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UNDERSTANDING SOCIODEMOGRAPHIC DISPARITIES IN MATERNAL-FETAL SURGERY STUDY PARTICIPATION

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Abstract

BACKGROUND/PURPOSE: Although maternal-fetal surgery to treat fetal anomalies such as spina bifida continues to grow more common, potential health disparities in the field remain relatively unexamined. To address this gap, we identified maternal-fetal surgery studies with the highest level of evidence and analyzed the reporting of participant sociodemographic characteristics and representation of racial and ethnic groups.

METHODS: We conducted a systematic review of the scientific literature using biomedical databases. We selected randomized control trials (RCTs) and cohort studies with comparison

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Author Contributions

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

groups published in English from 1990 to May 5th, 2020. We included studies from across the globe that examined the efficacy of fetal surgery for twin–twin transfusion syndrome (TTTS), obstructive uropathy (OU), congenital diaphragmatic hernia (CDH), myelomeningocele (MMC), thoracic lesions, cardiac malformations, or sacrococcygeal teratoma (SCT). We determined the frequency of reporting of age, gravidity/parity, race, ethnicity, education level, language spoken, insurance, income level, and relationship status. We identified whether sociodemographic factors were used as inclusion or exclusion criteria. We calculated the racial and ethnic group representation for studies in the United States using the participation prevalence ratio (PPR).

RESULTS: We included 112 studies (10 RCTs, 102 cohort) published from 1990–1999 (8%), 2000–2009 (30%), and 2010–2020 (62%). Most studies were conducted in the U.S. (47%) or Europe (38%). The median sample size was 58. TTTS was the most common disease group (37% of studies), followed by MMC (23%), and CDH (21%). The most frequently reported sociodemographic variables were maternal age (33%) and gravidity/parity (20%). Race and/or ethnicity was only reported in 12% of studies. Less than 10% of studies reported any other sociodemographic variables. Sociodemographic variables were used as exclusion criteria in 13% of studies. Among studies conducted in the U.S., White persons were consistently overrepresented relative to their prevalence in the U.S. disease populations (PPR 1.32 – 2.11), while Black or African American, Hispanic or Latino, Asian, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander persons were consistently underrepresented (PPR 0–0.60).

CONCLUSIONS—Sociodemographic reporting quality in maternal-fetal surgery studies is poor and inhibits examination of potential health disparities. Participants enrolled in studies in the U.S. do not adequately represent the racial and ethnic diversity of the population across disease groups.

Keywords

maternal-fetal surgery; fetal therapy; health equity; health disparities

INTRODUCTION

Maternal-fetal surgery to treat fetal anomalies continues to grow more common. For example, the number of fetal therapy centers in North America has increased from approximately 15 in 2000 to 45 in 2020 [1, 2]. Fetal surgery can be beneficial for the prenatal treatment of anomalies such as spina bifida and congenital diaphragmatic hernia among others. However, potential health disparities in the field remain relatively unexamined.

It is unclear whether social determinants of health (e.g., socioeconomics, environment, cultural drivers, etc.) play a role in who has access to and undergoes maternal-fetal surgery, and what populations may have certain types of positive or negative outcomes. Race, ethnicity, and other socioeconomic factors have been shown to play a significant role in the pathogenesis of some diseases treated with maternal-fetal surgery [3]. It is vital that their potential role in the safety and efficacy of interventions be examined. Studies of the National Spina Bifida Patient Registry have identified outcome variations associated with socioeconomic factors, however it is unclear how these compare in patients who had prenatal vs. postnatal interventions [4]. Fetal surgery can place a significant social burden on

families (e.g., stressors associated with weeks of required maternal bed rest) and identifying social considerations may be important in influencing outcomes [5]. Lower socioeconomic status and longer distance to a tertiary care center (where fetal centers are commonly located) are associated with poor outcomes in the broader perinatal population [6] [7]. Maternal and infant morbidity and mortality rates disproportionately affect racial and ethnic minority populations, and therefore, examining potential health disparities is critical as the field of maternal-fetal surgery continues to grow [3].

