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The Relationship of Recurrent Spontaneous Miscarriage with Reproductive Failure

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Recurrent miscarriage · Polycystic ovaries · Reproductive failure

Abstract
Objective: To investigate the reproductive performance of non-pregnant women with recurrent spontaneous miscarriage (RSM) and the association between RSM and polycystic ovary syndrome (PCOS) in reproductive failure. ***Subjects and Methods:*** Fifty non-pregnant women with 3 or more consecutive RSM attending our RSM clinic were evaluated prospectively. Detailed history and physical examination were completed. Extensive laboratory investigations, ultrasonographic, radiological and specialized procedures/tests were performed. Those patients who did not achieve pregnancy within the first 6 months of follow-up had appropriate treatment options implemented. The outcome of any subsequent pregnancies was analyzed. ***Results:*** The mean age of the patients was 33.8 ± 4.6 years (range 22–43 years). The aetiological factors associated with RSM were chromosome anomaly, uterine abnormality, antiphospholipid syndrome, PCOS and infections; 40% were 'unexplained'. Thirty patients (60%) were able to achieve viable pregnancies which progressed to term, resulting in live births. Fourteen of the other 20 patients had high body mass index (BMI) >30 and evidence of PCOS. Of these 20 patients, 13 eventually achieved pregnancies which ended again in first-second-trimester abortions (cause undetermined). The remaining 7 patients (4 with high BMI) who had a combination of male factor/protracted PCOS/ovarian failure did not achieve pregnancies. ***Conclusion:*** The association of RSM with PCOS resulted in poor reproductive performance, which may progress to reproductive failure.

Introduction

A number of women who are anxious to achieve pregnancy but are never able to do so or achieve non-viable pregnancies constitute a group generally referred to as cases of reproductive failure; such failure is a common and important cause of despair and sadness for the affected couple. These women/patients fall into two groups: (a) infertile patients who in spite of all modalities of treatment including assisted reproductive technology (ART) in some cases still do not achieve a pregnancy or achieve pregnancies which terminate in sporadic abortions and (b) patients who have recurrent spontaneous miscarriage (RSM) due to a variety of aetiological factors, whose pregnancies again terminate in miscarriages.

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RSM, defined as the occurrence of 3 or more consecutive spontaneous miscarriages, is in the spectrum of conditions that lead to or could terminate in reproductive failure. RSM is a complex problem facing the specialist obstetrician/gynaecologist. The aetiology of RSM is multifactorial although 50% are unexplained. Polycystic ovary syndrome (PCOS) is the commonest cause of infertility in women in the USA [1] and a frequent cause of infertility in Kuwait [2]. PCOS affects about 5–10% of women in the reproductive age group and is characterized by chronic anovulation, menstrual abnormalities, obesity and hyperandrogenism [3] in which insulin resistance is a prominent feature [4–6]. PCOS has been associated with RSM in many reports, although its exact role and mechanism in RSM are still uncertain [7–9]. PCOS has been associated with early RSM in 56% of the population [7, 8], while in Kuwait the incidence is reported to be 21.1% [9]. Obesity and high body mass index (BMI) have been associated with PCOS and obese women with PCOS are relatively unresponsive to the induction of ovulation by clomiphene citrate and other agents. Higher reproductive losses have been observed in patients with BMI >32 [10].

The aetiology of RSM has been extensively studied and calls for comprehensive investigations [8, 9]; some of these aetiological factors respond well to appropriate therapeutic measures and are followed by viable pregnancies. Antiphospholipid syndrome has been associated with RSM in many studies and has responded positively to a variety of therapeutic trials resulting in favourable outcome for mother and baby [11]. Methylenetetrahydrofolate reductase, C677T polymorphisms (and the related hyperhomocysteinaemia which may be readily corrected by folic acid administration in pregnancy) have also been associated with RSM in few reports. Thrombophilic defects such as deficiencies of anticoagulants (protein C, protein S and antithrombin III and inherited disorders of factor V Leiden and prothrombin G20210A mutation) have been also associated with RSM [8]. The scope of the contribution of these thrombophilic disorders to RSM is still being actively investigated in many centres while the therapy for these conditions (including thromboprophylaxis) has not been well established. In our practice we observed the relatively poorer performance of some of our patients who present with RSM, and some of them also have PCOS.

