

Birth Achieved After Effective Ovarian Stimulation Combined With Dexamethasone in a Patient With Resistant Ovary Syndrome: A Case Report and Review of the Literature

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Case report

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Abstract

Background: Resistant ovary syndrome (ROS) was a rare endocrine disorder and there have been few reports of live births. As the ovarian resistance to FSH leading the immature oocytes, some researchers reported few live births after in vitro maturation (IVM) of oocytes, but it didn't work in all ROS patients.

Case presentation: A 30-year-old woman was diagnosed as ROS. GnRH analogue triptorelin acetat was used to administer downregulation, combining with corticosteroid dexamethasone (administered orally at 0.75mg three times daily) from the beginning of the downregulation to the day of oocyte collection. After 28 days of downregulation, gonadotropin (Gonal-f 225 IU and HMG 150 IU per day at first) was given for hyperstimulation. On the 11th day of gonadotropin administration, 10000 IU of hCG was given. 36h later, oocytes were retrieved and followed by IVF procedure. Two months later, the frozen embryos were thawed and transferred. 8 metaphase II oocytes were retrieved and 3 embryos were developed, in which 1 embryo was transplanted after thawed. the β -hCG value in serum was 246.7 mIU/ ml. The patient got pregnant and gave a live birth at the 35th week of pregnancy by Caesarean section.

Conclusion This is the first report about treatment ROS patient with ovarian stimulation combined with dexamethasone. In some cases of ROS, high doses of exogenous gonadotropins in combination with immunosuppressive therapy could be an effective approach in patients with ROS.

Introduction

Resistant ovary syndrome (ROS) is a rare endocrine disorder. Its concept was firstly proposed by Moraes-Ruehsen and Seegar Jones at 1967 (**de Moraes-Ruehsen & Jones, 1967**). They found that some cases of premature ovarian failure (POF) patients had milder symptoms and were not sensitive to gonadotropin, referred to as the resistant ovary syndrome(**Jones & De Moraes-Ruehsen, 1969**), which is characterized by amenorrhea, normal sex characteristics and follicle number. Furthermore, the ovary of ROS patient is not sensitive to high dose of exogenous gonadotropin. To date, the level of antimullerian hormone (AMH) is included in the diagnostic criteria of ROS(**Rogenhofer et al., 2015**).

The etiology of ROS has not been elucidated, and its pathogenesis may be related to genetic or immune factors. A number of studies have shown that FSHR mutations is associated with ROS(**Aittomaki et al., 1995; Latronico & Arnhold, 2006; W. Li et al., 2017**). For instance, patients with p.N680S mutation needed a higher doses of FSH stimulation to get the normal serum estrogen level(**Greb et al., 2005; Pabalan et al., 2014; Perez Mayorga et al., 2000; Wunsch, Sonntag, & Simoni, 2007**), suggesting that FSHR(p.N680S) affects the sensitivity of ovaries to FSH, and Ser680-FSHR developed partial "resistance" to FSH. Besides genetic factors, immune factors may also contribute to ROS. Studies have shown that there may be autoimmunity antibody Ig-FSHR which makes the ovaries to not respond to gonadotropin stimulation(**Blecher, 1984; V. Chiauuzi, Cigorraga, Escobar, Rivarola, & Charreau, 1982; V. A. Chiauuzi, Bussmann, Calvo, Sundblad, & Charreau, 2004; Dragojevic-Dikic et al., 2010; Escobar, Cigorraga, Chiauuzi, Charreau, & Rivarola, 1982; Meldrum, Frumar, Shamonki, Benirschke, & Judd, 1980**). (The paragraph should be moved to the discussion part)

Although the syndrome of ROS is well defined, slow progress has been made in the treatment of ROS. At present, pregnancies obtained with self-oocytes are mainly achieved through hormone therapy(**Amos, 1985; Aslam, Gilmour, & McCune, 2004; Ezeh & Breeson, 1995; Jequier, 1990; Mueller, Berkholz, Dittrich, & Wildt, 2003; Nawroth & Sudik, 1999; Zielinska & Rzepka-Gorska, 2011**) or in vitro fertilization (IVF) after ovulation stimulation(**Rogenhofer et al., 2015**), as well as the acquisition of valid embryos through in vitro maturation (IVM)(**Galvao, Segers, Smitz, Toumaye, & De Vos, 2018; Grynberg et al., 2013; Y. Li, Pan, Yuan, Qiu, & Yang, 2016**). Other patients suffering from ROS who fail in obtaining self-oocytes have to be enrolled in the waiting list of oocytes donation(**Fraser, Russell, Greco, & Robertson, 1986; Koninckx & Brosens, 1977; Mori, Matsuoka, Aisaka, & Kigawa, 1985; Starup & Pedersen, 1978; Sung et al., 2012; Tolino, Romano, & Montemagno, 1984; Twigg, Wallman, & McElduff, 1996**). In this paper, we report a case of a patient diagnosed with ROS, who achieved clinical pregnancy, after treatment with high-dose gonadotropin and dexamethasone. This case report offers hints on a potential therapeutic for ROS.