A key component of examining health disparities, particularly in a relatively new field of health care such as maternal-fetal surgery, is to consider who is enrolled in the clinical studies that establish the efficacy of these new treatments. Sociodemographic information about study participants, such as their age, race, ethnicity, and socioeconomic status (SES), allow clinicians and other stakeholders to assess external validity and determine the applicability of a study's findings to their own patient population. Given that the efficacy and safety of maternal-fetal surgeries are likely influenced by the same set of social, economic, epigenetic, and environmental factors that contribute to excess maternal-child morbidity and mortality in the United Sates, underrepresentation of racial or ethnic minority or low SES groups in maternal-fetal surgery research may be hazardous [3, 8].

There are two important considerations regarding the representation of patient populations in research studies. First, it is important to determine whether study authors are reporting important characteristics of their study participants. Adequate reporting of sociodemographic data is necessary for stakeholders to evaluate external validity. Without the ability to understand how sociodemographic variables may have contributed to the evidence informing clinical practice, we impede our ability to explore health disparities, such as social determinants of health (e.g., socioeconomic barriers) and implicit bias.

A second consideration, among studies that do report the sociodemographic characteristics, is whether the patients included in a study sample are reflective of the people in the population who have the disease. In other words, are specific sociodemographic groups bearing a greater burden of disease in the broader population, but only representing a smaller proportion of study participants? For example, 33.3% of children born with spina bifida in the United States are Hispanic [9]. However, in the Management of Myelomeningocele Study (MOMS), a landmark randomized control trial demonstrating the benefits of fetal surgery for children born with spina bifida, only 3.8% of participants were Hispanic [10]. Little is known about whether such inequities are pervasive across the field of maternal-fetal surgery.

To examine potential health disparities in maternal-fetal surgery, we identified studies with the highest level of evidence, and analyzed the reporting of participant sociodemographic characteristics and representation of racial and ethnic groups.

MATERIALS AND METHODS

Data Collection

On May 5th 2020, we completed a comprehensive search of multiple databases for maternal-fetal surgery clinical studies. The search strategy was designed and conducted by an expert medical librarian (J.B.) with input from clinical and systematic review experts on the research team. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. The following databases were searched: included OVIDMedline ALL, OVIDEmbase, OVIDPsycINFO, CINAHL Complete, Cochrane CENTRAL, Web of Science, and ProQuest. To identify appropriate search terms, a Medical Subject Heading (MeSH) analysis was done using the Yale MeSH Analyzer and a gold standard set of key maternal-fetal surgery studies provided by members of the research team [12]. Relevant controlled vocabulary terms and synonymous free text words and phrases were used to capture the concept of fetal surgery. The medical librarian (J.B.) used key maternal-fetal surgery studies provided by the first author (A.W.) to validate the reliability of the searches. The search was also peer-reviewed by a second librarian. The first author (A.W.) and coauthor (A.L.) reviewed the first 100 articles derived from the first round of search results to refine search criteria and revise inclusion/exclusion criteria and finalized the search strategy. Further studies were identified by examining the reference lists of all included articles. The full search strategy is available upon request.

We selected randomized control trials (RCTs) and cohort studies with comparison groups published in English from 1990 to May 5th, 2020. RCTs and cohort studies are considered the highest standard for experimental therapeutic studies.[13] Thus, they shape clinical practice and play a critical role in the implementation of fetal surgery into healthcare. We included studies from across the globe that examined the efficacy of maternal-fetal surgery for twin–twin transfusion syndrome (TTTS), obstructive uropathy (OU), congenital diaphragmatic hernia (CDH), myelomeningocele (MMC), thoracic lesions, cardiac malformations, or sacrococcygeal teratoma (SCT). These conditions were selected in accordance with the Maternal-Fetal Surgical Procedures Technical Brief completed by The Agency for Healthcare Research and Quality's (AHRQ) in 2011.[14]

All abstracts and full texts were reviewed by at least 2 authors to ensure rigor (A.W., A.L., B.E., A.P., M.L.). The first author (A.W.) reviewed eligibility conflicts and, if needed, discussed them with the research team to reach consensus. To assess methodological quality, researchers used the Critical Appraisal Skills Program (CASP) Checklist for RCTs and cohort studies.[15]

