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Effect of Some Heavy Metals on Testosterone Hormone in Infertile Men

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Abstract

Background: Infertility is defined as a failure of achieve a pregnancy after one year and more of regular unprotected sexual intercourse. The exposure of reproductive system to heavy metals has also been associated with male infertility. A large number of metals are toxicants to the reproductive system and are suspected to be endocrine system disruptors.

Patients and methods: This study performed at the high institute of infertility diagnosis and assisted reproductive technologies in Al-Nahrain University and the Poisoning consultation center / specialized surgeries hospital in the Medical city in period from November 2018 to April 2019. Number of 150 men were enrolled in this study divided into two groups, the patient and the normal control groups. The infertile group included 100 men aged 20-50 years who they have abnormal seminal fluid analysis parameters. The second group included 50 healthy fertile men who have at least two children without any previous history of systemic diseases as a control group. Heavy metals and testosterone concentrations were estimated for all the study groups. Aim of current study are evaluation of some heavy metals concentrations, in serum and whole blood of groups. Assessment of testosterone hormone in serum of infertile men and healthy controls and study the correlation between this hormone and trace elements which were estimated among cases.

Results: The heavy metals Cu, Pb and Cd showed a highly significant increase ($p<0.01$) in the serum and blood of infertile men (159.77±8.49 µg/dl, 24.18±4.30µg/dl, 0.31±0.10 µg/dl) respectively when compared with their concentrations in healthy control men (125.14±10.12 µg/dl, 15.74±2.69 µg/dl, 0.16±0.03 µg/dl) respectively. The mean levels of Zn showed a highly significant decrease ($p<0.01$) in the serum of infertile men (70.82±9.48 µg/dl) compared to its mean level in the healthy control group (95.70±11.41 µg/dl). Serum testosterone hormone in infertile men (185.40±61.92 ng/ml) showed a highly significant decrease ($p<0.01$) as compared with those of healthy men (450.35±131.27 ng/ml). Serum copper level was negatively correlated with serum testosterone level among infertile men.

Conclusions: this study concluded that some heavy metals were shown to be an indicators for men infertility. Serum copper level was negatively correlated with serum Testosterone level among infertile men .This result can hypothesize that excess copper acts as a hormonal disrupter. The remaining heavy metals did not show significant correlation with the selected hormones.

Keywords: heavy metals, infertile male, testosterone hormone, lead, cadmium.

Introduction

Infertility was defined as inability to conceive after one year of regular unprotected intercourse [1]. So infertility is an ever increasing phenomenon in the modern urban societies generally, infertility affects about (10-15%) of the couples in the world[2].The cause of infertility in about (10%) of cases remains unexplained, and the couples are designated as normal infertile couples[3]. Male infertility is a common disorder that affects approximately (50%) of infertility cases in the world [4]. Therefore, male fertility depends upon the coordination between neural and hormonal mechanisms or between male reproductive system and these mechanisms, any hindering of at least one of these mechanisms will result in infertility [5]. The trace elements are micro nutritive elements that exist in minute quantities within the body mass and they are either important via playing different functional roles in the body or non-essential elements with negative effect on the human body even at very low concentrations [6]. Heavy metals are usually dense elements with potential toxicity, especially in environmental context [7]. They can be naturally obtained from the earth crust, and became concentrated because human activities. Heavy metals can enter human tissues via food, inhalation and manual handling [8]. Skin contact absorption, for instance soil contact, is another possible source of body contamination by heavy metals [9]. Because they are difficultly metabolized, toxic heavy metals can bioaccumulation in human's body [10]. Those heavy metals may combine with and interfere with the vital cellular element functions [11]. Because of sperm's oxidative damage and testicular apoptosis, exposure to heavy metals has also been associated with male infertility [12]. A significant increase in fertility associated with higher miscarriage rates have been noted in the partners of men working in lead battery factories, indicating harmful effects of heavy metals on reproductive success, large number of metals are toxicants to the reproductive system and are suspected to be endocrine system disruptors[13]. Human studies on metal exposure and unstable hormone levels to date are limited, despite the prevalence of exposure to many of the toxic metals, Cadmium and lead have been the most studied metals in relation to altered hormone levels [14].

