Full length article

Medical conditions associated with recurrent miscarriage—Is BMI the tip of the iceberg?

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ARTICLE INFO

ABSTRACT

Background: In contrast to sporadic miscarriage, recurrent miscarriage (RM) is a rare entity which affects 1% of couples attempting conception. It is distressing for couples and healthcare professionals as the aetiology is unclear with limited treatment options. Apart from anti-phospholipid syndrome (APS), the strength of associations between RM and commonly investigated endocrine, autoimmune, thrombophilic and uterine structural abnormalities remains uncertain and variable.
Objectives: To assess the prevalence of commonly investigated medical conditions associated with RM.
Study design: A 9-year retrospective analysis of a prospectively collected database was conducted for 592 patients seen between 2008 and 2016, in tertiary level RM clinic in South Africa.
Results: In this period, 592 patients were assessed. The mean age was 29.73 ± 5.46 (mean $\pm$ SD), gravidity 4.6 ± 1.82 and parity 0.98 ± 1.05. The mean number of miscarriages per patient was 3.34 ± 1.63, of which two-thirds (61.3%) were in the first trimester, a third (33%) in the second trimester and intrauterine fetal deaths (IUFDs) constituted 6% of total losses. Of the 50% of patients with no identified associated disorders, 15% were unexplained (investigations complete but no associations found), 10% became pregnant during investigation (investigations incomplete) and 25% were lost to follow-up (investigations incomplete). Nearly forty percent (38%) of patients had an associated endocrine disorder (22% PCOS, 11% IGT, 3% Diabetes Mellitus and 2% Thyroid Dysfunction) and 10% a uterine factor (4% Cervical Incompetence, 2% Fibroids, 2% Synechiae and 2% Anomalies). APS and Thrombophilias constituted 3% and 2% of patients respectively. The BMI (mean $\pm$ SD) amongst patients with Unexplained RM, PCOS and IGT were 28.85 ± 5.95, 30.86 ± 7.79 and 33.40 ± 6.47 respectively. Patients with IGT had significantly higher mean BMI in comparison to those with Unexplained RM $(p < 0.0001)^{***}$ and PCOS $(p < 0.001)^{**}$.
Conclusion: PCOS, IGT and Type II Diabetes are all likely surrogates for elevated BMI and constitute 70% of those women with RM and identified associated medical disorders. In our population, BMI seems to have a substantial impact on recurrent pregnancy loss and future studies should interrogate its effect on recurrent miscarriage.

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Introduction

The lack of a uniform definition of recurrent miscarriage (RM) is reflected in the varied international societal positions of what constitutes the condition. The American Society of Reproductive Medicine (ASRM) defines RM as "disease characterised by two or more failed clinical pregnancies", however there is recognition that three or more losses should be utilised for epidemiological studies [1]. The European Society of Human Reproduction's (ESHRE) early pregnancy special interest group (SIGEP) and the Royal College of Obstetricians and Gynaecologists (RCOG) define RM as three or more consecutive pregnancy losses occurring before 20 and 24 weeks gestation, respectively [2–4]. However defined, RM still remains a clinical challenge, as there is quite often no direct aetiology linked to the pregnancy losses, which is frustrating for caregivers and couples alike and makes management and counselling difficult. The sequelae of recurrent pregnancy loss include major psychological morbidity such as stress and depression as well as relationship and marital instability [5,6].

Unlike sporadic miscarriage, whose age-dependant incidence ranges from 10 to 15% below the age of 30 years and increases up to

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30% by the age of 39 years, largely due to embryonic aneuploidies [7], recurrent miscarriage is a much rarer phenomenon. The incidence of recurrent miscarriage is 1% in couples of reproductive age attempting conception, however this incidence is much higher than would be explained by statistical chances of recurrent sporadic losses alone [8]. This suggests, at least in pathophysiological terms, that RM is a unique entity and different to sporadic miscarriage.

Currently embryonic chromosomal abnormalities and antiphospholipid syndrome (APS) are the two main conditions for which an explanation can be offered to couples about their pregnancy losses [9,10]. However, other medical factors previously investigated in association with RM include endocrine [11], autoimmune[12–14], thrombophilic and uterine structural abnormalities [15], although the strength of these associations largely remains variable and uncertain.

This study therefore sought to assess the prevalence of commonly investigated medical conditions associated with recurrent miscarriage in a tertiary level Recurrent Miscarriage Clinic, in Cape Town, South Africa.

