

ORIGINAL ARTICLE

# Gastroschisis in Brazil within a Global Context

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## Abstract

**Introduction:** global disparity in outcomes of gastroschisis is visible. Survival rates in high-income countries have improved since 1960, and are currently around 100%, due to progress in pediatric surgery and neonatal intensive care. However, in low- and middle-income countries mortality rates can reach all cases.

**Objective:** this study aims to map the existing literature on gastroschisis in Brazil within a global context.

**Methods:** scoping Review. PubMed, Scielo Brazil, Biblioteca Virtual em Saúde (BVS) and Google Scholar, were searched from January 2000 to May 2020.

**Results:** eight studies met the inclusion criteria. The consolidated data of 912 patients were: Mean maternal age of 20.7 years, antenatal diagnosis rate of 80.2%, cesarean section rate of 77.7%. Mean of hospital stay of 40.8 days. Mean mortality rate of 25.3 %. Risk factors associated with death were: prematurity, low birth weight, low APGAR score, reinterventions, sepsis, birth-to-surgery interval greater than 4 hours, fewer prenatal visits, delayed prenatal diagnosis.

**Conclusion:** studies on gastroschisis in Brazil were scarce, most of carried out in southeast of country. This study suggests that there are regional contrasts on gastroschisis outcomes in Brazil. The worst results are in regions with low economic resources, a similar situation found in international literature. This review should be validated with future studies to investigate the situation of pregnant women with fetuses with gastroschisis, especially in low-resource regions, in Brazil.

**Keywords:** Brazil, congenital abnormalities, gastroschisis, newborn, pregnancy outcome.

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## Authors summary

### Why was this study done?

There are few publications on results of gastroschisis cohorts in low- and middle-income countries. This scope review aims to map the existing literature on gastroschisis in Brazil and to discuss the body of evidence available in a global context.

### What did the researchers do and find?

Studies on gastroschisis in Brazil have been scarce, most of them carried out in southeast of country. The data were consolidated and results suggest that there are regional contrasts in outcomes of gastroschisis in Brazil. Worst results are in regions with few economic resources, a situation similar to that found in the international literature.

### What do these findings mean?

It is expected to contribute to the policy makers and professionals involved in assisting patients with gastroschisis in obtaining better results in health care for this population.

## INTRODUCTION

Gastroschisis (GS) is a congenital anomaly that consists of abdominal organs externalization through a defect, which in most cases is to the right of the umbilical cord; the organs are not covered by membranes<sup>1</sup>. Its pathogenesis is related to abnormalities in “physiologic” umbilical herniation, which occurs between the fifth and tenth weeks of gestation<sup>2</sup>.

A global disparity in outcomes of GS is visible<sup>3</sup>. Survival rates in high-income countries (HICs) have improved since 1960 and are currently around 100%, due to progress in pediatric surgery and neonatal intensive care<sup>3</sup>. However, in low-income countries (LICs) mortality rates can reach all cases<sup>3</sup>. The lack of antenatal diagnosis, inefficiency in pre-hospital care, limited access to neonatal intensive care units (NICU), unavailability of pediatric surgery and total parenteral nutrition (TPN) are factors related to death in regions with low economic resources<sup>3</sup>.

There are few publications on outcomes of cohorts of gastroschisis in low-and middle-income countries LMICs<sup>3</sup>. Brazil is an upper-middle-income country with regional contrasts<sup>4</sup>. Southeast region has higher Human Development Indexes (HDI), more qualified health professionals and NICU beds than those in north and northeast regions of country<sup>5,6</sup>. This Scoping review aims to map the existing literature on GS in Brazil and within the global context.

## METHODS

### Study Design

The method of this scoping review was based on the format described by Arksey and O’Malley<sup>7</sup> and advanced by Levac *et al.*<sup>8</sup> included the following five main phases: (1) definition of the research question, (2) recognition of relevant studies, (3) selection of the study, (4) data mapping and (5) collating, summarizing and reporting the results. The specific question was: “What is the current state of evidence on the outcomes of patients with gastroschisis in Brazil?”