Materials and methods

This prospective study was performed at two main medical centers in Baghdad. The high institute of infertility diagnosis and assisted reproductive technologies in Al-Nahrain University and the Poisoning consultation center / specialized surgeries hospital in the Medical city/ Baghdad during the period from November 2018 to April 2019. A total number of 150 men were enrolled in this study who were divided into two groups, the patient and the normal control groups. The patient group included 100 men aged between 20-50 years. The second group included 50 healthy men who have at least two children without any previous history of systemic diseases as a control group. Heavy metals and trace element concentrations were estimated for all the study groups in this study. Frozen serum was allowed to thaw at room temperature, and assessment of inorganic elements Zn and Cu was performed by Flame atomic absorption spectrophotometry, while Cd was measured by graphite furnace atomic absorption spectrophotometry.

Results and Discussion

As depicted in table (1) serum copper concentration in infertile men group was 159.77±8.49 µg/dl, which was significantly higher than serum copper concentration of the healthy control group 125.14±10.12 (p< 0.01). Results agreed with [15] who found a significant increase ($p \leq 0.05$) in the concentration of Cd and Cu in the serum of infertile men who had azospermia & oligospermia in comparison with the control group [15]. Many human studies found negative correlations between Cu quantified in the body and spermatozoa quality parameters [16]. [17] Indicated that high doses of Cu had negative effects on sperm motility and mitochondrial activity [17]. Similar results were reported by [18] in human spermatozoa in Cu accumulation [18]. Table (1) also showed that serum zinc concentration in infertile group was 70.82±9.48 µg/dl which was a highly significantly lower than serum zinc concentration of the healthy group 95.70±11.41 (p< 0.01).

Result was compatible with [19] who showed serum zinc levels of patients with abnormal seminal fluid parameters were lower than those who have normal seminal fluid parameters [19], similar to the results of [20] who showed significant variation between serum zinc of infertile group & fertile group [20]. The most rapidly growing organs in the body are the gonads, and zinc metallo-enzymes are the vital enzymes involved in protein and nucleic acid synthesis, therefore, zinc deficiency can result in severe testicular damage such as atrophy of the testicular and inhibition of spermatid differentiation, decreases of testicular weight, gonads dysfunction and seminiferous tubule shrinkage [21] Data demonstrated in table 2 showed that blood lead concentration in infertile men was 24.18±4.30µg/dl, which was significantly higher than its concentration in the healthy control group 15.74±2.69 (p< 0.01). Results were compatible with a study of [22] who found a highly significant variation between their study groups [22]. And with [23] who found high levels of lead in the infertile men in comparison with the controls [23]. And also with [24] who found that Pb levels were significantly higher in infertile males (p=0.001) when compared with the control group [24]. Our results were also compatible with the results of [25] which showed that seminal and blood plasma cadmium as well as blood plasma lead levels were significantly higher (p<0.01) in azospermic and oligospermic men in comparison with normospermic men [25]. Results shown in table 1 indicated that mean blood cadmium concentration in the infertile male group was (0.31±0.10 µg/dl), which was significantly higher than its mean concentration in the healthy control group (0.16±0.03 (p< 0.01). Our results were compatible with [25] who reported that seminal and blood plasma cadmium as well as blood plasma lead were significantly higher (p<0.01) in azospermic and oligospermic men when compared with normospermic men [25]. However, [26] observed significant correlations between blood cadmium levels, volume of semen and immature forms of spermatozoa suggesting the need of further studies on blood and semen cadmium levels [26]. Data in table (1) demonstrated that mean serum testosterone concentration in infertile men was (185.40±61.92 µg/dl), which was highly significantly lower than its mean concentration in the healthy controls 450.35±131.27 (p< 0.01). These results were compatible with a study of [27] who reported a significant increased levels of testosterone and oestradiol in the control group compared with the infertile group

(P<0.001) [27]. Presence of testosterone, LH and FSH in general, is required for the quantitative production of spermatozoa. Spermatogenesis and development of reproductive organs require the testosterone hormone which is produced in the Leydig cells [28] . Testosterone plays an essential role in stimulation the synthesis of mitotic and meiotic deoxyribonucleic acid (DNA) in spermatogonia as well as the maintenance and induction of spermatogenesis. FSH acts directly on the seminiferous tubule, while the LH

causes indirect spermatogenesis stimulation through testosterone [29].

