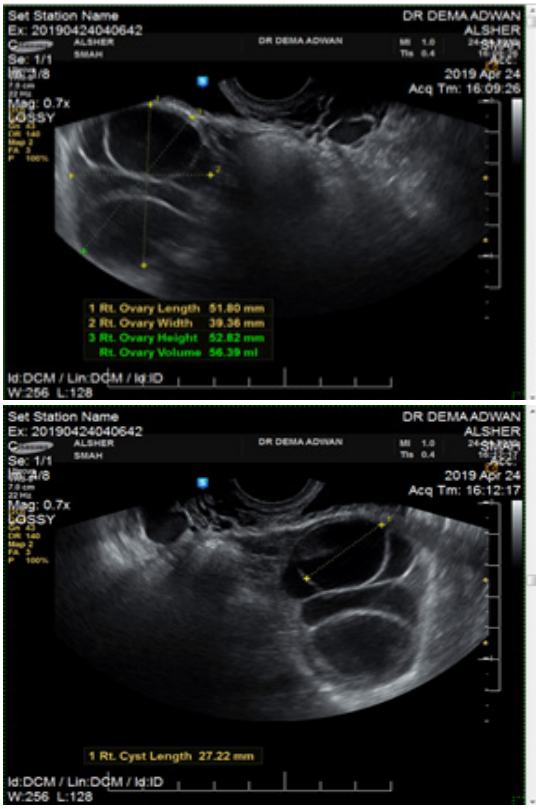


**Figure 1,2: Shows the formation of follicles on the right ovary with measurements after treatment.**

## DISCUSSION

We report a rare case of a patient with savage ovary syndrome who has responded successfully to treatment with Hydro cortisol, which may open the door to more studies on this way of treatment, the syndrome has been rarely reported in the literature so far.

Resistant ovary syndrome (ROS), first reported in 1969,[1] is a syndrome of unknown precise etiology, causes the patient to have either secondary or primary amenorrhea, despite the age-compatible number of small antral follicles. The syndrome also involves normal female habitus, normal chromosomes, with the gonadotropins elevated in blood to menopausal levels. However, the ovary does not response to the elevated gonadotropins.[2]

The syndrome has no precise known etiology. on one hand, some reports revealed that the resistance of the ovaries on Gonadotropins is due to an abnormal gonadotropin receptor protein or a defective activator protein.[3] On the other hand, many others suggest that the gonadotropin resistance in Savage Ovary Syndrome might be because the interactions of FSH and its receptor were abnormal, mostly secondary to autoimmune activities,[4,5] especially that many patients experienced the ROS after spontaneous conception, just like the case we report, which suggest the autoimmune cause[4,6] that might be the cause of the resumption of ovary activity in our patient after prescribing high doses of Hydro cortisol. Other reports of Insensitive Ovary Syndrome suggested that the syndrome is of genetic etiology, one of these reports revealed a genetic variant, I160T (NM_000145.3: exon 6: c.479 T>C: p.Ile160Thr, rs121909659), which is a mutation in extracellular ligand binding domain (7), another genetic variant was reported, N558H (NM_000145.3: exon 10: c.1672 A>C: p.Asn558His) which, as well as the other mutation

