Effect of Using Contraceptive on Anti-Mullerian Hormone in Egyptian Women

Magdy Mahmoud Mohamed[a], Eslam M. A. El-Nahrery[b], Heba Farouk Hegy [C]

[a] Department of Biochemistry Faculty of Science, Ain Shams University, Cairo, Egypt.
[b] Department of Chemistry (Biochemistry Branch), Faculty of Science, Suez University, Egypt
[c] M.sc Student at Department of Chemistry (Biochemistry Branch), Faculty of Science, Suez University, Egypt

Abstract: *May women used contraceptive in family planning there for, our objective in this stud y was to evaluate AMH in Egyptian women which use contraceptives. this study was conducted in 30 women use the oral contraceptive, divided into 15 women use Implanon and 15 use Depoprovera (18-3 5years) together with 15 age matched normal control women. Blood tests were collected in a fasting state, lipid profile, AMH were assessed. The mean± standard deviation of lipids profile (total cholesterol, triglycerides, LDL, HDL) and of AMH respectively in Implanon group were (15 3±25.6, 114.6±2 5.6, 86.7± 23.6, 43.1±9), and 1.5±.7 in Depoprovera group were (151±24.6, 96.8±25.8, 82.5±26.8, 49.1±9), 1.4±.6. While the mean and standard deviation of (total cholesterol, triglycerides, LDL, HDL) and of AMH respectively in control were (151.4±19.1, 103.7±15.6, 76.1±18.8), 2.2±0.4). There was significant rise in risk factor in both studied group when contrasted to control, and there was significant decrease in both treated groups in regards to HDL and AMH when contrasted with control.The study concluded that, risk factor of coronary heart disease is increase and AMH is decreased in women used Implanon and Depoprovera as contraceptive.*
Keywords: *lipid profile, AMH, Egyptian women.*

I. Introduction

One of the essential strategies for family planning includes the use of contraceptives, it is may be modern or traditional. One of the present day techniques incorporate the utilization of hormonal contraceptives, prepared as pill (oral) or infuse able *(Qazi, Hashmi, Raza, Soomro, & Ghauri, 2010).* Currently, more than 90 million women in 130 countries rely on upon infuse capable contraceptives to avoid pregnancies *(FDA, 2005).* Depomedroxy progesterone acetate (DMPA), a microcrystalline infuse capable suspension is a long acting, highly effective, reversible preventative and one of the real method for family planning *(Lande, 1995).* DMPA, promoted as Depo-Provera is a powerless and organic progestin controlled as a single 150 mg intramuscular infusion each three months. The contraceptive gives off an impression of being a powerful inhibitor of gonadotropin. It has a low disappointment rate; however, women who use this contraceptive may encounter some unfriendly effects *(Yadav et al., 2011).*

The single-rod implant table contraceptive device containing etonogestrel (Implanon) is embedded sub dermally in the upper arm and stays effective for 3 years. It has been available for over 10 years, but it has been widely marketed in the United States just since 2007. Insertion and removal of the Implanon requires specific training by the manufacturer *(Bonnema, McNamara, & Spencer, 2010).*

II. Subjects and Methods

This study was performed to assess the impact of Implanon and Depoprovera on serum lipoproteins and AMH in Egyptian women. Forty-five Egyptian women chose from family planning (15 women using Implanon, 15 women using Depoprovera and 15 women as control group), no women were suffering from hypertension, diabetes mellitus, irregular menstrual bleeding, anemia and known or suspected pregnancy. The study was performed as per Announcement of Helsinki and was approved by the Research Ethics Committee of Suez University, Egypt. An informed consent was obtained from all treated women and controls.

BMI was estimated using the equation

(Status, 1995),

$$\text{BMI (Kg} \div \text{m)} = \frac{\text{Body weight in kg}^2}{(\text{Height in meters})^2}$$

Biochemical analysis including assurance of triglycerides, total cholesterol, HDL, LDL by photometric method by using kits of Human Co. (Germany), determination of AMH by ELIZA method by kits from My Bio Source USA.

