Outcome of pregnancies in female patients with inflammatory bowel diseases treated with vedolizumab

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Abbreviations:
BIRD: Belgian IBD Research and Development group; CD: Crohn’s disease; CRP: C-reactive protein; EMA: European Medicines Agency; IBD: inflammatory bowel disease; IQR: interquartile range; IV: intravenous; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; PGA: physician global assessment; PROM: premature rupture of the membranes; FDA: Food and Drug administration; TNF: tumour necrosis factor; UC: ulcerative colitis; UST: ustekinumab; VDZ: vedolizumab

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ABSTRACT

Background and aims

Vedolizumab is an IgG1 anti-α4β7 integrin antibody approved for the treatment of inflammatory bowel diseases, but without clear safety data during conception, pregnancy and nursing. Animal studies showed that MAdCAM-1 is expressed by maternal vessels in the placenta and recruits α4β7-expressing cells that are considered important for maternal/foetal tolerance. Blocking this interaction by vedolizumab might affect this process. We aimed to evaluate pregnancy outcomes in vedolizumab treated female IBD patients.

Methods

We conducted a retrospective, multicentre Belgian observational study. Details on disease activity, prenatal complications, delivery and neonatal outcome were collected through a case report form.

Results

Twenty-four pregnancies were reported. Five women had active disease at conception and one patient flared during pregnancy. There were 23 live births. Complications were observed in 25% of pregnancies (premature rupture of membranes, pre-eclampsia, miscarriage, elective termination and stillbirth) and in 35% of infants (prematurity, intra-uterine growth retardation, small for gestational age and congenital malformations including hip dysplasia, pulmonary valve stenosis, and Hirschprung’s disease). Vedolizumab was continued throughout pregnancy in two females and stopped in the 1st and 2nd trimester in 5 and 16 patients, respectively. For live born children, the median (interquartile range) gestational age, weight and Apgar score 5 minutes after birth were 39 (37-39.6) weeks, 3270 (3080-3585) grams and 10 (9-10).

Conclusion

Although several complications were observed, both in mothers and newborns, no firm conclusions can be drawn. Awaiting prospective and controlled registries, vigilance and strict follow-up of pregnant patients treated with vedolizumab seems mandatory.

Keywords: Inflammatory bowel disease – pregnancy – vedolizumab
INTRODUCTION

Inflammatory bowel diseases (IBD), are characterized by chronic intestinal inflammation with a relapsing and remitting course, mostly affecting men and women of childbearing age.\(^{(1)}\) As active disease is associated with poor pregnancy outcome in women with IBD, it is crucial to achieve and maintain clinical remission prior to conception as well as throughout pregnancy.\(^{(2)}\) Although a wide variety of biologic therapies have shown efficacy in this situation, safety data are scarce.\(^{(2-4)}\) Most evidence for the use of biologicals in pregnancy exists for anti-tumour necrosis factor (anti-TNF) antibodies.\(^{(5, 6)}\) Anti-TNF agents are also the only biological agents included in the European guidelines on reproduction and pregnancy in IBD patients.\(^{(2)}\) Out of all the anti-TNF therapies, certolizumab pegol is considered the safest biological during pregnancy, since it does not cross the placental barrier.\(^{(6)}\) However, this pegylated anti-TNF agent is not available in most European countries.
Vedolizumab (VDZ) was approved by the European Medicines Agency (EMA) in 2014 for the treatment of moderate to severe Crohn’s disease (CD) and ulcerative colitis (UC) patients. VDZ is an intravenous humanized IgG1 monoclonal antibody targeting the interaction between α4β7 integrin and mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) in the gut. As VDZ is considered to be gut-focused, it is generally presumed that it has an excellent safety profile. However, safety data on VDZ exposure during pregnancy are very limited. Importantly, murine experiments have shown that MAdCAM-1 is expressed by maternal vessels during placental development and recruits α4β7-expressing cells of the macrophage/monocyte lineage, which are assumed to play a role in maternal/foetal tolerance. In humans, placental expression of MAdCAM-1 was confirmed, though it seems to be only expressed during the first trimester of pregnancy and is absent in the placenta at birth. It stands to reason that blocking this α4β7 integrin-MAdCAM-1 interaction by VDZ might affect pregnancy and lead to maternal and/or foetal complications. The aim of this study was therefore to evaluate the outcome of pregnancies in female IBD patients treated with VDZ.

