Clinical and neurodevelopmental outcome of prenatally diagnosed Wormian bones

OBJECTIVE: Wormian bones are isolated ectopic bones located in cranial sutures and fontanelles. The underlying pathogenesis of their formation is unknown. They have been found to be associated with craniosynostosis, osteogenesis imperfecta, genetic syndromes and head trauma; they can also be a normal variant.[1−12] This finding has been scarcely described in fetuses,[13,14] which precludes appropriate prenatal counseling.

This study aimed to determine the short- and long-term outcomes in fetuses diagnosed with Wormian bones.

STUDY DESIGN: This was a historic cohort study with postnatal follow-ups of the fetuses detected with at least one Wormian bone each during routine, detailed anomaly scans between 2013 and 2020. Excluded were cases with missing contact information and patients refusing to participate. The anomaly scans were performed by a single ultrasound expert (E.K.) at a single center. The indication for the scans was a routine anomaly scan, performed either in the early second trimester (14−17 weeks), the midtrimester (19−26 weeks), or the third trimester (>27 weeks). The data were collected from anomaly scan reports, and they included the gestational age at diagnosis, fetal biometry, the number of bones, and the associated anomalies. Postnatally, the parents were contacted and presented a semistructured telephone questionnaire (Table 1) addressing the demographic parameters and the peri- and postnatal outcomes, such as general pediatric health conditions and neurodevelopmental markers. For Autism Spectrum Disorder (ASD), only children aged 2 years and over were included for analysis, as this is considered as the minimal age for reliably diagnosing ASD.[15]

The examinations were performed transabdominally or transvaginally using a Voluson E6/E10 ultrasound machine (GE Healthcare, Milwaukee, WI). For the Voluson E10, either an RM6C abdominal probe or a RIC6-12-D vaginal probe was used. Generally, a transvaginal approach was used at 12 to 15.6 weeks of gestation, and a transabdominal approach was used from 16 weeks onward.

Fetal skull 3D/4D ultrasound imaging

A 3D Render Skeleton mode, as previously published,[16] was the preferred method for fetal skull image acquisition during fetal rest (Supplemental Video). The 3D box of interest was placed above the assumed location of the fontanelle. For posterior fontanelle imaging, the 3D box was extended to include the posterior part of the parietal bones and the occipital bone. The angle of acquisition was set at 40° to 60° to include the lambdoid suture bilaterally. For anterior fontanelle imaging, the 3D box was extended to include the superior part of the frontal bones and the anterior part of the parietal bones. The angle of acquisition was set at 40° to 60° to include the coronal suture bilaterally. An ideal image was expected when the 2D image was midsagittal with a good resolution. During fetal movement, either a 4D Skeleton Render mode or a 4D OmniView Skeleton mode was used. The former method, using a 4D box, was adjusted in the same manner as the 3D Render Mode. The 4D OmniView method, using an OmniView line, was set to a width of 12 to 20 mm and placed above and parallel to the fontanelle.

The study protocol was approved by the Institutional Ethical Committee (approval number 5345-18-SMC). Verbal consent was given at time of telephone interview.

Statistical analysis

The normality of the data was tested using the Shapiro−Wilk or Kolmogorov−Smirnov tests. The data are presented as median and interquartile range (IQR) or rate and percentage. A comparison between the unrelated continuous variables was conducted with the Student *t*-test or the Mann-Whitney U test as appropriate. The chi-square and Fisher's exact tests were used for comparison between the categorical variables. The prevalence of aberrant conditions in the study group was compared with that found in general population studies[17−20] using a one sample proportion Z test or the Fischer exact test, according to the pretest assumptions. Significance was accepted at $P<.05$. Statistical analyses were conducted using the IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY).