Progesterone and AMH were determination by ELIZA method by kits from Elab science Germany, and Glucose, AST and ALT were determined by using kits of Human Co. Germany. All biochemical parameters were performed for all treated women and controls.

III. Results

The mean± standard deviation of the Age and BMI, TG, TC, HDL, LDL, T. lipid, Risk Factor respectively in Implant group were33.0±5. 1, 30.1±5.0,33.0±5.1, 30.1±5.0, 114.6±25.6, 153.4±25.6, 43.9±5.5, 86.7±23.6, 400.1±67.1, 2.0±0.7 and for Depoprovera group were34.5±4.6, 31.6±4.5, 96.8±25.8, 151.0±24.6, 49.1±9.0, 82.5±26.8, 379.3±56.1, 1.8±0.8 while for control group were 30.9±5.0, 27±4.9, 103.7±15.6, 151.4±19.1, 54.5±6.1, 76.1±18.8, 385.7±41.2, 1.5±0.4. There was a significant decrease in HDL in both treated groups when compared to control group. And a significant increase in risk factor.

And for progesterone and AMH in Implant group were0.4±0.1, 1.5±0.7, in Depoprovera group 0.4±0.21.4±0.6 and in control group were 11.1±4.9, 2.2±0.4. A significant decrease in AMH and progesterone in both treated group when compared the control

Table 1 Descriptive Statistics Of All Groups

Group	IMPLANT	DEPOPROVERA	CONTROL
AGE	33.0±5.1	34.5±4.6	30.9±5.0
BMI	30.1±5.0	31.6±4.5	27±4.9
TG	114.6±25.6	96.8±25.8	103.7±15.6
Cholesterol	153.4±25.6	151.0±24.6	151.4±19.1
HDL	43.9±5.5	49.1±9.0	54.5±6.1
LDL	86.7±23.6	82.5±26.8	76.1±18.8
Lipid	400.1±67.1	379.3±56.1	385.7±41.2
Risk Factor	2.0±0.7	1.8±0.8	1.5±0.4
AST	14.5±2.1	12.6±2.0	13.6±2.5
ALT	22.3±3.8	19.6±2.8	20.0±3.8
Glucose	88.4±7.1	85.1±6.2	88.2±5.6
Progesterone	0.4±0.1	0.4±0.2	11.1±4.9
AMH	1.5±0.7	1.4±0.6	2.2±0.4

Table 2 Comparison between stated groups

Parameters	P value		
	IMPLANT vs. DEPOPROVERA	IMPLANT vs. CONTROL	DEPOPROVERA vs. CONTROL
HDL	0.1	0.0	0.0
Risk Factor	0.4	0.0	0.0
Progesterone	0.6	0.0	0.0
AMH	0.7	0.0	0.0
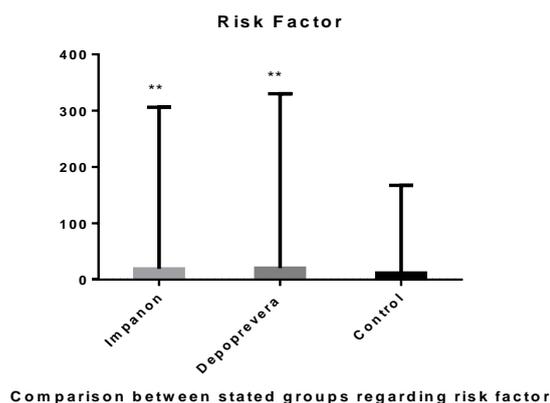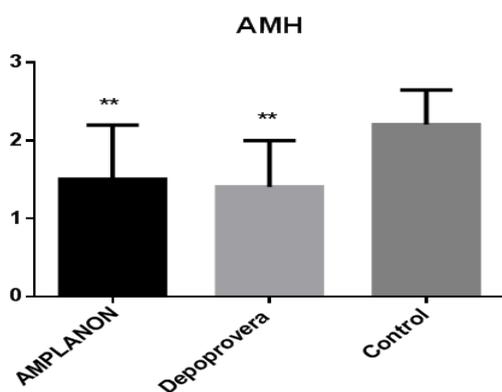
Comparison between stated groups regarding AMH

