

# Congenital Anomalies in the Offspring of Mothers With a Bicornuate Uterus

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**ABSTRACT.** *Background.* Most of the reports on mothers with bicornuate uterus analyze fertility, reproductive capacity, and pregnancy outcomes. Very few of them, however, mention the risk for congenital anomalies in their offspring. Further, to our knowledge, no epidemiologic studies estimating the risk for congenital defects and analyzing the type of anomalies observed in infants born to mothers with bicornuate uterus have been reported.

*Methods.* Using a case-control study series, we estimated the risk of congenital anomalies in the offspring of women with a bicornuate uterus. To identify the specific defects associated with the presence of a bicornuate uterus in the mother, we analyzed 26 945 consecutive malformed infants from the Spanish Collaborative Study of Congenital Malformations and assessed the frequency of congenital anomalies in the offspring of mothers with a bicornuate uterus and in those born to mothers with a normal uterus. We then calculated the relative frequency, which is the quotient of the frequency of the individual defects in each group. This figure expresses the times each congenital defect is more frequent in infants of mothers with a bicornuate uterus than in those born to mothers with a normal uterus.

*Results.* Offspring of mothers with a bicornuate uterus had a risk for congenital defects four times higher than infants born to women with a normal uterus. The risk was statistically significant for some specific defects such as nasal hypoplasia, omphalocele, limb deficiencies, teratomas, and acardia-anecephaly.

*Conclusions.* Offspring of mothers with bicornuate uterus are not only at high risk for deformations and disruptions, but also for some type of malformations. *Pediatrics* 1998;101(4). URL: <http://www.pediatrics.org/cgi/content/full/101/4/e10>; *bicornuate uterus, fertility*.

ABBREVIATIONS. ECEMC, Spanish Collaborative Study of Congenital Malformations; RF, relative frequency.

Most reports on mothers with bicornuate uterus analyze fertility, reproductive capacity, and the incidence of low birth weight, prematurity, miscarriages, and twinning.<sup>1-5</sup> Very few studies make reference to the occurrence of congenital

anomalies in the offspring other than vascular disruptions and deformations.<sup>6,7</sup> To our knowledge, no previous epidemiologic studies estimating the risk for congenital defects and analyzing the type of anomalies observed in infants born to mothers with a bicornuate uterus have been published.

We present an analysis of the risk for congenital anomalies in infants of mothers with a bicornuate uterus, using a case-control study. We also analyzed the type of congenital defects observed, using a large sample of malformed infants from a series of consecutive births.

## MATERIALS AND METHODS

Data were derived from the Spanish Collaborative Study of Congenital Malformations (ECEMC). This is a hospital-based case-control study and surveillance system. Each child born in any of about 75 participating hospitals from all over Spain was examined within the first 3 days of life to identify major and/or minor/mild defects. For each case, the next nonmalformed infant of the same sex born in the same hospital was selected as a control subject. Once the case and control infants had been identified, the same physicians interviewed their mothers to gather information on family history, obstetric data, and prenatal exposures, such as acute and chronic maternal diseases, drugs, alcohol, and other potential teratogens. In many instances, photographs, imaging studies, karyotypes, pathology reports, and other complementary studies are also available for review. The ECEMC methodology has been published in detail elsewhere.<sup>8,9</sup>

Because of the fact that the ECEMC case-control methodology is only used for liveborn infants, we calculated the risk (odds ratio) of mothers with a bicornuate uterus having a malformed infant using only liveborn cases and controls infants.

To identify the specific defects associated with the presence of bicornuate uterus in the mother, we divided our population of 26 945 live and stillborn malformed infants into two groups. One comprised the cases born to mothers with a bicornuate uterus (38 cases, 32 liveborn and 6 stillborn), the other, those born to mothers who had no evidence of a bicornuate uterus (26 907 cases). We selected all the defects present in infants born to mothers with a bicornuate uterus and then calculated the proportion of each particular defect in each of the two groups of mothers of malformed infants. Dividing the proportions observed in the group of mothers with a bicornuate uterus by the corresponding proportions found in the mothers without a bicornuate uterus, we obtained the relative frequency (RF). These ratios, or RF, express the times each congenital defect is more frequent among infants of mothers with a bicornuate uterus than in those born to mothers with a normal uterus. The Fisher exact *P* value was used to compare the different proportions.

## RESULTS

Table 1 shows that the relative risk for having a liveborn child with congenital defects in the group of women with a bicornuate uterus, was about four times higher than in women with a normal uterus. These results are statistically significant (*P* = .0002).

