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ORIGINAL ARTICLE

Diagnosis and management of the phenotypic spectrum of twins with Beckwith-Wiedemann syndrome

Jennifer L. Cohen[1,2] | Kelly A. Duffy[1] | Brian J. Sajorda[1] | Evan R. Hathaway[1] | Christina X. Gonzalez-Gandolfi[1] | Jennifer Richards-Yutz[2] | Andrew T. Gunter[3,4] | Arupa Ganguly[2] | Julie Kaplan[3,5] | Matthew A. Deardorff[1,2] | Jennifer M. Kalish[1,2]

[1]Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[2]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[3]Department of Pediatrics, Division of Genetics, University of Mississippi Medical Center, Jackson, Mississippi

[4]Humana, University of Mississippi Medical Center

[5]Division of Genetics, Department of Pediatrics, Nemours/Alfred I. DuPont Hospital for Children

Correspondence
Jennifer M. Kalish, Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, 3501 Civic Center Blvd, CTRB Rm 3028, Philadelphia, PA, 19104.
Email: kalishj@email.chop.edu

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Abstract

Beckwith-Wiedemann syndrome (BWS) is an overgrowth disorder with a heterogeneous phenotypic spectrum. There is an increased prevalence of monozygotic twinning in BWS. Given the epigenetic nature and phenotypic spectrum that defines BWS, twins are often discordant for clinical features, and clinicians are faced with the challenge of diagnosing and managing these twins. We present a cohort of multiple pregnancies in which one or more child from each pregnancy was diagnosed with BWS. We conducted a chart review of monochorionic and dichorionic gestations. Clinical scores for monochorionic twins demonstrated phenotypic discordance between the proband and twin. Based on linear regression analysis, a higher clinical score in the proband correlated with larger phenotypic discordance between twin siblings. Despite phenotypic discordance, however, we observed a consistent additive clinical score for a pregnancy (proband's plus twin's scores from a pregnancy). This idea of a finite degree of affectedness for a pregnancy implies a finite number of epigenetically affected cells. This further corroborates the idea that timing of monozygotic monochorionic twinning correlates with the disruption of establishment and/or maintenance of imprinting. The difference in clinical score between a proband and their twin may be due to diffused mosaicism, whereby there is an asymmetric distribution of affected cells among the multiple fetuses in a monozygotic monochorionic pregnancy, leading to a spectrum of variably affected phenotypes. Based on these findings, we recommend an algorithm for a conservative approach to clinically evaluate all children in a monozygotic multiple gestation affected by BWS.

KEYWORDS
Beckwith-Wiedemann syndrome, mosaicism, multiple gestation, tumor screening, twin

1 | INTRODUCTION

Beckwith-Wiedemann syndrome (BWS) is a multisystemic disorder that causes an overgrowth phenotype and can lead to embryonal tumors. BWS is diagnosed based on physical exam findings, organ differences, and pathologic features. Molecular testing can support the diagnosis of BWS, but in up to 20% of patients a molecular defect is not found, leading to reliance on clinical diagnosis (Brioude et al., 2018; Choufani, Shuman, & Weksberg, 2010). Clinical diagnosis is now aided by BWS clinical score from the summation of cardinal (2 points) and suggestive (1 point) features (Brioude et al., 2018). A clinical diagnosis of BWS can be confirmed if the score is ≥4, even in the absence of a molecular diagnosis (Brioude et al., 2018).

BWS is typically caused by an imprinting defect that alters gene expression, rather than a mutation or deletion in a single gene. It is specifically due to genetic or epigenetic changes on chromosome 11p15, for which there are multiple possible mechanisms. The most common epigenetic mechanism leading to BWS is a loss of methylation at imprinting control region 2 (KCNQ1OT1:TSS-DMR) on chromosome 11p15 (IC2 LOM) and the second most common cause is paternal uniparental disomy (pUPD) (Brioude et al., 2018). The syndrome can occur in a mosaic fashion, affecting certain cells and tissues of the body to varying degrees within a single patient. The occurrence of mosaicism within a single patient has further led to speculation of whether mosaicism exists among the different embryos in a multiple gestation affected by BWS. Furthermore, this is an intriguing question because there is a higher prevalence of multiple gestations in the BWS population compared to the general population (Weksberg et al., 2002).