Methods

A retrospective analysis of prospectively collected data from Groote Schuur Hospital's Recurrent Miscarriage Clinic Database, for patients assessed between 2008 and 2016, was conducted. The patient database has been approved by the Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town under the reference number (HREC 182/2015). Groote Schuur Hospital (GSH) is a tertiary level, University teaching hospital in Cape Town, South Africa.

GSH has a referral clinic for patients with recurrent miscarriage which was established in 1991. The criteria for assessment at the clinic are as follows; i) patients with a history of three consecutive first trimester miscarriages, ii) patients with a history of two consecutive second trimester miscarriages or iii) patients with a history of any combination of three consecutive miscarriages. Upon referral, patients are initially assessed clinically (including calculation of body mass index (BMI) in kg/m^2), and routinely investigated to exclude endocrine, autoimmune, thrombotic as

well as uterine structural abnormalities that may be associated with RM.

Embryonic karyotype does not form part of routine investigation as most patients present remote from the time of miscarriage and fetal tissue is not available. The endocrine assessment includes measurements of Thyroid Stimulating Hormone (TSH), Prolactin, and a glucose tolerance test (GTT) as well as transvaginal sonography and evaluation for chronic anovulation, clinical and/or biochemical hyperandrogenism for the diagnosis of polycystic ovary syndrome (PCOS) according to the Rotterdam criteria [16]. Autoimmune biochemical tests for exclusion of anti-phospholipid syndrome (APS) include anti-cardiolipin antibodies (ACA), Lupus anticoagulant (LAC) employing the Russel Viper Venom Test (RVVT) and anti-β2 glycoprotein-1. Protein C, S and Activated Protein C Resistance (APCR) are measured to screen for hereditary thrombophilias. Hysteroscopy and hysterosalpingography are utilised as screening tools for exclusion of uterine structural abnormalities. If indicated, laparoscopy, 3D-sonography or magnetic resonance imaging (MRI) may be performed. The BMI of each patient was categorised according to the World Health Organisation Classification.

Statistical analysis

One-way analysis of variance (ANOVA) followed by Dunn's multiple comparison test were performed to compare body mass indices across different diagnostic categories, using GraphPad Prism (version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com). In addition, descriptive statistics were computed using the same software and $p < 0.05$ defined statistical significance, where *, **, *** denoted $p < 0.05$; $p < 0.001$ and $p < 0.0001$ respectively.

Results

Between 2008 and 2016, five hundred and ninety-two patients (592) were entered into the database on their first visit, along with the investigations subsequently conducted and pregnancy outcomes. Data are presented as mean ± standard deviation (SD). The mean patient age was 29.73 ± 5.46, gravidity 4.6 ± 1.82, and parity
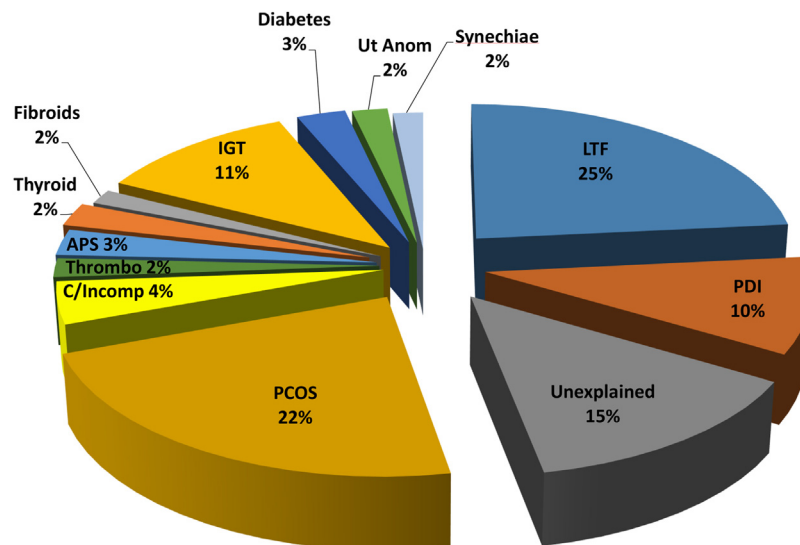

Fig. 1. The pie chart illustrates the prevalence of medical disorders associated with recurrent miscarriage at Groote Schuur Hospital. The following abbreviations are used, (APS) Antiphospholipid Syndrome, (C/Incomp) Cervical Incompetence, (IGT) Impaired Glucose Tolerance, (LTF) Loss to follow up, (PCOS) Polycystic Ovary Syndrome, (PDI) Pregnancy during Investigation, (Thrombo) Thrombophilia, (Ut Anom) Uterine Anomalies.