RHEUMATOLOGY

Rheumatology 2017;56:1272–1275
doi:10.1093/rheumatology/kex070
Advance Access publication 5 April 2017

Concise report

Pregnancy in polymyositis or dermatomyositis: retrospective results from a tertiary centre in China

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Abstract

Objective. To examine if patients with PM/DM are at higher risk of complicated pregnancies.

Methods. In a retrospective cohort in a large tertiary centre in North China, the outcomes of 144 pregnancies were evaluated in 62 women with PM/DM. Generalized linear mixed effect models were fitted to assess the effect of pregnancy occurring after disease on pregnancy outcomes including preterm birth (PTB), abortion (spontaneous or induced) and normal delivery. Adjustment for confounding factors including parity, maternal age and pregnancy–disease interval were achieved with a multivariable model.

Results. For women who became pregnant after disease onset, there was significantly higher risk of either PTB or spontaneous abortion (adjusted odds ratio, OR = 9.36, 95% CI: 1.10, 79.88; P = 0.041). The odds increase was more prominent if PM/DM was also active during pregnancy (adjusted OR = 435.35, 95% CI: 5.32, 35628.18; P = 0.007). Disease flare upon conception was observed in 4 of 22 post-PM/DM pregnancies (P = 0.125), and responded well to steroids and IVIG but resulted in PTB or spontaneous abortion.

Conclusion. PM/DM, especially those less well controlled, might contribute to an increased risk of complicated pregnancy.

Key words: polymyositis/dermatomyositis, pregnancy, outcome, generalized linear mixed effect models

CLINICAL SCIENCE

Rheumatology key message

- For women with polymyositis or dermatomyositis, especially when active, risk of complicated pregnancy should be anticipated.

Introduction

PM/DM is idiopathic inflammatory myopathy characterized by proximal muscle weakness, muscle inflammation and autoimmune abnormalities [1]. Though with a female predominance [2, 3], PM/DM affects women more often after their childbearing age, with an incidence peak at 40–65 years and proportion of PM/DM onset from age 25 to 34 years estimated to be 4–11% [3, 4]. This accounts for the small sample size of the few relevant studies. Conclusive interpretations are difficult, given the complex relationship between the two entities [5]. This retrospective study sought to evaluate the interaction between pregnancy and PM/DM, focusing on whether PM/DM has an adverse impact on subsequent pregnancy outcomes, and conversely can be triggered or exacerbated by pregnancy.

Methods

This retrospective, single-centre study was approved by the Ethics Committee of Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences. In accordance with the Declaration of Helsinki, informed consent was obtained from each patient. We searched the electronic medical

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Submitted 26 February 2016; revised version accepted 21 February 2017

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record database system of Peking Union Medical College Hospital from 1 January 2007 to 30 September 2013, obtaining 62 eligible cases. All cases were diagnosed and assessed at the department of rheumatology, met the Bohan & Peter Diagnostic Criteria [6] and reported at least one pregnancy. Cases with malignancy, SLE, SSc and APS were excluded. Age of disease onset, disease activity at pregnancy, treatment, obstetrical history and other relevant information were mainly confirmed and extracted from medical records. For the purpose of this study, exposure variables were obtained for each episode of pregnancy, whether before PM/DM (pre-PM/DM group), followed by postpartum PM/DM, complicated with gestational PM/DM onset or occurring after preexisting PM/DM (post-PM/DM group). These included temporal relationship with PM/DM, disease–pregnancy interval, maternal age, disease activity (determined by the presence of any of rash, muscle weakness and serum creatine phosphokinase elevation) and parity at pregnancy. The outcomes included preterm birth (PTB), defined as gestational age between 28 and 37 weeks at birth and spontaneous abortion (STA), defined as spontaneous embryonic/fetal loss before 20 weeks' gestation.

Statistical analysis

To compare pregnancy outcomes from the two major groups, pre-PM/DM and post-PM/DM, statistical tests were performed including Fisher's exact test and the Mann–Whitney test. Multiple comparisons were adjusted by the Bonferroni method. Nevertheless, these observations were neither independent nor paired. There were intrinsic correlations among pregnancies experienced by the same woman, forming a nested structure (supplementary Fig. S1, available at *Rheumatology* Online) that necessitated the use of a generalized mixed effect model with individuals entered as the random effect. The remaining exposure variables including temporal relation (categorical), pregnancy–disease interval (continuous and categorical), maternal age (continuous and categorical), disease activity (categorical) and parity (continuous) were selected as fixed effects based on previous knowledge and regardless of their significance when analysed separately. Odds ratios (ORs) with 95% CIs were calculated to estimate the association.

