Clinical Drug Investigation (2023) 43:109–117
https://doi.org/10.1007/s40261-022-01227-6

ORIGINAL RESEARCH ARTICLE

Use of Methotrexate in Girls and Women of Childbearing Age, Occurrence of Methotrexate-Exposed Pregnancies and Their Outcomes in Germany: A Claims Data Analysis

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Accepted: 14 November 2022 / Published online: 21 December 2022

Abstract

Background and Objective Methotrexate should be withdrawn before pregnancy because of its teratogenic potential. We aimed to describe the use of methotrexate in women of childbearing age in Germany and the occurrence and outcomes of pregnancies exposed to methotrexate.

Methods Using the German Pharmacoepidemiological Research Database (GePaRD, covering ~ 20% of the German population), we determined the age-specific and age-standardized prevalence of methotrexate use for each year between 2004 and 2019 among women aged 13–49 years (cross-sectional analyses). In a cohort analysis, we assessed the number and outcomes of pregnancies exposed to methotrexate in the critical time window. Exposure was defined as a dispensation overlapping with the onset of pregnancy or a dispensation in the first 8 weeks of pregnancy. For children born from exposed pregnancies, the mother's and children's data were linked and the occurrence of malformations was assessed by reviewing all available data of these children.

Results The age-standardized prevalence of methotrexate use per 1000 females increased from 1.5 in 2004 to 2.3 in 2019, i.e., by 52%. Overall, we identified 184 pregnancies exposed to methotrexate. Of these, 53% ended in a live birth (21% preterm) and 11% in an induced abortion. Among 81 live-born children linked to their mothers, five children (6%) had relevant malformations including congenital heart defects and musculoskeletal malformations.

Conclusions In Germany, the use of methotrexate in women of childbearing age has substantially increased since 2004. Despite the known teratogenic effect, there was a considerable number of exposed pregnancies. Also, malformations likely associated with methotrexate and thus avoidable were observed.

Key Points

Methotrexate use in women of childbearing age has increased by 52% since 2004.

A considerable number of pregnancies exposed to methotrexate and malformations in exposed children were observed.

1 Introduction

Methotrexate is used for various autoimmune disorders such as rheumatoid arthritis and Crohn's disease [1], i.e., disorders that also affect girls and women of childbearing age [2, 3]. Furthermore, it is used for the treatment of malignancies

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and the termination of ectopic pregnancies [4]. Methotrexate is a known teratogen and particularly in high doses—as used for the treatment of cancer and for inducing elective abortion—it has been associated with the 'fetal methotrexate syndrome' (also known as 'fetal aminopterin syndrome') including multiple malformations of the skull and limbs, cardiovascular and central nervous system anomalies, growth deficiency, and mental retardation [4–9]. The risk of malformations and fetal death under a low-dose treatment regimen, as used for rheumatoid arthritis, is supposed to be lower, but several studies show unambiguous results regarding the risks of methotrexate to the unborn child [5, 7, 10–12].

As methotrexate can show a delayed plasma elimination [13], it is recommended to withdraw the drug sufficiently before the beginning of pregnancy, though the recommended time interval varies between 1 and 3 [14] and up to 6 months before a planned pregnancy [15]. Monitoring the use of methotrexate in girls/women of childbearing age is thus of public health relevance, and even more so as pregnancies often occur unintendedly [16]. However, studies investigating the prevalence of methotrexate use in this population, time trends, and pregnancies occurring in women exposed to methotrexate are scarce. In a recent study from Germany, restricted to data from 2018 and data from one German statutory health insurance provider, the prevalence of methotrexate use (at least one dispensation in 2018) in girls/women of childbearing age was 262 per 100,000 for rheumatoid arthritis, and 10 per 100,000 for the oncologic indication. Three pregnancies with methotrexate dispensation during the first trimester were observed in this study. However, only deliveries in hospitals with at least 13 weeks of pregnancy were considered, and pregnancy outcomes such as induced abortions were not captured. Furthermore, there was no linkage of mothers and children to investigate potential malformations in the offspring [17].

