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ORIGINAL ARTICLE

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Is there a higher prevalence of pregnancy complications in a live-birth preceding the appearance of recurrent abortions?

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Abstract *Objective*: The present study was designed to evaluate the prevalence of pregnancy complications in a live-birth preceding the appearance of recurrent abortions. *Methods*: A case-control study comparing women who had at least two consecutive spontaneous abortions after one live birth with matched controls, without recurrent abortions, was performed. Cases were recruited from the Recurrent Abortions Clinic. The women in the control group were matched by the following parameters: age, pregnancy order and having had a live birth in the same year as the study group. Four controls were matched for each case. The analysis focused on the characteristics of the live-birth preceding the recurrent abortions of the study group and the births of the matched controls. *Results*: From Jan 2001 through Dec 2002, 140 women were examined in the Outpatient Clinic for Recurrent Abortions. Of these, 58 women who had a live-birth prior to at least two consecutive spontaneous abortions comprised the study group, which was compared with 232 controls. A statistically significant higher rate of preeclampsia (mild and severe) was found in a live-birth preceding recurrent abortions than in the matched controls (10.3 vs. 3.9%, $p = 0.047$). In addition, a nonsignificant trend was found for higher rates of non-reassuring fetal heart rate patterns (8.6 vs. 3.0%, $p = 0.055$) in this group. No other significant differences regarding maternal or neonatal complications such as placental abruption, intrauterine growth restriction, and intrauterine fetal death were noted between the groups. *Conclusions*: A live-birth preceding the appearance of recurrent abortions is associated with a higher rate of preeclampsia.

Keywords Recurrent abortions · Pregnancy complications · Preeclampsia · Thrombophilia

Introduction

Recurrent abortions are a common gynecological problem affecting 0.5–3% of pregnancies, causing much grief and distress [3, 6, 7]. Unfortunately, a definite cause has been established in less than 50% of the cases, leading to the frustration of both patient and caregiver [3, 6, 7]. Recurrent abortions are traditionally defined as three consecutive spontaneous abortions, with a recurrence rate of 33%. However, the risk of recurrence after two consecutive abortions is clinically similar to the risk of recurrence after three or more consecutive abortions and stands at 30% [3]. Thus, the 2001 American College of Obstetricians and Gynecologists (ACOG) recommendation is that women with two or more spontaneous consecutive abortions should be candidates for clinical and laboratory evaluation in order to find a possible etiology [3]. A distinction should be made between recurrent abortions and spontaneous sporadic abortions, which are defined as nonconsecutive pregnancy losses occurring sporadically during a woman's childbearing years. The prevalence of sporadic abortions is 10–15% of all diagnosed pregnancies [3]. While in the majority of cases single, sporadic and spontaneous abortions are attributed to a chromosomal abnormality; the etiologies of recurrent abortions are heterogenic [3,

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6]. Some of the causes of recurrent abortions are: chromosomal abnormalities of one or both parents, congenital uterine anomalies (bicorniate uterus and uteral septum), acquired uterine abnormalities (polyps, myomas and adhesions), and hormonal abnormalities (prolactin, thyroid and gonadotropin). Other important causes are the antiphospholipid syndrome and thrombophilic states that include antithrombin III deficiency, protein C deficiency, protein S deficiency, and genetic mutations in factor V, factor II and methylenetetrahydrofolate reductase (MTHFR) [3, 6]. Thrombophilia is defined as an elevated tendency of the blood to clot as a result of hereditary or acquired abnormalities [7, 17, 22]. Although the actual causes of recurrent abortions are unknown in at least half the patients, there are recent reports that connect thrombophilia to many of the cases that in the past were considered idiopathic [6].

During a normal pregnancy, the concentration and activity of certain proteins that are involved in blood clotting and fibrinolysis are altered. These changes might facilitate clotting and inhibit fibrinolysis; thus, enhancing the risk for thromboembolic events, especially in women with inherited or acquired defects that promote thrombosis [14, 17].

