PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pregnancy outcomes in Lebanese women with multiple sclerosis (the LeMS study): a prospective multicenter study
AUTHORS	Fares, Jawad; Nassar, Anwar; Gebeily, Souheil; Kobeissy, Firas; Fares, Youssef

VERSION 1 - REVIEW

REVIEWER	Said DANDACH The University of Bourgogne - FRANCE
REVIEW RETURNED	25-Jan-2016

GENERAL COMMENTS	I read the paper with interest. It discusses the outcomes of pregnancy in Lebanese female patients with multiple sclerosis. I am not aware of similar publications from the region on this issue. The paper is well written in terms of grammar and structure. It exhibits a clear methodology and approach. Few comments: 1) When stating the significant reduction in the relapse rate during pregnancy and in the first year postpartum, just focus on the p-value in between parentheses. 2) Why was the paired two-tailed t test used needs to be mentioned 3) The version of McDonald criteria needs to be mentioned. 4) Did any of the women get pregnant in the three years of follow up post partum? The paper is worthy of publication in BMJ Open.

REVIEWER	ABDEL RASSOUL Ronza INSERM U1141 France
REVIEW RETURNED	01-Feb-2016

GENERAL COMMENTS	Thank you for your consideration This study explores the influence of pregnancy on the MS patients in Lebanon. It includes 29 adult women who had been diagnosed with MS according to the McDonald criteria. These patients were under Interferon beta 1a treatment. This treatment was stopped 3 months before conception. The patients were followed up from 1 year before conception to 3 years after delivery. The annualised rate of relapse was calculated during this period. The study shows the disappearance of relapse in the pregnant MS

	patients. The annualized rate decreased significantly also in the first year after delivery when compared to the year before gestation, something which has not been demonstrated in previous papers. This study is the first in Lebanon, the Middle East and North Africa regions as far as I am aware, and it is promising for the MS patients. Many other studies in other countries with a higher number of women showed a significant decrease in the number of relapses during the third trimester of pregnancy, but this is the first study showing the absence of relapse during the entire period of pregnancy. However, I do have some minor comments that I would like the authors to address. - 25 out of 29 women had more than one pregnancy during this study. So based on the study's results, can we conclude the absence of a long term effect of pregnancy on patients at following gestations? Does the increasing number of gestations per woman decrease the number of relapses? - Which version of the McDonald criteria for the diagnosis of MS was used? And why was this criteria used? This needs to be mentioned. - How was the annualized rate of relapses calculated? This should be clarified. - Do you think that the environment or the genetic background has an effect on the pregnancy period or/and on the MS disease? especially in Lebanon where you show an absence of relapses during gestation? It would be important for a further research study. - Did the 7 women who decided to halt treatment on their own continue follow up with the neuro team? Did they have any recurrence of relapses whatsoever? Overall, I believe this study will have an impact in the MS field.

REVIEWER	Dr. Sanaa Nabha 23433 Hill Street, Dearborn heights, MI USA
REVIEW RETURNED	03-Feb-2016

GENERAL COMMENTS	Minor points 1) In the results section p. 7 line 23, it is stated that three (4.7 %) women had diabetes and three women (4.7 %) had hypertension. This is confusing, since it is stated in table 1 that 2 out of 29 (6.9 %) and 3 (10.3 %) had diabetes and hypertension, simultaneously. The authors should clarify these results, as 4.7% correspond to 3 out of 64 pregnancies. 2) If space is available, the data shown in figure 1 should also be presented in the form of a table. 3) On page 11, lines 38-42 in the discussion section, the statement "Confavreux et al. reported that women who chose to breast–feed experienced fewer relapses and had milder disability scores in the year before and during pregnancy in comparison with women who chose not to breastfeed" p.11, 38-42. This statement is not very accurate. In fact Confavreux et al., reported "that women who breast-fed their infants had a significantly lower rate of relapse then women who did not", when they evaluated the entire 33-month study period (year before pregnancy, during pregnancy and in the postpartum year).The sentence needs to be restated. 4) On page 12, lines 42-43, in the conclusions and implications, the statement "the profile of women and the management of MS shown

	in this study can help physicians guide women with MS who seek motherhood to decrease relapses during pregnancy and in the first year postpartum". This statement is not very clear and need to be clarified.

