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Paternal Exposure to Immunosuppressive and/or Biologic Agents and Birth Outcomes in Patients with Immune-Mediated Inflammatory Diseases

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Abstract

Background and Aims: We conducted a retrospective cohort study to inform the safety of exposure to immunosuppressive and/or biologic agents around conception in expectant fathers with immune-mediated inflammatory diseases (IMIDs) on birth outcomes.

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- Analysis and interpretation of data: JM, JL, SS
- Drafting of the manuscript: JM, SS
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- Approval of the final manuscript: JM, JL, WZ, GB, CDC, AGS, BSB, WJS, UM, SS
- Guarantor of the article: SS

Methods: Using a de-identified administrative claims database (OptumLabs® Data Warehouse), we identified 7,453 expectant fathers with IMIDs (inflammatory bowel diseases, rheumatoid arthritis, psoriasis/psoriatic arthritis, ankylosing spondylitis) linked to newborns, with peri-conception medication exposure between 38–60 weeks prior to newborn delivery date (34–58 weeks prior for pre-term newborns), and neonatal follow-up for 3 months after delivery date. Through logistic regression, adjusting for paternal age and race (and in a subset for maternal age, race, presence of IMIDs and non-singleton births), we compared the risk of major congenital malformations (primary outcome) and preterm birth and low birthweight in fathers exposed to thiopurines (n=461), methotrexate (n=171), TNFα antagonists (n=1082) or non-TNF-targeting biologic agents (n=132) vs. fathers not exposed to any of these medications (n=5607).

Results: As compared to unexposed fathers (3.4% prevalence of major congenital malformations), exposure to thiopurines (RR, 1.12 [95% CI, 0.66–1.76]), methotrexate (RR, 0.67 [0.21–1.55]), TNFα antagonists (RR, 1.14 [0.81–1.57]), and non-TNF-targeting biologic agents (RR, 1.75 [0.80–3.24]) was not associated with increased risk of major congenital malformations. No association was observed between paternal medication exposure and risk of preterm birth or low birth weight. Results were stable on sub-analyses of linked father-mother-newborn triads.

Conclusions: In a large cohort study of 7,453 expectant fathers with IMIDs, exposure to immunosuppressive or biologic agents around conception was not associated with increased risk of adverse birth outcomes.

Keywords

Teratogenicity; paternal; Crohn’s disease; immunomodulators; infliximab

INTRODUCTION

Immune-mediated inflammatory diseases (IMIDs) such as inflammatory bowel diseases (IBD), psoriasis and psoriatic arthritis (PsA), rheumatoid arthritis (RA) and ankylosing spondylitis frequently affect individuals of childbearing age. Both male and female partners have concerns about the effect of medications used to treat these IMIDs on fetal development and birth outcomes.[1, 2] Several studies have informed safety of maternal exposure to immunosuppressive and/or biologic agents on birth outcomes in patients with IMIDs.[3–6] However, there is limited evidence on the safety of immunosuppressive and/or biologic medications in men who wish to conceive.[7–9]

Based on preclinical studies, paternal exposure to medications may impact pregnancy through multiple mechanisms including: (a) genetic or chromosomal damage to spermatocytes; (b) impact of drugs and their metabolites on sperm maturation; and (c) direct impact of drug and their metabolites in seminal fluid on the uterus, and indirect systemic effect on females through absorption of seminal fluid by the vaginal mucosa.[7, 8, 10] Prior studies suggest paternal exposure to thiopurines, methotrexate and tumor necrosis factor [TNF]-α antagonists may not adversely affect birth outcomes, though they may be underpowered to detect small differences in risk of rare birth outcomes like major congenital anomalies.[11–13] Importantly, to our knowledge, there is no study on impact of paternal exposure to non-TNF-targeting biologics on birth outcomes in patients with IMIDs.

Using a large de-identified administrative claims database (OptumLabs® Data Warehouse) with linked father-offspring pairs, we conducted a retrospective cohort study evaluating birth outcomes in children fathered by men with IMIDs exposed to conventional immunosuppressive (thiopurines, methotrexate) or biologic agents (tumor necrosis factor [TNF]-α antagonists including infliximab, adalimumab, certolizumab pegol, golimumab and etanercept, and non-TNF-α-directed biologic agents including ustekinumab, vedolizumab, tocilizumab), within 3 months before conception. We hypothesized that as compared to expectant fathers not exposed to medications, paternal exposure to immunosuppressive or biologic agents within 3 months prior to conception would not be associated with increased risk of major congenital malformations and other adverse birth outcomes (preterm birth, low birth weight).

METHODS

Data source

We conducted a retrospective analysis of de-identified medical and pharmacy administrative claims from a large database, OptumLabs® Data Warehouse (OLDW), which includes commercially insured and Medicare Advantage enrollees throughout the United States.[14] The database contains data on more than 100 million enrollees, from geographically diverse regions across the United States, with greatest representation from the South and Midwest. Medical claims include International Classification of Diseases, Ninth Revision and Tenth Revision, Clinical Modification (ICD-9-CM; ICD-10- CM) diagnosis codes; ICD-9 and ICD-10 procedure codes; Current Procedural Terminology, Fourth Edition (CPT-4) procedure codes; Healthcare Common Procedure Coding System (HCPCS) procedure codes; site of service codes; and provider specialty codes. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996, and because this study involved analysis of preexisting de-identified data, it was exempted from institutional review board approval.

