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Prevalence of genital abnormalities in neonates

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Abstract

Objectives: To assess the prevalence of genital abnormalities among neonates in two public maternity-schools.

Methods: Case-control, cross-sectional descriptive study. Genital morphology of 2,916 neonates was assessed using a clinical protocol between 04/19/2010 and 04/18/2011. Control group included neonates without birth defects, born at the same maternity unit and in the same day in which a case was identified. Fisher and Kruskal-Wallis tests were used for statistics.

Results: The study identified 29 (1:100) neonates with genital abnormalities. Most of them were examined within 3 days of life and presented only one genital defect. Morphological abnormalities comprised: genital ambiguity (1/29), fusion of labia majora (1/29), micropenis (2/29), enlarged clitoris (6/29), hypospadia (9/29), and combined defects (4/29). Only one case reported the genital abnormality in the statement of live birth correctly. Prematurity occurred in 13/29 cases and was the only variable statistically associated with genital defects. Eight cases agreed on the complementary investigation of the genital defect, among which three were diagnosed with disorder of sex development.

Conclusions: There is a high prevalence of genital abnormalities in the maternity units included in the present study and most cases are under-diagnosed and under-reported. Our results reinforce the importance of a careful examination of genital morphology in neonatal period towards the recognition of minor defects that can be clinical features of a disorder of sex development.


Introduction

The development of sex in humans is a complex process that involves biological, psychological, and social phenomena. The first stage occurs at the moment of fertilization through the union between maternal and paternal chromosome complements.1,2

From the eighth week of gestation, undifferentiated tissues are transformed into gonads and internal and external anatomical structures typical of male or female genitalia. This process, governed by a web of genetic and hormonal mechanisms, corresponds to the pre-natal

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Development of biological sex, which will be completed in puberty.1-4

Based on the biologic structure, psychological and social phenomena will confer uniqueness to subjects regarding their gender identity and behavior, as well as their sexual orientation.2-4

Anatomical defects of the external genitalia may have genetic, non-genetic, or multifactorial etiology, resulting from the interaction gene/environment. These defects can be restricted to the genital tract or involve various anatomical sites, configuring dysmorphic syndromes.2,5 In both situations, genital abnormality may be the clinical expression of disorders of sex development (DSD).

The DSD are heterogeneous congenital conditions in which the development of chromosomal, gonadal or anatomic sex components is atypical. The clinical spectrum can range from mild morphological abnormalities in genitals that look male or female to the situation classified as genital ambiguity, in which it is not possible to recognize the biological sex of the newborn by physical examination.4,6,7 Clinical practice reveals, however, that the delimitation of the borders of normal morphology is not uniform. Thus, the literature provides some parameters to recognize abnormalities that require investigation of DSD. They are2-4:

1) In newborns with male genitalia aspect:
   a) Bilateral Cryptorchidism;
   b) Micropenis (penis length of less than -2.5 standard deviations for age);
   c) Isolated perineal hypospadia or light hypospadia with bilateral cryptorchidism or micropenis.

2) In newborns with genitalia of female aspect:
   a) Clitoral hypertrophy (diameter greater than 6 mm);
   b) Any degree of labial fusion, from posterior to complete;
   c) Mass is the inguinal area or labioscrotal folds.

Given the range of clinical presentations and the use of different inclusion criteria and methods for data collection, studies on prevalence of genital abnormalities have provided results ranging from 1:20,0008 to 1:4,5003 newborns.

Careful examination of the newborn’s external genitalia is not only important for early diagnosis and management of genital abnormalities, but also to register and obtain epidemiological information necessary for planning preventive actions in the field of public health.

In Brazil, a population-based registry of birth defects was introduced in 1999 by the inclusion of a field in the Statement of Live Birth (SLB) [Declaração de Nascido Vivo (DNV)], which is a document of mandatory completion. Records of this magnitude have potential to provide information about prevalence and risk factors for birth defects. From this information, it is possible not only to plan prevention policies and health care, but also to evaluate the effectiveness of implemented actions. Studies on the quality of this record have revealed, however, a high rate of under-reporting in the country as a whole.9-12

The objective of this study was to conduct an active search for newborns with genital abnormalities, verify the prevalence, and assess the records of these defects at two institutions in the municipality of Maceió, state of Alagoas.

Methods

This is a case/control, cross-sectional descriptive study. The active search for abnormalities was performed by direct examination of the external genitalia of infants in two maternity units, between 04/19/2010 and 04/18/2011. This search was suspended during 31 non-consecutive days, due to long holidays and closure of hospitals for infection control.