Case Presentation

Patient history

Patient Chen was a 30-year-old woman with BMI of 22.5, who was hospitalized due to secondary amenorrhea and infertility. Having been married for 10 years, she gave birth to a baby girl in 2009. Before coming to the center, the patient had undergone assisted reproductive technology (ART) in another hospital and failed to conceive, the detailed medical records of which was unavailable. Examination of her basic endocrine conditions (**Table 1**) indicated that the FSH value was higher than normal level, while the AMH concentration remained normal. Ultrasound scanning indicated that the uterine volume was relatively small (4.0cm*3.9cm*3.3cm). Sinus follicles more than 10 antral follicle were observed in both ovaries. Blood tests and genetic analysis excluded lupus erythematosus, multiglandular insufficiency, diabetes and myasthenia gravis, and chromosomal abnormalities (Fragile X syndrome, Turner syndrome, and Swyer syndrome). The patient has a karyotype of 46, XX.

According to the 5th semen analysis standard of world health organization, the husband's sperm concentration and motility were in the normal range, sperm acrosomal enzyme activity was normal. The study was conducted in accordance with the ethical guidelines of the institution concerned and with the informed consent of the patient.

Table 1 Hormonal profile

	2019-3-14	2019-4-12
FSH, IU/L (N early follicular phase: 2.5 - 10.2)	42.37	40.8
LH, IU/L (N early follicular phase: 1.9 - 12.5)	15.13	11.49
E2, pg/mL (N early follicular phase: 11 - 69)	15	11
AMH, ng/mL (N: 2.1 - 6.5)	6,29	6.14
T, nmol/L (N: 0.7 - 3.1)	1.8	–
P, ng/mL (N early follicular phase: 0.38 - 2.28)	0.15	–
PRL, mIU/L (N: 72 - 511)	408.94	–
FT3, pmol/L (N: 4 - 10)	4.92	–
FT4 pmol/L (N: 9 - 25)	18.39	–
TSH, mIU/L (N: 0.3 - 5.0)	3.01	–
AFC (2 - 12 mm) (N: 12 - 24)	> 20	28

Abbreviations: N, normal ranges; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E2, Estradiol; AMH, anti-mullerian hormone; T, testosterone; P, progesterone; PRL, prolactin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; AFC, antral follicle count.

Controlled Ovarian Hyperstimulation and IVF

After administrated on March 4, 2019, the patient received two cycles of ovarian hyperstimulation (Table 2). The first one (May 19, 2019) was started with 3.75 mg of GnRH analogue triptorelin acetate injection (FERRING, Switzerland), and gonadotropin (300IU/d, 15d) at cycle day 30, which was abandoned due to follicular dysplasia. Then the second cycle started at July 6, 2019, when the patient was first given a 3.75 mg of triptorelin acetate injection for down-regulation on the second day of menstruation. Controlled ovarian hyperstimulation was initiated at day 30 with daily subcutaneous injections of gonadotropin recombinant FSH (Gonal-f Merck Serono, Darmstadt, Germany) 225 IU/d and HMG 150 IU/d for 3 days and then daily Gonal-f 225 IU/d, HMG 225 IU/d and Luveris (Merck Serono, Darmstadt, Germany) 75 IU/d for 7 days. During the hyperstimulation period, the folliculometry with ultrasonography, and estradiol, luteinizing hormone, follicle-stimulating hormone and progesterone were measured to monitor follicular maturation. Then 10,000 IU human chorionic gonadotropin (HCG) was administered (lizho pharmaceuticals, China) with s.c. injection. 36h later ultrasound guided transvaginal follicular aspiration was performed under the negative pressure of 110 mmHg (14.7 kpa) using a single lumen aspiration needle (Cook; William Cook Australia Pty Ltd, Australia). A total of 8 Metaphase II (MII) oocytes were collected. After in vitro fertilization 3 embryos were vitrified and cryopreserved, and the remaining embryos were discarded.

