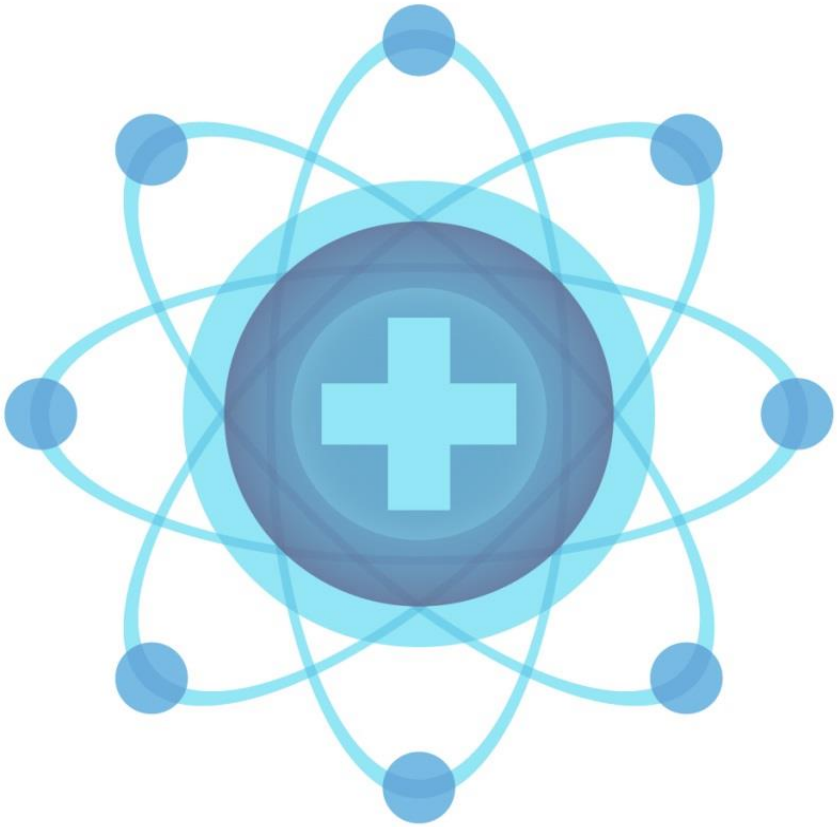

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Compleks pregravid preparation in the prevention of miscarriage in women with hyperandrogenism

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Abstract: Hyperandrogenism is diagnosed in almost 10% of women worldwide and impairs the reproductive system: menstrual disorders are diagnosed in 50-70% of patients, infertility in 60-80% of cases and miscarriage in 20-30% of cases. Comprehensive corrective pre-pregnancy treatment was used in these patients, and its efficacy was confirmed by the onset of pregnancy and normalization of the hormonal background.

Keywords: hyperandrogenism, hormonal background, pregravidarial preparation.

Miscarriage (MC) and infertility in women of fertile age is a very urgent medical and social problem. Hyperandrogenism (HA) is rightfully recognized as one of the causes of these conditions and a common risk factor for pathology of the reproductive system. GA is quite widespread in women of reproductive age. Violation of the secretion of androgens by the adrenal glands and ovaries, impaired metabolism of the hormones produced and leads to HA [4]. In almost ¾ women, HA causes disorders of menstrual and reproductive functions, which leads to infertility [1].

During pregnancy, women with HA often experience complications: the threat of termination of pregnancy, ischemic-cervical insufficiency (ICI), placental dysfunction, and the threat of premature birth. One or more of these complications cause miscarriage (FB) or premature birth [4].

Russian scientists cite some figures: SPB is noted in 20% of women, and in 80% in the first trimester. Endocrine pathology, in particular HA, is the cause of habitual miscarriages in every fifth pregnant woman [2].

Pregnant women with GA have a proven high risk of perinatal complications; therefore, at the stage of pregnancy planning, pregravid preparation is mandatory in order to minimize the negative effects of an excess of androgens on pregnancy and reduce the incidence of complications [11].

HA in women also disrupts the reproductive system: menstrual irregularities (MC) are noted in 50-70% of patients, infertility - in 60-80%, NB - in 20-30%. Consequently, GA is not only a medical, but also a social problem, since against the background of internal and external changes occurring in a woman's body, the psychoemotional state changes and the quality of life decreases [9].

