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Intrinsic Risk for Poor Outcome in Neonates Born with Gastroschisis: A Systematic Review

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Abstract

Background: Intrinsic risk (IR) in a surgical neonate is the risk for complication, poor outcome, or death that an infant carries at birth, prior to medical or surgical intervention. We examine the recent literature to identify and categorize the factors that influence IR in gastroschisis and to study the usefulness of this literature for estimating IR.

Method: PubMed and OVID were searched for studies published from January 1, 2003, through June 8, 2013, using the search term "gastroschisis risk." English-language articles that examined the effects of maternal, fetal or neonatal factors identifiable prenatally or at the time of birth were reviewed.

Results: Eighty studies were reviewed (median sample size = 102). The majority were retrospective in design. Sixty-two potential IR factors fell into four categories: maternal, prenatal, delivery and patient factors at birth. While 40% of studies performed multivariable analyses, the majority included postnatal characteristics as predictor variables, limiting their usefulness in prenatal and perinatal decision making.

Conclusion: The current literature does not provide a robust understanding of the factors that influence IR in gastroschisis. The impediments to estimation of IR in gastroschisis include retrospective study design, inadequate sample size, reliance on univariate analyses, and inclusion of postnatal factors in multivariable analysis.

ABBREVIATIONS

GPS: Gastroschisis Prognosis Score; SNAP-II: Score for Neonatal Acute Physiology II; SNAPPE-II: Score for Neonatal Acute Physiology Perinatal Extension II

INTRODUCTION

In neonatal surgery, intrinsic risk refers to the risk an infant carries at the time of birth for complication, poor outcome, or death. Notably, intrinsic risk is the risk inherent prior to any post-birth intervention, medical or surgical. It is important that intrinsic risk be calculable at the time of birth, or even predictable prenatally, to allow for the earliest possible risk-stratification. This, in turn, can impact the way we provide care for mothers and fetuses and allow prospective identification of the resources that infants will require when they are born. Ensuring that patients are born in environments with resources that meet their needs can reduce the necessity, risk and cost of patient transfer, minimize separation of mother and child, and improve patient outcomes.

The process of estimating intrinsic risk in surgical neonates might be best illustrated from the body of literature on gastroschisis, one of the most common neonatal surgical problems. Approximately 1800 infants (1 in 2229 live births) are born with gastroschisis annually in the United States [1]. As a group, these patients have a 3% to 4% mortality rate and among the longest hospital stays of all infants with birth defects [2,3]. Since gastroschisis is more common than other neonatal surgical problems, infants with gastroschisis have been the subject of much study by those specializing in neonatology, pediatric surgery and maternal-fetal medicine.

In this paper, we review the last decade of literature on the measurement of intrinsic risk in neonates with gastroschisis. Our goals are to identify and categorize the factors that influence intrinsic risk and study the usefulness of this literature for estimating it. We identify the current impediments and delineate opportunities for increasing the understanding of intrinsic risk and for developing more robust methods of timely risk-stratification in surgical neonates.

MATERIAL AND METHODS

PubMed and OVID were searched from January 1, 2003 to June 8, 2013 using the search terms "gastroschisis risk" and "gastroschisis outcome." To minimize variation in treatment environment, only articles reporting on infants cared for in developed regions (North America, Europe, Japan, Australia, New Zealand) [4] were included in our review.

Study selection

Titles and abstracts were screened and all English-language articles that investigated maternal, fetal or neonatal factors identifiable prenatally or at the time of birth were selected for review. All outcomes were included. Case reports of rare findings were included only if the finding reported was not studied statistically in another paper included in this review. Multiple studies reporting data from a single data set were included if the factors studied were not duplicative.

Papers focusing on medical or surgical treatment, descriptive reports of single cohorts, papers lacking statistical comparison of groups, and review articles were excluded. Inclusion and exclusion criteria were determined *a priori*.

Data extraction and classification

Each article was systematically reviewed by one author (L.E.C.) and the following information collected:

1. Year published
2. Clinical specialty of authors (neonatology, pediatric surgery, maternal-fetal medicine)
3. Study design (retrospective study, prospective study, systematic review, case report)
4. Data source (single/multiple institution(s), regional/national database)
5. Sample size of gastroschisis patients
6. Risk factor(s) reported
7. Risk factor(s) analyzed for effect
8. Outcome(s) of interest
9. Statistical approach (univariable analysis, multivariable analysis)

We defined a retrospective study as one in which the database was produced from a past series of cases without a planned data collection protocol developed in advance, and a prospective study as one in which a protocol detailing the risk factors to collect and the data collection methods were specified prior to data collection on new patients.