RESULTS: Overall, 70 patients carrying 72 pregnancies affected by 1 or more Wormian bones were identified. Of these, 62 patients were successfully contacted, and they consented to complete the follow-up questionnaire for 64 pregnancies (2 patients had recurring Wormian bones in 2 subsequent pregnancies). Table 2 summarizes the perinatal characteristics and postnatal outcomes. The Wormian bones were isolated in 68.06% (49/72) of cases, whereas 31.94% (23/72) had additional minor anomalies, most commonly an absent 12th rib detected in 13.9% (10/72) of fetuses. The median gestational age at detection was 22.1 weeks. The earliest diagnosis was achieved at 13.3 weeks. Chromosomal abnormalities were detected in 5.4% (2/37) of the cases. One of them was a Trisomy 21 case that also had an echogenic cardiac focus and an aberrant right subclavian artery. Another other case was a balanced translocation with an isolated Wormian bone. Postnatally, 30.16% (19/63) received some form of developmental intervention. The prevalence of ASD and epilepsy was found to be 5.8% (3/52) and 3.2% (2/63), respectively. Only the rate of the absent 12th rib was found to be significantly higher than the population ($P<.0001$). Over 96% (61/63) of children attended normal educational

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TABLE 1
Wormian bones semistructured questionnaire

Maternal and Paternal Demographic Data:
1. What is your marital status?
2. What is your (maternal) level of education? Primary, Secondary, Tertiary
3. What is your partner's (paternal) level of education? Primary, Secondary, Tertiary
Maternal General Health Condition:
1. Are you generally healthy?
2. Do you have any chronic conditions?
3. Do you take any medications on a regular basis?
4. Do you have any gynecology-related conditions?-Polycystic ovary syndrome, irregular menses, endometriosis, adenomyosis, obesity, infertility, other.
5. Did you undergo any surgeries?
6. Maternal Birth date.
7. Paternal birth date.
8. Weight before index pregnancy.
9. Height.
10. Do you smoke?
11. Have you or your partner undergone genetic mutation carrier screening testing?
Pregnancy Follow-up:
1. Gravidity
2. Parity
3. Number of Living children
4. Was this pregnancy conceived spontaneously or via assisted reproductive technology? (Controlled ovarian stimulation, intrauterine insemination, invitro fertilization). For invitro fertilization treatments:
a. Was intracytoplasmic sperm injection technique used?
b. Were the embryos transferred fresh or frozen?
5. Did you smoke during pregnancy?
6. Did you take any medications during pregnancy?
7. Was your Nuchal Translucency exam normal? What was the Nuchal Translucency value measured?
8. Were your First and second trimester biochemical analyte assay normal?
a. 1st human chorionic gonadotropin levels
b. Pregnancy-associated plasma protein A
c. Alpha fetoprotein levels
d. 2nd human chorionic gonadotropin levels
e. Unconjugated estriol 3 levels
9. Did you undergo noninvasive pregnancy testing?
a. Indication
b. Gestational week
c. Was the test normal? If not, please elaborate
10. Did you undergo an Amniocentesis test?
a. Indication
b. Gestational week

(continued)

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TABLE 1
Wormian bones semistructured questionnaire *(continued)*

- c. Was the fetus karyotype normal? If not, please elaborate
- d. Was the chromosomal microarray analysis normal? If not, please elaborate

11. Sonographic exam:
    - a. Gestational Week
    - b. Was it a routine exam or was it indicated because of a specific prior finding? Please elaborate
    - c. Other than the Wormian bone, were there any additional findings (Placental/Fetal/Amniotic)?
12. Have you experienced any pregnancy complications? Please elaborate
    - a. Gestational Diabetes
        - i. Were you treated by diet only?
        - ii. Were you treated with medication (Insulin/other)?
    - b. Premature contractions/Preterm birth
    - c. Preeclampsia
    - d. Gestational Hypertension
    - e. Cholestasis
    - f. Placental abruption
    - g. Fetal growth restriction
    - h. Other
13. Were you monitored at a high-risk clinic?
    - a. Indication
    - b. duration

Birth and Neonatal Period Details:

1. Where did you give birth? (Hospital name/Clinic/Home delivery)
2. What was mode of delivery? (normal vaginal delivery, vacuum extraction, Elective cesarean section, emergency cesarean section, vaginal birth after cesarean)
3. Was the delivery spontaneous or induced
4. Gestational age at birth
5. Birth weight
6. For preterm birth:
    - a. Duration of hospital stay
    - b. Neonatal complications
7. For term birth:
    - a. Were there any neonatal complications?
    - b. Were there any maternal complications?
    - c. Was the neonatal hospitalization duration extended? If so, please elaborate
8. Was the child in need of medical follow-up? Please elaborate

