

**UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA  
DOCTORAL SCHOOL**

**DOCTORAL THESIS**

**IMPACT OF CONTRACEPTIVE METHODS ON FEMALE  
FERTILITY**

**~ ABSTRACT ~**

**PhD Advisor:**

**Prof. Univ. Dr. NOVAC Liliana**

**PhD Candidate:**

**NICULESCU Gabriela**

**CRAIOVA**

**2015**

<b>TABLE OF CONTENTS</b>	
<b>STATE OF THE ART</b>	<b>pag.3</b>
<b>IMPACT OF CONTRACEPTIVE METHODS ON FEMALE FERTILITY</b>	<b>pag.6</b>
<b>Material and method</b>	<b>pag.6</b>
<b>Results</b>	<b>pag.7</b>
Biostatistics analysis of the study lot	<b>pag.7</b>
Immunologic analysis of the ovarian reserve by the use of specific biomarkers	<b>pag.9</b>
<b>CONCLUSIONS</b>	<b>pag.10</b>
<b>REFERENCES</b>	<b>pag.11</b>

## **STATE OF THE ART**

Women who choose to use reversible contraceptive methods in order to prevent an unwanted pregnancy do that for a variety of reasons, many times according to the age and/ or stage of their individual life. Many intend to postpone their pregnancy and at the same time remaining fertile. These categories include young teenagers and adults who wish to prevent a pregnancy until their social/ educational/ occupational/ financial goals have been reached.

Women have a fundamental right to decide if and when to have children, but more than 222 million in the entire world are in the impossibility of having access to modern contraceptives when they need them.

In the five decades since the birth control pill was traded for the first time in the United States of America, the number of contraceptive products available for women extended considerably. Nevertheless, these overwhelming innovations were adaptations of current technologies which offer variations per hormone doses rather than real technological discoveries. At the same time, there is a current issue related to the high rate of unwanted pregnancies in the United States and in the entire world.

Improvement of reproduction health is essential so as to reach the Millennium Development Goals regarding the improvement of maternal health, reduction of infant mortality and eradication of extreme poverty (1).

This means that women should have access to efficient methods of fertility control. Promotion of family planning, so that women can avoid an unwanted pregnancy is essential for the World Health Organization, with the purpose of improving maternal health and it is fundamental to achieve the Millennium Development Goals in this respect (2).

It is estimated that 90% of abortion-related morbidity and mortality and 20% of the one related to pregnancies, as well as 32% maternal deaths could be prevented by using efficient contraception methods (3).

The preoccupation regarding the possible fertility damage after having used oral contraceptives increased over the last two decades and temporary delays in conception were reported (4).

The longest delay in conceiving a baby is experienced by women who interrupted injectable methods of contraception. In its recommendations guide, the World Health Organization states that women's fertility will immediately return after having interrupted the contraceptive methods, except for injectable progesterone - Depot medroxyprogesterone (DMPA) or Norethisterone enanthate (5).

Moreover, based on the recommendation of the World Health Organization, the average time necessary to conceive after the last injection is between 6 and 10 months. That means that the average rate of conception capacity come-back after the use of injectable contraceptives is 1-4 months longer compared to other contraception methods (6).

Oral contraceptives remain a frequent choice among women. Approximately 30% of the feminine population uses them every year as their favourite contraception method. The conception rate at 12 months related to formers users of oral contraceptives varies from 72% to 94%. This is comparable to the general population. (7)

However, the effect of using oral contraceptives over a long period of time on pregnancies was prospectively assessed only in two studies, without reporting any association between the use of oral contraceptives and a fecundity state: Wiegratzet in 2006 and Cronin in 2009. One of these studies also analysed the type of oral contraceptives and the time necessary to obtain a pregnancy (TNS) but only an insignificant association was found concerning these parameters (8).

Depot medroxyprogesterone is associated to a prolonged amenorrhea and an anovulation after the last injection, which was proved to cause a delay in coming back to fertility (9). It acts as an inhibitor of gonadotropin, thus preventing follicular ageing and ovulation.