MATERIALS AND METHODS

Patient population

We conducted a multicentre (n=11), Belgian, retrospective study in which members of the Belgian IBD Research and Development group (BIRD), were asked to report all pregnancies exposed to VDZ between March 2009 (when VDZ became available through clinical trials) and February 2018. Details on disease activity, prenatal complications, delivery and neonatal outcome were collected through a case report form (Supplementary figure 1).
Data collection

Data were retrospectively collected at all participating centres by review of medical records and delivery reports after ethical approval by the Ethics Committee of the University Hospitals Leuven, Leuven, Belgium (S60985). In addition, the mothers were contacted to provide information about infections, vaccinations and hospitalizations of the children during the first year of life. Preconception data included patient characteristics at conception [IBD diagnosis and previous IBD related medical history, obstetrical history (number of previous pregnancies, miscarriages and elective terminations as well as possible complications and outcomes of previous pregnancies), comorbidity, C-reactive protein (CRP) level prior to conception, disease activity based on physician global assessment (PGA) and concomitant use of medication at conception]. PGA options correspond to “active disease”, “flare” or “remission” and were based on the clinical judgement of the treating gastroenterologist.

The information collected during pregnancy consisted of the following: date of conception, smoking and drinking habits during pregnancy, use of folic acid supplementation, dose and duration of VDZ therapy, reason for VDZ discontinuation in pregnancy, other IBD medication during pregnancy [including topical therapy, mesalamine, systemic steroids, immunomodulators, anti-TNF therapy and ustekinumab (UST)], disease activity (PGA) and changes in treatment (dose escalation or de-escalation, change in time interval or initiation of other treatments) per trimester of pregnancy and complications such as placenta praevia, (pre)-eclampsia, infections during pregnancy, intra-uterine growth retardation, foetal loss or elective termination and premature rupture of the membranes (PROM). In addition, we collected mode and term of delivery and newborn characteristics and complications (gestational age, sex, birth weight, Apgar scores at minute 1 and 5, congenital malformations, intensive care unit admission, allergies, vaccinations, breastfeeding, severe infectious complications and malignancies occurring in the first year of life). Regarding severe infections or malignancies we collected data on the date of diagnosis, type of infection or tumour, need for hospitalization and length of hospitalization, treatment and outcome. In case of missing data the general practitioners were contacted to retrieve the information.

Outcomes and definitions
The primary aim of this study was to assess pregnancy outcome in vedolizumab treated female IBD patients. These include: the number of live births, stillbirths (defined as foetal loss after 20 weeks post-conception\(^\text{15}\)), miscarriages and elective terminations, preterm delivery (defined as any delivery before 37 weeks of gestation\(^\text{16}\)), mode of delivery (instrumental delivery, caesarean section, vaginal delivery), infection, (pre-) eclampsia, placenta praevia or chorioamnionitis and IBD flare during pregnancy. Secondary outcomes include neonatal complications such as intra-uterine growth retardation, low birth weight (defined as birth weight less than 2500 grams in a child born at term)\(^\text{16}\), small for gestational age (defined as weight below the 10\(^\text{th}\) percentile in regards to gestational age)\(^\text{17}\), low Apgar score (score <7 at minute 5)\(^\text{18}\), congenital anomalies, admission to neonatal intensive care unit, serious infection or malignancy the first year of life or at last follow-up. The first trimester was characterized as the time from conception until week 13 of gestation, the second trimester from week 13 to 26 and the third trimester from week 26 until delivery. Severe infectious complications in the newborn were regarded as infectious complications requiring or prolonging hospitalisation. IBD disease activity was retrospectively assessed at conception and during each trimester of pregnancy by using PGA.