Specific approach to father-offspring linkage: A family identifier field in OLDW allowed identification of multiple enrollees under the same medical plan, with each new addition (including newborns) being linked to the same plan at birth. Through this approach, with some assumptions on biologic plausibility (of paternal age) and conventional societal norms (biologic paternity in family), we identified linked father-offspring dyads with very high degree of certainty. In both the mother and father linkage approaches, there is some error around linking newborns to the correct parents. Per an internal analysis at OLDW and in a very small percentage of cases, newborns may be linked to multiple mothers or fathers in the event there are multiple women or men of qualifying age enrolled under the same medical plan and/or there was an administrative error in generating/processing enrolment data. We dropped these parent-newborn dyads from our cohort and analyses; since this phenomenon is rare, the impact on cohort size was negligible.

Cohort identification

We identified a cohort of men aged 20–55 years, with at least 2 medical claims coded for an IMID (IBD, psoriasis or PsA, RA, ankylosing spondylitis) greater than 30 days apart from

an ambulatory visit encounter, between January 1, 2005 to December 31, 2018, with evidence of at least 1 linked newborn during this period. From this cohort, we included only men with continuous enrollment for at least 18 months prior to newborn's earliest effective date in health plan (=newborn delivery date, also referred to as index date in this analysis) and continuing for at least 3 months after newborn delivery date.

Paternal exposure to medications

Fathers with IMID were considered exposed to medications in the peri-conception period if they had at least 1 medical claim (for infusions for specialty medications) or pharmacy claim (for self-administered specialty medications) for medications of interest within 38 to 60 weeks prior to newborn delivery date for term newborns; for pre-term newborns, this window of exposure was 34 to 58 weeks prior to delivery date.[15] In prior studies, date of conception is approximately 39 weeks prior to delivery date for term newborns, and 35 weeks for pre-term newborns.[16] A 12-week window was chosen since spermatogenesis takes 70–90 days in humans, and that cut-off can evaluate the toxic effects of a medication exposure on sperm development and thus potential offspring;[12, 17] an additional 10 weeks was added to account for medication fill duration. Primary exposures of interest included: (1) thiopurines, (2) methotrexate, (3) TNFα antagonists including infliximab, adalimumab, certolizumab pegol, golimumab and etanercept, and (4) non-TNFα-targeting biologics including ustekinumab, vedolizumab and tocilizumab. Combination therapy with biologics and immunomodulators (thiopurines or methotrexate) was considered a secondary exposure of interest.

Fathers with IMID not exposed to any of these medications (i.e., not receiving refills) in the 38 to 60 week period prior to newborn delivery date (or 34 to 58 week period for pre-term newborns) formed the "unexposed" cohort.

Newborn outcomes

The primary outcome of interest was risk of major congenital malformations. This was based World Health Organization criteria and identified as at least 2 ICD-9/10 codes for the same congenital malformations in the newborn (Supplementary Table 1); this definition has been validated with a positive predictive value >80% and used in prior studies.[18–21]

Secondary outcomes of interest included risk of (1) preterm birth (<37 weeks of gestation) and (2) low birth weight (<2500g at birth), All were identified using two ICD9/10 codes reported within 90 days after delivery date in infant records.[18, 22] Since family linkage between fathers and newborns was only possible for live births, we were unable to ascertain outcomes like infertility, abortion or stillbirth.

Covariates

In evaluating the association between exposure (paternal use of immunosuppressive or biologics agents in the peri-conception period) and outcomes (major congenital malformations), there were few confounders (that influence both exposure and outcome). We accounted for paternal age, race, and type of IMID. For a subset of patients (n=4685, 63% of cohort), where mother was identifiable under the same family ID (when both

partners are in the same health plan at time of delivery), a full linkage of father-mother-baby was also performed. In this sensitivity analysis, we accounted for important maternal health aspects including maternal age, race, multiple gestations (twins, triplets, and quadruplets) and maternal IMIDs. Details of maternal health conditions, drug exposures and pregnancy-related complications were not deemed to be confounders, since they were very unlikely to influence paternal drug exposure.

Statistical Analysis

For our primary analysis, we compared unadjusted prevalence of adverse birth outcomes by any immunosuppressive and specific type of paternal medication exposure using unexposed fathers as reference category, to calculate prevalence relative risk (RR) with 95% CI. We subsequently performed multivariable logistic regression analyses, adjusting for paternal age and race. For a subset of patients with complete father-mother-baby linkage, we performed additional adjusted analyses accounting for maternal age, race, multiple gestation and presence of IMIDs. To account for variability in coding and treatment patterns over time, we performed unadjusted analyses split by every 5 years (2005–09, 2010–14, 2015–18). Post-hoc, based on reviewers' comments, we performed additional analyses to evaluate stability of the association by age of father at conception (≤35y vs. >35y) and disease type (IBD vs. non-IBD).

