

**Role of Antiphospholipid Antibodies in Unexplained Recurrent Abortion and Intrauterine Fetal Death**Alaa El-Deen M. Ismail<sup>1</sup>, Ebtessam M El-Gezawy<sup>2</sup>, Tahra Sherif<sup>2</sup> and Khalid A Nasif<sup>3</sup><sup>1</sup>Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Egypt.<sup>2</sup>Department of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt.<sup>3</sup>Department of Biochemistry, Faculty of Medicine, Minia University, Egypt[dr.alaa\\_ismail@yahoo.com](mailto:dr.alaa_ismail@yahoo.com)

**Abstract: Background:** Women with antiphospholipid antibodies (aPL) have a significant risk of reproductive failure and adverse pregnancy outcomes, the recurrent miscarriages, intrauterine fetal deaths, and intrauterine fetal growth restriction is significant among these patients. Women with a history of recurrent abortion and unexplained fetal death or a history of recurrent thrombotic episodes should be screened for the presence of antiphospholipid antibodies. We studied the incidence of anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) factor in recurrent unexplained miscarriages and intrauterine fetal deaths. **Subjects and Methods:** We performed a cohort study among women who attended the department of Obstetrics and Gynecology, Assiut University hospitals, Assiut, Egypt, between October 2007 and October 2011 after being referred due to recurrent miscarriage ( $\geq 2$  consecutive pregnancy losses). All women underwent a standardized investigation sequence. Women with other reasons for recurrent miscarriage were excluded. Lupus anticoagulants and Anticardiolipin antibodies were performed for all cases. **Results:** A total of 927 women met the selection criteria, 164 women were selected for this study by virtue of having unexplained recurrent fetal wastage. These comprised 140 cases of recurrent ( $\geq 3$ ) mainly first and sometimes second trimester abortions and 24 cases of recurrent ( $\geq 2$ ) late intrauterine fetal death. An increased incidence of anticardiolipin antibodies was found in women with unexplained recurrent fetal loss. Lupus anticoagulants was found in forty five (45) cases (27.4%) anticardiolipin antibodies IgM and or IgG positive cases shows prevalence of fifty eight (58) cases (35.4%). The prevalence of APS in the studied group was seventy eight (78) cases (47.6%). **Conclusions:** All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for aPL.

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**Keywords:** Antiphospholipid antibodies, anticardiolipin; antiphospholipid syndrome; recurrent pregnancy loss.

**1. Introduction**

A miscarriage is a pregnancy that ends spontaneously before the fetus has reached a viable gestational age, while IUFD is defined as fetal death after the age of viability which differ internationally between 20-24 weeks of gestation [1].

Recurrent miscarriage is common, with an incidence of 0.4–2% amongst couples who try to conceive (depending on the definition of two or three consecutive miscarriages) [2,3]. Major determinants of the prognosis following recurrent miscarriage are maternal age, the number of preceding miscarriages, and whether or not an underlying cause is found. Therefore, diagnosing an underlying cause is essential for appropriate counseling of couples with recurrent miscarriage. Known risk factors for recurrent miscarriage include anatomical, hormonal or chromosomal abnormalities and the antiphospholipid syndrome (APS) [4]. However, the cause of recurrent miscarriage remains unexplained in more than 50% of couples with recurrent miscarriage [5,6].

Antiphospholipid syndrome is an acquired condition, defined as the presence of thrombosis or

pregnancy loss or maternal morbidity and persistent circulating antiphospholipid antibodies (aPL) in plasma [6, 7]. The prognosis of a subsequent pregnancy in women with APLAs and recurrent miscarriage is not clearly elucidated. Most descriptions stem from randomized trials that have assessed the efficacy of aspirin, with or without heparin, to improve the live birth rate in women with APLAs after recurrent miscarriage [8]. Because participants in trials do not necessarily reflect the general population, these results are not easily translated to daily practice.