To shed further light on this topic, we aimed to (i) investigate the use of methotrexate among girls and women of childbearing age in Germany over time, (ii) describe the specialty of prescribing physicians, and (iii) characterize the occurrence and the outcomes of pregnancies exposed to methotrexate, including the potential presence of malformations among exposed children.

2 Methods

2.1 Data Source

We used the German Pharmacoepidemiological Research Database (GePaRD), which is based on claims data from four statutory health insurance providers in Germany and currently includes information on approximately 25 million individuals who have been insured with one of the participating providers since 2004 or later. In addition to demographic data, GePaRD contains information on drug dispensations as well as outpatient (i.e., from general practitioners and specialists) and inpatient services and diagnoses. Per data year, there is information on approximately 20% of the general population and all geographical regions of Germany are represented [18, 19].

In GePaRD, the Anatomical Therapeutic Chemical (ATC) code is used to identify drugs dispensed in the outpatient setting. The drugs relevant for this study were identified based on the ATC codes for methotrexate L04AX03 and M01CX01. Diagnoses in GePaRD are coded according to the International Classification of Diseases 10th Revision, German Modification (ICD-10-GM). For research on drug utilization and safety during pregnancy, algorithms to identify and classify pregnancy outcomes [20, 21], to estimate the beginning of pregnancy [22], and to link mothers with their newborns [23] have been developed for GePaRD.

2.2 Study Design and Study Population

2.2.1 Prevalence of Use Among Girls/Women of Childbearing Age

To determine the prevalence of use for methotrexate over time, we conducted year-wise cross-sectional analyses from 2004 to 2019. For each calendar year, we included all girls/women in the numerator who had at least one dispensation of methotrexate, were aged between 13 and 49 years in the respective year, and were actively insured on 30 June of that year. In the denominator, we included all girls/women aged between 13 and 49 years in the respective year and actively insured on 30 June of that year.

2.2.2 Identification of Exposed Pregnancies

Using the algorithm for pregnancy outcomes, we identified pregnancies ending between 2004 and 2019 and occurring among girls/women aged 13–49 years at pregnancy onset. A pregnancy was classified as exposed to methotrexate during early pregnancy if the exposure window assigned to the last dispensation before pregnancy overlapped with the first day of pregnancy or if there was a dispensation in the first 8 weeks of pregnancy. The latter time period was restricted to 8 weeks rather than 12 weeks because it seems thus more likely that the dispensed drug was actually used during the first trimester. The exposure window was defined as the dispensation date plus the number of defined daily doses (DDDs) in the package or in the injection. In a sensitivity analysis, we further extended the exposure window by 3 months to take into account delayed elimination because of pharmacokinetic properties [13]. In order to assess exposure status, continuous health insurance of the mother before the

onset of pregnancy was required for at least the number of days covered by the largest available package of methotrexate plus, for the sensitivity analysis, the time period required for extension of the exposure window.

Given that there may partly be no outcome recorded for incomplete pregnancies in claims data (e.g., spontaneous abortions not requiring medical treatment, induced abortions without a medical indication), which would therefore remain undetected if only applying the outcome algorithm, we also searched for this type of incomplete pregnancy. To qualify for this category, there had to be at least a code indicating the expected delivery date and another indicator of a pregnancy (e.g., a pregnancy-related examination) within a plausible time interval after the onset of pregnancy. We determined the exposure status of these pregnancies as described above. Pregnancies still ongoing at the end of observation in GePaRD were included in the analysis determining the number of exposed pregnancies but not in the description of the distribution of pregnancy outcomes because information on their outcomes was not available yet.

