Supplemental table e1 Adverse pregnancy outcomes

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Preg 8** | **Preg 35** | **Preg 64** | **Preg 19** | **Preg 32** | **Preg 2** | **Preg 3** | **Preg 28** | **Preg 71** | **Preg 88** |
| Pregnancy outcomes | Term live birth | Preterm birth in gw 35+4 (twin pregnancy) | SA in gw 11+1 | Preterm birth in gw 35+5 | Preterm births in gw 29+1 | Preterm births in gw 33+6 | Preterm births in gw 36+1 | Preterm births in gw 34+4 | Planned preterm births in gw 34+1 | Preterm births in gw 35+5 |
| Anomaly | ventricular septum defect | atrium septum defect with pulmonary stenosis | fetal hydrops | mild hydronephrosis | umbilical hernia | no | no | no | no | no |
| Major congenital anomaly | yes | yes | no | no | no | no | no | no | no | no |
| Mothers disease | RRMS | RRMS | NMOSD | RRMS | RRMS | RRMS | RRMS | RRMS | autoimmune myositis | NMOSD |
| Mothers age at conception | 31 years | 27 years | 25 years | 25 years | 38 years | 35 years | 32 years | 38 years | 20 years | 28 years |
| Exposure | OCR | OCR | RTX | OCR | RTX | OCR | RTX | OCR | RTX | RTX |
| Exposure duration | 131 days after LMP | 11 days after LMP | 49 days before LMP | 6 days before LMP | 94 days before LMP | 9 days after LMP | 34 days before LMP | 42 days before LMP | 109 days after LMP | 148 days after LMP |
| Anti-CD20-mAbs dosis | 300 mg | 600 mg | 1000 mg | 600 mg | 500 mg | 300 mg | unk | 600 mg | 1000 mg | 500 mg |
| Anti-CD20-mAbs cycle | 1 | 3 | 5 | 2 | 7 | 1 | 2 | 1 | 1 | 1 |
| Steroids during pregnancy | 5 days à 1000mg in gw 18 | no | no | no | no |  |  |  | 80mg/d during entire pregnancy | 1300 mg in gw 18 |
| IA/PLEX during pregnancy | no | no | no | no | no | no | no | no | no | 5 cycles IA in gw 18 and 5 cycles PLEX in gw 20 |
| smoking during pregnancy | no | yes, during first trimester | no | no | no | no | no | no | no | no |
| Concomitant drug exposure | third alemtuzumab cycle 9 months before LMP;  insulin during entire pregnancy | cetirizine and salbutamol according to demand | general anesthesia (unknown indication) one month after LMP | progesterone 200mg one month after LMP;  progesterone 200mg in gw 33 | modafinil 100mg/day during entire pregnancy due to fatigue; progesterone; fosfomycine, cefixime, azithromycin and fluomizin; intravenous immunoglobulins 10g every 4 weeks | fingolimod 0.5 mg up to gw 2 | no | progesterone in gw 7 | tazobactam/piperacillin 3x4.5g, clarithromycin 2x500 mg and aciclovir 3x750 mg | no |
| Co-morbidities | Diabetes type I | allergic asthma | no | vaginal bleeding; premature labor | cervical insufficiency;  intermittent urinary tract infections and vaginal mycosis; hypogammaglobulinemia (IgA: 55mg/dl; IgM: 12mg/dl) | no | no | vaginal bleeding;  hypothyroidism | pneumocystis jirovecii infection; genital herpes infection PcP, steroid induced hypertonia; preeclampsia; cushing’s syndrome | no |
| potential reasons for preterm birth |  | twin pregnancy; cervical insufficiency |  |  | cervical insufficiency; intermittent urinary tract infections and vaginal mycosis |  |  |  | planned preterm birth due to worsening of myositis and pre-eclampsia |  |

Abbreviations: gw = gestational week, SA = spontaneous abortion, RRMS = relapsing remitting multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, RTX = rituximab, OCR = ocrelizumab, LMP = last menstrual period, anti-CD20-mAb = anti CD20 monoclonal antibodies, unk = unknown, IA = immunoadsorption, PLEX = plasma exchange, IgA = immunoglobulin A, IgM = immunoglobulin M

Supplemental table e2 severe maternal infections during pregnancy and infant infections leading to hospitalization