Table (1): Descriptive table between patient group and control group regarding (Zn µg/dl, Cu µg/dl, Pb mg/dl, Cd µg/dl Testosterone ng/ml).

	Groups	No.	Mean ±Std.	t-test	P-Value	C.S
Cu	Cases	100	159.77±8.49	22.065	.000	P<0.01(HS)
	Control	50	125.14±10.12			
Zn	Cases	100	70.82±9.48	14.140	.000	P<0.01(HS)
	Control	50	95.70±11.41			
Pb	Cases	100	24.18±4.30	12.684	.000	P<0.01(HS)
	Control	50	15.74±2.69			
Cd	Cases	100	0.31±0.10	10.478	.000	P<0.01(HS)
	Control	50	0.16±0.03			
Testosterone	Cases	100	185.40±61.92	16.822	.000	P<0.01(HS)
	Control	50	450.35±131.27			

Comparison between levels of testosterone, copper, zinc, lead, and cadmium in table 2 and figures 1, 2, 3, and 4 showed that serum zinc levels was negatively correlated with serum copper levels.

Table (2): Simple Correlation between items with each other from cases

		Testosterone	Cu	Zn	Pb	Cd
Testosterone	r	1				
	P-Value					
Cu	r	-.068	1			
	P-Value	.503				
Zn	r	.138	-.880**	1		
	P-Value	.171	.000			
Pb	r	-.088	.809**	-.851**	1	
	P-Value	.382	.000	.000		
Cd	r	-.041	.718**	-.776**	.907**	1
	P-Value	.689	.000	.000	.000	

**. Correlation is significant at the 0.01 level (P<0.01)

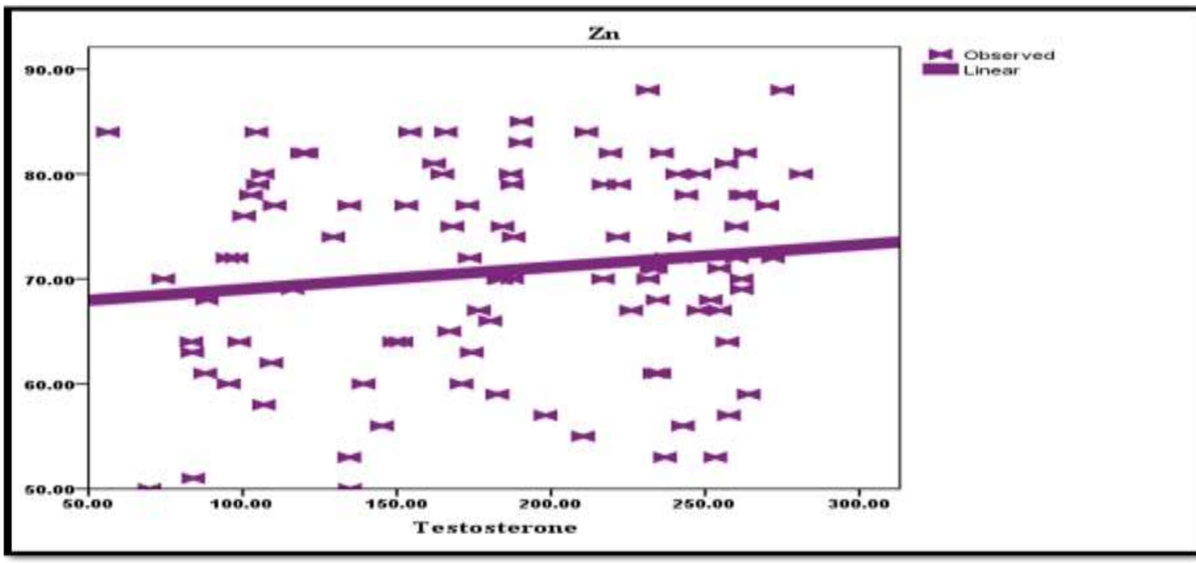

Figure 1: Regression between Testosterone (ng/ml) and Zn (μg/dl)