2.2.3 Exploration of Potential Malformations Among Exposed Children

For exposed pregnancies ending in a live birth, we applied the algorithm linking mothers with their newborns [23] to explore potential congenital malformations in the children. Among linked children, we identified those with any malformation code (ICD-10-GM Q00–Q99) occurring up to 1 year after birth. Subsequently, profiles were reviewed taking into account all available information in GePaRD on these children until the end of their observation period in GePaRD (end of insurance, death or end of the study period, i.e., 31 December, 2019) in order to verify the occurrence of malformations. This patient profile review was performed independently by two reviewers. In this review, we considered the diagnoses in the context of the patients' history (e.g., gestational age at birth or chromosomal abnormalities as potential alternative explanations for malformations) and took into account information supporting or confirming the presence of malformations (e.g., whether it was coded in the inpatient setting, whether there were repeated diagnoses or specific treatments/surveillance examinations). Disagreement between the reviewers regarding the certainty of malformations was solved by consensus.

2.3 Data Analysis

In the cross-sectional analyses, we determined age-specific and age-standardized prevalence for each year, using the age distribution of the German female population on 31 December, 2019 as the reference. We used 5-year age groups (except for age group 13–15 years), as this was a good compromise between the sample size and homogeneity within groups. To describe the prescribing physicians, we considered all methotrexate dispensations in the respective year among included girls/women and assigned the specialty of the prescribing physician based on the information contained in the individual physician number [24].

As to pregnancies, we determined the number of those classified as exposed overall and described the mothers' age at pregnancy onset as well as the pregnancy outcomes.

The distribution of continuous variables was summarized as mean and median [interquartile range], while categorical variables were expressed as frequency counts (percentages). We conducted all statistical analyses using the software SAS version 9.4, SAS Institute Inc., Cary, North Carolina, USA.

3 Results

3.1 Prevalence of Use Among Girls/Women of Childbearing Age

Overall, the number of girls and women of childbearing age with at least one dispensation of methotrexate ranged from 5418 to 9768 per year. The age-specific and age-standardized prevalence of use per 1000 girls/women is displayed in Fig. 1. The age-standardized rate increased by 52% during the study period, from 1.51 in 2004 to 2.30 in 2019. In relative terms, the highest increase during the study period was observed in the age groups 13–15 years (0.44/1000 in 2004 vs 1.01/1000 in 2019, i.e., increase by the factor 2.3), 16–20 years (0.52 vs 1.04, i.e., increase by the factor 2.0), and 21–25 years (0.56 vs 1.10 i.e., increase by the factor 2.0), whereas in absolute terms, the highest increase occurred in the age group 46–49 years (3.57 vs 5.42). The proportion of girls/women treated with methotrexate ≤40 years increased over time, it ranged between 39.5% in 2008 and 49.2% in 2019 (see Electronic Supplementary Material [ESM]). Table 1 shows, for each year during the study period, the specialty of the prescribing physician for all prescriptions filled by girls or women of childbearing age. The proportion of methotrexate prescriptions issued by rheumatologists increased during the study period, from 34% in 2009 to 46% in 2019, whereas the proportion issued by general practitioners and specialists for internal medicine decreased in the same time interval (from 25% in 2009 to 13% in 2019 and from 21% in 2009 to 14% in 2019, respectively).

3.2 Characterization of Exposed Pregnancies

Overall, we identified 184 pregnancies classified as exposed during early pregnancy, occurring in 176 women (a flow chart is provided in the ESM). The median age of these women was 33 years at pregnancy onset. The distribution of