To characterize twins, chorionicity (the number of placentas in a pregnancy) and zygosity (the degree of genetic similarity between twins), must be considered. Monozygotic twins arise from one fertilized egg, while dizygotic twins arise from two eggs at a single ovulation, fertilized by two different sperm (Hoekstra et al., 2008). The timing of twinning in embryogenesis is correlated to the chorionicity of the pregnancy: dichorionic, diamniotic twinning (two placentas) occurs between days 0 to 3 of embryogenesis, while monochorionic, diamniotic twinning (one placenta) occurs between days 4 to 7 of embryogenesis (Hall, 2003).

The diagnosis and management of a multiple gestation affected by BWS has been a long-standing question. Monozygotic twins are typically discordant for the syndrome and the question often arises whether to test and conduct tumor surveillance on only the proband who presents to medical attention, or to further investigate the twin sibling(s). It has long been hypothesized that certain factors may predispose to both twinning and the syndrome itself (Berry, Belton, & Chantler, 1980; Bliek et al., 2009; Bose, Wilkie, Madlom, Forsyth, & Faed, 1985; Weksberg et al., 2002). Despite BWS not being a monogenic disease, several groups have noted that the twin sibling of a patient with BWS may present with the same molecular blood test result as the proband (Bliek et al., 2009). Previous work has examined the blood and skin fibroblasts of the twin sibling and noted concordance of the blood tests and discordance with skin fibroblast analysis (Weksberg et al., 2002), indicating that the methylation blood tests in twins may be unreliable. Potential confounding factors for the concordant blood results include shared placental vascular connections in utero (Hall, 1996b; Weksberg et al., 2002), or a shared hematopoietic stem cell population of abnormally methylated cells (Bliek et al., 2009; Hall, 2003). These factors have created the clinical challenge of how to diagnose and manage a monozygotic twin.

Here, we present a large cohort of multiple gestation patients with BWS, and highlight the variability of phenotype and molecular testing results of the twin sibling(s), allowing us to re-examine clinical practices and consider updating management guidelines. With this data, we propose an algorithm with which to manage multiple pregnancies in which at least one child has BWS.

2 | METHODS

2.1 | Patient selection

This research was approved by the Institutional Review Board (IRB) at Children's Hospital of Philadelphia (CHOP IRB 13–010658). Consent was obtained from all participants and/or their guardians. Eligible patients included those who were part of a multiple gestation for whom molecular testing results were positive for the proband. We excluded multiple gestations from the study if chorionicity of the pregnancy was unknown. Probands with a clinical diagnosis of BWS and negative molecular testing were also excluded. Twenty-six multiple gestations fit our inclusion criteria, and to our knowledge, only one of these twenty-six gestations has been previously reported in the literature (Smith et al., 2006). For comparative analysis, we additionally included a group of randomly selected singleton patients (n = 40) for whom quantitative IC2 LOM data was available.

A chart review was conducted to collect clinical information on patient sex, molecular testing results, and presence of BWS features. Additional information for multiple gestation patients was collected related to chorionicity and zygosity of the pregnancy, use of assisted reproductive technology (ART) for conception, the number of fetuses in original gestation, and the number of live born children per pregnancy. The BWS clinical score for each patient was determined by criteria described in Brioude et al. (Brioude et al., 2018). The additive clinical score for each multiple gestation pregnancy was determined by the sum of the clinical score for each child in the gestation. In multiple gestations, the proband was defined as the more phenotypically affected patient in the gestation and the twin was defined as the less phenotypically affected patient in the gestation. The twins were considered to be clinically affected if their BWS clinical score was ≥4. For comparative analyses, the multiple gestation cohort was divided into two groups based on chorionicity (monochorionic (MC) and dichorionic (DC)). The singleton gestation cohort was also divided into two groups based on the quantitative degree of loss of methylation (LOM) at imprinting control region 2 (IC2): non-mosaic LOM was defined as IC2 methylation <2.5% and mosaic LOM was defined as IC2 methylation ≥2.5%.

2.2 | Statistical analysis

Data were analyzed using Graphpad Prism Version 6.0c and SPSS version 25. Independent t-tests and linear regression analyses were performed to compare the BWS clinical score between groups, and relative risk was calculated to predict the likelihood of monozygotic monochorionic twins being phenotypically unaffected. For all analyses, the sole monozygotic monochorionic quadruplet gestation in our cohort was excluded, as there was not a large enough sample size of quadruplet gestations in the cohort to conduct appropriate and meaningful comparison. The two triplet gestations in the cohort each had one monochorionic twin pair within the triplet, therefore, we analyzed these gestations as either a monochorionic or dichorionic twin pair, based on the proband patient's chorionicity. Results were considered statistically significant when $p < .05$.