Table 3 Correlation between AMH and other studded Parameters in Implanon group

Parameters	R	P value
Progesterone	0.953**	0.000
Lipid	0.960**	0.000
Risk Factor	0.962**	0.000
AMH	0.983**	0.000

HDL
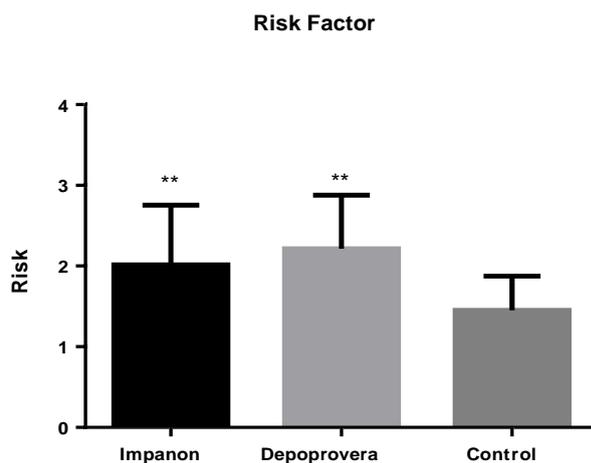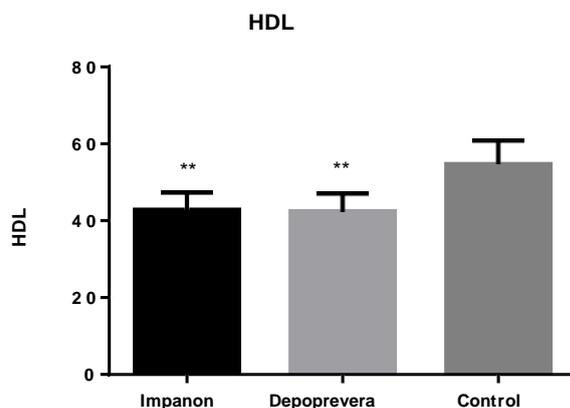
Risk Factor

Correlation between Progesterone and other studded parameter in Depoprovera group