We therefore decided to evaluate further patients with RSM who have failed to achieve pregnancies, establish the factors involved and to explore the linkage between RSM and reproductive failure.

Subjects and Methods

Fifty non-pregnant women with 3 or more RSM attending our RSM clinic constituted the subjects studied. A detailed history of all previous miscarriages was obtained from the patients to establish the pattern of the miscarriages. A comprehensive past medical, surgical, obstetric and gynaecological history and social biodata were also recorded. All the patients had a complete physical examination including height and weight measurements. Extensive laboratory investigations were requested and ancillary investigations including ultrasonography, radiological and specialized procedures and tests were performed in order to establish the aetiological factors. The following investigations were performed for all the cases of RSM: complete blood count, urine/blood tests to exclude renal disorders, endocrinological evaluation (screening for hyperprolactinaemia, thyroid disorders, disorders of the pituitary-ovarian axis and diabetes mellitus), and bacteriological tests (endocervical and high vaginal swab tests for bacterial vaginosis and other bacterial infections), viral and parasitic serology tests for herpes, cytomegalovirus, rubella, parvovirus and toxoplasmosis. Other tests were parental karyotype studies, hysterosalpingography and transvaginal ultrasonography and Doppler studies. The diagnosis of PCOS was based on the typical transvaginal ultrasound finding of enlarged ovaries containing ten or more follicles, 2–8 mm in diameter, arranged in the typical necklace appearance. Biochemistry tests were performed in 10 cases of PCOS and detailed insulin resistance tests were not performed although fasting glucose and insulin levels were determined and the fasting glucose-to-insulin ratio was calculated in 5 cases; the ratio of <4.5 is diagnostic of insulin resistance. Hysteroscopy and laparoscopy were also performed in 7 patients to confirm/treat uterine and ovarian disorders. The methodology for the diagnosis of antiphospholipid syndrome, one of the most frequently encountered associated causes of RSM in our clinic, and the treatment administered to patients with the syndrome were as outlined in a previous publication [11]. The diagnosis of antiphospholipid syndrome was based on the combination of the clinical criteria which were the presence of a clinical event such as recurrent pregnancy loss (RSM in this study), and or venous/arterial thrombosis and the presence of a positive laboratory finding such as the presence of positive antiphospholipid antibodies which were either anticardiolipin or lupus anticoagulant (or both in 3 cases) and/or thrombocytopenia. Anticardiolipin antibodies (ACL IgM, IgG) were estimated using the enzyme-linked immunosorbent assay while lupus anticoagulant was estimated by initial screening with activated partial prothrombin time followed by the dilute Russell's viper venom time. Positive antiphospholipid antibody test usually meant lupus anticoagulant was present/absent and the ACL antibodies were elevated on at least two occasions 6 weeks apart (the normal values of these antibodies for our laboratory are: ACL IgM <9.80 MPL units/ml and IgG <13.30 GPL units/ml). Patients diagnosed as having antiphospholipid syndrome were treated with low-dose aspirin (100-mg tablet daily) and twice-daily unfractionated heparin (mini-heparin) or low molecular weight heparin subcutaneously daily at the appropriate doses during the pregnancy.