Risk factors reported in each study either as independent or dependent variables were recorded. A variable was categorized as an *intrinsic risk factor* if information about that variable could be known at the time of birth or prenatally with current technology (e.g., prenatal sonographic findings, birth weight). Conversely, a variable was considered a postnatal factor if information about the variable can only be known after the time of birth such as treatment type or patient outcome (e.g., type of surgical closure, days on mechanical ventilation).

Definition of usefulness for estimating intrinsic risk

A highly useful study was defined as one that performed multivariable analysis and included at least five intrinsic risk factors, and no postnatal factors, in the final prediction model.

Statistical analysis

Descriptive statistics were used to characterize the group of articles reviewed. Wilcoxon Rank Sum test was used to compare groups since variables were generally not normally distributed. A P value of <.05 was considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The PubMed and OVID searches generated 301 unique English language citations, which were reviewed at the title level. Of these, 234 underwent abstract review, and 95 underwent full text review. Eighty (80) publications met our inclusion criteria and were included in this study. A summary of study characteristics is shown in (Table 1).

Specialty contribution

Pediatric surgeons were the largest contributors to this body of literature, followed by maternal-fetal medicine specialists, then neonatologists. Forty-seven (47) articles were published by authors from a single specialty (31 pediatric surgery, 15 maternal-fetal medicine, 1 neonatology). Twenty-eight articles were the collaborative work of two specialties, and all three specialties were represented in just five of the 80 publications reviewed.

Study design

Most studies were retrospective (n = 73, 91.3%, including two case reports); few were prospective (n = 6, 7.5%). The remaining study was a systematic review investigating the effect of bowel dilatation on outcomes. The two case reports were included because they reported unique risk factors not studied in the other papers reviewed and might be important in future investigation. While there are few prospective studies, it is important to note that their findings are similar to those of the body of retrospective literature.

Sample size and data source

The median sample size for all 80 studies was 102 (range: 6 to 4344). Seventeen (21.3%) studies had a sample size under 50, and 12 (15%) had a sample size over 500. More than half the studies reported data from a single institution and a third of the studies were analyses of data from regional or national databases. Database studies had a significantly larger sample size (median = 402, IQR: 303 – 631) than institution-based studies (median = 71, IQR: 45 – 105) (P < .0001).

Intrinsic risk factors

A total of 62 factors that may contribute to intrinsic risk were reported in the 80 papers reviewed. These factors naturally fall into the following four categories: maternal factors (18), prenatal factors (20), delivery factors (8), and patient factors

Table 1: Study Characteristics.

Study Attributes	No. (%) of Studies (Total = 80)
Year published	
2003 to 2007	28 (35.0%)
2008 to 2013	52 (65.0%)
Author specialty	
Surgery	60 (75.0%)
Maternal-fetal medicine	44 (55.0%)
Neonatology	14 (17.5%)
Study design	
Retrospective,including case reports	73 (91.3%)
Prospective	6 (7.5%)
Systematic review	1 (1.3%)
Data source	
One institution	45 (56.3%)
Two institutions	5 (6.3%)
Three institutions	1 (1.3%)
Five institutions	1 (1.3%)
Eleven institutions	1 (1.3%)
Regional or national database	26 (32.5%)
N/A (systematic review)	1 (1.3%)
Sample size,median (range)	102 (6 to 4344)
<50	17 (21.3%)
50 to 100	23 (28.8%)
100 to 500	28 (35%)
>500	12 (15%)
No. of intrinsic risk factors reported in study as independent or dependent variables,median (range)	8 (1 to 29)
1 to 10	62 (77.5%)
11 or more	18 (22.5%)
Statistical analysis	
Univariate only	44 (55.0%)
Multivariable	32 (40%)
N/A (case report or systematic review)	4 (5.0%)
No. of IR variables analyzed in univariate studies (n=44)	19 (43.2%)
1	25 (56.8%)
2 or more	
Variables in multivariable analyses (n = 32)	
Types of variables	
Intrinsic risk factors only	15 (46.9%)
Intrinsic risk factors and postnatal factors	17 (53.1%)
No. of intrinsic risk variables	
1 to 4	11 (34.4%)
5 or more	21 (65.6%)

at birth (16) (Table 2). The variables most frequently analyzed were gestational age at birth (30 studies), complex gastroschisis (26 studies), birth weight (22 studies) and mode of delivery (20 studies). Only 6 variables were studied 10 or more times as predictor variables. Fifteen variables were only studied once, and 8 variables that my potentially influence intrinsic risk were reported only as dependent variables and not studied as predictor variables.