The examination of newborns was performed daily by a properly trained group of eight medical students. The training included both medical knowledge and subjective aspects of the approach inherent to diagnosis of DSD and the information given to parents about the abnormalities detected. Attitudes towards maternity professionals and parents were discussed and agreed upon before the start of data collection. For ethical reasons, the terms “genital ambiguity” and “DSD” were not used during the screening stage, only after the confirmation of abnormalities in visits to genetic outpatient clinics.

For data collection, there was a protocol with specific fields to register the following abnormalities:

- Genitalia with masculine aspect: non-palpable gonads or with any degree of bilateral cryptorchidism; stretched penile length below -2.5 standard deviations for age; gonads with larger diameter less than 8 mm; inguinal mass; any degree of hypospadia. For premature evaluation, the assessment of penile size used the distribution of measures for children born between 24 and 36 weeks of gestation as a reference.13
- Genitalia with female aspect: clitoral diameter greater than 6 mm (including preterm infants); palpable gonad in a labioscrotal fold; any degree of fusion of labia majora; inguinal mass.
- Genitalia unclassifiable based on physical examination, defined as ambiguous.

The depended outcome variable was the presence of one or more genital abnormalities. The independent variables and their respective categories of analyses were:

- Maternal residence: capital and countryside of Alagoas;
- Gestational age: < 37 weeks (preterm) and ≥ 37 weeks (term);
- Birth weight: < 2,500 g (low) and ≥ 2,500 g (adequate);
- Age of the newborn at the time of examination: < 3 days and ≥ 3 days;
- Sex registered on the SLB: male, female, unknown, and blank;
- Registration of congenital abnormality on the SLB: yes, no, unknown, and blank;
- Attendance at the follow-up reevaluation visit: yes and no;
- Genital abnormalities still present at clinical reevaluation: yes and no.

Data were tabulated and analyzed using the Epi-Info™ version 3.5.2. Initially, descriptive analysis of the 2,916 newborns was performed. To test associations between categorical variables, a control group was formed by births without morphological abnormalities, which occurred on the same day and the same hospital where a case was detected. Once matching criteria was applied, the control group consisted of 87 newborns. Fisher’s exact test was used for analysis of categorical variables, and Kruskal-Wallis, for equality of means. The level of significance adopted was of 5% ($p < 0.005$).

Cases with suspected DSD were sent to molecular study conducted by the Interdisciplinary Group for the Study of Disorders of Sex Differentiation and Center for Molecular Biology and Genetic Engineering of Universidade Estadual de Campinas.

This study was approved by the Research Ethics Committees of both institutions involved, according to procedure numbers #010367/2009-29 and #1433/2010.

Results

In the period between 04/19/2010 and 04/18/2011, there were 3,271 births in the maternity units studied. Out of this total, 3,009 (92%) newborns were examined, and 93 were excluded a posteriori, based on the criteria established in research methods (33 by multiple congenital defects, 14 by death before the exam and 46 by birth elsewhere).

Among 2,916 infants who composed the sample, 1,633 (56%) births occurred in maternity 1, and 1,283 (44%), in maternity 2. Age at examination ranged from 0-38 days with mean of 1 day and standard deviation of 2 days, and 2,718 (93.2%) patients were examined before completing 72 hours of life.

The present study found 29/2,916 (prevalence of 1:100) cases with some genital abnormality detected at physical examination. Among positive cases, predominated births in maternity 1 and mothers living in the countryside of Alagoas. Most of them were examined before reaching 72 hours of life, had weight equal or greater than 2.500 g and gestational age equal or longer than 37 weeks (Table 1). There were no statistically significant differences between cases and controls in relation to birthplace, maternal residence, age at first exam and incidence of low weight. Prematurity rates, however, were significantly higher in the case group ($p = 0.02$). Nevertheless, premature cases and controls presented comparable gestational ages ($p = 0.12$), with means of 34 (standard deviation of 1.6) and 34.7 (standard deviation of 1.8) weeks, respectively.

The distribution of cases by type of genital abnormality, information written on the SLB, attendance at the follow-up outpatient clinical reassessment, and the situation of genital abnormality are presented in Table 2. The most frequent genital abnormality was hypospadias, with a prevalence of 1:324, followed by bilateral cryptorchidism and clitoral hypertrophy. Obvious genital ambiguity occurred in one case. The analysis of SLB showed that only one newborn had the sex field marked as “unknown” and that five had the congenital defects field filled with “yes” (Table 2).