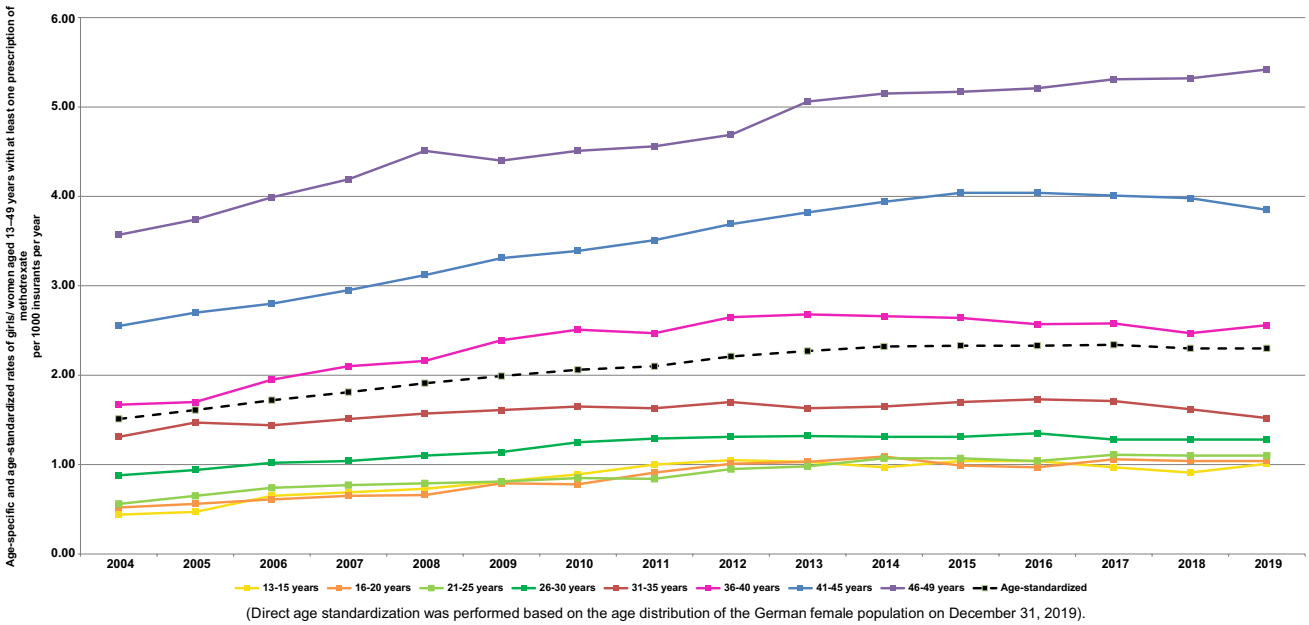

Fig. 1 Age-specific and age-standardized prevalence of methotrexate use per 1000 girls/women aged 13–49 years and calendar year

these pregnancies according to the year of pregnancy onset is shown in the ESM. One hundred and ten pregnancies were defined as exposed because of dispensations overlapping with pregnancy onset, 57 had a dispensation in the first 8 weeks of pregnancy, and for 17 pregnancies, both held true. For exposed pregnancies that were no longer ongoing at the end of the observation period ($N = 168$), the distribution of pregnancy outcomes is summarized in Table 2. A total of 53% of exposed pregnancies ($n = 89$) ended in a live birth, thereof 21% ($n = 19$) classified as preterm births, 11% ($n = 19$) in an induced abortion, and 4% in a spontaneous abortion ($n = 6$). For 46 pregnancies (27%), no outcome was recorded (i.e., they are assumed to also be abortions). In sensitivity analyses extending the exposure window by 3 months before pregnancy, the number of exposed pregnancies increased to 385 and was thus twice as high as in the base-case analysis.

3.3 Characterization of Exposed Children

For 81 out of the 89 live-born children exposed during pregnancy, the mother's and baby's data could be linked. Of these, five children (6%) had malformations that were considered as certain based on profile reviewing: two children had a defect of the heart; one of these children also had a musculoskeletal malformation. Further, two children were affected by malformations of the musculoskeletal system and one child had a nervous system anomaly (see Fig. 2).

4 Discussion

In this population-based study covering 20% of the German population, we found that the age-standardized prevalence of methotrexate use among girls and women of childbearing age increased by more than 50% between 2004 and 2019 in Germany. This increase was particularly pronounced in girls/women up to the age of 25 years. Across the whole study period, between 40% and 49% of users were aged ≤ 40 years, i.e., in age groups in which pregnancies typically occur. Overall, we identified 184 pregnancies exposed to methotrexate at the onset of or in early pregnancy. About half of these pregnancies ended in a live birth and among live births, about 6% had malformations. According to sensitivity analyses taking into account the delayed elimination of methotrexate, the number of exposed pregnancies may even be twice as high because methotrexate was stopped too shortly before pregnancy, i.e., pregnancy started prior to sufficient plasma elimination of methotrexate.