The term “ovarian reserve” refers to the capacity of ovaries to produce oocytes which can be fertilized within a very short period of time. The assessment of ovarian reserve was difficult to obtain in routine clinical practice as no biomarker with a sufficient clinical precision was easily accessible. Clinical publications which spread quickly confirm that the AMH values from the serum as useful clinical measure, available on a large scale, first of all quantitative, of ovarian reserve is more precise than the serum values of the separate follicle-stimulating hormone (FSH) (10).

The AMH value from the serum, regardless of the age, in order to foretell birth rate or quality of the oocyte, remained controversial. Currently, despite all that, the data available suggest that the serum levels for AMH taken individually cannot be used to advise a patient if natural conception is possible or not. (11).

The diminution of the ovarian function or of the “reserve” is apparently owed to the reduced number of ovarian primordial follicles. In theory, the direct products of granular cells could reflect better the ovarian secretory capacity and the number of follicles. Inhibin B is one of these products which regulate the FSH secretion with a negative feedback. Ovary ageing is accompanied by a diminution of Inhibin B. The serum rate for Inhibin B in incipient

follicular phase can be an adequate marker of ovarian follicular reserve and of the fertility potential (12).

Based on a fix range between menopause and an accelerated decline of ovarian reserve the hypothesis that up to 10% of the women from the general population can suffer a “premature ovarian ageing” was issued (13).

Knowing these aspects of the ovarian function would be of value in many circumstances, both clinical and social/ personal, as well as valuable in the promotion or understanding of the manner in which reproductive life duration can be regulated (14).

Many times women ignore the advice to avoid a delay of conception over the age of 30 but studies suggest that customized instruments of risk assessment such as RO testing can actually increase an individual’s motivation for a positive change.

A low RO screening result is more likely to convince a woman to present her plans for natural conception or, alternatively, to explore the vitrification of the oocyte in a stage when these approaches still have reasonable perspectives of success (15).

Women who are aware of the risk of developing premature ovarian ageing choose a non-hormonal type of contraception.

Since 10% of the women show risks of premature ovarian ageing, it is suggested a new paradigm of offering young women an assessment of the RFO before beginning hormonal contraception during family planning sessions. Together with an adequate counselling, this new paradigm can improve women’s autonomy over the health of their reproduction function or not.

## **IMPACT OF CONTRACEPTIVE METHODS ON FEMALE FERTILITY**

### **Material and method**

The prospective study performed included two lot of patients selected from the casuistry of the Family Planning Cabinet from Scornicesti Hospital and of Planning Cabinet within “Filantropia” Municipal Clinical Hospital from Craiova, cases studied over the period 2009-2014. There were selected a number of 428 patients who were assigned in two lots, as follows:

1. A lot made up of 288 patients who represented users of oral hormonal contraceptives;
2. A lot made up of 140 patients who represented users of injectable hormonal contraceptives with progesterone.

We drew up an initial assessment chart of the case based on which we included/excluded the cases in this study.

The assessment and blood biochemical investigations were carried out in the haematology laboratory within “Filantropia” Municipal Clinical Hospital from Craiova. The investigations for the analysis of ovarian reserve biomarkers AMH and Inhibin B were performed within Synevo laboratory. The informed consent for the use of personal data for the purpose of this study was obtained from the patients included in this study. The study was approved by the Ethics Commission of the University of Medicine and Pharmacy of Craiova. In order to take statistical data the program Microsoft Excel (Microsoft Corp., Redmond, WA, USA) was used together with XLSTAT lot for MS Excel (Addinsoft SARL, Paris, France) and the program IBM SPSS Statistics 20.0 (IBM Corporation, Armonk, NY, USA).

## **Results**

### **Biostatistics analysis of the study lot**

The purpose of this study was to mention the physiopathological implications and the practical importance of fertility resettlement, that is the occurrence of a desired pregnancy, after the contraceptive method ceased and so as to have a unitary research we chose only hormonal contraception used by the studied patients.