Results of correlation of progesterone in the Depoprovera show positive correlation with Lipid, Risk Factor and AMH, and negative correlation with other parameters table**4**
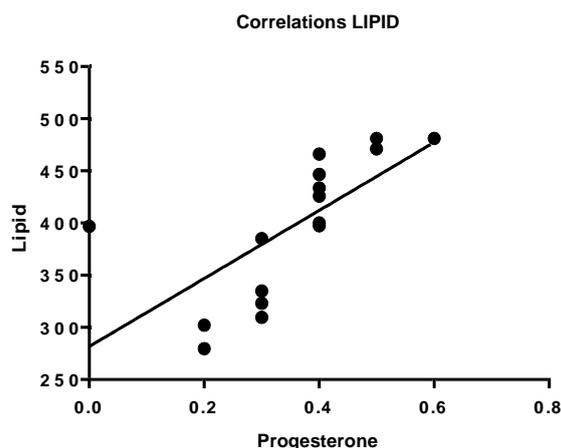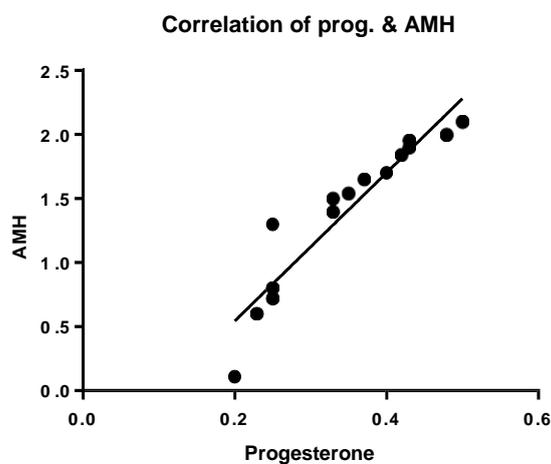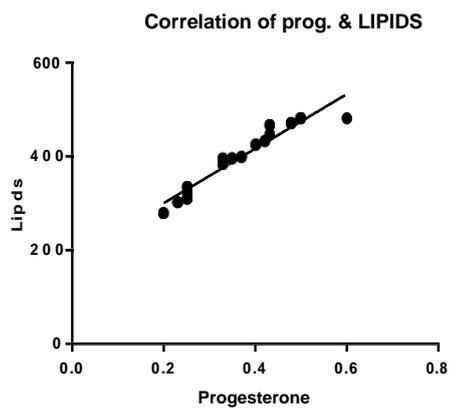
Correlations LIPID
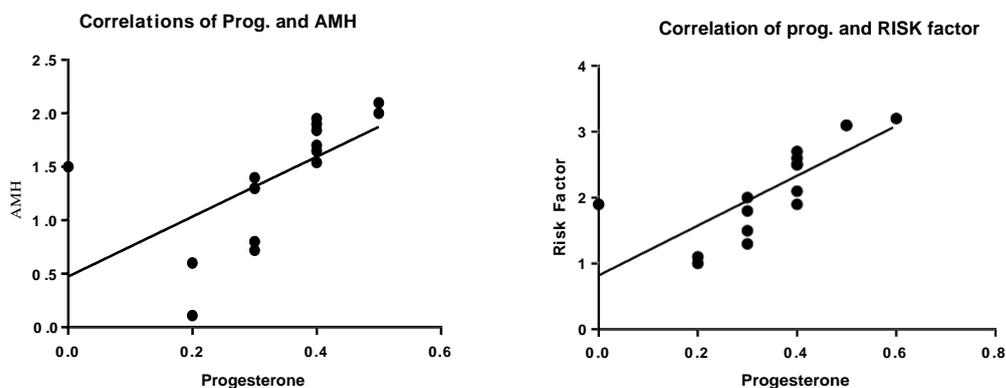
Table 4 Correlation between Progesterone and other studded parameter in Depoprovera group.

Parameters	R	P value
Lipid	.986**	<0.000
Risk Factor	.970**	<0.000
AMH	.943**	<0.000

Correlation between AMH and Parameters in Depoprovera:
Results of correlation of AMH in the Depoprovera show positive correlation with progesterone, Lipid and Risk Factor, and no correlation with other parameters table 5.

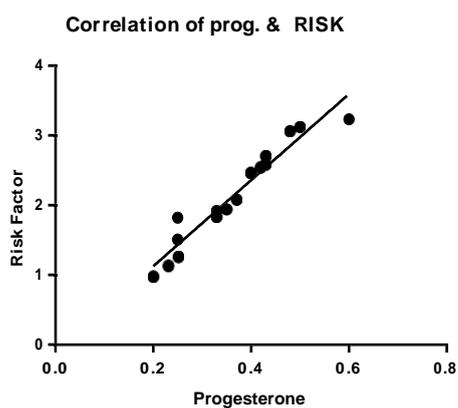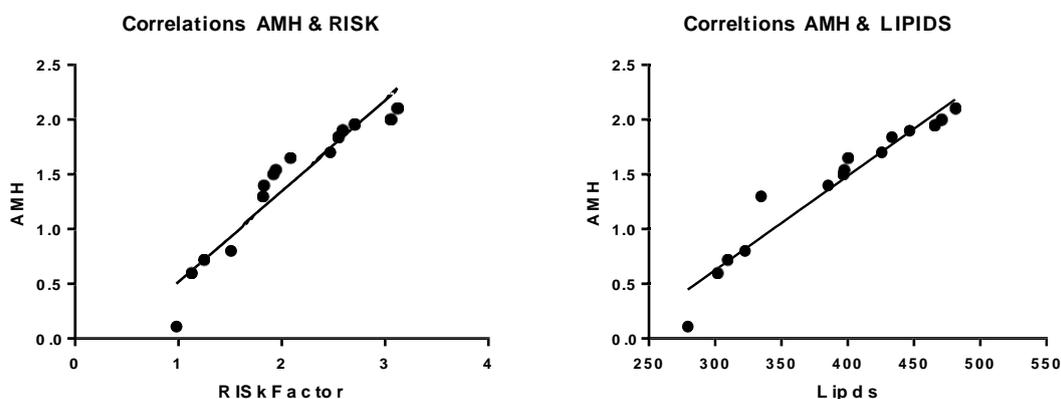**Table 5** Correlation between AMH and other studded parameters in all groups.