Child and family details:

1. Gender
2. Date of birth
3. Siblings:
    - a. Order of siblings in the family
    - b. Age of siblings

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TABLE 1
Wormian bones semistructured questionnaire *(continued)*

c. Medical history
d. Neurocognitive and developmental history of siblings—normal/abnormal, please elaborate
4. Extended family neurocognitive and developmental history—normal/abnormal, please elaborate
5. Affected Child Medical history:
1. Was your child born with any genetic condition or anatomical malformation? Please elaborate
2. Was your child in need of a medical follow-up after birth? Please elaborate
3. Current height
4. Current weight
5. Was your child diagnosed with any chronic illnesses? (Condition, age at diagnosis, tests performed, treatments, current status)
6. Has your child taken any medications, vitamins, or food supplements? please elaborate (medication name, indication, dosage, age, duration)
7. Was your child ever hospitalized?
a. Reason for admission
b. Medical care and testing during hospitalization
c. Number of days
d. Diagnosis at discharge
8. Did your child undergo any surgeries or ambulatory procedures?
a. At what age?
b. For what indication?
c. What was the outcome?
d. Were there any complications?
9. Did your child undergo head imaging scan (computed tomography/magnetic resonance imaging/ultrasound)?
a. At what age?
b. For what indication?
c. Were there any findings?
10. Did your child suffer from any visual impairment?
a. What type of impairment?
b. Was it uni/bilateral?
c. At what age was the child diagnosed?
d. What treatment did your child receive?
e. Did it resolve? Or is it a permanent condition?
11. Did your child suffer from any hearing impairment?
a. What kind of impairment?
b. Was it uni/bilateral?
c. At what age was the child diagnosed?
d. What treatment did your child receive?
e. Did it resolve? Or is it a permanent condition?
Systems scan:
For any condition, please elaborate:
- What kind of impairment?
- Age of diagnosis?

(continued)

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TABLE 1
Wormian bones semistructured questionnaire *(continued)*

- Treatment received?
- Did it resolve or is it a permanent condition?
- Does this condition require routine follow-up?

1. Does your child suffer from any respiratory tract impairment?
2. Does your child suffer from any heart disease/malformation/condition?
3. Does your child suffer from any vascular diseases?
4. Does your child suffer from any gastrointestinal disease/malformation/condition?
5. Does your child suffer from any genitourinary disease/malformation/condition?
6. Does your child suffer from type 1 diabetes?
7. Does your child suffer from any other endocrinological impairments?
8. Does your child suffer from any skin related conditions?
9. Does your child suffer from any ophthalmic related conditions?
10. Does your child suffer from any ENT-related conditions?
11. Does your child suffer from any allergies/food sensitivities?
12. Does your child experience now or in the past from any physical disability?

Was he entitled of a disability expense for his condition?

13. Does your child suffer from any musculoskeletal related conditions?
14. Does your child experience any seizures? Was he ever diagnosed with epilepsy?
15. Does your child suffer from any other neurological (central or peripheral nerve systems) related conditions?
16. Does your child suffer from any malignancies or benign tumors?

Neurological and cognitive development:

1. What is your child dominant hand (right/left/undetermined)
2. Has your child experienced any gross motor developmental delays? Please elaborate
3. Has your child experienced any fine motor developmental delays? Please elaborate
4. Has your child experienced any language developmental delays? Please elaborate
5. Has your child experienced any social/cognitive developmental delays? Please elaborate
6. Did your child use any developmental therapy services?

for each service please elaborate (indication, age at therapy, duration)

a. Occupational therapy?
b. Speech therapy?
c. Physiotherapy?
d. Psychotherapy?
e. Emotional therapy?
f. Neurologist and developmental center follow-up
g. Dietician?
h. Other?