**Vedolizumab administration**

Since March 2009, VDZ has been used for treatment of IBD patients as part of multiple trials.\(^\text{7,8}\) In Belgium, classical induction with commercial VDZ for both UC and CD consists of a dose of 300mg intravenous (IV) at weeks 0, 2 and 6 followed by an 8 weekly intravenous maintenance dose of 300mg. Of note, most patients with CD receive an extra induction dose of 300mg IV VDZ at week 10. Patients who lose response to VDZ throughout follow-up can be optimized to 300mg IV every 4 weeks through a medical need program, provided that objective signs of disease relapse are present.

**Statistical analysis**

Descriptive statistics were used to display the results. For nominal data, proportions and percentages were reported whereas for (non-parametric) continuous data medians with interquartile ranges (IQR)
were presented. IBM SPSS Statistics 25.0 software package (Armonk, NY, USA) was used. A p-value <0.05 was regarded as statistically significant.

RESULTS

Study population

Eleven Belgian hospitals reported 24 pregnancies in 24 unique women with IBD treated with VDZ since March 2009. Four women (17%) were included in the GEMINI trials at the time of conception and had to discontinue the study agent per protocol. However, after being excluded from the trial, two of those patients still received vedolizumab through a medical need program. All other women (n=20, 83%) were treated with vedolizumab in routine clinical practice at the time of conception or during pregnancy. Three pregnancies did not lead to a live birth. The remaining twenty-one pregnancies led to twenty-three live births (61% female), which included two dizygotic pairs of twins.

Maternal baseline characteristics and medication use in pregnancy

Maternal characteristics are displayed in Table 1. All but two women were on VDZ maintenance treatment at conception either every 8 (n=17) or 4 weeks (n=5), with one patient needing dose optimization in the second trimester to VDZ 300mg every 4 weeks. The two exceptions include patients that received VDZ induction therapy at week 4 of pregnancy, due to either disease activity or loss of response to anti-TNF therapy, not knowing they were pregnant. Figure 1 shows the use of vedolizumab at conception and during pregnancy.

At conception, five women had clinically active disease. Disease activity persisted until the first trimester of pregnancy in two and until the second trimester in one patient respectively. The remaining two patients had incessant disease activity throughout pregnancy. One patient, who was in remission at conception, flared during the third trimester of pregnancy. The latter patient started VDZ therapy in combination with prednisolone suppositories at gestational week 4 after loss of response to anti-TNF therapy. After induction, topical steroids could be stopped and VDZ was given at a dose of 300mg IV every 8 weeks until gestational week 22 when the last infusion was given. During the third trimester of pregnancy, topical steroids were restarted because of a flare.
VDZ could be stopped in the first or second trimester of pregnancy in 5 and 16 cases, respectively. Two patients continued VDZ infusions throughout pregnancy due to persistent disease activity, and one patient was still using VDZ when she miscarried at week 6. In 87% of patients (n=20) VDZ was stopped after multidisciplinary consultation. In one case, VDZ was stopped at the request of the patient because of arthralgia, despite having active disease. Postpartum 86% (18/21) of patients that had stopped VDZ in pregnancy restarted VDZ therapy. No allergic reaction after re-induction was identified. Concomitant medication during pregnancy is shown in supplementary figure 2. Mesalamine, anti-TNF therapy and azathioprine were used as part of maintenance treatment, whilst steroids were initiated either because of active disease (n=2) or erythema nodosum (n=1).

**Pregnancy outcomes and complications**

Previous pregnancies were reported in 63% (15/24) of the women and these pregnancies were complicated in 47% (7/15) of cases. These included pregnancy and neonatal complications such as antenatal hydronephrosis, IBD flare during pregnancy, PROM, preterm delivery and a history of multiple miscarriages. Only one of these patients now had an uncomplicated pregnancy.