The most common pathology leading to HA in women is PCOS; it is diagnosed in three out of 4-5 women [5, 6, 7, 10]. Clinical symptoms of PCOS are well diagnosed: MC disorders, infertility, hirsutism. Pregnancy is possible only after

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effective medical correction of the condition (treatment of infertility by stimulating ovulation) or surgical treatment [3].

Diagnosis of PCOS is based on the results of clinical, hormonal and ultrasound studies. The history should focus on oligomenorrhea with menarche, anovulation, primary infertility, early multiple SPD [3].

These facts involuntarily suggest that the attitude of the female population to such a formidable pathology as GA is not serious, which is most likely explained by the lack of knowledge of women about this pathology and the lack of active educational work at the level of primary health care, the media and the state as a whole.

Correction and prevention of HA should be carried out starting with pregravid preparation and continued in early pregnancy. The duration of correction for each patient is individual and depends on the severity of the obstetric and gynecological history, the severity of clinical and biochemical symptoms of HA and concomitant somatic pathology. In women with infertility and / or with the usual SPD, correction implies the restoration of reproductive function and the preservation of the subsequent pregnancy with the minimization of androgen-dependent complications.

Correction of GA and treatment of NECJ is extremely necessary both from the point of view of the health of each individual woman and the female population as a whole, and therefore the composition of the population and fertility in it.

Objective: to develop and evaluate the effectiveness of diagnostic markers of complex corrective pregravid preparation in terms of the relationship between hormonal status and biochemical markers of the endometrium in women with hyperandrogenism.

Material and research methods:

We examined 146 women of reproductive age 21-35 years (the average age of the examined patients was 27.8 ± 2.89) with reproductive disorders (primary / secondary infertility, early SPD) against the background of clinical and / or biochemical symptoms of GA in history. Group I included 62 patients with PCOS with pre-obesity and degree I obesity (BMI within 25-34.9 points) aged 21 to 35 years, the average age was 28.2 ± 1.34 years. Group II included 64 patients with PCOS and normal body weight (BMI in the range of 18.5-24.9 points) aged 23 to 35 years, the average age was 29.8 ± 1.25 years.

The control group (CG) included 20 pregnant women 22-34 years old without GA and with physiological hormone levels, with normal BMI, identical with the studied patients in terms of age and presence of extragenital pathology (mean age 29.1 ± 1.16 years).

We studied the prevailing nature of the distribution of subcutaneous fat (SFA) along the waist circumference (OT), with OT less than 80cm, the female (gynoid) type of SSS distribution was ascertained, and with OT over 80cm, the visceral (android) type.

The severity of hirsutism was assessed according to the Ferriman-Gallwey scale [8], calculating the "hirsut number" in points, the norm was taken as a sum of 7-

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12 points, moderate hirsutism was stated with a hirsut number of 20-25 points, pronounced hirsutism - more than 25 points.

Laboratory studies of the condition of the patients of all groups, including the control group, were carried out in parallel with the clinical examination for the first time upon treatment, then again 2 weeks after the completion of the course of pre-gravid preparation.

The laboratory examination consisted of standard and specific tests, based on the purpose and objectives of the study, its specificity and design: general clinical analysis of blood and urine, biochemical blood test, indicators of various links of hemostasis, levels of steroid hormones in serum and saliva, determination of infectious markers, which meant taking venous and peripheral blood and urine strictly on an empty stomach, excluding fatty and salty foods and spices the day before.

The study of hormones in the blood serum and saliva in all patients of the main and CG implied the determination of gonadotropic hormones (LH, FSH), total testosterone, estradiol, progesterone, 17-ONP, DHEA-S, glycodelin (PP14) and IPFR-1. The results obtained for the patients of the main group were compared with the results for women in the CG. The hormonal background was studied in the first phase of MC, in dynamics after corrective therapy before pregnancy.

The main groups of patients were divided by us according to the type of pregravid corrective therapy, each into 2 subgroups A and B.

