

### (資料 3) OTIS Autoimmune Diseases in Pregnancy Study

#### (1) Birth outcomes in women who have taken adalimumab in pregnancy: A prospective cohort study

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**Background:** Information is needed on the safety of adalimumab when used in pregnancy for the treatment of certain autoimmune diseases.

**Methods and findings:** Between 2004 and 2016, the Organization of Teratology Information Specialists Research Center at the University of California San Diego conducted a prospective controlled observational cohort study in 602 pregnant women who had or had not taken adalimumab. Women in the adalimumab-exposed cohort had received at least one dose of the drug in the first trimester for the treatment of rheumatoid arthritis or Crohn's Disease (N = 257). Women in the disease comparison cohort had not used adalimumab in pregnancy (N = 120). Women in the healthy comparison cohort had no rheumatic or inflammatory bowel diseases (N = 225). Women and their infants were followed to one year postpartum with maternal interviews, medical records abstraction, and physical examinations. Study outcomes were major structural birth defects, minor defects, spontaneous abortion, preterm delivery, pre and post-natal growth deficiency, serious or opportunistic infections and malignancies. 42/602 (7.0%) of pregnancies were lost-to-follow-up. 22/221 (10.0%) in the adalimumab-exposed cohort had a live born infant with a major birth defect compared to 8/106 (7.5%) in the diseased unexposed cohort (adjusted odds ratio 1.10, 95% confidence interval [CI] 0.45 to 2.73). Women in the adalimumab-exposed cohort were more likely to deliver preterm compared to the healthy cohort (adjusted hazard ratio [aHR] 2.59, 95% CI 1.22 to 5.50), but not compared to the diseased unexposed cohort (aHR 0.82, 95% CI 0.66 to 7.20). No significant increased risks were noted with adalimumab exposure for any other study outcomes.

**Conclusions:** Adalimumab exposure in pregnancy compared to diseased unexposed pregnancies was not associated with an increased risk for any of the adverse outcomes examined. Women with rheumatoid arthritis or Crohn's Disease were at increased risk of preterm delivery, irrespective of adalimumab exposure.

#### (2) Birth Outcomes in Women Who Have Taken Hydroxychloroquine During Pregnancy: A Prospective Cohort Study

**Objective:** Findings from previous small studies have been reassuring regarding the safety of treatment with hydroxychloroquine (HCQ) during pregnancy. In one recent study, it was demonstrated that the frequency of major birth defects was increased in women who had received HCQ at a dose of  $\geq 400$  mg/day during pregnancy. This study was undertaken to examine pregnancy outcomes among women following the use of HCQ.

**Methods:** The study cohort comprised pregnant women who were prospectively enrolled in the MotherToBaby/Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Study and were receiving treatment with HCQ. For the control groups, disease-matched women without HCQ exposure and healthy women were randomly selected from the same source, with subject matching using a 1:1 ratio. Data were collected through interviews, medical records, and dysmorphology examinations. Pregnancy outcome measures included the presence or absence of major and minor birth defects, rates of spontaneous abortion, rates of preterm delivery, and infant growth measures.

**Results:** Between 2004 and 2018, 837 pregnant women met the criteria for study inclusion, including 279 women exposed to HCQ during pregnancy and 279 women in each unexposed control group. Sixty pregnant women (7.2%) were lost to follow-up. Among the women with live births, major birth defects occurred as a pregnancy outcome in 20 (8.6%) of 232 women with HCQ exposure in the first trimester, compared to 19 (7.4%) of 256 disease-matched unexposed controls (odds ratio [OR] 1.18, 95% confidence interval [95% CI] 0.61-2.26) and 13 (5.4%) of 239 healthy controls (adjusted OR 0.76, 95% CI 0.28-2.05). Risks did not differ in women who were receiving an HCQ dose of  $\geq 400$  mg/day. No pattern of birth defects was identified. There were no differences in the rates of spontaneous abortion or preterm delivery between groups. Occurrence of infant growth deficiencies did not differ in the HCQ-exposed group compared to the disease-matched unexposed control group, except in the infant's head circumference at birth (adjusted OR 1.85, 95% CI 1.07-3.20).

**Conclusion:** In this study, there was no evidence of an increased risk of structural birth defects or other adverse outcomes among women receiving HCQ during pregnancy, with the exception of infant head circumference at birth. For pregnant women being treated with HCQ, these findings are reassuring.

- (3) Risk of infantile hemangiomas in the offspring of women with autoimmune disease and the pathogenic implications of these lesions

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The purpose of this study was to analyze the risk of maternal autoimmune disease or associated treatments on infantile hemangiomas (IHs), a common benign vascular tumor in infants, and to better understand how maternal chronic inflammation may play a factor in the pathogenesis of these lesions. Eligible women from the United States and Canada who enrolled before 19 weeks' gestation and delivered at least one live born infant were recruited as part of the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project from 2004-2013. A total of 51/969 (5.3%) and 8/240 (3.3%) infants with IH were born to mothers with and without autoimmune disease, respectively (OR 1.61; 95%CI, 0.75-.44). The presence of ulcerative colitis (UC) in the mother was significantly associated with IH in the child (OR 3.46; 95%CI, 1.29-9.26). The five largest IH occurred within the autoimmune disease cohort and to women taking a biologic medication. These results imply that UC may be a risk factor for IH development, and that chronic inflammation may influence the development of these lesions. This potential link between IH and autoimmune disease warrants further investigation.