All analysis was conducted in a secure Windows virtual machine provide by OptumLabs. We used DBVisualizer 10.0 (Stockholm, Sweden) for database management and R version 3.5.3 (Vienna, Austria) for statistical analysis. Due to re-identification risk based on OLDW policy, cells with less than 11 total events reported were labeled as <11.

RESULTS

Paternal Characteristics

Overall, 266,333 men with covered medical and pharmacy claims with 2 or more codes for IMIDs were identified between 2005 to 2018. After applying our inclusion and exclusion criteria, our final cohort included 7,453 father-newborn dyads (Figure 1). Overall, psoriasis/PsA (43%) and IBD (41.3%) were the most common IMIDs (Table 1). Of 7,453 father-newborn dyads, 1,846 (24.8%) were classified as being exposed to immunosuppressive or biologic medication in the peri-conception period: 461 (25.0%) to thiopurines, 171 (9.3%) to methotrexate, 1,082 (58.6%) to TNFα antagonists, and 132 (7.1%) to non-TNFα-targeting biologics (ustekinumab in 114 patients, vedolizumab in 18 patients). Overall, 214 patients were exposed to a combination of biologic agents and immunomodulators. Approximately, 3.8% prospective fathers were hospitalized within 6 months, prior to conception. On examining comorbidities, 7.9% prospective fathers were diagnosed with hypertension, 2.9% with diabetes mellitus, 2.3% were obese, and 4.7% were diagnosed with depression, with no differences between fathers exposed and unexposed to immunosuppressive and/or biologic agents. Total 4,685 patients had a complete linkage of father-mother-newborn triads (62.9%), of whom 1,148 (24.5%) fathers were classified as exposed (Supplementary Table 2). Approximately 2.9% mothers were diagnosed with IMIDs.

Primary outcome: Major Congenital Malformations

Overall, approximately 3.5% of newborns were born with major congenital malformations, with anomalies of the cardiovascular system and urinary system being most common. Table 2 details the risk of major congenital malformations by exposure type and reports unadjusted and adjusted risk by different paternal medication exposure type. There was no significant association between paternal exposure to any immunosuppressive or biologic medication and risk of major congenital malformations. Specifically, no association was observed between exposure to thiopurines (RR, 1.12; 95% CI, 0.66–1.76), methotrexate (RR, 0.67; 95% CI, 0.21–1.55), TNFα antagonists (RR, 1.14; 95% CI, 0.81–1.57), and non-TNF-targeting biologic agents (RR, 1.75; 95% CI, 0.80–3.24) and risk of major congenital malformations. Exposure to combination therapy was also not associated with increased risk of major congenital malformations (5.6% prevalence of major congenital malformations; RR, 1.68; 95% CI, 0.9–2.82). No specific signals were observed for major cardiovascular congenital malformations with exposure to thiopurines (vs. unexposed: adjusted RR, 1.23; 95% CI, 0.52–2.48), methotrexate (adjusted RR, 0.48; 95% CI, 0.03–2.12), TNFα antagonists (adjusted RR, 1.28; 95% CI, 0.73–2.10) and non-TNF-targeting biologic agents (adjusted RR, 0.62; 95% CI, 0.03–2.74).

Sensitivity analysis: On limiting analysis to father-mother-newborn triads, similar results were observed (Table 2). Paternal exposure to thiopurines, methotrexate, TNFα antagonists and non-TNF-targeting biologic agents was not associated with increased risk of major congenital malformations after adjusting for paternal age and race, and maternal age, race, presence of immune-mediated inflammatory diseases, and multiple gestation. Paternal exposure to combination therapy in this cohort was also not associated with increased risk of major congenital malformations (adjusted RR, 1.43; 95% CI, 0.61–2.78).

By time period of birth, there was a slight increase in overall risk of major congenital malformations (2005–09, <2.5%; 2010–14, 3.5%; 2015–18, 4.7%), but no significant differences were observed in risk in fathers exposed vs. unexposed to immunosuppressive or biologic medications. Associations were stable on post-hoc subgroup analysis by age of father at conception (≤35y vs. >35y) and disease type (IBD vs. non-IBD) (Supplementary Table 3 and 4).

