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# Autoantibodies in pregnancy wastage: perspectives and challenges

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## ABSTRACT

**Background:** Repeated failure is a serious problematic in which numerous issues show a vital part such as anticardiolipin antibodies (ACA) and antinuclear antibodies (ANA).

**Objectives:** The goal of this investigation learning was to approximation anticardiolipin (IgG) and antinuclear (IgG) antibodies in patients of recurring unsolved pregnancy damage and intrauterine fatal demises (IUFD).

**Methods:** One hundred & twenty (120) women were enrolled in this prospective case-controlled study from Maternity Hospital, Erbil City, Iraq. Altogether patients needed absent finished a consistent examination order. They were (60) patients with a past of three & additional attacks of previous abortions and (60) well pregnant. Entirely remained separated for ANA-IgG, ACL-IgG in serum.

**Results:** It was noted that (19/60, 31.7%) of the patients & (7/60, 11.67%) healthy control were positive for ACL-IgG with a mean concentration of 38±10.3 IU/ml in the patient's

group, and 11.6±4.4 IU/ml in the healthy control with highly significant at (p≤0.01). It was shown from the results that (15/60, 25%) of the patients & (6/60, 10%) healthy control were positive for ANA-IgG with a mean concentrations of (6.2 ± 0.4) IU/ml in the patients group, and (0.75±0.325) IU/ml in the healthy control with significant at (p≤0.05). The occurrence of both ACL &ANA among the seropositive patients cases were 8/19 (42.11%), whereas 11/19 (57.89%) among the seronegative patient's cases with a significant difference regarding the distribution of ANA in both ACL-positive & ACL-negative cases (P<0.05).

**Conclusions:** Anticardiolipin and Antinuclear antibodies constitute an important cause of recurrent mid-trimester abortion in Iraqi, women.

**Keywords:** Anticardiolipin Antibodies (ACA), Recurrent Abortion, Antinuclear Antibodies (ANA), Intrauterine Fetal Deaths (IUFD).

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## INTRODUCTION

Unsolved repeated pregnancy loss is consistently full as extra than two consecutive pregnancy wounded. It originates in around 1% of the overall universal residents concentrating to consume offspring. Autoimmunity achieves a significant part in regular pregnancy loss. It has been decided that immunologic individuality might be a reason in several of such suitcases. The pretentious women have typically no further symbols or indications mentioning an autoimmune illness. Antiphospholipid disorder is an inessential complaint, distinct as the existence of thrombosis or pregnancy loss or motherly sickness and continuous mingling Antiphospholipid Antibodies (APL) in plasma [1, 2]. Now, Antiphospholipid Antibodies (APL) are existence observed as the greatest commonly developed danger issue for thrombophilia as they are accountable for clots in the placental blood vessels producing foetal progress delay and as a treatable reason for persistent pregnancy loss [3]. APS can reason preeclampsia (18%), pregnancy-induced hypertension, foetal demise (7%), hindrance (31%), untimely labour (43%), miscarriage, and eventually

unproductiveness [4, 5]. APS disorder cumulative a varied cluster of circulating antibodies contrary to anionic phospholipids with the greatest vital ones are antiphosphatidyl choline, anticardiolipin antibodies (ACA), antiphosphatidylserine, lupus anticoagulants and antinuclear antibodies (ANA) [6, 7]. Inflated levels of immune markers of varies kinds of antiphospholipid antibodies are assumed to be anxious with an immune response to an inserting embryo on trophoblast intracellular combination, hormone discharge and attack may cause initial pregnancy loss. Once placentation is established, thrombogenic act ideas to diminished placental perfusion and following infarction [8]. As for the pathogenesis of APS, there are quite a lot of recognized clarifications connecting to the pathogenic part of APLs which displays expatriate placental purpose. In pregnancy, placenta is the mark organ of APS, where ischemic infarctions change due to intimal propagation, fibrinoidnecrosis and intraluminal thrombosis of the spiral arteries [8, 9, 10]. Arachidonic acid metabolites variation found in the placenta in occurrence of APLs. In the endothelial cells, APLs disturb the construction of prostacyclins which theatres a chief part via serving vasodilatation besides blocking platelet aggregation subsequent in the collection of the procoagulant thromboxane A2. On the other way, after connecting with placental anticoagulant proteins, APLs limit the performance of ordinary anticoagulants [9, 11]. Furthermore, in the first trimester of pregnancy, APLs may cause ataxia of placentation and embryonal implantation by exactly constraining hormonal excretion and violence of trophoblasts [9, 12]. This study aimed to determine the serological levels of anticardiolipin antibodies and antinuclear antibodies among the recurrent aborting women.

