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Effect of biologicals and JAK inhibitors during pregnancy on health-related outcomes in children of women with inflammatory bowel disease

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ABSTRACT

Current guidelines advise to maintain immunomodulators and biologicals in pregnant patients because relapse of inflammatory bowel is associated with unfavourable pregnancy outcome. With the exception of Methotrexate, IBD therapy seems not to be related to an increase of congenital malformations or infections requiring hospitalisation of the babies, although the effect the on the developing immune system of the exposed infants remains unknown. In this review we will focus on the effect of IBD drugs on health-related outcomes in children taking into account possible long-term effects of biologicals and immunomodulators, which are transferred across the placenta.

Introduction

Pre-conception counselling women with inflammatory bowel disease (IBD) is challenging but extremely important. Many women with IBD are afraid that IBD might lead to complications during pregnancy or immunosuppressive medication might harm the neonate [1]. Voluntary childlessness is increased in women with IBD and is associated with lack of knowledge of how IBD and immunosuppressive medication might influence the outcome of pregnancy and the neonate [2,3]. Women who receive pre-conception counselling are less likely to be voluntarily childless [3]. Relapse of IBD has been associated with unfavourable pregnancy outcomes with an increased risk of spontaneous abortion, prematurity and low birth weight [4,5]. Therefore current guidelines advise to maintain IBD drugs such as immunomodulators and biologicals during pregnancy [6,7]. Most IBD drugs are considered of low risk during pregnancy, since no increase of congenital malformations has been reported so far [8–10]. However the effects on the developing immune system of infants, especially of those drugs transferred across the placenta remain uncertain as published cohorts are mostly small and retrospective.

Anti-Tumor Necrosis Factor alpha therapy

Anti-Tumor Necrosis Factor alpha (anti TNFα) inhibits the biological function of the pro-inflammatory cytokine TNFα by neutralization of soluble and membrane bound TNFα. Several different TNFα inhibitors have been shown to be effective in IBD and are currently used: Infliximab, Adalimumab and golimumab are all monoclonal (IgG1) immunoglobulins blocking TNFα, whereas certolizumab is a pegylated Fab-fragment binding TNFα [11,12].

Like other maternal immunoglobulins anti TNFα drugs are transferred across the placenta passively in low amounts throughout pregnancy [12]. Nearly all anti -TNFα drugs also have the ability to actively pass the placenta during the second half of

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pregnancy using the neonatal Fc receptor on the placenta. This results in high concentrations of anti- TNFα in the neonate, sometimes exceeding the maternal concentration by a factor 2 at birth [12–15]. Intrauterine exposure extends beyond the neonatal period because of the long half-life of this biological in infants, which is at least twice as long as in adults [16]. Anti- TNFα can still be detected in the child 12 months after birth [16,17]. Certolizumab pegol does not bind the neonatal Fc receptor and concentrations of certolizumab are very low or undetectable in cord blood [18,19].

Most safety data about the effect of intra uterine exposure are from studies with adalimumab and infliximab. Data on golimumab are scarce [20,21]. A recent case report did however describe maternal-fetal transfer of golimumab resulting in golimumab concentration (with last dose given 4 days before birth) in the neonate of 8 μg/ml (121% of maternal concentration) [20]. Given the mechanism of action the effect of intra uterine exposure to golimumab might be comparable to adalimumab and infliximab. Long-term effects of exposure to certolizumab are probably less likely since certolizumab concentrations are very low or undetectable in cord blood.

Risk of congenital malformations and unfavourable neonatal pregnancy outcome

Intra uterine exposure of infants to anti TNFα has not been associated with adverse pregnancy outcomes such as spontaneous abortions premature birth, low birth weight or congenital malformations [8–10,22,23].

Anti TNFα and the developing immune system

Concerns might be raised about the effect of anti TNFα on the developing immune system of the exposed children. Anti TNFα drugs might have a direct effect on the immune system during pregnancy but also on the developing immune system after birth.

