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Pregnancy termination following prenatal diagnosis of anencephaly or spina bifida: a systematic review of the literature

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Abstract

Background—In regions where prenatal screening for anencephaly and spina bifida is widespread, many cases of these defects are prenatally diagnosed. The purpose of this study was to estimate the frequency of termination of pregnancy (TOP) following prenatal diagnosis of anencephaly or spina bifida and to investigate factors associated with TOP that might lead to selection bias in epidemiologic studies.

Methods—We included articles indexed in Medline and Embase between 1990 and May 2012 reporting the frequency of TOP following prenatal diagnosis of anencephaly or spina bifida with English-language abstracts, ≥20 prenatally diagnosed cases, and at least half of the study years in 1990 or later. We summarized the frequency of TOP across studies using random-effects meta-analysis and stratified results by fetal and study characteristics.

Results—Among the 17 studies identified, 9 included anencephaly and 15 included spina bifida. Nine were from Europe, 6 were from North America, and 1 each was from South America and Asia. The overall frequency of TOP following prenatal diagnosis was 83% for anencephaly (range: 59–100%) and 63% for spina bifida (range: 31–97%). There were insufficient data to stratify the results for anencephaly; TOP for spina bifida was more common when the prenatal diagnosis occurred <24 weeks gestation, with defects of greater severity, and in Europe versus North America.

Conclusions—Because underascertainment of birth defects might be more likely when the pregnancy ends in TOP and TOP is associated with fetal characteristics, selection bias is possible in epidemiologic studies of anencephaly or spina bifida.

Keywords

anencephaly; meta-analysis; prenatal diagnosis; spina bifida; termination of pregnancy

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.
INTRODUCTION

Neural tube defects (NTDs) are birth defects caused by failure of the neural tube to close completely, resulting in incomplete formation of the brain or spinal cord (Botto et al., 1999; Mitchell et al., 2004). The two most common types of NTDs are anencephaly, characterized by absence of much of the skull and brain, and spina bifida, a herniation of neural tissue through an incompletely formed spine (Botto et al., 1999). Anencephaly is a lethal condition and liveborn infants typically survive less than one day (Jaquier et al., 2006; Obeidi et al., 2010). The severity of spina bifida is more variable. Complications of spina bifida can lead to death; however, this is not the most common outcome, with over 90% of liveborn infants with spina bifida in the United States surviving the first year of life with varying levels of sensory loss and paralysis (Bol et al., 2006; Doherty and Shurtleff, 2006).

Screening for elevated maternal serum alpha-fetoprotein levels in the second trimester of pregnancy can identify over two-thirds of fetuses with open neural tube defects (defects that are not covered by skin), including almost all fetuses with anencephaly (Cameron and Moran, 2009; Driscoll et al., 2009). The rapid increase in use of second and third trimester ultrasonography since the 1970s has led to prenatal ultrasounds becoming a common and effective method for prenatal screening for and detection of NTDs and other birth defects (Peller et al., 2004). Given the often severe nature of NTDs, termination of pregnancy (TOP) is common following prenatal diagnosis if the diagnosis is made early enough for this to be an available option (Mansfield et al., 1999).

The increasing frequency of prenatal diagnosis and TOP has important implications for the interpretation of results from epidemiologic studies of birth defects such as NTDs, for which both prenatal diagnosis and TOP are relatively common. Not all fetuses with NTDs are able to be included in epidemiologic studies. Cases from pregnancies ending in TOP are more difficult to ascertain than those ending in live birth and typically require inclusion of additional case ascertainment sources. Descriptive studies underestimate the number of pregnancies with recognized NTDs when only live births are included or some proportion of affected pregnancies resulting in TOPs is missed (Roberts et al., 1995; Bower et al., 2001; Cragan and Gilboa, 2009). In etiologic studies, exclusion or incomplete ascertainment of NTDs among TOPs can lead to selection bias when the exposure of interest is associated with likelihood of TOP (Cragan and Khoury, 2000). Clinical studies of long-term outcomes following infants from birth might not be useful for counseling parents with prenatally diagnosed fetuses about prognosis if liveborn infants represent only a small, selected subset of all affected pregnancies.

