SMFM Statement: **Ultrasound Screening for Fetal Microcephaly Following Zika Virus Exposure**

Microcephaly is a condition in which the size of the head is smaller than expected for age. This condition in fetuses and infants has been associated with the recent outbreak of Zika virus. Due to this association, the CDC, ACOG, and SMFM have suggested prenatal ultrasound evaluation for fetal microcephaly in pregnant women who have been infected or potentially exposed (1,2). However, the diagnosis of microcephaly by prenatal sonography is not always straightforward. Given the complexity of prenatal diagnosis of microcephaly, the purpose of this document is to review the ultrasound criteria for the diagnosis following exposure to the Zika virus.

Various national and international agencies have recommended prenatal ultrasound for evaluation for fetal microcephaly in women who have travelled to any of the high-risk areas for Zika exposure during pregnancy (1-3). At present, however, there are limited data available regarding criteria for diagnosis of fetal microcephaly in the setting of Zika infection or exposure. In addition, the natural history of fetal microcephaly associated with Zika virus is unknown; although, recent reports describe cases of microcephaly after maternal infection (4, 5). In most cases, it is difficult to differentiate between constitutionally small head size versus pathologic microcephaly, and available data regarding prenatal diagnosis of microcephaly are based on small numbers of cases of varying etiologies.

In cases in which the fetal head circumference (HC) measures >2 standard deviations (SD) below the mean, we recommend that a detailed neurosonographic examination be performed (6), as some fetuses with HC >2SD due to *in utero* infection will have findings such as periventricular and intraparenchymal echogenic foci, ventriculomegaly, cerebellar hypoplasia,

microcephaly and cortical abnormalities (4,5). In addition, assessment of the profile can be helpful as the forehead is often sloping in pathologic microcephaly, and demonstration of this finding should increase the index of suspicion. We recommend that isolated fetal microcephaly should be defined as fetal HC $\geq$ 3SD or more below the mean for gestational age (see Table 1), and the diagnosis of pathologic microcephaly is considered certain when the fetal HC is $\geq$5 SD (7,8). If the HC by prenatal ultrasound is >2 SD below the mean, a careful evaluation of the fetal intracranial anatomy is indicated. If the intracranial anatomy is normal, we recommend follow up ultrasound in 3-4 weeks.

Data regarding the neonatal outcomes of fetal microcephaly are limited to small case series (9,10), and specific to Zika infection only as case reports (4, 5). A recent report presented one case of ultrasound-diagnosed microcephaly also with intracranial findings correlated with post mortem pathology (4). Another reported two cases of prenatal microcephaly associated with Zika infection and both had intracranial findings (5). In a case series of 20 fetuses with prenatal diagnosis of microcephaly, a HC that was between 2SD and 3SD below the mean was associated with a normal HC at birth in 90% of cases (9). In another study of 42 cases of fetal microcephaly with HC > 3 SD below the mean, 40% of infants were found to a have normal HC at birth (10).

Of note, many ultrasound reporting packages report HC percentiles and not SD and often the lowest reported is < 5^{th} %ile. In such cases, use of Table 1 is suggested to determine the number of SD below the mean for gestational age, as this is the most validated reference standard for the diagnosis of microcephaly.

In summary, this statement outlines the prenatal ultrasound diagnostic criteria for microcephaly and what is currently known about the predictive value for microcephaly at birth.

The current CDC, ACOG, and SMFM guidance recommends serial ultrasounds, every 3-4 weeks, with evidence of maternal infection. These recommendations further suggests that serial ultrasounds can be considered for women who have traveled to endemic areas but have no evidence of infection, as Zika infection can be asymptomatic. At present, there are very limited data with respect to the natural history and outcomes of fetal microcephaly in the setting of Zika infection or exposure. As new data emerge, these recommendation may change. In addition, diagnostic testing, surveillance, and management of suspected prenatal Zika exposure and infection is evolving and will continue to change as new data become available. For additional information, go to www.smfm.org/education/zika, http://www.acog.org/About-ACOG/ACOG-Departments/Zika-Virus,or http://www.cdc.gov/zika/pregnancy/index for Zika virus infection during pregnancy.

Recommendations:

1. If the HC by prenatal ultrasound is >2 SD below the mean, a careful evaluation of the fetal intracranial anatomy is indicated. If the intracranial anatomy is normal, we recommend follow up ultrasound in 3-4 weeks.

2. We recommend that isolated fetal microcephaly should be defined as fetal HC ≥3SD or more below the mean for gestational age. The diagnosis of pathologic microcephaly is considered certain when the fetal HC is ≥5 SD. A detailed neurosonographic examination should be performed and follow-up ultrasound done in 3-4 weeks.

3. If a reporting package for fetal biometry provides HC measurements as a percentile, Table 1 can be used to determine the SD, which is necessary in most cases to identify true microcephaly.

References

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Table 1. Means and Standard deviations of the head circumference as a function of Gestational Age

		Head circumference (mm): **SD Below Mean**				
Gestational Age (Weeks)	**Mean (mm)**	**-1**	**-2**	**-3**	**-4**	**-5**
20	175	160	145	131	116	101
21	187	172	157	143	128	113
22	198	184	169	154	140	125
23	210	195	180	166	151	136
24	221	206	191	177	162	147
25	232	217	202	188	173	158
26	242	227	213	198	183	169
27	252	238	223	208	194	179
28	262	247	233	218	203	189
29	271	257	242	227	213	198
30	281	266	251	236	222	207
31	289	274	260	245	230	216
32	297	283	268	253	239	224
33	305	290	276	261	246	232
34	312	297	283	268	253	239
35	319	304	289	275	260	245
36	325	310	295	281	266	251
37	330	316	301	286	272	257
38	335	320	306	291	276	262
39	339	325	310	295	281	266
40	343	328	314	299	284	270
41	346	331	316	302	287	272
42	348	333	319	304	289	275

Adapted from: Chervenak FA, Jeanty P, Cantraine F, Chitkara U, Venus I, Berkowitz RL, et al. The diagnosis of fetal microcephaly. Am J Obstet Gynecol. 1984;149:512-7.