Data Analysis

Sociodemographic characteristics examined included age, gravidity/parity, race, ethnicity (or other population group variables for non-U.S. countries), education level, language spoken, insurance (U.S. only), income level, and relationship status. Although insurance status is not typically reported in clinical trial publications, many of the cohort studies in our sample were retrospective chart reviews of procedures already implemented into standard clinical practice. Therefore, patients were likely not receiving care under an experimental protocol

and insurance coverage may have been necessary to access the procedures. We analyzed the percent of papers reporting each sociodemographic variable. We also identified whether sociodemographic factors were used as inclusion or exclusion criteria. Finally, we examined racial and ethnic group representation relative to their representation in populations affected by disease. We used the metric of participation-to-prevalence ratio (PPR), which is calculated by dividing the percentage of racial and ethnic groups among study participants by the percentage of racial and ethnic groups in the disease population [16–19]. The denominators were obtained from research reporting the most recent population-based data representing national disease burden. The interpretation of PPR values was based on established thresholds where less than 0.8 indicates underrepresentation; greater than 1.2, overrepresentation; and close to 1.0, adequate representation [16–19]. Participation-to-prevalence ratio calculations were only possible for studies conducted solely in the U.S. that reported the race or ethnicity of their sample and had conditions with recent U.S. population-based data stratified by racial or ethnic groups.

RESULTS

We identified 13,346 articles, of which 1,151 underwent full-text review, and 112 met the criteria for inclusion in the analysis (shown in Fig. 1). No studies were excluded after quality appraisal. We included 112 studies (10 RCTs, 102 cohort) published from 1990–1999 (8%), 2000–2009 (30%), and 2010–2020 (62%) (show in Table 1). Of the 102 cohort studies, 75% were retrospective and 25% were prospective. Most studies were conducted in the U.S. (47%, 6 RCTs, 48 cohort) or Europe (38%, 4 RCTs, 38 cohort). The median sample size was 58. TTTS was the most common disease group (38%, 4 RCTs, 38 cohort), followed by MMC (23%, 3 RCTs, 23 cohort), and CDH (21%, 2 RCTs, 21 cohort).

Sociodemographic characteristics of the study samples were rarely reported (shown in Fig. 2). Only 33% of the included studies reported maternal age (6 RCTs, 31 cohort), 20% reported childbearing history (gravidity/parity) (3 RCTs, 19 cohort), 12% reported race and/or ethnicity (2 RCTs, 11 cohort) (no studies reported other population group variables), 4% reported level of education and relationship status (1 RCT, 3 cohort), 1% reported income level (1 cohort), and 0 studies reported the language spoken by participants. None of the studies conducted in the U.S reported the insurance status of the participants. Of the 47 studies conducted solely within the U.S., only 12 (26%, 1 RCT, 11 cohort) reported race or ethnicity. Congenital diaphragmatic hernia had the highest percentage of studies reporting sociodemographic variables (44%) followed by myelomeningocele (35%). Of the studies reporting race and/or ethnicity, all but 1 were published after 2009.

For most studies, eligibility criteria focused on medical variables such as obstetric history, gestational age, fetal condition severity, the presence of other fetal anomalies. For example, most cohort studies were retrospective and reported limited eligibility criteria (e.g., all consecutive patients diagnosed with TTTS before 28 weeks' gestation between January 1993 and December 2007 were included). Sociodemographic variables were used as exclusion criteria in 13% of studies (12 cohort studies, 2 RCTs). Of these 14 studies, six reported using the MOMS criteria, but did not explicitly state what these criteria included or how they were evaluated. The MOMS trial, which was included in this review, excluded non-US residents

and those with no support person, inadequate support at home for pregnancy, inadequate understanding of risks and benefits of the procedure, or an inability to comply with medical restrictions for follow up (e.g., significant decrease in maternal activity)[10]. The remaining seven studies that used sociodemographic variables as exclusion criteria, but did not report using the MOMS criteria, described a variety of requirements including country or state residency and the ability to understand the potential risks and benefits of the maternal-fetal procedure. Most studies did not report data on those who were excluded or declined to participate, and almost no studies described the details of psychosocial exclusion. For example, one study excluded six people due to “psychosocial factors” but did not specify what these included or how they were assessed [20].