During the whole period of down-regulation and controlled ovarian hyperstimulation the patient was orally administered dexamethasone at 0.75mg daily.

Table 2 Cycle characteristics and results in patient with resistant ovary syndrome

Cycle No.	Protocol	Hormon	Total gonadotropin (IU)	Days of stimulation	Serum E2 on oocyte retrieval day (pg/mL)	Numbers of follicles (>14mm)	MI	D3 embryo	The Result
1	Long GnRH agonist	Triptorelin Acetate Injection	3000	14	--	Follicular dysplasia	0	0	Cycle the cancel
2	Long GnRH agonist	Triptorelin Acetate Injection	4800	10	1973	8	8	3	Pregnant

Abbreviations: GnRH, gonadotropin-releasing hormone; MI, Metaphase II oocytes; D3, the third day.

Frozen-thawed embryo transfer and follow-up

2 months after the second ART cycle, hormone replacement cycle for Endometrial preparation was started at day 3 of menstrual cycle, consisting of 5 days with 4 mg and then 5 days with 6 mg of estradiol valerate tablets (Bayer, Germany). Endometrial thickness was 7 mm at day 13, and 9 mm at day 16 after additional 3 days with 8 mg of estradiol valerate. The serum E₂ at day 16 was 346 pg/mL. Progesterone (0.05 ng/MI) and human chorionic gonadotropin (HCG, 10000 IU) were injected at the night of day 16.

Progesterone luteal support with vaginal tablets containing 40 mg of progesterone (Utrogestan, Besins, Paris, France) daily was started on day 17, and continued until the day of the hCG test and, if pregnant, until 10 weeks of pregnancy.

One embryo was thawed at day 20 (14 CII) and transplanted. Serum value of β-hCG was 246.7 mIU/mL at 13th day after the transfer, and vaginal ultrasonography showed clinical pregnancy 28 days after. The pregnancy evolved without complications until the 35th weeks, when the patient had oligohydramnios and gave birth to a baby girl by Caesarean section. The fetus weight 2200 g and was in good health.

Table 3 Cases of ROS received pregnancy through different treatments

Author	Patient No.	Age at intake	Type of infertility	BMI (kg/m ²)	Basal AFC	AMH (µg/L)	Ovarian histology	E2	FSH	Ig-FSHR	Infertility treatments before pre
Amos, W. L., Jr. (1985)(Amos, 1985)	1	41	Secondary	NA	NA	NA	NA	NA	88.4 IU/L	NA	HRT
Jequier, A. M. (1990)(Jequier, 1990)	2	28	Secondary*	NA	NA	NA	NA	31-52 pmol/L	125 U/L	NA	HRT
	3	30	Secondary*	NA	NA	NA	normal ovarian stroma and follicles	76 pmol/L	range seen in postmenopausal women	NA	HRT
Nawroth, F. and R. Sudik (1999) (Nawroth & Sudik, 1999)	4	32	Secondary	NA	NA	NA	NA	NA	NA	NA	HRT
Mueller, A., et al. (2003)(Mueller et al., 2003)	5	26	Primary	NA	NA	NA	normal density of follicles	NA	70 IU/L	NA	HRT
Aslam, M. F., et al. (2004)(Aslam et al., 2004)	6	19	Secondary	NA	NA	NA	NA	NA	133.9 U/L	NA	HRT
	7	24	Secondary	27	NA	NA	NA	NA	Higher than normal	NA	HRT
Zielinska, D. and I. Rzepka-Gorska (2011)(Zielinska & Rzepka-Gorska, 2011)	8	31	Secondary	NA	NA	NA	NA	18.1 pg/ml	58.2 IU/mL	NA	HRT
Ezeh, U. I. O. and A. J. Breeson (1995) (Ezeh & Breeson, 1995)	9	32	22	NA	NA	NA	NA	39 pmol/L	95-115 IU/L	NA	Ovarian Hyperstim
Rogenhofer, N., et al. (2015) (Rogenhofer et al., 2015)	10	26	Secondary	22	15	2.1	NA	28.7 pg/mL	50.8 U/mL	antibodies directed to hMG but not to recFSH	Controlled Ovarian Hyperstim and IVF
Grynberg, M., et al. (2013)(Grynberg et al., 2013)	11	29	primary	normal	23 and 18	4.50 and 4.36	NA	<15	40.3 and 38.4 mIU/mL	NA	IVM
Li, Y., et al. (2016) (Y. Li et al., 2016)	12	33	Secondary*	NA	25	12.27	NA	260.57 pmol/l	41.99 IU/L	NA	IVM
Galvao, A., et al. (2018)(Galvao et al., 2018)	13	29	primary	27.7	37	8.6	NA	NA	27.7 IU/L	NA	IVM
	14	36	primary	18.9	40	2.11	NA	NA	7.9 IU/L	NA	IVM
	15	23	primary	24.8	50	2.88	NA	NA	49.1 IU/L	NA	IVM

