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The incidence of apparent congenital urogenital anomalies in North Indian newborns: A study of 20,432 pregnancies

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Abstract
Introduction and objectives: Over the last few decades, congenital anomalies of the urogenital system have increased globally as a consequence of advanced maternal age at pregnancy and developments in assisted reproductive techniques. The aim of this study was to determine the incidence of apparent congenital urogenital anomalies in North Indian newborns and the causative factors.
Subjects and methods: The data of all newborns delivered at our institute between September 2012 and August 2014 were collected for this prospective study. The predetermined data format included the newborns' birth weight and gestational age, the maternal age, parity and infertility treatment, if any. Newborns weighing less than 1000 g or born before 32 weeks of gestation were excluded from the study.
Results: During the study period, 20,432 deliveries were recorded (10,952 male and 9480 female babies). Apparent urogenital congenital anomalies were diagnosed in 799, with an incidence of 39.1 per 1000 newborns. The most common anomaly was cryptorchidism found in 678 newborns, while hypospadias was noted in 61, ambiguous genitalia in 34, congenital hernia/hydrocele in 20 and an exstrophy–epispadias complex in 5 children. Prune belly syndrome was seen in 1 newborn. Newborns weighing less than 2500 g had a higher proportion of anomalies (9.64%) in comparison to those weighing over 2500 g (1.99%) ($p = 0.0001$). A maternal age >30 years, parity >2 and infertility treatment were recorded in 5.40%, 4.93% and 9.80%, respectively, and all were independently associated with an increased risk of urogenital anomalies ($p = 0.0001$).

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Conclusions: The incidence of apparent congenital urogenital anomalies was 3.91%. Infertility treatment, parity >2 and a maternal age >30 years were independently associated with an increased risk of congenital urogenital anomalies.

Introduction

According to the WHO, the term "congenital anomalies" should be confined to structural defects present at birth. External risk factors have been well established and can be avoided, yet, the exact etiology of congenital anomalies remains unknown. A general surveillance program, carried out since 1960 in order to monitor the incidence of congenital anomalies in various populations around the world, has shown birth prevalence of congenital anomalies to vary significantly from country to country [1]. These variations are due to social, racial, ecological and economic factors [2,3]. Congenital anomalies contribute significantly to preterm birth and are a leading cause of fetal death, as well as of childhood and adult morbidity. Congenital anomalies have increased globally in the last few decades due to advanced maternal age at pregnancy and developments in assisted reproductive techniques. Studies suggest that the use of fertility drugs and progesterone support in pregnancy increase the risk of premature birth, small for gestational age embryos and birth defects [4–6]. An advanced maternal age at pregnancy and a parity $\geq$2 are known risk factors for congenital urogenital anomalies. It has also been found that there is a higher incidence of congenital anomalies in male compared to female children and in children with a below-normal birth weight at delivery [7]. The most common congenital urogenital anomalies mentioned in the literature are undescended testis in 1–4% of full term and 1 to 45% of preterm male newborns [8,9], hypospadias in 3–5/1000 live births [10], exstrophy–epispadias complex in 1/10,000–50,000 live births [11], prune belly syndrome in 1/29,000–40,000 live births [12] and congenital inguinal hernia/hydrocele in 1.2% [13]. In an epidemiological study carried out in Germany, the incidence of ambiguous genitalia was found to be 2/10,000 births per year. [14]

It is important to know the distribution and incidence of various congenital anomalies for every country and even for every community. To improve the quality of life, early recognition of correctable anomalies is essential to make sure that they can be treated in time. This prospective study was carried out in order to determine the incidence of various apparent congenital anomalies of the urogenital system in North Indian newborns and to identify probable risk factors leading to the same.

Subjects and methods

For this prospective cohort study, we collected the data of all newborns delivered at our institute between September 2012 and August 2014. After clearance from the institution's Ethical Committee and obtaining the informed consent from the parents, all newborns were examined clinically by a trained pediatric and urology resident right after birth and before discharge from the hospital. Neonates with recognized anomalies were re-examined for confirmation by a consultant urologist. The predetermined format for data collection included the newborns' birth weight and gestational age as well as information on the mothers such as age, parity and infertility treatment, if any (clomiphene citrate, progesterone or any other drug), and any previous history of a malformed baby. To keep the study sample representative of the normal population, newborns with a birth weight of less than 1000 g and/or born before 32 weeks of gestation were excluded as these children are known to have a higher incidence of anomalies in comparison to full-term babies.