## MATERIALS AND METHODS

### The training procedure and Specimen

This learning was conducted from September 2017-September 2019, at Maternity Hospital, Erbil City, Iraq. Researches for the hormonal assess and infections (CMV, rubella and toxoplasmosis) were negative. The inclusion criteria were patients with a history of three or more consecutive early pregnancy losses, patients with a history of hepatitis or brucellosis involved. One hundred and twenty women (60 aborted and 60 fit panels) were registered in this case-control study. The controls were women with normal pregnancy who were para 3 and gravida 4. The diagnosis was accepted rendering to medical standards and fractional

thromboplastin time [13]. The barring principles were the subsequent: an antiquity of uterine anomalies; diabetes mellitus; thyroid disease; aspirin, heparin, antibiotics or corticosteroid intake; embryo anomalies; long-lasting systemic disease counting lupus, autoimmune diseases, hypertension, asthma, and cardiopulmonary diseases and a preceding antiquity of asymptomatic urinary tract infection.

**Ethical consideration**

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The Ethics Committee of Erbil Polytechnic University, Iraq/ Erbil Medical Technical Institute approved the protocol. Informed consent was obtained from all. The severely designated patient's assembly required olden times of three or extra consecutive primary pregnancy losses.

**Analytical Methods**

A 5ml aliquot of blood was occupied after separately patient. The divided serum was kept at -30°C till examined for ACL, ANA, anti-Brucella antibodies &HBs Ag. Discovery of ACL IgG was achieved via the ELISA method as defined by the constructer of the kit (ACL ELISA Kit, ORGENTEC, GERMANY). The result was referred to as negative if it is ≤ 15 GPLU/ ml and positive if it is >20 GPLU/ml. The serum samples were also subjected to ELISA Specific ANA as described by the manufacturer (Diagnostic Automation, Woodland Hills, California, USA). ELISA test system is designed to detect IgG class antibodies to a variety of common nuclear antigens in human sera. The result was referred as negative if OD Ratio Negative Specimens= < 0.90, Equivocal Specimens= 0.91 to 1.09 and positive if it is= > 1.10, Cut off OD = 0.198. Index Values or OD ratios = Specimen OD / Cut off OD calculated as suggested by the manufacturer, the sensitivity and specificity of the kit are 96.6% and 100% respectively.

**Statistical analysis**

Information was articulated as mean ± standard aberration, proportions and varieties as suitable. Judgements were complete via Student t-test, Chi-squared test (x2) consuming standard comp-rations in calculator manually. The consequences were described with p≤ 0.05 as the recognized equal of implication.

## RESULTS

Table (1) shows the delivery of ACL in the patients & control groups. In the patient's group, (19/60, 31.7%) had a positive ACL-IgG elevation with a range and mean of (25.3 – 64.1) IU/ml and (38.4 ± 10.3) IU/ml respectively. In the control group, (7/60, 11.7%) had a positive ACL elevation with a range and with mean of (8.5–19.4) IU/ml and (11.6 ± 4.4) IU/ml respectively. The difference in the number of individuals with positive ACL and the averages among together collections was extremely substantial through using Chi-square and the Student t-test respectively ($p \leq 0.01$).

Table (2) illustrates the dispersal of ANA in the patients & control group. In the patient's group, (15/60, 25%) had a positive ANA-IgG elevation with a range and mean as showing (0.25-4.4) IU/ml and (6.2 ± 0.4) IU/ml respectively. In the controls group, (6/60, 10%) had a positive ANA elevation with a range and mean of (0.5 - 0.9) IU/ml and (0.75±0.325) IU/ml respectively. The difference in the number of individuals with positive ANA and the means between equally clusters was very important by using Chi-square and the Student t-test respectively ($p \leq 0.01$).

