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Fingolimod, teriflunomide and cladribine for the treatment of multiple sclerosis in women of childbearing age: description of drug utilization and exposed pregnancies in Germany

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Abstract

Background

Authorizations of fingolimod, teriflunomide and cladribine were accompanied by risk minimization measures concerning their teratogenic potential. Real-world data on their use are scarce. We aimed to assess trends in the use of fingolimod, teriflunomide and cladribine among women of childbearing age, estimate the number of pregnancies occurring under treatment and explore the occurrence of malformations in newborns exposed during early pregnancy in Germany.

Methods

Using the German Pharmacoepidemiological Research Database (GePaRD, claims data from ~20% of the German population), we determined annual age-standardized prevalences of fingolimod, teriflunomide and cladribine use from their authorization until 2019 among women aged 13-49 years (cross-sectional analyses). In longitudinal analyses, we estimated the number of exposed pregnancies by assessing whether there was an overlap between the exposure windows assigned to dispensations and the onset of pregnancy or a dispensation in the first eight weeks of pregnancy. For live births, a mother-baby linkage was performed. All available data of children with in-utero exposure and malformation codes in the first year of life were reviewed to verify the occurrence of congenital malformations.

Results

For fingolimod, the age-standardized prevalence of use per 1,000 females increased from 0.14 in 2011 to 0.46 in 2019; for teriflunomide, from 0.06 in 2013 to 0.28 in 2019; for cladribine, from 0.01 in 2017 to 0.07 in 2019. The proportion of users aged ≤40 years was 60% for fingolimod, 45% for teriflunomide and 65% for cladribine. We identified 136 pregnancies exposed to fingolimod, 50 to teriflunomide and one to cladribine. For fingolimod and teriflunomide, respectively, 72% and 62% of exposed pregnancies ended in a live birth. Mother-newborn linkage was successful in 64 (fingolimod)

and 20 (teriflunomide) live-born children. Among these, there were six with relevant malformations (mainly heart defects) for fingolimod and two for teriflunomide.

Conclusion

Use of fingolimod, teriflunomide and cladribine among women of childbearing age has substantially increased in Germany. A high proportion of users was in age groups in which pregnancies typically occur. Despite risk minimization measures, early pregnancy exposure to these drugs was observed.

Keywords

Multiple Sclerosis, Fingolimod, Teriflunomide, Cladribine, Pregnancy, Drug Utilization

1 Introduction

Fingolimod (FGL), teriflunomide (TFL) and cladribine (CLA) have been licensed by the European Medicines Agency (EMA) for the treatment of relapse remitting multiple sclerosis (MS) since 2011, 2013 and 2017, respectively. Due to their teratogenic potential, risk minimization measures concerning women of childbearing age have been in place for all three medications since their authorization (EMA, 2012, 2013, 2017). All three medications are contraindicated during pregnancy and a negative pregnancy test is required prior to treatment initiation. Further, treatment is indicated only in women of childbearing age using reliable contraception (EMA, 2021a, b, 2022).

In case a pregnancy occurs under treatment with FGL, TFL or CLA, treatment has to be discontinued (EMA, 2021a, b, 2022). However, stopping treatment does not translate into immediate termination of potential teratogenicity. FGL and TFL are eliminated slowly from the plasma, which may, on average, take as long as two months for FGL and eight months for TFL from the time point of treatment cessation (EMA, 2021a, b). Consequently, also pregnancies beginning after treatment with FGL or TFL but prior to the end of the respective delayed elimination period may be exposed to potentially harmful plasma concentrations. Thus, effective contraception is required for an additional two and eight months after FGL and TFL treatment cessation, respectively (EMA, 2021a, b). Conversely, CLA is eliminated rapidly from the body. However, due to its potential to interfere with DNA synthesis, effective contraception must be taken for up to six months after CLA treatment cessation (EMA, 2022; Giovannoni et al., 2020).

Monitoring the utilization of teratogenic drugs among girls and women of childbearing age including changes over time is important to determine whether risk minimization measures are adequate or require adaptation. However, population-based studies on the utilization of disease-modifying drugs for the treatment of MS in this group are scarce (Duchesneau et al., 2022; Grandt et al., 2021). The aim of this study was i) to describe the utilization of FGL, TFL and CLA in girls and women of childbearing age in Germany including temporal trends from their authorization through 2019, ii) to describe the occurrence of pregnancies and their outcomes (e.g. live births, induced abortions) among

women taking these drugs, considering also possible exposure due to delayed elimination, and iii) to explore potential malformations among children exposed to FGL, TFL or CLA in early pregnancy.