Parameters	Control		Implanon		Depoprovera	
	r	P value	r	P value	r	P value
Progesterone	.082	<0.040	.984**	<0.001	0.918**	<0.001
Lipid	.772	0.887	697**	<0.005	0.977**	<0.001
Risk Factor	.082	0.040	.584*	0.022	0.936**	<0.001

**. Correlation is significant at the 0.01 level (2-tailed).

IV.   Discussion

One of the main methods of family planning involves the use of contraceptives and this may be modern or traditional. One of the modern methods include the use of hormonal contraceptives, prepared as pill (oral) or inject able suspension (Qazi et al., 2010). This study was performed to evaluate the effect of Implanon and Depoprovera on AMH and serum lipoproteins in Egyptian women users

Forty-five Egyptian women were selected from family planning Outpatient clinic of Ras Gharib general hospital during the period from 2014 to 2015. Woman in the study were divided into three groups, group A: containing 15 women using Implanon, group B: containing 15 women using Depo-Provera and group C: 15 age-matched healthy women.

There were no statistically significant differences were observed between Implanon & Depoprovera in (TG, HDL, TC, LDL, AST, ALT, Risk Factor, lipid and Glucose) after 6 months' treatment compared with control group while there was a high significant increase in risk factor in treated gropes when compared to control group but, our results show a high significant decrease HDL, progesterone and AMH in both treated groups when compared to control group $p<0.001$

There has been considerable debate about the effect of Depo-Provera® (DMPA) on lipid metabolism Some studies have reported that DMPA does not exert any effect on various lipoproteins and lipid components **(Faddah, Al-Rehany, Abdel-Hamid, & Bakeet, 2005)** , our study is disagreed with Kaunitz and Faddah data , where it is remarkably noticed that no significant change in the HDL-C levels of DMPA users in our study, non-significant change with TC and TG like our results , the studies by **(Faddah et al., 2005; Fahmy, Khairy, Allam, Gobran, & Alloush, 1991)** which showed a decrease in high-density lipoprotein cholesterol (HDL-C) levels in DMPA users and significant increase in serum LDL, and no changes in serum cholesterol or triglycerides. These findings were similar to *(Ahmed, Hussein, & Talib, 2015)*

Our results are agreed with the numerous studies of effect of contraception on AMH which reported that significant AMH levels on HC or to reduce it significant,**(Bentzen et al., 2012)** *Bentzen, et .al., 2012*, reported that AMH levels were 29.8% lower in OC users than controls. The reduction in AMH was more pronounced with increasing duration of contraception. Confirmed by **(Dólleman, 2013)** *Dólleman,* et. al.*, 2013*

And*van den Berg et al. (2010)***(van den Berg et al., 2010)** who showed a significant increase in serum AMH concentration after termination of oral contraceptives*,* a small randomized trial recently confirmed largely these findings . The study population consisted of 42 healthy women randomized to use for 9 weeks an OC in the form of either an oral pill ($n = 13$), a trans dermal patch ($n = 15$), or a vaginal ring ($n =14$). After 9 weeks of contraceptive use, serum AMH levels decreased significantly by almost 50% as compared to baseline in all treatment group **(Kallio et al., 2013).**

Lastly, Arbo et al. **(Arbo et al., 2007) s**tudied 20 women and showed that administration of oral contraceptives in the luteal phase in one menstrual cycle may lead to a lower AMH concentration in the follicular phase in the following menstrual cycle.

