

UNIVERSITÀ DEGLI STUDI DI PADOVA  
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Tesi di Laurea Magistrale

UTILIZZO DI UNA DIETA SPECIFICA PER RIDURRE LA POSOLOGIA  
DELLA TERAPIA ORMONALE SOMMINISTRATA ALLE DONNE  
CANDIDATE A PMA E PER IMPLEMENTARNE L'EFFICACIA

USE OF A SPECIFIC DIET TO REDUCE THE POSOLOGY OF HORMON  
THERAPY ADMINISTERED TO WOMEN CANDIDATES FOR MAP AND TO  
IMPLEMENT ITS EFFECTIVENESS

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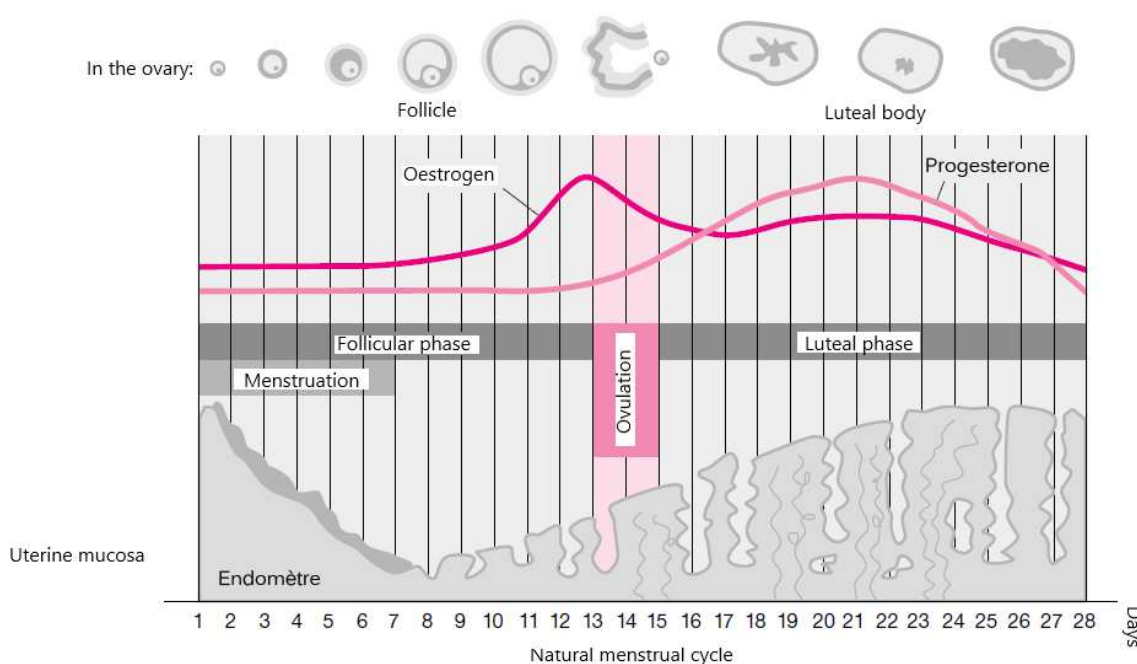
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## INTRODUCTION

PMA or medical assisted procreation, is a technique that helps couples having problems in having a child, aiming to discover what is the problem in the couple and solve it with different techniques. Often there is the necessity to give a hormonal treatment to the female partner of the couple to induce ovarian multiple follicular stimulation. In this study we will discuss the use and the effects of the therapeutic hormones and the possibility to integrate a specific diet to reduce the hormone posology and increase the quality of the PMA process. In particular I will focus on a possible further explanation on how it could be possible to modulate oestrogens and progesterone treatment with the use of a specific diet.