Of the 13 studies that reported race or ethnicity, 12 were conducted solely within the U.S (6 MMC, 5 TTTS, 1 various thoracic lesions) and one was conducted as a multisite study in the UK, Ireland, Scotland, and the Netherlands (1 OU). Because we found no population-based data applicable to the obstructive uropathy and thoracic lesions studies, we were only able to calculate participation-to-prevalence ratios for the MMC and TTTS studies. The most recent population data for spina bifida came from the National Birth Defects Prevention Network (NBDPN) which did not differentiate between types of spina bifida (e.g., MMC, occulta, closed neural tube defects, or meningocele) [21]. Because MMC is the most common type of spina bifida reported prenatally or at birth, we applied these data for comparison to study samples [22]. Finally, there is very limited data on TTTS incidence. TTTS only occurs in monochorionic pregnancies, which are shown to have no relationship with race or ethnicity. Therefore, we used estimates of monochorionic twins (1/300 pregnancies) from the 2019 National Vital Statistics Report to calculate PPR for TTTS studies [23].

In the MMC studies, no racial or ethnic groups were adequately represented (shown in Fig. 3). White persons represented 44% of the U.S. spina bifida population but 93% of the maternal-fetal surgery MMC study samples and therefore were overrepresented (PPR 2.11) [21]. Hispanic or Latino persons were the most meaningfully underrepresented group in MMC studies as they accounted for 40% of the U.S. spina bifida population but only 10% of the study samples (PPR 0.25). Black or African American persons represented 9% of the U.S. spina bifida population and only 3% of the study samples (PPR 0.26), while Asian persons represented 2% of the U.S. spina bifida population and 0.4% of the study samples (PPR 0.22). Similarly, no racial or ethnic groups were adequately represented in the TTTS studies. White persons represented 53% of the estimated U.S. monochorionic twin population but 73% of maternal-fetal surgery TTTS study samples and were therefore overrepresented (PPR 1.37). Hispanic or Latino persons accounted for 24% of the population but only 7% of the study samples (PPR 0.27). Black or African American persons accounted for 15% of the population but only 11% of the study samples (PPR 0.75). Asian persons represented 7% of the population but only 3% of the study samples (PPR 0.38). Therefore, these three groups were underrepresented in maternal-fetal surgery TTTS studies. No other racial or ethnic groups were listed as participants in the MMC or TTTS studies (e.g., American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander).

DISCUSSION

Our analysis highlighted the critical gaps in sociodemographic reporting and representation of racial and ethnic groups in maternal-fetal surgery studies with the highest levels of evidence. Most maternal-fetal surgery studies included in our systematic review did not report the sociodemographic characteristics of their samples. Furthermore, White persons were consistently overrepresented relative to their prevalence in the U.S. disease populations, while Black or African American, Hispanic or Latino, Asian, American Indian or Alaska Native, and Native Hawaiian or Other Pacific Islander persons were consistently underrepresented.

The need to standardize and promote the collection and reporting of race, ethnicity, and other sociodemographic factors is not unique to the field of maternal-fetal surgery. Many influential organizations in health care have set clear reporting standards, yet our findings build upon a body of literature which suggest poor reporting in other fields as well [24–26]. For example, in 2014 researchers examining minority participation in cancer trials found the percentage of manuscripts reporting participant race and ethnicity data ranged from only 1.5% to 58% [26]. Similarly, in a recent study of US-based vaccine trials from 2011 to 2020, only 58% of trials reported race and only 34% reported ethnicity [27]. Race and ethnicity are not the only sociodemographic variables that lack adequate reporting in clinical research. Even in leading medical and surgical journals, authors were found to infrequently report RCT participant socioeconomic status, educational levels, marital status, and language spoken [28]. This corresponds with our findings in which less than 10% of studies reported any of these variables.