There is hardly any other study to which we can compare our findings. A study analyzing claims data from one German statutory health insurance provider for the year 2018 did not report the age-standardized prevalence of methotrexate use but only the overall number of methotrexate users among all girls/women aged 13–49 years ($N = 5173$) [17]. This yields a crude prevalence of 262 per 100,000, which is thus not very different from the age-standardized prevalence of 230 per 100,000 observed in our study. Time trends of methotrexate use among women of childbearing age were not analyzed in this study nor, to the best of our

Table 1 Specialty of physicians prescribing methotrexate to girls/women of childbearing age in the respective study year[a]

Specialty of prescribing physician	Study year															
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	N = 14,242	*N* = 15,499	*N* = 17,887	*N* = 19,091	*N* = 20,099	*N* = 22,277	*N* = 23,130	*N* = 23,170	*N* = 25,975	*N* = 27,627	*N* = 28,107	*N* = 28,331	*N* = 27,909	*N* = 27,476	*N* = 26,290	*N* = 25,736
Specialist for internal medicine/rheumatology[b]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3175 (15.8%)	7640 (34.3%)	8934 (38.6%)	9157 (39.5%)	10,413 (40.1%)	11,053 (40.0%)	11,290 (40.2%)	11,842 (41.8%)	11,926 (42.7%)	11,929 (43.4%)	11,558 (44.0%)	11,888 (46.2%)
Specialist for internal medicine	7491 (52.6%)	8198 (52.9%)	9483 (53.0%)	10,419 (54.6%)	7538 (37.5%)	4729 (21.2%)	4484 (19.4%)	4276 (18.5%)	4699 (18.1%)	4762 (17.2%)	4736 (16.8%)	4520 (16.0%)	4439 (15.9%)	4263 (15.5%)	4117 (15.7%)	3674 (14.3%)
General practitioner	4517 (31.7%)	4820 (31.1%)	5195 (29.0%)	5200 (27.2%)	5263 (26.2%)	5535 (24.8%)	5058 (21.9%)	4922 (21.2%)	5282 (20.3%)	5296 (19.2%)	5154 (18.3%)	5089 (18.0%)	4636 (16.6%)	4190 (15.2%)	3758 (14.3%)	3393 (13.2%)
Dermatologist	303 (2.1%)	344 (2.2%)	412 (2.3%)	537 (2.8%)	609 (3.0%)	686 (3.1%)	812 (3.5%)	998 (4.3%)	1275 (4.9%)	1450 (5.2%)	1608 (5.7%)	1604 (5.7%)	1685 (6.0%)	2019 (7.3%)	1901 (7.2%)	1734 (6.7%)
Others	1889 (13.3%)	2101 (13.6%)	2751 (15.4%)	2908 (15.2%)	2901 (14.4%)	2490 (11.2%)	2207 (9.5%)	2316 (10%)	2469 (9.5%)	2837 (10.3%)	3091 (11%)	3008 (10.6%)	2884 (10.3%)	2821 (10.3%)	2701 (10.3%)	2797 (10.9%)
Assessment of specialty not possible	42 (0.3%)	36 (0.2%)	46 (0.3%)	27 (0.1%)	613 (3.0%)	1197 (5.4%)	1635 (7.1%)	1501 (6.5%)	1837 (7.1%)	2229 (8.1%)	2228 (7.9%)	2268 (8.0%)	2339 (8.4%)	2254 (8.2%)	2255 (8.6%)	2250 (8.7%)

[a]In 2008, the lifelong physician number was introduced that includes more detailed information on the specialty of the respective physician than the number used before. Therefore, e.g., rheumatologists can only be identified since mid-2008