TNFα has been shown to be important in the development of the immune system in mice. Mice with a TNFα deficiency show an increased susceptibility to infection, reduced delayed hypersensitivity response and a decreased humoral immune response. Although immunoglobulin class switch does occur in these mice, they have a deregulated humoral response to antigens, exemplified by a lack of splenic primary B cell follicles and follicular dendritic cells [24]. TNFα also regulates growth and functional activities of normal T cells and is able to induce the formation of regulatory T-cells. Hypothetically anti-TNFα could have an effect on the developing immune system in humans as well, although TNFα is not completely absent after intra uterine exposure.

Recently a study of T and B cell subsets in children, in utero exposed to infliximab or adalimumab monotherapy (n = 11), or to a combination of thiopurines with either adalimumab or infliximab (n = 4) was published. Children of mothers with IBD, exposed to certolizumab pegol monotherapy (n = 4) were considered reference population. In children exposed to combination therapy a trend toward reduction in three B cell subsets and lower frequency of certain T cells was seen [25]. It was suggested that the reduction in B cell subsets were an effect of combination therapy rather than purely anti-TNFα since TNF- deficient mice did not exhibit a reduction of plasmablasts or memory B cells. Statistical significance was not reached, but numbers were small.

Extensive immunological tests in another small study have shown a decreased response after mycobacterial challenge, a more immature B and T helper phenotype and a decreased regulatory T cell frequency [26].

Neutropenia has been described in adults using anti-TNFα therapy [27] as well as in infants after intra uterine exposure [26,28]. In a small case series 4 newborns with in utero exposure to anti-TNFα were reported with severe neutropenia and subsequent development of skin infections (n = 3) and *Enterobacter cloacae* diarrhea (n = 1). Treatment of the infants consisted of granulocyte-colony stimulating factor (G-CSF) and antibiotics. Neutropenia resolved within the first year of life [28]. In the previously mentioned small study [26] neutrophil counts below the reference range in the cord blood of two out of six neonates exposed to anti-TNFα were found. One of them was also exposed to steroids and the other was exposed to anti-TNFα and azathioprine. A severe neutropenia at 3 months of age in one and moderate neutropenia in two out of six patients was observed. None of them suffered of skin infections [26].

Vaccination of children after exposure to anti- TNFα therapy

Currently it is advised to avoid live attenuated vaccines (i.e. BCG, measles-mumps, rubella MMR) until the levels of anti-TNFα are undetectable [7,29], as there has been one report of an infant, who died after a Bacillus-Calmette- Guérin (BCG) vaccination associated with exposure to anti-TNFα in utero [30].

Besides safety issues, the effectiveness of vaccination in children exposed to anti-TNFα have has also been questioned. Studies in adults with IBD using immunosuppressive drugs have shown that the response to 23-valent pneumococcal vaccine is decreased [31–33]. The response to conjugated pneumococcal vaccine is better [34,35], but the seroprotective rate 2 months after vaccination is still lower in IBD patients using anti-TNFα (86.6%) than in those patients on non-immunosuppressive drugs (95.5%) [34]. Several studies report insufficient levels of Pertussis antibodies in adults [36–38]. But a more recent study showed that the rate of children and adolescents (11–18 years old) with combined immunosuppression who reached adequate booster response to Pertussis vaccination was 90% and comparable to healthy controls [39].

There have been some studies on vaccination response in infants exposed to anti-TNFα in utero (Table 1), but most studies measured vaccine response cross sectionally at different ages, which makes interpretation of results difficult [14,40–45]. In some of these reported children inadequate response to vaccination was found, but numbers were too small to draw any conclusions. In a retrospective study of 25 children, older than 12 months (14–70 months), who were exposed to infliximab or adalimumab in utero the response on vaccinations for *S. Pneumoniae,* mumps, measles, rubella and diphtheria were normal in all 15 children measured. Serological response to *H Influenzae* was detectable in all children, but levels were below protective value in 6 of 17 children. Hypogammaglobulinemia was also found in 7 of 17 children (41%) [46]. In a recent larger study from the same research group, including these previous results, serological response to vaccination to *H Influenzae* was found to be inadequate in 17 out of 49 (34.7%) exposed children at a mean age of 34 months [44]. Moreover 9 out of 37 children (24.3%) had inadequate response to Mumps measured at age 38.9 months. Interestingly though inadequate responses to H *Influenzae* and Mumps were also found in the control group. Response to other vaccination including *Streptococcus Pneumoniae*, tetanus, diphtheria, measles and rubella were considered normal. Interpretation of these data is difficult: measurement of vaccination response should ideally be performed one month after vaccination [47] and in these children, responses were performed almost two years after primary vaccination.