Sensitivity analysis was performed with two aspects: first, to examine whether excluding women under 35 years old at the time of data collection would change the result, which was concerned with measurement bias due to insufficient follow-up; and second, to check if four censored disease activity records could change the result by assuming all possible activity profiles and refitting the model.

A dependent sample sign test was performed to infer whether disease flare upon pregnancy happens more than due to chance. Two-tailed $P < 0.05$ was regarded as significant. Categorical variables were presented as frequency (percentage) and quantitative variables as both mean (S.D.) and median (first and third quartile). Statistic analysis was performed with R statistical software version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 62 PM/DM women (48 DM, 14 PM) had 144 pregnancies. Overall, they were characterized by (i) maternal age composition with strong resemblance to the nationwide sample survey [7], and (ii) time lapse between disease onset and pregnancy: 75% women had onset of disease after 30 years of age, while 75% became pregnant before the age of 29 years (Table 1).

Among the 144 pregnancies, 118 (81.9%) occurred before PM/DM, 22 (15.3%) after PM/DM, 2 (1.4%) followed by postpartum PM/DM and 2 (1.4%) coincided with gestational PM/DM. For the two major groups, the post-PM/DM group had significantly older age, shorter pregnancy–disease interval, a higher proportion of PTB and outcome collection (OC) of PTB and STA (36.4% *vs* 9.3%, $P = 0.0026$), and a lower proportion of normal delivery. After Bonferroni adjustment, only results of pregnancy–disease interval, OC and PTB remained statistically significant (supplementary Table S1, available at *Rheumatology* Online).

A dependent sample sign test inferred that disease exacerbation (18.2%) was not significant upon pregnancy ($P = 0.125$). The feature and trigger of these cases, together with those complicated with gestational or postpartum disease onset, are documented in supplementary Table S2, available at *Rheumatology* Online.

Generalized linear mixed effect models

Of pregnancies that occurred before PM/DM, 11 (9.3%) resulted in either PTB or STA. While in the post-PM/DM group, 8 (36.4%) had this OC. To test the hypothesis whether PM/DM or active PM/DM at pregnancy could have any impact on pregnancy outcome in a way independent of known risk factors including maternal age, parity and pregnancy–disease interval [8, 9], two generalized linear mixed effect models were constructed, each with the binomial variable (presence/absence of PM/DM or active PM/DM) as fixed effect and individual woman as random effect (see supplementary Fig. S2, available at *Rheumatology* Online, for model diagnostics). Occurring after PM/DM was significantly associated with OC (adjusted OR = 9.36, 95% CI: 1.10, 79.88; $P = 0.041$). The OR estimates increased dramatically to 435.35 (95% CI: 5.32, 35628.18; $P = 0.007$) if PM/DM was also active during pregnancy (Table 2; supplementary Fig. S3, available at *Rheumatology* Online). Furthermore, the discrimination capacity of these two models was examined by receiver operating characteristic curves. Both performed well in distinguishing complicated from normal pregnancy outcome, with area under the curve above 0.9 (supplementary Fig. S4, available at *Rheumatology* Online).

Neither maternal age nor pregnancy disease interval had a statistically significant association with OC, whether analysed as a continuous or categorical variable (Table 2; supplementary Table S3, available at *Rheumatology* Online). Sensitivity analysis excluding pregnancy from

Table 1 Characteristics of 62 PM or DM patients grouped by temporal relationship between disease onset and pregnancy

Variable	Total	Before PM/DM	After PM/DM	Postpartum PM/DM	Gestational PM/DM
Patients, n (%)	62 (100.0)	49 (79.0)	15 (24.2)	2 (3.2)	2 (3.2)
Gravidity, mean (S.D.)	2.3 (1.2)	2.5 (1.3)	2.2 (1.2)	1, 4[a]	1, 4[a]
1, n (%)	19 (30.6)	13 (26.5)	4 (26.7)	1 (50.0)	1 (50.0)
2–4, n (%)	39 (62.9)	32 (65.3)	9 (60.0)	1 (50.0)	1 (50.0)
⩾5, n (%)	4 (6.5)	4 (8.2)	2 (13.3)	0 (0.0)	0 (0.0)
Age of disease onset, years				22, 26[a]	38, 26[a]
Mean (S.D.)	34.6 (7.7)	37.7 (5.3)	25.8 (6.2)		
Median (IQR)	37.0 (30.0–41.0)	37.7 (33.8–42.0)	23 (22.5–28.5)		
Comorbidities, n (%)					
Interstitial lung disease	29 (46.8)	27 (55.1)	5 (33.3)	1 (50.0)	0 (0.0)
Tuberculosis	5 (8.1)	4 (8.2)	1 (6.7)	0 (0.0)	0 (0.0)
Hypertension	2 (3.2)	1 (2.0)	2 (13.3)	0 (0.0)	0 (0.0)
Diabetes mellitus	2 (3.2)	0 (0.0)	1 (6.7)	0 (0.0)	1 (50.0)