Of the current pregnancies, as mentioned above, three did not lead to a live birth including an early miscarriage at 6 weeks of gestation in a patient with a history of idiopathic miscarriages. Underlying active disease, though not obvious clinically, may be an explanation for the miscarriages. The second case was an active termination at week 9 of gestation due to relational problems and thus independent of underlying IBD. The last one was a stillbirth at 22 weeks of gestation because of chorioamnionitis in a patient with a history of a late preterm delivery at 36 weeks. After foetal loss, this patient was switched to UST because of persistent disease activity. Since switching her therapy, she has gotten pregnant twice with the first pregnancy ending in a miscarriage at week 4. The second pregnancy was complicated by cervical insufficiency. She had to be hospitalized from week 23 until 32 due to risk of extreme premature delivery and eventually delivered at week 37. Other pregnancy complications included pre-eclampsia (n=1) and PROM (n=2).

**Infants’ baseline characteristics and neonatal complications**
In the 23 children that were born alive, the median gestational age, Apgar score at minute 5, and birth weight were respectively 39 weeks (IQR 37-39.6), 10 (IQR 9-10) and 3270 grams (IQR 3080-3585). The majority of children (65%, n=15) did not experience complications, however three children were born with a congenital anomaly including hip dysplasia (n=1), congenital pulmonary valve stenosis (n=1) and Hirschsprung’s disease (n=1). Medication to which these children were exposed in utero is displayed in Table 2. Furthermore, four infants were born late premature (week 34-36.5) and one child, part of a twin, was small for gestational age (2390g at week 37). This twin also experienced intra-uterine growth retardation. The proportion of neonatal complications to adverse pregnancy outcomes are displayed in supplementary figure 3. Twelve children were breastfed (12/23=52%). All newborns old enough to receive vaccinations were vaccinated according to the standard Belgian regimen (n=20) with 45% (9/20) receiving Rotavirus vaccination. No allergies or adverse reactions to vaccinations were reported. Only one child was hospitalized during the first year of life due to fever of unknown origin, but so far no other serious infections or malignancies have been reported. The median follow-up time of the children was 23 weeks (IQR 10-60).
DISCUSSION

This study reports on the outcome of 24 pregnancies in VDZ treated female IBD patients, which resulted in 23 live births including 2 dizygotic twins. In our cohort, 25% of the pregnancies were complicated and 35% of the infants experienced problems, including three children with congenital anomalies. To our knowledge, this is the largest cohort study reporting on pregnancy outcomes in female patients treated with VDZ. IBD typically affects women at a childbearing age\(^{(20)}\) and prior studies have shown that disease activity at any time in pregnancy, rather than medication used to treat IBD, is the most important risk factor for unfavourable pregnancy outcome.\(^{(2, 16)}\)

In accordance with the Food and Drug Administration (FDA), VDZ can be used in pregnancy, despite the fact that studies on fetotoxicity in humans are lacking and no long-term data are available.\(^{(21)}\) Furthermore, IBD is associated with adverse events in pregnancy such as preterm delivery, low birth weight, small for gestational age, pre-eclampsia, miscarriages and elective terminations.\(^{(22, 23)}\) In addition, one study showed that children born to women with UC had a higher risk for congenital malformations.\(^{(23)}\) However, so far no other study was able to confirm this.\(^{(24)}\) Although our retrospective study did not include a control group, we observed complications of which the frequencies were in the same range as those reported in previous historical case series with other biologic agents.\(^{(25-27)}\) Most of these complications such as preterm delivery, small for gestational age, miscarriage and stillbirth can be explained by underlying active IBD disease. In our relatively small cohort, the major confounding factor for poor pregnancy outcome seems to be the presence of active disease at conception and during pregnancy. Although the number of patients with active disease
reported in our study was low, this was based on PGA and not on objective measures of disease activity. In addition, 45% of women did have an elevated CRP before conception, which also suggests the presence of active disease making these women more at risk for pregnancy complications. In addition, the child that was small for gestational age was part of a twin and these pregnancies are themselves considered as being high-risk. Regarding the congenital anomalies described in this manuscript (hip dysplasia, congenital pulmonary valve stenosis, and Hirschsprung’s disease), no association was found between the mechanism of action of VDZ and the underlying molecular pathways of these malformations. However, based on our study a possible causal relationship between VDZ and the mentioned complications cannot be excluded or confirmed due to the low number of patients and the presence of other underlying risk factors (mainly active disease) that may have contributed to these complications. The same probably goes for other anomalies that have been reported in the literature such as agenesis of the corpus callosum in a child of a healthy volunteer exposed to VDZ. In addition, the pregnancy complications mentioned in our cohort (PROM, pre-eclampsia, elective termination and spontaneous miscarriage) are also seen with IBD patients not treated with biologicals or treated with biologic agents other than VDZ. Thus, these complications are presumably also connected to the disease itself rather than the medication that was used.