A successful pregnancy is very much dependent on sufficient development of a functioning placenta. The perfusion to the placenta might be impaired due to thrombosis resulting from microthrombi in the placental vascular bed. These microthrombi might cause multiple infarcts that eventually may lead to pregnancy complications [11, 14, 17, 22]. Lately, several studies [7, 11, 14, 17, 22] have reported an association between thrombophilia and the pregnancy complications of preeclampsia [10, 15], placental abruption [28], and intrauterine growth restriction (IUGR) [19]. However, there are conflicting arguments in the literature as to whether this association actually exists. Assuming that there is an association, the question arises as to whether pregnancy complications (as a clinical presentation of thrombophilia) could be seen in live-birth pregnancies preceding recurrent abortions. We hope that in the future, treatment would be considered earlier for women with pregnancy complications and thus prevent the appearance of recurrent abortions.

The present study aimed to evaluate the prevalence of pregnancy complications (such as preeclampsia, placental abruption and IUGR) prior to the appearance of recurrent abortions.

Materials and methods

This study received the approval of the "Helsinki" Committee of the Soroka University Medical Center, Israel. The population of this study was female patients from the Recurrent Abortions Clinic of the Soroka University Medical Center in Israel. Soroka University Medical Center is a tertiary teaching center located in the City of Beer-Sheba, where most births in the south of Israel occur and where most women of the south are treated. The cases under study were women who had at least two consecutive spontaneous abortions after having had at least one live birth. The clinic treated 140 women between the years of 2001 and 2002, out of which 58 were secondary aborters.

The control group was selected from birth discharge records of women who delivered in the Department of Obstetrics and Gynecology of the Soroka University Medical Center. The women in the control group were matched by the following parameters: they had a live birth in the same year as that of the women in the study group who had their first spontaneous abortion; they had the same number of pregnancies, were the same age and were members of the same ethnic group (i.e., Jewish or Bedouins) as the women in the study group. Four controls were matched for every case. We used a design which compared the characteristics of the pregnancy preceding the abortions of the women in the study group to that of the corresponding pregnancy of the women in the control group. The following obstetric risk factors were evaluated: previous caesarian section (CS), mild and severe preeclampsia [4], IUGR, placental abruption, gestational and pre-gestational diabetes mellitus [5], hydramnios (amniotic fluid index >24 cm) or oligohydramnios (amniotic fluid index <5 cm), presence of premature rupture of membranes (PROM), (i.e., rupture of membranes before the commencement of the labor process), previous perinatal death, and second trimester bleeding.

The following pregnancy, labor and delivery complications were assessed: induction of labor, malpresentations, nonreassuring fetal heart rate (FHR) patterns, meconium-stained amniotic fluid, and labor dystocia.

The following birth outcomes and neonatal complications were recorded: perinatal mortality, Apgar scores of less than 7 (taken at 1 and 5 min postpartum), and postpartum hemorrhage.

To test the statistical significance of the categorical variables, the χ^2 test or Fisher's exact test were used, as deemed appropriate. To test the statistical significance of the continuous variables, the t-test was used. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed with the SPSS package (SPSS, Chicago, IL, USA).

Results

From Jan 2001 through Dec 2002, 140 women were examined in the Soroka University Medical Center's Outpatient Clinic for Recurrent Abortions. Fifty-eight of these women had a live birth prior to at least two consecutive spontaneous abortions and therefore were included in this study. The matched controls consisted of 232 women.

Table 1 shows clinical and demographic characteristics of the groups. The distributions of matched parameters: maternal age, ethnicity, and gravidity were statistically similar in the case and control groups. The number of pregnancies prior to the live birth ranged from one to eight.