Secondary Outcomes

Preterm birth: Overall, 7.3% of newborns were born pre-term, with comparable prevalence in newborns born to fathers not exposed to immunosuppressive or biologic medications in the peri-conception period (7.3%) vs. those exposed to medications (7.4%). Table 3 details the prevalence of preterm birth by exposure type and reports unadjusted and adjusted risk by different paternal medication exposure type. There was no significant association between paternal exposure to any immunosuppressive or biologic medication and preterm birth. Specifically, no association was observed between exposure to thiopurines (adjusted RR, 1.12; 95% CI, 0.80–1.52), methotrexate (adjusted RR, 0.49; 95% CI, 0.20–0.98), TNFα antagonists (adjusted RR, 1.10; 95% CI, 0.87–1.37) and non-TNF-targeting biologic agents (adjusted RR, 0.72; 95% CI. 0.31–1.36) and risk of preterm birth. Exposure to combination therapy was also not associated with increased risk of preterm birth (7.5%

prevalence of preterm birth; adjusted RR, 1.02; 95% CI, 0.60–1.59). On limiting analysis to father-mother-newborn triads, similar results were observed (Table 3). By time period of birth, there was a slight decrease in overall risk of preterm birth (2005–09, 9.4%; 2010–14, 8.2%; 2015–18, 3.6%), but no significant differences were observed in risk in fathers exposed vs. unexposed to immunosuppressive or biologic medications.

Low birth weight: Overall, 4.3% newborns were low birth weight, with comparable prevalence in newborns born to fathers not exposed to immunosuppressive or biologic medications in the peri-conception period (4.2%) vs. those exposed to medications (4.4%). Table 4 details the prevalence of low birth weight by exposure type and unadjusted and adjusted risk by different paternal medication exposure type. There was no significant association between paternal exposure to any immunosuppressive or biologic medication and preterm birth. Specifically, no association was observed between exposure to thiopurines (adjusted RR, 1.15; 95% CI, 0.73–1.72), methotrexate (adjusted RR, 0.68; 95% CI, 0.25–1.46), TNFα antagonists (adjusted RR, 1.10; 95% CI, 0.81–1.47) and non-TNF-targeting biologic agents (adjusted RR, 0.70; 95% CI, 0.22–1.62) and risk of low birth weight. Exposure to combination therapy was also not associated with increased risk of low birth weight (5.1% prevalence of low birth weight; adjusted RR, 1.20; 95% CI, 0.63–2.06). On limiting analysis to father-mother-newborn triads, similar results were observed (Table 4). By time period of birth, there was a slight decrease in overall risk of preterm birth (2005–09, 5.8%; 2010–14, 5.0%; 2015–18, 1.6%), but no significant differences were observed in risk in fathers exposed vs. unexposed to immunosuppressive or biologic medications.

Associations between paternal exposure to specific medications and preterm birth and low birth weight were stable on post-hoc subgroup analysis by age of father at conception (≤35y vs. >35y) and disease type (IBD vs. non-IBD) (Supplementary Table 3 and 4).

DISCUSSION

While several studies have informed safety of maternal exposure to immunosuppressive and/or biologic agents on birth outcomes in patients with IMIDs, there has been limited assessment of the impact of paternal exposure to these medications on birth outcomes. In this large claims-based analysis with unique linkage of fathers and newborns (and mothers for approximately 2/3rd of cohort), we made several key observations on peri-conception exposure to immunosuppressive or biologic agents in expectant fathers with IMIDs on newborn outcomes. First, we confirmed prior observations reporting no increase in the risk of major congenital malformations, preterm birth or low birth weight with paternal exposure to conventional immunosuppressive agents like methotrexate or thiopurines, or to TNFα antagonists. Second, we observed no association between paternal exposure to non-TNF-targeting biologic agents and adverse neonatal outcomes. Overall, these findings are very reassuring to expectant fathers and mothers with IMIDs, that exposure of IMID-directed pharmacotherapy does not appear to increase the risk of major adverse birth outcomes. These findings fill an important evidence gap and support continuing pharmacotherapy without interruption in fathers planning conception.

Preclinical studies have suggested that immunosuppressive and biologic agents may impact male fertility and mediate teratogenicity. In mouse studies, mercaptopurine exposure has been associated with occult sperm damage and higher rates of embryonic resorption and spontaneous abortion.[23] Methotrexate has been associated with reversible oligospermia and altered spermatogenesis and cytotoxicity.[10] However, human studies on potential impact of paternal exposure to immunosuppressive and/or biologic agents have previously not observed any clinically meaningful difference in the risk of adverse neonatal outcomes. In a Danish nationwide cohort study, investigators found no increase in rate of adverse birth outcomes (congenital anomalies, preterm birth and small for gestational age) in children fathered by men exposed to thiopurines (n=699) or methotrexate (n=193), as compared to non-exposed controls.[24–26] Similarly, in a prospective study of 115 pregnancies after paternal exposure to thiopurines, there was no significant difference in rates of congenital anomalies, though rates of elective termination of pregnancy and spontaneous abortions were higher.[11] Our study confirms prior findings on the safety of paternal exposure to thiopurines and methotrexate in expectant fathers in the peri-conception period.

Data on safety of biologic agents in men wishing to conceive has been limited. In three studies totaling to <100 men exposed to TNF-α antagonists, no significant increase in congenital anomalies was observed.[13, 27, 28] In a Danish nationwide cohort study of 372 men exposed to TNF-α antagonists, offspring of men exposed to TNFα antagonists were 1.7 times as likely to be small for gestational age, though this was not statistically significant (95% CI, 0.94–3.09); no increased risk of congenital malformations or preterm birth was observed.[12] In this study with 1,082 expectant fathers exposed to TNF-α antagonists around conception, we found no increase in the likelihood of major congenital malformations, preterm birth and low birth weight.