Another study compared vaccination response for *H Influenzae* and tetanus between 42 children exposed to biologicals and 8 children exposed to either other immunosuppressive drugs or no immunosuppressive drugs. No significant differences were found, but overall response rates were lower than historically reported

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Table 1
Reported vaccination response after intra uterine exposure to anti-TNFα because of maternal IBD.

Study	Biological (number of patients)	Age at measurement of response	Outcome vaccination response	Significant other outcomes
Bortlik 2014 [46] Retrospective multicentre cohort study	Infliximab (n = 22) Adalimumab (n = 3)	At least one year of age	6/15 inadequate response to Hib vaccine 15/15 adequate response to *Streptococcus Pneumoniae,* mumps, measles, rubella and diphtheria vaccines	4/25 serious infections requiring hospitalisation 17/17 T en B cel-subsets normal 7/17 mild hypogamma-globulinemia (IgA and/or IgG) 25/25 normal growth 1/25 mild psychomotor developmental delay
Beaulieu 2017 [45] Prospective multicentre cohort study, sub-study of the Pregnancy in IBD and Neonatal Outcomes (PIANO) registry	Infliximab (n = 27) Adalimumab (n = 7) Certolizumab (n = 3) Ustekinumab (n = 2) Natalizumab (n = 2) Vedolizumab (n = 1)	At least 7 months of age	27/38 adequate response to Hib vaccine 33/41 adequate response to tetanus vaccine Response to Hib and tetanus comparable to 8 controls (maternal IBD not exposed to anti- TNFα; but other immunosuppressive drugs), but lower than historically reported	
Duricova 2019 [44] Retrospective multicentre controlled cohort study, including children of the previous published study by Bortlik et al. [46]	Infliximab (n = 54) Adalimumab (n = 18)	Median age 34 months (IQR 16.8–61.0) Median age 38.7 months (IQR 24.9 –67.9)	17/49 inadequate response to Hib vaccine (also inadequate in 14/16 controls) 9/37 inadequate response to mumps vaccine (also inadequate in 3/13 controls) Adequate response to *Streptococcus Pneumoniae* (45/46), tetanus (47/49), diphtheria (48/49), measles (36/37) and rubella (36/37) vaccines	No increased risk of infections, use of antibiotics or allergies Growth and psychomotor development similar to controls
De Lima 2018 [48] Single centre Cross sectional, controlled cohort study	Infliximab (n = 8) Adalimumab (n = 7)	12 months	15/15 response to hepatitis B vaccine adequate	Growth, number of infections treated with antibiotics, chronic diseases, allergies, eczema comparable to controls (maternal IBD not exposed to anti- TNFα)
Mahadevan 2006 [41] Prospective cohort study, data from the PIANO registry (abstract)	Infliximab (n = 8)	Mean 13 months (6–28 months)	7/8 adequate response to Hib vaccine 8/8 adequate response to tetanus vaccine	6/8 normal IgG, IgA; 4/6 low IgM
Sheibani 2016 [43] Prospective cohort study, data from the PIANO registry	Infliximab (n = 10) Adalimumab (n = 2)	Median age 10 months (6–28 months	11/12 adequate response to tetanus vaccine 11/12 adequate response to Hib vaccine	5/10 low IgM, 10/10 normal IgG and IgA No serious infections
Vasiliauskas 2006 [40] casereport	Infliximab (n = 1)	6 months	adequate response to Hib, *Streptococcus Pneumonia* and tetanus vaccine	Normal T en B cel-subsets, IgG, IgA, IgM and in vitro lymphoproliferative responses to non-specific mitogens Normal growth and development, no infections during first year of life
Zelinkova 2011 [14] Prospective case series	Infliximab (n = 4)	6 months	2/2 adequate response to Hib and *Streptococcus Pneumonia* vaccines	Normal development and no infections during follow up 4–11 months

[45]. A study on the effectiveness of hepatitis B vaccination in children born to IBD mothers did not observe a difference between response to hepatitis B vaccination in 15 children exposed to anti TNFα compared to 12 children not exposed to anti TNFα [48].