Cryptorchidism was defined as the absence of one or both testes in the scrotum. The presence of a retractile testis was excluded. Hypospadias was defined as the presence of an abnormal ventral opening of the urethral meatus with dorsal hooding. Genital phenotypes where the external genitalia did not have the typical appearance of either a boy or a girl were considered as ambiguous and were mainly divided in male or female predominant genitalia. Male predominant genitalia included proximal hypospadias with no palpable gonads and hypospadias with micropenis, no palpable gonads or one palpable gonad. Female predominant genitalia were considered in newborns with female external genitalia and a gonadal mass in the labia or labial fusion and/or clitoral enlargement. Exstrophy–epispadias, cloacal exstrophy, superior vesical fissure, classical exstrophy and epispadias were noted as per the standard definitions. Congenital inguinal hernia/hydrocele were defined as translucent inguinal/inguinoscrotal swelling with cough impulse.

The incidence of hypospadias, undescended testis and congenital hernia/hydrocele was calculated using live male births as denominator, but the incidence of exstrophy–epispadias complex, prune belly syndrome, ambiguous genitalia and the overall incidence of apparent congenital urogenital anomalies were calculated per total live births. The Chi-square test was used for comparative analysis, while logistic regression analysis was used to determine independent factors predictive of reproductive disorders, with a p value <0.05 considered as statistically significant. All statistical analyses were performed using the SYSTAT software.

Results

In total, 20,432 deliveries (10,952 males and 9480 females) were registered during the study period. The sex ratio was 866 female per 1000 male children. In 34 newborns the sex could not be determined, and these infants were considered as having ambiguous genitalia. The incidence of congenital urogenital anomalies was 39.1 per 1000 births (3.91%; $n = 799$). The most common urogenital anomaly was undescended testis seen in 678 babies, followed by hypospadias diagnosed in 61 and congenital hernia/hydrocele in 20 children. An exstrophy–epispadias complex was found in 5 children with one patient having isolated epispadias. Only one child had prune

belly syndrome. Out of 34 patients with ambiguous genitalia 22 had male predominant genitalia. The 12 patients with female predominant genitalia had clitoral enlargement ($n=7$) and labial fusion ($n=5$). Among the 61 hypospadias cases, distal, mid and proximal hypospadias were found in 36 (59.01%), 16 (26.22%), and 9 (11.42%) subjects, respectively.

In this study, 5142 babies were born by mothers of advanced maternal age (>30 years); 278 of these babies were found to have urogenital anomalies (5.40%, $p=0.0001$). With maternal age advancing to more than 35 years, the incidence of anomalies increased to 13.33%.

There was an increase in urogenital anomalies in subsequent pregnancies, with a parity >2 being an independent risk factor for the development of urogenital anomalies. In this study, a parity >2 resulted in 228 infants with birth defects (4.93%, $p=0.0001$).

A total of 3122 pregnancies were achieved after infertility treatment. Of these babies, 306 were born with birth defects (9.80%) which was statistically highly significant ($p=0.0001$) (Table 1).

A gestational age <37 weeks was also significantly associated with birth defects seen in 456 children (9.89%, $p=0.0001$). Infants weighing 2500 g or less (9.64%) were more prone to birth defects than those weighing over 2500 g (2.68%). Statistical analysis showed that a low birth weight was a significant risk factor for congenital urogenital anomalies ($p=0.0001$) (Table 2).

Discussion

The knowledge of the incidence of congenital anomalies is important for planning health services in a specific country. It helps in planning the budget as well as measures for the management and the prevention of the disorders. It also helps to establish a program raising awareness of congenital urogenital anomalies and their management. This is important as many parents of children born with a congenital anomaly develop a feeling of guilt and are overwhelmed by the unexpected situation. This may lead to a late presentation of the patients to the hospital, especially in developing countries. Cases of hypospadias patients aged 27 and female epispadias patients aged 26 and 23 years have been reported [15,16]. Knowing the incidence of these congenital urogenital anomalies will not only help to diagnose them, but it will also help the parents to cope with the situation and to decide on timely surgery. It will also help to prepare the parents for the outcome of surgery, thus establishing the bond of confidence between parents and treating surgeon [17].

There are many published studies on the incidence of congenital anomalies and the evaluation of different associated variables, but none of them is focussed on urogenital congenital anomalies alone. Indian studies on congenital anomalies report an incidence of genitourinary anomalies between 0.43% and 6.22%, showing an increasing number of congenital anomalies with time [18–21]. In their study "The prevalence of congenital anomalies in Europe", Dolk et al. [22] reported anomalies of the genito-urinary system in 3.1 per 1000 births. The present study shows a higher percentage

Table 1 Relationship between different variables and uro-genital anomalies.