3 | RESULTS

3.1 | Characteristics of the multiple gestation cohort

Demographic and characteristic data of the multiple gestation cohort are summarized in Table 1. The majority of monochorionic gestations were female–female and half of the dichorionic gestations were male–male. Use of assisted reproductive technology was more common among the dichorionic group. The most common molecular defect found among all multiple gestations was IC2 LOM.

Among the monochorionic multiple gestations, 12/13 pairs (92%) had molecular testing of blood for all children in the pregnancy and one twin (1/13) was not tested. Concordant blood testing results with the proband were found in 11/12 twins tested; the remaining twin's results were reported by the lab initially as "inconclusive," followed by a negative test result. Secondary tissue analysis (skin, saliva, buccal swab) was performed in 4/12 twins (33%), all of which were negative. 5/13 twins (38%) had a BWS clinical score of ≥4, confirming some degree of phenotypic concordance with the proband. After eliminating shared features of a monochorionic pregnancy (polyhydramnios, placentomegaly, or placental mesenchymal dysplasia) for these five twins' clinical scores, all five still had an affected clinical score (range 4–8). Of these five twins, four had one or more cardinal features and concordant blood methylation testing with their proband.

The dichorionic cohort (n = 13 pregnancies) had no known instances of concordant molecular blood tests. Three of the 13 dichorionic twins (23%) were molecularly tested, one of whom had clinical features consistent with a diagnosis of BWS, and all three had negative testing results.

3.2 | Phenotype comparisons between patients of multiple gestations with BWS

The average BWS clinical score was found to differ significantly (p < .0001) between both the dichorionic proband (mean = 8.9 ± SEM = 0.51) and twin (mean = 0.38 ± SEM = 0.31) and the monochorionic proband (mean = 7.8 ± SEM = 0.65) and twin (mean = 2.8 ± SEM = 0.58). Linear regression analysis demonstrated a significant positive correlation between the clinical score of the proband and phenotypic discordance (or gap in clinical score) with their monochorionic monozygotic twin (Figure 1). Cross-tabulation in SPSS demonstrated that twins were more likely to be phenotypically unaffected (clinical score <4) if their proband had a clinical score greater than 8 (RR = 2.250 [1.084–4.671]) or less than 6 (RR = 1.833 [1.069–3.144]). Twins of probands with a clinical score of 6–8 were less likely to be unaffected (RR 0.375 [0.153–0.917]), indicating that these twins are more likely to be affected.

No statistically significant difference was found in the additive clinical score of a multiple pregnancy (proband plus twin) when comparing all multiples conceived through assisted reproductive technology (ART) to those naturally conceived (p = .1463). Similarly, no significant difference was observed between the additive clinical scores based on ART use within the monochorionic pregnancies (p = .1822) or dichorionic pregnancies (p = .7440).

TABLE 1 Characteristics of multiple gestation cohort

Demographics		Total number of pregnancies (n = 26)	Monochorionic multiple pregnancies (n = 13)	Dichorionic multiple pregnancies (n = 13)
Sex	Female–female	14	12	2
	Male–male	7	1	6
	Female–male	5	n/a	5
Zygosity	Monozygotic (identical)	15	13	2
	Dizygotic	8	0	8
	Unspecified	3	0	3
Molecular epigenotype	IC2 LOM	21	12	9
	IC1 GOM	2	1	1
	pUPD	3	0	3
Assisted reproductive technology used	Yes	13	5	8
	No	13	8	5
Multiple gestation category originally noted in pregnancy	Twin	20	10	10
	Triplet	5	2	3
	Quadruplet	1	1	0
Multiple gestation category based on liveborn infants	Singleton	1	1	0
	Twin	22	10	12
	Triplet	2	1	1
	Quadruplet	1	1	0

Abbreviations: IC2 LOM, Loss of methylation at imprinting control Region 2; IC1 GOM, Gain of methylation at imprinting control Region 1; pUPD, Paternal uniparental disomy; n/a, Not applicable.