Abbreviations: BMI, body mass index; AFC, antral follicle count; AMH, anti-mullerian hormone; HRT, Hormone Replacement Therapy; IVM, in vitro maturation; ART, assisted reproductive technologies; recFSH, ; FSHR, ; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; HP-hMG, highly purified human menopausal gonadotropin; 17β-E2, estradiol-17β; NA, not applicable.

*One live birth after spontaneous birth

Discussion And Conclusion

In this paper, we reported the clinical pregnancy treatment of one ROS patient. The first ovarian hyperstimulation cycle induced little ovarian response. Prior to the second cycle, we detected the presence of Ig-FSHR in the peripheral blood of the patients. Then we started the second cycle of ovarian hyperstimulation, while using of the immunosuppressant dexamethasone in the process of down-regulation and hyperstimulation, so as to reduce the FSHR antibody level in

peripheral blood. The patient finally obtained 8 mature oocytes and frozen 3 embryos. Two months later, one embryo was thawed and transferred, finally the patient got clinical pregnancy and live birth.

Infertility is a huge problem for people of reproductive age with ROS, and the chances of having children with their own oocytes are unpredictable. The treatments of ROS has been under exploration. In previous cases of successful pregnancy, treatments were mainly conducted through hormone replacement therapy, controlled ovarian hyperstimulation, and IVM (**Table 3**). In early cases, different hormone replacement therapies were often used to restore normal menstruation(Fraser et al., 1986; Koninckx & Brosens, 1977; Mori et al., 1985; Starup & Pedersen, 1978; Sung et al., 2012; Tolino et al., 1984; Twigg et al., 1996). Later, it was found that patients with secondary ROS could obtain pregnancy through periodic estrogen administration(Jequier, 1990). For hormone therapy of ROS, estradiol, clomiphene, high-dose hMG and estradiol were commonly used(Mori et al., 1985). However, ROS showed significant individual differences. Some cases of ROS could even recover spontaneously(Mueller et al., 2003), while other ROS had amenorrhea in general, but could get pregnant through hormone therapy more than once(Aslam et al., 2004). Therefore, the treatment of ROS is also according to the severity of the disease.

Some researchers considered that the different basic FSH levels can evaluate the degrees of ovarian follicle resistance to FSH more accurately than the follicle numbers(**Huang et al., 2017**). In views of our opinion, although the grading of ROS according to FSH levels can preliminarily determine the severity of ROS, it is not rigorous, because there were only 6 cases in this report, and the case reported by Galvao also proved that(Galvao et al., 2018) patient with normal FSH level could showed obvious resistance to gonadotropin stimulation. So, we considered that the FSH level can only reflect the follicular reactivity to ovulation drugs from one side, which can only be used for reference in the selection of treatment plan.

In fact, there was heterogeneity in different ROS patient, and the etiology may involve gene mutation(Latronico & Arnhold, 2006; W. Li et al., 2017) and autoimmune disorders(V. Chiazuzzi et al., 1982; Escobar et al., 1982). ROS can only be treated effectively if the causes of ROS are clearly identified. Although some research reported the IVM could be as one of the treatment of ROS(Galvao et al., 2018), the etiology of the patients were still unknown. The association between ROS and autoimmune was first proposed in 1982 (V. Chiazuzzi et al., 1982; Escobar et al., 1982). The authors found that gonadotropin resistance has the same immune mechanism as myasthenia gravis, and they confirmed that the serum of this patient contained a substance similar to gamma globulin, which inhibited the specific binding of FSH to the receptor in vitro, this could be the reason of the ovary's non-response to gonadotropin stimulation. In 2004, Chiazuzzi VA found that in their study, all the ROS patients had circulating immune complex in the serum, which might block the binding of FSH to its receptor(V. A. Chiazuzzi et al., 2004).