REVIEWER	Mohamad Saad, PhD University of Washington, Seattle, USA Department of Biostatistics
REVIEW RETURNED	11-Feb-2016

GENERAL COMMENTS	This is a paper by Fares J. et al., untitled "Pregnancy outcomes in Lebanese women with multiple sclerosis (the LeMS Study): a prospective multicenter study." The authors study the relapse rates of MS women before, during, and after pregnancy, in a Lebanese population. The findings of this paper are interesting. They replicate results from existing literature. In addition, they show that the relapse rate does not increase in the first year postpartum as shown in previous studies, which is important to highlight. The paper is nicely written and the data and results are well described. I have just one comment: did the authors explore possible differences between the MS Lebanese women and the MS patients used in existing literature that might decrease the relapse rate? Authors should discuss that a little bit more. I also have some minor comments: 1. On line 19 and 23 (Page 4), the word "affect" did not show well. 2. The first sentence in the Statistical analysis has to be re-phrased in order to be clearer.

VERSION 1 – AUTHOR RESPONSE

Response to Comments from Reviewer 1:
Dandach, Said
The University of Bourgogne – France

- Comment: When stating the significant reduction in the relapse rate during pregnancy and in the first year postpartum, just focus on the p-value in between parentheses.

Reply: Thank you for your comment. We fixed this issue in the two places where we report this variable.

o In the abstract: In comparison with the pre-pregnancy year, in which the mean relapse rate ± standard error was 0.17±0.07, there was a significant reduction in the relapse rate during pregnancy and in the first year postpartum (P=0.02), but an increase in the second year postpartum (0.21±0.08).

o In the Results (MS Relapses section): In comparison with the pre-pregnancy year, in which the mean ± standard error relapse rate was 0.17±0.07, there was a significant reduction in the relapse rate during pregnancy and in the first year postpartum (P=0.02), but an increase in the relapse rate the second year after delivery (0.21±0.08).

- Comment: Why was the paired two-tailed t test used needs to be mentioned?

Reply: Thank you for your remark. We have added an explanation as to why we chose this test to the Statistical Analysis section of the Methods: "The paired t-test was used as it calculates the difference within each before-and-after pair of measurements, determines the mean of these changes, and reports whether this mean of the differences is statistically significant."

- Comment: The version of McDonald criteria needs to be mentioned.

Reply: Thank you for your comment. The version of the McDonald criteria used is that of 2010. This is now mentioned in the Methods (Participants section): "To be included, women had to have clinically diagnosed definite MS according to the 2010 McDonald criteria, clinical and paraclinical tests and

quantitative or qualitative abnormalities in immunoglobulins in the cerebrospinal fluid. In addition, they had to have become pregnant after the onset of MS. The 2010 McDonald criteria allowed a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with past criteria."
- Comment: Did any of the women get pregnant in the three years of follow up post partum?
Reply: No, none of the women got pregnant in the three years postpartum. This information has been added to the Results (Pregnancy Characteristics section): "None of the women got pregnant in the three years postpartum."

Response to Comments from Reviewer 2:
Abdel Rassoul, Ronza
INSERM U1141, France
- Comment: 25 out of 29 women had more than one pregnancy during this study. So based on the study's results, can we conclude the absence of a long term effect of pregnancy on patients at following gestations? Does the increasing number of gestations per woman decrease the number of relapses?
Reply: We found no evidence that multiple gestations may alter the progression of MS. We found no evidence of an association between multiple gestations and relapses in the women of the study. This is stated in the Results (Pregnancy Characteristics section): "We found no evidence of an association between any of the pregnancy characteristics and other known risk factors."
- Comment: Which version of the McDonald criteria for the diagnosis of MS was used? And why was this criteria used? This needs to be mentioned.
Reply: We used the 2010 McDonald criteria, along with clinical and paraclinical tests and quantitative or qualitative abnormalities in immunoglobulins in the cerebrospinal fluid. The 2010 McDonald criteria allowed a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with past criteria. It also clarified and simplified the diagnostic process with fewer required MRI. This has been added to the Methods (Participants section): "To be included, women had to have clinically diagnosed definite MS according to the 2010 McDonald criteria, clinical and paraclinical tests and quantitative or qualitative abnormalities in immunoglobulins in the cerebrospinal fluid. In addition, they had to have become pregnant after the onset of MS. The 2010 McDonald criteria allowed a more rapid diagnosis of MS, with equivalent or improved specificity and/or sensitivity compared with past criteria. It also clarified and simplified the diagnostic process with fewer required MRI."
- Comment: How was the annualized rate of relapses calculated? This should be clarified.
Reply: We have included this in the Methods (Demographic and Outcome Measures section): "…and mean annualized relapse rate before, during and after pregnancy (calculated as the ratio between the number of relapses experienced by each woman and the number of years for each period)…"
- Comment: Do you think that the environment or the genetic background has an effect on the pregnancy period or/and on the MS disease? especially in Lebanon where you show an absence of relapses during gestation? It would be important for a further research study.
Reply: Thank you for your comment. We hypothesized in the Future Research section that "women's genetics, lifestyle, mental wellbeing, high vitamin D3, coenzyme Q-10 and magnesium sulfate supplementations may generate a protective effect against relapses."
- Comment: Did the 7 women who decided to halt treatment on their own continue follow up with the neuro team? Did they have any recurrence of relapses whatsoever?
Reply: Yes, the seven women continued follow up with neuro specialists; they decided to halt treatment though. No, they did not have a recurrence of relapses.