### Data sources

Search was performed in PubMed, Scielo Brazil, Biblioteca Virtual em Saúde (BVS). We limited our search to studies published in English and Portuguese, in the period between January 2000 and May 2020.

Search: The descriptors “Gastroschisis and Brazil” and “Gastroquise” were adopted, and the inherent

operational properties of each database were observed. The search and selection process were carried out independently by two authors (ALN and VMM), who read the title and the summary of the publications.

### Study selection

The inclusion criteria were original publications on GS carried out in the NICU in Brazil. The exclusion criteria were studies that included other major congenital malformations, duplicate databases, case reports, unpublished theses or dissertations, editorials, letters from readers, qualitative studies, presentations at scientific events, book chapters, classes, research carried out exclusively with fetuses (fetal medicine) and experimental research on animals.

The flowchart of the study was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (figure 1)<sup>9</sup>.

The following data were extracted: geographic region of Brazil, research period, site of study, study design, prenatal and postnatal variables. These two latter variables comprised the following parameters: Prenatal care and delivery variables: maternal age (mean) and antenatal diagnosis (%), route of delivery (vaginal or cesarean section), place of birth (inborn or outborn), gender, birth weight (grams) and gestational age (weeks). Postnatal variables: GS simple or complex gastroschisis (CG) (with atresia, stenosis, volvulus, ischemia, necrosis)<sup>10</sup>. Type of wall closure (primary closure or silo placement), TPN (mean time or percentage of use), mechanical ventilation “MV” (mean time or percentage of use), sepsis, time to first enteral feeding (mean of days), time to full enteral feeding (mean of days), hospital length of stay (mean of days), mortality rate (%) and total number of patients.

## RESULTS

Eight studies met inclusion criteria. Table 1 shows included studies<sup>11-18</sup>.

### Outcomes extracted from included studies

Outcomes of 912 patients were verified. The smallest number of individuals observed was 31 and the largest was 207<sup>13,18</sup>. Table 2 shows variables of prenatal care and delivery and table 3 variables of post-surgical care.