Table (3) showed that from (19) ACL- positive recurrent aborting women, 8 (42.11%) women had a positive elevation of both ACL-IgG & ANA-IgG, while the rest 11 (57.89%) women had normal levels of ANA. whereas in the (41) ACL–negative recurrent aborting women 7 (17.07%) had a positive elevation of ANA, while the rest 34 (82.93%) women had normal levels of ANA. Chi x2 test showed a significant difference regarding the distribution of ANA in both groups ($p \leq 0.05$).

**Table 1. Distribution of ACL +ve cases in both patients & controls with their mean ± standard deviation and the range of concentrations observed.**

| Groups | ACL + Positive | ACL - Negative | Total | Mean ± S.D (IU/ml) | Range (IU/ml) |
|---|---|---|---|---|---|
| Patients | 19 (31.67%) | 41 (68.33%) | 60 | 38.4 ± 10.3 | 25.3 – 64.1 |
| Control | 7 (11.67%) | 53 (88.33%) | 60 | 11.6 ± 4.4 | 8.5 – 19.4 |
| Total | 26 | 94 | 120 | | |

The chi-square statistic is 7.0704. The *p*-value is .007837. This result is significant at $p < 0$ .01.

Student t test revealed this difference is considered to be extremely statistically significant $p \leq 0.01$.

t = 6.5976 d.f = 24

**Table 2. Distribution of ANA +ve cases in both patients & control groups with their mean ± standard deviation and the range of concentrations observed.**

| Groups | ANA **+** Positive | ANA - Negative | Total | Mean ± S.D (IU/ml) | Range (IU/ml) |
|---|---|---|---|---|---|
| Patients | 15 (25%) | 45 (75%) | 60 | 6.2 ± 0.4 | 0.25 - 4.4 |
| control | 6 (10%) | 54 (90%) | 60 | 0.75 ± 0.325 | 0.5 - 0.9 |
| Total | 21 | 99 | 120 | | |

The chi-square statistic is 4.6753. The *p*-value is .030599. This result is significant at $p < 0.05$

Student t test revealed this difference is considered to be extremely statistically significant $p \leq 0.01$.

t= 29.5592 d.f =19

Negative Specimens = < 0.90, Equivocal Specimens = 0.91 to 1.09, Positive Specimens = > 1.10, Cut off OD = 0.198

**Table 3. Distribution of ANA status in both the ACL positive and ACL negative women in the patient's group.**

| Patients'Group | ACL **+** positive | ACL - negative | Total |
|---|---|---|---|
| ANA **+** Positive | 8 (42.11%) | 7 (17.07%) | 15 |
| ANA - Negative | 11 (57.89%) | 34 (82.93%) | 45 |
| Total | 19 | 41 | 60 |

The chi-square statistic is 4.3389. The *p*-value is .037251. This result is significant at $p < 0.05$

## DISCUSSION

The result of the present study demonstrated that 19/60 (31.67%) of the aborted women attended the motherliness hospital in Erbil city had a raised level of ACL-Ab. Many studies agreed with our results that are found a significant association between repeated miscarriage and presence of high level of ACL- Abs. for example in Iraq studies done by Jawadet al. [13] found (17.6%) the rate of ACL-Abs. in pregnant women with fetal losses. Another study by Risan [14], Hanan S.H [15], found the 10 (33.34%) had ACL- IgM & ACL-IgG from 30 women with repeated miscarriage in Diyala and Babylon. This result is in parallel to studies by Zakariaet al. [16], Amel AA Al Samarraiet al. [17] where the prevalence of ACL among women with RPL were (31.7%), (26.5%) which were higher than control women group (8.3%), (6.6% )respectively. The results are consistent with the previous reports that 8–42% of recurrent pregnancy loss is due to positive ACL [18, 19, 20]. A study from Jordan in 2001, originate that in a set of 26 women distinct as characteristic abortion, 19.23% required constructive ACL- Abs as associated with control cluster Daboubi [21]. Festen MR et al. [22] reported that the rate of anticardiolipin antibody was 15% among patients with previous fetal loss of unexplained origin. Erkan D [23] clarified that the prevalence of anticardiolipin antibodies in patients with recurrent pregnancy loss was 20%. Zolghadriet al. [24] reported from Shiraz Iran, that the prevalence of anticardiolipin antibody in patients with recurrent pregnancy losses was 11.6%. A study in India by Velayutha Prabhu [25] found that 40% of patients with recurrent abortion had a positive result for ACL. Another study by Bayoumiet al. [26] clarified that the presence of high ACL level 4/23 (17.4%) is a major cause of recurrent fetal loss and many pregnancies can be saved if diagnosed and treated adequately. Tebo AE et al. [27] concluded that the presence of persistence LA activity or antibodies against either ACL or B2GP1 of IgG and or/IgM isotope is currently the cornerstone for laboratory diagnosis of APS. The presence of ACL has been noted in the sera of women who had a recurrent abortion for which no cause has been found. There is an association between the ACL and recurrent pregnancy loss [7]. The IgG APL of each phospholipids were more prevalent and were found frequently in women with recurrent pregnancy loss and IgG ACL is reported to be more strongly associated with clinical events than IgM ACL [28, 29]. In contrast, other studies showed no such a relation between the presence of ACL and recurrent abortion [30, 31]. Another study which was carried out in Sari (North of Iran) by