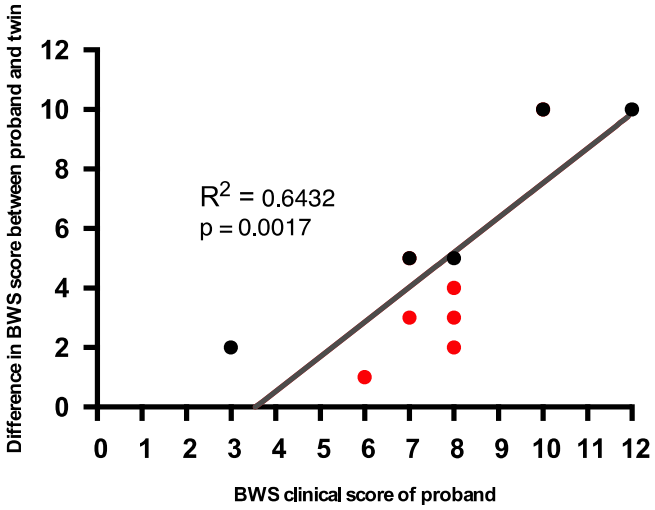

FIGURE 1 Linear regression showing clinical scores for 12 monochorionic twin pairs (there are only 10 distinct data points shown due to overlapping score pairs). The data points represent the BWS clinical score of the more affected twin of the gestation (proband) on the X axis, in relation to the difference in clinical score between the proband and twin sibling on the Y axis. The red data points represent the most phenotypically concordant twin pairs (difference ≤4). The best-fit line R^2 = .6432 with statistical significance (p = .0017) [Color figure can be viewed at wileyonlinelibrary.com]

3.3 | Phenotype comparisons between singletons and multiple gestations with BWS due to IC2 LOM

Singleton and multiple gestation patients were grouped according to chorionicity, degree of affectedness (proband or twin), and quantitative methylation results as applicable. The average clinical score between the groups was then calculated and compared (Figure 2). The results displayed a gradient in level of affectedness (as determined by clinical score) with DC twins as the least affected group and non-mosaic LOM singleton patients as the most affected group. Similar clinical scores were observed between mosaic LOM singleton patients and MC probands, with a moderately affected phenotype. In concordance with this observation, 5/5 MC probands with quantitative methylation data had results consistent with mosaic LOM.

The additive clinical score of IC2 LOM multiple gestation pregnancies (DC or MC) was also compared with the clinical score of singleton IC2 LOM groups (non-mosaic or mosaic). The average additive clinical score of MC (10.6 ± SEM = 0.86) and DC (9.8 ± SEM = 0.86) gestations was significantly higher than the average clinical score of mosaic LOM singleton patients (7.1 ± SEM = 0.48), p = .0005 and p = .0067, respectively. No significant differences were observed between the average additive clinical score of the MC or DC gestations and non-mosaic LOM singleton patients (10.4 ± SEM = 0.53), p = .8051 and p = .5275, respectively.

3.4 | Highlighted patients from the multiple gestation cohort

One monochorionic pair (multiple Pregnancy 1) presented with a proband who was selectively reduced due to a prenatally noted severe phenotype (omphalocele, organomegaly, macroglossia) with IC2 LOM on amniocentesis. The live born twin sister presented to medical attention with a BWS clinical score of 8 (macroglossia, lateralized overgrowth, placental mesenchymal dysplasia, nevus simplex, and ear