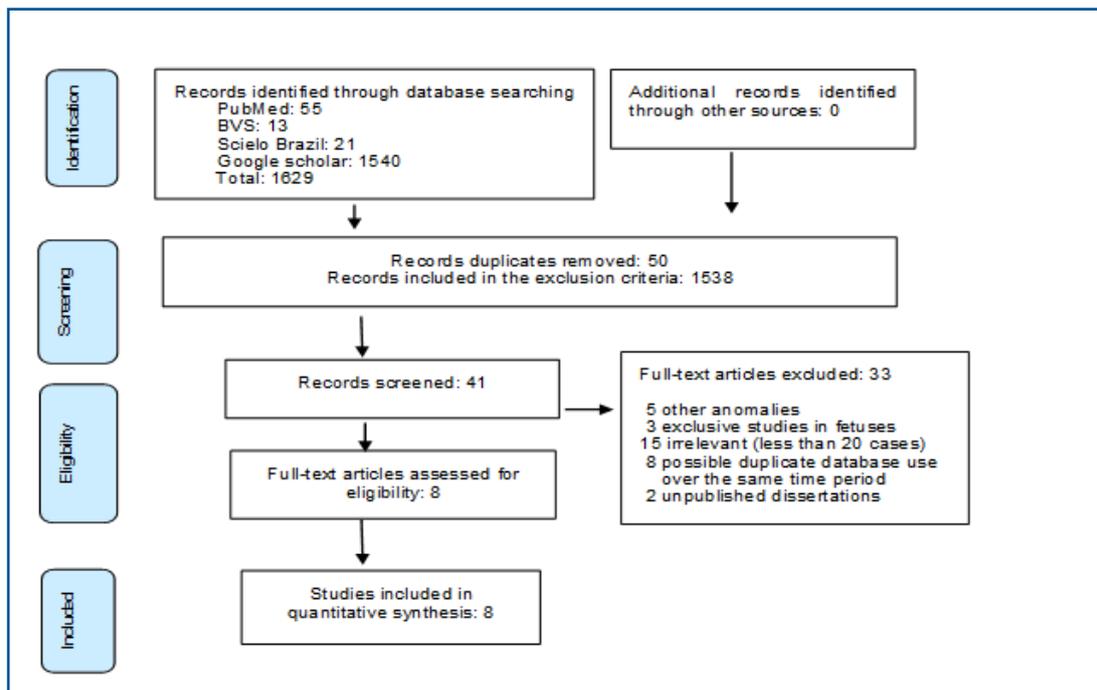


Figure 1: Flowchart of Search Process (PRISMA-ScR)<sup>9</sup>.

Table 1: Relevant included studies on gastroschisis outcomes conducted in Brazil.

Authors/year	Region	Site	Design	Objective
Martins <i>et al.</i> <sup>11</sup> 2016-2019	Southeast	IFF <sup>a</sup>	prospective	to describe the clinical outcomes and surgical characteristics of gastroschisis
Bilibio <i>et al.</i> <sup>12</sup> 2010-2015	North	FSCMPA <sup>b</sup>	retrospective	to evaluate the prognostic factors related to mortality in neonates with gastroschisis,
Osmundo Jr <i>et al.</i> <sup>13</sup> 2005-2017	Southeast	HC-FMUSP <sup>c</sup>	retrospective	to investigate the association of spontaneous labor onset with neonatal outcomes in pregnancies with fetal gastroschisis.
Miranda <i>et al.</i> <sup>14</sup> 1989-2013	Southeast	HC-UFMG <sup>d</sup>	retrospective	to test the hypothesis that some interventions had a favorable effect on mortality and morbidity
Carvalho <i>et al.</i> <sup>15</sup> 2009-2013	Southeast	UNIFESP-EPM <sup>e</sup>	retrospective	to evaluate postnatal outcomes in fetuses with gastroschisis
Calcagnotto <i>et al.</i> <sup>16</sup> 1992-2012	South	HCPA <sup>f</sup>		to analyze the perinatal mortality rate in cases of gastroschisis
Tannuri <i>et al.</i> <sup>17</sup> 2003-2009	Southeast	HC-FMUSP, FCMUNICAMP <sup>g</sup> FMRP-USP <sup>h</sup>	retrospective	to analyze the morbidity of newborns after gastroschisis closure, at three tertiary university centers
Vilela <i>et al.</i> <sup>18</sup> 1995-1999	Southeast	IMIP <sup>i</sup>	retrospective	to determine the frequency of postoperative death and to identify factors associated with adverse prognosis in gastroschisis

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**Table 2:** Variables of prenatal care and delivery.

Variables	Brazil	Martins et al. <sup>11</sup>	Bilibio et al. <sup>12</sup>	Osmundo Jr et al. <sup>13</sup>	Miranda et al. <sup>14</sup>	Carvalho et al. <sup>15</sup>	Calcagnotto et al. <sup>16</sup>	Tannuri et al. <sup>17</sup>	Vilela et al. <sup>18</sup>
Maternal age (y <sup>a</sup> /mean/SD <sup>b</sup> )	20.7	21 (±5.1)	19.7 (±3.7)	21 (±4.1)	21 (±5.1)	21.2 (±3.6)	21.5	20.1 (±4.5)	
Antenatal diagnosis (%)	80.2	96	55.1	100	84	100	92.2	82.2	32.3
Caesarean (%)	77.7	67	67.7	91.3	83.3	90.9	92.2	84.7	45
Outborn (%)	20.8	13	53.2	0	15.3	0	0		64.5
Female (%)	49.4	53	47.8		50.6	40.9		54.6	
Birth weight (g <sup>c</sup> ) (mean/SD/%)	2302	2339 (±492)	2302 (±464)	2347 (±454)	2308 (±492)	2349 (±514)	2269	2200	>2500g/54.8%