In our study we used two types of hormonal contraceptives: oral contraception and hormonal injectable contraception with Depo-Provera.

The average age for study enrolment was  $31.72 \pm 6.03$  years standard deviation. The minimum age was 19 and the maximum age was 42.

The necessary time to obtain a pregnancy was observed with all the patients regardless of the contraceptive method used. Only 4.21% of the cases conceived in the first 3 months, of all the investigated cases. In the following 3-6 months after ceasing to administer contraception a percentage of 38,79% of the cases conceived. Over the period 6-12 months the percentage of obtaining a pregnancy was 33,88%. After 12-18 months a percentage of 17,29% obtained a pregnancy and in the time range of 18-24 months after the interruption of the contraceptive method 5,84% of the cases studied conceived. Thus, the period with the lowest percentage of pregnancies obtained was represented by the first 3 months and the period of 18-24 months. Over the period comprised between 3 months and 12 months from the interruption of contraception there were the most obtained pregnancies in a percentage of 72,67%.

Putting aside the time necessary so as to obtain a pregnancy according to the contraceptive method used we noticed that, in the case of oral contraception, most of the cases, 55,56%, obtained a pregnancy within the time range of 3-6 months from the interruption of contraception while in the case of injectable contraception the time necessary to obtain a pregnancy was later, after 6-12 months from the interruption of contraception. In the same context, in the first 3-6 months after the injectable contraception was interrupted a pregnancy was obtained in a percentage of only 4,29% and after 6-12 months, in the case of oral contraception, there was a higher percentage of pregnancies obtained, of 19,79 % of the cases.

In the first 3 months, most of the pregnancies, 4,86% were obtained after the use of oral contraception, compared to injectable contraception when a pregnancy was obtained only in 2,86% of the cases. In the following period of 12-18 months after the contraception was interrupted the rate of obtaining a pregnancy was close as value to the 2 contraceptive

methods, 18,57% in the case of injectable contraception compared to 16,67% in the case of oral contraception. Over the last period of time, the furthest from the interruption of contraception, 18-24 months, most of the cases, 11,43% obtained a pregnancy while, in the same period of 18-24 months only 3,13% of the cases showed this delay in conceiving.

Statistical analysis showed us that according to the contraceptive hormonal method used, either injectable or oral, related to the time necessary to obtain a pregnancy, we have a highly significant statistical signification, with  $p < 0.0001$ , so TNS is correlated with the type of contraception used.

The analysis of the average time necessary to obtain a pregnancy showed us that in the case of oral contraceptives the average time necessary to obtain a pregnancy was  $7,84 \pm 4,94$  months standard deviation, and in the case of injectable contraceptives the average time necessary to obtain a pregnancy was longer, of  $11,13 \pm 4,83$  months standard deviation. The average time necessary on both lot studied was of  $8,91 \pm 5,16$  months standard deviation.

We tried to see if there is a connection between the time necessary to obtain a pregnancy and the age when menarche is installed. In this case, statistical analysis showed us that we do not have a meaningful statistical significance, with  $p = 0.380$ ,  $p > 0,05$ , by correlating the age of menarche and the type of contraception with the time necessary to obtain a pregnancy.

Statistical analysis showed us that we do not have a meaningful statistical significance, with  $p = 0.824$ ,  $p > 0,05$  by correlating the average age of the patients and the type of contraception with the time necessary to obtain a pregnancy.

The statistical calculation of the average age for the first use of contraceptives does not show significant statistical changes,  $p = 0.960$ ,  $p > 0.05$ . Nevertheless, there is a highly significant difference ( $p$  Chi square = 0,00013,  $p < 0,001$ ) regarding the ages at the first use of contraceptives between patients from lot CI (injectable contraceptives) and the ones from the lot CO (oral contraceptives), the ones from the lot CO falling in the categories 20-24 de years and 30-34 years in a greater percentage, while the ones in the lot CI, being in a larger percentage, 40% compared to ~23% in the group 25-29 years.