Ours is one of the first studies evaluating birth outcomes with paternal exposure to non-TNF-targeting biologic agents, particularly ustekinumab and vedolizumab. Vedolizumab has not been associated with an impact on semen quality, which is the standard surrogate marker of male fertility.[29] There are no published data on the impact of ustekinumab on spermatogenesis and male fertility. Similar to TNF-α antagonists, we observed no increase in the risk of major congenital malformations, preterm birth and low birth weight. Maternal exposure to ustekinumab may be associated with a slightly higher risk of major congenital malformations as compared to TNF-α antagonists and vedolizumab in a systematic review.[30] However, the rate of major congenital malformations with ustekinumab exposure was 5%, similar to background risk of major malformations in unexposed women.

There are several unique strengths of our analysis, including: (a) innovative use of an administrative claims database to identify linked father-newborn dyads, and a subset of father-mother-newborn triads, (b) assessment of medication exposure by examining refills (and infusions for infliximab and vedolizumab) around conception, rather than relying only on prescriptions, and (c) using a validated claims-based approach to identify major congenital malformations and other adverse birth outcomes with high positive predictive value. Rates of major congenital malformations, preterm birth and low birth weight were very similar to rates observed in the general population using a variety of outcome ascertainment approaches.[31, 32] However, our study also had important limitations. First,

despite the high positive predictive value of our claims-based approach to identify major congenital malformations and other adverse birth outcomes, we may have misclassified some outcomes; however, we believe any misclassification would be non-differential. Second, we did not evaluate the effect of paternal IMID disease activity, and maternal drug exposures on risk of adverse birth outcomes; however, these are not true confounders since these factors do not simultaneously affect (paternal) exposure and (neonatal) outcomes. We focused only on birth outcomes on live births; we could not examine the potential impact of paternal exposure to pharmacotherapy around conception on risk of stillbirth, abortions or fertility. We were unable to account for exposure to smoking or alcohol in fathers and mothers. Our cohort had limited ethnic diversity. Finally, we recognize that dispensed medication may not necessarily equate medication intake at time of conception.

In summary, in large claims-based analysis of 7,453 expectant fathers with IMIDs linked to newborns, we confirmed that exposure to conventional immunosuppressive agents like methotrexate or thiopurines, or to biologic agents including TNFα antagonists and non-TNF-targeting biologic agents in the conception period, does not increase the risk of major congenital malformations, preterm birth and low birth weight. These findings are reassuring, and fill an important evidence gap on male-mediated teratogenicity. Future studies evaluating the impact of paternal and maternal exposure to non-TNF-targeting biologic agents and targeted small molecule inhibitors on newborn outcomes are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Gallinger ZR, Rumman A, Nguyen GC. Perceptions and Attitudes Towards Medication Adherence during Pregnancy in Inflammatory Bowel Disease. J Crohns Colitis 2016;10:892–7. [PubMed: 26896087]
2. Selinger CP, Eaden J, Selby W, et al. Inflammatory bowel disease and pregnancy: lack of knowledge is associated with negative views. J Crohns Colitis 2013;7:e206–13. [PubMed: 23040449]
3. Lichtenstein GR, Feagan BG, Mahadevan U, et al. Pregnancy Outcomes Reported During the 13-Year TREAT Registry: A Descriptive Report. Am J Gastroenterol 2018;113:1678–1688. [PubMed: 30022113]
4. Luu M, Benzenine E, Doret M, et al. Continuous Anti-TNFalpha Use Throughout Pregnancy: Possible Complications For the Mother But Not for the Fetus. A Retrospective Cohort on the French National Health Insurance Database (EVASION). Am J Gastroenterol 2018;113:1669–1677. [PubMed: 29961771]
5. Mahadevan U, McConnell RA, Chambers CD. Drug Safety and Risk of Adverse Outcomes for Pregnant Patients With Inflammatory Bowel Disease. Gastroenterology 2017;152:451–462 e2. [PubMed: 27769809]
6. Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy. Gastroenterology 2016;150:734–757 e1. [PubMed: 26688268]
7. Micu MC, Ostensen M, Villiger PM, et al. Paternal exposure to antirheumatic drugs-What physicians should know: Review of the literature. Semin Arthritis Rheum 2018;48:343–355. [PubMed: 29502800]
8. Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: A systematic review and analysis of published evidence. Semin Arthritis Rheum 2018.
9. Hammami MB, Mahadevan U. Men With Inflammatory Bowel Disease: Sexual Function, Fertility, Medication Safety, and Prostate Cancer. Am J Gastroenterol 2020;115:526–534. [PubMed: 32022719]
10. Saxena AK, Dhungel S, Bhattacharya S, et al. Effect of chronic low dose of methotrexate on cellular proliferation during spermatogenesis in rats. Arch Androl 2004;50:33–5. [PubMed: 14660169]
11. Hoeltzenbein M, Weber-Schoendorfer C, Borisch C, et al. Pregnancy outcome after paternal exposure to azathioprine/6-mercaptopurine. Reprod Toxicol 2012;34:364–9. [PubMed: 22609326]