<sup>a</sup>Y Years, <sup>b</sup>SD Standard deviation, <sup>c</sup>G grams

**Table 3:** Variables of post-surgical care

Variables	Brazil	Martins et al. <sup>11</sup>	Bilibio et al. <sup>12</sup>	Osmundo Jr et al. <sup>13</sup>	Miranda et al. <sup>14</sup>	Carvalho et al. <sup>15</sup>	Calcagnotto et al. <sup>16</sup>	Tannuri et al. <sup>17</sup>	Vilela et al. <sup>18</sup>
CG <sup>a</sup> (%)	22.9	11		15.9	14.7		59.4	13.5	
Primary closure (%)	64.8	76	65.5	82.6	50	65.8	68.8	68.1	41.9
Time on TPN <sup>b</sup> (mean/ %)	26.2	23	19.8		29			33.2	83.9%
Time to the first enteral feeding (mean)	20.5	16			21			24.7	
Time to full enteral feeding (mean)	30	24		28.5				37.6	
Time on MV <sup>c</sup> (mean /%)	6.9	5.5	9.7	2.3	12			4.9	41.9%
Sepsis (%)	53.2	34.5		53.6	76.9	52.5	50	40.5	64.5
Hospital length of stay (mean)	40.8	36	32.3	37	46	52.7		41.2	
Mortality (%)	25.3	4.2	51.2	10.6	26.9	20.5	23.4	14.1	51.6
N	912	79	168	207	156	44	64	163	31

<sup>a</sup>CG Complex gastroschisis; <sup>b</sup>TPN Total parenteral nutrition; <sup>c</sup>MV Mechanical ventilation

### Risk factors for mortality and other associations

Three studies verified the risk factors associated with death. Calcagnotto *et al.*<sup>16</sup> found prematurity (p=0.03), low weight at birth (p=0.001), low APGAR score (p=0.03), reinterventions (p=0.001) and sepsis (p=0.008). Vilela *et al.*<sup>18</sup> observed birth weight less than 2 500 g (p= 0.03), birth-to-surgery interval greater than 4 hours (p=0.04) and need of mechanical ventilation (p=0.02). Bilibio *et al.*<sup>12</sup> found fewer prenatal visits (p=0.004), delayed prenatal diagnosis (p=0.005), low birth weight (p=0.001), intestinal injury (p=0.001) and sepsis (p=0.001).

Moreover, spontaneous labor in preterm infants was associated with CG (p=0.002) and short bowel syndrome (p=0.013) when compared to preterm indicated deliveries<sup>13</sup>. Low postoperative serum sodium and albumin levels were associated with prolonged MV time<sup>17</sup>. CG group had a significantly smaller defect size (p=0.04), more surgical reinterventions (p=0.001), and worse clinical outcomes than simple group, with start of feeding 1.5 times longer (p=0.001), time of total parenteral nutrition use twice as long (p=0.001), and length of hospital stay 2.5 times longer<sup>11</sup>. Patients who

underwent sutureless technique had significantly fewer wound infections ( $p=0.01$ ) and a decreased duration of MV than sutured patients ( $p=0.001$ )<sup>11</sup>. Results before and after a protocol of care package were measured<sup>14</sup>. When compared to the previously cohort, patients had higher rates of prenatal diagnosis ( $p=0.001$ ), delivery at a tertiary center ( $p=0.001$ ), early closure ( $p=0.001$ ), primary repair ( $p=0.01$ ), monitoring of bladder pressure ( $p=0.001$ ), PICC placement ( $p=0.001$ ), early initiation of enteral feeding ( $p=0.001$ ), and lower rates of electrolyte disturbances ( $p=0.001$ )<sup>14</sup>.