Antiphospholipid antibodies are a family of approximately 20 antibodies directed against negatively charged phospholipid binding proteins. To diagnose APS, it is mandatory that the woman has two positive tests at least 12 weeks apart for either lupus anticoagulant (LA) or anticardiolipin antibodies (aCL) of immunoglobulin G and/or immunoglobulin M class present in a medium or high titer over 40 g/l or ml/l, or above the 99<sup>th</sup> percentile). In the detection of lupus anticoagulant, the dilute Russell's viper venom time test together with a platelet neutralization

procedure is more sensitive and specific than either the activated partial thromboplastin time test or the kaolin clotting time test [9].

If a value  $> 95^{\text{th}}$  centile is used to define positivity, an individual will have a 64% chance of positive test result from one of these 20 antibodies. However, only the LA and aCL (IgM and IgG subclass but not IgA), have been shown to be of clinical significance. Testing for antiphospholipid antibodies other than LA and aCL is uninformative [8].

The inhibitory effect of aPL on trophoblast intercellular fusion, hormone production and invasion may cause pregnancy loss. Once placentation is established, this thrombogenic action leads to decreased placental perfusion and subsequent infarction [10].

The aim of this work is to evaluate the prevalence of Anti phospholipids syndrome in these cases and the relation between the level and the type of the antibody on the pregnancy outcome.

## 2. Subjects and Methods:

This study was carried out in the department of Obstetrics and Gynecology, Assiut University hospitals, Assiut, Egypt, between October 2007 and October 2011.

Nine hundred and twenty seven cases of the recurrent pregnancy losses were recruited from the outpatient clinic after exclusion of the possible etiological factors (from the history and detected investigations). All cases of recurrent fetal wastage were studied, from these one hundred sixty four (164) women were selected for this study by virtue of having unexplained recurrent fetal wastage. These comprised one hundred forty cases (140) of recurrent ( $\geq 3$ ) mainly first and sometimes second trimester abortions and twenty four (24) cases of recurrent ( $\geq 2$ ) late intra uterine fetal death.

In all cases full history and complete physical examinations including body weight, height and body mass index were done. Exclusion of the endocrinal abnormalities including signs of hirsutism and thyroid abnormalities were done. Ultrasound examination was done to exclude anatomical causes in the uterus and exclusion of polycystic ovaries (PCO). All women underwent a standardized investigation sequence, as previously reported [11, 12].

### Inclusion criteria:

These patients were considered as cases with recurrent fetal losses if they have the following criteria:

- 1-Three or more recurrent miscarriage (whether primary or secondary) before 20 weeks gestation.
- 2-Two or more recurrent unexplained intra-uterine fetal deaths (IUFD) whether primary or secondary.

### Exclusion Criteria:

1. Consanguineous marriage.

2. Uterine abnormalities: Fibroid, congenital anomalies, incompetent internal OS, and uterine hypoplasia (from detected investigations as ultrasound and hystosalpingography, and uterine sound).
3. Increased percentage of abnormal forms of sperms in semen analysis (from detected semen analysis done for cases of recurrent primary first trimester abortion).
4. Diabetes mellitus (Known from the history or from detected random blood sugar more than 200 mg/ml).
5. Essential hypertension (Known from the history).
6. Patients with thyroid dysfunction (Known from the history or from detected investigation; abnormal low or high  $T_3$ ,  $T_4$  and /or TSH).
7. Patients with uterine surgery before recurrent pregnancy losses (Cesarean section or previous myomectomy or D & C .....etc).
8. Rh isoimmunization (Known from the history or from detected Rh- negative blood grouping).
9. Previous history of late IUFD exclusion of ante partum hemorrhage, umbilical cord prolapse and abruptio placentae were done.

The selected patients belonged to the age group of 22-35 and they were thoroughly investigated for all baseline blood parameters, and other infectious diseases including metabolic diseases. All other pathologies were ruled out except anti-phospholipid antibodies.

Screening for LA was performed by the Kaolin Cephalin Clotting Time (KCCT) utilizing sensitive reagents and by the Dilute Russell's Viper Venom Time (DRVVT) with a neutralization procedure using frozen-thawed platelets (Dade Behring). For This test collection of blood was of (9 vol.) in 0.109 M (i.e., 3.2 %) trisodium citrate anticoagulant (1 vol.). Use sample collection tubes made of plastic or siliconized glass. Centrifugation of blood samples for 15 minutes at 2,500 rpm, collection of the plasmas in plastic tubes. Plasmas remain stable for 4 hours at  $20 \pm 5^{\circ}\text{C}$ .

