

Statistical Correlations of the Spontaneous Abortion with Trombophilia and Other Associated Pathologies

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ABSTRACT: 15-20% of all known pregnancies progress with a miscarriage or an ectopic pregnancy. The recurrent miscarriage is a delicate clinical situation because with all the advances in genetic and immunologic research the incriminating factors haven't been discovered yet. The treatment is also subject to controversies, being perceived as either ineffective or aggressive. A number of 376 pregnant women with a gestational age smaller than 12 weeks have been selected, 226 of them with spontaneous abortion. In the study group of patients with previous spontaneous abortions we have found a series of associated pathology. From the cases with secondary non idiopathic recurrent miscarriage we have identified 4 cases of thrombophilia with antiphospholipid syndrome, 2 cases of thrombocytosis, one case of autoimmune thyroiditis, one case of uterine tumor, one case of MTHFR C homozygous thrombophilia and one case of FVL heterozygous thrombophilia. Knowing the correlations between the recurrent miscarriage and the hereditary thrombophilia as well as the options of treatment for increasing the chances of having a pregnancy with a normal evolution direct the doctors in testing the patients with recurrent miscarriage for hereditary thrombophilia.

KEYWORDS: recurrent miscarriage, trombophilia, associated diseases

Introduction

The early loss of pregnancy represents a negative experience both for the patient as well for the physician. Unfortunately, pregnancy loss is the most common complication of human gestation. Most of these losses are not recognized and are usually discovered before or with the next menstruation.

15-20% of all known pregnancies progress with a miscarriage or an ectopic pregnancy. Approximately 5% of the couples attempting to get pregnant have 2 consecutive miscarriages and about 1% of the couples have 3 or more consecutive miscarriages.

The recurrent miscarriage is a delicate clinical situation because with all the advances in genetic and immunologic research the incriminating factors haven't been discovered yet. The treatment is also subject to controversies, being perceived as either ineffective or aggressive.

It is very important to make the couples which are eager for answers and solutions to understand that this pathology may be very frustrating for the physicians as well.

Materials and method

The conducted prospective study comprised two lots of patients selected from the patients of

the 1st Clinic of Obstetrics and Gynecology of the Filantropia Municipal Hospital in Craiova. The patients have been selected after the completion of the initial evaluation chart and the informed consent forms. The study has been approved by the Ethics Commission of UMF Craiova.

A number of 376 patients have been selected and then divided into 2 groups:

The first group included 150 women with normal pregnancies, with a gestational age smaller than 12 weeks and induced abortion (an evacuation curettage was requested).

The second group comprised of 226 women with pathological pregnancy, with gestational age smaller than 12 weeks and spontaneous abortion.

Out of the 226 women with spontaneous abortion we have identified the patients with recurrent miscarriages being included in this category the patients with a minimum of 3 miscarriages, subdividing this group into 2 smaller subgroups:

a subgroup that included 43 women patients with recurrent miscarriage

a second subgroup that comprised the rest of the patients, 183 women, with 1-2 miscarriages in the past that were not defined as recurrent miscarriages.

The secondary data processing, the calculation of the fundamental statistical

parameters, the median and standard deviation, their relationship – the variation coefficient and their graphical representation have been conducted using Microsoft Office Excel software and the Pivot Tables, Functions-Statistical, Chart and Data Analysis modulus commands. To complete the normality tests for statistical analysis (Shapiro-Wilks and Anderson-Darling) and the Student and Mann-Whitney-Wilcoxon tests we have used commands from the XLSTAT module and the help of SPSS software.

Results

The analysis of the questionnaires completed after anamnesis and clinical examinations carried out we selected patients and reveal the data in the present study. The data has been statistically processed and the statistical analysis of the data has been conducted by using statistic indicators applied to the studied cases and in accordance with the indices and the scores calculated for the pregnant women.

We identified the cases that have investigated and found to have a definite pathology in abortions occurred before, aiming to select among patients with RSA those with idiopathic recurrent spontaneous abortion (IRSA).

We have individualized a number of 29 cases with idiopathic recurrent spontaneous abortion (IRSA) and the other 14 cases with non idiopathic recurrent spontaneous abortion (NIRSA) have been classified according to the obstetrical antecedents of the patients in:

-primary spontaneous recurrent abortion – the patient didn't have any previous births – 4 cases

-secondary spontaneous recurrent abortion – the patient had one or more previous births - 10 cases.