A reassessment at the genetics outpatient clinic was offered to the 29 positive cases. Of this total, four (13.8%) died before the scheduled date, and 11 (38%) did not attend. The positive cases who died had complications related to low birth weight (630 g), prematurity, septicemia and hemorrhagic syndrome. One of these infants had major midline malformations including holoprosencephaly. There were no statistically significant differences between cases who attended and those who did not attend the visit in relation to the origin of the mother ($p = 0.55$).

Children’s age at the time of clinical reassessment ranged from 2 to 31 days, with mean of 15 days and standard deviation of 9 days. The clinical situation was maintained in eight (57%) and had regressed in six (43%) cases. In the latter group, abnormalities were cryptorchidism (4) and clitoromegaly (2). There were no statistically significant differences between these groups regarding age at the first examination ($p = 0.88$), age at clinical reevaluation ($p = 0.43$), incidence of low birth weight ($p = 0.15$) and prematurity ($p = 0.47$).

In the group of eight newborns who remained with genital abnormality, four did not adhere to the proposed research and monitoring in the genetics and psychology integrated outpatient clinic. Among these, three had hypospadias, and one bilateral cryptorchidism.

Table 3 presents the summary of genetic and clinical characteristics of the four cases that entered the outpatient clinic and remained under monitoring.

Among these, one was defined as isolated hypospadias, one with congenital adrenal hyperplasia due to 21-hydroxylase deficiency, and two had clinical and laboratory
conditions suggestive of partial androgen insensitivity syndrome. Despite the loss of cases through the process of diagnostic investigation, the prevalence of DSD in the sample was, at least, 1.03:1,000.

**Discussion**

The maternity units involved in this study are references on high risk maternal and child health care in the state of Alagoas. Located in the capital (Maceió), they are linked to

**Table 1** - Distribution of characteristics of mothers and newborns in case and control groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case group (n = 29)</th>
<th>Control group (n = 87)</th>
<th>Total (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birthplace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1</td>
<td>20 (69%)</td>
<td>50 (57%)</td>
<td>70 (60.4%)</td>
</tr>
<tr>
<td>M2</td>
<td>9 (31%)</td>
<td>37 (43%)</td>
<td>46 (39.6%)</td>
</tr>
<tr>
<td>Odds ratio (95%CI): 0.2-1.5</td>
<td>p = 0.19*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capital</td>
<td>11 (38%)</td>
<td>50 (57%)</td>
<td>61 (53%)</td>
</tr>
<tr>
<td>Countryside</td>
<td>18 (62%)</td>
<td>37 (43%)</td>
<td>55 (47%)</td>
</tr>
<tr>
<td>Odds ratio (95%CI): 0.8-5.8</td>
<td>p = 0.05*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 days</td>
<td>28 (97%)</td>
<td>83 (95%)</td>
<td>111 (95.7%)</td>
</tr>
<tr>
<td>≥ 3 days</td>
<td>1 (3%)</td>
<td>4 (5%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Odds ratio (95%CI): 0.1-68.7</td>
<td>p = 0.63*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2,500 g</td>
<td>14 (48%)</td>
<td>33 (38%)</td>
<td>47 (40.5%)</td>
</tr>
<tr>
<td>≥ 2,500 g</td>
<td>15 (52%)</td>
<td>54 (62%)</td>
<td>69 (59.5%)</td>
</tr>
<tr>
<td>Odds ratio (95%CI): 0.5-3.8</td>
<td>p = 0.22*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 37 weeks</td>
<td>14 (48%)</td>
<td>23 (26%)</td>
<td>37 (32%)</td>
</tr>
<tr>
<td>≥ 37 weeks</td>
<td>15 (52%)</td>
<td>64 (74%)</td>
<td>79 (68%)</td>
</tr>
<tr>
<td>Odds ratio (95%CI): 0.9-6.7</td>
<td>p = 0.02*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95%CI = 95% confidence interval; M1 = maternity 1; M2 = maternity 2.
* Fisher's exact test.