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 (Haug and Schink, 2021; BIPS, 2020). 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 institutional review board review.

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 L04AA27 (FGL), L04AA31 (TFL) and L04AA40 (CLA). 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 (Mikolajczyk et al., 2013; Wentzell et al., 2018), to estimate the beginning of pregnancy (Schink et al., 2020) and to link mothers with their newborns (Garbe et al., 2011) 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 prevalence of use for FGL, TFL and CLA over time, we conducted year-wise cross-sectional analyses for each of these three drugs (2011-2019 for FGL, 2013-2019 for TFL and 2017-2019 for CLA). For each calendar year, we included all girls/women in the numerator who had at least one dispensation of the respective drug and were aged between 13 and 49 years in the respective year, and were actively insured on June 30 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 June 30 of that year.

2.2.2 Identification of exposed pregnancies

Using the algorithm for pregnancy outcomes (Mikolajczyk et al., 2013; Wentzell et al., 2018), we identified pregnancies ending between 2011 and 2019 and occurring among girls/women aged 13–49 years at pregnancy onset. A pregnancy was classified as exposed to the respective drug during early pregnancy if i) the exposure window assigned to the last dispensation before pregnancy overlapped with the first day of pregnancy or ii) there was a dispensation in the first eight weeks of pregnancy. The exposure window mentioned above was defined as the dispensation date plus the number of defined daily doses in the package plus, if relevant, an additional extension to take into account delayed elimination due to pharmacokinetic properties (FGL: extension by 2 months, TFL: extension by 8 months) (EMA, 2021a, b). 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 the respective drug plus, if relevant, the time period required for extension of the exposure window (see above). Given that certain incomplete pregnancies in claims data may have no outcome recorded (e.g., spontaneous abortions not requiring medical treatment, induced abortions without medical indication) and would, therefore, remain undetected when only applying the outcome algorithm (Mikolajczyk et al., 2013; Wentzell et al., 2018), we specifically searched for this type of incomplete pregnancies. To qualify for this type of incomplete pregnancy, 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 with missing information on the outcome due to insufficient follow-up time were classified into a separate category.

2.2.3 Exploration of potential congenital malformations among exposed children

For exposed pregnancies ending in a live birth, we applied the algorithm linking mothers with their newborns (Garbe et al., 2011) to explore potential congenital malformations in the children. Among linked children, we identified those with any malformation code (Q00-Q99) occurring up to one year after birth. Subsequently, profiles were reviewed taking into account all available information in GePaRD on these children in order to verify the occurrence of malformations. The profile reviews were conducted independently by two reviewers. Consensus was reached in a subsequent case conference. While reviewers were instructed to consider certain objective criteria confirming the occurrence of relevant malformations, such as the presence of inpatient codes, repeated coding and treatment or monitoring of the malformations, they were specifically asked to apply their clinical judgement in light of the overall patient history (including, for example, the evaluation whether malformations may be attributable to the gestational age at birth, chromosomal abnormalities, etc.). In doing so, the primary focus was on malformations categorized as "major" as suggested by EUROCAT, but so-called "minor" malformations were also considered if treatment (e.g. surgical) or other information (e.g. physical impairment, malformation-related complications) indicated a higher level of severity (EUROCAT, 2018).

2.3 Data analysis

In the cross-sectional analyses, we determined—for each drug and year—age-specific and age-standardized prevalences, using the age distribution of the German female population on 31 December 2019 as reference. Furthermore, we described the medical specialty of the prescribing physicians.

As for pregnancies, we determined the number of those classified as exposed overall and by calendar year. We described the mothers' age at pregnancy onset and the pregnancy outcomes. In sensitivity analyses, we explored the impact of the delayed elimination of FGL and TFL on our results. We,

therefore, examined to which extent the number of exposed pregnancies decreased when omitting the two- and eight-month extensions of the exposure windows. In another sensitivity analysis, we explored if the number of pregnancies exposed to TFL increased when extending the exposure window assigned to the last dispensation before pregnancy by 24 months given that in some cases plasma elimination of TFL may last 24 months (EMA, 2021a). We also examined whether the identified pregnancies were preceded by a dispensation of a substance recommended for accelerated elimination, i.e. activated charcoal or cholestyramine, within 24 months prior pregnancy onset (EMA, 2021a).