## MENSTRUAL CYCLE



All the procedures in PMA (in Italy is called PMA but abroad is ART for Artificial Reproductive Technology) go around the menstrual cycle that need to be always strictly monitored all along it's different phases<sup>1</sup> that are:

- Menstruation; this first phase last 4 days and is when the endometrium shed causing the bleeding. During this phase, inside the ovaries, the new follicles are growing thanks to the hypothalamus that produces GnRH (gonadotropin releasing hormone) that stimulate the adenohipophysis to produce FSH that is the mainsignal starting the ovarian follicles maturation. Now the follicles passed from the primordial to the primary stage.
- Proliferative or follicular; we are now in the pre-ovulatory phase when the ovarian follicles reach the maturation. During this phase, the follicles are still stimulated with FSH that makes them grow from primary to secondary follicles and later as tertiary. When the follicles reach the secondary stage they start to produce oestrogens that stimulate the preparation of the uterus (gradual thickening of the endometrium) for embryo implantation. On average, the follicular phase lasts about 9-10 days reaching day13-14 of all the period. Among all menstrual cyclephases, it is the one with the most variable duration: it tends to decrease around menopause and ends when the level of luteinizing hormone, released by the adenohipophysis, increases dramatically (peaks). The LH peak causes the release of the oocyte from the ovarian follicle (ovulation) and marks the beginning of the next phase.
- Ovulation; here the plasma levels of LH reach a threshold leading to the protrusion of the dominant follicle to the ovary surface causing it's rupture with consequent expulsion of the oocyte within the Fallopien tubes. The plasma levels of FSH start to decrease.
- Secretive phase; even called post-ovulatory or luteal phase, starting when the broken follicle became an hemorrhagic body due to the emptying in blood of his cavity and becoming later a luteal body.Those 2 shape (hemorrhagic body and luteal body) of the follicle start producing progesterone that together with the oestrogens cause the thickening of the endometrium to prepare the uterus in enriching it with fluids and nutrients in case an embryo is implanted, . This phase lasts about 12 days (from day 15 to day 26) and can end up in 2 different ways: if the oocyte hasn't been fertilized or in general if there is not an implant in the endometrium, the luteal body degenerates becoming a *Corpus albicans* and leading to the last phase; if the implantation of the embryo occurs, the cells located around the developing embryo begin to produce a hormone called human chorionic gonadotropin, which keeps going on the luteal body activity and its production of progesterone until the fetus is able to produce its own hormones.

- Ischemic phase or premenstrual phase; occurs only when the embryo has not been implanted so that the luteal body became a *Corpus albicans* ending the progesterone and oestrogen production, causing a sharp drop in the levels of these hormones that lead to the start of the menstruation phase.

## **WHAT IS PMA (ART)**

To maximise the results, the hormonal therapy in PMA acts in the different stages of the period but not all the couples have the same medical problem and of course there are different strategies according to each specific infertility cause. For this reasons, PMA centres have 3 levels of treatment with which they can treat the patients<sup>2</sup>.

Level 1- including one technique: the intra-uterine insemination. Here, during the follicular phase, the follicle growth is monitored and possibly stimulated with FSH thus to increase the rate of oocyte survival. Once reached the maturation of the follicle (after about 14 days), HCG is administered, that is an LH analogue, this cause after 36h the extrusion in the tube of the oocyte (ovulation). At this point a gynaecologist, about at the 36<sup>th</sup> hours insert with a catheter the semen in the uterus. After this phase there is the luteal phase that is supported with injection of oestrogen and progesterone.

Level 2- this level is also called IVF (in vitro fertilization), hormonally speaking the there is a first injection of FSH but of larger doses, because we are now trying to maturate all the follicles that are released at period day 0 and all along the maturation phase there is still a monitoring of the condition of the patient and her ovarian follicles. At the 14<sup>th</sup> day the ovulation is induced with HCG injectioun. After around 36 hours the woman is submitted to a procedure called follicle pick-up where all the oocyte present within the ovarian follicles that are mature are picked up, in an operating room and transferred in the laboratory for other operations. At the moment the oocytes arte picked up from the follicles, those became instantly hemorrhagic bodies that will eventually became luteal bodies. Those luteal bodies won't be able to produce enough oestrogen and progesterone to supplement the growing of the endometrium and the other functionality. Thus, for this reason, there is a periodic injection of those lacking or insufficient hormones to help the woman bodyto prepare for the future implant of the embryo/s. In the meanwhile, in the laboratory several