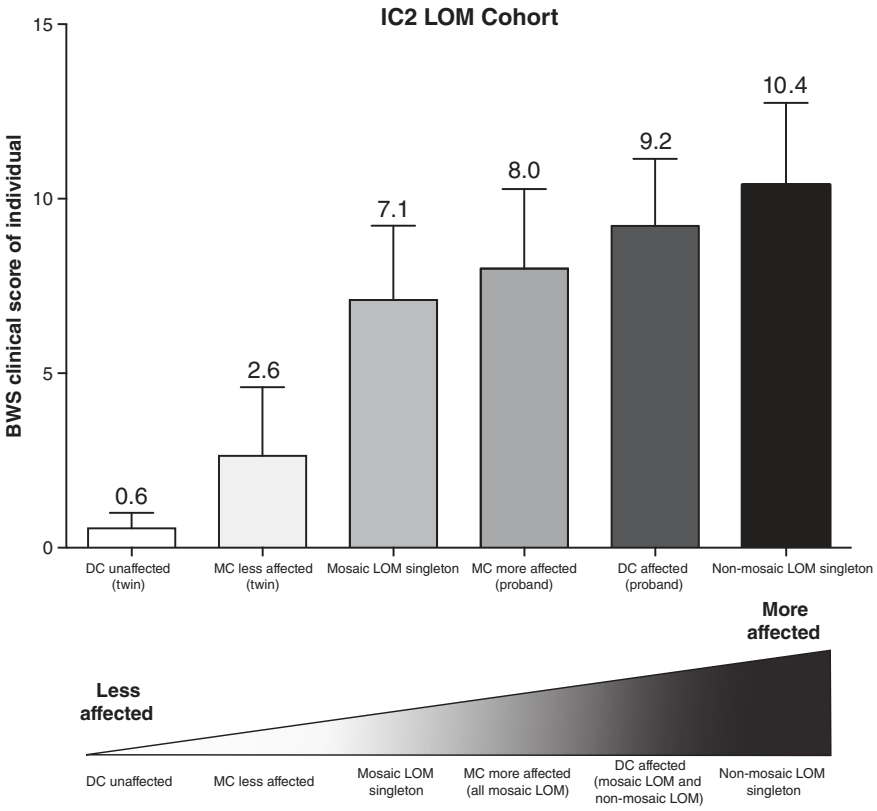

FIGURE 2 Depiction of BWS average clinical scores for a cohort of patients with IC2 loss of methylation (LOM) as their molecular diagnosis. Average clinical score for a cohort of individuals is depicted above the respective bar in the graph. Abbreviations: MC, monochorionic; DC, dichorionic; mosaic LOM, mosaic loss of methylation at IC2; non-mosaic LOM, non-mosaic loss of methylation at IC2

crease). If we eliminate placental mesenchymal dysplasia from the score (as this is a shared feature in a monochorionic pregnancy), her corrected clinical score is 6. Her blood testing was positive for BWS, but her buccal swab methylation was negative, demonstrating phenotype/epigenotype discordance within a single patient.

Two pairs of naturally conceived monozygotic dichorionic twins (multiple Pregnancies 2 and 3) both demonstrated molecular discordance with their proband, but each pair demonstrated a different degree of phenotypic discordance. A female–female pair (multiple Pregnancies 2) presented with a proband who had a clinical score of 10 and non-mosaic IC2 LOM, while the monozygotic dichorionic twin presented with a clinical score of 4 (lateralized overgrowth, nevus simplex, umbilical hernia) and showed negative IC2 LOM testing on blood. Conversely, in a male–male pair (multiple Pregnancy 3), the proband had a clinical score of 8 with pUPD, and his monozygotic dichorionic twin showed consistent discordance—negative molecular testing and a clinical score of 0.

A spontaneous monochorionic monozygotic quadruplet gestation (multiple Pregnancy 4) resulted in four female children, all of whom tested positive on methylation testing and were mosaic for IC2 LOM. The clinical scores for the children were as follows: proband's score was 9, followed by 3, 3, and 1 for her monozygotic sisters. None of the monozygotic sisters demonstrated a cardinal feature of BWS, compared to the two cardinal features noted in the proband.

4 | DISCUSSION

Based on the data presented here, we advocate that probands presenting with a concern for BWS should be clinically evaluated and molecularly tested based on clinical criteria, to counsel families appropriately (Brioude et al., 2018). Based on our series, we urge that the probands' monozygotic monochorionic, or monozygotic dichorionic twin sibling should be clinically evaluated by a geneticist. It has previously been suggested that molecular testing for BWS in twins can be unreliable (Bliek et al., 2009; Hall, 2003; Weksberg et al., 2002). This is demonstrated well by multiple Pregnancy 1 in our cohort, and by the three other twins in our monochorionic cohort who tested positive on blood and negative on secondary tissue.

Our cohort demonstrates the variability in degree of phenotypic discordance among BWS multiple pregnancies. Previous reports of BWS twins have shown that the majority of monozygotic twins show discordant phenotypes (Berry et al., 1980; Bose et al., 1985; Chien, Lee, Tsai, & Wang, 1990; Clayton-Smith, Read, & Donnai, 1992; Franceschini, Guala, Vardeu, & Franceschini, 1993; Gaston et al., 2001; Leonard et al., 1996; Litz, Taylor, Qiu, Pescovitz, & de Martinville, 1988; Lubinsky & Hall, 1991; Olney, Buehler, & Waziri, 1988; Orstavik, Tommerup, Eiklid, & Orstavik, 1995), however, concordant monozygotic twins have also been reported, with one more severely affected than the other (Clayton-Smith et al., 1992). Furthermore, even in the discordant pairs, the "unaffected" twins are noted to have some mild manifestations associated with BWS (Olney et al., 1988; Orstavik et al., 1995). These observations are trends we have confirmed through our data. One novel observation from our data set, however, is that a proband with a more moderate BWS score (specifically a score of 6–8), is more likely to have a twin sibling who is affected with a clinical score of 4 or greater (Figure 1). Interestingly, another imprinting disorder due to the inverse epigenetic changes at 11p15.5, known as Russell-Silver syndrome, has been previously shown to be predominantly discordant in monozygotic twin pairs in the case reports described, with only one concordant case recently reported (Riess et al., 2016). While discordance is expected in twins due to postzygotic events such as BWS (Machin, 1996), our observation highlights that one cannot assume that discordance translates to unaffected.