We conducted all statistical analyses using the software SAS version 9.4.

3 Results

3.1 Prevalence of use among girls/women of childbearing age

Overall, we identified 3,963 girls/women aged 13–49 years with at least one dispensation of FGL (2011–2019), 2,396 with at least one dispensation of TFL (2013-2019), and 351 with at least one dispensation of CLA (2017-2019). The age-standardized prevalence of FGL use per 1,000 girls/women increased from 0.14 in 2011 to 0.46 in 2019. For TFL, it increased from 0.06 in 2013 to 0.28 in 2019, and for CLA, it increased from 0.01 in 2017 to 0.07 in 2019. For FGL and TFL, there was no further increase in prevalence after 2016 in women ≤40 years. Age-specific and age-standardized prevalences over the study years are shown in Figure 1.

Each calendar year, the proportion of girls/women with at least one dispensation of the respective drug aged ≤40 years was roughly 60% for FGL, 45% for TFL and 65% for CLA. Information on the prescribing physician was available for 89% of all dispensations for FGL, 92% for TFL and 76% for CLA. Of those with known information, the proportion prescribed by neurologists was 95% for FGL, 95% for TFL and 93% for CLA.

3.2 Characterization of exposed pregnancies

Overall, we identified 136 pregnancies classified as exposed during early pregnancy for FGL, 50 for TFL and one for CLA. For FGL, the number of exposed pregnancies per calendar year ranged from 3 in 2011 to 27 in 2017, and for TFL from 0 in 2013 to 16 in 2017. The pregnancy exposed to CLA started in 2018. The majority of pregnancies occurred in women aged ≤40 years (FGL: 96%, TFL: 88%, CLA: 100%).

For exposed pregnancies that were no longer ongoing at the end of the observation period (118 for FGL, 42 for TFL and one for CLA), the distribution of pregnancy outcomes is summarized in Table 1. For FGL, 72% (n=85) of exposed pregnancies ended in a live birth, 8% (n=10) in an induced abortion and 3% (n=4) in a spontaneous abortion. For 17 pregnancies (14%), no outcome was recorded (i.e. they are assumed to also be abortions). For TFL, the proportion of live births was lower (62%, n=26) and accordingly, the proportion of incomplete pregnancies was higher (induced abortion: 19% (n=8),

spontaneous abortion: 0% (n=0), no outcome recorded: 19% (n=8)). For the pregnancy exposed to CLA, no pregnancy outcome was recorded.

In sensitivity analyses omitting the two-month extension of the exposure period for FGL, the number of exposed pregnancies decreased to 99 (from 136). For TFL, it decreased to 24 (from 50) when the eight-month extension of the exposure period was omitted, while it increased to 60 when the exposure window was extended by 24 instead of eight months. In 19 of those 60 pregnancies, there had been at least one dispensation of cholestyramine in the 24 months prior to the onset of pregnancy. No dispensation of activated charcoal was observed in this time period.

3.3 Characterization of exposed children

In the 85 pregnancies exposed to FGL and ending in a live birth, mother-newborn linkage was successful in 64 cases. In six of these children (9%), relevant congenital malformations were observed. Four children had defects of the heart, one child had a limb anomaly and one child had both a malformation of the nervous system and defects of the heart (Figure 2A). In two cases, there was neither an overlap between FGL supply and the onset of pregnancy nor a dispensation during the first eight weeks of pregnancy, but the pregnancy occurred during the additional two-month period of delayed plasma elimination.

In the 26 pregnancies exposed to TFL and ending in a live birth, 20 children could be linked to their mothers. Two of these children (10%) had relevant congenital malformations. One child had a gastro-intestinal malformation and one child had both a defect of the heart and a nervous system anomaly (Figure 2B). In both cases, there was neither an overlap between TFL supply and the onset of pregnancy nor a dispensation during the first eight weeks of pregnancy, but the pregnancy occurred during the additional eight-month period of delayed plasma elimination.

4 Discussion

In this large, population-based study, we found a substantial increase in the use of FGL, TFL and CLA since their authorization through 2019 among women of childbearing age in Germany. The vast majority of dispensations of FGL, TFL and CLA was prescribed by neurologists. For FGL and TFL there was no further increase in prevalence after 2016 in women ≤40 years, but the proportion of users in age groups in which pregnancies typically occur was high across the whole study period and for all three drugs. Even though risk minimization measures are in place, we observed 187 pregnancies likely exposed to one of these drugs in a time window most critical for the development of the child. In 9-10% of children born from these pregnancies, we observed relevant malformations, for FGL particularly defects of the heart. In half of the children with relevant congenital malformations, the mothers became pregnant after FGL and TFL treatment cessation but prior to sufficient plasma elimination.