Similar to the lack of sociodemographic reporting, the lack of adequate representation persists in the face of standards set by major organizations. For example, in 2014 the Food and Drug Administration launched an action plan to improve demographic subgroup analysis in the evaluation of new therapeutics [29]. This plan included a specific focus on postmarketing studies because they are meant to address the well-known underrepresentation of demographic subgroups in premarketing studies. However, in a recent analysis researchers found that demographic representation in postmarketing studies was not significantly different from premarketing studies where Black patients were significantly underrepresented [30]. These and other studies have also highlighted a lack of representation of groups based on other sociodemographic characteristics such as age, socioeconomic status, insurance type, and family structure [26, 31, 27, 30]. It is likely that maternal-fetal surgery studies have similar underrepresentation, but we are unable to assess most of these variables because so few studies have reported them.

The underrepresentation of most racial and ethnic groups found in this systematic review highlights the ongoing challenge of recruiting diverse samples in clinical research. The field likely faces common obstacles to participation of racially and ethnically diverse patients that virtually all healthcare focused studies face. Barriers to participation in RCTs and cohort studies include influences of systemic racism such as mistrust, a lack of access to tertiary care centers, a lack of comfort with the clinical research process, a lack of information about clinical research, and time and resource constraints [32]. Some of the recruitment

challenges in maternal-fetal surgery may relate to patients' racial or ethnic group, while some may be more closely related to economics (e.g., inflexible work schedules), culture (e.g., different beliefs about health and health care), or language/literacy (e.g., complex informed consents)[33]. Historically, very few sponsors, institutions, and investigators have been willing to conduct any interventional studies with pregnant women, and so maternity care practices may also be unaware of the needs and opportunities for pregnant patients in clinical research [34]. A lack of study team outreach to community practices can lower providers' willingness to promote clinical studies to their patients and can lower pregnant people's willingness to join studies [35]. Since most of the cohort studies in our sample were retrospective chart reviews of procedures already implemented into standard clinical practice, their lack of racial and ethnic diversity suggests disparities in clinical care, as well as in research. Many of the hypothesized barriers to maternal-fetal surgery research participation would also apply to clinical care (e.g., lack of access to tertiary care centers, time and resource constraints.)

Finally, our analysis provides important insights into barriers that may be more unique to maternal-fetal surgery and affect some groups more than others, such as commonly used psychosocial exclusion criteria. Almost half of the 14 studies that reported psychosocial exclusion variables used the MOMS trial criteria [10]. These criteria are more subjective than the medical criteria (e.g., inadequate support at home, inadequate understanding of risks and benefits of the procedure) and may be influenced by implicit bias. In particular, the "inability to comply with medical restrictions for follow up" (e.g., significant decrease in maternal activity) may present an unequal barrier to minority and lower SES populations who may be less able to take time off from work or get help caring for other children at home. Although these criteria were designed to protect pregnant people, they may also have negative effects that justify further investigation.

Limitations

Findings from this systematic review must be understood in the context of the following limitations. First, this study is limited to only the conditions and treatments included in the AHRQ Maternal-Fetal Surgical Procedures Technical Brief, which excluded some procedures (e.g., intra-uterine transfusions) [14]. Second, it is unclear how race or ethnicity was captured by researchers in the studies reporting those sociodemographic variables (e.g., self-reported, extracted from medical record). Third, we were unable to calculate PPR for many conditions due to a lack of racial and ethnic study data as well as a lack of disease prevalence data stratified by racial and ethnic groups. For MMC and TTTS we used the larger populations of spina bifida and monochorionic twins as a substitute for the missing exact condition-specific data. Finally, population-based data representing disease prevalence came from two U.S. datasets – The National Vital Statistics System (NVSS) and The National Birth Defects Prevention Network (NBDPN). These databases do not capture incidence of congenital anomalies that resulted in termination of pregnancy or fetal demise. This may skew the true prevalence of these diseases and thus the PPR calculations. However, there is significant variability in the rate of termination of pregnancy for fetal anomaly (TOPFA) based on race, socioeconomic status, and geographic location, which may mitigate any confounding influence [36].