Although there were evidences that ROS was highly linked to autoimmune disorder, few cases have been reported in which Ig-FSHR antibody activity was detected or corresponding immunotherapy was given in patients with ROS. In 2015, Rogenhofer described a ROS patient getting pregnancy through controlling stimulate ovulation. In their results, resistance to HMG positive signals were detected in the sera, so they chose recombinant follicle element of beta and high purity HMG for ovarian stimulation scheme and got a good ending, this was a good case for symptomatic treatment on the basis of cause. (Rogenhofer et al., 2015)

In this paper, we detected Ig-FSHR antibody activity in patient's serum. Using standard Long GnRH agonist scheme, with large dose of gonadotropin, combining with immunosuppressive dexamethasone, the patient eventually got pregnancy. We provided possible hints in ROS treatment.

In general, ROS is closely related to autoimmunity, so we should identify the cause and then targeted treatment be carried out, which may greatly increase the success rate of ROS patients. For some patients with abnormal immunity of ROS, it can be an effective method to treat with large dose of gonadotropin drugs in combination with immunosuppressive agents.

Declarations

Ethics approval and consent to participate

This survey was approved by the Ethical Committee of Center of Reproductive Medicine Tongji Medical College (2019-04). Informed consents were obtained from participant involved in our study.

Consent for publication

Not applicable.

Availability of data and materials

Full availability of data and material are declared. Extra data is available by emailing Wenpei Xiang

Competing interests

The authors declare that they have no competing of interest.

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None.

Authors' contributions

Huiying Li was responsible for drafting the manuscript. Tianli Chang helped to diagnosis, treatment, literature research and manuscript writing. Hongbei Mu and Qiaojuan Mei helped to write the part of the manuscript and storage of data. Wenpei Xiang contributed to diagnosis, treatment plan and guideline of this study and manuscript revising. All authors read and approved the final manuscript.