Variables	No. of pregnancies.	No. of birth defect	Percentage	*p*-Value
Maternal age(years)				
20–24	4123	109	2.63%	0.0001
25–29	11,258	412	3.66%	0.07
30–34	4602	206	4.47%	0.02
35-older	540	72	13.33%	0.0001
Previous pregnancies				
0	9720	346	3.56%	0.1
1	6086	225	3.40%	0.3
2 or more	4626	228	4.93%	0.0001
Infertility treatment	3122	306	9.80%	0.0001
Birth weight (g)				
Less than1500	408	71	17.40%	0.0001
1500–2499	4708	422	8.96%	0.0001
2500 or more	15,316	306	1.99%	0.07
Gestational age (wks)				
32 to 37	4608	456	9.89%	0.0001
37 or more	12,762	343	2.68%	
History of previous malformed babies	208	11	5.28%	0.42

Table 2 Factors predictive of uro-genital anomalies.

Variable	No. of pregnancies	Number and percentage	*p*-Value
Age 20–24 yrs	4123	109 (2.63%)	0.0001
Age >30 yrs	5142	278 (5.40%)	0.0001
Age >35 yrs	540	72 (13.33%)	0.0001
Parity (>2)	4626	228 (4.93%)	0.0001
Infertility treatment	3122	306 (9.80%)	0.0001
Low birth weight (<2500)	5116	493 (9.64%)	0.0001
Gestational age <37 wks	4608	456 (9.89%)	0.0001

(3.91%) as compared to previous studies because our institute, which is a tertiary care center, had referral cases of complicated pregnancies and pregnancies following infertility treatment, which may have increased the number of preterm deliveries and babies with a below-normal birth weight. The proportion of mothers aged above 30 in the present study was much higher than that reported in the study conducted by Datta and Chaturvedi [23] (25.16% vs. 3.22%), which may be a significant factor for the occurrence of anomalies. Another reason for a higher percentage of urogenital anomalies in our study may be due to the fact that most of the reported studies did not include undescended testes [18,19,23–25] which were the most common anomaly in our study. Sunethri Padma et al. reported anomalies in 6.22% which is higher than in our study and may be a result of the inclusion of still births and autopsy reports [21].

Patel and Adhia [24] reported preterm pregnancies and a below-normal birth weight in 4.40% and 31.62% of their cases, respectively. Although the number of preterm pregnancies was significantly higher in our study (22.55%), the incidence of below-normal birth weight was almost the same (25.03%). As for the correlation between birth weight and anomalies, a statistically significant increase in the occurrence of anomalies was found in babies weighing below 2500 g. Chaturvedi and Banerjee [18] and Parmar et al. [25] recorded a below-normal birth weight (<2500 g) in 57.1% and 79% of congenitally malformed babies, respectively, as compared to 61.7% malformed babies in the present study. An association between a below-normal birth weight and anomalies has also been documented in numerous other studies [19,25–27].

In the present study, the highest incidence of congenital anomalies (13.33%) was observed in mothers aged above 35 years, the next in order being the age group 30 –35 years (4.47%). This is similar to the observations made by Grover et al. [28] and Khanum et al. [29], while Chinara et al. [30] and Kulshrestha et al. [19] reported the highest incidence in mothers aged between 30 and 35 years (3% and 2%). In our study, we also found a significant number of children with anomalies ($p = 0.0001$) born by mothers aged 20–24 years, which is similar to the study of Mathur et al. [31] who even found that mothers aged between 17–25 years were most prone to having malformed babies. In a study of 1422 pregnancies in North East England and North Cumbria, Tennent et al. [32] found evidence of an association between maternal age, young and advanced, and the risk of certain structural (i.e. non-genetic) congenital anomalies.

Bhat [17] and Chinara et al. [30] found that parity had no effect on the incidence of malformation, as the incidence was 1.9% in both primipara and multipara mothers. In contrast, we found a significant correlation between a higher parity (>2) and congenital anomalies, which is similar to the observation made by Khanna and Prasad [33] (37.83%) and McIntosh et al. [34] (8.3%) who also found an increased incidence of congenital anomalies after the third pregnancy.

While clomiphene citrate used for the treatment of infertility has only been reported to cause multiple pregnancies but no congenital malformations [34,35], progesterone support during pregnancy is a known risk factor for urogenital anomalies [36]. The same observation was made in our study: the group of patients treated for infertility had a higher incidence of malformation (9.80%, $p = 0.0001$).

Studies done on congenital anomalies in general also suggest that an advanced maternal age and a low birth weight, as well as preterm and infertility treatment increase the risk of birth defects [18,20,26,27].