Real-world data on the use of FGL, TFL and CLA in girls/women of childbearing age are scarce. There are, for example, population-based studies from the U.S. and from France describing the use of disease-modifying drugs among pregnant women, i.e. they did not report prevalence of use among women of childbearing age (Blotière et al., 2021; Illoh et al., 2018; MacDonald et al., 2019). A recent study from Germany—restricted to data from 2018—reported that 54 and 29 per 100,000 females aged 13 – 49 years received a prescription for FGL and TFL, and 5 per 100,000 had a prescription for CLA for any indication (MS or hematological malignancy) (Grandt et al., 2021). These data are consistent with our results for 2018. Only five pregnancies with first-trimester exposure were observed in this study, but the investigation of pregnancies was restricted to those with a minimum duration of 33 weeks, an inpatient delivery in 2018 and also delayed elimination of FGL and TFL was not considered. Unlike in our study using the expected delivery date to estimate the onset of pregnancy (Schink et al., 2020), this study used ICD-10-GM codes (O09) providing only a rough estimate of gestational length. Therefore, the risk of misclassifying early pregnancy exposure was higher (Grandt et al., 2021). Another recent study using claims data from the U.S. described trends in the use of disease-modifying treatment from 2010 to 2019 among girls and women of reproductive age with a

diagnosis of MS (Duchesneau et al., 2022). This study showed an overall increase in monthly age- and region-standardized prevalence of FGL and TFL use over the study period. FGL reached its peak prevalence in 2017 and remained one of the three most commonly used disease-modifying drugs by 2019. CLA use was not investigated (Duchesneau et al., 2022). The peak in 2017 for FGL resembles the pattern we observed in our study for FGL and TFL use in women ≤40 years. The fact that there was no further increase after 2016 may be due to other new disease-modifying therapies. In Germany, alemtuzumab was launched on the market in 2013, dimethyl fumarate in 2014, peginterferon beta-1a in 2014, CLA in 2017 and ocrelizumab in 2018.

In our study, the majority of users of FGL, TFL and CLA was in age groups in which pregnancies typically occur (≤40 years of age). These findings and the fact that we actually observed 187 pregnancies likely exposed to these drugs in a critical time window imply that continuous monitoring of the implementation of risk minimization measures will remain important in the future. Drawing more attention to the vulnerable time period after treatment cessation of FGL and TFL may be relevant given that pregnancies beginning after treatment with FGL or TFL but prior to the end of the respective delayed elimination period may be exposed to potentially harmful plasma concentrations. In our sensitivity analyses, there was a considerable decrease in the number of exposed pregnancies when those two- and eight-month time periods were omitted from the estimation of exposure periods: for FGL, the number of exposed pregnancies decreased to 99 (from 136) and for TFL, it decreased to 24 (from 50). In other words, 27% of a total of 136 pregnancies exposed to FGL and 52% of a total of 50 pregnancies exposed to TFL occurred after FGL and TFL treatment cessation and prior sufficient plasma elimination, respectively. Also, in half of the children with relevant congenital malformations the mother became pregnant during this time period.

In our study, we observed relevant malformations in six out of 64 children (9%) with early pregnancy exposure to FGL and in 2 out of 20 children (10%) exposed to TFL. In 2019, recommendations for the treatment with FGL in girls and women of childbearing age were tightened based on post-marketing EUROCAT data suggesting a two-fold increased risk of major congenital malformations among infants with in-utero exposure. Heart, kidney and musculoskeletal malformations were described most

commonly (EMA, 2019). For TFL and CLA, recommendations so far mainly rely on the teratogenic potential shown in animal studies. Consequently, the current results are a valuable contribution to the limited human data that have been acquired so far. In line with previous findings, we mainly observed defects of the heart in children exposed to FGL during pregnancy. As described in the EUROCAT data, we found atrial and septal defects as well as further defects of the Teratology of Fallot (pulmonary valve stenosis, discordant ventriculoarterial connection) (BfArM, 2019). Our study was not designed to assess relative risks by comparing exposed and unexposed pregnancies and in addition, the number of exposed children was limited. Nevertheless, it is remarkable that the proportion of children exposed to FGL showing heart defects, for example, was 8% and, thus, more than 10 times higher than the proportion expected based on data from EUROCAT (~0.6% of live births with heart defects in 2019) (EUROCAT, 2022).