Conclusion

Sociodemographic reporting quality in maternal-fetal surgery studies is poor, which limits external validity and inhibits examinations of potential health disparities. Studies in the U.S. do not adequately represent disease populations, even when minority racial or ethnic groups are most burdened by the disease. Sociodemographic reporting standards and diversity enrollment targets should be established for maternal-fetal surgery studies to improve generalizability and representation. Inclusion of diverse participants may lead to more robust and comprehensive data that expands our understanding of potential sociodemographic differences in access to care, decision-making, treatment responses, and outcomes.

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Data Availability Statement

The data used in this study are publicly available.

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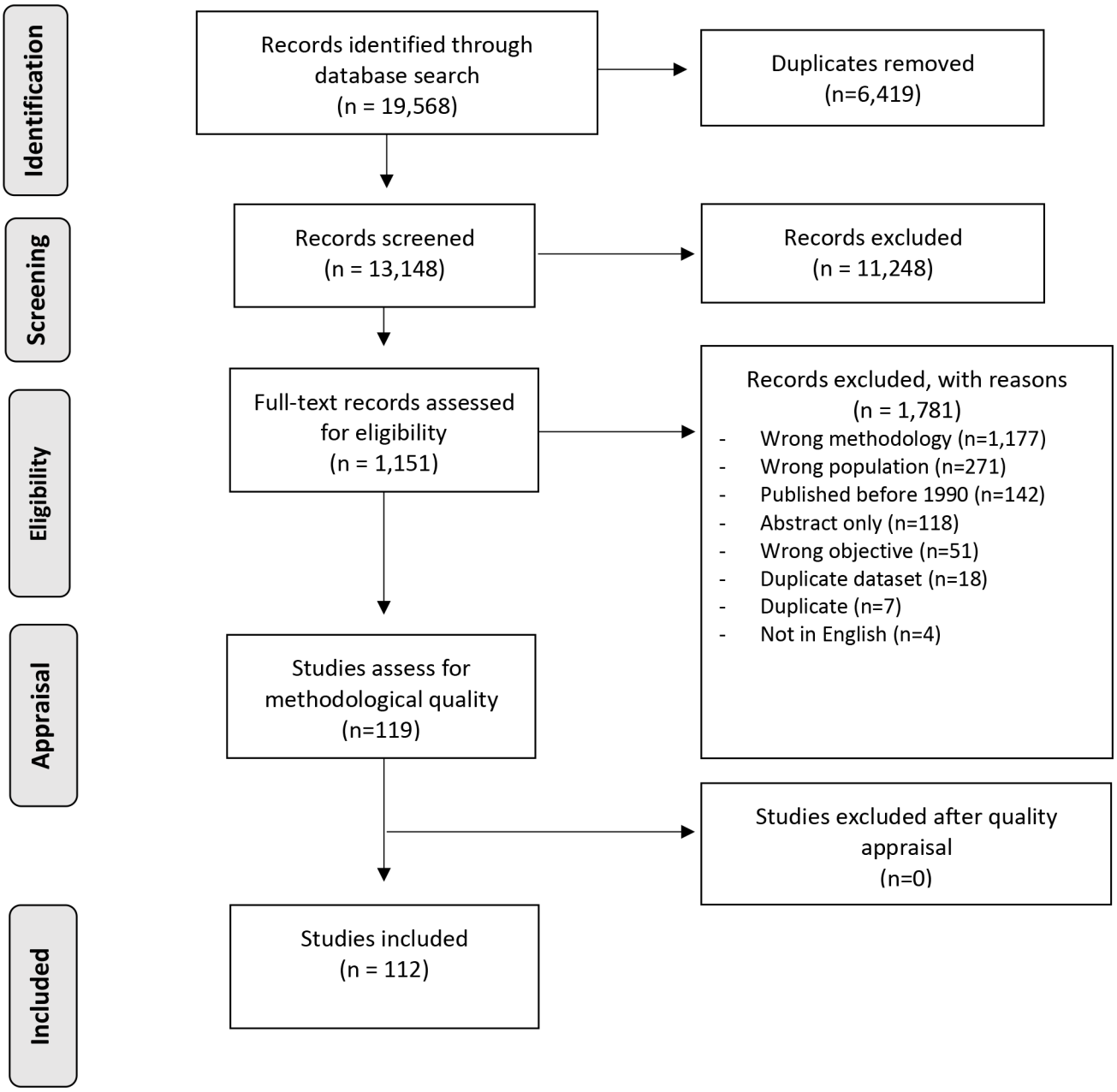