Type of statistical analysis

A slight majority of studies (n=44, 55.0%) solely performed univariate analyses, and 32 (40.0%) performed multivariable analyses. Two case reports [74,76] and a systematic review [41] constituted the remainder of the reviewed articles. Of the 32 studies reporting multivariable analyses, 17 included postnatal factors in addition to intrinsic risk factors as predictor variables in their analyses.

The postnatal variables that were included in the multivariable analyses were type of surgical closure, days to surgical closure, number of operations, days on mechanical ventilation, time to initiate feeds, time to full enteral feeds, days on total parenteral nutrition, incidence of cholestasis, and type of hospital environment in which the infant was treated. These postnatal variables represent the dimensions of practice variability and patient outcome, and their inclusion as predictor variables in an analysis stymies the ability to study and understand intrinsic risk.

Outcomes analyzed

The neonatal outcomes investigated in the 80 studies included the following: complex gastroschisis (collectively includes bowel atresia, perforation, necrosis, volvulus and/or the requirement for intestinal resection) [85], ability to perform primary surgical closure, number of surgeries, time to initiate feeds, time to full feeds, days on total parenteral nutrition, days on mechanical ventilation, occurrence of infectious complications, length of stay, hospital charges, and mortality.

Highly useful studies and their findings

None of the six prospective studies performed multivariable analysis, and therefore none met our definition of a highly useful study.

Six retrospective studies met our definition of a highly useful study. The characteristics and findings of these studies are listed in decreasing order of sample size in (Table 3). Of note, four are database analyses, and two report data from a single institution. None of the intrinsic risk variables in these studies were collinear. Taking these studies in aggregate, the factors that were shown to increase intrinsic risk were: maternal factors (single parent status, geographic isolation from pediatric surgical center, maternal cocaine use); prenatal factors (amniotic fluid anomaly, intrauterine growth restriction); and patient factors at birth (lower gestational age at birth, bowel necrosis, number of associated malformations).

DISCUSSION

This review shows that despite publication of a large number of studies and the development of several risk indices in the past decade, we do not yet have a useful risk index that can be widely used to calculate intrinsic risk in patients with gastroschisis. By focusing on intrinsic risk and making robust, complete models, we can develop a tool for matching postnatal resources to the high risk neonates' needs to reduce their risk of poor outcome. This would facilitate getting the highest risk neonates to settings where resources are adequate to handle them more safely.

A surgical neonate's overall risk is cumulative and dynamic over the continuum of their fetal and neonatal experience. The distinct phases in this continuum include the prenatal period, delivery, immediate post-birth period, pre-intervention period, medical and surgical intervention, and the post-intervention period. Together, variables in the first three time periods (prenatal, delivery, and immediate post-birth periods)

Table 2: Intrinsic Risk Factors Reported.