All the patients were followed up in the clinic to await spontaneous pregnancies. Those patients who failed to achieve spontaneous pregnancies within the first 6 months were further evaluated for causes of reduced fertility and appropriate treatment options including ART implemented. The protocol for the induction of ovulation for all the cases of PCOS (no spontaneous ovulation/pregnancy recorded in these cases) included the use of clomiphene citrate in

standard graduated doses with progression to the use of gonadotropin injections; a combination therapy of either clomiphene citrate and gonadotropin injections or clomiphene citrate and metformin tablets was also utilized in 3 clomiphene-resistant cases. Laparoscopic ovarian drill was offered to 1 patient while ART was offered to those patients who qualified for such specialized treatment.

It is noteworthy to point out that the period of 6 months was selected as the point to commence further evaluation and treatment because of the great anxiety expressed by our patients over their failure to achieve pregnancies. So it was not possible to wait for the normal period of 1 year before commencing further investigations and treatment.

Results

The mean age of the patients was 33.8 ± 4.6 years (range 22–43 years). Thirty patients (60%) were able to achieve viable pregnancies which progressed to term resulting in live births. Thirteen patients (26%) achieved pregnancies which ended mostly in first (85%) or second (15%) trimester abortions. The remaining 7 patients (14%) failed to achieve pregnancies.

The aetiological factors associated with RSM were varied and are given in table 1. Some patients had more than one aetiological factor. PCOS and infections (bacterial vaginosis in particular) were the aetiological factors in 40% of the patients; many of these patients also presented with diabetes mellitus, hypothyroidism and cervical incompetence. Antiphospholipid syndrome was detected in 10 patients (20%) and has remained the most frequently encountered single aetiological factor associated with RSM in our clinic population. In 40% of the patients, the cause of the miscarriage was regarded as 'unexplained' since no specific aetiological factor could be detected.

Chromosome anomaly was detected in 6% of the patients (3 cases). One of these patients, a 35-year-old woman, is a case of Turner's mosaic with chromosome pattern of 45XO, 46XX and 47XXX; she had a history of 6 previous first-trimester miscarriages. She also had features of PCOS. Although her pregnancy was complicated by insulin-dependent diabetes mellitus and pregnancy-induced hypertension it progressed to term ending in a delivery of a healthy baby by lower segment caesarean section. The other 2 patients with karyotype abnormalities who had miscarriages again were (a) a 39-year-old patient with a balanced chromosome translocation (13/14) and history of 1 living child, 3 intra-uterine fetal deaths and 14 miscarriages and (b) a 40-year-old woman with chromosome inversion with 2 living children and 8 previous miscarriages, respectively.

Table 1. Aetiology of recurrent abortion in non-pregnant patients (n = 50)

Aetiology	Cases	
	n	%
Chromosome anomaly (parental karyotype studies)	3	6
Uterine anomaly	3	6
Antiphospholipid syndrome	10	20
PCOS infections[1]	20	40
Cervical incompetence	4	8
Hypothyroidism	2	4
Poorly controlled diabetes	2	4
Unexplained/idiopathic	20	40

There was a combination of aetiological factors in the patients studied. Antiphospholipid syndrome was diagnosed as previously reported [11].

[1] Miscellaneous subgroup: cases with PCOS also presenting with or without infections (bacterial vaginosis etc.).

Table 2. The status of non-pregnant patients achieving no viable pregnancy (n = 20)

Aetiological factor of recurrent miscarriage	Cases		Outcome of pregnancy
	n	%	
Antiphospholipid syndrome	3	15	A
Hypothyroidism	2	10	NP
Poorly controlled diabetes	1	5	NP
PCOS/infections[1]	17	85	A[2]
Chromosome anomaly	1	5	A

There was a combination of aetiological factors in these patients. Four patients were still not pregnant because of a combination of male factor/PCOS. A = Miscarriage (first/second trimester); NP = not pregnant.

[1] Miscellaneous subgroup.

[2] 13 pregnancies ended in abortions.