Those patients who showed negative for the above said tests were selected for the next step of aPL screening test. Serum is the recommended sample for the evaluation of aCL. Therefore, for the present investigation blood (3ml) was collected from the women who had experienced an abortion or IUFD in non pregnant state. The blood sample was then allowed to clot for 30 min-1h and serum was collected from the sample. The serum was again centrifuged at 4000 rpm at  $10^{\circ}\text{C}$  in cooling centrifuge and then the purified serum sample was used for further evaluation. Serum samples were evaluated to see the presence of aCL (IgG and IgM).

Anticardiolipin antibodies estimation was done by the ELISA technique as described by Luzzana *et*

al.,[13]. The procedure is according to the direction of manufacturers[14]. The result, which was calculation against concentration, was interpreted in (U/ml) units: For IgG(U/ml) <10 negative, and >10 positive and IgM(U/ml) <7 negative and <7 positive.

#### Statistics:

The prevalence of the (antiphospholipid antibodies) was evaluated and the mean values were calculated. The two tailed t -test was performed to find out significance variance of positive aCL among the total test population by using SPSS statistical software, 9th Version; SPSS Inc., Chicago, IL, USA. Non parametric data was analyzed by Chi-Square test or Fischer exact test when appropriate. Statistical significance was assumed when *p* value < 0.05.

#### 3. Results:

A total of 927 women met the selection criteria, of whom (25%) were diagnosed with APLAs. Baseline characteristics are listed in Table (1) and they were similar in women with APLAs and women with unexplained recurrent miscarriage.

One hundred sixty four (164) women were selected for this study by virtue of having unexplained recurrent fetal wastage. These comprised one hundred forty cases (140) of recurrent ( $\geq 3$ ) mainly first and sometimes second trimester abortions and twenty four (24) cases of recurrent ( $\geq 2$ ) late intrauterine fetal death. The clinical criteria of the both groups showed no significant difference (Table 2).

The prevalence of APLAs antibodies among the studied group (164 cases) showed that LA was found in forty five cases (27.4%). Anticardiolipin antibodies IgM and or IgG positive cases shows prevalence of fifty eight cases (35.4%). Antiphospholipid syndrome can be diagnosed if the case contains one or more of the previous three antibodies. The prevalence of APS in the studied group was diagnosed in seventy eight cases (47.6%), (Table 3).

The prevalence of positive cases of APA and the mean values of ACA (IgM & IgG) and LA1/ LA2 titre among the positive cases were studied. We found that LA was positive in forty two cases (29.8%) of abortion group, while in IUFD group was three cases (12.5%) "*P* = 0.299". (Table 4)

As regard ACA (IgM), we found that positive cases were (32cases, 22%) in abortion group while it was 3 cases (12.5%) in IUFD group (*P*=0.225). Regarding ACA (IgG) positive cases in abortion group was (44 cases (31%) while they were (6 cases, 25%) in IUFD group with no statistical significance.

The correlation between the number of abortion and increasing maternal age, weight, BMI, and APA was evaluated. All of them show highly significant positive correlation (*P*= 0.025,0.006 and 0.004).Table (5).

The association between APLAs antibodies showed that LA positive cases were associated with ACA IgM and/or IgG positive cases were found in fifty one (51) cases (31.09 %)Table |(6).

#### 4. Discussion

The loss of fetus at any stage during pregnancy is a devastating event for a woman and her family .The grief reaction follow the pregnancy loss is sever and similar to that following the death of an adult family member [15].

The causes of fetal loss are myriad, and many will have implication for future pregnancy [16].