Risk of infections after exposure to anti- TNFα therapy

A higher rate of infections in children exposed to the combination of anti-TNFα and thiopurines in utero was found in a prospective study in 80 children. Children were compared to children exposed to anti TNFα monotherapy, but not to an unexposed group [16]. Larger and more recent studies though seem reassuring on the rate of infections, at least on the rate of infections requiring hospitalisation of children exposed to anti-TNFα.

In a cohort of 53 children, who were exposed to anti TNFα in utero and of whom data were retrospectively collected by using questionnaires, the rate of infections was comparable to non-exposed children during the first year of life. These children, however, were advised not to attend normal day care [9]. A larger European retrospective observational study, also using questionnaires, found an incidence rate of serious infections, requiring hospitalisation of 2.8% per person in 388 children exposed to anti TNFα with (n = 99) or without (n = 289) thiopurines. This was comparable to children of women with IBD, unexposed to anti TNFα or thiopurines [49]. But the majority of children (62%) were not exposed during the third trimester and data considering anti TNFα concentration in cord blood or children were lacking. None of mentioned studies provide information about the occurrence of mild infections.

A retrospective cohort study using data from the French national health system database identified 799 children born to mothers using anti-TNFα during pregnancy because of IBD [50]. Compared to non-exposed children the anti-TNFα exposed children were more often born prematurely and preterm birth was associated to a higher risk of in-hospital infections. The overall rate of infections (community acquired and in-hospital) was 43.7% and comparable to the non-exposed group. Using a medico-administrative database however cannot exclude some bias: recurrent less severe infections not needing direct medical care will not be reported in these databases but could imply subtle influences on the developing immune system.

Another retrospective cohort study using a medico-

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administrative database in Canada identified 100 babies born to 90 mothers using anti-TNFα because of an auto-immune disease [51]. Fifty percent of mothers were diagnosed with IBD. The occurrence of serious infections requiring hospitalisation in these children ranged from 0 to 7% depending on concomitant exposure to other immunosuppressive drugs during pregnancy, but statistical analysis did not show an association between anti-TNFα exposure and serious infections in the first year of life.

Although the rate of infections, requiring hospitalisation are reassuring the fact that these data are generated in a population with high vaccination coverage should be taken into account. In the Netherlands vaccination rates are dropping and this might impose more risk in future.

Auto immune disease and malignancies

Theoretically transplacental exposure to anti-TNFα might affect anti-tumor surveillance as TNFα amongst others regulates cell proliferation, differentiation, survival and apoptosis [52]. IBD patients treated with anti-TNFα inhibitors in combination with thiopurines seem to have an increased risk of developing lymphoma [53–56].

Currently no increase in neoplasms has been observed in children exposed to anti-TNFα during pregnancy, although the length of follow up is limited [49].

The development of autoimmune diseases such as TNFα agonist-induced lupus-like syndrome (TAILS) might be another concern might be. This has not been reported in children after intra-uterine exposure to our knowledge. The incidence of allergies does not seem to be increased compared to the general population [46,48,49].

Anti-integrins: vedolizumab

Vedolizumab is an anti-α4β7 integrin IgG1 monoclonal antibody, selectively modulating trafficking of memory B cells to the inflamed gut. Vedolizumab targets the interaction between anti-α4β7 and mucosal vascular adressin cell adhesion molecule 1 (MAdCAM), which is expressed in the gut, but is also expressed by maternal vessels in the placenta [57]. In animal models the importance of integrins during placentation and embryogenesis has been shown [58]. Mutations in the α4 subunit gene in mice cause dysfunctional placentation and consequently to the death of the embryo [59].