Quantifying the frequency of TOP and factors associated with TOP is important for understanding how underascertainment of cases might affect study results. A systematic review of studies published between 1987 and 1995 estimated that 84% and 64% of pregnancies known to be affected with anencephaly and spina bifida, respectively, ended in TOP (Mansfield et al., 1999). Since that review was published, no further summary of the frequency of TOP has been performed to determine if these estimates still accurately reflect the present-day situation. The purpose of the present analysis is to estimate the proportion of pregnancies ending in TOP following prenatal diagnosis of anencephaly or spina bifida.
during a time period when ultrasonography was widely used for prenatal diagnosis of NTDs and to investigate factors associated with TOP that could contribute to selection bias in epidemiologic studies of these defects.

METHODS

Search Strategy

We included epidemiologic studies indexed in Medline and Embase from 1990 through May 2012 that reported both the number of cases of anencephaly or spina bifida prenatally diagnosed in a specific time period and the number of these cases in which the pregnancy outcome was TOP. The search strategy included search terms and synonyms for "neural tube defect", "anencephaly", "spina bifida", "prenatal diagnosis", and "pregnancy termination" (Appendix). We identified additional studies by searching reference lists of included articles and by using Google Scholar to search for more recently published articles citing the included studies. Information abstracted from each article included location and dates of participant recruitment, number of prenatally diagnosed cases of anencephaly or spina bifida, the number of these cases with TOP as the pregnancy outcome, and fetal and study characteristics such as defect type and the country where the study was conducted (described in further detail below).

Inclusion and Exclusion Criteria

Two types of studies were eligible for inclusion: studies following a prospective or retrospective cohort of prenatally diagnosed fetuses to determine outcome of pregnancy and studies using birth defects surveillance or registries that ascertain prenatally diagnosed cases and pregnancies ending in TOP (although ascertainment might not be complete). Additional inclusion criteria were: an English-language abstract, pregnancy outcome known for at least 20 prenatally diagnosed cases of anencephaly or of spina bifida, and at least half the study years in 1990 or later. We restricted our analysis to studies of at least 20 prenatally diagnosed cases to ensure the estimates were fairly stable. The restriction to studies mostly conducted in 1990 or later was made because after this time fetal ultrasound was in widespread use in most countries monitoring neural tube defects and the decision to continue or end an affected pregnancy would have likely involved not only serum screen results but also ultrasound confirmation of the specific defect.

We excluded studies that analyzed only fetuses with both NTDs and other specific non-NTD diagnoses (e.g., studies of fetuses with both NTDs and chromosomal abnormalities) or specific indications on ultrasound (e.g., studies of fetuses with both NTDs and increased nuchal translucency). We also excluded studies conducted exclusively in non-singletons. When two studies included information from overlapping populations, we included the most recent study or the study with the largest catchment area (e.g., a national study would be chosen over a regional study). Studies were also excluded if they were conducted in a location where no TOP was reported because it was not legally permitted at any gestational age.
Statistical Analyses

In each study, we calculated the frequency of TOP as the number of pregnancies ending in TOP among those in which a prenatal diagnosis was made and pregnancy outcome was known. We used random-effects meta-analysis of proportions to calculate the combined frequency of TOP and 95% confidence interval (CI) across studies. The $I^2$ statistic and 95% uncertainty interval (UI) were used to quantify between-study heterogeneity. $I^2$ ranges from 0 to 100% and is an estimate of the proportion of variability that is attributable to between-study variability as opposed to chance. Values of 25%, 50%, and 75% have been suggested as rough indications of low, moderate, and high proportions of between-study heterogeneity (Higgins et al., 2003). Analyses were conducted using the ‘meta’ package in R (www.r-project.org).

In some studies, pregnancies were lost to follow-up and the outcome of pregnancy was unknown. When this occurred, we restricted the analysis to the subset of pregnancies with known outcomes to make these studies comparable to studies which reported no pregnancies lost to follow-up; it was often not possible to determine if a study truly had no pregnancies lost to follow-up or if these pregnancies were excluded prior to analysis. If this restriction decreased the number of cases in the study to less than 20, the article was considered to be ineligible for inclusion.

If fetuses undergoing surgery for in utero spina bifida repair had been excluded from the original study, we added them back into our analysis and categorized them as pregnancies not ending in TOP.