Therefore we have identified 15 cases of primary idiopathic spontaneous recurrent abortion, 14 cases with secondary idiopathic spontaneous recurrent abortion, 4 cases of primary non idiopathic spontaneous recurrent abortion and 10 cases of secondary non idiopathic spontaneous recurrent abortion.

In the study group of patients with previous spontaneous abortions we have found a series of associated pathology. Out of the total of 226 patients with spontaneous abortion included in the study group, 110 did not present any associated pathology. In this category we have included the subgroup of patients with idiopathic spontaneous recurrent abortion (29 cases), the rest of the patients being diagnosed with

hematologic disorders: 16 cases of confirmed thrombophilia and 2 cases of thrombocytosis. The tumors and the uterine malformations were found in 28 patients with non recurrent spontaneous abortion The most frequent pathology in these cases was comprised of local and general infections (31 cases).

Table 1. Type of recurrent spontaneous abortion in the studied groups

Miscarriage type	Cases	%
Primary idiopathic recurrent miscarriage	15	34.88
Secondary idiopathic recurrent miscarriage	14	32.56
Primary recurrent miscarriage	4	9.3
Secondary recurrent miscarriage	10	23.26
Total	43	100

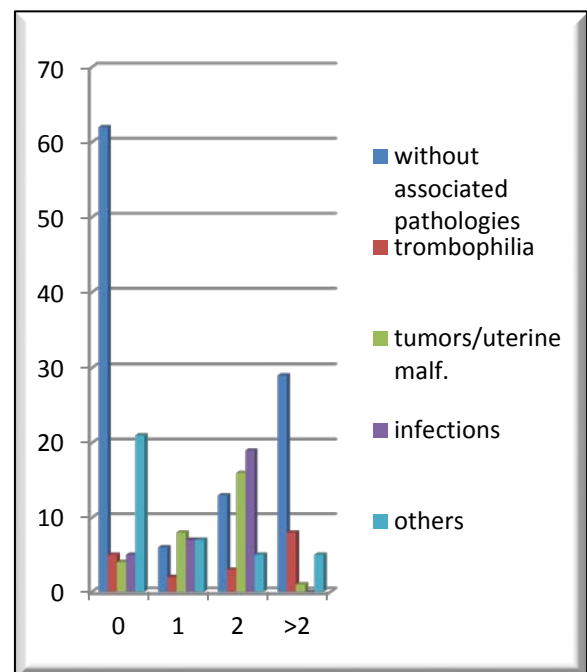


Fig.1. The relationship between associated diseases and prior spontaneous abortions

Comparing the median age of the two study groups we found a statistically significant difference between the median age of patients in the study group and the control group, with p <0.05, which shows that age is a marker that may influence the production of recurrent abortion.

Table 2. The comparing of median age of the two study groups

Age(years)	Spontaneous abortion group	Control group
Median	29.73	27.48
Standard deviation	6.02	5.38
C.V. (%)	20.29%	19.58%
p test Student	0.002666	<0.05

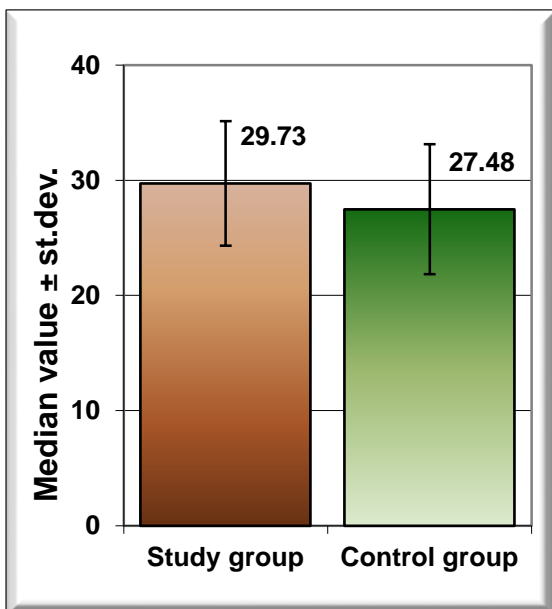


Fig.2. The comparing of median age of the two study groups

Table 3. The comparing of median age of patients with recurrent spontaneous abortion (RSA) with those of other patients with non-recurrent spontaneous abortion (NRSA)

Age	Spontaneous abortion		
	With ASR	Without ASR	Total
Median	32.30	27.85	28.69
Standard deviation	5.41	5.65	5.86
C.V. (%)	16.76%	20.29%	20.43%
p Mann-Whitney	< 0.0001 significantly high		

Comparing the ages of patients with recurrent spontaneous abortion (RSA) with those of other patients with non recurrent spontaneous abortion (NRSA) in the study group, we obtained a highly significant difference (p Mann-Whitney <0.0001).

