

Successful in vivo conceptions in women with low AMH levels- a case series

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Introduction:

Anti-Mullerian Hormone (AMH) is a glycoprotein, a member of transforming growth factor super family, produced by the granulosa cells surrounding each oocyte in the developing follicles [Usta 2012, Leader 2014]. The assessment of AMH level predicts poor or over response in ART cycles. Additionally measurement of AMH level is used to predict diminished ovarian reserve, age of menopause, polycystic ovary syndrome (PCOS), ovarian reserve after cancer and surgical treatment and pregnancy outcomes in ART helping to individualize treatment strategy [Usta 2012, Grynnerup 2014]. Hormone secreted in large amounts leads to anovulation observed in patients with PCOS. AMH level reflects the ovarian reserve therefore is used as a sensitive marker of ovarian reserve and aging. When ovarian reserve diminishes it is the first marker which decreases [Usta 2012]. Before puberty serum level of AMH is undetectable. After puberty it reaches maximal concentration and then gradually declines reflecting reduction in follicular reserve reaching undetectable levels after menopause [La Marca 2005].

AMH probably take a part in the regulation of release from the primordial follicle pool, arranging the pace at which follicle starts meiosis and growth and the rate of set down of the primordial follicle pool [Usta 2012, Grynnerup 2014].

Due to this characteristic AMH is widely used in the assessment of infertile couples. Decision making is based on the obtained results therefore women with low and very low levels of AMH are considered to be poor candidates for in vivo conceptions after ovarian induction and are referred to the ART centers for protocols often with donor eggs [Gleicher 2010].

Objective:

To describe the case series of infertile couples with low AMH level treated with NPT in Maternity and Life Clinic in Lublin (Poland).

Material and methods:

This study is a retrospective analysis of medical records of nine couples with very low level of AMH treated with NPT who had successfully conceived. The relevant data were abstracted from medical records and entered into a computerized database, with manual verification. Obtained data were analyzed statistically (Statistica Stat-Soft). Also review of english language literature in Pubmed was conducted on the role and utility of AMH in the treatment of infertile couples.

Results:

The mean age of women was 36 year, mean duration of infertility was 64,5 months. The level of AMH range between <0,1-0,8 ng/ml. Four couples were offered ART, but they didn't accept this option. All couples decided to undergo treatment with NaProTechnology in Maternity and Life Clinic in Lublin. During first month of the treatment all women had blood tests for the assessment of the level of follicle stimulating hormone (FSH), lutropin, progesterone, oestradiol, prolactin (also after stimulation with metoclopramide), testosterone, vitamin D, thyroxine and free thyroid hormones and specific antibodies. Additionally test for food intolerance and oral glucose tolerance test with the assessment of insulin levels were done. After blood tests hyperprolactinemia, Hashimoto disease and insulin resistance were diagnosed in 4, 2, and 1 cases respectively. All couples learned how to monitor their biological markers of fertility using Creighton Model FertilityCare System (CrMS) to identify especially `peak-day` (the day preceding ovulation with the best quality of mucus). Each month seven days after `peak day` serum levels of oestradiol and progesterone were assessed. Also ultrasound follicle tracking was performed once to confirm follicle rupture and assess the diameter of follicle and thickness of endometrium. Women with diagnosis of hyperprolactinemia were treated with bromocriptine. Patients with insulin resistance received metformin, patient with Hashimoto disease low dose of thyroid hormone. Women with low progesterone level on the 7th day after `peak day` received luteal phase support (oral or vaginal progesterone). Couples with low quality of mucus received mucus enhancers. The median time from beginning of NPT treatment to conception was 11,6 months. In 4 cases letrozole was used for induction of ovulation, other conceived after standard NPT protocol. One couple had full term, one preterm live birth, 3 women are pregnant, 4 had miscarriages.