[b]Exemplified by 2019, we also determined the number of girls/women with at least one dispensation prescribed by a rheumatologist. This proportion was 54%, i.e., higher than the proportion of prescriptions issued by a rheumatologist, which may indicate rheumatologists partly only initiate therapy that is then continued by a general practitioner or another specialty

Table 2 Distribution of pregnancy outcomes in pregnancies exposed to methotrexate in early pregnancy ($N = 168$)[a]

Outcome of exposed pregnancies	*n* (%)
Live births	89 (52.98)
Thereof preterm birth, *n* (% of live births)	19 (21.35)
Still birth	0 (0.00)
Induced abortion	19 (11.31)
Ectopic pregnancy or molar pregnancy	8 (4.76)
Spontaneous abortion	6 (3.57)
No pregnancy outcome was recorded[b]	46 (27.38)

[a]Pregnancies that were still ongoing at the end of the observation period are not listed here as the outcome could not be determined yet (applied to 16 pregnancies)

[b]There were clear indicators of a pregnancy but no outcome was recorded. It can be assumed that these pregnancies ended in a spontaneous abortion not requiring medical care or an induced abortion not reimbursed by the health insurance

knowledge, in any other study. We can therefore only compare our findings on time trends to a data source reporting, for each year, the total number of DDDs dispensed to all persons with statutory health insurance in Germany (i.e., no denominator/prevalence estimate, no restriction to girls/women of childbearing age). Even though comparability is limited, this report confirms a substantial increase in the use of methotrexate for the ATC code M01CX01 between 2011 and 2019 (2011: 52 million dispensed DDDs [25]; 2019: 83 million dispensed DDDs [26]), and it also increased for the oncological ATC code [27]. The increase in the prevalence of methotrexate use may have different reasons. First, the prevalence of the autoimmune diseases treated with methotrexate has increased [3, 28]; second, it may have been a stepwise process until changes in guidelines were fully adopted in the real-world setting. In rheumatoid arthritis, for example, methotrexate has been recommended as part of the initial treatment strategy for patients with active rheumatoid arthritis and been considered an anchor drug due to its efficacy and long-term safety [29–31] for many years, while it was used only sporadically until the mid-1980s. A study from Germany conducting annual cross-sectional analyses among 38,723 outpatients with rheumatoid arthritis showed that in 2007, 56% of patients were treated with methotrexate [32], while for several other countries (e.g., Denmark, Norway, Brazil) higher proportions were reported in the 2000s [33].

Irrespective of the reasons underlying the increased use of methotrexate in girls/women of childbearing age, this trend deserves attention due to the teratogenic potential of this drug. For regulatory agencies, it is important to know which kinds of physicians are relevant regarding the communication of risks. Our study suggests that the importance of rheumatologists as physicians prescribing methotrexate has substantially increased in recent years (46% of all dispensations in 2019). The high proportion of rheumatologists is also consistent with the recommendation that rheumatologists should primarily care for patients with rheumatoid arthritis and also for musculoskeletal manifestations in patients with psoriatic arthritis [29–31, 34]. However, because of the heterogeneity of indications, other specialties as well as general practitioners are relevant target groups. Regarding psoriatic arthritis, guidelines recommend considering methotrexate at an early stage of the disease [34]. In 2019, 7% of dispensations of methotrexate were issued by dermatologists. The use of methotrexate is also recommended in Crohn's disease but only if azathioprine or 6-mercaptopurine is not tolerated [35], which may explain part of the dispensations issued by specialists of internal medicine other than rheumatologists.

Our analyses on the occurrence of pregnancies exposed to methotrexate indeed indicate that there may be a need to further increase the awareness of the risks of methotrexate among physicians who prescribe this drug to girls/women of childbearing age, also with respect to the delayed plasma elimination. In our sample covering 20% of the German population, we identified 184 pregnancies exposed to methotrexate in the critical time window, i.e., it can be estimated that there were 920 such pregnancies in the whole of Germany between 2004 and 2019; taking into account the delayed plasma elimination of methotrexate, there were 385 exposed pregnancies, corresponding to an estimated number of 1925 pregnancies throughout Germany. The finding that 6% of live-born children exposed to methotrexate in early pregnancy showed a malformation confirms the known risk of this drug to the unborn child. Moreover, the fact that for 11% of exposed pregnancies in our study an induced abortion was coded, as compared to 3.6% if all pregnancies in GePaRD are considered [21], might partly be due to in utero diagnoses or suspicions of malformations.