7. For pre-school-age children:

a. Is your child at daycare or homecare?
b. Does your child attend a regular daycare or a special needs daycare?
c. Does your child attend a special needs lingual or communication daycare?

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TABLE 1
Wormian bones semistructured questionnaire *(continued)*

8. For school-age children:
a. Is your child home-schooled?
b. If not, is he attending a normal educational public school or is he attending a special needs school?
c. Please compare his abilities with other children at his class:
i. Reading—less than/equal to/better than his classmates
ii. Writing—less than/equal to/better than his classmates
iii.Math—less than/equal to/better than his classmates
9. Neurocognitive Evaluations:
a. Has your child been evaluated for or diagnosed with any of the following learning disabilities:
i. Dyslexia
ii. Dysgraphia
iii.Dyscalculia
b. Has your child been evaluated for or diagnosed with ADHD/ADD?
i. Was Has never been evaluated
ii. Evaluated and diagnosed (age)
iii.Currently being evaluated
iv.Evaluated and ruled out
c. Has your child been evaluated for or diagnosed with Autism Spectrum Disorder?
i. Has never been evaluated
ii. Evaluated and diagnosed (Asperger/Rett/pervasive developmental disorders/other, age, evaluation details)
iii.Currently being evaluated
iv.Evaluated and ruled out

systems. None of the children were diagnosed or suspected to have osteogenesis imperfecta or craniosynostosis.

Solitary vs multiple Wormian bones

A comparison of prenatal and postnatal characteristics (invitro fertilization, fetal growth restriction, chromosomal abnormality, ASD, etc.) between solitary vs multiple Wormian bones is presented in Table 3. Half of the cohort had 1 bone (36/72) and half had multiple bones (35/72 had 2, 1/72 had 3 bones). No statistically significant differences were detected among the groups.

CONCLUSION: Fetal Wormian bones are probably a normal variant and should not be scanned for routinely. The risk for chromosomal abnormality in this condition does not seem to be increased compared with the general population. Although some cases may develop mild developmental delays, parents can be reassured to expect a typical neurodevelopmental outcome.

This is a large cohort of fetal Wormian bones. Given the paucity of data in the current literature, the clinical significance of Wormian bones is still debated in the pediatric and adult populations. Some reports consider this entity as either a normal variant or an acquired condition secondary to head trauma and skull manipulations as practiced in some cultures.[1,2] Other studies have found an association of this phenomenon with skeletal dysplasia,[6,9] osteogenesis imperfecta,[2,4,12] and craniosynostosis[2,21,22] and also with rare conditions such as Menkes Disease,[23] Robinow Syndrome,[7] Primrose Syndrome[9] and ARID2 mutations.[10,24]

The current study provides an informative description of this condition in a cohort of 72 fetuses. Wormian bones could be detected as early as 14 weeks of gestation. They were usually isolated and presented a normal perinatal outcome. Most of the children had normal long-term outcomes, were generally healthy, and attended normal educational systems. This is in agreement both with the study by Jeanty et al,[13] consisting of 4 prenatally detected cases and with a large pediatric population study,[1] which concluded that Wormian bones should be considered a normal variant.

In contrast to postnatally detected Wormian bones, fetal Wormian bones were not found to be associated with osteogenesis imperfecta, craniosynostosis, or other skeletal dysplasia. This discrepancy could have a few possible explanations. First, it has been suggested that in osteogenesis imperfecta, there are usually >10 bones.[4] None of the fetuses

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TABLE 2
Perinatal and postnatal characteristics and outcomes of fetuses with Wormian bones