To investigate factors potentially associated with TOP, we categorized studies according to study design (cohort vs. surveillance or registry), case type (all cases vs. isolated defects), defect type (open vs. closed, for spina bifida only), geographic region (Europe vs. North America), and gestational age at prenatal diagnosis (<24 weeks vs. ≥24 weeks); we identified this set of variables after reading the included articles and determining what information was available. If results were reported for more than one stratum (e.g., results for open and closed defects presented separately within the same article), the article was included once in each category. For these stratified analyses, we did not restrict our analyses to subgroups with 20 or more prenatally diagnosed cases. We compared meta-analysis results across strata using a two-sided Z-test for proportions.

RESULTS

We identified 15 articles meeting inclusion criteria using the search strategy (Harmon et al., 1995; Forrester and Merz, 2000; Waller et al., 2000; Olde Scholtenhuis et al., 2003; Biggio et al., 2004; Garne et al., 2005; Ghi et al., 2006; Nikkila et al., 2006; Tairou et al., 2006; D’Addario et al., 2008; Poretti et al., 2008; Aguilera et al., 2009; Amari et al., 2010; Lu et al., 2011; Machado et al., 2012). One additional article was found using Google Scholar (this article had cited one of the articles identified using the search strategy) (Adama van Scheltema et al., 2003) and one article was known to the authors and included (Shulman et al., 1994). Of these 17 included articles, 9 reported information on anencephaly and 15 on
spina bifida. Nine articles were from Europe, 6 were from North America, 1 was from South America, and 1 was from Asia.

**Frequency of TOP in Included Studies**

The overall frequency of TOP following prenatal diagnosis in the 9 studies of anencephaly was 83% (95% CI, 70–93%) by random-effects meta-analysis and ranged from 59% to 100% in individual studies (Table 1). In the 15 studies of spina bifida, the overall frequency of TOP by random-effects meta-analysis was 63% (95% CI, 51–74%) and estimates from individual studies ranged from 31% to 97%. There was substantial between-study heterogeneity in each meta-analysis (anencephaly $I^2 = 95\%$, spina bifida $I^2 = 95\%$).

**Factors Investigated in Association With Frequency of TOP**

There were few studies of anencephaly available to investigate factors associated with frequency of TOP between studies; therefore, only results for spina bifida are shown (Table 2). No study provided data to evaluate associations between maternal sociodemographic characteristics and TOP after prenatal diagnosis of spina bifida.

**Geographic region**—In both North America and Europe, the frequency of TOP following prenatal diagnosis of spina bifida was variable. Estimates ranged from 31% to 82% in North America and from 41% to 89% in Europe. Overall, TOP following prenatal diagnosis was more common in Europe (66%) than North America (50%).

**Study design**—Of the 15 studies, 5 used data from birth defect surveillance or registries and the remainder followed a cohort of prenatally diagnosed fetuses for pregnancy outcome. All cohort studies were hospital-based and used records of prenatal diagnoses as the source of data. Of the 5 surveillance or registry studies, 2 had hospital-based case ascertainment and the rest had multiple sources of hospital- and non-hospital-based ascertainment. Estimates from studies using surveillance or registries were similar to those from cohort studies (64% vs. 62%); however, results from the surveillance and registry studies stratum were heavily influenced by two studies with large sample size ($n >100$) and high prevalence of TOP (>75%) (Garne et al., 2005; Lu et al., 2011).

**Case type**—Five studies presented analyses restricted to fetuses with isolated spina bifida and the remainder included all types of cases. TOP was more common in studies including all types of cases than those restricted to fetuses with isolated defects (66% vs. 56%).

**Defect type**—Two studies presented results for closed spina bifida and five for open spina bifida. In the two studies of closed spina bifida, the frequency of TOP was 22% and 50% (combined frequency: 33%), but both estimates were based on small subgroup analyses within each study and included fewer than 10 prenatally diagnosed fetuses. For open spina bifida, the estimates ranged from 36% to 91% (combined frequency: 60%).

**Gestational age at prenatal diagnosis**—Four studies (all from Europe) reported frequency of TOP stratified by gestational age at prenatal diagnosis (<24 versus ≥24 gestational weeks). TOP was more common when prenatal diagnosis was made <24 weeks
rather than later (86% vs. 27%). Gestational age at prenatal diagnosis appeared to be responsible for some of the between-study variability (Table 3). For example, the overall frequency of TOP was lower in the Netherlands (49%) than other European countries (78%), but once restricted to prenatal diagnoses made <24 weeks, the Netherlands and other European countries had similar estimates (92% vs. 91%). Nevertheless, between-study heterogeneity remained high after stratifying on gestational age (<24 weeks: $I^2 = 62\%$, ≥24 weeks: $I^2 = 78\%$).