Intrinsic Risk Factor	No. of Studies Investigating Variable as Predictor	Studies Including Each Risk Factor [Reference number]
Maternal factors		
Age	9	[5-13]
Race	5	[8,9,12,14,15]
Educational level	2	[9,12]
Marital status	1	[8]
Income level	1	[8]
Location of residence	4	[8,9,12,15]
Population density of residential area	1	[8]
Insurance status	1	[16]
Smoking	3	[8,13,17]
Illicit drug use	2	[8,17]
Alcohol consumption	2	[8,17]
Parity	3	[9,12,15]
Complicated pregnancy	1	[18]
History of prior fetus with gastroschisis	1	[15]
Level of prenatal care	2	[9,19]
Not studied: body mass index,occupation,prescription medication use	n/a	
Prenatal factors		
Diagnosis	5	[6,15,20-22]
Monitoring	3	[19,23,24]
Cardiac monitoring	1	[25]
Intrauterine growth restriction	4	[11,26-28]
Gestational age at diagnosis	5	[27-31]
Sonographic findings:		
Bowel Dilatation	15	[26,27,30-42]
Intra- vs. extra-abdominal bowel dilatation	4	[27,30,32,33]
Single vs. multiple dilated loops	2	[27,38]
Bowel wall thickness	5	[26,27,32,34,35]
Bowel matting	2	[32,44]
Bowel peristaltic abnormality	2	[11,32]
Echogenic bowel	1	[32]
Gastric dilatation	5	[27,32,45-47]
Liver herniation	1	[48]
Ventral wall character	1	[47]
Abnormal amniotic fluid volume	6	[11,15,18,26,28,49]
Amniotic fluid lipase	1	[50]
Not studied: multiple pregnancy,amniotic fluid alpha-feto protein level,chorioamnionitis	n/a	
Delivery factors		
Inborn vs. outborn (required transfer)	5	[18,34,43,51,52]
Time to closure (delay due to transfer)	3	[18,40,53]
Time of day	3	[7,54,55]
Spontaneous vs. elective	6	[22,56-60]
Labor and rupture of membranes	2	[24,61]
Meconium-stained amniotic fluid	3	[18,44,45]
Mode of delivery (Cesarean vs. vaginal)	20	[6,7,12,13,17,22,31,34,43,49,52,54,58,61-67]
Delivery plan	1	[7]
Patient factors at birth		
Gender	6	[6,7,24,31,62,63]
Gestational age	30	[7,13,16,17,20,22-24,28,31,34,42,43,48,49,53-55,60,62-67,69-73] [6,7,13,16,22,24,31,34,42,43,48,54,55,62-67,69,70,72]
Birth weight	22	[13,63]
Apgar score [68]	2	[53-55,70]
SNAP-II score (Score for Neonatal Acute Physiology version II) [86]	4	[74] [6,73]
Defect side	1	[65,75]
Defect size	2	[76]
Closed gastroschisis	2	
Vanishing gastroschisis	1	[53,70]
Bowel characteristics:		[6,71]
GPS (Gastroschisis Prognosis Score) [70]	2	[3,16,18,20,22,24,34,36,39,46,49,51,56,57,62,64,65,70,72,73,77-82]
Peel	2	
Complex gastroschisis[a]	26	[5,14-16,31,46,49,51,63,83] [84]
Associated congenital anomalies	10	
C-reactive protein	1	
Not studied: meconium aspiration, umbilical artery pH	n/a	

[a]Complex gastroschisis includes bowel atresia, perforation, necrosis, volvulus, or requirement for intestinal resection [85]

Table 3: Study Characteristics and Findings from Highly Useful Studies.

Author (year)	Sample Size	Data source	Intrinsic Risk Variables in Multivariable Analysis					Outcome Variable(s)	Statistically Significant Findings
			No.	Maternal	Prenatal	Delivery	Patient		
Brindle (2012) [8]	535	National database	5	Marital status, race, illicit drug use, cocaine use, geographic isolation	-	-	-	Prenatal care, mode of delivery, delivery center	Single parent status was associated with absence of prenatal care. Isolation from pediatric surgical center was associated with cesarean delivery. Cocaine use was associated with failure to deliver at the planned center.
Cowan (2012) [70]	409	National database	7	-	-	-	Birth weight, gestational age, [a]SNAP-II, matting, atresia, perforation, necrosis	Mortality	Necrosis independently predicted mortality
Emusu (2005) [9]	368	State database	6	Age, race, education, residence, parity, level of prenatal care	-	-	-	Birth weight, gestational age	Infants born to teenage mothers were at greater risk for low birth weight and very preterm birth (<33wk gestational age)
Snyder (2011) [24]	167	Single institution	6	Prenatal counseling	-	Mode	Gender, birth weight, gestational age, [b]complexgastroschisis	Duration on parenteral nutrition	Lower gestational age and presence of complex gastroschisis predicted longer time on parenteral nutrition
Pasquier (2007) [15]	99	Regional database	8	Race, residence, family history, parity	Diagnosis, amniotic fluid anomaly	Delivery in facility with neonatal surgical resources	Number of malformations	Mortality	Presence of amniotic fluid anomaly and presence of multiple malformations was associated with greater mortality
Nicholas (2009) [11]	80	Single institution	5	Age	Hyperperistalsis, oligohydramnios, polyhydramnios, [c]IUGR	-	-	Composite neonatal adverse outcome	IUGR was predictive of composite neonatal adverse outcome (mortality, complex gastroschisis, >2 surgeries, feeding difficulty, sepsis, length of stay)

[a]SNAP-II: Score for Neonatal Acute Physiology version II [86]
[b]Complex gastroschisis includes bowel atresia, perforation, necrosis, volvulus, or requirement for intestinal resection [85]
[c]IUGR – intrauterine growth restriction

sequentially and cumulatively contribute to an infant's intrinsic risk.