The collaborating hospitals used VDZ in pregnancy in a similar way as anti-TNF therapy since they are both IgG1 monoclonal antibodies. So, when feasible and as is customary in Europe, VDZ therapy was stopped during the second trimester of pregnancy. However, applying identical rules to VDZ and anti-TNF therapy in pregnancy may not be appropriate since VDZ has a longer half-life than anti-TNF agents. Therefore, discontinuation of VDZ in the 2nd trimester may lead to significantly higher serum levels in the infant compared to infliximab, which theoretically may have implications regarding the administration of live-attenuated vaccines as well as the newborn’s risk of infections. Currently, European and American guidelines do not recommend the administration of live-attenuated vaccines the first 6 months of life in children exposed to biologicals in utero. In Belgium, this only concerns Rotavirus vaccination. However, these guidelines are based solely on treatment with anti-TNF therapy since data regarding live-attenuated vaccination in VDZ exposed children is absent. Why 45% of the infants in our population received Rotavirus vaccination despite active discouragement
remains unknown. Nevertheless, no adverse events were documented after vaccination. Meanwhile, response to non-live vaccines was shown to be normal in children exposed to biologicals in utero. However, this should be interpreted with caution as only one child was exposed to VDZ. Another concern that may arise is the possible effect of biologicals on the development of the infant’s immune system and infection risk. First, trials with anti-TNF therapy reported conflicting results. Preliminary data from the PIANO registry showed a higher risk of infection in newborns exposed to a combination of anti-TNF therapy and immunomodulator. On the contrary, the recently published TEDDY study demonstrated reassuring results in a similar population of children. Furthermore, studies on the effect of anti-TNF exposure in utero on the development of the infant’s immune system also resulted in inconsistent results. However, there is no evidence available on the effect of VDZ on the immune system and infection risk of the newborn, so no recommendations can be made. In our study, only one child was hospitalized for an infection the first year of life, tough this should be interpreted with caution due to the short follow up time postpartum.

Regarding lactation in females treated with VDZ, only three studies have been published so far: one in monkeys receiving a supratherapeutic dose of VDZ and two in humans. The studies demonstrated the presence of VDZ in breast milk, yet in very small doses. In addition, it is presumed that these small amounts of VDZ will be degraded in the infant’s gastrointestinal tract and thus will not substantially impact the immune system. In spite of the current knowledge, only 52% of children in our population were breastfed. No explanation could be found, but despite recommendation of breastfeeding, mothers may still have concerns about neonatal exposure to medication through breastmilk.

Hence, the main emphasis should still be on the preconception consultation in which concerns with respect to medication use, breastfeeding and vaccination should be addressed. Furthermore, the importance of good disease control should be stressed and the physician should make sure that the patient understands the value of disease control prior to conception as well as during pregnancy.

Our study has some limitations with the main one being the low number of cases and the fact that no control group was used, because this prevents us from drawing firm conclusions regarding the use of VDZ in pregnancy. For this, we need to await the results of large ongoing prospective registries in the
years to come. Although our cohort reflects real world data, it contains a very heterogeneous group of patients as can be derived from the diverse use of concomitant medication, the different setting of vedolizumab initiation (placebo controlled trial vs. daily clinical practice) and the onset of vedolizumab initiation (since months, started just before or just after conception). Second, although we asked to report all pregnancies under vedolizumab, the retrospective nature of this study makes it prone to selection bias in which either patients with unfavourable pregnancy outcomes might be over-reported or early miscarriages might have been missed. Indeed, patients may not always inform their treating gastroenterologists of their pregnancy. Finally, disease activity was retrospectively assessed using the PGA, which is known to correlate poorly with endoscopic and biological disease activity, as reflected in the fact that only 5 women were assessed as having clinically active disease, however biologically 45% had an elevated CRP. Missing of other objective markers of disease activity like endoscopic evaluation or faecal calprotectin is therefore also a limitation, and underlying active disease remains a major confounding factor in our cohort.