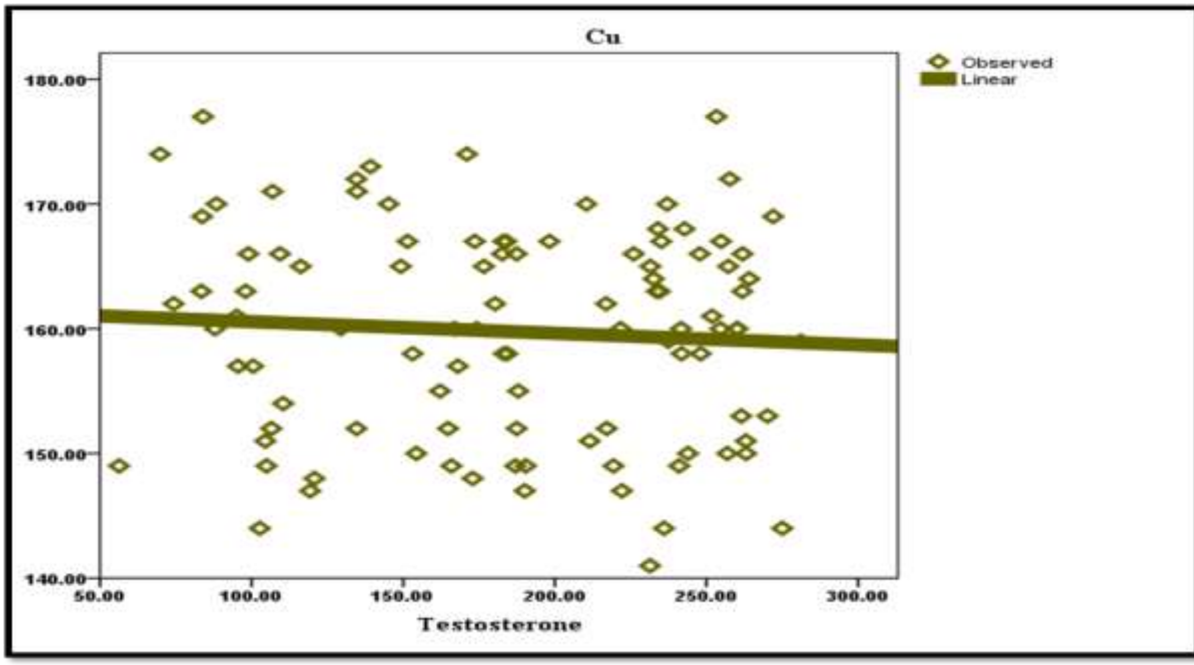

Figure 2: Regression between Testosterone (ng/ml) and Cu (µg/dl)

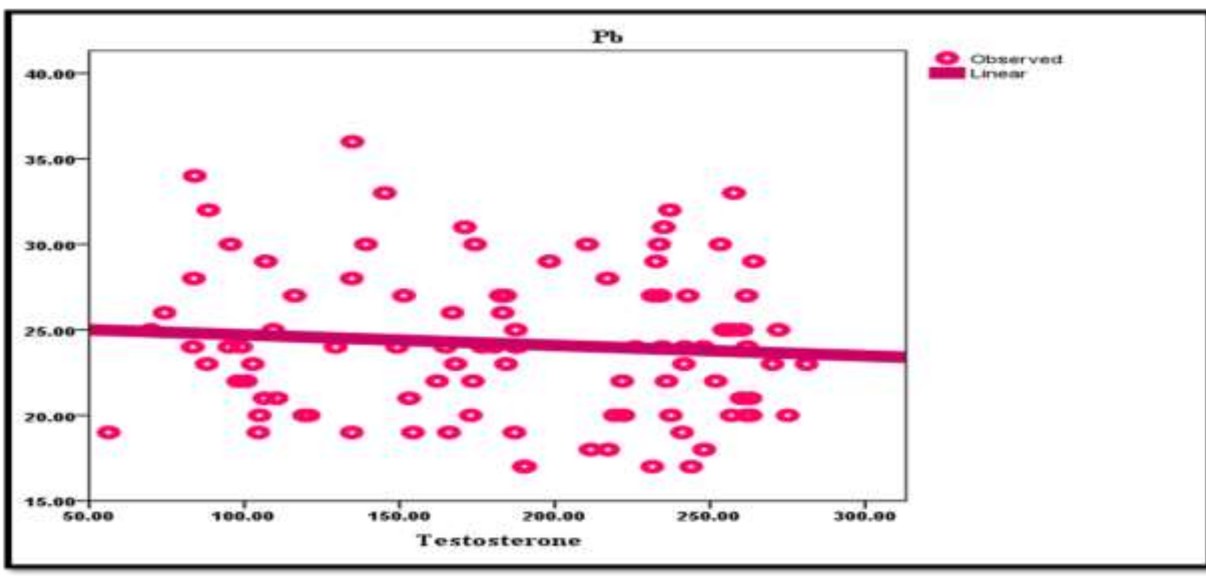

Figure 3: Regression between Testosterone (ng/ml) and Pb (µg/dl)