12. Larsen MD, Friedman S, Magnussen B, et al. Birth Outcomes in Children Fathered by Men Treated with Anti-TNF-alpha Agents Before Conception. Am J Gastroenterol 2016;111:1608–1613. [PubMed: 27619836]
13. Wallenius M, Lie E, Daltveit AK, et al. No excess risks in offspring with paternal preconception exposure to disease-modifying antirheumatic drugs. Arthritis Rheumatol 2015;67:296–301. [PubMed: 25418443]
14. Evans M. Healthcare data mining. OptumLabs collaborative begins to offer insights about what works. Mod Healthc 2015;45:24–6.
15. Anderson TS, Xu E, Whitaker E, et al. A systematic review of methods for determining cross-sectional active medications using pharmacy databases. Pharmacoepidemiol Drug Saf 2019;28:403–421. [PubMed: 30761662]
16. Margulis AV, Setoguchi S, Mittleman MA, et al. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf 2013;22:16–24. [PubMed: 22550030]
17. Mosesso P, Palitti F. The genetic toxicology of 6-mercaptopurine. Mutat Res 1993;296:279–94. [PubMed: 7680107]
18. Palmsten K, Huybrechts KF, Kowal MK, et al. Validity of maternal and infant outcomes within nationwide Medicaid data. Pharmacoepidemiol Drug Saf 2014;23:646–55. [PubMed: 24740606]
19. Cooper WO, Hernandez-Diaz S, Gideon P, et al. Positive predictive value of computerized records for major congenital malformations. Pharmacoepidemiol Drug Saf 2008;17:455–60. [PubMed: 18081215]
20. Fan H, Gilbert R, O'Callaghan F, et al. Associations between macrolide antibiotics prescribing during pregnancy and adverse child outcomes in the UK: population based cohort study. BMJ 2020;368:m331. [PubMed: 32075790]
21. Huybrechts KF, Bateman BT, Pawar A, et al. Maternal and fetal outcomes following exposure to duloxetine in pregnancy: cohort study. BMJ 2020;368:m237. [PubMed: 32075794]
22. Palmsten K, Bandoli G, Watkins J, et al. Oral Corticosteroids and Risk of Preterm Birth in the California Medicaid Program. J Allergy Clin Immunol Pract 2020.
23. Ligumsky M, Badaan S, Lewis H, et al. Effects of 6-mercaptopurine treatment on sperm production and reproductive performance: a study in male mice. Scand J Gastroenterol 2005;40:444–9. [PubMed: 16028439]
24. Friedman S, Larsen MD, Magnussen B, et al. Paternal use of azathioprine/6-mercaptopurine or methotrexate within 3 months before conception and long-term health outcomes in the offspring-A nationwide cohort study. Reprod Toxicol 2017;73:196–200. [PubMed: 28844800]
25. Winter RW, Larsen MD, Magnussen B, et al. Birth outcomes after preconception paternal exposure to methotrexate: A nationwide cohort study. Reprod Toxicol 2017;74:219–223. [PubMed: 29080667]
26. Norgard BM, Magnussen B, Larsen MD, et al. Reassuring results on birth outcomes in children fathered by men treated with azathioprine/6-mercaptopurine within 3 months before conception: a nationwide cohort study. Gut 2017;66:1761–1766. [PubMed: 27456154]
27. Eck LK, Jensen TB, Mastrogiannis D, et al. Risk of Adverse Pregnancy Outcome After Paternal Exposure to Methotrexate Within 90 Days Before Pregnancy. Obstet Gynecol 2017;129:707–714. [PubMed: 28277353]
28. Weber-Schoendorfer C, Hoeltzenbein M, Wacker E, et al. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. Rheumatology (Oxford) 2014;53:757–63. [PubMed: 24369411]
29. Grosen A, Bungum M, Hvas CL, et al. Vedolizumab Does Not Impair Sperm DNA Integrity in Men With Inflammatory Bowel Disease. Gastroenterology 2019;156:2342–2344. [PubMed: 30849317]
30. Nielsen OH GJ, Juhl CB, Streett SE, Maxwell C. Biologics for Inflammatory Bowel Disease and their Safety in Pregnancy: A Systematic Review and Meta-analysis. Clin Gastroenterology Hepatol 2020.
31. Mai CT, Isenburg JL, Canfield MA, et al. National population-based estimates for major birth defects, 2010–2014. Birth Defects Res 2019;111:1420–1435. [PubMed: 31580536]