Existing risk models

Cowan et al.'s Gastroschisis Prognostic Score (GPS) [70], derived by surgeon observation of the presence or absence of four features of intestinal injury within 6 hours of birth, and significantly predicts morbidity and mortality. It has proven to be significant despite inter-surgeon variability in observation, but does not incorporate other important factors such as the infant's gestational age, birth weight and physiology that will likely further increase the score's predictive power. Complementary to the GPS, are the SNAP-II (Score for Neonatal Acute Physiology II) [86], which includes six physiologic elements and SNAPPE-II (Score for Neonatal Acute Physiology Perinatal Extension II) [86], which adds birth weight, small for gestational age status and Apgar score to the SNAP-II. While the SNAP-II and SNAPPE-II are well-validated for mortality risk assessment in non-surgical neonates, their applicability to the surgical neonate is limited because they do not account for the surgical diagnosis, most likely the strongest contributor to risk.

Son et al.'s risk-adjustment method for surgical newborns incorporates surgical diagnoses, clinical data and risk of mortality [87]. Their model allows hospitals to benchmark their performance in non-cardiac surgery in full-term infants. However, their model is limited in terms of predicting an infant's intrinsic risk for three reasons. First, and most importantly, their model predicting mortality includes risk of mortality as a predictor variable; to develop their model, they assigned each procedure to a mortality risk category based on in-hospital mortality in the dataset, then used the mortality risk variable in their model to predict mortality. Second, their study did not include premature infants, a significant population with unique risk. Third, maternal demographic characteristics, which can strongly influence risk, were not included in the model.

Barriers to estimating intrinsic risk

In the current literature on gastroschisis we have identified barriers to our understanding of intrinsic risk in three major areas: study design, the selection of risk factors, and analytic strategy.

Study design

More than 90% of the studies reviewed, including all six high quality studies, were retrospective in nature. While retrospective studies can be of very high quality, the results of their analyses can carry with them the attendant biases and disadvantages of retrospective study design. However, one must note that it is not possible to study intrinsic risk using the gold-standard in study design; the randomized controlled trial, because randomization of intrinsic risk factors is not possible. Prospective observational designs are preferred over retrospective designs because they allow selecting the most appropriate population to study, planning the most predictive risk factors to measure, and instituting accurate data collection protocols with quality control procedures.

In light of these issues, to answer the question of intrinsic risk, we propose a focus on prospective study design and data collection. While this could be accomplished in single or multiple centers, note that sample size was a significantly limiting factor in many studies in this review. We therefore champion the establishment of regional or national registries. This review included 26 studies that were database analyses. As a group, database studies had a significantly larger sample size than institution-based studies, suggesting that databases, if they contain the right information, can support robust analyses. In the United States, this highlights the important role that groups such as the Children's Hospitals Neonatal Consortium, in partnership with surgical organizations, can play in studying intrinsic risk in surgical neonates.

Selection of risk factors

While 62 different intrinsic risk factors were reported in the 80 studies reviewed, few of them have been studied adequately; 23 were studied once or not at all, as predictor variables. The infrequency of their inclusion should not lead one to assume that they are unimportant. In fact, we recommend that they undergo rigorous statistical assessment in the future to definitively delineate their contribution to intrinsic risk. In addition, there appears to be variability in definition of intrinsic risk factors and outcomes. We advocate for development of consensus surrounding these as this will be critical to interpretation of future systematic reviews and attempts at meta-analyses of intrinsic risk factors.

Of the six most commonly studied risk factors, half of them (bowel dilatation, complex gastroschisis, associated congenital anomalies) are fixed and cannot be altered by the clinician. The other three risk factors (mode of delivery, gestational age, birth weight) are potentially amenable to intervention by influencing mode and timing of delivery. We recommend continued investigation of all factors that have the potential to influence intrinsic risk. Ultimately, the fixed risk factors that are significant will be useful in categorization of risk, and clinicians can develop management guidelines to mitigate the risk contribution of the variables they can affect.

Notably, few studies have focused on maternal sociodemographic factors. This should be a high priority for research because the identification of sociodemographic factors associated with significant risk will allow early identification of high-risk populations. This can then form the basis for development and employment of different prenatal management and surveillance strategies to minimize neonatal risk.

Analytic strategies

Our ability to learn about intrinsic risk has been impaired by 1) frequent limitation of studies to univariate analyses, 2) the small number of variables included in multivariable analyses, and 3) inclusion of postnatal factors as predictor variables in multivariable analyses. Given these findings, we make the following recommendations for future analytic strategies.