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| --- | --- | --- | --- | --- | --- |
|  | **Preg 5** | **Preg 32** | **Preg 71** | **Preg 2** | **Preg 14** |
| maternal/infant infection | maternal | maternal and infant | maternal | infant | infant |
| infection | agranulocytosis associated herpes infection | mother: intermittent urinary tract infections and vaginal mycosis; hypogammaglobulinemia (IgA: 55mg/dl; IgM: 12mg/dl)  infant: bronchitis | pneumocystis jirovecii infection | respiratory syncytial virus (RSV) | hospitalization due to fever of unknown origin |
| mothers disease | RRMS | RRMS | autoimmune myositis | RRMS | RRMS |
| mothers age at conception | 37 years | 38 years | 20 years | 35 years | 33 years |
| exposure | RTX | RTX | RTX | OCR | OCR |
| exposure duration | 66 days before LMP | 94 days before LMP | 109 days after LMP | 9 days after LMP | 99 days before LMP |
| anti-CD20-mAbs doses | 500 mg | 500 mg | 1000 mg | 300 mg | 300 mg |
| anti-CD20-mAbs cycle | 11 | 7 | 1 | 1 | 1 |
| pregnancy outcomes | term live birth | preterm birth in gw 29+1 | planned preterm birth in gw 34+1 | preterm birth in gw 33+6 | term live birth |
| other potential immunosuppressive drugs during pregnancy | progesterone gw2-12 due to previous spontaneous abortion | progesterone due to cervical insufficiency | prednisolone 80 mg during entire pregnancy | fingolimod 0.5 mg up to gw 1+2 |  |
| further drug exposure during pregnancy | aciclovir 400mg in gw 22 due to herpes infection | modafinil 100mg/day during entire pregnancy due to fatigue; fosfomycine, cefixime, azithromycin and fluomizin due to intermittent urinary tract infections and vaginal mycosis; intravenous immunoglobulins 10g every 4 weeks due to hypogammaglobulinemia (IgA: 55mg/dl; IgM: 12mg/dl) | tazobactam/piperacillin 3x4.5g, clarithromycin 2x500 mg and aciclovir 3x750 mg due to pneumocystis jirovecii and genital herpes infection |  | citalopram 10 mg up to gw 5 |
| B-cell counts | decreased in gw 3  depleted in gw 32 | mother: unk  infant: normal | depleted in gw 15  decreased in gw 35 | Unk | decreased |

Abbreviations: IgA = immunoglobulin A, IgM = immunoglobulin M, RRMS = relapsing remitting multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, RTX = rituximab, OCR = ocrelizumab, LMP = last menstrual period, anti-CD20-mAb = anti CD20 monoclonal antibodies, gw = gestational week, unk = unknown

Supplemental table e3 Clinical characteristics of MS/NMOSD patients who started anti-CD20 therapy before pregnancy and experience a relapse during pregnancy or during 6 months postpartum

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| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Preg 6** | **Preg 14** | **Preg 17** | **Preg 32** | **Preg 79** | **Preg 74\*** | **Preg 81** |
| disease | RRMS | RRMS | RRMS | RRMS | RRMS | NMOSD | NMOSD |
| age at conception | 37 years | 33 years | 30 years | 38 years | 27 years | 24 years | 36 years |
| No DMTs before anti-CD20-mAbs | 3 | 6 | 1 | 6 | 4 | 1 | 3 |
| Last DMT before anti-CD20-mAbs | IVIG | NTZ | DMF | DMF | NTZ | Aza | MMF and oral prednisolone |
| number of relapses in the year before pregnancy | 1 (before initiation of RTX) | 0 | 0 | 0 | 0 | 2 (before initiation of RTX) | 0 |
| Anti-CD20 Therapy | RTX | OCR | RTX | RTX | RTX | RTX | RTX (+prednisolone) |
| Anti-CD20-mAbs cycles before pregnancy | 1 | 1 | 1 | 7 | 4 | 1 | 6 |
| Last anti-CD20 therapy before relapse (months) | 16 | 2 | 21 | 11 | 19 | 10 / 13 | 7 |
| DMT at relapse | no | yes (44 days after OCR) | no | no | no | no | yes (prednisolone 2mg/d) |
| number of relapses during pregnancy | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| gw of relapse |  |  |  |  |  |  | 33 |
| Relapse treatment during pregnancy |  |  |  |  |  |  | 5x1000 mg steroids |
| Number of relapses up to 6 months postpartum | 1 | 1 | 1 | 1 | 1 | 2 | 0 |
| Time to relapse postpartum (months) | 5 | 3 | 2 | 1 | 3 | 1 / 3 |  |
| treatment after relapse | IVIG | OCR | none | RTX | RTX | RTX | RTX |
| CD20 positive cells in blood at relapse (yes/no) | unk | unk | unk | yes | yes | yes/yes | yes |
| Baseline EDSS before pregnancy | 2.5 | 3.5 | 1.5 | 4 | 3.5 | 3 | 3.0 |
| EDSS end of pregnancy | 2.5 | 3.5 | 0 | 4 | 2.5 | 3 | 4.0 (during relapse) |
| EDSS postpartum | 2.5 | 3.5 | 2 | 4 | 3.0 | 3 | 3.5 |

RRMS = relapsing remitting multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorders, DMT = disease modifying therapy, anti-CD20-mAb = anti CD20 monoclonal antibodies, MMF = mycophenolate mofetil, IVIG = intravenous immunoglobulins, NTZ = natalizumab, DMF = dimethyl fumarate, Aza = azathioprine, OCR = ocrelizumab gw = gestational week, RTX = rituximab, unk = unknown, EDSS = expanded disability status scale

\* *Pellkofer HL et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology. 2011;76(15):1310-5*