But our results regarding AMH level are disagree with**(Li, Wong, Yeung, Ho, & Ng, 2011)**(*Li, et. al., 2011)* measured serum AMH concentration before and 3–4 months after use of hormonal contraception, administered as combined oral contraceptive pill (n=23), combined inject able contraceptives (n=23), progestogen-only inject able (n=20) or levonorgestrel intrauterine devices (n = 20): no significant differences in serum AMH were found between pre- and post-treatment measurements within all treatment group

Other studies were disagreed with our result **(Somunkiran, Yavuz, Yucel, & Ozdemir, 2007)**;*(Deb et al., 2012);(Streuli et al., 2008);(Andersen, Witjes, Gordon, & Mannaerts, 2011)* which reported that serum AMH concentration did not change significantly during oral contraceptive treatment In our study there were significant positive correlation between AMH and age in control group(r=o.956 ,p<0.000)

our results are agreed with the literature of **(Lie Fong et al., 2012)**,**(La Marca et al., 2012)**, **(Nelson et al., 2014)**,**(Leader et al., 2012)** *and (Seifer, Baker, & Leader, 2011)* reported that AMH correlate with age , similar observation was reported by **(Himabindu et al., 2013)** *HimabinduY,et.al.,2013* that significant differences were found in AMH levels between positive and negative pregnancy subjects in the age group of 35 and above, but not in the age group below 35 years. There were positive correlations between AMH and other ovarian reserve markers and clinical pregnancy outcome in this age group.

He H, et.al. 2011 reported that from 25 years of age AMH declines to undetectable levels at menopause. Also from our results we observed that correlation between AMH and progesterone in Implanon group is positive (p<0.000) and positive correlation between AMH and progesterone in Depoprovera group (p<0.000)

Our results are agreed with that **(Imboden et al., 2015)** *Kollmann Z,et.al.,2015* reported that significant positive correlation between AMH and progesterone may suggest progesterone as a factor influencing AMH secretion and **(Jeppesen et al., 2013)**(*Jeppesen, et al.,2013)* reported that AMH gene expression showed a significant inverse correlation with corresponding follicular fluid concentration of estradiol and positive correlations with follicular fluid concentrations of testosterone and progesterone, and no relationship with follicular fluid and rostenedione**.**

But our results are disagreeing with **(Bungum et al., 2011)** *bungum, et. al., 2011* reported that significant positive correlation between AMH and LH concentration was seen over the 24-h period (p< 0.001)

V.   Conclusion
The results of this study indicate increased in AMH together with increased risk for cardiovascular disease in women use oral contraceptives. However, this hypothesis still remains to be proven in prospective long-term follow-up studies of women with PCOS.

Conflict of Interest

References

[1]. Ahmed, I. T., Hussein, A. H., & Talib, A. (2015). Lipid Profile Changes in Women in Reproductive Age Group Using Injectable Medroxypogesterone Acetate Contraception.

[2]. Andersen, A. N., Witjes, H., Gordon, K., & Mannaerts, B. (2011). Predictive factors of ovarian response and clinical outcome after IVF/ICSI following a rFSH/GnRH antagonist protocol with or without oral contraceptive pre-treatment. Hum Reprod, 26(12), 3413-3423. doi: 10.1093/humrep/der318

[3]. Arbo, E., Vetori, D. V., Jimenez, M. F., Freitas, F. M., Lemos, N., & Cunha-Filho, J. S. (2007). Serum anti-mullerian hormone levels and follicular cohort characteristics after pituitary suppression in the late luteal phase with oral contraceptive pills. Hum Reprod, 22(12), 3192-3196. doi: 10.1093/humrep/dem258

[4]. Bentzen, J., Forman, J. L., Pinborg, A., Lidegaard, Ø., Larsen, E., Friis-Hansen, L., . . . Andersen, A. N. (2012). Ovarian reserve parameters: a comparison between users and non-users of hormonal contraception. Reproductive biomedicine online, 25(6), 612-619.