Discussion:

AMH level is used as a sensitive marker of ovarian reserve and aging therefore women with low level of this hormone are referred for in vitro fertilization. Age of women plays an important role in the treatment of infertile couples therefore many physicians want to use fast track for the treatment and offer women with potential low ovarian reserve artificial reproductive techniques before treatment and trial of conception in vivo. In our opinion despite this situation we should always perform complete diagnostics to search for basic conditions which may negatively influence fertility potential of the couple. In many cases of idiopathic infertility after detailed diagnostics we can find pathologic conditions which can be treated successfully without need of advanced reproductive techniques.

All presented couples underwent treatment according to the principles of NPT. NPT is a systemic and integrated approach to infertile couples developed by Thomas Hilgers and Pope Paul VI Institute from Omaha in US which monitors and maintains a women's reproductive and gynecological health. It provides medical and surgical treatment which cooperates completely with the reproductive system [Stanford 2008].

In described cases five couples conceived in vivo after standard NPT protocol which included use of CrMS, luteal phase support, treatment of hyperprolactinemia in two cases, insulin resistance in another two cases and thyroid dysfunction in one case. Another four couples required induction of ovulation. For this purpose we used letrozole (LTZ). LTZ is an aromatase inhibitor very effective in induction of ovulation especially in patients with PCOS after failed stimulation with clomiphene citrate (CC). Use of LTZ has many advantages compared to therapy with CC e.g. no negative antiestrogenic effects on endometrium and endometrial and cervical mucus, more monofollicular cycles, lower risk of ovarian hyperstimulation syndrome, normal negative feedback mechanism for FSH in the brain, lesser need for ovulation tracking [Ghomian 2015]. LTZ was given always on 3rd day of the cycle in doses ranges from 7,5 mg to 20 mg. Rupture of follicle was stimulated additionally by gonadotropin injection HCG 5000-10000 IU. In two cases pregnancy was achieved after initial treatment with LTZ, two other need nine and twelve cycles with LTZ. In Poland LTZ is not registered for the purpose of ovulation induction.

It is believed that serum AMH levels are better marker for ovarian reserve than FSH or inhibin because its level remains stable during menstrual cycle. However recent studies show that AMH level may change during one cycle due to physiological fluctuations. Also medications, surgical procedures and laboratory methodology may influence AMH measurement [Leader 2014]. In our opinion caution should be required when interpreting single AMH assessment and single result should not be decisively a proof of low ovarian reserve and an indication for ART without trial of conception in natural or induced cycle.

Conclusions:

Women with low level of AMH may benefit from treatment with NaProTechnology and achieve pregnancy without need of artificial reproductive techniques. NPT is a useful and efficient tool for the diagnosis and treatment of infertile couples. Single measurement of AMH should be interpreted with caution due to its biological fluctuations. Letrozole is effective for induction of ovulation in patients with low AMH.

Table 1. Characteristic of couples – medical history

No	Age	AMH level (ng/ml)	Duration of infertility (years)	Pregnancy in the past	Miscarriage in the past	Live birth in the past	IUI	Referred to IVF
1	44	0,1	7	Yes	Yes	No	No	No
2	40	0,14	10	Yes	Yes	No	No	No
3	36	0,5	6	Yes	Yes	No	No	No
4	34	0,1	6	No	No	No	Yes	Yes
5	34	0,1	6	Yes	Yes	No	Yes	Yes
6	42	0,1	2	No	No	No	No	No
7	28	0,7	2	No	No	No	No	No
8	31	1	3	No	No	No	No	Yes
9	30	0,8	4	Yes	Yes	No	No	Yes

Table 2. Characteristic of couples – NPT treatment

No	Induction of ovulation (letrozole)	Duration of treatment with NPT (months)	Number of cycles with letrozole	Full-term live birth after NPT	Preterm live birth after NPT	Miscarriage after NPT
1	No	2	0	No	No	Yes
2	Yes	22	9	No	No	Yes
3	Yes	5	2	No	No	Yes
4	No	4	0	No	No	Yes
5	No	11	0	?	?	?
6	No	2	0	No	Yes	No
7	No	1	0	?	?	?
8	Yes	7	1	Yes	No	No
9	Yes	36	12	?	?	?

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