A specific strength of our study is the large claims database that has been shown to be representative of persons with statutory health insurance in Germany in terms of drug dispensations [36]. The available data allowed us to assess trends in methotrexate dispensations over a 15-year period. Since we used claims data, our analysis was not affected by recall or non-responder bias. Additionally, the sophisticated methods we developed for GePaRD (i) to identify pregnancy outcomes [21], which was further optimized to capture incomplete pregnancies, (ii) to link mothers' and babies' data [23], and (iii) to estimate the beginning of pregnancy predominantly based on the estimated date of delivery [22], which is expected to minimize the misclassification of gestational age, are strengths of our study.

Our study also has limitations. First, as in all pharmacoepidemiological studies, there is uncertainty whether patients filling a prescription are actually taking the drug

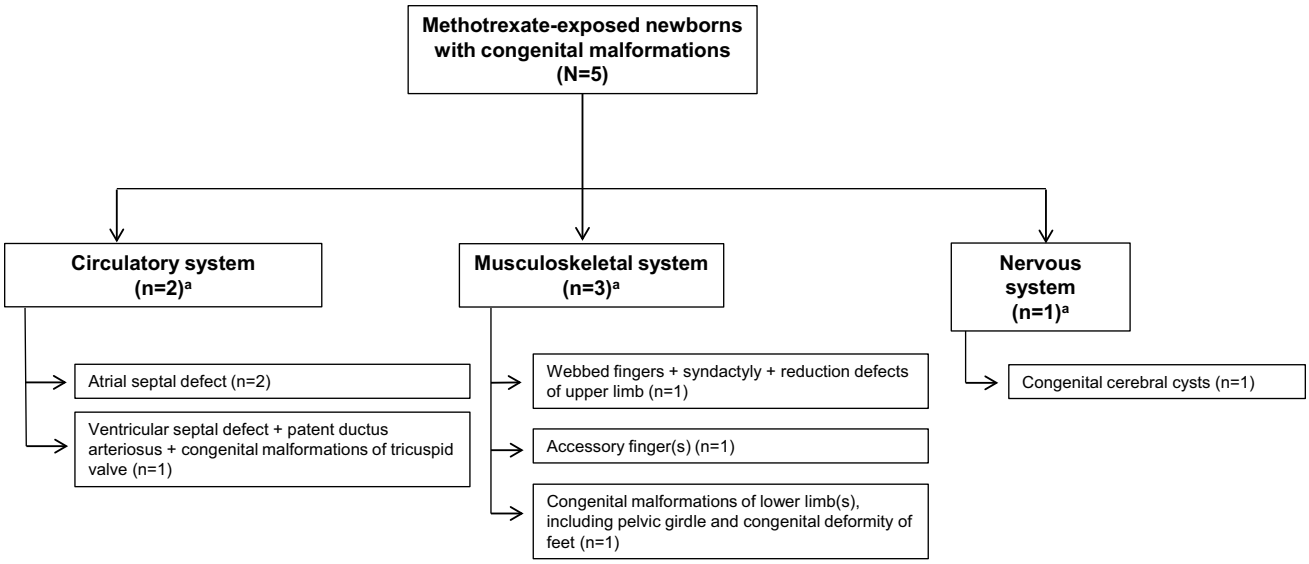

Fig. 2 Malformations observed in children exposed to methotrexate in early pregnancy