In comparing BWS multiple pregnancy patients to singleton patients, we note that probands who are part of a twin gestation are not significantly different in terms of clinical score from their singleton counterparts. There appears to be a trend, however, that the monochorionic proband from a multiple pregnancy is more similar in clinical score to the mosaic singletons compared to the non-mosaic singletons (Figure 2). This is an intriguing observation, as the more mosaic a patient is, the more difficult it may be to predict the location and degree of organ involvement, burden of epigenetic aberration, and associated tumor risk. This is therefore an argument in favor of a conservative approach to conduct BWS tumor screening in the clinically affected (albeit less affected) twin patient.

Previous research has proposed that an epigenetic event prior to twinning leads to the formation of two different clonal populations of cells; these different cell clones repulse one another and trigger the twinning event, leading to separate cell masses (Hall & Lopez-Rangel, 1996; Machin, 1996; Weksberg et al., 2002). It has been previously theorized that the methylation defect and twinning are so closely correlated that all BWS patients result in twins but sometimes one fetus is resorbed early in pregnancy (Bliek et al., 2009; Landy & Keith, 1998). These postulations may be supported by the occurrence in our series of three triplet pregnancies that spontaneously became twin pregnancies (Table 1).

The previously proposed mechanism for twin discordance involves failure of methylation maintenance by Dnmt1o (DNMT1 oocyte) at the S phase of one cell cycle during or just before the twinning event occurs (Bestor, 2003). There is a skew toward females in BWS twins, which has been hypothesized to be secondary to X-inactivation, with the time delay in embryogenesis allowing for developmental errors to occur, including a failure of methylation maintenance (Goodship, Carter, & Burn, 1996; Hall, 1996a, 1996b; Lubinsky & Hall, 1991; Orstavik et al., 1995; Weksberg, Shuman, & Smith, 2005). The high prevalence of monozygotic females in our cohort supports these possible explanations.

The idea of mosaicism leading to discordance among monozygotic twins has been previously established (Hall, 1996b; Machin, 1996; Saul, Schwartz, & Stevenson, 1990), along with the notion of unequal cell dispersal in the inner cell mass during early postzygotic events (Hall, 1996a; Machin, 1996; Weksberg et al., 2002). The data presented in our series support the mechanism that the epigenetic event causing BWS is a trigger to the twinning process and that the affected cells from this event diffuse among the embryos in a multiple pregnancy, creating a mosaic distribution. This diffused mosaicism of BWS cells is likely responsible for the variable phenotypic spectrum we observe.

Twinning, the degree of BWS affectedness, and the degree of mosaicism are all likely due to the timing of embryologic twinning relative to the timing of the epigenetic aberration. The proposed theory

