RESEARCH PROJECT

1. Title

Biological therapy in women with immune-mediated inflammatory rheumatic diseases: influence on pregnancy outcomes

2. Background

With the increasing use of biological drugs in rheumatic immune-mediated diseases, questions about their side effects and interaction with reproduction and pregnancy arise. There is no conclusive evidence on fetal safety of immunomodulatory medications.

The safety of biologic agents during pregnancy is still being investigated. However, studying the influence of this kind of treatment in pregnancy is challenging because pregnant women are usually excluded from clinical trials. There is some information about this theme but usually involving patients with bowl inflammatory disease. In Portugal there is a lack of studies about biological treatment in female rheumatic patients who got pregnant. It is known that an increased risk of infection is a concern for all biologics. Anti-TNF treatment is the best well-studied biological drug in pregnancy. Apparently, the exposure to anti-TNF therapies at conception or during early pregnancy is not associated with adverse pregnancy outcomes or any increase in congenital abnormalities, when compared to unexposed females. However, the exposure in late pregnancy is associated with high drug levels in the newborn and their long-term effects on children remain unknown.

3. Rationale

Because human experience is still extremely limited, these drugs should be avoided during pregnancy or used only when no other option is available for treatment of serious maternal disease. Although there is no clear medical evidence on randomized controlled trials, observational studies are important in order to give us some information about fetal prognosis and safety.

4. Study aims

. Primary aim - To identify successful pregnancy defined as “Live birth at term with no malformation and no complications”

. Secundary aims

_ To identify gestational complications and adverse birth outcomes

- Live births
- Spontaneous abortion

- Neonatal death
- Intrauterine death
- Intrauterine growth restriction
- Premature delivery
- Congenital malformations
- Neonatal lupus

_ Disease flare- ups

_ Need for treatment with other drugs

5. Methods

1. Type of study: Retrospective cohort study
2. Study population:

Inclusion criteria

- Women with immune-mediated rheumatic diseases receiving biological therapy.
- Women who became pregnant during the biological treatment.

Expected sample size: There are currently about 65 female patients under biological treatment who got pregnant. We estimate a sample of 70 patients.

3. Database:

- Data will be collected from the Rheumatic Diseases Portuguese Registry (Reuma.pt). It will include patient demographics characteristics, diagnosis, disease duration (years), autoimmune profile, comorbidities, disease activity in the last visit previous to became pregnant, current therapy, pregnancy outcome, disease flare-ups and need for treatment with other drugs (csDMARD´s, Corticosteroids), bDMARD´s therapy (previous, current, after pregnancy diagnosis: stop bDMARDs vs continue treatment, time of last administration (weak of pregnancy))
- Past obstetric history (collected during one consultation or, if it's not possible, with a phone call)

4. Data analysis

- A descriptive analysis will be performed: categorical variables will be described using absolute and relative frequencies; for continuous data mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be calculated.

6. Description of variables

- Demographic data: age, race and ethnicity, height and weight.

- Co-morbidities: Hyperuricemia, Arterial Hypertension, Diabetes Mellitus, Dyslipidemia, smoking and alcoholic habits.
- Past obstetric history (pregnancy number, pregnancy follow-up (primary care physicians, gynecologist, high risk consult), type of delivery, birth weight, live birth at term/preterm, abortion, neonatal or intrauterine death, congenital malformations, lupus neonatal, voluntary or medical termination of pregnancy).
- Diagnosis including disease duration (years).
- Patient Global Health Assessment and Physician Global Disease Assessment - Recorded data on patient's and physician assessment of disease per standard of care. (if available)
- Health Assessment Questionnaire (HAQ) and EQ-5D - Recorded data on patient's HAQ and/or EQ-5D, if available.
- Disease activity by DAS 28 for rheumatoid arthritis and ASDAS for spondyloarthritis patients. Then, to standardize the different diseases included, it will be used a qualitative evaluation scale: disease remission/inactive, low disease activity, moderate disease activity and high disease activity.
- Laboratorial findings: Erythrocyte Sedimentation Rate, C-Reactive Protein, autoimmune profile (ANAs, ENAs, dsDNA, ACL, FR, CCP)
-Current therapy: csDMARDs and bDMARDs (treatment duration; previous, current, after pregnancy diagnosis: stop bDMARDs vs continue treatment; time of last administration (weak of pregnancy)), corticosteroids (mean dose previous of pregnancy and mean dose during pregnancy), NSAIDs (dose, treatment duration, treatment during 1st and/or 2nd and/or 3rd trimester)
- Successful pregnancy: Live birth at term with no malformation and no complications.
- Gestational complications and adverse birth outcomes: Live births, spontaneous abortion, neonatal death, intrauterine death, intrauterine growth restriction, premature delivery, congenital malformations, lupus neonatal
- Disease flare- ups
- Need for treatment with other drugs

7. Expected results and possible limitations

-We expected to characterize the target population at a national level and try to improve the best approach to these female patients. The pregnancy section is relatively recent and may not be adequately fulfilled, introducing a potential selection bias in the inclusion of patients.

8. Calendar of task

- Data collection of patients until November.
- Presentation of the results in the CPR (May 2018)
    . Abstract submission (deadline February 2018).
- Submit as publication to Acta Reumatologia Portuguesa.

9. Proponent

Luisa Brites

10. Institutions

The project is open to all National Centers interested to cooperate.

11. Co-authors

All clinicians who actively work on the project will be co-authors with a maximum of 2 co-authors per participating institution.

12. Funding and conflicts of interest

No conflicts of interest and no external funding to declare.

13. Ethical considerations

This study will be submitted for evaluation and approval to a competent Ethics Committee. Results will be presented in an objective way and will not be hidden or manipulated.

14. References

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