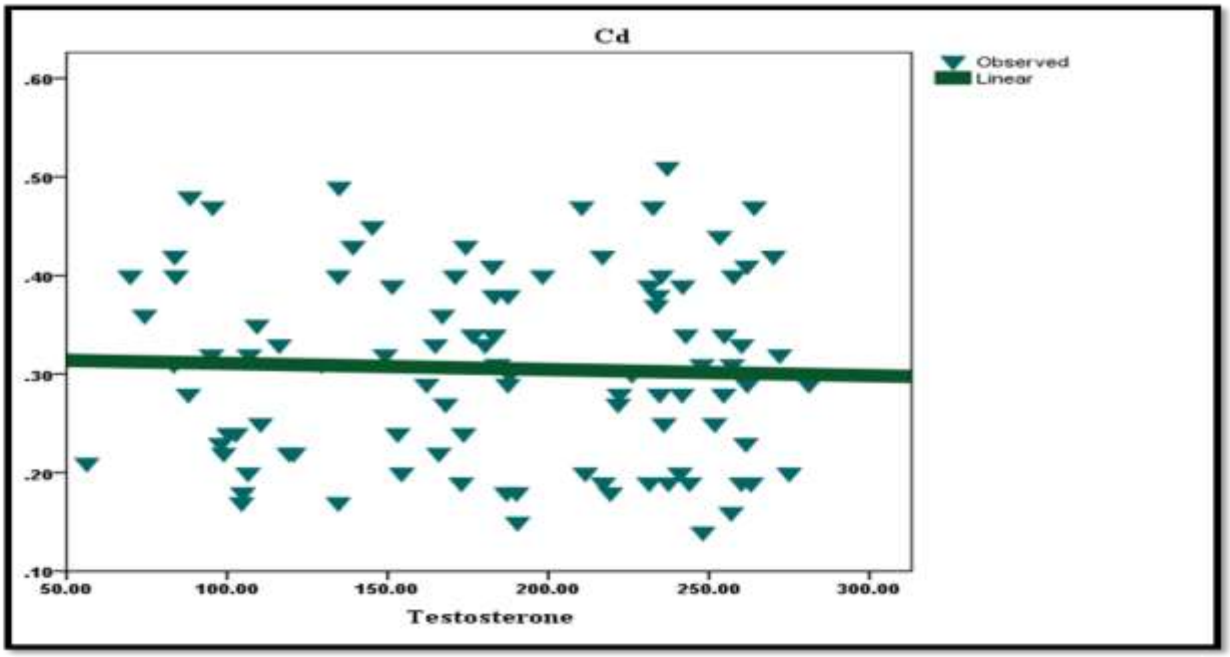

Figure 4: Regression between Testosterone (ng/ml) and Cd (µg/dl)

This result agreed with the study of [15] who found a significant low serum in infertile men with high copper levels of the same samples [15]. The same table also demonstrated a positive correlation between blood lead levels and serum copper levels and this result was in agreement with the study of [30] who showed an increase in lead and copper levels in infertile men with a significant difference ($p<0.005$), and they also found significant increase in all heavy metals including Lead Pb, Magnesium Mg, Cadmium Cd, Iron Fe, Chromium Cr, copper Cu and Cobalt Co [30]. There was also a negative correlation between serum lead levels and serum zinc levels when compared with the findings of [30].