## DISCUSSION

In this review, mean maternal age was 20.7 years (19.7 to 21.5 years). The lowest mean was reported in a region with the second lowest HDI in country<sup>5</sup>. In 2013, a Brazilian study showed a trend towards earlier first pregnancy among women from the north region (19.4 years) compared to the ones from the southeast region (21.9 years). These figures indicated a higher prevalence of early pregnancy in the poorest region of country<sup>19</sup>. By way of comparison, the mean maternal age in this review was lower than ones reported in similar studies from Canada (23.3 years), U.S. (22.2 years) and France (25 years)<sup>20-22</sup>.

Rates of antenatal diagnosis of GS vary considerably according to the country's economic status. Whilst in HICs GS is antenatally diagnosed in between 68% to 100% of cases<sup>21,23</sup>, in LMICs this rate is much lower, ranging from 4.7% to 46%<sup>24-26</sup>. In our review the antenatal diagnosis total rate was 80.2% (32.2% to 100%). Studies carried out in poorest regions had lower rates of antenatal diagnosis and this indicate failures in the local health system. The antenatal diagnosis allows the proper differentiation with omphalocele, distinction between simple gastroschisis and CG, childbirth planning and family counseling<sup>27</sup>.

Cesarean rates vary among the Brazilian regions. According to a previous study, in country's low resource region operative deliveries rates ranged from 35% to 45%, whilst in the high resource region the same rates ranged between 55% and 65%<sup>28</sup>. In HICs cesarean rates ranged from 31.5% to 68%<sup>20,22,23</sup>, and in LMICs between 5% and 76.3%<sup>24,26,29</sup>. In the current study, cesarean rate was 77.7% (45% to 92.2%). However, were higher in studies carried out in high resource settings of Brazil. The best route of birth in fetuses with GS remains controversial<sup>27,30</sup>. Purported benefits of inducing labor close to term include reducing the exposure of the intestine to amniotic fluid and reducing serious intestinal injuries. On the other hand, this procedure increases the risk of conditions related with prematurity, such as respiratory distress and other comorbidities<sup>27</sup>.

In this review, mean rate of outborn patients was 20.8% (0% to 64.5%). However, were more frequent in studies carried out in poorest region of the country. The rates of outborn in LMICs ranged from 46.8% to 100%<sup>24,26,29</sup>, whilst in HICs these rates varied between 2.9% and 62.5%<sup>20,22,23</sup>. After the diagnosis of GS is confirmed, the pregnant woman should be forwarded to a tertiary referral center for high-risk births, wherein fetal

medicine, pediatric surgery, NICU, and nutritional teams are accessible<sup>27,30</sup>.

Regarding the features related to newborns, the mean of birth weight was 2 302 g (2 200 g to 2 349 g). Studies carried out around the world have found birth weight ranging from 2 232 g to 2 549g<sup>20,22,26,29</sup>. Female gender rate was 49.4% (40.9% to 54.6%), similar to studies found in the international literature<sup>20,22-24,26</sup>. The mean gestational age of this review was 36.2 weeks (35.9 to 37.6 weeks); full-term births were more frequent in studies carried out in poorest region of Brazil and were similar to rates found in LMICs<sup>26,29</sup>. The lower gestational age reflects the use of protocols for monitoring pregnancy during prenatal care, including the induction of delivery close to term in high-income health care systems<sup>20,22,23</sup>.

CG offers additional challenges to the treatment of this anomaly, since the affected newborns are more prone to multiple surgeries and long-term TPN, more vulnerable to sepsis and death<sup>10,30</sup>. In this current review, the CG rate of 22.9% (11% to 59.4%) were similar to those reported in studies from other countries<sup>22,23,25,29</sup>.