This shows that an administration of hormonal contraceptives at a younger age has an influence over the time necessary to obtain a pregnancy.

The average duration of using hormonal contraception was  $4,89$  years  $\pm 1,77$  standard deviation in the case of oral contraceptives and  $4,26$  years  $\pm 1,49$  standard deviation in the case of injectable contraceptives. The statistical calculation of the average duration of contraceptive use shows highly significant statistical changes,  $p = 0.00034$ ,  $p < 0.0001$ .

In this case we can state that the duration of use in the case of hormonal contraceptives can influence the time necessary to obtain a pregnancy; the longer the duration, the more delayed the moment of conception can be.

The statistical analysis on the involvement of the contraception time in obtaining a pregnancy after having interrupted the contraception showed us statistically significant values,  $p= 0.000$ ,  $p>0.001$ , the average time to obtain a pregnancy being of 7.84 months  $\pm 4,97$  standard deviation in the case of oral contraceptives and 11.13 months  $\pm 4,83$  standard deviation in the case of injectable contraceptives. Thus, the use of injectable contraceptives leads to a longer time to obtain a pregnancy after interrupting this type of contraception.

In the formula of oral contraceptives used by the women in our study we found Drospirenona, Desogestrel, Gestodene and LNG, levonorgestrel which was present both in monophasic oral contraceptives and in the three-phase ones. By comparing the different types of progestatives within oral contraceptives we found the existence of highly significant differences ( $p$  ANOVA=0,000135  $p<0,001$ ), drospirenone having the longest duration necessary in order to obtain a pregnancy compared to LNG or three-phase oral contraceptives EE+LNG.

### **Immunologic analysis of the ovarian reserve by the use of specific biomarkers**

The statistical analysis of the AMH values according to the type of contraception shows us a highly meaningful significance,  $p < 0,0001$ , which shows us that the low values of AMH are positively correlated with the delay in the occurrence of a pregnancy in the case of these women with a diminished ovarian reserve. The difference between the AMH values with the patients from lot CO (oral contraceptives) (1,52 ng/ml) and lot CI (injectable contraceptives) (2,01 ng/ml) is highly significant from the statistical point of view, the outcome of the Student test being  $p=0,00000718$ , thus much below 0,001, the maximum level for high significance (99,9% trust as difference observed, not only a coincidence).

The statistical analysis of the values of Inhibin B according to the type of contraception shows us a meaningful statistical significance,  $p = 0,002$ ,  $p<0,05$ , which denotes that the low values of Inhibin B are positively correlating with the delay in the occurrence of a pregnancy in the case of these women with a diminished ovarian reserve, but the positive statistical correlation is poorer than in the case of AMH.

## CONCLUSIONS

❖ The statistical analysis of patients' age distributed according to the type of contraceptive used showed that we do not have a statistically significant rate,  $p=0,824$ , so  $p>0,005$ .

❖ In the case of oral contraception, most of the cases, 55,56% obtained a pregnancy in the range 3-6 months after having interrupted the contraception, while in the case of injectable contraception the necessary time to obtain a pregnancy was longer, after 6-12 months from the interruption of the contraception.

❖ The analysis of the average necessary time to obtain a pregnancy showed us that in the case of oral contraception the average necessary time to obtain a pregnancy was 7,84 months and in the case of injectable contraception, the average necessary time to obtain a pregnancy was longer, of 11,13 months.

❖ The statistical analysis showed us that we do not have a meaningful statistical significance, with  $p=0.824$ ,  $p>0,05$ , by correlating the patients' average age and the type of contraception with the necessary time to obtain a pregnancy.

❖ There is a highly significant difference ( $p$  Chi square=0,00013,  $p<0,001$ ) regarding the age at the first use of contraceptives between patients from lot CI and the ones from lot CO. This shows that an administration of hormonal contraception at younger ages has an influence over the time necessary to obtain a pregnancy.