**Table 2** - Distribution of positive cases regarding the type of genital abnormality detected, registration of sex and congenital malformation in the Statement of Live Birth, attendance at clinical reevaluation, and situation of genital abnormality

<table>
<thead>
<tr>
<th>Genital abnormality</th>
<th>n (%)</th>
<th>SLB - Sex</th>
<th>SLB - Congenital defects</th>
<th>Clinical reassessment</th>
<th>Maintenance of the condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M</td>
<td>F</td>
<td>U</td>
<td>Y</td>
</tr>
<tr>
<td>Hypospadia</td>
<td>9 (31%)</td>
<td>9</td>
<td>–</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Bilateral cryptorchidism</td>
<td>6 (20.6%)</td>
<td>5</td>
<td>–</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clitoris &gt; 6 mm</td>
<td>6 (20.6%)</td>
<td>–</td>
<td>6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Combined defects</td>
<td>4 (13.8%)</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Micropenis</td>
<td>2 (7%)</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Fusion of labia majora</td>
<td>1 (3.5%)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Obvious ambiguity</td>
<td>1 (3.5%)</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>29 (100%)</td>
<td>19</td>
<td>9</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

F = female; M = male; N = no; SLB = Statement of Live Birth; U = unknown; Y = yes.
* Bilateral cryptorchidism + micropenis.
† Micropenis + glandular hypospadia; bilateral cryptorchidism + glandular hypospadia; clitoral hypertrophy + posterior labial fusion.
Table 3 - Genetic and clinical characteristics of the cases under monitoring

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Genital abnormality</th>
<th>Legal sex</th>
<th>Karyotype</th>
<th>Mutation</th>
<th>Parental consanguinity</th>
<th>Familial recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated hypospadi</td>
<td>Hypospadi</td>
<td>M</td>
<td>46,XY</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PAIS</td>
<td>Hypospadi</td>
<td>M</td>
<td>46,XY</td>
<td>Study in progress</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PAIS</td>
<td>Hypospadi + micropenis</td>
<td>M</td>
<td>46,XY</td>
<td>Study in progress</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CAH†</td>
<td>Genital ambiguity</td>
<td>F</td>
<td>46,XX</td>
<td>p.Q318X + p.R356W (pat)</td>
<td>+*</td>
<td>+‡</td>
</tr>
</tbody>
</table>

(* = absent; (+) = present; CAH = congenital adrenal hyperplasia; F = female; M = male; mat = mutation inherited from the mother; PAIS = partial androgen insensitivity syndrome; pat = mutation inherited from the father.
* Parents are third cousins.
† Salt-loser phenotype.
‡ Recurrence in a sister.

Two public universities and are fully financed by the Brazilian National Health System. Both have rooming, neonatal intensive care unit and intermediate care, comprising a total of 127 beds.

According to data from the Municipal Health Secretariat of Maceió, together, these two maternity units account for 20% of births occurred in the capital and 9% of births occurred in the state of Alagoas. The mean annual live births in both, in the period 2004-2009, was 5,284, with 53% in maternity 1, and 47% in maternity ward 2.

Also according to the same source, in the period of data collection for this study, there were only 3,271 births at the two maternity units, due to structural problems that led to the temporary closure. Despite this, the proportion of births in each maternity was maintained throughout the year and was repeated in the sample that comprises this study. The absence of statistically significant differences between cases and controls in relation to birthplace and age at first examination indicates that the sample was homogeneous.

In general, it is expected that 2-5% of live births worldwide have functional or morphological congenital defects. The diversity of criteria used in epidemiological studies to define genital abnormalities, genital ambiguity, and DSD hinders comparative analysis of the prevalence of these defects in different populations.

Based on the criteria adopted in the present investigation, we obtained overall prevalence of an abnormality in every 100 live births. This result, quite high considering the group of structural birth defects, may reflect the comprehensiveness of criteria used in this study. The age at which infants were examined is another aspect to consider, since some genital abnormalities, such as enlargement of the clitoris and cryptorchidism may be transient. In these situations, one must consider prematurity as an intervenient factor, since in about 30% of preterm infants, the testicles becomes eutopic in the period between 6 and 12 months old. Specifically regarding clitoris hypertrophy, scarcity of adipose tissue in the vulva of preterm children can give the impression of clitoral hypertrophy. On the other hand, a recent study showed that the measure of the clitoris has a negative relationship with weight and length of the newborn and, therefore, with gestational age.

In this study, over 90% of newborns had up to 72 hours of life at the time of examination. Bilateral cryptorchidism (6/29) and clitoris hypertrophy (6/29) corresponded, together, to 40% of diagnoses. Prematurity was the only variable significantly associated with the presence of genital abnormality, even when the cases of cryptorchidism (p = 0.04) were excluded.