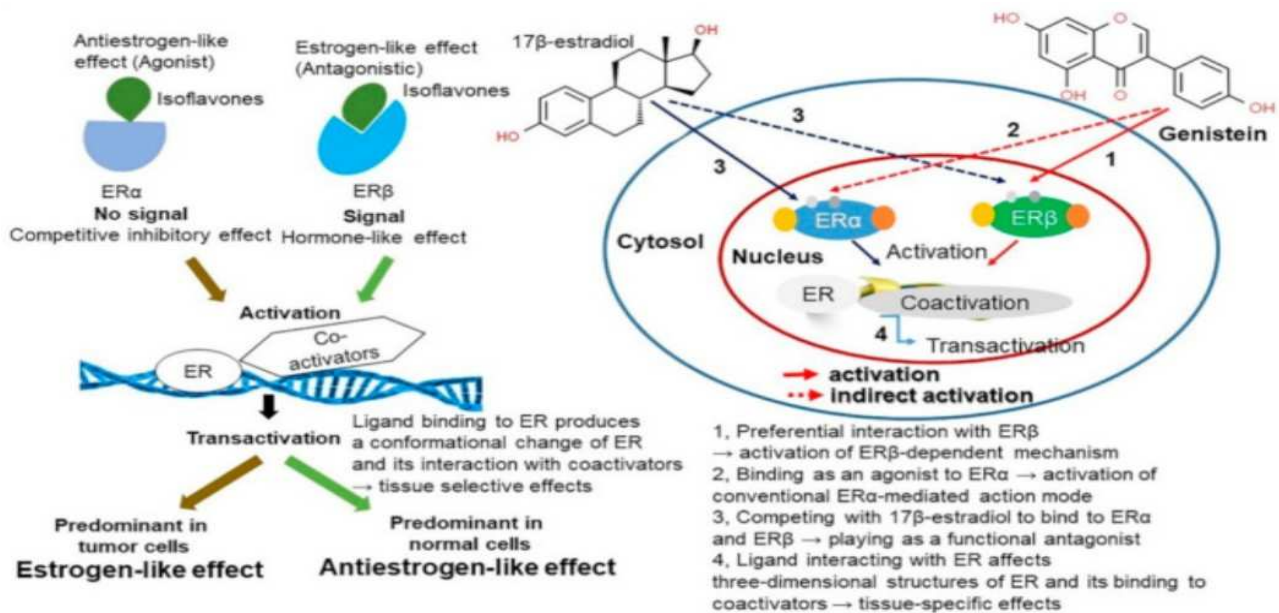
procedure are made up to fertilize each retrieved oocyte that, if fertilized and progressing to embryo phase, after around 5 days will be transferred within the uterus.

Level 2+ - this is a particular procedure that we can call heterologous and is when there is an oocyte picked up from another donor woman because there are several different medical problems that prevent the patient from producing oocytes by her own. In this case the patient is subjected to a series of oestrogen injections to induce the preparation of the endometrium. During those days there are several monitorages of the condition of the endometrium and, when it is thick enough, the therapy changes and besides the oestrogen, even the progesterone is injected (progesterone dose > oestrogen dose) to trigger a modification of the endometrium in luteal endometrium that is now ready to allow the implant of the transferred embryo previously fertilized in the lab using the donor oocyte and the sperm coming from the partner or from a donor too.

## **FOODS THAT CAN HELP**

As you noticed, during the different phases of the “period” there are 4 hormones that are crucial: FSH, oestrogens, LH and progesterone. Those are usually administered via injections that can be singular like for the LH or periodical, like the oestrogens and the progesterone. The repetitive administration of those exogenous hormones with the fact that the woman has to go every time in the clinic and undergo a new injection can cause an increase of the stress level. Several studies analysing the association between stress level and infertility<sup>3-4-5-6</sup> demonstrate that it is possible that during a stressing period the fertility decreases due to different factors. For this reason the possibility to integrate a diet that can reduce the hormonal therapy can be a way to improve the efficacy of all the treatment. Among the 4 main hormones the LH is impossible to modulate with a diet approach because it needs to have a sharp increase only in 1 day, the FSH is difficult to modulate but there is something that could help in its modulation, the other 2 due to their long lasting in the different phases of the period allowing, at least, the possibility to make an approach with the “food therapy”.

For the oestrogens, food that are able to increase they're amount in the body are mainly soy and soy derivatives. Those aliments thanks to the high amount of phytoestrogens<sup>7-8-9-10</sup> content have the possibility to increase the overall oestrogen level in the blood. In addition a correct administration of those foods has been demonstrated to have anticarcinogenic effect due to they're isoflavonoids, in particular ganistein.