Pregravid preparation of patients A of subgroups I and II of groups consisted of standard conservative treatment, including biguanides (metformin 500 mg), stimulation of ovulation with agonists and antagonists of gonadotropin-releasing hormones, anti-estrogen drugs (clomiphene citrate) at 50-100 mg / day. under the control of ultrasound. We performed ultrasound to monitor the dynamics of follicle growth. Starting from the 14th day of the menstrual cycle, the patients took gestagens (dydrogesterone 10/20 mg or micronized progesterone 100 mg (daily dose - 200-300 mg), continuing their intake with the onset of pregnancy. micronized progesterone was extended to 36 weeks to reduce the risk of complications at various gestational times.

Pregravid preparation of patients in subgroups I and II of groups consisted of standard conservative treatment, adherence to a healthy lifestyle, exclusion from the diet of foods from fast-dissolving glucose and with a high index of insulin resistance. In order to increase the sensitization of cells to insulin, myoinositol 750 mg (daily dose up to 4000 mg) was included in the standard treatment. Stimulation of ovulation was carried out by agonists and antagonists of gonadotropin-releasing hormones, anti-estrogen drugs (clomiphene citrate) at 50-100 mg / day. under the control of ultrasound. With the onset of biochemical pregnancy, metformin was canceled, while myoinositol was continued**.**

Results of our own research

At the initial visit, all patients had complaints of primary or secondary infertility, MC, violations of MC disorders. When analyzing morphograms in pregnant women of groups I and II, an insignificant difference in body type was

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noted. Most patients of group I were diagnosed with male type of hair growth, visceral type of obesity was diagnosed in 22.58% (n = 14) from puberty, in the remaining 77.42% (n = 48) - in the post-pubertal period (Table 1). In group II, the picture was similar - 81.25% (n = 52) had a female type of body structure.

Table 1. Data of anamnesis and examination of patients of groups I and II and CG

Options	I group (n=62)	II group (n=64)	CG (n=20)
Primary infertility	44 (70,97%)	14 (21,88%)	--
Secondary infertility	14 (22,58%)	47 (73,44%)	--
Early pregnancy loss	26 (41,94%)	17 (26,56%)	--
MC violations	52 (83,87%)	46 (71,88%)	--
Male body type	60 (96,77%)	52 (81,25%)	--
Female body type	2 (3,23%)	12 (18,75%)	20 (100%)
Hirsutism scores	22,7±1,5	22,2±1,6	4,7±0,68
Acne	10 (16,13%)	9 (14,06%)	--
Striae	38 (61,29%)	26 (40,63%)	--
Acanthosis nigroid	14 (22,58%)	8 (12,50%)	--

The diagnosis of PCOS was made taking into account the history, complaints and results of laboratory and instrumental research methods. We studied the hormonal background on days 2-3 with natural or induced MC - an increase in total testosterone up to 4.12 ± 0.26 ng / ml, DHEA-S - 9.83 ± 0.35 μmol / L, LH - 13.51 ± 1.79 IU / L, FSH - 5.34 ± 0.55 IU / L, growth of 17-ONP no more than 1.85 ± 0.75 ng / ml, LH / FSH ratio - 2.78 ± 0.75, those. exceeding more than 2, which is a diagnostic criterion for PCOS, was typical for all women in the main groups.

Signs of PCOS by ultrasound on the 3-7th day of the MC (an increase in the volume of the ovaries by more than 10 cm3 due to a hyperechoic stroma with many (more than 10-12) diffusely and / or along the periphery in the form of a necklace of follicles, up to 8-10 mm in size, compaction ovarian capsules) were found in the majority of women in the main groups. Visualization of such a picture is typical for women with GA.

The hormonal background in GA differs sharply from the CG indicators, so all indicators differ significantly ($p < 0.05$), with the exception of FSH and 17-SNP, the differences of which are not statistically significant ($p \geq 0.05$), which, apparently, associated with the nature of the GA - SKPJ. Also, some vitamin D deficiency was noted in patients of the main groups.

The levels of thyroid-stimulating hormone in the patients of the main groups were almost twice as high as those in the CG, and the indicators of prolactin were one and a half times higher than those in the CG in the blood serum and in saliva, and the indicators of the I group were significantly higher than the levels of the II group of patients ($p < 0.05$).