Thus, the patients with recurrent spontaneous abortion from our study had a median age of

32.3 years while the median age of other patients with miscarriage, but without recurrence was 27.85 years.

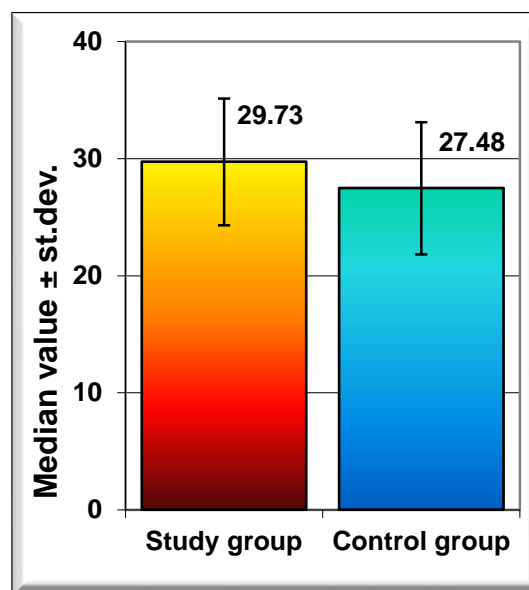


Fig.3. The comparing of median age of patients with recurrent spontaneous abortion (RSA) with those of other patients with non-recurrent spontaneous abortion (NRSA)

The results are not surprising, because the patients in the group with RSA have at least three previous miscarriages, so they have a long obstetrical history.

Patients in the study group were divided according to gestational age at the time of abortion and serum levels of chorionic gonadotropin, as follows:

Preclinical miscarriage - when gestational age was less than 5 weeks and the βhCG below 1500 IU;

Clinical Miscarriage - when gestational age was more than 5 weeks also classified into:

- Clinical miscarriage class I - for pregnancies with a gestational age between 6 weeks and 9 weeks and 6 days and
- Clinical miscarriage class II - for pregnancies with gestational age between 10 and 12 weeks of gestation.

Most of the miscarriages occurred at gestational ages from 6 weeks to 9 weeks and 6 days (73.45%).

The differences between the group of patients with recurrent miscarriage and miscarriage were not statistically significant for all three categories of spontaneous abortion (Chi square p= 0.787514).