Data on vedolizumb during pregnancy are limited. As with other IgG1 antibodies vedolizumab placental transfer is expected, especially during the third trimester. Vedolizumab has a longer half-life than adalimumab or infliximab and would theoretically result in significant concentrations in the neonate, even if vedolizumab would be discontinued in the third trimester [60,61]. But in the Pregnancy in the Inflammatory Bowel Disease and Neonatal Outcome (PIANO) registry the serum level in the exposed child at birth was half of serum level of the mother [62]. Another small report of two pregnant women with IBD also showed lower vedolizumab cord blood levels than maternal levels at birth [63]. Last infusion of vedolizumab in these women had been at 10 and 5 weeks before birth. A low detectable level of vedolizumab was found in one of two children at 6 months of age. In a recent prospective cohort study of 21 pregnant women, spontaneous abortion seemed more frequent in women treated with vedolizumab as compared to anti TNFα or conventional treatment for IBD [64]. The authors suggest that more severe and refractory IBD could be a confounder and explanation for this finding, but larger studies are needed to draw any conclusions.

Risk of congenital malformations and unfavourable neonatal pregnancy outcome

Theoretically blocking integrin function during pregnancy could impose a higher risk for spontaneous abortion or congenital malformations [58].

A report of the outcome of 24 unplanned pregnancies in women treated with vedolizumab in 6 different clinical trials showed 5 elective abortions, 4 spontaneous abortions and 11 live births. Congenital malformation (corpus callosum agenesis and left frontal polymicrogyria) occurred in one child. Two births were premature. Post marketing safety data of an additional 81 pregnancies in women recorded 4 live births and 11 spontaneous abortions. Data of the other 66 pregnancy outcomes were missing [65].

Recently a Belgian multicentre retrospective cohort study, including 24 pregnancies in 24 women with IBD using vedolizumab, reported 2 spontaneous abortions/still births and 23 life births [66].Two patients continued vedolizumab throughout pregnancy because of persistently active IBD. Four children were born premature and one (part of a twin) was small for gestational age. Congenital malformations occurred in 3 children (hip dysplasia, congenital pulmonary valve stenosis and Hirschsprung disease).

Vedolizumab and the developing immune system

To date no data are available concerning immunological development in children exposed to vedolizumab during pregnancy. Animal studies in pregnant cynomolgus monkeys receiving 10 mg/kg (expected maximum human dose) or 100 mg/kg (10-fold expected human dose) vedolizumab every 2 weeks, showed no changes in white blood cell counts and differentiation at 28 days, 120 days and 6 months after birth.

Vaccination of children after exposure to vedolizumab

Data on vaccination response in exposed children is limited. In a study of 54 adults treated with vedolizumab the response to hepatitis B vaccination was comparable to placebo. The response to oral cholera vaccination however was reduced, probably reflecting the gut selective mechanism of action of vedolizumab [67]. In the previous mentioned Belgian study no adverse events after vaccination (including live attenuated rotavirus in 9 children) were observed in 20 exposed children [66]. Beaulieu et al. included one child exposed to vedolizumab in their previous mentioned study on response to vaccination after intra uterine exposure to biologicals [45].

Risk of infections after exposure to vedolizumab

Data concerning the risk of infection in children who were exposed during pregnancy are scarce. Given the working mechanism of vedolizumab an increased rate of (gastro-intestinal) infections might be expected in exposed children. Safety data in patients with IBD using vedolizumab show no increased risk of infection [68]. In a small prospective study in 21 children treated with vedolizumab respiratory tract infections were the most frequent occurring infections and occurred 5 times during the follow up period of 22 weeks after initiation of vedolizumab [69]. In the Belgian study 1 of 23 children exposed during pregnancy, was admitted to hospital during the first year of life because of fever of unknown origin [66].

Autoimmune disease and malignancies

During follow up of 23 exposed children no malignancies have

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been reported but follow up of infants was short with a median of 23 weeks [66]. The risk of malignancies does not seem to be increased in patients treated with vedolizumab either [68].