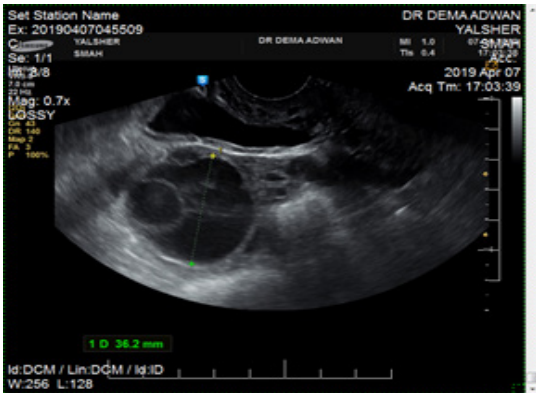


**Figure 3: Shows cyst formation on the left ovary after treatment.**

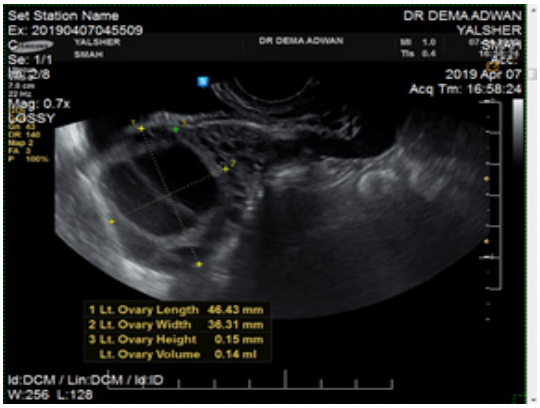


**Figure 4: Shows the formation of follicles on the left ovary with measurements after treatment.**

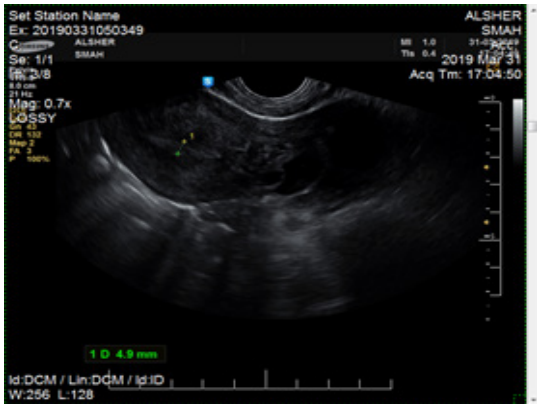


**Figure 5: Shows the thickness of the endometrium before starting cortisone therapy.**

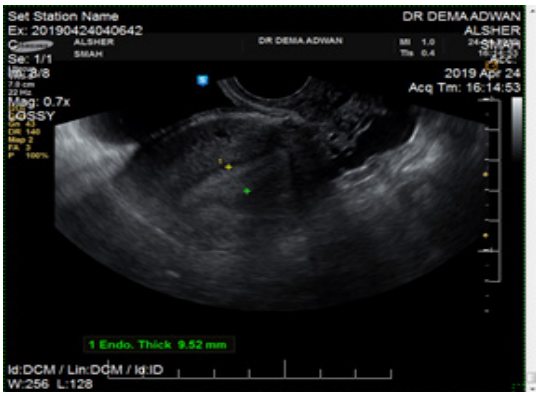


**Figure 6: shows the thickness of the endometrium after application of treatment.**

Written informed consent was obtained from the patient for publication of this case report and accompanying images*

mentioned above, considered responsible of savage syndrome in the reported case.[4,7]

In patients with primary or secondary amenorrhea, ovary reserve should be measured by measuring serum levels AMH, with the important measurement of antral follicle count by transvaginal ultrasound as lately the ovarian biopsy has not been done to measure antral follicle count with the existence of high resolution transvaginal ultrasound;[2] in Premature Ovary Insufficiency, FSH, AMH and antral follicle count are found to be in accordance.[8] On the other hand, in Resistant Ovary Syndrome (ROF), FSH levels are found to be elevated, despite the normal levels of AMH and antral follicle count.[9]

We found some reports of successful live birth in women with ROF following *in vitro* maturation of oocytes[2,10,11] in addition of the first one in 2013.[9] A patient experienced first real menstrual bleeding for 7 years, just after she stopped receiving replacing hormone therapy, which caused gonadotropin rebound phenomenon.[12] Furthermore, a patient got effective ovarian stimulation after FSH receptors upregulation due to endogenous gonadotropins down regulation by using of cyclic hormone supplementation with oral estradiol with levonogestril.[6] Another patient got spontaneously pregnant twice while receiving replacing hormone therapy, which she started 6 years ago, with a twin delivered by one of her two pregnancies.[10] A resumption of ovarian function was reported just after ovarian biopsy, too.[13] Our patient started to have spontaneous menstrual bleeding just after oral therapy with Hydrocortison.

## CONCLUSION

This case shows the importance of further studying patients with secondary amenorrhea and high levels of gonadotropins and not to treat them all as premature ovary insufficiency patients, just like our patient was firstly treated for a long time. Instead, ovary reserve should be precisely measured and further investigated. In addition, this case highlights the potential benefit of the treatment of Savage Ovary Syndrome patients with hydrocortison, the role of hydrocortison in the treatment of such patients should be further studied, which might be a promising therapy for these patients.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The author declares that there is no conflict of interest

## ABBREVIATIONS

**ROF:** Resistant Ovary Syndrome; **IOS:** Insensitive Ovary Syndrome; **FSH;** Follicular stimulating hormone; **LH:** Luteinizing hormone; **AMH:** Anti-Müllerian Hormone; **HRT:** Hormone replacement therapy; **CPD:** Cephalopelvic disproportion; **MRI:** Magnetic resonance imaging.

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