Glomahammadet al. [32] showed that the prevalence of anticardiolipin antibody in patients was not significant and it was not the cause of recurrent abortion and fetal death. Spegirionet al. [33] mentioned that some published investigations did not identify any association between antiphospholipid antibodies and reported miscarriages, but other studies did and this demonstrates the need for further studies using a larger number of individuals and standardization of the investigational methods. Ebadiet al.[34] reported that although in some reports the prevalence of antiphospholipid antibodies is higher in patients than control, actually the frequencies are only marginally greater than in the normal population, and this could be owing to absence of occurrence of a typical evaluate for determining antibodies.

Here are facts signifying that antiphospholipid antibodies encourage thrombosis concluded any one or further of numerous apparatuses: 1-antiphospholipid antibody interfering with endogenous anticoagulant instruments (disturbance of the annexin A5 anticoagulant shield [35], reserve of protein C pathway, embarrassment of antithrombin); 2-compulsory and beginning of platelets; 3-augmented thromboxane creation by platelets; 4-interacting with endothelial cells and inducing expression of adhesion molecules and tissue aspect, and thus a prothrombotic national happens as a outcome of the response between APA with cellular antigens together with platelet and endothelial cell membrane protein [36] and 5-declined prostacyclin creation by endothelial cells [37]. The exact mechanism of interaction of APL with surface molecules of HUVEC was not understood, investigators started to study signalling pathways within the ECs after their interaction with APL. Incubation of human umbilical vein endothelial cells (HUVEC) with APL resulted in a redistribution of nuclear factor κB (NFκB) from the cytoplasm to the nucleus Dunoyer-Geindre S et al. [38]. The effects of APL on the ECs are outlined in following: increased expression of adhesion molecules (ICAM-1, VCAM-1, and E-selectin), β2GPI - dependent effect, increased synthesis and secretion of proinflammatorycytokines (IL-1, IL-6 , IL-8), tissue factor expression/up regulation of TF Murine, increased endothelin-1 (ET-1), induction of apoptosis [39, 40].

In current education, antinuclear antibodies were start in 15(25%) of the aborted women with RPL and 6 (10%) in the control group, which had attended the maternity hospital in Erbil city. Antinuclear antibodies (ANA) may also be associated with reproductive failure, but in low titre appear to be relatively non- specific, and it has been recently shown

that they are found in 9% of normally fertile women [40]. This result is in parallel to studies by Anupriya A et al. [41], Garcia et al. [42] and Nakatsuka et al. [43] where the prevalence of ANA among women with RPL were (30%), 30% and 43.5% which were higher than control women group (8.3%), 6.6% and 22.4%, respectively. Morteza M et al. [44] had reported a high prevalence of ANA (13.21%) among patients with both explained and unexplained pregnancy losses. Sakthiswary R et al. [45] concluded that the existence of antinuclear antibodies may predict for a higher chance of pregnancy loss in cases with history of previous recurrent pregnancy loss. Shoenfeldet al. [46] had found a higher prevalence of antinuclear antibodies in patients with autoimmune disease. However, the incidences of ANA and Anti-ds DNA in the our learning were contradictory with a homework in Italy that had revealed a occurrence of 51.5% for ANA and 39% and for anti-ds DNA in women with persistent failure and these incompatible consequences may be due to alteration in the genetic greasepaint among the inhabitants of the existing study and Italian females [47].