CONCLUSION

This is the largest cohort study reporting on pregnancy outcomes in patients treated with VDZ. Although the number of pregnancies remains low and no guidelines are available, our results support the fact that VDZ should only be used in pregnancy if the benefits for the mother outweigh the potential risks for mother and (unborn) child. In the future, results from ongoing registries will hopefully shed more light on the safety of VDZ in pregnancy and lactation. Furthermore, large prospective studies are needed, not only on pregnancy outcomes with VDZ, but also regarding VDZ trough levels in mother and newborn. In addition, the function of the α4β7-MAdCAM1 interaction in
the placenta should be further explored. In the meanwhile, vigilance and strict follow-up of pregnant patients with IBD treated with VDZ are warranted.

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CONFLICTS OF INTEREST

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REFERENCES


LEGENDS FIGURES/TABLES

Table 1 displays the baseline maternal characteristics.

Table 2 shows the medication to which the three children born with anomalies were exposed during pregnancy.

Figure 1 shows the use of vedolizumab at conception and during pregnancy.

Supplementary figure 1 displays the case report form that was used to collect data.

Supplementary figure 2 shows the concomitant medication that was used at conception and throughout pregnancy.

Supplementary figure 3 displays the proportion of neonatal complications to adverse pregnancy outcomes.
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (IQR) at IBD diagnosis (years)</strong></td>
<td>23 (19-27)</td>
</tr>
<tr>
<td>Crohn’s disease (%)</td>
<td>15/24 (62.5%)</td>
</tr>
<tr>
<td>Ulcerative colitis (%)</td>
<td>9/24 (37.5%)</td>
</tr>
<tr>
<td><strong>Disease localization (Montreal, %)</strong></td>
<td></td>
</tr>
<tr>
<td>L1: Ileal</td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>L2: Colonic</td>
<td>1/15 (7%)</td>
</tr>
<tr>
<td>L3: Ileocolonic</td>
<td>13/15 (86%)</td>
</tr>
<tr>
<td>L4: Upper GI involvement</td>
<td>0/15 (0%)</td>
</tr>
<tr>
<td>E1: Proctitis</td>
<td>0/9 (0%)</td>
</tr>
<tr>
<td>E2: Left-sided colitis</td>
<td>7/9 (78%)</td>
</tr>
<tr>
<td>E3: Extensive colitis</td>
<td>2/9 (22%)</td>
</tr>
<tr>
<td><strong>Disease behaviour CD (Montreal, %):</strong></td>
<td></td>
</tr>
<tr>
<td>B1: Inflammatory</td>
<td>6/15 (40%)</td>
</tr>
<tr>
<td>B2: Strictureing</td>
<td>4/15 (27%)</td>
</tr>
<tr>
<td>B3: Penetrating</td>
<td>5/15 (33%)</td>
</tr>
<tr>
<td><strong>Perianal disease (%)</strong></td>
<td>9/15 (60%)</td>
</tr>
<tr>
<td><strong>History of intestinal resection (%)</strong></td>
<td>6/24 (25%)</td>
</tr>
<tr>
<td><strong>Median (IQR) age at conception (years)</strong></td>
<td>32 (26-34)</td>
</tr>
<tr>
<td><strong>Median (IQR) disease duration at conception (years)</strong></td>
<td>8 (5-11)</td>
</tr>
<tr>
<td><strong>Median (IQR) duration of VDZ therapy at conception (months)</strong></td>
<td>8 (4-12)</td>
</tr>
<tr>
<td><strong>CRP &lt;5mg/l at conception</strong></td>
<td>12/22 (55%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>IBD medication at any point in pregnancy (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Systemic mesalamine</td>
<td>6/24 (25%)</td>
</tr>
<tr>
<td>Topical steroids</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>4/24 (17%)</td>
</tr>
<tr>
<td>Immunomodulators</td>
<td>4/24 (17%)</td>
</tr>
<tr>
<td>Anti-TNF therapy</td>
<td>1/24 (4%)</td>
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<tr>
<td><strong>Comorbidity (%)&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
</tr>
<tr>
<td>Inflammatory disorder</td>
<td>3/24 (13%)</td>
</tr>
<tr>
<td>Hypothyroidism (treated)</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td>Other</td>
<td>2/24 (8%)</td>
</tr>
<tr>
<td><strong>Usage during pregnancy (%)</strong></td>
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<tr>
<td>Smoking</td>
<td>3/24 (13%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>2/24 (8%)</td>
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<tr>
<td>Folic acid supplementation</td>
<td>23/24 (96%)</td>
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<tr>
<td><strong>Active disease during pregnancy (%)</strong></td>
<td></td>
</tr>
<tr>
<td>First trimester</td>
<td>5/24 (21%)</td>
</tr>
<tr>
<td>Second trimester&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3/22 (14%)</td>
</tr>
<tr>
<td>Third trimester&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3/21 (14%)</td>
</tr>
<tr>
<td><strong>Number of previous pregnancies (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9/24 (37.5%)</td>
</tr>
<tr>
<td>1-2</td>
<td>14/24 (59%)</td>
</tr>
<tr>
<td>3 or more</td>
<td>1/24 (4%)</td>
</tr>
<tr>
<td><strong>Mode of delivery</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Caesarean section</td>
<td>5/22 (23%)</td>
</tr>
<tr>
<td>Vaginal delivery</td>
<td>17/22 (77%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes patients with unknown CRP values.