First, the ability to predict intrinsic risk will hinge on appropriate multivariable analyses. Such analyses should include as many variables as possible that are known prenatally or at the time of birth as predictor variables (Table 2); the larger the pool of predictors, the greater the likelihood that the final multivariable model will capture all the dimensions of intrinsic risk. With this in mind, however, care must be taken not to include collinear variables in regression analyses since this may mask the true effect of the collinear factors.

Since the goal is to predict risk for poor outcome at time of birth, and not to predict the ultimate outcome, it is critical not to include postnatal treatment or outcome variables as predictor variables in the analysis. This detail is important because inclusion of postnatal factors as predictor variables controls for these factors in the analysis and renders the results useless for developing a model that can be applied before birth or at the time of birth.

Study limitations

While the goal of this study was to examine the literature in regard to intrinsic risk, the contribution of intrinsic risk is to an infant's overall risk is unknown. Patient outcome is ultimately influenced by intrinsic risk and extrinsic risk, which is the risk associated with medical and surgical interventions after birth. Robust scientific knowledge surrounding both intrinsic risk and extrinsic risk is necessary to understand the relative contributions of each so that we may focus our clinical and research efforts.

Another limitation of this review is its restriction to risk modeling of only one surgical diagnosis, gastroschisis, when mortality risk assessment is important across the entire range of neonatal surgical conditions. The restriction was necessary because of the voluminous literature that has accumulated on risk assessment. Additional limitations include the aforementioned weaknesses of the individual studies and the heterogeneity of the studies.

The importance of intrinsic risk and risk stratification

Health care continues to focus heavily on enhancing systems of care to improve patient outcomes. Critical in this effort will

be the optimization of resources within the field of children's surgery, such that children are treated in environments with resources that match their needs [88]. It is important to note that resources are the focus and not the type of hospital as necessary resources may exist in both free-standing children's hospitals as well as highly-resourced adult general hospitals. The ability to accurately risk stratify patients will be central to the success of such efforts to identify the appropriate hospital for each child. Intrinsic risk represents an infant's innate risk for bad outcome. Understanding this risk, and being able to calculate and acknowledge it will enable physicians and health systems to reap the benefits of early risk stratification.

Prenatally, prediction of intrinsic risk will undoubtedly have a large influence on prenatal counselling [89]. Specialists in maternal-fetal medicine, neonatology and pediatric surgery can also use this information to influence prenatal testing and surveillance. Prenatal estimation of intrinsic risk will also enable prediction of the infant's needs at birth, thus facilitating the prospective matching of infants with delivery hospital resources. At birth, low intrinsic risk can obviate the need for transfer from the birth hospital to a higher-level facility, where such transfer is risky to the infant, socially suboptimal for the family, and costly to the health care system. Conversely, high intrinsic risk may demonstrate that the need to transfer outweighs these other considerations. It will benefit hospitals and health systems to risk-stratify patients as early as possible so that patients' needs can be identified and they can be cared for in the appropriate environment.

In conclusion, the current literature does not allow a good understanding of intrinsic risk in gastroschisis, one of the most frequently occurring prenatally-detectable congenital surgical diagnoses. Future studies focused on intrinsic risk are warranted given the implications for research and health care delivery. In regard to research, reliable calculation of intrinsic risk will allow a risk-stratified approach to studying post-natal interventions. By combining intrinsic risk with postnatal clinical data, researchers will be able to study risk-adjusted outcomes, and therefore have greater ability to define best practices for cohorts of surgical neonates. Understanding the factors that contribute to intrinsic risk will impact health care delivery in a broader way. Reliable risk estimation will allow providers to prospectively intervene to reduce postnatal risk. In the future, intrinsic risk can help determine the most appropriate hospital environment for the delivery of an infant, where mothers plan to deliver at or near hospitals that have the resources their baby will need at birth. Implemented regionally or nationally, the impact of such change should be measurably positive for patients, their families, the health care system and society.

CONTRIBUTORS' STATEMENTS

Li Ern Chen: Dr. Chen conceptualized and designed the study, conducted the data collection and analyses, drafted the initial manuscript, revised the manuscript and approved the final manuscript as submitted.

James E. Moore and Robyn Horsager-Boehrer: Drs. Moore and Horsager-Boehrer critically reviewed the manuscript and approved the final manuscript as submitted. Robert W. Haley: Dr. Haley designed the study, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

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DISCLAIMER

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