Parameter	Prevalence	Population studies	Relative risk	*P* value	95% confidence Interval
Multiple bones (up to 3)	50 (36/72)	N/A			
Posterior fontanelle Wormian bone	98.6 (71/72)	N/A			
Gestational age at detection	22.1 (21.6–22.6)	N/A			
Associated anomalies[a]	31.9 (23/72)	N/A			
Termination of pregnancy	1.56 (1/64)	N/A			
Gestational age at delivery (wk)	39 (38–40)	N/A			
Birthweight (g)	3200 (2875–3460)	N/A			
Preterm delivery	4.8 (3/63)	N/A			
Male gender	59.4 (38/64)	N/A			
Fetal growth restriction	4.8 (3/63)	N/A			
Age at time of questionnaire (y) range	3.4 (2.1–5) 0.7–8.1	N/A			
Chronic conditions[b]	17.5 (11/63)	N/A			
Use of developmental therapy services[c]	30.16 (19/63)	N/A			
Type of educational system					
Normal	96.8 (61/63)	N/A			
Special education	3.2 (2/63)				
Absent 12th rib[d]	13.9 (10/72)	1.75 (33:1885)[18]	7.9	<.0001	7.2–20.6
Epilepsy[e]	3.2 (2/63)	0.77 (7.7:1000)[17]	4.12	.09	N/A
Autism spectrum disorder[e,f]	5.8 (3/52)	1.56 (1:64)[19]	3.7	.23	N/A
Chromosomal abnormalities[e]	5.4 (2/37)	1.8 (16:890)[20]	3	.16	N/A

Data are presented as median (interquartile range) or percent (number/total number), as appropriate. Clopper-Pearson interval was performed to calculate the confidence interval.

[a] Absent 12th rib, ventricular septal defects, cardiac echogenic foci, aberrant right subclavian artery, pyelectasis, double collecting system; [b] Asthma (N=3), Allergy (N=9); [c] Including physiotherapy, and emotional, speech, or occupational therapy; [d] Z test for 1 proportion performed to compare to population rate; [e] Fisher exact test performed in conditions detected in <5 cases; [f] Children <2 years were excluded, which is the minimal age for diagnosing autism.

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in our cohort had >3 bones. Second, several studies have shown that Wormian bones might appear postnatally secondary to intentional cranial stress, suggesting that not all are congenital.[4,22,25] Thus, it remains to be determined whether Wormian bones might be a direct consequence and not merely a marker of disease in skeletal dysplasia.

The strengths of the study are its precedence as the largest cohort of fetal Wormian bones and the only study to address the long-term outcome. The study limitations should also be discussed. The background characteristics of the study group, such as the high in vitro fertilization rates (20.3%), might not reflect those of the general population, diminishing the extent of the study's external validity. Another possible limitation is recall bias, which might have influenced the accuracy of the data retrieved through the study questionnaire. To minimize recall bias, premeditated questions targeting major events such as hospital admissions, surgical interventions, or medical follow-up, were included. Similar parameters were addressed in 2 forms of questions to verify the reliability of the parents' responses. A comparison with a control group of fetuses without Wormian bones could have further supported the conclusions of the study. Further studies are needed to confirm the findings of this preliminary study.

To conclude, fetal Wormian bones are probably a normal variant and should not be scanned for routinely. When prenatally detected, a meticulous scan should be performed to rule out the associated anomalies, especially skeletal. Genetic consultation should be considered in nonisolated cases. Although some cases may develop mild developmental delays, parents can be reassured to expect a typical neurodevelopmental outcome.

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TABLE 3
Solitary vs multiple Wormian bones

Factors	Solitary bone (n = 33)	Multiple bones (n = 31)[a]	*P* value
Invitro fertilization pregnancy	18.2 (6/33)	22.6 (7/31)	.66
Male gender	69.7 (23/33)	48.4 (15/31)	.08
Fetal growth restriction[b]	6.3 (2/32)	3.2 (1/31)	1
Chromosomal abnormality	9.5 (2/21)	0	.5
Nonisolated Wormian bones	27.3 (9/33)	45.2 (14/31)	.14
Epilepsy[b]	6.3 (2/32)	0	.5
Use of developmental therapy services[b,c]	28.1 (9/32)	32.3 (10/31)	.72
Autism spectrum disorder[b,d]	6.9 (2/29)	4.3 (1/23)	1

Data are presented as percent (number/total number).

[a] Thirty cases had 2 bones and 1 case had 3 bones; [b] One case of pregnancy termination owing to Trisomy 21; [c] Including physiotherapy, and emotional, speech, or occupational therapy; [d] Children <2 years were excluded, which is the minimal age for diagnosing autism.

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