Our findings thus support the concern that FGL and TFL are harmful for children exposed during early pregnancy. Generally, the treatment of girls and women of childbearing age and during pregnancy with chronic diseases requires a careful weighting of the health of the mother on the one hand and the potential drug-related risks for the unborn child on the other hand. In case of MS, it may be feasible to avoid potentially teratogenic substances in girls and women of childbearing age as there are treatment alternatives: for example, there is strong evidence to conclude that beta-interferon and glaritamer acetate exposure during pregnancy has no teratogenic effects. In case of natalizumab and dimethyl fumarate, there has been no clear indication for an increased risk of malformations, but data on exposed pregnancies are limited. For the treatment of relapses, high-dose glucocorticosteroids may be applied after the first trimester (Hemmer, 2021).

There are limitations that need to be taken into consideration when interpreting our results. First, we assumed that patients claiming their prescriptions are actually taking their treatment but this may not always be the case. Second, given that information on the prescribed dose is not available in German claims data, we used the defined daily dose which may have over- or underestimated exposure windows. Third, while our study was designed to describe prevalence of use and pregnancies occurring under treatment with the drugs, our database would not have been suited to assess whether

risk minimization measures are followed on an individual level. This would have required comprehensive information on contraceptive measures, which is limited in GePaRD as in most other claims databases (Schink et al., 2021). Fourth, we would like to stress that based on the current data, no conclusions on outcomes of CLA-exposed pregnancies may be drawn as the available observation time of CLA use was limited (2017-2019) and only a single pregnancy exposed to CLA with no documented pregnancy outcome was observed. Fifth, with regard to pregnancy outcomes and malformations, our study was merely descriptive. Estimating causal effects 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. For TFL, such a study would also need to consider utilization of drugs accelerating plasma elimination (cholestyramine, activated charcoal). In our study, there was a dispensation of cholestyramine in about one third of exposed pregnancies within 24 months before their onset. Furthermore, such a study would need to take into account MS relapses of the mother as this might have an impact, for example, on the proportion of pregnancies ending in an induced abortion. Sixth, 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.

Specific strengths of our study are the large database covering approximately 20% of the German population as well as the methodology specifically developed to use GePaRD for research on drug utilization and safety in pregnancy. This includes i) an algorithm to estimate the onset of pregnancy based on the expected delivery date, which is expected to minimize misclassification of gestational age (Schink et al., 2020), ii) an algorithm for the identification of pregnancy outcomes which was further optimized regarding incomplete pregnancies (Mikolajczyk et al., 2013; Wentzell et al., 2018), and iii) an algorithm to link newborns to their mothers (Garbe et al., 2011), which allowed us to systematically assess potential malformations in exposed children. Unlike previous studies, we also considered the delayed elimination of FGL and TFL and conducted sensitivity analyses on how this affects the number of exposed pregnancies.

In conclusion, the use of FGL, TFL and CLA among women of childbearing age has substantially increased in Germany since their authorization. A high proportion of users was in age groups in which pregnancies typically occur. There were 186 pregnancies exposed to FGL and TFL and relevant malformations were observed in exposed children, supporting the need for monitoring risk minimization measures.

Credit Author Statement

Katharina Platzbecker: Methodology, Writing – Original Draft, Visualization

Nadine Wentzell: Methodology, Writing – Review & Editing

Bianca Kollhorst: Methodology, Software, Formal Analysis, Writing – Review & Editing

Ulrike Haug: Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding Acquisition

Conflict of Interest

The authors 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 (PASS) 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.