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References

1. Aittomaki, K., Lucena, J. L. D., Pakarinen, P., Sistonen, P., Tapanainen, J., Gromoll, J., . . . Delachapelle, A. (1995). MUTATION IN THE FOLLICLE-STIMULATING-HORMONE RECEPTOR GENE CAUSES HEREDITARY HYPERGONADOTROPIC OVARIAN FAILURE. *Cell*, *82*(6), 959-968. doi:10.1016/0092-8674(95)90275-9
2. Amos, W. L., Jr. (1985). Pregnancy in a patient with gonadotropin-resistant ovary syndrome. *American journal of obstetrics and gynecology*, *153*(2), 154-155. doi:10.1016/0002-9378(85)90101-2
3. Aslam, M. F., Gilmour, K., & McCune, G. S. (2004). Spontaneous pregnancies in patients with resistant ovary syndrome while on HRT. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*, *24*(5), 573-574. Retrieved from <Go to ISI>://MEDLINE:15369944
4. <https://www.tandfonline.com/doi/abs/10.1080/01443610410001722707>
5. Blecher, M. (1984). Receptors, antibodies, and disease. *Clin Chem*, *30*(7), 1137-1156. Retrieved from <http://clinchem.aaccjnl.org/content/clinchem/30/7/1137.full.pdf>
6. Chiauzzi, V., Cigorruga, S., Escobar, M. E., Rivarola, M. A., & Charreau, E. H. (1982). Inhibition of follicle-stimulating hormone receptor binding by circulating immunoglobulins. *J Clin Endocrinol Metab*, *54*(6), 1221-1228. doi:10.1210/jcem-54-6-1221
7. Chiauzzi, V. A., Bussmann, L., Calvo, J. C., Sundblad, V., & Charreau, E. H. (2004). Circulating immunoglobulins that inhibit the binding of follicle-stimulating hormone to its receptor: a putative diagnostic role in resistant ovary syndrome? *Clinical Endocrinology*, *61*(1), 46-54. doi:10.1111/j.1365-2265.2004.02054.x
8. de Moraes-Ruehsen, M., & Jones, G. S. (1967). Premature ovarian failure. *Fertil Steril*, *18*(4), 440-461.
9. Dragojevic-Dikic, S., Marisavljevic, D., Mitrovic, A., Dikic, S., Jovanovic, T., & Jankovic-Raznatovic, S. (2010). An immunological insight into premature ovarian failure (POF). *Autoimmun Rev*, *9*(11), 771-774. doi:10.1016/j.autrev.2010.06.008
10. Escobar, M. E., Cigorruga, S. B., Chiauzzi, V. A., Charreau, E. H., & Rivarola, M. A. (1982). Development of the gonadotrophic resistant ovary syndrome in myasthenia gravis: suggestion of similar autoimmune mechanisms. *Acta endocrinologica*, *99*(3), 431-436. doi:10.1530/acta.0.0990431
11. Ezeh, U. I. O., & Breeson, A. J. (1995). Spontaneous pregnancy following pretreatment with gonadotrophins in a patient with resistant ovary syndrome. *Journal of Obstetrics and Gynaecology (Abingdon)*, *15*(6), 423-424. doi:10.3109/01443619509009184
12. Fraser, I. S., Russell, P., Greco, S., & Robertson, D. M. (1986). Resistant ovary syndrome and premature ovarian failure in young women with galactosaemia. *Clinical reproduction and fertility*, *4*(2), 133-138. Retrieved from <Go to ISI>://MEDLINE:3091236
13. Galvao, A., Segers, I., Smits, J., Tournaye, H., & De Vos, M. (2018). In vitro maturation (IVM) of oocytes in patients with resistant ovary syndrome and in patients with repeated deficient oocyte maturation. *Journal of assisted reproduction and genetics*. doi:10.1007/s10815-018-1317-z
14. Greb, R. R., Grieshaber, K., Gromoll, J., Sonntag, B., Nieschlag, E., Kiesel, L., & Simoni, M. (2005). A common single nucleotide polymorphism in exon 10 of the human follicle stimulating hormone receptor is a major determinant of length and hormonal dynamics of the menstrual cycle. *J Clin Endocrinol Metab*, *90*(8), 4866-4872. doi:10.1210/jc.2004-2268
15. Grynberg, M., Peltoketo, H., Christin-Maitre, S., Poulain, M., Bouchard, P., & Fanchin, R. (2013). First Birth Achieved After In Vitro Maturation of Oocytes From a Woman Endowed With Multiple Antral Follicles Unresponsive to Follicle-stimulating Hormone. *Journal of Clinical Endocrinology & Metabolism*, *98*(11), 4493-4498. doi:10.1210/jc.2013-1967
16. Huang, B., Xu, P., Liu, M., Fu, Y., Xu, J., Zeng, Y., . . . Liu, J. (2017). [Grading and etiology of ovarian resistant syndrome]. *Chinese Journal of Practical Gynecology and Obstetrics*, *33*(09), 963-966.
17. Jequier, A. M. (1990). Conception in the resistant ovary syndrome occurring during hormone replacement therapy: a report of 2 cases. *The Australian & New Zealand journal of obstetrics & gynaecology*, *30*(2), 176-178. doi:10.1111/j.1479-828X.1990.tb03257.x
18. Jones, G. S., & De Moraes-Ruehsen, M. (1969). A new syndrome of amenorrhoea in association with hypergonadotropism and apparently normal ovarian follicular apparatus. *Am J Obstet Gynecol*, *104*(4), 597-600.
19. Koninckx, P. R., & Brosens, I. A. (1977). The Gonadotropin-Resistant Ovary Syndrome as a Cause of Secondary Amenorrhea and Infertility. *Fertility and Sterility*, *28*(9), 926-931. doi:10.1016/S0015-0282(16)42792-5
20. Latronico, A. C., & Arnhold, I. J. P. (2006). Inactivating mutations of LH and FSH receptors—from genotype to phenotype. *Pediatric endocrinology reviews : PER*, *4*(1), 28-31. Retrieved from <Go to ISI>://MEDLINE:17021580
21. Li, W., He, W., Zhou, L., Hu, X., Li, S., Gong, F., & Tan, Y. (2017). Study of two Chinese families affected with resistant ovarian syndrome resulted from novel mutations of FSHR gene. *Zhonghua yi xue yi chuan xue za zhi = Zhonghua yixue yichuanxue zazhi = Chinese journal of medical genetics*, *34*(2), 196-199. doi:10.3760/cma.j.issn.1003-9406.2017.02.009
22. Li, Y., Pan, P., Yuan, P., Qiu, Q., & Yang, D. (2016). Successful live birth in a woman with resistant ovary syndrome following in vitro maturation of oocytes. *Journal of Ovarian Research*, *9*(54). doi:10.1186/s13048-016-0263-6