Cryptorchidism, defined as an abnormally positioned testis, affects about 1 to 4% of full and 1 to 45% of preterm male neonates [8]. A similar incidence (6.19% of live male neonates) was observed in our study. The exact etiology of cryptorchidism has not been clearly identified. However, the high incidence of cryptorchidism among first-degree relatives of study participants suggests a genetic contribution to this congenital anomaly [9], and epidemiological data on maternal factors such as gestational diabetes, smoking and exposure to environmental chemicals suggest the effect of environmental factors [33]. Similarly, intrauterine growth restriction leading to preterm birth and below-normal birth weight at delivery are also associated with an increased risk of cryptorchidism [37,38]. Birth weight alone is significantly correlated with cryptorchidism, irrespective of the duration of gestation [39,40]. We also found that a low birth weight was an independent factor for an increased risk of cryptorchidism as well as other congenital urogenital anomalies ($p = 0.0001$).

Hypospadias has been reported to be present in approximately 1 in 250 newborn males (0.4%) [10], which is similar to the incidence seen in our study (0.55% live male neonates). The risk of hypospadias is 12 to 20-fold higher among first-degree relatives, suggesting a genetic contribution [41]. But also environmental factors, especially chemicals such as endocrine disruptors, exogenous sex hormones and other medications increase the risk of hypospadias [42]. A higher incidence of hypospadias is found in children with below-normal birth weight at delivery and in premature babies. Preterm birth has been reported to be associated with a 9-fold increased risk of hypospadias in a study carried out by Preiksa et al. [39]. Maternal factors like diet devoid of fish and meat, obesity and maternal hypertension also increase the chances of hypospadias [43] but we did not look for these factors. In the present study, distal, mid and proximal hypospadias was found in 59.01%, 26.22% and 14.75%, respectively, which is nearly similar to the findings of other published by Canon et al. (coronal/distal in 60.7% of cases, mid penile/subcoronal, in 18.8%, and perineal/proximal penile in 4.6%) [44].

The reported incidence of bladder exstrophy is 1 in 10,000–50,000 (0.01–0.05%) [11]. Our findings with an incidence of 0.024% fall in the same range.

In a multinational study on the incidence of the exstrophy–epispadias complex, Lancaster [45] found that bladder exstrophy rather tended to occur in newborns of younger mothers, while a higher parity increased the risk of bladder exstrophy rather than the risk of epispadias. A report from Israel indicated a 10-fold increase of bladder exstrophy in children delivered by mothers who had received their last dose of progesterone in the earlier part of the first trimester [46]. In contrast, in a large epidemiological survey of 214 families with the exstrophy–epispadias complex carried out by Gambhir et al., no association with parental age, maternal reproductive history or peri-conceptual maternal exposure to alcohol, drugs, chemical noxae, radiation or infection was found [47]. Our findings were similar in that all 4 cases of exstrophy–epispadias complex occurred in female children born by mothers of different age and parity, without any history of infertility treatment and progesterone exposure. Only one male child had isolated epispadias.

The incidence of ambiguous genitalia of 2 per 10,000 births per year (0.02%) found in an epidemiological study carried out in Germany was lower than that found in the present study (0.16%), which may be due to the fact that they followed children up to a higher age at which a definite diagnosis of the child's gender could be made in many cases [14]. On the other hand, our findings are similar to those of an Indian study performed by Datta and Chaturvedi (0.13%) [23].

The incidence of prune belly syndrome (1 in 29,000–40,000 live births [12]) and congenital hernia/hydrocele (1.2% [13]) reported in the literature is similar to our study.

In this study, there was an average number of 866 female per 1000 male children. This sex ratio is lower than the National and State female-to-male sex ratios of 940:1000 and 926:1000, as well as those of the nearby states of Punjab (893:1000) and Haryana (877:1000). The lower number of female children may be due to the female foeticide practice in some regions [48].

Conclusions

In our study, the incidence of apparent congenital anomalies of the genitourinary system was 3.91%. Infertility treatment, increased maternal age and a parity >2 increased the risk of below-normal birth weight at delivery and preterm birth, resulting in a statistically significant increase of genitourinary anomalies.

With an emphasis on "small family" norms (two-child family) and population control it is necessary to identify anomalies to ensure early surgical intervention and prevent crippling of infants with external urogenital anomalies. The average female-to-male sex ratio was lower than both the state and national ratios which points to the importance of the "Save-the-Girl-Child" campaign in our region.

Conflict of interest

None declared.

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None declared.

Ethical committee approval

Approved.

Authors' contributions

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