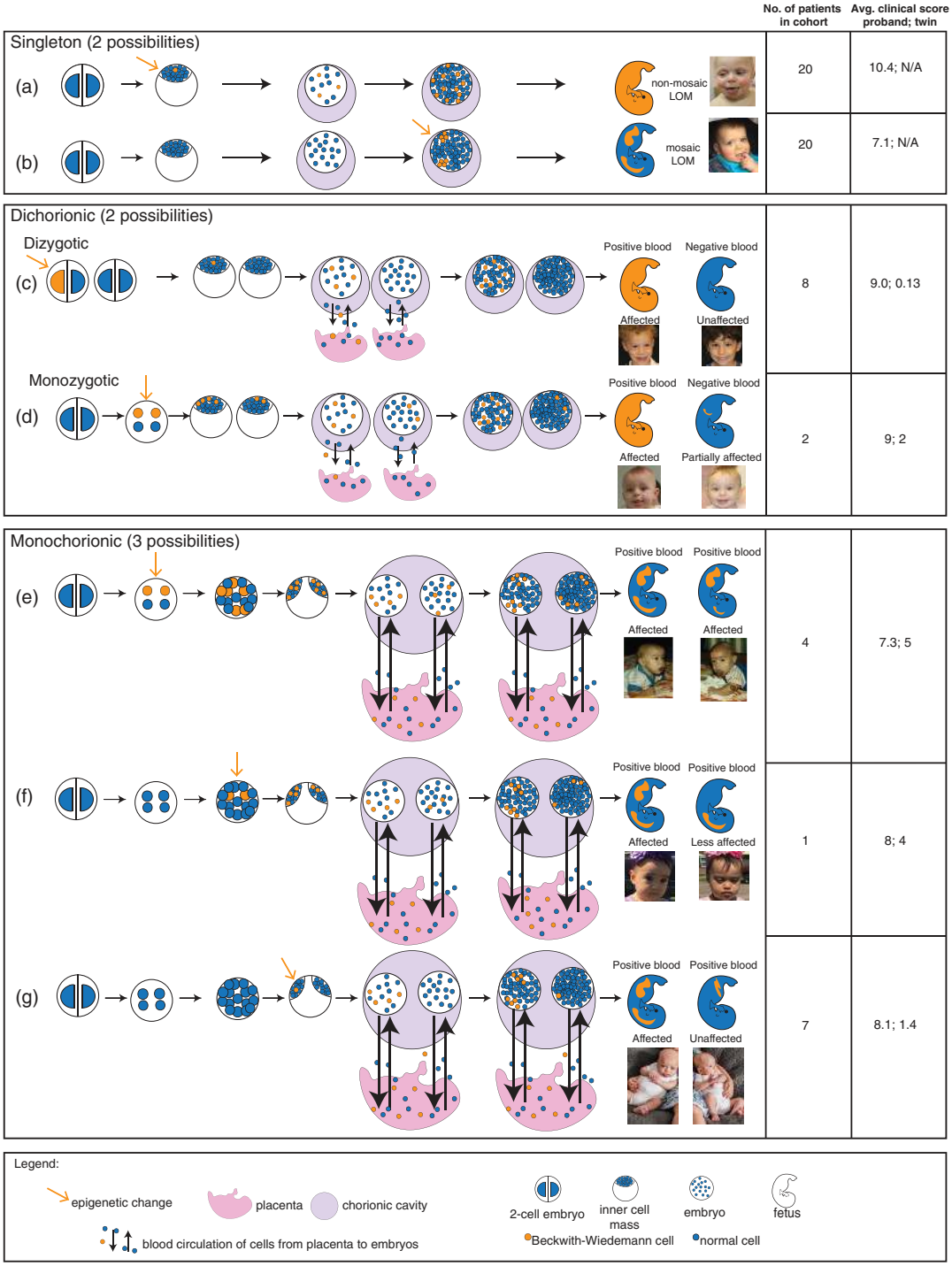

FIGURE 3 Depiction of the proposed relationships between an imprinting event and the occurrence of twinning in embryogenesis, and a proposed mechanism of "diffused mosaicism" to explain phenotypic variability in the monochorionic twin cohort. (a) Non-mosaic LOM singleton; (b) mosaic LOM singleton; (c) dizygotic dichorionic discordant twins; (d) monozygotic dichorionic partially discordant twins (twin may be partially affected or unaffected); (e) monozygotic monochorionic concordant twins; (f) monozygotic monochorionic partially discordant twins; (g) monozygotic monochorionic discordant twins. A delay between the epigenetic event and twinning allows time for affected cell propagation, leading to two concordant embryos (e). When the twinning event occurs immediately following the epigenetic event, there is less time for affected cell division and dispersion, leading to two discordant embryos. For each category (a–g), the number of applicable pregnancies from our presented cohort is listed, followed by the average BWS clinical score for each child in the pregnancy (proband and twin, where applicable). The photographs depict representative patients from our cohort for each category