but we assume that for severe chronic diseases such as those treated with methotrexate, this limitation is less relevant. Second, given that information on the prescribed dose is not available in German claims data, we used the defined daily dose, which may have overestimated or underestimated exposure windows. Third, we decided against analyzing the ATC code L04AX03 and M01CX01 separately because, as these codes are defined, this would not be meaningful to conclude on the indication. The indication of a prescription is not recorded in claims data. For several drugs, it has been shown that it is possible to estimate the indication based on hierarchical algorithms that combine and classify all information available on the patient, but this was beyond the scope of our study. Fourth, it should be noted that we cannot rule out that methotrexate may have been used to treat an ectopic pregnancy within the first 8 weeks after the onset of pregnancy. It is used for the treatment of ectopic pregnancies, but there are also other treatment options [37]. Even though the proportion of ectopic pregnancies in our study (4.8%) was slightly higher than estimated for all pregnancies in Germany (1.3–2.4%, [37]) the absolute number of ectopic pregnancies was still low (eight pregnancies). Therefore, we do not think that this had a relevant impact on our results. Finally, it is important to note that our study was not designed to estimate the causal effects of methotrexate exposure during pregnancy. This would have required another design including the consideration of relevant confounders, as well as a larger sample of exposed children, which might be achieved by a consortium of large databases in a future study. With regard to the malformations observed in children exposed during pregnancy, we conducted an in-depth patient profile review based on all diagnoses and procedure codes available in GePaRD but did not have additional clinical data.

5 Conclusions

Our study showed that the use of methotrexate in women of childbearing age has substantially increased since 2004. Despite the known teratogenic effect, there was a considerable number of pregnancies exposed to methotrexate in early pregnancy or in the 3 months prior. The malformations we observed in children born from exposed pregnancies point to the risks of methotrexate to the unborn child. Overall, our study emphasizes the need for appropriate counseling by physicians prescribing methotrexate to girls/women of childbearing age in order to avoid malformations due to this drug, which includes the use of effective contraception and the change of treatment well before pregnancy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40261-022-01227-6.

Acknowledgements The authors thank Marieke Niemeyer and Philipp Alexander Volkmar for statistical programming of the analysis datasets and double-independent programming of results as well as all statutory health insurance providers that provided data for this study, namely AOK Bremen/Bremerhaven, DAK-Gesundheit, Die Techniker (TK), and hkk Krankenkasse.

Authors' Contributions NW and UH: study concept and design, analysis and interpretation of data, drafting of the manuscript, critical revision of manuscript. JR: interpretation of data, critical revision of manuscript. BK: study concept and design, statistical analysis,

critical revision of manuscript. The final version of the manuscript was approved by all authors.

Declarations

Funding The study was funded by the German Federal Institute for Drugs and Medical Devices, Bonn (BfArM, V-18281/68605/2019-2020). Open Access funding enabled and organized by Projekt DEAL.

Conflicts of Interest/Competing Interests Nadine Wentzell, Bianca Kollhorst, Jonas Reinold, and Ulrike Haug are working at an independent, non-profit research institute, the Leibniz Institute for Prevention Research and Epidemiology - BIPS. Unrelated to this study, BIPS occasionally conducts studies financed by the pharmaceutical industry. Almost exclusively, these are post-authorization safety studies requested by health authorities. The design and conduct of these studies as well as the interpretation and publication are not influenced by the pharmaceutical industry. The study presented was not funded by the pharmaceutical industry and was performed in line with the ENCePP Code of Conduct.

Ethics approval In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law. All involved health insurance providers as well as the German Federal Office for Social Security and the Senator for Health, Women and Consumer Protection in Bremen as their responsible authorities approved the use of GePaRD data for this study. Informed consent for studies based on claims data is required by law unless obtaining consent appears unacceptable and would bias results, which was the case in this study. According to the Ethics Committee of the University of Bremen, studies based on GePaRD are exempt from an institutional review board review.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material As we are not the owners of the data, we are not legally entitled to grant access to the data of the GePaRD. In accordance with German data protection regulations, access to the data is granted only to BIPS employees on the BIPS premises and in the context of approved research projects. Third parties may only access the data in cooperation with BIPS and after signing an agreement for guest researchers at BIPS.

Code availability Not applicable.

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