DISCUSSION

Among the studies identified in this review, 83% of pregnancies known to be affected with anencephaly and 63% of those known to be affected with spina bifida ended in TOP. However, no study presumably had 100% sensitivity for ascertaining NTDs and sensitivity likely varied between included studies. Because epidemiologic studies and surveillance programs are more likely to underascertain pregnancies prenatally diagnosed and ending in TOP than those ending in live births (Cragan et al., 1995), these are likely to be underestimates of the prevalence of TOP.

These estimates are similar to those from a previous systematic review of the frequency of TOP published over a decade ago: 84% (95% CI, 82–86%) for anencephaly and 64% (95% CI, 61–67%) for spina bifida (Mansfield et al., 1999). Although the similarity between estimates in the present and previous reviews suggests that the likelihood of TOP following prenatal diagnosis of anencephaly or spina bifida has not appreciably changed over time, the overlap in the study years and differences in the inclusion and exclusion criteria between reviews make any direct comparison of results difficult. A study analyzing time trends within a single population would be needed to confirm if there have been changes in the proportion of pregnancies ending in termination over time.

With a substantial proportion of pregnancies ending in TOP following prenatal diagnosis, investigators should be aware that epidemiologic studies conducted only among live births include a highly selected sample of the total population of fetuses with NTDs. Previous studies have reported that maternal characteristics such as education, age, and race/ethnicity are associated with the outcome of NTD-affected pregnancies (Velie and Shaw, 1996; Parks et al., 2011); however, these studies have not separated the effects of these characteristics on the decision to terminate a pregnancy following prenatal diagnosis from their effects on access to or uptake of prenatal diagnosis. Two studies included in this review investigated maternal characteristics associated with TOP following prenatal diagnosis. One reported no difference in maternal age, gravidity, parity, or history of spontaneous abortions between pregnancies ending in TOP compared to other pregnancy outcomes following prenatal diagnosis of anencephaly (Machado et al., 2012). The second did not present results separately for each NTD type (anencephaly, spina bifida, and encephalocele) but found that TOP following prenatal diagnosis of NTDs was more common in older than younger mothers, in Asian compared to white mothers, and in certain areas of their study catchment area in Hawaii (Forrester and Merz, 2000). Because these characteristics are associated with TOP and therefore inclusion in the study, selection bias is possible in studies investigating these factors in relation to NTD etiology (Cragan and Khoury, 2000). Further studies will be
needed to evaluate whether these and other maternal and fetal characteristics are associated with TOP following prenatal diagnosis for different NTD subtypes.

Regional differences in average gestational age at prenatal diagnosis are a possible explanation for some of the observed between-study variability in frequency of TOP. Greater frequency of TOP is expected at earlier gestational ages because many regions have laws restricting the gestational ages at which TOP may be performed. These results suggest the importance of considering characteristics that delay prenatal diagnosis as potential sources of selection bias. As an example, ultrasound visualization of the fetal anatomy and prenatal diagnosis of birth defects is more difficult in obese mothers than normal weight mothers (Hendler et al., 2004; Dashe et al., 2009). If the ultrasound examination must be repeated later in pregnancy to complete the fetal anatomic examination or if an accurate diagnosis cannot be made, obese mothers might have on average a later gestational age at prenatal diagnosis than non-obese mothers and therefore be less likely to be able to consider a TOP (Hendler et al., 2004; Phatak and Ramsay, 2010). As a result, non-obese mothers might be more likely to have a TOP than obese mothers and cases of NTDs among non-obese mothers might be missed, creating a potentially spurious association between prepregnancy obesity and NTDs.