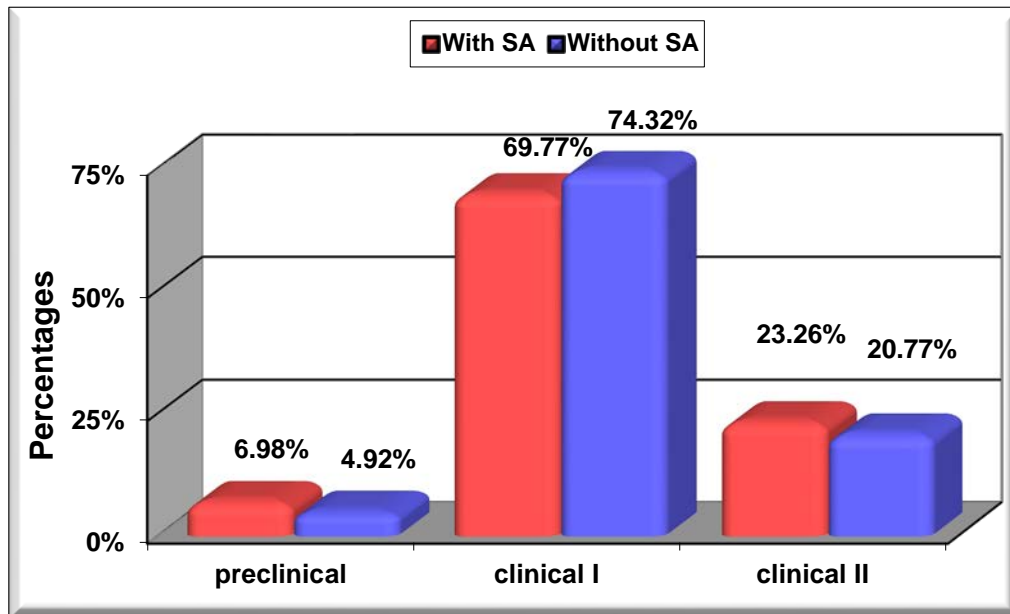


Fig.4. The comparing of groups according to the miscarriage classification

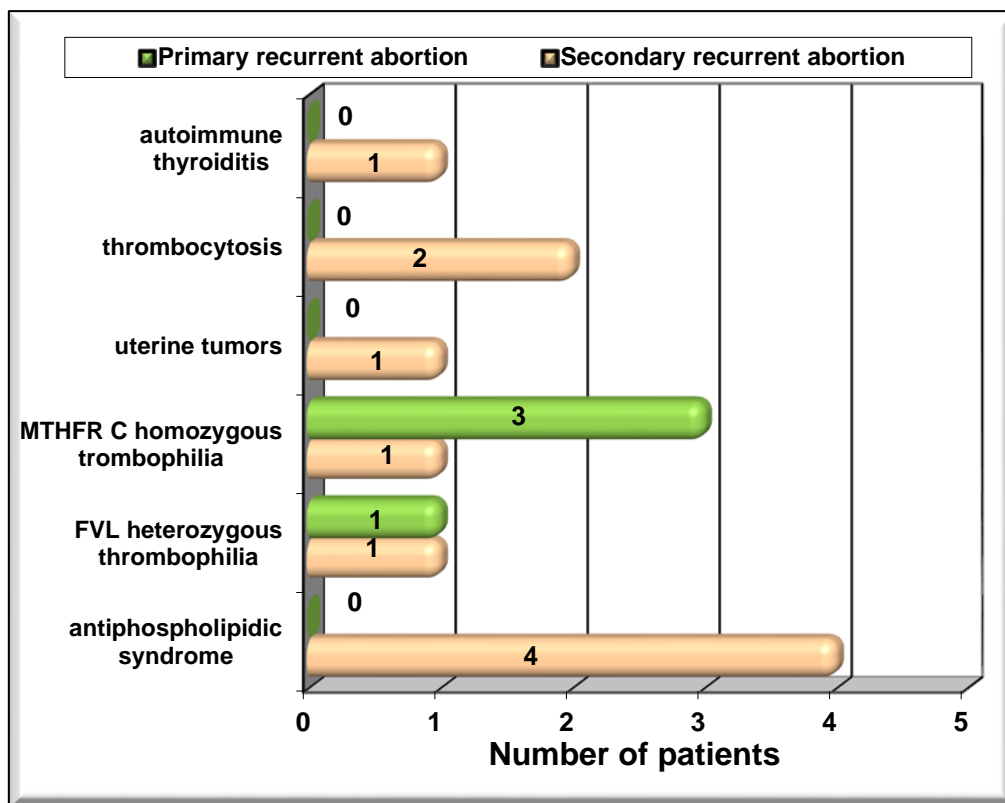


Fig.5. Diseases associated with recurrent spontaneous abortions

From the group of 43 patients with recurrent spontaneous abortion in 14 cases investigations conducted revealed the presence of associated pathologies that can be incriminated in the etiology of miscarriage. The 14 cases were divided according to the type of disease associated with.

In three of the cases with primary nonidiopathic recurrent spontaneous abortion the investigations showed the presence of homozygous MTHFR C thrombophilia, and in one case the presence of heterozygous FVL thrombophilia.

Table 4. Diseases associated with recurrent spontaneous abortions

Diseases associated with RSA	Primary recurrent miscarriage	Secondary recurrent miscarriage
Autoimmune thyroiditis	0	1
Thrombocytosis	0	2
Uterine tumors	0	1
Homozygous MTHFR C thrombophilia	3	1
Heterozygous FVL thrombophilia	1	1
Antiphospholipid syndrome	0	4

In secondary non idiopathic recurrent spontaneous abortions we have identified 4

cases of thrombophilia with antiphospholipidic syndrome, 2 cases of thrombocytosis, one case of autoimmune thyroiditis, one case of uterine tumors, one case of MTHFR C homozygous thrombophilia and one case of FVL heterozygous thrombophilia.

In all the 183 patients in the study group that haven't been diagnosed with recurrent spontaneous abortion the clinical and paraclinical investigations have shown a series of associated pathology. The most common associated pathology was represented by local and general infections (16.94%), especially uterine infections (endometritis, endometriometritis).