We stated that there was no difference in the LH / FSH ratios in all groups between the studies in blood serum and in saliva, which proves the consistency of the

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study of the hormonal background of patients with HA and PCOS in terms of concentration in saliva.

Analysis of statistical processing revealed the presence of a significant ($p < 0.05$) average strength of the correlation between BMI and IPFR-1, in group I patients ($r = 0.48$), with glycodelin ($r = 0.47$), androstenedione ($r = 0.50$), free testosterone ($r = 0.42$), hirsutism scores ($r = 0.44$). We stated that there was no correlation between the above parameters in the control group of patients ($r < 0.23$). We found strong direct correlations between BMI and the level of dihydrotestosterone ($r = 0.60$) and glycodelin PP14 ($r = 0.58$).

In patients with GA, a significant ($p < 0.05$) direct relationship was found between the scores of hirsutism and the levels of the following hormones: androstenedione ($r = 0.51$), free testosterone ($r = 0.47$), glycodelin ($r = 0.48$), IPFR-1 ($r = 0.46$). A significant ($p < 0.05$) average strength direct relationship was found between the level of glycodelin and the levels of IPFR-1 ($r = 0.40$), androstenedione ($r = 0.41$), free testosterone ($r = 0.44$).

The indicators of the hormonal background of the patients of the main and control groups when measured in saliva were displayed more accurately and had many correlations identical to the blood indicators within the measurement, but at the same time, the levels of free testosterone and DHEA-S in saliva were significantly higher in the patients of the main groups, it should also be taken into account that the collection of saliva and its study is much easier, therefore, the main hormones were measured by us by the level of their concentration in saliva.

Table 2. Hormonal background of patients of groups I and II and CG before corrective therapy

Options	Group I (n = 62)		Group II (n = 64)		KG (n = 20)	
	In blood	In the saliva	In blood	In the saliva	In blood	In the saliva
Thyroid stimulating hormone, μIU / ml	3,4±0,35*	3,2±0,32*	3,3±0,34*	3,2±0,31*	1,9±0,28	1,5±0,27*
Prolactin, μIU / ml	612,3±22,4*	594,9±22,9*	439,8±23,4*	499,3±22,1*	413,7±24,2	337,6±22,5
Total testosterone, ng / ml	2,17±0,15*	1,65±0,12*	2,01±0,16	1,89±0,13*	2,71±0,15	1,51±0,13
Total testosterone, ng / ml	4,32±0,37*	4,09±0,35*	4,12±0,36*	3,75±0,28*	3,87±0,09	3,27±0,10
Free testosterone, pg / ml	4,79±0,13*	4,4±0,15*	3,98±0,15*	3,75±0,16*	1,2±0,15	0,8±0,10
Dihydrotestosterone, pg / ml	450,3±12,4*	415,6±12,3*	395,2±16,3*	327,3±12,4*	191,9±11,4	116,7±10,3
Androstenedione, nmol / l	13,5±3,9*	13,1±3,4*	11,7±3,25*	11,5±3,3*	0,89±0,25	0,90±0,20
Dihydroepiandrosterone sulfate, μmol / l	13,55±0,55*	12,09±0,60*	10,82±0,63*	10,11±0,60*	6,8±0,16	5,04±0,13
17-hydroxyprogesterone, ng / ml	1,85±0,75	1,79±0,80	1,49±0,68	1,45±0,60	1,02±0,20	0,97±0,18
LH, IU / l	13,51±1,79*	12,47±1,89*	11,8±1,4*	10,09±1,25*	8,5±0,95	7,8±0,86
FSH, IU / l	5,9±0,50	5,6±0,35	5,34±0,45	5,01±0,25	5,5±0,15	5,3±0,19
LH / FSH	2,28±0,75*	2,28±0,65*	2,19±0,28*	2,02±0,55*	1,56±0,22	1,52±0,35
Glycodelin PP14, μg / ml	14,81±0,91*	--	18,72±0,85*	--	33,58±1,35	--
IPFR-1, ng / ml	537,08±35,6*	--	496,23±36,2*	--	367,5±26,8	--
25-OH D3	22,63±1,65		29,57±1,79		31,89±1,87	

Note:* – statistically significant intergroup differences I and II relative to the control group ($p<0,05$).