Of the 20 patients who did not achieve viable pregnancies (table 2) 14 had high BMI >30 and 17 evidence of PCOS. In addition, 6 of 17 (35%), had bacterial vaginosis that was diagnosed from endocervical and high vaginal swabs, while other bacterial infections were diagnosed in another 2 patients. The organisms cultured in the patients with bacterial vaginosis included *Gardnerella vaginalis, Ureaplasma urealyticum, Mobilincus* and *Mycoplasma hominis.* Three of the 6 patients with bacterial vaginosis in this subgroup also had other aetiological factors (uterine anomaly, cervical incompetence and diabetes mellitus). The main disease profile of 13 patients with nonviable pregnancy were significant features of PCOS and high BMI. In addition to PCOS with high BMI in 4 out of 7 patients who did not achieve pregnancies, premature ovarian failure was diagnosed in 2 patients while male factor was an associated aetiological factor in another 3.

Discussion

The aetiological factors associated with RSM remain an active area of research. Our current study has further confirmed the aetiological factors which have been reported in previous studies [7–9, 12]. Quite a high proportion of cases of RSM still remain 'unexplained' as were 40% of the miscarriages in this study. Many studies, especially those focusing on immunological factors, are in progress to identify and help to unravel some of these unexplained aetiological factors.

Polycystic disease of the ovaries, especially when associated with high BMI of >30, has a contributory role in the aetiology of RSM and it has been associated with high reproductive losses [10], a finding consistent with our results. The exact mechanism is not yet known. However, obesity and abnormal endocrine metabolism have been implicated in the pathogenesis linking PCOS and RSM in these patients. Insulin resistance and hyperinsulinaemia have also been associated with RSM [13] and with PCOS [14–19].

Recent studies have detected high levels of plasminogen activator inhibitor (PAI) activity, a significant inhibitor of fibrinolysis, in women with PCOS [20–23]; some other reports have, however, failed to confirm any elevation of PAI activity in PCOS [24]. High levels of PAI activity have been reported in women with early recurrent unexplained miscarriage [25, 26], while another study [21] confirmed a positive association between PAI activity and miscarriages and adverse pregnancy outcome in patients with PCOS. From these reports, it can be deduced that high levels of PAI may play a direct role in the pathophysiology of spontaneous miscarriages. It is therefore tempting to speculate that at least some of the unexplained aetiological factors involved in RSM could be due to high level of PAI. The high levels of PAI activity reported above may lead to miscarriages through various pathways including inhibition/impairment of plasmin activity, thereby inhibiting plasmin-dependent proteolysis, with failure of lysis of thrombi in the placenta and ultimately thrombotic placental insufficiency; such abnormality occurring in early pregnancy may also lead to impaired trophoblastic development and poor placentation [15, 25, 26].

Many therapeutic measures including the use of metformin therapy [5, 11, 14, 27] have been utilized to achieve pregnancy in PCOS patients. ART has also been applied in the management of PCOS patients with varying degrees of success. At times when pregnancies did occur, the outcome was RSC, as demonstrated in this study in which 26% did not achieve viable pregnancy. It is pertinent to state here that the probability of achieving live birth in subsequent pregnancies after a variety of treatment methods for RSM is in the range of 50–70% [28, 29], also similar to our result of 60%. Some patients with RSM will therefore continue to present as cases of reproductive failure and also to be visualized as people who have a poor reproductive performance and a poor obstetric history.

It is our opinion that induction of ovulation in the patients with PCOS should commence with clomiphene citrate therapy and ultimately progress through the usual pathway of therapy to combination treatment as outlined earlier and such therapy should include the addition of metformin.

Metformin therapy in patients with PCOS has been associated with a reduction in the levels of PAI activity, fasting serum insulin levels and insulin resistance [15, 20, 21] and also with a reduction of hyperinsulinaemia [19]. In a recent study involving patients on metformin therapy [15] a positive correlation was demonstrated between the fasting serum insulin and PAI activity; first trimester spontaneous miscarriages in the patients with PCOS were reduced from 73 to 10% ($p < 0.002$) [15]. Since metformin and other related drugs have so far provided some positive results in patients with PCOS and RSM, we believe that such therapeutic trials should continue.