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**TABLE 1.** Case-Control Study: Risk for Congenital Defects in Infants of Mothers With Bicornuate Uterus

	Mother With Bicornuate Uterus		Total	OR = 3.91 CI (1.73–9.19) P = .0002
	Yes	No		
Cases	32	24 931	24 963	
Controls	8	24 374	24 382	

Table 2 depicts all defects observed in infants born to mothers with a bicornuate uterus and their RF, in relation to the infants of mothers without a bicornuate uterus. Table 2 indicates that five congenital anomalies (nasal hypoplasia—or flat nasal bridge, omphalocele, limb deficiencies, teratoma, and acardia-anencephaly) were significantly more frequent in infants born to mothers with a bicornuate uterus. Other defects, such as microcephaly, microtia, esophageal atresia, syndactyly, limb contractures, scoliosis, and micrognathia, presented a RF >1 but did not reach the level of statistical significance. The frequency of the rest of studied defects had a RF of nearly 1, indicating that their frequencies were similar in both study groups of mothers, suggesting that these defects were not related to the mother's uterine malformation.

### DISCUSSION

Our data show that mothers with a bicornuate uterus have about four times the risk of having live-born infants with congenital defects than mothers with a normal uterus. To our knowledge, this is the first time this risk has been quantified using a case-control approach.

Previous authors<sup>6,7</sup> have suggested a relationship between maternal bicornuate uterus and congenital deformations and vascular disruptions in their offspring. However, these reports were based

on clinical observations and not on epidemiologic studies. In our data, cases with deformations (limb contractures, scoliosis, nasal hypoplasia, micrognathia, and clubfoot) constituted 34.2% (13/38) of total cases, which is similar to previously reported risk.<sup>7</sup> However, as shown in Table 2, nasal hypoplasia was the only deformation that we found to be statistically related with this maternal uterine defect. Other deformations, such as micrognathia, scoliosis, limb contractures, and clubfoot, were more frequent in infants of these mothers but the difference with infants of mothers with normal uterus did not reach the level of statistical significance. This could be a consequence of the sample size.

Limb deficiencies also occurred more commonly in mothers with a bicornuate uterus ( $P < .01$ ). The true frequency of these anomalies among infants of mothers with a bicornuate uterus is probably higher because of the type of limb deficiencies included in both groups. Although these consisted of hypoplasia of metacarpals/tarsals or phalanges, short hands, and absence of fingers in infants of mothers with a bicornuate uterus, they included all types of limb deficiencies in the offspring of mothers with a normal uterus.

An unexpected observation was that omphalocele, teratoma, and acardia-anencephaly were much more frequent in infants of mothers with a malformed uterus than in those born to mothers with a normal uterus. The possible relationship between these malformations and a bicornuate uterus has not been previously reported in the literature. A possible explanation is that they represent vascular disruptions caused by compression or other factors. In our data, we observed that mothers with a bicornuate uterus had vaginal bleeding significantly more frequent than mothers with a normal uterus (54.1% vs 14.1%).

**TABLE 2.** Frequency of the Different Types of Congenital Anomalies Among Children Born to Mothers With and Without Bicornuate Uterus\*

Type of Defect	Mothers With Bicornuate Uterus		Mothers With Normal Uterus		RF
	N	%	N	%	
Microcephaly	1	2.63	308	1.14	2.31
Nasal hypoplasia	4	10.53	410	1.52	6.93§
Micrognathia	3	7.89	697	2.59	3.05
Preauricular tag	3	7.89	1584	5.89	1.34
Microtia	1	2.63	225	0.84	3.13
Esophageal atresia	1	2.63	278	1.03	2.55
Omphalocele	2	5.26	193	0.72	7.31†
Limb deficiencies	5	13.16	966	3.59	3.67‡
Club foot	5	13.16	3941	14.65	0.90
Syndactyly	2	5.26	885	3.29	1.60
Hypospadias	3	7.89	2562	9.52	0.83
Ortolani +	3	7.89	4305	14.65	0.90
Limb contractures	2	5.26	789	2.93	1.80
Scoliosis	1	2.63	95	0.35	7.51
Teratoma	1	2.63	22	0.08	32.88†
Acardia-anencephaly	1	2.63	7	0.03	87.67‡
Total cases	38	100	26 907	100	—

\* RF, relative frequency: quotient between the two previous percentages. An infant could have more than one of the deformations or the other anomalies.

†  $P < .03$ .

‡  $P < .01$ .

§  $P < .003$ .

This bleeding may have also increased the risk for vascular problems that gave rise to disruptions. With regard to omphalocele, it may be hypothesized that the malformed uterus, by altering the location of the embryo, may interfere with the normal morphogenetic movements and, thus, lead to this defect. It is difficult to explain pathogenetically the observed high frequency of infants with a teratoma or acardianencephaly in mothers with bicornuate uterus. However, one could speculate that they might result from abnormalities in the migration and differentiation processes secondary to the anomalous location of the embryo.

In conclusion, mothers who have bicornuate uterus are at high risk not only for fertility problems and other abnormal outcomes of pregnancy,<sup>1-5,10</sup> but also for infants with deformations, disruptions, and even some malformations.

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