[5]. Bonnema, R. A., McNamara, M. C., & Spencer, A. L. (2010). Contraception choices in women with underlying medical conditions. Am Fam Physician, 82(6), 621-628.

[6]. Bungum, L., Jacobsson, A. K., Rosen, F., Becker, C., Yding Andersen, C., Guner, N., & Giwercman, A. (2011). Circadian variation in concentration of anti-Mullerian hormone in regularly menstruating females: relation to age, gonadotrophin and sex steroid levels. Hum Reprod, 26(3), 678-684. doi: 10.1093/humrep/deq380

[7]. Deb, S., Campbell, B. K., Pincott-Allen, C., Clewes, J. S., Cumberpatch, G., & Raine-Fenning, N. J. (2012). Quantifying effect of combined oral contraceptive pill on functional ovarian reserve as measured by serum anti-Mullerian hormone and small antral follicle count using three-dimensional ultrasound. Ultrasound Obstet Gynecol, 39(5), 574-580. doi: 10.1002/uog.10114

[8]. Dólleman, M. (2013). Fertility Forecasting: Advances in the Role of Ani-Müllerian Hormone as a Reproductive Biomarker.

[9]. Faddah, L., Al-Rehany, M., Abdel-Hamid, N., & Bakeet, A. (2005). Oxidative stress, lipid profile and liver functions in average Egyptian long term depo medroxy progesterone acetate (DMPA) users. Molecules, 10(9), 1145-1152.

[10]. Fahmy, K., Khairy, M., Allam, G., Gobran, F., & Alloush, M. (1991). Effect of depo-medroxyprogesterone acetate on coagulation factors and serum lipids in Egyptian women. Contraception, 44(4), 431-444.

[11]. Himabindu, Y., Sriharibabu, M., Gopinathan, K., Satish, U., Louis, T. F., & Gopinath, P. (2013). Anti-mullerian hormone and antral follicle count as predictors of ovarian response in assisted reproduction. J Hum Reprod Sci, 6(1), 27-31. doi: 10.4103/0974-1208.112377

[12]. Imboden, S., Papadia, A., Nauwerk, M., McKinnon, B., Kollmann, Z., Mohr, S., . . . Mueller, M. D. (2015). A comparison of radiocolloid and indocyanine green fluorescence imaging, sentinel lymph node mapping in patients with cervical cancer undergoing laparoscopic surgery. Annals of surgical oncology, 22(13), 4198-4203.

[13]. Jeppesen, J. V., Anderson, R. A., Kelsey, T. W., Christiansen, S. L., Kristensen, S. G., Jayaprakasan, K., . . . Yding Andersen, C. (2013). Which follicles make the most anti-Mullerian hormone in humans? Evidence for an abrupt decline in AMH production at the time of follicle selection. Mol Hum Reprod, 19(8), 519-527. doi: 10.1093/molehr/gat024

[14]. Kallio, S., Puurunen, J., Ruokonen, A., Vaskivuo, T., Piltonen, T., & Tapanainen, J. S. (2013). Antimullerian hormone levels decrease in women using combined contraception independently of administration route. Fertil Steril, 99(5), 1305-1310. doi: 10.1016/j.fertnstert.2012.11.034

[15]. La Marca, A., Spada, E., Grisendi, V., Argento, C., Papaleo, E., Milani, S., & Volpe, A. (2012). Normal serum anti-Mullerian hormone levels in the general female population and the relationship with reproductive history. Eur J Obstet Gynecol Reprod Biol, 163(2), 180-184. doi: 10.1016/j.ejogrb.2012.04.013

[16]. Lande, R. E. (1995). New era for injectables. Population Reports. Series K: Injectables and Implants(5), 1-31.