The rate of primary wall closure surgery found in this review of 64.8% (41.9% to 76%) was close to studies conducted in HICs<sup>22,23,31</sup>. This procedure, when performed immediately after birth, offers some advantages such as early positioning of the intestine back to its appropriate location and a reduction of the risk of injuries due to mechanical exposure. However, this technique is not always possible or safe, particularly in the presence of friable, distended intestinal loops or narrow intra-abdominal cavities, due to the risk of compartment syndrome<sup>32</sup>.

The mean time of TPN use was 26.2 days (19.8 to 33.2 days). Studies carried out in high resource settings of Brazil showed a mean time of TPN use similar to HICs<sup>20,22,23</sup> and higher than those observed in MICs<sup>26,29</sup>. Maintaining a newborn on TPN is a challenge, since this procedure requires a trained team in techniques for the insertion and maintenance of intravenous catheters and handling these solutions<sup>3</sup>. In regions with few resources, these therapeutic options are not available and this may result in shorter survival times for patients with GS and reflect the shorter duration of TPN use observed in LMICs<sup>3</sup>.

The mean time to the first enteral feeding in this study was 20.5 days (16 to 24.7 days), and close to that found in the international literature<sup>20,25</sup>. The mean time to full enteral feeding of 30 days (24 to 37.6 days) was higher than those found in studies performed in HICs (24 to 26 days)<sup>22,23</sup>. Most patients with simple GS start an enteral diet around the second week of life, whereas cases of CG require prolonged fasting due to intestinal complications<sup>32</sup>.

The mean time under MV in this review was 6.9 days (2.3 to 12 days), and similar to studies carried out in HICs and MICs (4 to 9.5 days)<sup>20,22,23,26,29</sup>. Patients in LIC studies did not have access to MV<sup>26,33</sup>.

The mean sepsis rate observed in this study of 53.2% (34.5% to 76.9%) were higher than in reports from HICs (19% to 36.2%)<sup>22,23</sup>, and were close to those observed in MICs (54% to 83%)<sup>25,26,29</sup>.

The mean of length of stay observed in this review of 40.8 days (32.3 to 52.7 days) was higher than studies performed in HICs (34 to 37 days)<sup>20,23,31</sup>. In LMICs this period ranges from 17 to 34 days<sup>24-26,29,34</sup>. The long hospital stay reflects the complications of GS, which evolve with the need for several secondary surgeries, prolonged fasting and can delay the motor development of newborns<sup>32,35</sup>. A short length of stay is related to care failures and high death rates in the first weeks of life<sup>3</sup>.

The mortality rates observed in this study was 25.3% (4.2% to 51.6%). It was noted that in studies performed in high resource setting, in Brazil, the mortality rates (4% to 26.8%) were close to those observed in MICs (12% to 39.1%)<sup>26,29</sup>, and were far from those of HICs (1.4% to 3.5%)<sup>20,22,31</sup>. In low resource setting of the country, these rates (51.6% and 51.2%) were similar to those in LICs (58%)<sup>34</sup>.

Vulnerabilities in prenatal care, access to health services and postoperative care were risk factors associated with death observed in this review; and these findings are similar to those obtained in LICs<sup>3</sup>. In HICs, the outcome of death is no longer used as a primary result in cases of simple GS, as these rates negligible<sup>20</sup>. However, a recent study found birth weight, Apgar score at 5 min, and complex gastroschisis was able to predict mortality<sup>23</sup>. Another study found no statistically significant trends in the overall mortality for gastroschisis<sup>31</sup>.

In most recent studies in reference centers of high resource setting in Brazil, the use of protocols for the standardization of conduct in GS has been noted with good results. A research group composed of English and African investigators proposed three levels of intervention in cases of GS that could improve the outcomes in these patients in places with limited resources. At the micro level, educational programs aimed at neonatal resuscitation (pre- and intra-hospital), training of a multidisciplinary team and the involvement of parents in monitoring the provision of care. At the macro level, the incorporation of ultrasound in prenatal care and logistics for the provision of TPN and MV. At the global level, GS has been suggested as a sentinel condition for assessing the capacity of services to provide care in cases of neonatal surgical emergencies in general in LMICs<sup>3</sup>. The importance of these guidelines has been supported by a recent study in Uganda that achieved a 40% reduction in mortality rates after the implementation of the micro-level intervention protocol<sup>34</sup>.