❖ The duration of use of hormonal contraceptives can influence the time necessary to obtain a pregnancy; the longer the duration, the more delayed the moment of conception can be, with statistically high significant changes,  $p=0.00034$ ,  $p<0.0001$ .

❖ The statistical analysis of the AMH values according to the type of contraception shows us a highly meaningful statistical significance,  $p < 0,0001$ , which shows us that the low values of AMH are positively correlated with the delay of a pregnancy occurrence with these women having a diminished ovarian reserve.

❖ The statistical analysis of the Inhibin B values according to the type of contraception shows us a meaningful statistical significance,  $p = 0,002$ ,  $p<0,005$ , which shows us that the low values of Inhibin B are positively correlated with the delay of a pregnancy occurrence with these women having a diminished ovarian reserve, but the positive statistical correlation is poorer than in the case of AMH.

## REFERENCES

1. United Nations Population Fund: State of the world population 2004. The Cairo consensus at ten: population, reproductive health and the global effort to end poverty. New York: UNFPA; 2004
2. World Health Organisation: Making Pregnancy Safer: Annual Report 2007. Geneva: World Health Organisation; 2008
3. Collumbien M, Gerressu M, Cleland J. Non-use and use of ineffective methods of contraception. In Ezzati M, Lopez AD, Rodgers A et al (eds.). Comparative quantification of health risks. Geneva: World Health Organization, 2004:1255–1319
4. Farrow A, Hull MG, Northstone K, Taylor H, Ford WC, Golding J. Prolonged use of oral contraception before a planned pregnancy is associated with a diminution risk of delayed conception, *Hum Reprod.* 2002 ;17(10):2754-61
5. World Health Organization, Selected practice recommendations for contraceptive use, 2004; Second edition:8, Department of Reproductive Health and Research Family and Community Health, Geneva, 2004
6. Shulman L, Westhoff C. Return to fertility after use of reversible contraception, *Dialogues in contraception*, 2006;10(1):1-8
7. Wiegatz I, Mittmann K, Dietrich H, Zimmermann T, Kuhl H. Fertility after discontinuation of treatment with an oral contraceptive containing 30 microg of ethinyl estradiol and 2 mg of dienogest. *Fertil Steril.* 2006;85(6):1812-1819.
8. Cronin M, Schellschmidt I, Dinger J. Rate of pregnancy after using drospirenone and other progestin-containing oral contraceptives. *Obstet Gynecol.* 2009;114:616–622
9. Liao PV, Dollin J. Half a century of the oral contraceptive pill: historical review and view to the future, *Can Fam Physician.* 2012 Dec;58(12):e757-60
10. Practice Committee of the American Society for Reproductive Medicine Testing and interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril* 2012; 98:1407–1415
11. Iliodromiti S, Kelsey TW, Wu O, et al. The predictive accuracy of anti-mullerian hormone for live birth after assisted conception: a systematic review and meta-analysis of the literature. *Hum Reprod Update* 2014; 20:560–570
12. Nancy A, Brenda S, Karl R, Teresa K, Patrick M, William J, Michael R. Age-Related Analysis of Inhibin A, Inhibin B, and Activin A Relative to the Intercycle

Monotropic Follicle-Stimulating Hormone Rise in Normal Ovulatory Women. *Clin Endocrinol Metab*, 2004; 89(6): 2977-2981

13. Nelson SM. Biomarkers of ovarian response: current and future applications. *Fertil Steril* 2013; 99:963–969

14. Kelsey TW, Wright P, Scott M, et al. A validated model of serum anti-mullerian hormone from conception to menopause. *PLoS One*. 2011; 6:e22024

15. Tremellen K, Savulescu J. Ovarian reserve screening: a scientific and ethical analysis, *Hum Reprod*. 2014;29(12):2606-14