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During the treatment, pregnancy occurred in 88.89% (n = 56) patients: 26 (83.87%) from group Ib and 30 (93.75%) from group IIb. Of all our patients who became pregnant, 39.42% (n = 41) became pregnant during the first 2 months, and 60.58% (n = 63) during the 3rd - 4th months of corrective pregravid preparation. In the control group, this ratio was 60% (n = 12) to 40% (n = 8), respectively. There was no statistically significant difference in the timing of pregnancy between the subgroups, despite the difference in BMI and corrective pregravid preparation.

After the completion of the complex corrective pregravid preparation of the patients of both groups, the level of almost all hormones in the study groups was comparable, however, within each group, the levels of hormones significantly differed between the subgroups.

In Ia and IIa subgroups, the levels of hormones in the blood serum and saliva differ more from the norm than the indices of the Ic and IIc subgroups. There were statistically significant differences in the levels of total and free testosterone, dihydrotestosterone, androstenedione, dihydroepiandrosterone sulfate and glycodelin ($p < 0.05$).

Attention should be paid to statistically significant differences between the two subgroups of corrective pregravid training, which indicates a clear higher efficiency of the complex training offered by us, which also has a good effect on patients in subgroup I of group with preobesity and obesity of I degree ($p < 0.05$) , but the expected best efficacy was obtained by us in subgroup II of group of patients with normal body weight.

It should be noted that the level of vitamin D in the blood serum of patients has normalized, and we have achieved greater success in this aspect in the subgroups of the main groups, the difference is significant ($p < 0.05$).

The levels of thyroid-stimulating hormone and prolactin by the end of pregravid preparation were slightly lower in the B groups of both main groups. The LH / FSH ratio in all subgroups in serum and saliva was identical, which again confirms the possibility of monitoring the effectiveness of therapy by the concentration of hormones in saliva.

Table 3. Hormonal background of patients of the main groups and CG after corrective pregravid therapy

Options	I A group (n=31)		I B group (n=31)		II A group (n=32)		II B group (n=32)	
	In blood	In the saliva	In blood	In the saliva	In blood	In the saliva	In blood	In the saliva
Thyroid stimulating hormone, μIU / ml	2,5±0,35	1,6±0,30	2,1±0,34	1,4±0,29	2,4±0,32	1,6±0,29	2,2±0,31	1,7±0,28
Prolactin, μIU / ml	291,1±32,4	196,8±28,4	270,6±32,8	204,8±29,2	296,3±30,4	201,9±25,5	259,6±27,8	198,3±20,8
Total testosterone, ng / ml	2,78±0,15*	2,46±0,12*	2,45±0,15*	2,09±0,10*	2,21±0,17	2,08±0,14	1,88±0,08	1,64±0,07
Free testosterone, pg / ml	2,41±0,18*	2,15±0,14*	1,73±0,16*	1,62±0,14*	1,55±0,15	1,34±0,13	0,97±0,10	0,81±0,09
Dihydrotestosterone, pg / ml	252,1±13,6*	224,9±12,5*	223,6±13,4*	209,4±12,9	224,7±11,8	210,1±11,5	197,6±10,4	170,9±10,1
Androstenedione, nmol / l	10,04±3,9*	9,07±3,8*	8,27±3,7*	7,09±3,4*	9,4±3,35	7,13±3,25	7,44±3,15	6,81±2,95
Dihydroepiandrosterone sulfate, μmol / l	9,37±1,85*	8,14±1,82*	6,02±1,78*	5,78±1,73*	6,13±1,63	5,04±1,58	4,31±1,23	4,04±1,18
17-hydroxyprogesterone, ng / ml	1,23±0,84	1,13±0,80	1,08±0,82	0,94±0,56	1,11±0,60	0,96±0,45	0,95±0,35	0,84±0,30
LH, IU / l	8,93±1,25	8,18±1,22	7,87±1,15	7,66±1,12	7,61±1,13	7,54±1,11	6,73±1,08	6,33±1,05
FSH, IU / l	5,39±0,55	5,21±0,41	5,36±0,38	5,07±0,35	5,76±0,32	5,43±0,29	5,58±0,34	5,31±0,25
LH / FSH	1,58±0,31	1,57±0,21	1,47±0,28	1,51±0,21	1,32±0,22	1,38±0,22	1,21±0,30	1,19±0,31
Glycodelin PP14, μg / ml	25,31±0,82*		31,74±0,84		27,67±0,80*		33,51±0,56	
IPFR-1, ng / ml	413,98±36,2		376,31±35,4		387,63±34,5		365,8±27,9	
25-OH D3	42,7±2,75*		51,37±2,86		43,56±2,71*		54,87±2,65	