23. Meldrum, D. R., Frumar, A. M., Shamonki, I. M., Benirschke, K., & Judd, H. L. (1980). Ovarian and adrenal steroidogenesis in a virilized patient with gonadotropin-resistant ovaries and hilus cell hyperplasia. *Obstetrics and gynecology*, *56*(2), 216-221. Retrieved from <Go to ISI>://MEDLINE:7393511
24. Mori, H., Matsuoka, R., Aisaka, K., & Kigawa, T. (1985). Sporadic ovulation in a case of resistant ovary syndrome. *Asia-Oceania journal of obstetrics and gynaecology*, *11*(3), 357-362. Retrieved from <Go to ISI>://MEDLINE:3910009
25. <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/j.1447-0756.1985.tb00755.x>
26. Mueller, A., Berkholz, A., Dittrich, R., & Wildt, L. (2003). Spontaneous normalization of ovarian function and pregnancy in a patient with resistant ovary syndrome. *European Journal of Obstetrics Gynecology and Reproductive Biology*, *111*(2), 210-213. doi:10.1016/s0301-2115(03)00211-2
27. Nawroth, F., & Sudik, R. (1999). Pregnancy and hormone replacement therapy in a patient with resistant ovary syndrome. [Schwangerschaft unter Hormonersatztherapie bei einer Patientin mit einem passageren "Resistant-Ovary-Syndrome"]. *Zentralblatt fur Gynakologie*, *121*(5), 255-257. Retrieved from <Go to ISI>://MEDLINE:10408080
28. Pabalan, N., Trevisan, C. M., Peluso, C., Jarjanazi, H., Christofolini, D. M., Barbosa, C. P., & Bianco, B. (2014). Evaluating influence of the genotypes in the follicle-stimulating hormone receptor (FSHR) Ser680Asn (rs6166) polymorphism on poor and hyper-responders to ovarian stimulation: a meta-analysis. *J Ovarian Res*, *7*, 285. doi:10.1186/s13048-014-0122-2
29. Perez Mayorga, M., Gromoll, J., Behre, H. M., Gassner, C., Nieschlag, E., & Simoni, M. (2000). Ovarian response to follicle-stimulating hormone (FSH) stimulation depends on the FSH receptor genotype. *J Clin Endocrinol Metab*, *85*(9), 3365-3369. doi:10.1210/jcem.85.9.6789
30. Rogenhofer, N., Pavlik, R., Jeschke, U., Wypior, G., Ochsenkuehn, R., & Thaler, C. J. (2015). Effective Ovarian Stimulation in a Patient with Resistant Ovary Syndrome and Antigonadotrophin Antibodies. *American Journal of Reproductive Immunology*, *73*(2), 185-191. doi:10.1111/aji.12306
31. Starup, J., & Pedersen, H. (1978). Hormonal and ultrastructural observations in a case of resistant ovary syndrome. *Acta endocrinologica*, *89*(4), 744-752. doi:10.1530/acta.0.0890744
32. Sung, M., Kim, K.-T., Lee, K.-B., □□□, □□□, □□□, . . . □□□. (2012). A case of resistant ovary syndrome. [□□□ □□□□□ 1□]. *Obstetrics & Gynecology Science*, *55*(12), 1039-1042. doi:10.5468/kjog.2012.55.12.1039
33. Tolino, A., Romano, L., & Montemagno, U. (1984). Resistant ovary syndrome and fertility. *Acta Europaea fertilitatis*, *15*(3), 175-177. Retrieved from <Go to ISI>://MEDLINE:6485708
34. Twigg, S., Wallman, L., & McElduff, A. (1996). The resistant ovary syndrome in a patient with galactosemia: A clue to the natural history of ovarian failure. *Journal of Clinical Endocrinology and Metabolism*, *81*(4), 1329-1331. doi:10.1210/jc.81.4.1329
35. Wunsch, A., Sonntag, B., & Simoni, M. (2007). Polymorphism of the FSH receptor and ovarian response to FSH. *Annales D Endocrinologie*, *68*(2-3), 160-166. doi:10.1016/j.ando.2007.04.006
36. Zielinska, D., & Rzepka-Gorska, I. (2011). Pregnancy in a patient with resistant ovary syndrome - a case report. *Ginekologia Polska*, *82*(10), 785-787. Retrieved from <Go to ISI>://WOS:000296301400010