Figure 1.
PRISMA flow chart

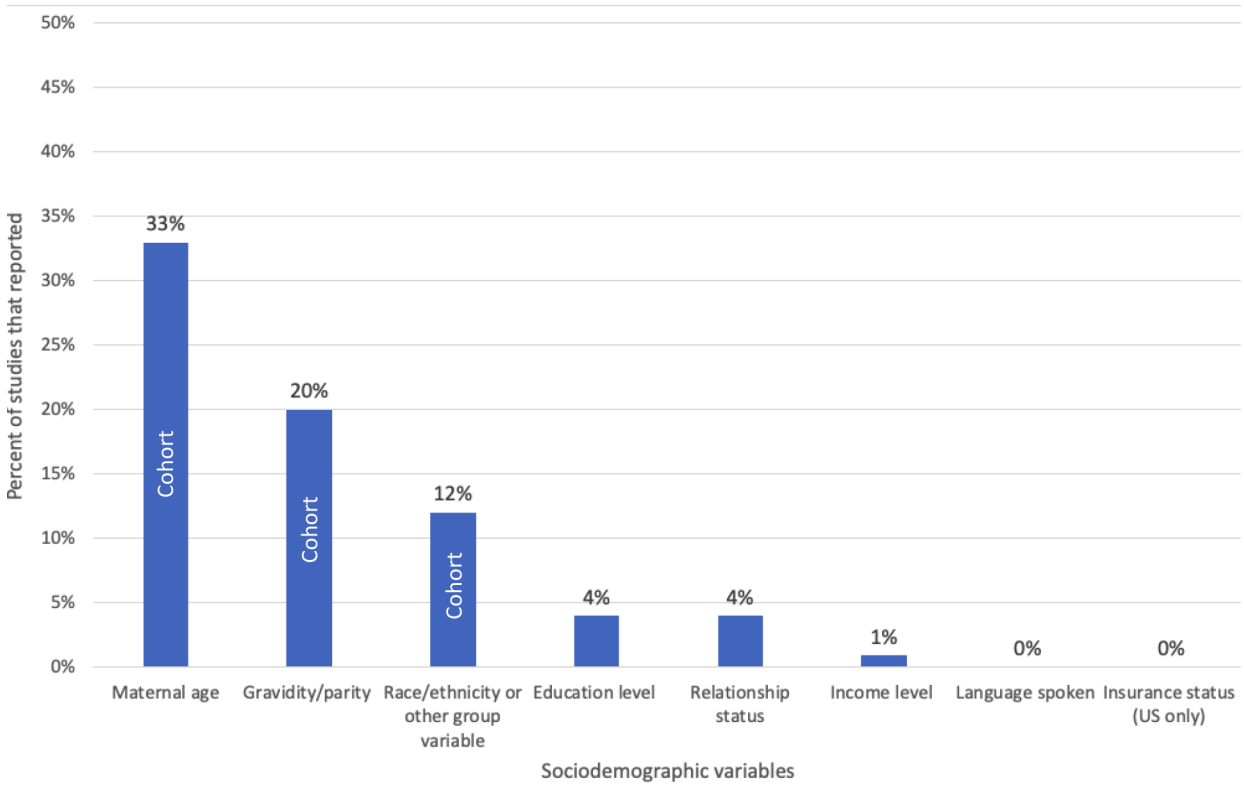

Figure 2.
Sociodemographic reporting by variable

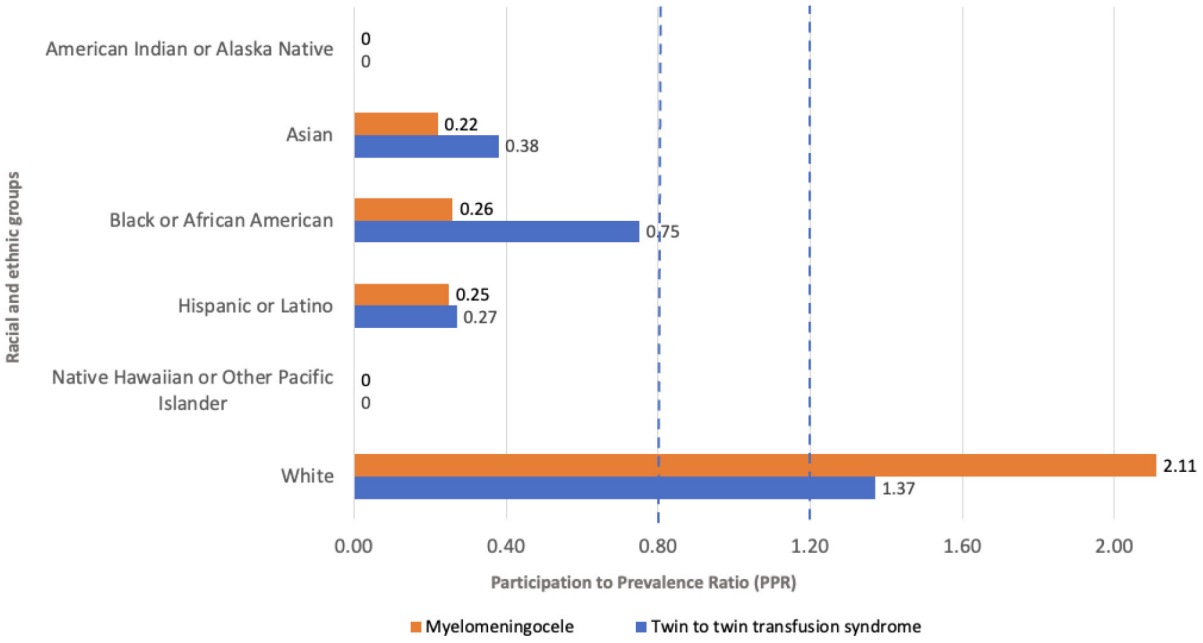

Figure 3.

Participation-to-prevalence ratios (PPRs) for myelomeningocele and twin-to-twin transfusion maternal-fetal surgery studies.

The vertical dashed line at participation to prevalence ratio (PPR) of 0.8 indicates that lower values represent underrepresentation, and the dashed line of 1.2 indicates that higher values represent overrepresentation. Values from 0.8 to 1.2 indicate that the proportion of the group in the study almost equals its proportion in the U.S. disease population.

Table 1.

Characteristics of primary study sample

Conditions (n)		**Twin–twin transfusion syndrome (41) [37–78]**	**Myelomeningocele (26) [79–88, 10, 89–102]**	**Congenital diaphragmatic hernia (23) [103–125]**	**Obstructive uropathy (8) [126–133]**	**Thoracic lesions (7) [134–140]**	**Cardiac defects (3) [141–143]**	**Sacrococcygeal teratoma (3) [144–146]**
Location	U.S.	13	19	6	2	5	1	1
	Outside U.S.	21	7	17	6	2	0	2
	U.S. + Outside	6	0	0	0	0	0	0
	Unspecified	2	0	0	0	0	2	0
Study type	RCT	4	3	2	1	0	0	0
	Prospective cohort study	12	2	7	1	0	1	0
	Retrospective cohort study	26	21	14	6	7	2	3
Years		1997–2019	1999–2020	1997–2020	1994–2020	2005–2018	2009–2018	2011–2017
Number of sites (av.)		1–11 (2)	1–3 (1)	1–5 (1)	1–21 (4)	1–2 (1)	1–15 (7)	1–2 (1)
Sample size (av.)		14–666 (118)	5–293 (75)	11–191 (63)	23–111 (47)	9–294 (68)	67–270 (136)	13–112 (49)