In this review notice that publications on GS conducted in Brazil were scarce, most of carried out in southeast of country, with small sample size, heterogeneous methodology, not all variables were present in the included studies and only one study was

multicentric. These characteristics are typical of studies on gastroschisis carried out in other countries, which has made it difficult to carry out classic systematic reviews<sup>36</sup>.

This study has several limitations. Firstly, the variables were studied heterogeneously and not all were present in the included studies. Secondly, all studies reported data on patients who had access to tertiary referral centers and under this aspect, they may not represent the entire population of patients who were born with gastroschisis in Brazil. Finally, in some studies there were periods of achievement with prolonged time differences, which may not reflect the reality of current assistance in those places.

The gaps observed in this review suggest that future studies in Brazil may be carried out with the cooperation between the tertiary reference services in GS with multicentric research and elaboration of consensus protocols on which outcomes should be verified, for better quality of care.

## CONCLUSION

In summary, these clinical findings based on this review suggest that there are regional contrasts in studies conducted on gastroschisis in Brazil. The worst outcomes are in regions with low economic resources, similar situation found in international literature. However, these results should be validated with future studies to investigate the situation of pregnant women with fetuses with gastroschisis, especially in low-resource regions in Brazil.

## Contributions

Muniz V.M., Salaroli L.B. and Zandonade E. had the original concept and design of the study. Muniz V.M. and Netto A.L. performed data collection. Muniz V.M. performed data analysis, under supervision of Salaroli L.B. and Zandonade E. Muniz V.M. and Netto A.L. wrote the first draft, which was approved by all of the authors.

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## Conflicts of Interest

Nothing to declare.

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## Resumo

**Introdução:** a disparidade global nos resultados da gastrosquise é visível. Taxas de sobrevivência em países de alta renda melhoraram desde 1960 e atualmente estão em torno de 100%, devido ao progresso da cirurgia pediátrica e da terapia intensiva neonatal. No entanto, em países de média e baixa renda, as taxas de mortalidade continual elevadas.

**Objetivo:** este estudo tem como objetivo mapear a literatura existente sobre gastrosquise no Brasil e discutir as evidências disponíveis em um contexto global.

**Método:** revisão de escopo. Foram pesquisados o PubMed, o Scielo Brasil, a Biblioteca Virtual em Saúde (BVS) e o Google Scholar no período de janeiro de 2000 a maio de 2020.

**Resultados:** oito estudos preencheram os critérios de inclusão e os dados encontrados de 912 pacientes foram: idade materna média de 20.7 anos, média do diagnóstico antenatal de 80.2%, taxa média de cesarianas de 77.7%, tempo de permanência hospitalar médio de 40.8 dias e taxa média de mortalidade 25.3%. Os fatores de risco associados ao óbito encontrados foram a prematuridade, baixo peso ao nascer, APGAR baixo, reintervenções cirúrgicas, sepse, intervalo nascimento-cirurgia maior que 4 horas, poucas consultas do pré-natal e diagnóstico antenatal tardio.

**Conclusão:** estudos sobre gastrosquise no Brasil são escassos, a maioria realizada no Sudeste do país. Os piores desfechos estão em regiões com poucos recursos econômicos, situação semelhante à encontrada na literatura internacional. Esta revisão deve ser validada com estudos futuros que investiguem a situação de gestantes portadoras de fetos com gastrosquise, especialmente em regiões de poucos recursos, no Brasil.

**Palavras-chave:** Brasil, anomalias congênitas, gastrosquise, recém-nascido, resultado da gravidez

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