[17]. Leader, B., Hegde, A., Baca, Q., Stone, K., Lannon, B., Seifer, D. B., . . . Baker, V. L. (2012). High frequency of discordance between antimullerian hormone and follicle-stimulating hormone levels in serum from estradiol-confirmed days 2 to 4 of the menstrual cycle from 5,354 women in U.S. fertility centers. Fertil Steril, 98(4), 1037-1042. doi: 10.1016/j.fertnstert.2012.06.006

[18]. Li, H. W. R., Wong, C. Y. G., Yeung, W. S. B., Ho, P. C., & Ng, E. H. Y. (2011). Serum anti-müllerian hormone level is not altered in women using hormonal contraceptives. Contraception, 83(6), 582-585.

[19]. Lie Fong, S., Visser, J., Welt, C., de Rijke, Y., Eijkemans, M., Broekmans, F., . . . Fauser, B. (2012). Serum anti-müllerian hormone levels in healthy females: a nomogram ranging from infancy to adulthood. The Journal of Clinical Endocrinology & Metabolism, 97(12), 4650-4655.

[20]. Nelson, S. M., Iliodromiti, S., Fleming, R., Anderson, R., McConnachie, A., & Messow, C. M. (2014). Reference range for the antimullerian hormone Generation II assay: a population study of 10,984 women, with comparison to the established Diagnostics Systems Laboratory nomogram. Fertil Steril, 101(2), 523-529. doi: 10.1016/j.fertnstert.2013.10.021

[21]. Qazi, H. A., Hashmi, A., Raza, S. A., Soomro, J. A., & Ghauri, A. (2010). Contraceptive methods and factors associated with modern contraceptive in use. Journal of family and reproductive health, 4(1), 41-46.

[22]. Seifer, D. B., Baker, V. L., & Leader, B. (2011). Age-specific serum anti-Mullerian hormone values for 17,120 women presenting to fertility centers within the United States. Fertil Steril, 95(2), 747-750. doi: 10.1016/j.fertnstert.2010.10.011

[23]. Somunkiran, A., Yavuz, T., Yucel, O., & Ozdemir, I. (2007). Anti-Müllerian hormone levels during hormonal contraception in women with polycystic ovary syndrome. European Journal of Obstetrics & Gynecology and Reproductive Biology, 134(2), 196-201.

[24]. Status, W. P. (1995). The Use and Interpretation of Anthropometry. Report of a World Health Organization Expert Committee. Geneva, Switzerland: World Health Organization.

[25]. Streuli, I., Fraisse, T., Pillet, C., Ibecheole, V., Bischof, P., & De Ziegler, D. (2008). Serum antimüllerian hormone levels remain stable throughout the menstrual cycle and after oral or vaginal administration of synthetic sex steroids. Fertility and sterility, 90(2), 395-400.

[26]. van den Berg, M. H., van Dulmen-den Broeder, E., Overbeek, A., Twisk, J. W., Schats, R., van Leeuwen, F. E., . . . Lambalk, C. B. (2010). Comparison of ovarian function markers in users of hormonal contraceptives during the hormone-free interval and subsequent natural early follicular phases. Hum Reprod, 25(6), 1520-1527. doi: 10.1093/humrep/deq071

[27]. Yadav, B. K., Gupta, R. K., Gyawali, P., Shrestha, R., Poudel, B., Sigdel, M., & Jha, B. (2011). Effects of long-term use of depo-medroxyprogesterone acetate on lipid metabolism in Nepalese women. The Korean journal of laboratory medicine, 31(2), 95-97.

[28]. Netsh wlan set hostednetwork mode=allow ssid=Islam key=12345678