Response to Comments from Reviewer 3:
Nabha, Sanaa
23433 Hill Street, Dearborn heights, MI, USA
- Comment: In the results section p. 7 line 23, it is stated that three (4.7 %) women had diabetes and

three women (4.7 %) had hypertension. This is confusing, since it is stated in table 1 that 2 out of 29 (6.9 %) and 3 (10.3 %) had diabetes and hypertension, simultaneously. The authors should clarify these results, as 4.7% correspond to 3 out of 64 pregnancies.
Reply: Thank you for your comment. This is now fixed. Indeed, we mean that 3 of the 64 pregnancies (4.7%) occurred in 3 of the 29 women (10.3%) who had chronic hypertension and another 3 of the 64 pregnancies (4.7%) occurred in 2 of the 29 women (6.9%) who had pre-gestational diabetes. However, these pregnancies did not have any complications. We now clearly state this in the Results (Pregnancy Characteristics section): “Three pregnancies (4.7 %) occurred in women who had pre-gestational diabetes mellitus and another three pregnancies (4.7 %) occurred in women who had chronic hypertension.” We hope that this now clearer.
- Comment: If space is available, the data shown in figure 1 should also be presented in the form of a table
Reply: Thank you for your suggestion. We have added a Table 2 in the Results (MS Relapses section): “Table 2: Relapses of Multiple Sclerosis during pregnancy among 29 Lebanese women.”
- Comment: On page 11, lines 38-42 in the discussion section, the statement “Confavreux et al. reported that women who chose to breast–feed experienced fewer relapses and had milder disability scores in the year before and during pregnancy in comparison with women who chose not to breastfeed” p.11, 38-42. This statement is not very accurate. In fact Confavreux et al., reported “that women who breast-fed their infants had a significantly lower rate of relapse then women who did not”, when they evaluated the entire 33-month study period (year before pregnancy, during pregnancy and in the postpartum year).The sentence needs to be restated.
Reply: Thank you for your remark. We have restated this sentence. It is now as follows: “Confavreux et al.10 reported that women who chose to breast-feed experienced significantly fewer relapses and had milder disability scores in the year after pregnancy in comparison with women who chose not to breast-feed.”
- Comment: On page 12, lines 42-43, in the conclusions and implications, the statement “the profile of women and the management of MS shown in this study can help physicians guide women with MS who seek motherhood to decrease relapses during pregnancy and in the first year postpartum”. This statement is not very clear and need to be clarified.
Reply: Thank you for your comment. We have rephrased the statement as follows: “The characteristics and lifestyle of the women in the study can serve as a model to other women with MS who seek motherhood. Furthermore, the medical management presented in the LeMS study can be a guide to physicians in their future dealings with similar cases.”

Response to Comments from Reviewer 4:
Saad, Mohamad
University of Washington, Seattle, USA
Department of Biostatistics
- Comment: I have just one comment: did the authors explore possible differences between the MS Lebanese women and the MS patients used in existing literature that might decrease the relapse rate? Authors should discuss that a little bit more.
Reply: Thank you for your suggestion. In the Discussion, we have explored the similarities and differences between our sample and other samples from similar studies. The additions and changes have been highlighted in red in the text.
o 1st paragraph of the discussion: “In line with other studies in the literature,10,15-19 all the women in our study had RRMS. However, our sample was unique in the sense that all women did not smoke, drink alcohol or use drugs. All women were primiparous, had planned for the pregnancies, had stopped treatment three months before conception, reported no pregnancy or delivery complications, had no birth defects or diseases postpartum and were capable of breastfeeding.”
Comparison to Similar Studies:
♣ “The relapse rate in our study ranged between 0 and 0.21 which is the lowest among all the previous similar studies: Confavreux et al.10 reported relapse rates that ranged between 0.20 and

1.20, Fernandez Liguori et al.16 had relapse rates ranging between 0.04 and 0.82, Jalkanen et al.17 reported relapse rates that ranged between 0.40 and 1.40, Salemi et al.18 had relapse rates ranging between 0.36 and 0.72, and Fragoso et al.19 reported relapse rates that ranged between 0.29 and 1.37."