Severity of the defect is another important consideration for continuing or terminating a pregnancy following prenatal diagnosis (Evans et al., 1996; Peller et al., 2004; Shaffer et al., 2006). Pregnancies complicated by a severe NTD or one accompanied by multiple major malformations might be more likely to end in TOP than an isolated NTD or a less severe case. Severity of the defect is more relevant for spina bifida than anencephaly because the latter is uniformly lethal. In our review there was little information on the effect of severity of spina bifida on likelihood of TOP, but the results suggested a higher frequency of TOP for fetuses with open defects compared to those with closed defects. This point is important when results from studies reporting clinical outcomes such as shunting or mobility impairment are used to counsel families with a prenatally diagnosed fetus on long-term prognosis. Consideration should be given to the possibility that the fetuses most likely to be liveborn and to have follow-up information available are those with the least severe defects; thus, results from studies based on liveborn infants might not be generalizable to all prenatally diagnosed fetuses.

Incomplete ascertainment of cases of anencephaly or spina bifida among pregnancies ending in TOP also pose problems for evaluating population-based interventions for the prevention of these defects. For example, using data from surveillance to evaluate the success of folic acid fortification programs is difficult because of the high frequency of prenatal diagnosis and TOP and the difficulty in separating the effects of the intervention from changes in prenatal diagnosis and TOP over time (Besser et al., 2007); in this situation, alternate strategies such as bio-monitoring might be warranted (Oakley et al., 2008).

One limitation of this study was the inability of our search strategy to identify all relevant articles. Restricting the search databases to Medline and Embase likely resulted in missed articles in languages other than English and articles from journals not indexed by these databases, particularly those outside North America and Europe.
proportion of pregnancies with prenatal diagnosis ending in TOP is not a common study objective, this information is often presented in the text and not the abstract. There might be other articles reporting the frequency of TOP following prenatal diagnosis not captured by a search strategy that exclusively searches abstracts; this could affect our conclusions if study results systematically differ between studies identified and not identified by our search strategy. A second limitation of our analysis was the exclusion of prenatally diagnosed fetuses with unknown pregnancy outcomes by us or by authors of the included studies. This exclusion would likely produce underestimates of the frequency of TOP if pregnancies with unknown outcomes might be more likely to represent TOP than the more easily ascertained live births. Third, estimates from each study were variable. Although we presented a summary frequency of TOP to capture the overall state of the available literature, the frequency of TOP likely varies by region. Given the evidence available in the literature, it was not possible to determine if this variability was due to differences in attitudes toward TOP, timing of prenatal diagnosis, laws restricting TOP, case ascertainment procedures, or other reasons.

Our results suggest, in accordance with previous studies, that TOP is the most common outcome of pregnancy following prenatal diagnosis of anencephaly and spina bifida, particularly when the prenatal diagnosis is made prior to 24 weeks of gestation. The relatively small proportion of fetuses with NTDs presenting as live births will present challenges to investigators conducting studies in which not all NTD-affected pregnancies among TOPs are included. A better understanding of factors associated with TOP following prenatal diagnosis of anencephaly or spina bifida will provide much needed information on the potential for selection bias in etiologic studies and generalizability in studies of the prognosis of prenatally diagnosed fetuses.

LITERATURE CITED


### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Years</th>
<th>Anencephaly&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Spina Bifida&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
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<td>56/85 66</td>
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<td>Birmingham, USA</td>
<td>1996–2000</td>
<td>20/56 36</td>
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<td>Forrester 2000</td>
<td>Hawaii, USA</td>
<td>1986–1997</td>
<td>64/78 82</td>
<td>32/65 49</td>
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<td>1995</td>
<td>23/36 64</td>
<td>10/27 37</td>
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<td>Harmon 1995</td>
<td>Indianapolis, USA</td>
<td>1988–1994</td>
<td>19/61 31</td>
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<td>Shulman 1994</td>
<td>Memphis, USA</td>
<td>1988–1993</td>
<td>18/22 82</td>
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<td>Amari 2010</td>
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<td>68/103 66</td>
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<td>Garne 2005</td>
<td>Europe&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1995–1999</td>
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<td>Olde Scholtenhuis 2003</td>
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<td>Asia</td>
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<tr>
<td>Lu 2011</td>
<td>China&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2008–2009</td>
<td>174/174 100</td>
<td>137/141 97</td>
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</table>

<sup>a</sup> Overall proportion of pregnancies ending in TOP are 83% (95% confidence interval 70–93%) for anencephaly and 63% (95% CI, 51–74%) for spina bifida.