32. Martin JA, Hamilton BE, Osterman MJK, et al. Births: Final Data for 2017. Natl Vital Stat Rep 2018;67:1–50.

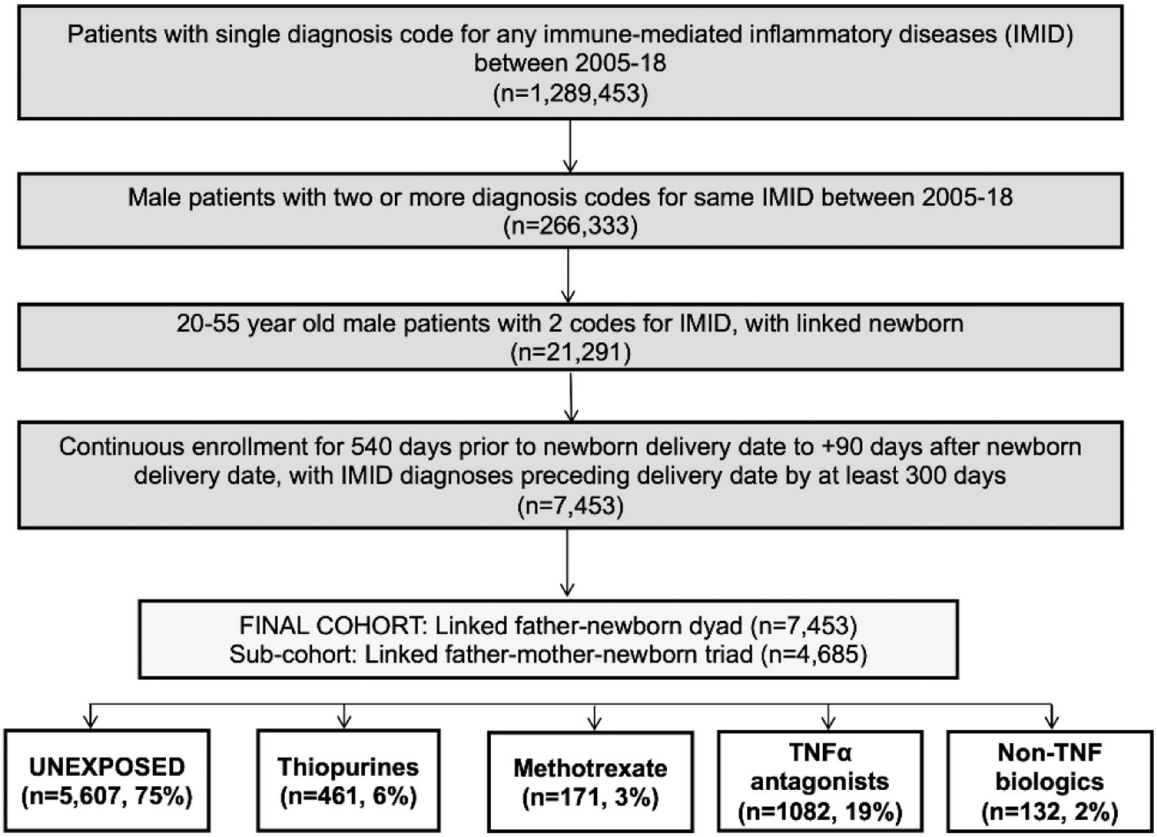

Figure 1.
Patient selection flowchart

Table 1.

Baseline characteristics of fathers in all linked father-newborn dyads.

Paternal characteristics	Full Cohort (N=7453)	Unexposed (N=5607)	Immunomodulators* (N=632)	TNFα antagonists (N=1082)	Non-TNFα biologics (N=132)
Age at conception, mean (SD)	35.8 (5.6)	35.9 (5.6)	Thiopurines: 35.1 (5.6) Methotrexate: 37.0 (7.0)	35.3 (5.2)	36.7 (5.4)
Race					
• White	5126 (68.8%)	3801 (67.8%)	457 (72.3%)	775 (71.6%)	93 (70.5%)
• Non-White	2327 (31.2%)	1806 (32.2%)	175 (27.7%)	307 (28.4%)	39 (30.0%)
Type of IMID					
• IBD	3075 (41.3%)	1984 (35.4%)	>453 (>71.7%)*	<619 (<57.2%)*	>19 (>14.4%)*
• RA	608 (8.2%)	403 (7.2%)	88 (13.9%)	105 (9.7%)	12 (9.1%)
• AS	566 (7.6%)	442 (7.9%)	<11 (<1.7%)*	>102 (>9.4%)*	<11 (<8.3%)*
• Ps/PsA	3204 (43%)	2778 (49.5%)	80 (12.7%)	256 (23.7%)	90 (68.2%)

[Abbreviations: AS=Ankylosing Spondylitis, IBD=Inflammatory Bowel Disease, Ps/PsA=Psoriasis/Psoriatic arthritis, RA=Rheumatoid Arthritis]

*Values suppressed intentionally to avoid back-counting small cell size per OptumLabs policy. To maintain the de-identified nature of the Optum Labs Data Warehouse, all summary tables or summary charts must adhere to cell size suppression policy set by CMS (Centers' for Medicare and Medicaid Services) for reporting cell size. Based on this policy, no cell value less than 11 may be displayed for patient data. No cell can be reported that allows a value of 1 to 10 to be derived from other reported cells or information.