Approximately suitcases of RM may have a non-thrombotic etiology. The indication for this derives from lessons reportage antinuclear antibodies (ANA) and anti-double stranded DNA amongst womenfolk with recurring mistake [48]. These antibodies were also a shared result In Italian [47] and Colombian women folk [49] with repeated miscarriage during the first trimester of pregnancy.

Antinuclear antibodies may interfere with the formation and maturation of placenta which would eventually lead to an early fetal loss. Yielding of antibodies versus histone proteins may procure to the brisk of the autoimmune process in mother and thereby end up in abortion.

Antinuclear antibodies (ANAs) are a specific class of autoantibodies that tend binding and destroying certain structures within the nucleus of the cells [50]. The mechanism by which ANAs cause pregnancy loss is not known well but based on an assumption that suggests antinuclear antibodies give rise to inflammation of the uterus that does not permit it to be a suitable host for implantation of the embryo [51].

In this study, from (19) ACL-positive recurrent aborting women, 8 (42.11%) women had a positive elevation of both ACL-IgG & ANA-IgG, while the rest 11 (57.89%) women had normal levels of ANA. whereas in the (41) ACL–negative recurrent aborting women 7 (17.07%) had a positive elevation of ANA, while the rest 34 (82.93%) women had normal levels of ANA which had attended the maternity hospital in Erbil city. Antiphospholipid

syndrome can be classified as primary or secondary. The primary form occurs in the absence of related or base diseases, being more common than the secondary [52], which is characterized by the association with a large spectrum of illnesses [53].

This result is in parallel to studies by Kwaket al. [54] in a study of patients with recurrent abortions reported a 10% to 15% increase in the incidence of antibodies to both phospholipids and nuclear epitopes with each group of higher gravidity. Creaghet al. [55] also reported a higher frequency of lupus anticoagulant and ACA in patients with recurrent abortions. While our result disagreement with a study done by Ahmed M. Bahar [56] concluded that, no association or correlation was found between the ACA and the ANA as there was only one patient who was positive for both antibodies. This lack of association has also been reported by Fort et al. [57]; and it indicates that the population of ACA positive recurrent aborts is a different subgroup from those who are ANA positive. In the existing learning, the repeated miscarriage was more associated with the primary antiphospholipid disorder rather than with secondary antiphospholipid disease, that from 19/60 (31.67%) had an elevated level of ACL IgG antibodies only 11/19 (57.89%) of women who were positive only for ACL-IgG had primary APS, while 8/19 (42.11%) women had a positive elevation of both ACL-IgG & ANA-IgG antibodies with secondary antiphospholipid syndrome. This result is in parallel to studies concluded that, no association or correlation was found between the ACA and the ANA as there was only one patient who was positive for both antibodies [58]. This lack of association has also been reported by Fort et al [57]; and it indicates that the population of ACA positive recurrent aborts is a different subgroup from those who are ANA positive. Existence ANA and Antids-DNA with parallel occurrences was stated in Spanish females with regular insufficiencies [48]. Additional study described that the first trimester of pregnancy was start to be related with the improved positivity of ANA and Antids-DNA in Colombian womenfolk [37]. Though, the incidences of ANA and Anti-ds DNA in the present study were incompatible with a study in Italy that had exposed a rate of 51.5% for ANA and 39% and for Anti-ds DNA in females with repeated lapse and these disagreeing outcomes may be due to variance in the genetic greasepaint amongst the populace of the present study and Italian ladies [49].

## CONCLUSION

In conclusion, a high serum anticardiolipin and antinuclear antibodies are not uncommon in women with unexplained recurrent miscarriage, suggesting the possible role of an autoimmune disorder on abortion, at least in a subgroup of patients. Thus, females deprived of an autoimmune syndrome antiquity, but with difficulties throughout pregnancy, have an elevated number of autoantibodies. Further research in this topic that the manifestation of autoantibodies is temporary particularly restricted to gestation or post-delivery or prognostic of upcoming immune-related diseases are to be done in near future so that we prevent recurrent fetal wastage.

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