**Table (1):** Clinical characteristics of women with history of recurrent pregnancy loss referred to Assiut University hospitals during the period of the study:

| Character                                   | Abortion<br>n = 805 | IUFD<br>n = 122 | P value |
|---|---------------------|-----------------|---------|
| Age (years)<br>(mean $\pm$ SD)              | 27.2 $\pm$ 5.3      | 29 $\pm$ 5.5    | 0.08    |
| Weight (Kg)<br>(mean $\pm$ SD)              | 80.2 $\pm$ 7.2      | 78.8 $\pm$ 8.1  | 0.07    |
| Height (Cm)<br>(mean $\pm$ SD)              | 162 $\pm$ 4.2       | 160.3 $\pm$ 5   | 0.09    |
| BMI (Kg/m <sup>2</sup> )<br>(Mean $\pm$ SD) | 30.56 $\pm$ 2       | 30.78           | 0.13    |
| Hb % (gram/dl)<br>Mean $\pm$ SD             | 11.3 $\pm$ 0.99     | 11.2 $\pm$ 0.89 | 0.14    |

**Table (2):** Clinical characteristics of the studied group (164 cases of RM and IUFD).

| n = 164  |                |
|--|----------------|
| Age (Years) (mean years $\pm$ SD)                        | 26.4 $\pm$ 5.3 |
| Residency (n. & %)                                       |                |
| Rural  | 76 (46.3%)     |
| urban  | 88(53.7%)      |
| Weigh (kg) Mean $\pm$ SD                                 | 68.9 $\pm$ 8.8 |
| Height (cm) Mean $\pm$ SD                                | 160.2 $\pm$ 6  |
| Body mass index (BMI) mean $\pm$ SD<br>Kg/m <sup>2</sup> | 26.9 $\pm$ 3.6 |
| Blood group  |                |
| O (n. & %)   | (35.3%)        |
| A (n. & %)   | (28.7%)        |
| B (n. & %)   | (22%)          |
| AB (n. & %)  | 23<br>(14%)    |
| Hb% gram (mean $\pm$ SD)                                 | 11.5 $\pm$ 0.9 |

**Table (3):** Prevalence of possible Antiphospholipid antibodies in the studied groups:

| N = 164                             |     |          |
|-------------------------------------|-----|----------|
| Lupus Anticoagulant (LA)            | 45  | (27.4%)  |
| ACA IgM + ve (only)                 | 35  | (21.4 %) |
| IgG + ve (only)                     | 50  | (30.5 %) |
| ACA                                 |     |          |
| IgM and IgG + ve                    | 27  | (16.5%)  |
| IgG or IgM + ve                     | 31  | (18.9%)  |
| Both are - ve                       | 106 | (64.6%)  |
| All -ve (3Abs) (ACA IgM/IgG and LA) | 86  | (52.4%)  |
| One of them + ve (of the 3 tests)   | 78  | (47.6%)  |

**Table (4):** Prevalence of positive APA (LA and ACA) among studied groups:

| N = 164   |  |                                       |                         |
|---|--|---------------------------------------|-------------------------|
| Markers   | Abortion<br>n = 140                    | IUFD<br>n = 24                        | P<br>value              |
| Lupus Anticoagulant (LA)<br>(n. & %)<br>Mean ± SD | 42<br>(29.8%)<br>2.28 ± 0.45           | 3<br>(12.5%)<br>2.87 ± 0.15           | 0.299<br>0.004          |
| ACA<br>IgM<br>Mean ± SD                           | 32<br>(22%)<br>22.66 ±                 | 3<br>(12.5%)<br>27.33 ±               | 0.225                   |
| IgG<br>Mean ± SD                                  | 5.30<br>44<br>(31%)<br>21.98 ±<br>3.26 | 4.51<br>6<br>(25%)<br>25.50 ±<br>3.67 | 0.235<br>0.410<br>0.005 |
| ACA<br>Both (IgM and IgG) +ve<br>cases            | 24<br>(17%)                            | 3<br>(12.5%)                          | 0.60                    |
| ACA<br>Both (IgM and IgG)<br>-ve cases            | 88<br>(63.1%)                          | 18<br>(73.9%)                         | 0.60                    |

**Table (5):** The correlation between the number of abortion and Antiphospholipid antibodies level, age, weight and BMI.