A high percentage of cases (14.21%) has been diagnosed consecutive to the echoFig.and histopathological exams with partial or complete hydatidiform mole. 11.48% of the patients presented in the medical history human assisted reproductive techniques.

Table 5. Diseases associated with recurrent and non-recurrent spontaneous abortions

Spontaneous abortion pathology	Spontaneous abortion		
	With RSA	Withouth RSA	Total
Embryonic abnormal karyotype		7	7
DM (diabetes)		5	5
Infections		31	31
Uterine malformations		11	11
Mole		15	15
Complete mole		1	1
Incomplete mole		1	1
Partial mole		9	9
AHR (assisted human reproduction)		21	21
Blood Diseases	8	10	18
Endocrine diseases (autoimmune thyroiditis)	1	2	3
Antiphospholipid syndrome	4	1	5
Uterine tumors	1	17	18
Withouth	29	52	81
Total	43	183	226

Table 6. Diseases associated with non-recurrent spontaneous abortions

Non-recurrent spontaneous abortions pathology	Cases	Percent
Infections	31	16.94%
Mole	26	14.21%
AHR (assisted human reproduction)	21	11.48%
Uterine tumors	17	9.29%

Uterine malformations	11	6.01%
Embryonic abnormal karyotype	7	3.83%
DM (diabetes)	5	2.73%
Blood Diseases	10	5,46%
Endocrine diseases	2	1,09%
Antiphospholipid syndrome	1	0,54%
Withouth	52	28,41%

Uterine tumors (fibroids, endometrial polyps) may be a cause of miscarriage also isolated (9.29%) and recurrent. Uterine malformations identified by clinical examination, ultrasound or hysterosalpingography were considered causes of miscarriage in 6.01% of cases.

In other cases were involved embryonic abnormal karyotype (3.8%) or maternal diabetes (2.73%). In an important number of cases (28.41%) was not identified a pathology that could be associated with miscarriage.

Discussions

A series of specialized studies have shown that mothers over 40 years of age and immunologic factors are the most common factors associated with an abnormal evolution of the pregnancy [1]. Another study conducted on a group of women with infertility disorders of immune etiology show that although the chances of a successful conception decrease after mother's 40 years of age, the percentage of pregnancies doesn't also decrease with age [2].

A study conducted on a group of patients over 35 years of age and recurrent miscarriage has shown that fetal chromosomal anomalies are responsible for the majority of the abortions, other causes being incriminated in only 20% of the cases [3].

Comparing the median age of the patients in the 2 studied groups we have found a significant statistical difference between the median age of the patients in the study group and the median age of the patients in the control group, with a $p < 0.05$ indicating that age is a marker that might have an influence in the recurrent miscarriage occurrence.

The patients with recurrent miscarriage in our study had a median age of 32.3 years while the patients with simple miscarriages had a median age of 27.85 years.

Comparing the age of the patients with recurrent miscarriage and the age of patients with non-recurrent miscarriage we have obtained a very significant statistical difference (p Mann-Whitney < 0.0001).

Recent studies have shown that women with recurrent miscarriage have a tendency to lose the pregnancy at the same gestational age. That is why we believe that in these idiopathic situations the causes of the loss of pregnancy are specific to a certain gestational age and that further investigations should be aimed towards these causes [4].

In a recent study, Ticconi C. and his collaborators have found antithyroid auto antibodies in 28.75% of the patients with recurrent miscarriages compared with 13% found in patients included in the control group. 91.3% of the patients with recurrent miscarriages found with antithyroid auto antibodies also tested positive for other auto antibodies. Therefore some authors have concluded that the antithyroid antibodies and especially TG-Ab are associated with recurrent miscarriages and can be the expression of a more complex pathology of the maternal immune system. Antithyroid auto antibodies can play a role in the recurrent miscarriage regardless of the thyroid hormonal status [5].

In all the studied cases we have discovered only one case of associated autoimmune thyroiditis. The rest of the cases lacked any thyroid pathology. Therefore we could not establish any correlations between these elements.

Approximately 1-5% of the patients trying to conceive have recurrent miscarriages. For 50% of those patients the cause of anterior abortions is unknown. The hereditary thrombophilia such as the mutation of the factor V Leiden, the mutation of the prothrombin gene (PT 20210A) and the deficiencies in natural anticoagulants such as protein C, protein S and antithrombin are associated with recurrent miscarriage.