♣ "Among women in this study, interferon beta 1-a treatment was stopped three months before conception as a precautionary measure to avoid pregnancy complications or birth defects. Fernandez Liguori et al.16, van Walderveen et al.21 and Sandberg-Wollheim et al.22 reported that high doses of interferon beta increased spontaneous abortions and incidence of major birth defects (e.g. Down syndrome, hydrocephalus, abnormalities in the X chromosome, etc.). Several other studies suggest that, whenever possible, interferon beta treatment should be discontinued prior to conception.21-28 However, similar women in other studies continued to receive treatment throughout pregnancy."

♣ "Most similar studies reported complications during and after pregnancy.10,15-19 Our study, however, reported no obstetric complications; all of the pregnancies were full-term and resulted in live births."

- Comment: On line 19 and 23 (Page 4), the word "affect" did not show well.

Reply: Thank you for your remark. This could possibly be due to the PDF conversion. We hope this issue is now fixed:

o Line 19: "Furthermore, concerns about the progression of neurological disability over time affected family planning choices."

o Line 23: "Women with MS were naturally fretful as to how pregnancy would affect their disease, how the disease might modify pregnancy outcomes, and in particular, how the disease or the medications they were taking could affect the fetus."

- Comment: The first sentence in the Statistical analysis has to be re-phrased in order to be clearer.

Reply: Thank you for your comment. It has now been rephrased to make it clearer.

"The relapse rates for each woman during each trimester of pregnancy and the 3 years postpartum were compared with the relapse rate during the year before pregnancy by means of paired, two-tailed t-tests. The paired t-test was used as it calculates the difference within each before-and-after pair of measurements, determines the mean of these changes, and reports whether this mean of the differences is statistically significant. The effects of other demographic, pregnancy and infant-related variables on the course of MS were analyzed using logistic regression, as they were thought to be associated with the presence or absence of a relapse in the postpartum phase. P-values <0.05 were considered statistically significant for all analyses (95% confidence interval). All statistical analyses were performed with SPSS for Windows software version 23 (IBM SPSS, 2015)."

VERSION 2 – REVIEW

REVIEWER	Said DANDACH The University of Bourgogne - France
REVIEW RETURNED	22-Mar-2016

GENERAL COMMENTS	No technical errors, it is comprehensive and justified.

REVIEWER	ABDEL RASSOUL Ronza INSERM (Institut National de la Sante et Recherche Medicale), FRANCE
REVIEW RETURNED	22-Mar-2016

GENERAL COMMENTS	This study explores the course of pregnancy in MS patients in Lebanon. Similar studies have already been published (PRIMS for example) but as far as I am aware, there has not been similar

	studies in the MENA region before. The authors show that relapses significantly decrease in the first year postpartum, something which has not been demonstrated in previous papers. Therefore, in terms of originality, the paper is not lacking. This study is clear and rigorous. Overall, I believe this study will have an impact in the MS field.

REVIEWER	Sanaa Nabha Dearborn Heights, Michigan, USA
REVIEW RETURNED	25-Mar-2016

GENERAL COMMENTS	This is a very interesting manuscript describing pregnancy outcomes in Lebanese women with multiple sclerosis. The authors have done a good job describing their work and interpreting it within the context of the scientific literature. Additionally, the authors have clarified all the reviewers concerns, and addressed the individual points raised by the reviewers. Therefore, I strongly recommend this manuscript for publication. Minor point: Page 16, line 31, reference 33. Ueda A, Kondoh E, … Magnesium sulphate can prolong pregnancy in patients with severe early-onset preeclampsia. Please replace "J Matern Fetal Neonatal Med 2015. In press" by J Matern Fetal Neonatal Med 2016 Jan 14; 1-6

REVIEWER	Mohamad Saad, PhD University of Washington, Department of Biostatistics
REVIEW RETURNED	28-Mar-2016

GENERAL COMMENTS	The authors have answered my concerns in a rather convincing way.