Table 2.

Risk of **major congenital malformations** by paternal medication exposure status in the peri-conception period in father-newborn dyads: (1) unadjusted, (2) adjusted for paternal age and race (model 1), and (3) adjusted for paternal age and race, and maternal age, race, presence of immune-mediated inflammatory diseases, and multiple gestation in subset of father-mother-newborn linked triads (model 2)

Exposure	Major congenital malformations	Unadjusted relative risk (95% CI)	Model 1; Adjusted RR (and 95% CI)	Model 2; Adjusted RR (and 95% CI)
Unexposed	190 (3.4%)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Any immunosuppressive or biologic medications	70 (3.8%)	1.12 (0.85–1.45)	1.13 (0.86–1.47)	1.05 (0.73–1.48)
Methotrexate	<11 (<6.4%) *	NR *	0.67 (0.21–1.55)	0.29 (0.02–1.27)
Thiopurines	17 (3.7%)	1.09 (0.64–1.71)	1.12 (0.66–1.76)	1.40 (0.78–2.31)
TNFα antagonists	>31 (>2.9%) *	NR *	1.14 (0.81–1.57)	0.91 (0.56–1.40)
Non-TNFα biologics	<11 (<8.3%) *	NR *	1.75 (0.80–3.24)	2.07 (0.74–4.38)
Combination therapy (biologics + thiopurines or methotrexate)	12 (5.6%)	1.65 (0.89–2.77)	1.68 (0.90–2.82)	1.43 (0.61–2.78)

* Values suppressed intentionally, and unadjusted relative risk not reported, to avoid back-counting small cell size per OptumLabs policy.

Table 3.

Risk of **preterm birth** by paternal medication exposure status in the peri-conception period in father-newborn dyads: (1) unadjusted, (2) adjusted for paternal age and race (model 1), and (3) adjusted for paternal age and race, and maternal age, race, presence of immune-mediated inflammatory diseases, and multiple gestation in subset of father-mother-newborn linked triads (model 2)

Exposure	Preterm birth	Unadjusted relative risk (95% CI)	Model 1; Adjusted RR (and 95% CI)	Model 2; Adjusted RR (and 95% CI)
Unexposed	407 (7.3%)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Any immunosuppressive or biologic medications	136 (7.4%)	1.01 (0.84–1.22)	1.02 (0.84–1.23)	1.00 (0.77–1.28)
Methotrexate	<11 (<6.4%) *	NR *	0.49 (0.20–0.98)	0.32 (0.05–0.99)
Thiopurines	37 (8%)	1.11 (0.79–1.50)	1.12 (0.80–1.52)	0.77 (0.45–1.23)
TNFα antagonists	>77 (>7.1%) *	NR *	1.10 (0.87–1.37)	1.22 (0.90–1.61)
Non-TNFα biologics	<11 (<8.3%) *	NR *	0.72 (0.31–1.36)	0.76 (0.19–1.90)
Combination therapy (biologics + thiopurines or methotrexate)	16 (7.5%)	1.03 (0.61–1.60)	1.02 (0.60–1.59)	0.94 (0.44–1.71)

* Values suppressed intentionally, and unadjusted relative risk not reported, to avoid back-counting small cell size per OptumLabs policy

Table 4.

Risk of **low birth weight** by paternal medication exposure status in the peri-conception period in father-newborn dyads: (1) unadjusted, (2) adjusted for paternal age and race (model 1), and (3) adjusted for paternal age and race, and maternal age, race, presence of immune-mediated inflammatory diseases, and multiple gestation in subset of father-mother-newborn linked triads (model 2)

Exposure	Low birth weight	Unadjusted relative risk (95% CI)	Model 1; Adjusted RR (and 95% CI)	Model 2; Adjusted RR (and 95% CI)
Unexposed	238 (4.2%)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Any immunosuppressive or biologic medications	81 (4.4%)	1.03 (0.80–1.31)	1.05 (0.81–1.34)	0.98 (0.68–1.37)
Methotrexate	<11 (<6.4%) *	NR *	0.68 (0.25–1.46)	0.59 (0.10–1.89)
Thiopurines	22 (4.8%)	1.12 (0.71–1.68)	1.15 (0.73–1.72)	0.84 (0.41–1.54)
TNFα antagonists	>37 (>3.4%) *	NR *	1.10 (0.81–1.47)	1.12 (0.73–1.66)
Non-TNFα biologics	<11 (<8.3%) *	NR *	0.70 (0.22–1.62)	0.53 (0.03–2.26)
Combination therapy (biologics + thiopurines or methotrexate)	11 (5.1%)	1.21 (0.63–2.07)	1.20 (0.63–2.06)	1.20 (0.46–2.50)

* Values suppressed intentionally, and unadjusted relative risk not reported, to avoid back-counting small cell size per OptumLabs policy.