Note: * – statistically significant differences between A and B subgroups of both groups (p<0,05).

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Attention should be paid to statistically significant differences between the two subgroups of corrective pregravid training, which indicates a clear higher efficiency of the complex training offered by us, which also has a good effect on patients in subgroup I of group with preobesity and obesity of I degree ($p < 0.05$) , but the expected best efficacy was obtained by us in subgroup II of group of patients with normal body weight.

Conclusion

For the most part, it is advisable to measure hormonal levels by studying the saliva of patients, given the presence of strong correlations between the levels of hormones in serum and saliva.

The study of free testosterone, DHA-C glycodelin and IPFR-1 already at the stages of pregravid preparation as a marker of the processes occurring in the body of women, especially in the presence of PCOS and HA, is of great diagnostic value.

The proposed and tested by us complex corrective pregravid training of patients with HA and PCOS with normal body weight, as well as with preobesity and obesity of the 1st degree, showed greater efficiency, manifested in a greater proportion of pregnant patients relative to standard pregravid training.

References

1. Manukhin I.B., Tumilovich L.G., Gevorkyan M.A. Gynecological Endocrinology: Clinical Lectures. - M .: GEOTAR-Media, 2013 .-- 272 p.

2. Mordyk A.V., Novitskaya E.L., Puzyreva L.V. et al. The main causes of fetal loss syndrome (literature review) // Ural Medical Journal. - 2016. - No. 2 (135). - p. 18-21

3. Mukhtarov T.A., Molchanova I.V., Skvortsov V.V. Congenital adrenogenital syndrome // Nurse. - 2017. - No. 1. - P. 31-34

4. Sidelnikova V.M. Endocrinology of pregnancy in health and disease. - M., MEDpress-inform, 2009 .-- 352 p.

5. Bednarska S., Siejka A. The pathogenesis and treatment of polycystic ovary syndrome: What's new? // Adv Clin Exp Med. - 2017. - Vol. 26, no. 2. - P. 359-367.,

6. Bousmpoula A., Kouskouni E., Benidis E. et al. Adropin levels in women with polycystic ovaries undergoing ovarian stimulation: correlation with lipoprotein lipid profiles // Gynecol Endocrinol. - 2018. - Vol. 34, No. 2. - P. 153-156,

7. Carmona-Ruiz I.O., Saucedo-de la Llata E., Moraga-Sánchez M.R. et al. Polycystic ovary syndrome: is there a rise in the prevalence? // Ginecol Obstet Mex. - 2015. - Vol. 83, No. 12. - P. 750-759,

8. Ferriman D.M., Gallwey J.D. Clinical assessment of body hair growth in women // The Journal of Clinical Endocrinology & Metabolism. - 1961. Vol.21, No. 11. - p.1440-1447, https://doi.org/10.1210/jcem-21-11-1440

9. Kellesarian S.V., Malignaggi V.R., Kellesarian T.V. et al. Association between periodontal disease and polycystic ovary syndrome: a systematic review // Int J Impot Res. - 2017. - Vol. 29, No. 3. - P. 89-95

10.5281/zenodo.5713450
10. Li D., Li C., Xu Y. et al. Differential Expression of microRNAs in the Ovaries from Letrozole-Induced Rat Model of Polycystic Ovary Syndrome // DNA Cell Biol. - 2016. - Vol. 35, No. 4. - P. 177-183
11. Mossa F, Latham KE, Ireland JJ, Veiga-Lopez A. Undernutrition and hyperandrogenism during pregnancy: Role in programming of cardiovascular disease and infertility. // Mol Reprod Dev. 2019 Vol.86 (9) - p1255-1264