Table 2 presents maternal and neonatal pregnancy and delivery complications of the two groups. A higher rate of preeclampsia (mild or severe) was found in the live-birth preceding recurrent abortions as compared to the matched controls (10.3 vs. 3.9%, $p=0.047$). In addition, a higher rate of non-reassuring FHR patterns were observed in cases than in controls; this difference had borderline statistical significance (8.6 vs. 3.0%, $p=0.055$) in this group. A combined measure of complications that were previously shown to be associated with thrombophilia [9, 10, 14, 15, 19, 28] such as IUGR, preeclampsia, placental abruption, and suspected fetal distress was calculated. However, no statistical signifi-

Table 1 Maternal and neonatal clinical and demographic characteristics of the live births preceding recurrent abortions vs. matched controls

Characteristics	Cases ($n=58$)	Controls ($n=232$)	p value
Maternal age (years ± SD)[a]	27.45 ± 5.67	27.47 ± 5.6	
Ethnicity[a]			
Bedouin	67.9%	67.9%	
Jewish	32.1%	32.1%	
Gravidity[a]			
1	13.8%	13.8%	
2–5	75.9%	75%	
>5	10.3%	10.3%	
Parity (mean ± SD)	2.86 ± 1.61	3.09 ± 1.64	0.33
1	18.9%	17.2%	
2–5	74.1%	74.6%	
>5	6.9%	8.2%	
Gestational age (weeks ± SD)	38.69 ± 3.35	39.16 ± 2.33	0.21
24–36.9 weeks	10.3%	10.3%	
37–41.9 weeks	82.7%	84.9%	
>42 weeks	6.9%	4.7%	
Neonate gender			0.71
Male	46.5%	51.3%	
Female	53.5%	48.7%	
Birth weight (kg ± SD)	3.07 ± 0.67	3.13 ± 0.55	0.48
<2.5 kg	15.5%	10.8%	
2.5–4 kg	81%	86.2%	
>4 kg	3.4%	3%	

[a]Matching variables
Data are presented as percentages or means ± SD and p values for statistical significance

Table 2 Maternal and neonatal complications. *IUGR* intrauterine growth restriction, *FHR* fetal heart rate, *PROM* premature rupture of membranes

Complication	Cases ($n=58$)	Controls ($n=232$)	p value
IUGR	2	8	1.00
Preeclampsia (mild or severe)	6	9	0.047
Mild	3	5	0.14
Severe	3	4	0.15
Placental abruption	0	3	0.38
Nonreassuring FHR patterns	5	7	0.055
Oligohydramnios	1	3	1.00
Hydramnios	6	11	0.12
Diabetes mellitus	2	7	1.00
PROM	7	15	0.15
Cord around the neck	8	35	0.80
Malpresentations	7	26	0.85
Apgar score <7			
1 min	5	11	0.21
5 min	1	1	0.27
Labor dystocia	1	2	0.56
Meconium-stained amniotic fluid	8	37	0.68
Induction of labor	15	57	0.83
Cesarian section	9	30	0.65
Postpartum hemorrhage	0	1	0.61
All complications	36	152	0.62

cant differences were noted between the cases and the controls regarding combined complications (15.5 vs. 8.6%, $p=0.12$). There were no cases of perinatal mortality in our study population.

The results did not change substantially when considering the matched design and using conditional logistic analysis.

Discussion

Considerable progress has been made in recent years in the identification and understanding of inherited and acquired hypercoagulable disorders that promote thrombosis, collectively termed thrombophilia. In the present study, we examined the hypothesis that an increased risk of thrombophilia associated pregnancy complications (IUGR, preeclampsia, placental abruption, and suspected fetal distress) is associated with recurrent abortions. Accumulating evidence has indicated that thrombophilia has a negative impact on pregnancies. While several studies have reported a relationship between maternal thrombophilic defects and adverse pregnancy outcomes [9, 10, 14, 15, 19, 23, 28], others have not been able to make such an association [8, 13, 16]. Pregnancy complications such as severe preeclampsia, uterine growth restriction and placental abruption are the leading causes of perinatal morbidity and mortality [13–15, 19, 26–28]. Although the pathophysiology of these complications is unknown, it may be associated with inadequate maternal-fetal circulation resulting from haemostatic disturbances. Vascular lesions (single and multiple infarcts and fibrinoid necrosis of decidual vessels) are a common finding in placentas of women with severe pregnancy complications [17].