Asherman syndrome subsequent to repeated curettages after repeated miscarriages, abortions and postpartum haemorrhage has been associated with RSM and it is also a documented factor in secondary infertility (repro-

ductive failure) and menstrual disorders. This syndrome has rarely been encountered in our patients with RSM.

This was a preliminary study and as such the number of patients was limited to only 50. Hence the need for more structured larger long-term prospective studies which would investigate more the unexplained aetiological factors and possible association of insulin resistance and hyperinsulinaemia with RSM and with RSM and PCOS, respectively.

Such studies should incorporate further therapeutic trials (preferably randomized double-blind placebo-controlled studies) using metformin and related drugs.

Conclusions

The findings of this study indicate a linkage between RSM and reproductive failure. The association of RSM with PCOS resulted in poor reproductive performance that could progress to reproductive failure.

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References

1 Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R: Effects of metformin on spontaneous and clomiphene-induced ovulation in polycystic ovary syndrome. N Engl J Med 1998;338:1876–1880.
2 Omu AE, Ismail AA, Al-Qattan F: Infertility in Kuwait. Int J Gynecol Obstet 1999;67:113–114.
3 Franks S: Polycystic ovary syndrome. N Engl J Med 1995;333:835–861.
4 Dunaif A, Segal KR, Futterweit W, Dobrjansky A: Profound peripheral insulin resistance, independent of obesity in polycystic ovary syndrome. Diabetes 1989;38:1165–1174.
5 Ehrmann DA, Sturis J, Byrne MM, Karrison T, Rosenfield RL, Polansky KS: Insulin secretory defects in polycystic ovary syndrome: Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. J Clin Invest 1995;96:520–527.
6 Apter D, Butzow T, Langhlin GA, Yen SS: Metabolic features of polycystic ovary syndrome are found in adolescent girls with hyperandrogenism. J Clin Endocrinol Metab 1995;80:2966–2973.
7 Clifford K, Rai R, Watson H, Reagan L: An informative protocol for the investigation of recurrent miscarriage: Preliminary experience of 500 consecutive cases. Hum Reprod 1994;9:1328–1332.
8 Royal College of Obstetricians and Gynaecologists (RCOG): The Management of Recurrent Miscarriage. Guidelines No. 17. London, RCOG, 1998, pp 1–10.
9 Diejomaoh MFE, Al-Azemi M, Jirous J, Bandar A, Egbase P, Al-Sweih N, Al-Othman S: The aetiology and pattern of recurrent pregnancy loss. J Obstet Gynaecol 2002;22:62–67.
10 Sills ES, Levy DP, Wittkowski K, Perloe M: Preliminary experience with metformin treatment of polycystic ovary syndrome: Reproductive outcomes among 20 consecutive patients. Fertil Steril 1999;72:S187–S188.
11 Diejomaoh MF, Al-Azemi MM, Bandar A, Egbase PE, Jirous J, Al-Othman S, Bukhadour N, Al-Sweih N: A favourable outcome of pregnancies in women with primary and secondary recurrent pregnancy loss associated with antiphospholipid syndrome. Arch Gynecol Obstet 2002;266:61–66.
12 Kutteh WH, Pasquarette MM: Recurrent pregnancy loss; in Advances in Obstetrics and Gynaecology. St Louis, Mosby Year Book, 1995, vol 2, pp 147–177.
13 Craig LB, Ke RW, Kutteh WH: Increased prevalence of insulin resistance in women with a history of recurrent pregnancy loss. Fertil Steril 2002;78:487–490.