Anti IL12/23: ustekinumab

Ustekinumab is a monoclonal IgG1 antibody that prevents interleukine-12 (IL-12) and interleukine-23 (IL-23) to interact with their receptors on immune cells through binding to the p40 subunit, which is present in both interleukines. IL12 and IL23 play an important role in inflammatory diseases, including psoriasis and IBD [70], but might also play a role in uterine physiology and establishing pregnancy [71]. Ustekinumab is actively transported cross the placenta, especially in the third trimester. Concentrations of ustekinumab in cord blood were higher than maternal serum levels, similar to anti-TNFα [62,72]. In a recent case report of one pregnant women, who continued ustekinumab until 8 weeks before delivery, the cord blood level was almost ten-times higher than the maternal trough level directly after birth [73].

Risk of congenital malformations and unfavourable neonatal pregnancy outcome

No increased risk of spontaneous abortions or congenital malformations was seen in 65 pregnant women, exposed to at least one dose of ustekinumab (most of them treated for psoriasis, 3 women with IBD) [70,74].

Ustekinumab and the developing immune system

Immunological studies in infants after intra uterine exposure have not been performed. Animal studies in pregnant macaques, using high doses of ustekinumab showed no adverse effects on their offspring. Immunophenotyping, immunohistopathology of lymphoid tissues and T-dependent antibody responses were normal [75].

Vaccination of children after exposure to ustekinumab

There are no data on vaccination response in children exposed to ustekinumab during pregnancy, but data in adult patients treated with ustekinumab seem reassuring.

In 60 adults treated because of psoriasis, response to 23-valent pneumococcal vaccine and tetanus toxoid was adequate in 96.6% and 84.7% of respectively [76]. This was comparable to control psoriasis patients not receiving systemic treatment. Recently a another study showed that response rate to hepatitis B vaccination was higher in patients using ustekinumab as compared to patients using infliximab or adalimumab [77].

Risk of infections after exposure to ustekinumab

Data of patients treated with ustekinumab because of IBD do not show an increased risk for serious infections [70]. To our knowledge there are however no data available about the risk of infection in children exposed in utero.

Autoimmune disease and malignancies

The risk of autoimmune disease and malignancies after intra uterine exposure is unknown. No increased risk of the occurrence of malignancies has been reported in patients treated with ustekinumab [70].

JAK inhibitors: tofacitinib

Tofacitinib is an oral inhibitor of the Janus kinase (JAK) family of kinases, including JAK1 and JAK3. Through inhibition of JAK1 and JAK3 tofacitinib inhibits signal transduction of several interleukins and interferon, resulting in immunomodulation [78]. Recently the European Medicines Agency (EMA) has recommended not to prescribe tofacitinib in patients who are at risk of pulmonary thromboembolism as a higher risk of pulmonary thromboembolism has been described in patients with RA using tofacitinib 10 mg twice daily [79].

Studies on transplacental transport are lacking but given the small size of tofacitinib, it is considered reasonable that tofacitinib will be able to cross the placenta [80,81].

Congenital malformations and unfavourable neonatal pregnancy outcome

Animal studies have shown tofacitinib to be teratogenic in rabbits and in rats using dosages 13 to 146 times the recommended dose of 5 mg twice daily [82]. Amongst others ventricular septal defects, skeletal malformations and reduced foetal weight were described. For this reason the current EMA recommendation is that tofacitinib is contraindicated during pregnancy [79]. Outcomes of tofacitinib safety databases of ulcerative colitis were recently reported and combined with previously reported data from safety databases for rheumatoid arthritis and psoriasis [80,81]. A total of 74 maternal exposed pregnancies were described of which 37 resulted in healthy new-borns. Congenital malformation (pulmonary valve stenosis) was described in 1 neonate. Spontaneous abortion occurred in 12 pregnancies, 13 pregnancies were terminated for medical reasons and in 11 pregnancies outcome was pending or mother was lost to follow up. In addition, amongst 42 maternal exposed pregnancies from non-interventional studies or spontaneous adverse events reporting, 7 healthy new-borns, 1 child with a malformation (ventricular septum defect), 3 spontaneous abortions, 1 medical terminations and 33 cases pending or lost to follow up were described [80]. The risk for malformations or spontaneous abortions seemed consistent with background risk in the general population.