<sup>b</sup> Includes patients with unknown comorbidity data.

<sup>c</sup> Second trimester includes third trimester.

<sup>d</sup> Third trimester includes first and second trimesters.

*Mode of delivery includes patients with unknown delivery data.

Table 1: baseline maternal characteristics
CRP: C-reactive protein; IBD: inflammatory bowel disease; IQR: interquartile range; TNF: tumour necrosis factor

a: 2 CRP values missing from patients included in Millennium trial; b: Inflammatory disorders include psoriasis and IBD-related arthropathy. Hypothyroidism was treated adequately; c: exclusion of patient with early miscarriage and patient with elective termination; d: extra exclusion of patient with immature partus. *Patient with early miscarriage and elective termination were excluded.
Table 2: pregnancy details of children with congenital anomaly

<table>
<thead>
<tr>
<th>Congenital anomaly</th>
<th>VDZ dose</th>
<th>Co-medications</th>
<th>VDZ stop (gestational week)</th>
<th>Delivery</th>
<th>Birth weight (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital pulmonary valve stenosis</td>
<td>300mg, Q4W</td>
<td>5-ASA</td>
<td>18</td>
<td>38w3d</td>
<td>3495</td>
</tr>
<tr>
<td>Hip dysplasia</td>
<td>300mg, Q8W</td>
<td>None</td>
<td>20</td>
<td>40w1d</td>
<td>3270</td>
</tr>
<tr>
<td>Hirschprung’s disease</td>
<td>Induction at week 4</td>
<td>Anti-TNF (week 0-4) Local steroids (week 0-38)</td>
<td>22</td>
<td>39w</td>
<td>3305</td>
</tr>
</tbody>
</table>

Q4W: vedolizumab every 4 weeks; Q8W: vedolizumab every 8 weeks.
Figure 1: Use of vedolizumab at conception and throughout pregnancy

* 2 patients not yet on vedolizumab. °All patients on vedolizumab. ²Exclusion of patient with early miscarriage and elective termination. ³Extra exclusion of patient with immature partus.