Conclusions

The heavy metals Cu, Pb and Cd showed a highly significant difference in infertile men compared to the healthy control men, indicating that the alteration in heavy metal metabolism may be related to the development and even progress of infertility among men. The mean levels of Zn showed a highly significant decrease in the serum of infertile men compared to the healthy control group. According to the results of the present study, all heavy metals were shown to be indicators for men infertility. Serum testosterone hormone in infertile men showed a highly significant decrease as compared with those of healthy men. Serum copper level was negatively correlated with serum Testosterone level among infertile men .This result can hypothesize that excess copper acts as a hormonal disrupter. The heavy metals should be monitored routinely in male infertility, which could be helpful in improving the general health conditions and reducing progression of the disease.

Conflict of Interests.
There are non-conflicts of interest

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الخلاصة

الخلفية: يتم تعريف العقم على أنه فشل في تحقيق الحمل بعد عام واحد وأكثر من الاتصال الجنسي غير المحمي بانتظام. ارتبط تعرض الجهاز التناسلي للمعادن الثقيلة أيضًا بالعقم عند الرجال. وهناك عدد كبير من المعادن عبارة عن مواد سامة للجهاز التناسلي ويشتبه في كونها مضطربة لنظام الغدد الصماء.

المرضى والطرق: أجريت هذه الدراسة في المعهد العالي لتشخيص العقم والتقنيات المساعدة الإنجابية في جامعة النهرين ومركز استشاري التسمم / مستشفى الجراحات التخصصية في مدينة الطب في الفترة من نوفمبر 2018 إلى أبريل 2019. كان عدد الرجال 150 المسجلين في هذه الدراسة مقسمة إلى مجموعتين ، المريض ومجموعات المراقبة الطبيعية. وشملت مجموعة المرضى 100 رجل تتراوح أعمارهم بين 20–50 سنة. شملت المجموعة الثانية 50 رجلاً يتمتعون بصحة جيدة ولديهم طفلان على الأقل دون أي تاريخ سابق للأمراض الجهازية كمجموعة مراقبة. تم تقدير تركيزات المعادن الثقيلة لجميع مجموعات الدراسة. الهدف من الدراسة الحالية هو تقييم بعض تركيزات المعادن الثقيلة ، في الدم والدم الكامل للمجموعات. تقييم هرمون التستوستيرون في مصل الرجال المصابين بالعقم والضوابط الصحية ودراسة العلاقة بين هذا الهرمون والعناصر النزرة التي قدرت بين الحالات.

النتائج : أظهرت تراكيز المعادن الثقيلة وهي كل من النحاس والرصاص والكادميوم زيادة معنوية عالية وتحت مستوى احتمالية اقل من 0.010.01 في مصل دم و دم الرجال العقيمين حيث سجلت (139.7± 8.49 Mg/dl, 24.18 ± 4.30 Mg/dl, 0.31 ± 0.10 Mg/dl) على التوالي وعند المقارنة مع التراكيز في مصل الدم و دم الرجال السليمين (السيطرة) كانت النتائج على التوالي (125.14 ± 10.12 Mg/dl, 15.24 ± 2.69 Mg/dl, 0.16 ± 0.03 Mg/dl) كما أظهرت متوسطات عنصر الزنك (القصدير) انخفاضا معنويا عاليا عند مستوى احتمالية اقل من 0.01 (70.82±9.48Mg/dl) في مصل دم الرجال العقيمين مقارنة مع مجموعة السيطرة حيث كانت كما أظهرت تراكيز هرمون الشحمون الخصوي انخفاضا معنويا عاليا وتحت مستوى احتمالية اقل من 0.01 (185.40 ± 61.92 Ng/dl) (450.35±131.27 Ng/dl) بالمقارنة مع مجموعة الرجال السليمين كذلك كانت علاقة الارتباط لمستويات تراكيز عنصر النحاس وهرمون الشحمون الخصوي في مصل الدم عكسية عند الرجال العقيمين.

الاستنتاجات: خلصت هذه الدراسة إلى أن بعض المعادن الثقيلة أظهرت أنها مؤشرات لعقم الرجال. ارتبط مستوى النحاس في المصل سلبًا بمستوى هرمون التستوستيرون في المصل لدى الرجال المصابين بالعقم، وهذه النتيجة يمكن أن تفترض أن النحاس الزائد يعمل كمضاد هرموني. لم تظهر المعادن الثقيلة المتبقية ارتباطًا كبيرًا بالهرمونات المحددة.

الكلمات الدالة: المعادن الثقيلة، العقم، العقم التيستوستيرون التناسلي الذكري.