Table 2 Generalized mixed effect linear model (binomial distribution): preterm birth and spontaneous abortion as dependent variable

PTB and STA (OC)	Adjusted OR (95% CI)	P-value
Occurring after PM/DM	9.36 (1.10, 79.88)	0.041
After active PM/DM[a]	435.35 (5.32, 35628.18)	0.007
Maternal age	1.10 (0.89, 1.37)	0.385
Pregnancy–disease interval	1.02 (0.86, 1.21)	0.810
Parity	0.94 (0.47, 1.87)	0.852

[a]PM/DM were active during pregnancy. OC: outcome collection; OR: odds ratio; PTB: preterm birth; STA: spontaneous abortion.

woman younger than 35 at data collection confirmed the association between post-PM/DM pregnancy and OC (supplementary Table S3, available at *Rheumatology* Online).

Discussion

In this retrospective single centre study, PM/DM was independently associated with subsequent PTB or STA. This age/disease duration-independent effect became more prominent if PM/DM was poorly controlled. Individually, PTB and STA occurred at a higher rate after PM/DM onset than before, but sample size of the present study was insufficient to analyse these two outcomes separately (supplementary Table S4, available at *Rheumatology* Online).

In a recent multicentre study including 33 post-PM/DM pregnancies from 23 women, PM was proposed as a risk factor for complicated pregnancies including PTB, fetal loss and ectopic pregnancy (OR = 1.923), and so was active disease during or before conception [10]. Earlier small case series have similar observations [5, 11].

To the contrary, quite good maternal and fetal outcomes have been reported. Fernandez *et al*. [9] analysed 102 pregnancies in 51 women. No difference was detected in terms of both maternal and fetal outcomes between the 14 pre-PM/DM and 104 post-PM/DM pregnancies, after adjusting for maternal age and pregnancy–disease interval. In parallel with this observation, underlying disease was quiescent in all post-PM/DM pregnancies. Informatively, nine (64.3%) experienced significant disease improvement upon conception. These led the authors to speculate that pregnancy could be a favorable situation where disease remission might be expected, an informative observation not repeated in our study.

Overall, these studies including the present one have consistently emphasized the critical role of good control of disease in optimizing pregnancy outcomes in PM/DM women. Obstetrical and rheumatological consultations are aimed at providing advice on planning of conception and tuning therapy based on both disease and pregnancy status. Glucocorticoids and IVIG are the mainstay of treatment for active disease. Some studies associate gestational exposure to corticosteroids with slightly increased risk of premature birth [12] and fetal oral cleft [13]. These adverse outcomes have seldom been reported in PM/DM. Further investigation is needed. Efficacy and safety of IVIG has been well documented in the pregnant with other rheumatologic diseases [14] and are no doubt useful in managing PM/DM, particularly refractory cases. In our single case treated with IVIG (4.5 g in three consecutive days), short term remission was achieved but accompanied by PTB.

Our study can be criticized for insufficient follow-up time, which could cause misclassification bias due to pregnancy not yet observed. Nevertheless, we endeavoured to confirm the essential findings with the use of sensitivity analysis. Recall bias, which is intrinsic to

retrospective study design, was minimized by adherence to recorded data. The generalizability of our results is limited by the nature of the tertiary referral centre, where patients have more severe or refractory diseases. Another shortcoming was the sample size, which limited the accuracy of the estimated ORs, as reflected by the wide CIs. The introduction of random effect in the statistical model and the intrinsic clinical heterogeneity further contribute to this. Thus the results should be viewed with caution, awaiting external validation by larger sample size.

Despite these shortcomings, we endeavoured to improve the validity of the present study. We excluded malignancies and overlap with other CTDs that might interfere with the interpretation of pregnancy outcomes [15–17]. Our study population had pregnancy age distribution reflective of the nationwide sample survey [7], adding up to external validity. Moreover, by fitting a mixed effect logistic regression model with individual as nested random effect, correlation of multiple pregnancies per women was properly adjusted. With multivariable analysis, we were able to find robust association between the combined outcomes and post-PM/DM pregnancy after adjusting for parity, maternal age and disease duration. These findings were further confirmed by sensitivity analysis that excluded those with insufficient follow-up time.

Funding: This work was supported by the National Natural Sciences Foundation of China (30872333 and 81072404).

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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