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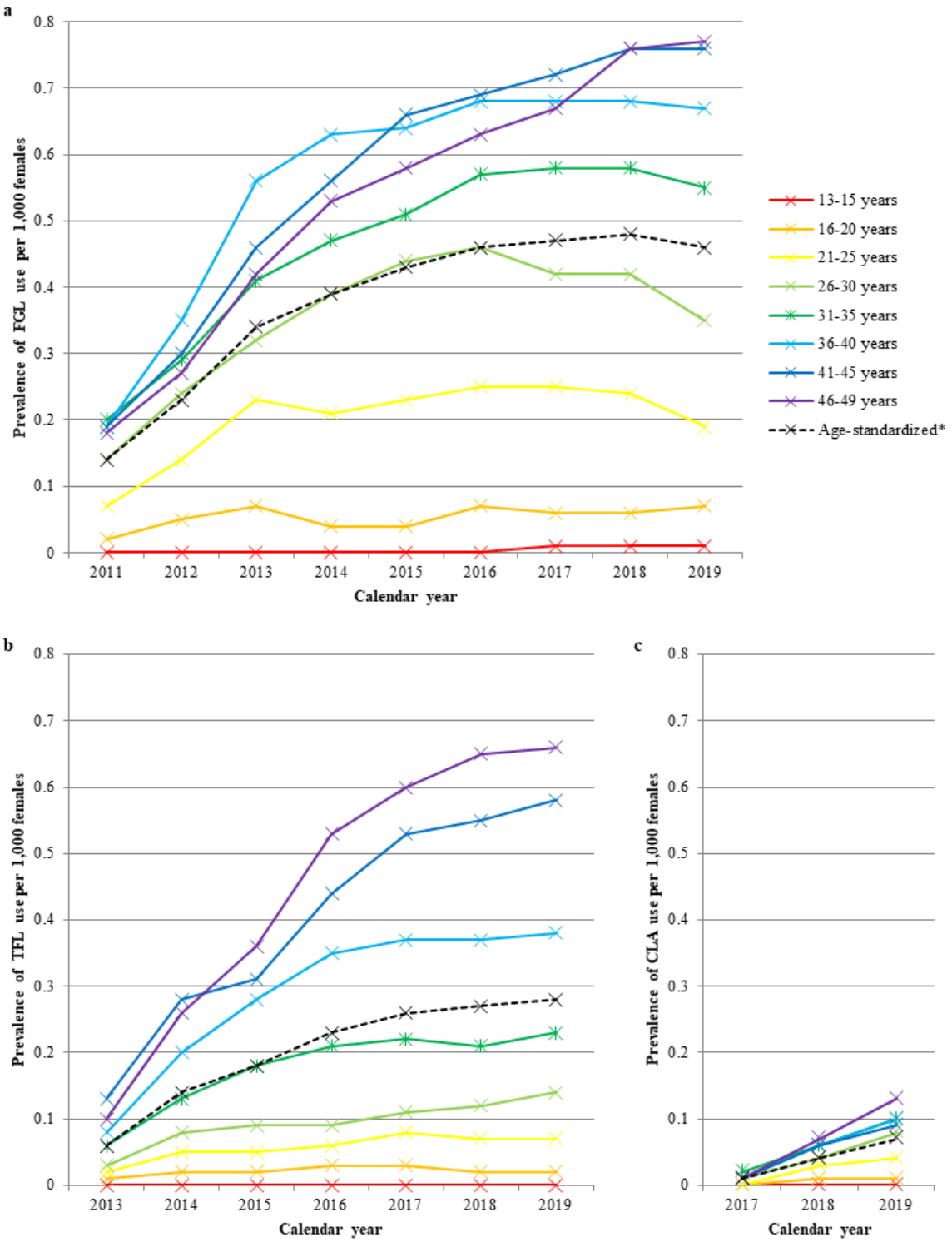

Figure 1. Age-specific and age-standardized* prevalences of **(a)** FGL, **(b)** TFL and **(c)** CLA use per 1,000 girls/women aged 13-49 years and calendar year.

* For age-standardization, the female German population of December 31st, 2019 served as standard population.