<sup>b</sup> Number of pregnancies ending in termination of pregnancy/number of fetuses prenatally diagnosed.

<sup>c</sup> Belgium (Antwerp, Hainaut), Bulgaria (Sofia), Croatia, Denmark (Funen County), France (Paris, Strasbourg), Germany (Maine, Saxony-Anhalt), Italy (Campania, Tuscany), Malta, Portugal (South), Spain (Asturias, Basque Country), Switzerland (Vaud), and the United Kingdom (Wales).
Amsterdam, Rotterdam, Utrecht.

Shanxi and Shandong provinces.
Table 2
Proportion of Pregnancies Affected by Spina Bifida Ending in Termination Following Prenatal Diagnosis From Random-Effects Meta-Analysis, by Fetal and Study Characteristics.

<table>
<thead>
<tr>
<th>Geographic region</th>
<th>Number of Studies</th>
<th>Summary Frequency of TOP, % (95% CI)</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Range of Estimates</th>
<th>95% (95% UI)</th>
</tr>
</thead>
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<td>All studies</td>
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<td>63 (51–74)</td>
<td></td>
<td>31–97</td>
<td>95 (93–96)</td>
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<tr>
<td>Geographic region</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>8</td>
<td>66 (53–77)</td>
<td>0.09</td>
<td>41–89</td>
<td>92 (86–95)</td>
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<tr>
<td>North America</td>
<td>6</td>
<td>50 (35–64)</td>
<td></td>
<td>31–82</td>
<td>85 (70–93)</td>
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<tr>
<td>Study design</td>
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<tr>
<td>Cohort</td>
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<td>62 (49–73)</td>
<td>0.85</td>
<td>31–89</td>
<td>90 (84–94)</td>
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<td>Surveillance or registry</td>
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<td>64 (39, 85)</td>
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<td>Case type</td>
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<td>All cases</td>
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<td>66 (54–78)</td>
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<td>Defect type</td>
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<tr>
<td>Open</td>
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<td>60 (39–80)</td>
<td>0.09</td>
<td>36–91</td>
<td>94 (89–97)</td>
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<tr>
<td>Closed</td>
<td>2</td>
<td>33 (12–58)</td>
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<td>22–50</td>
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<td>Gestational age at prenatal diagnosis</td>
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<tr>
<td>&lt;24 weeks</td>
<td>5</td>
<td>86 (79–91)</td>
<td>&lt;0.01</td>
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<td>62 (60–86)</td>
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<td>≥24 weeks</td>
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<td>27 (14–43)</td>
<td></td>
<td>16–41</td>
<td>78 (40–92)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; UI, uncertainty interval.

<sup>a</sup> Studies do not sum to total because studies can be counted in more than one or in no category.

<sup>b</sup> Two-sided Z-test for proportions.

<sup>c</sup> Studies with lowest and highest estimates.

<sup>d</sup> Too few studies to estimate \( I^2 \) and 95% UI.
Table 3

Proportion of Pregnancies Affected by Spina Bifida Ending in Termination Following Prenatal Diagnosis, by Gestational Age at Prenatal Diagnosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>All Fetuses</th>
<th>Prenatal Diagnosis</th>
<th>Prenatal Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n/N</td>
<td>&lt; 24 Weeks</td>
<td>≥ 24 Weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Game 2005</td>
<td>Europe(^b)</td>
<td>297/385</td>
<td>77</td>
<td>253/278</td>
</tr>
<tr>
<td>Aguiler 2009</td>
<td>United Kingdom</td>
<td>53/74</td>
<td>72</td>
<td>50/65</td>
</tr>
<tr>
<td>Amari 2010</td>
<td>Germany</td>
<td>68/103</td>
<td>66</td>
<td>63/74</td>
</tr>
<tr>
<td>Olde Scholtenhuis 2003</td>
<td>Netherlands</td>
<td>43/88</td>
<td>49</td>
<td>35/38</td>
</tr>
</tbody>
</table>

\(^a\) Number of pregnancies ending in termination of pregnancy/number of fetuses prenatally diagnosed.

\(^b\) Belgium, Bulgaria, Croatia, Denmark, France, Germany, Italy, Malta, Portugal, Spain, Switzerland, and the United Kingdom. Fetuses with unknown gestational age at prenatal diagnosis excluded from “All Fetuses” column.