From all the cases with non idiopathic recurrent miscarriage 3 cases presented MTHFR C homozygous thrombophilia and only one case presented FVL heterozygous thrombophilia.

From the cases with secondary non idiopathic recurrent miscarriage we have identified 4 cases of thrombophilia with antiphospholipid

syndrome, 2 cases of thrombocytosis, one case of autoimmune thyroiditis, one case of uterine tumor, one case of MTHFR C homozygous thrombophilia and one case of FVL heterozygous thrombophilia.

Knowing the correlations between the recurrent miscarriage and the hereditary thrombophilia as well as the options of treatment for increasing the chances of having a pregnancy with a normal evolution direct the doctors in testing the patients with recurrent miscarriage for hereditary thrombophilia. Even so, the association of recurrent miscarriage and hereditary thrombophilia is not very strong and, furthermore, there is no data to indicate that using anticoagulants could increase the chances of having a pregnancy with a normal evolution in these patients [6].

A certain group of women with infertility of unknown etiology can present subfertility because their pregnancies are lost before they can be clinically recognized. To determine if pre-clinical early miscarriages occur frequently in patients with infertility of unknown etiology there were serially measured the urinary concentrations of hCG in order to compare the number of pre-clinic early miscarriages after spontaneous conception in patients with infertility of unknown etiology comparatively with a group of healthy women. The obtained data does not support the hypothesis that recurrent pre-clinical early miscarriages can be represented like infertility of unknown etiology [7].

In the studied groups, the majority of the spontaneous abortions occurred between 6 weeks and 9 weeks and 6 days (73.45%) of gestational age – therefore we can consider them as class I clinical spontaneous abortions. The differences between the group of patients with recurrent spontaneous abortion and the group of patients with spontaneous abortion were statistically insignificant for all the three categories of spontaneous abortions – pre-clinical, clinical class I and clinical class II (p Chi square = 0.787514).

Conclusions

In our study the incidence of recurrent spontaneous abortion comprised 19.02% of the patients with spontaneous abortion. The incidence of idiopathic spontaneous recurrent

abortion comprised 67.44% of the total number of patients with recurrent spontaneous abortion and 12.83% of the total number of patients with spontaneous abortion.

Comparing the average age of the two groups we have observed a significant statistical difference between the median age of the patients in the study group and the patients in the control group (p test Student 0.002666<0.05). Patients with spontaneous abortion have had a median age of 29.65 years, which was higher than the patients requesting an abortion that had a median age of 27.48 years.

The majority of spontaneous abortions occurred between 6 weeks and 9 weeks and 6 days of gestational age (73.45%), qualifying as class I clinical spontaneous abortion.

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References

1. Caetano MR, Couto E, Passini R Jr, Simoni RZ, Barini R. Gestational prognostic factors in women with recurrent spontaneous abortion. Sao Paulo Med J. 2006 Jul 6;124(4):181-5
2. Ruiz AM, Kwak JY, Kwak FM, Beer AE. Impact of age on reproductive outcome in women with recurrent spontaneous abortions and infertility of immune etiology. Am J Reprod Immunol. 1996 Apr;35(4):408-14.
3. Marquard K, Westphal LM, Milki AA, Lathi RB. Etiology of recurrent pregnancy loss in women over the age of 35 years. Fertil Steril. 2010 Sep;94(4):1473-7.
4. Heuser C, Dalton J, Macpherson C, Branch DW, Porter TF, Silver RM. Idiopathic recurrent pregnancy loss recurs at similar gestational ages. Am J Obstet Gynecol. 2010 Oct;203(4):343.e1-5.
5. Ticconi C, Giuliani E, Veglia M, Pietropolli A, Piccione E, Di Simone N. Thyroid autoimmunity and recurrent miscarriage. Am J Reprod Immunol. 2011 Dec;66(6):4529.
6. de Jong PG, Goddijn M, Middeldorp S. Testing for inherited thrombophilia in recurrent miscarriage. Semin Reprod Med. 2011 Nov;29(6):540-7
7. Koot YE, Boomsma CM, Eijkemans MJ, Lentjes EG, Macklon NS. Recurrent pre-clinical pregnancy loss is unlikely to be a 'cause' of unexplained infertility. Hum Reprod. 2011 Oct;26(10):2636-41

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