Tofacitinib and the developing immune system

To our knowledge there are no data on the development of the immune system in children exposed in utero to tofacitinib. Neutropenia has been described in adult patients treated with tofacitinib [83].

Vaccination after exposure to tofacitinib

There are no reports on vaccination response in children exposed during pregnancy, but concerns might be raised when data on exposed adults are taken into account. In 102 adult patients using tofacitinib for rheumatoid arthritis (RA) vaccination response after polysaccharide pneumococcal vaccine was decreased compared to placebo, whereas response to influenzae vaccine was comparable [84]. Satisfactory response to vaccination, defined as a twofold or more rise against 6 or more of 12 pneumococcal serotypes, was achieved in 45.1% of patients on tofacitinib versus 68.4% of RA patients receiving placebo. In another study amongst 60 adult psoriasis patients using tofacitinib more than 80% of patients had measurable titers to each serotype after 13-valent pneumococcal conjugate vaccination and fourfold rise of tetanus toxoid was seen in 60% of patients [85].

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Risk of infections after exposure to tofacitinib

In a systematic review and meta-analysis on the efficacy and safety of oral JAK inhibitors in adults with IBD the rate of infections was found to be increased as compared to placebo, particularly for herpes zoster [86]. There no data on the rates of infections after exposure in utero.

Autoimmune disease and malignancies

The risk of malignancies or auto immune diseases has not yet been studies in children exposed to oral JAK inhibitors during pregnancy. In adults treated with oral JAK inhibitors the risk for malignancies does not seem to be increased, but most studies are relatively small and follow up was short [86].

Summarizing data and implications for care of exposed children

Maintaining disease remission during pregnancy in women with IBD is important to secure a healthy outcome of pregnancy for both mother and child. Current guidelines therefore advise to maintain IBD medication, including biologicals during pregnancy. Recent data in children exposed to anti TNFα during pregnancy seem reassuring as far as congenital malformations and serious infections requiring hospital admission are concerned. Effects on the developing immune system however cannot be excluded: one infant died after BCG vaccination and some cases of neutropenia with skin infections needing G-CSF have been reported. Moreover, small studies have shown subtle changes in T and B cell subsets, decreased response after mycobacterial challenge and vaccine response rates lower than historically reported. Furthermore, the reassuring data on infection rates are only in infections requiring hospitalisation and are generated in a population with high vaccination coverage. In the Netherlands vaccination rates are dropping and this might impose more risk in future. Any firm conclusions at this stage are impossible given the small size and retrospective design of most studies.

Parents-to-be should be informed about the limited knowledge on long term effects of exposure to biologicals and JAK inhibitors in utero, the importance of administration of inactivated vaccines and the fact that live-attenuated vaccines should be withheld until biologicals are no longer detectable in their child. Given the limited data on long term effects follow up of children exposed to biologicals seems warranted. We would suggest measuring drug level at birth and to check for neutropenia in cord blood. The functional capacity of the immune system can be evaluated by measuring response to routinely administered inactivated vaccines during the first months of life. If an adequate response is lacking, administrating a booster vaccine might be considered. Follow up in a prospective study design to evaluate the necessity of immunological follow up is suggested.

Practice points

- Relapse of IBD during pregnancy is associated with unfavourable pregnancy outcome. Therefore, current guidelines advise to maintain immunosuppressive drugs during pregnancy.
- The risk of congenital malformation and serious infections requiring hospital admission does not seem to be increased in children exposed to anti TNFα during pregnancy, but the effect on the developing immune system is uncertain. Safety data on children exposed to vedolizumab, ustekinumab and tofacitinib are limited and conclusions on the use of these drugs cannot be drawn.
- Administration of live attenuated vaccines should be withheld as long as the biologicals or JAK inhibitor is still detectable.

Research agenda

- Follow up of children exposed to biologicals during pregnancy in a prospective study design is necessary to evaluate both short term and long-term effects on the developing immune system.
- New biologicals, JAK inhibitors or other first in-class drugs with immune suppressive action require extensive evaluation in pregnancy including placental transfer, drug levels at birth and health-related outcome in new-borns.

Declaration of competing interest

Jantien Wieringa: None.

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