| Numbers of abortion (164) |                  |         |
|---------------------------|------------------|---------|
|                           | Co-efficient (R) | P value |
| APA                       | 0.163            | 0.038   |
| Age                       | 0.175            | 0.025   |
| Weight                    | 0.212            | 0.006   |
| BMI                       | 0.227            | 0.004   |

**Table (6):** The association between different antiphospholipid antibodies among the positive cases of the studied group:

| Number (N) = 164                     | Number (N) and<br>Percentage(%) |
|--------------------------------------|---------------------------------|
| Cases positive for both LA & ACA IgM | 14 (8.5 %)                      |
| Cases positive for both LA & ACA IgG | 24 (14.6 %)                     |
| Cases positive for all               | 13 (7.9 %)                      |

The risk of recurrence depends upon the cause of the first pregnancy loss, but adverse pregnancy outcomes appear to be more common in these women. Their pregnancy should be regarded as high risk and monitored accordingly [17].

Known causes of maternal defects include coagulation disorders, auto-immune defects [18]. The etiology in approximately 50% in recurrent pregnancy loss is unknown [19]. The exact prevalence of the etiological factors remains unclear.

Primary antiphospholipid syndrome has been associated with adverse pregnancy outcomes including three or more consecutive pregnancy losses

of morphologically normal fetuses [8].

The primary antiphospholipid syndrome refers to the association between APL with recurrent miscarriage, late pregnancy loss, and/or thrombosis and thrombocytopenia. Although more than 20 antibodies directed against phospholipid binding proteins have been described, in terms of pregnancy morbidity, only the aCL and LA antibodies are thought to be clinically relevant [20].

In the current study, one hundred sixty four cases of unexplained pregnancy loss (recurrent abortion and IUFD) were included; we found that the prevalence of APS among those cases was 47.6%. The results are consistent with the previous reports that 8-42% of recurrent pregnancy loss is due to positive aCL. [21-23]

Additionally, our results indicated that 45% of women with recurrent pregnancy loss were positive for LA and this is consistent with Velayuthaprabhu and Archunan, 2005 [24]. The presence of aCL has been noted in the sera of women who had a recurrent abortion for which no cause has been found. [25, 26]. There is an association between the aCL and recurrent pregnancy loss. Previous studies have subsequently confirmed the adverse effect of aCL on pregnancy with the experimental mouse model. The experimental induction of APS causes the increased resorption rate and at the same time decreased placental and embryos weight in pregnant mice [27].

Lupus anticoagulant was positive in 29% of recurrent abortion and 12, 5% of late IUFD group, ACA IgG positive was 31% in abortion group and 25% on IUFD group.

Anticardiolipin IgG antibodies seem to be better predictors of the fetal outcome although the presence of IgM antibodies is not without risk to the fetus [25].

Abd El Aal, et al., 1999 found strong relation between anti cardiolipin antibodies (IgM/IgG) and lupus anticoagulant [28]. They found that ACA were twice of lupus anticoagulant. Gezer et al., 2003 found that ACA is five times more often than LA in patient with APS. [29]. In our current study, we found that ACA is higher than lupus anticoagulant, (ACA, 35.4 % & LA 27%) .

There is strong correlation between number of abortions and the level of LA, and with level of ACA [28]. In our current study we found that only correlation between number of abortion and LA but not with either anticardiolipin antibodies IgM or IgG.

This is with agreement of our study (Negative predictive value with LA 84.2% and with ACA IgM 85%).

There was positive the correlation between the number of abortion and the increasing maternal age, weight, BMI, and APA.

**Conclusion,**

All women with recurrent first-trimester miscarriage and all women with one or more second-trimester miscarriage should be screened before pregnancy for antiphospholipid antibodies and this in agreement with Royal College of Obstetricians and Gynaecologists (RCOG) 2011 recommendations for the investigation of couples with recurrent pregnancy loss. The type and the level of each antibodies affect the pregnancy outcome in patients with APS. Large numbers of patients is needed to evaluate these findings and to compare this with other APS antibodies.

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