Miscarriage is a common and significant problem, since 20% of women have at least one fetal loss and 5% have two or more spontaneous losses. Furthermore, 30–40% of recurrent fetal losses remain unexplained, even after standard gynecological, hormonal and karyotype investigations [24]. There are conflicting reports in the literature relating to inherited thrombophilia and recurrent pregnancy loss. In some studies an association was found between thrombophilia and recurrent pregnancy loss [1, 2, 7, 18, 20, 25]. Sarig et al. [25], in a prospective cohort study, found one or more thrombophilic defects in two thirds of the patients with idiopathic pregnancy losses, while 21% of women with pregnancy wastage had two or more thrombophilic defects. However, not all authors support this relationship [12, 20, 21]. Rai et al. [21] did not find differences in the frequency of the Factor V Leiden allele among women with a history of recurrent early or late miscarriage, and the control group.

Due to the costly investigation of inherited thrombophilia and given the present data, together with conflicting results of studies regarding the presence and magnitude of the association between inherited thrombophilia and fetal loss, there is insufficient evidence to

include inherited thrombophilias in the initial evaluation of recurrent pregnancy loss [1, 11]. At present, a consensus has not been reached as to which haemostatic investigations can best identify pregnancies at greatest risk of miscarriage and later complications [23]. There is a need to find clinical alternatives to identify these pregnancies. In search of such a clinical alternative, we evaluated complications of pregnancies that ended in live-births, of women that later had recurrent miscarriages and compared them to pregnancies of matched controls that did not suffer from recurrent miscarriages.

Since thrombophilia might be a leading cause of both recurrent miscarriages and pregnancy complications, we hypothesized that there would be an increased risk of thrombophilia associated pregnancy complications (IUGR, preeclampsia, placental abruption, and suspected fetal distress) in pregnancies ending in live-births of women that later developed recurrent miscarriages. The only statistically significant difference found in our study was a higher rate of preeclampsia in pregnancies preceding the appearance of recurrent abortions. There was a nearly threefold increased risk for preeclampsia in live-birth pregnancies preceding recurrent abortions (OR 2.86, $p = 0.047$). These findings are compatible with observations made by other investigators [15]. Kupferminc et al. [15] observed that in women who had pregnancy complications and who have thrombophilias, the types of complications in sequential pregnancies can vary.

When we compared pregnancy and delivery complications in the live-births preceding recurrent abortions, we found a threefold increased risk of suspected fetal distress (i.e., non-reassuring FHR patterns) that was borderline significant ($p = 0.055$). This finding might be explained by problems in the uterine-placental circulation.

Our study was not without limitations. First, due to the small size of the study group ($n = 58$), some of our findings may have been lacking power and did not achieve statistical significance. Second, the population of our study group was comprised of women from the recurrent abortions clinic of the hospital. This medical center treats most women in the South of Israel. However, we believe that the clinic sees only a small portion of the women suffering from recurrent abortions and therefore may not adequately represent the entire population of recurrent aborters. Third, we did not test for inherited thrombophilic defects. Therefore, the association we found between pregnancy complications and recurrent abortions in later pregnancies could not be attributed, with certainty, to thrombophilia.

In conclusion, a live-birth preceding the appearance of recurrent abortions was found to be associated with a higher rate of preeclampsia. Since thrombophilia might be a leading cause for both recurrent abortions and pregnancy complications, further prospective studies of a larger scale should be undertaken in order to adequately evaluate the clinical alternative for inheritable thrombophilic defect testing.

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