#### (4) Well-Controlled Rheumatoid Arthritis and Juvenile Idiopathic Arthritis With a Disease Worsening in Late Pregnancy

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Objective: To investigate whether the discontinuation of tumor necrosis factor inhibitors (TNFi) during pregnancy is associated with any changes of the disease course in women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA).

Methods: Pregnant women with RA and JIA from the US and Canada were enrolled in the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project, a prospective cohort study. Information about medication and disease activity (patient-reported outcome measures) was collected prior to gestational week 20 and at gestational week 32. Associations between patterns of TNFi continuation or discontinuation and disease activity changes were tested in unadjusted and multivariate analyses.

Results: Among 490 women (397 with RA, 93 with JIA) enrolled between 2005 and 2017, 122 (24.9%) discontinued a TNFi before gestational week 20, 201 (41.0%) received a TNFi

beyond week 20, and 167 (34.1%) did not receive a TNFi during pregnancy. At the time of enrollment, disease activity was low to minimal in 72.9% of women. TNFi discontinuation was not associated with a clinically important worsening of patient reported outcome measures at the third trimester. Univariate but not multivariate analysis showed that women receiving TNFi beyond week 20 were more likely to experience improved disease activity scores at the third trimester.

Conclusion: Discontinuing TNFi before gestational week 20 seems feasible in women with RA and JIA who enter pregnancy with well-controlled disease.

#### (5) Factors Associated With Preterm Delivery Among Women With Rheumatoid Arthritis and Women With Juvenile Idiopathic Arthritis

Arthritis Care Res (Hoboken). 2019 Aug;71(8):1019-1027. doi: 10.1002/acr.23730. Epub 2019 Jul 4.

Objective: Pregnant women with inflammatory arthritis may be at increased risk for preterm delivery (PTD), yet it is unclear what drives this risk. This aim of this prospective cohort study of pregnant women with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), or healthier comparison women was to analyze the independent effects of maternal disease activity, medication use, and comorbid pregnancy conditions on PTD risk.

Methods: Women were enrolled before 19 weeks completed gestation as part of the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project. Data on pregnancy events, medications, disease activity, and outcomes were obtained by maternal report and validated by medical records. Poisson regression with robust standard errors estimated risk ratios (RR), multivariable adjusted risk ratios (ARRs), and 95% confidence intervals (95% CIs).

Results: A total of 657 women with RA, 170 with JIA, and 564 comparison women without autoimmune disease who delivered live born infants, from 2004 to 2017 were included for analysis. Both the RA and JIA groups had an increased risk of PTD versus the comparison group (RR 2.09 [95% CI 1.50-2.91] and RR 1.81 [95% CI 1.14-2.89], respectively). Active RA at enrollment (ARR 1.58 [95% CI 1.10-2.27]) and any time during pregnancy (ARR 1.52 [95% CI 1.06-2.18]) was associated with PTD. Corticosteroid use in every trimester was associated with an approximate 2- to 5-fold increased risk for PTD for both arthritis groups, independent of disease activity.

Conclusion: Women with RA and women with JIA are at increased risk for PTD.

Maternal disease activity and corticosteroid use may contribute to some of this excess risk.

(6) Potentially modifiable risk factors for adverse pregnancy outcomes in women with psoriasis

Br J Dermatol. 2010 Aug;163(2):334-9. doi: 10.1111/j.1365-2133.2010.09899.x. Epub 2010 Jun 9.

**Background:** Data on pregnancy outcomes among women with psoriasis are lacking. However, there are several known comorbidities of psoriasis, including obesity, smoking and depression, each of which increases the risk for negative birth outcomes.

**Objectives:** To determine if pregnant women with psoriasis have an excess of potentially modifiable risk factors for adverse pregnancy outcomes.

**Methods:** Prospectively collected data from the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project were analysed to compare the prevalence of selected risk factors between 170 pregnant women with psoriasis and 158 nondiseased controls.

**Results:** Women with psoriasis were more likely to be overweight/obese prior to pregnancy ( $P < 0.0001$ ), to smoke ( $P < 0.0001$ ), or to have a diagnosis of depression ( $P = 0.03$ ), and were less likely to have been taking preconceptional vitamin supplements ( $P = 0.004$ ). After controlling for race/ethnicity and socioeconomic status, women with psoriasis were 2.37 (95% confidence interval 1.45-3.87) times more likely to be overweight/obese as women without psoriasis. Duration of disease, age at onset, measures of disease impact during pregnancy, or use of biologics in pregnancy were not significant predictors of overweight/obesity in the subset of psoriatic women.

**Conclusions:** Pregnant women with psoriasis may be at increased risk for adverse pregnancy outcomes due to comorbidities or other health behaviours associated with the disease. These should be taken into consideration during clinical treatment of women with psoriasis who are in their childbearing years.