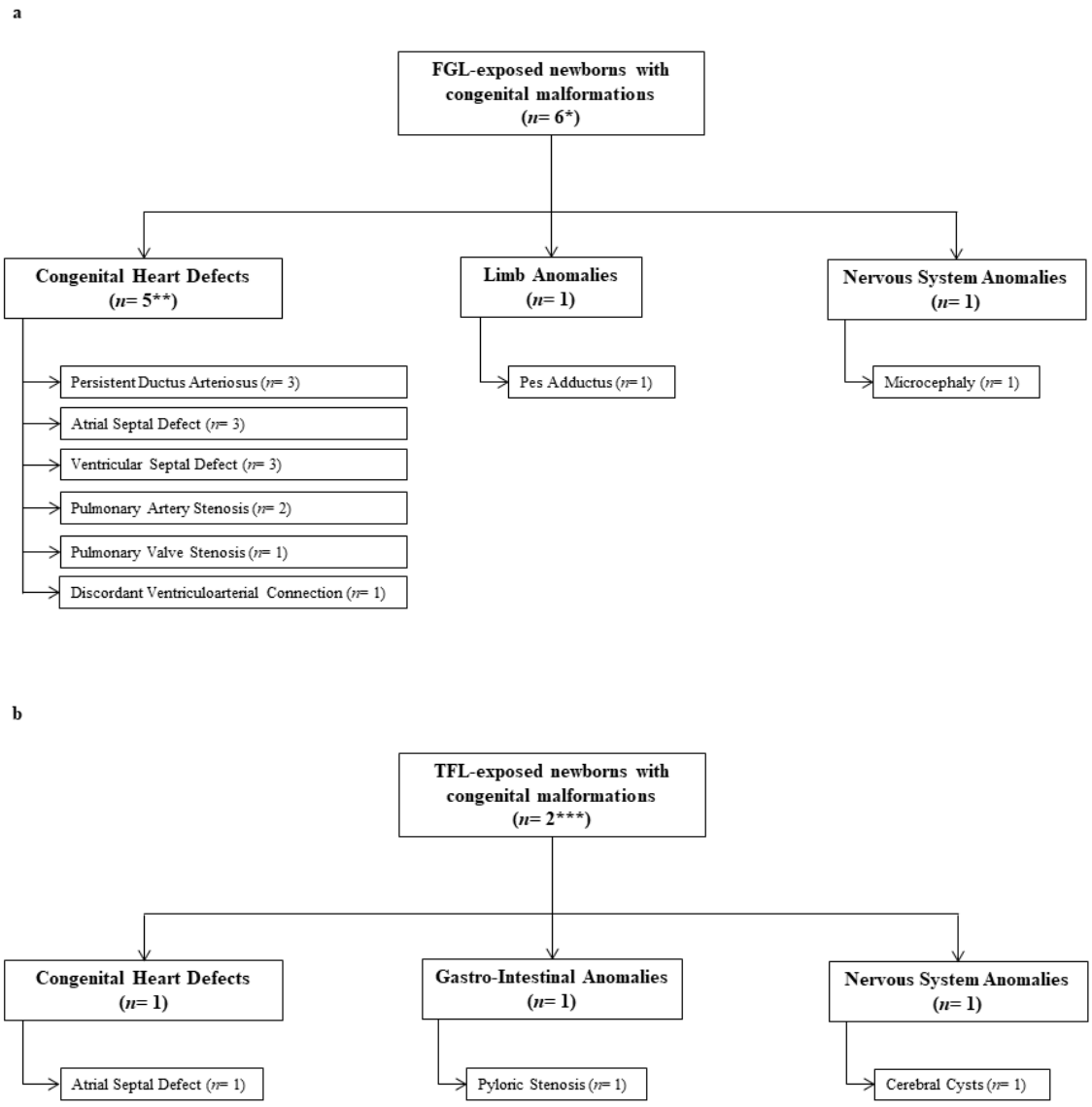

Figure 2. Malformations observed in children exposed to **(a)** FGL and **(b)** TFL during pregnancy.

* One child had malformations involving multiple organ systems (congenital heart defects and nervous system anomaly).
** Three children had multiple defects of the heart.
*** One child had malformations involving multiple organ systems (congenital heart defect and nervous system anomaly).

Table 1. Distribution of pregnancy outcomes in pregnancies exposed to FGL, TFL and CLA.

	Pregnancies exposed to FGL N=118*	**Pregnancies exposed to TFL** N=42*	**Pregnancies exposed to CLA** N=1*
Live birth	85 (72.0%)	26 (61.9%)	0 (0.0%)
Of those: Preterm birth	5 (4.2%)	2 (4.8%)	0 (0.0%)
Still birth	1 (0.8%)	0 (0.0%)	0 (0.0%)
Induced abortion	10 (8.5%)	8 (19.0%)	0 (0.0%)
Ectopic pregnancy or molar pregnancy	1 (0.8%)	0 (0.0%)	0 (0.0%)
Spontaneous abortion	4 (3.4%)	0 (0.0%)	0 (0.0%)
No pregnancy outcome was recorded**	17 (14.4%)	8 (19.0%)	1 (100%)

* 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 18 pregnancies for FGL and 8 pregnancies for TFL).

** 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.