14 Unluhizarci K, Kelestimur F, Bayram F, Sahin Y, Tutus A: The effects of metformin on insulin resistance and ovarian steroidogenesis in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 1999;51:231–236.
15 Glueck CJ, Phillips H, Cameron D, Sieve-Smith L, Wang P: Continuing metformin throughout pregnancy in women with polycystic ovary syndrome appears to safely reduce first-trimester spontaneous abortion: A pilot study. Fertil Steril 2001;75:46–52.
16 Kocak M, Caliskan E, Simsir C, Haberal A: Metformin therapy improves ovulatory rates, cervical scores, and pregnancy rates in clomiphene citrate-resistant women with polycystic ovary syndrome. Fertil Steril 2002;77:101–106.
17 Vandermolen DT, Ratts VS, Evans WS, Stovall DW, Kauma SW, Nestler JE: Metformin increases the ovulatory rate and pregnancy rate from clomiphene citrate in patients with polycystic ovary syndrome who are resistant to clomiphene citrate alone. Fertil Steril 2001;75:310–315.
18 Dunaif A, Segal KR, Shelley DR, Green G, Dobrjansky A, Licholai T: Evidence for distinctive and intrinsic defects in insulin action in polycystic ovary syndrome. Diabetes 1992;41:1257–1266.
19 Kolodziejczyk B, Duleba AJ, Spaczynski RZ, Pawelczyk L: Metformin therapy decreases hyperandrogenism and hyperinsulinaemia in women with polycystic ovary syndrome. Fertil Steril 2000;73:1149–1154.
20 Velazquez E, Mendoza SG, Wang O, Glueck CJ: Metformin therapy is associated with a decrease in plasma plasminogen activator inhibitor-1, lipoprotein (a), and immunoreactive insulin levels in patients with polycystic ovary syndrome. Metabolism 1997;46:454–457.
21 Glueck CJ, Wang P, Sieve-Smith L, Fontaine R, Tracy T, Moore SK: Plasminogen activator inhibitor activity: An independent risk factor for the high miscarriage rate during pregnancy in women with polycystic ovary syndrome. Metabolism 1999;48:1589–1595.
22 Glueck CJ, Wang P, Sieve-Smith L, Fontaine R, Tracy T: Metformin-induced resumption of normal menses in 39 of 43 (91%) previously amenorrheic women with polycystic ovary syndrome. Metabolism 1999;48:511–519.
23 Sampson M, Kong C, Patel A, Unwin R, Jacobs HS: Ambulatory blood pressure profiles and plasminogen activator inhibitor (PAI-1) in lean women with and without the polycystic ovary syndrome. Clin Endocrinol 1996;45:623–629.
24 Atiomo WU, Fox R, Condon JE, Shaw S, Friend J, Prentice AG, Wilkin TJ: Raised plasminogen activator inhibitor-1 (PAI-1) is not an independent risk factor in the polycystic ovary syndrome (PCOS). Clin Endocrinol 2000;52:487–492.
25 Gris JC, Ripart-Neveu S, Maugard C, Tailland ML, Brun S, Courtieu C, Biron C, Hoffet M, Hedon B, Mares P: Prospective evaluation of the prevalence of haemostasis abnormalities in unexplained primary early recurrent miscarriages. The Nimes Obstetricians and Haematologists (NOHA) study. Thromb Haemost 1997;77:1096–1103.
26 Gris JC, Neveu S, Mares P, Biron C, Hedon B, Schved JF: Plasma fibrinolytic activators and their inhibitors in women suffering from early recurrent abortion of unknown etiology. J Lab Clin Med 1993;122:606–615.
27 Velazquez E, Acosta A, Mendoza SG: Menstrual cyclicity after metformin therapy in polycystic ovary syndrome. Obstet Gynecol 1997;90:392–395.
28 Warburton D, Fraser FC: Spontaneous abortion risks in man: Data from reproductive histories collected in a medical genetics unit. Am J Hum Genet 1964;16:1–25.
29 Stirrat GM: Recurrent miscarriage: Definitions and epidemiology. Lancet 1990;336:673–675.