For the progesterone is more complicate because there aren't progesterone containing foods, however is possible to act in it's physiological production phase improving the amount of mineral and vitamins that our body need to create the molecule. The nutrients that our body need to create the progesterone are zinc and B group vitamin (specially B12), omega 3 and antioxidant foods. Some example of those aliments<sup>11</sup>, for each nutrient are:

- Foods rich in zinc: in this group of foods we can find seeds, nuts, legumes or mushrooms.
- Vitamin B: foods such as bananas, avocados, corn or oats.
- Omega 3: oily fish, shellfish, olive oil or avocado.
- Foods rich in antioxidants: fruits and vegetables with vitamin C, green leafy vegetables, tomatoes, watermelon or legumes

For the FSH there should be the possibility to increase it's level thanks to a fruit call Maca<sup>12-13</sup> (*Lepidium peruvianum Chacon*). The literature regarding the effect of this fruit is very contrasting but there are some studies that affirm that Maca fruit is able to increase the level of FSH in the body.

Effect of ethanol extract of *L. meyenii* on serum hormone levels in OVX rats (n=10 per group)

	Sham	OVX	<i>L. meyenii</i> (g/kg)		DES
			0.096	0.24	
12 week					
E2 (mg/L)	19.37±8.22	15.20±7.86	16.78±6.37	18.61±8.45	23.62±9.59 <sup>e</sup>
T (ng/L)	42.4±10.1	25.4±9.2 <sup>b</sup>	14.8±7.3 <sup>b,c</sup>	27.7±21.6	10.2±2.1 <sup>b,d</sup>
FSH (IU/L)	1.97±0.51	3.78±0.63 <sup>b</sup>	3.65±1.69	2.95±1.75	2.14±0.85 <sup>d</sup>
28 week					
E2 (mg/L)	11.88±6.26	7.29±2.81 <sup>a</sup>	10.28±3.33 <sup>e</sup>	8.28±2.98	11.66±2.33 <sup>d</sup>
T (ng/L)	21.5±7.6	9.7±4.7 <sup>b</sup>	7.3±6.1 <sup>b</sup>	10.9±4.1 <sup>b</sup>	4.7±0.1 <sup>b,d</sup>
FSH (IU/L)	3.14±1.00	8.05±3.04 <sup>b</sup>	3.92±1.21 <sup>d</sup>	3.69±2.66 <sup>d</sup>	2.053±0.79 <sup>d</sup>

All values are expressed as mean±S.E.M, OVX = Ovariectomized, DES = Diethylstilbestrol, <sup>a</sup>P<0.05 vs sham, <sup>b</sup>P<0.01 vs sham, <sup>c</sup>P<0.05 vs OVX, <sup>d</sup>P<0.01 vs OVX.

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## HOW, WHY AND WHEN SHOULD WE INTEGRATE THOSE FOODS

According to those foods and the different level of PMA procedures, is possible to think about different diet protocols to follow. For the women that are following the first level of PMA there is the possibility to intervene after the ovulation phase. The idea is to integrate progesterone pro diet integrating all the nutrient explained before in order to help with the develop of the embryo. Here the integration of oestrogen shouldn't be necessary because in this phase it's produced in a low amount while the major hormone is the progesterone. For the woman that undergo a second level PMA is possible to have the same food diet that there is at the first level, the only difference is for the heterologous. With them is possible to start integrate the oestrogen diet during the stimulation phase, once the endometrium reach the correct thick will be possible to begin the effect of the progesterone diet. The most important thing is to understand how and when the effects of the integration with the diet appear in the body in order to maximize the effect.



## **CONCLUSIONS**

With this scheme should be possible to increase the fertility rate in a PMA centre thanks to the fact that the non exogenous hormones in the body are able to improve the quality of the follicle, the oocyte and even of the embryo and his implant in the endometrium and the major thing is that along with the increase of the fertility rate will be a decrease with the repetition of the treatment for the couples, avoiding them to face different failure; in addition there's the possibility to modified all the hormone injection system using less hormones for each woman. Until now this remain only an hypothesis based on personal work and different studies that need to be verified or not according to the future results of clinical study.

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