While analyzing, separately, the most frequent genital defect in the sample, hypospadias, there was a prevalence of 1:324. This finding is in line with publications devoted specifically to this abnormality, whereby the prevalence varies from 1:300 to 1:1,000 births, reaching 1:100-80 when there is positive familial history.

In recent years, there has been a global trend of rising prevalence of this defect, probably related to environmental exposure to drugs with estrogen or anti-androgen action, with ability to unbalance the relationship androgen/estrogen or interfere in the biosynthesis of sexual steroids. Although these factors have not been investigated in this study, the absence of statistically significant differences between cases and controls in relation to maternal origin suggests the absence of preferential exposure to risk factors for hypospadias in the population living in the capital compared to that living in the countryside of Alagoas.

Analyzing, on the other hand, the most severe genital abnormality, i.e., the case of obvious genital ambiguity, the prevalence was 1:2,916. Despite the considerable difference
in the overall prevalence of genital abnormalities (1:100) and hypospadias (1:324), the result is still quite high compared to the global prevalence of 1:4,500 births\(^3\) and of 1:6,900 births in South America.\(^8\) Despite the loss of monitoring of some cases and the small sample size, the incidence of DSD in this sample was at least 1.03:1,000, higher than those described in other studies, which ranged from 1:4,500\(^3\) to 1:20,000.\(^8\) Given these results, the occurrence of under-diagnosis and under-reporting of genital defects in retrospective epidemiological studies is a possibility that should be considered.

Only in one newborn the field sex of the SLB was filled as “unknown”, and the defect, correctly described in the area for the registration of birth defects. Surprisingly, the abnormality detected in this case was bilateral cryptorchidism. Among the five infants who had the field congenital defects filled with “yes” as an answer, the abnormalities documented were bilateral cryptorchidism, hypospadias, and micropenis. It was noteworthy that the only newborn with obvious genital ambiguity had its sex registered as female and the alternative “no” checked in the field for the registration of birth defects.

Data suggest that the recognized under-diagnosis and under-reporting of congenital anomalies in Brazil\(^9\)-\(^12\) are problems that, in Alagoas, include genital abnormalities. This result is worrying because this is a group of birth defects whose detection does not require the use of additional tests, unlike what happens, for instance, in cases of cardiac, gastrointestinal, or central nervous system malformations, for which imaging exams are necessary.

All 29 newborns with genital abnormalities were referred for further clinical evaluation at the genetics outpatient clinic. Excluding the cases that died before the consultation, the attendance rate was 56%. The absence of statistically significant differences between cases who attended and those who did not attend the consultation in relation to maternal origin (whether capital or countryside) suggests that there were no difficulties in accessing available health care.

Apparently, poor adherence is related to perception of genital abnormality as a non-significant health problem. This attitude may reflect the lack of importance given to the abnormality or even its non-recognition by the pediatrician/neonatologist, which reinforces the aforementioned problem of under-diagnosis and under-reporting and the important role played by the “first doctor”.\(^22\)

In the group of infants who attended the outpatient clinical reassessment, the condition remained in eight and regressed in six. Age, incidence of low birth weight, and prematurity did not behave differently in these two groups. Thus, possible explanations for the regression of the abnormalities are:

- a) spontaneous resolution, e.g., testicular descent;
- b) error on measurements of the penis and clitoris.

A diagnostic evaluation of DSD as well as integrated genetic and psychological assistance were offered to the parents of eight newborns with genital abnormality at the outpatient clinic that is linked to the present study. Half the cases abandoned monitoring without performing the exams, which, again, suggests that the family does not perceive the genital defect as a health problem, or has difficulties in dealing with this type of abnormality. The impact and perception of parents about the diagnosis are the object of a qualitative study conducted by this research group and, given its specificity, it is reported separately.

The present study found a high prevalence of genital defects in the maternity units studied, as well as evidence of under-diagnosis and under-reporting. DSD was defined in three cases among those who remained under follow-up. In two of these cases, the genital abnormality leading to specific diagnostic investigation was subtle.

The results of this research reinforce the importance of careful examination of infants’ external genitalia, aiming to identify subtle morphological abnormalities that can constitute DSD.

The early diagnosis and treatment as well as family involvement are essential to a comprehensive health care for these individuals. Given the complexity and the biopsychosocial impact of DSD, we suggest more emphasis of residency programs and continuing education of pediatricians and neonatologists to increase awareness about appropriate screening and registration of genital defects.

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