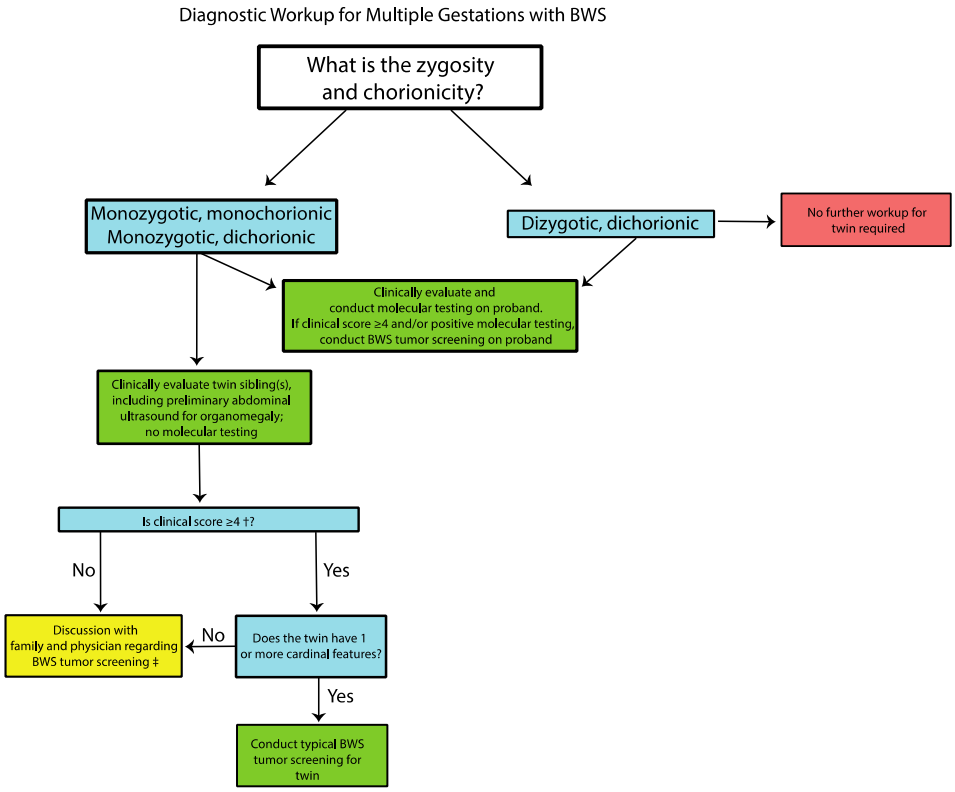

FIGURE 4 Proposed algorithm for clinical management of multiple gestations in which at least one child is affected with Beckwith-Wiedemann syndrome. Legend: † Clinical score excluding shared pregnancy factors (i.e., placental mesenchymal dysplasia, placentomegaly, polyhydramnios)‡ No data currently to support or refute the necessity of tumor screening in this instance [Color figure can be viewed at wileyonlinelibrary.com]

of "diffused mosaicism" is presented in Figure 3, which delineates the presumed time points at which the epigenetic event occurred relative to twinning and chorionicity determination, followed by the resultant phenotypes of singleton and multiple gestation patients with BWS. In singleton gestations, we propose that the epigenetic aberration occurs earlier in embryogenesis in non-mosaic patients (Figure 3a) and later in mosaic patients (Figure 3b). In dichorionic gestations, the timing of the event is likely determined by zygosity, occurring earlier in dichorionic dizygotic pregnancies (Figure 3c) than dichorionic monozygotic pregnancies (Figure 3d). In monochorionic pregnancies, an early epigenetic change affects both twins and can result in twins with positive molecular testing who are either equally affected (Figure 3e) or phenotypically affected to unequal degrees (Figure 3f). The more discordant phenotype between twins (Figure 3f) is likely due to the change occurring slightly later than in equally affected twins. The epigenetic change likely occurs even later in twins who both have positive molecular testing in blood, but with one clinically affected and the other completely unaffected (Figure 3g). This is similar to patients frequently reported in the literature, in which the concordant molecular test is thought to be due to shared placental circulation (Weksberg et al., 2002). While buccal swab has been previously proposed as the preferred and more reliable methylation test for twins due to this confounder of shared placental circulation (Bliek et al., 2009), our cohort includes a set of twins (multiple Pregnancy 1), in which the negative buccal swab was discordant with the patient's own affected clinical phenotype.

It is important to know both the zygosity and chorionicity of a multiple pregnancy patient to be able to treat and counsel appropriately. The rarer instances of monozygotic dichorionic twinning in our cohort suggest that chorionicity may strongly impact blood methylation testing results, but zygosity may play a more crucial role in determining clinical phenotype. This may result in a twin patient with a clinical diagnosis of BWS, yet negative molecular testing (Figure 3d). It is therefore important to clinically evaluate not only monozygotic monochorionic multiples, but also monozygotic dichorionic multiples, as the twin in these instances may be phenotypically affected.

In our cohort, there is no significant difference between a monochorionic pregnancy's average additive clinical score (more affected proband plus less affected twin) compared to a dichorionic pregnancy's clinical score (affected proband plus unaffected twin). Both of these two scores are most similar to that of a singleton patient with non-mosaic, rather than mosaic, loss of methylation. These equivalencies lead to the idea of a finite number of affected cells being changed during an epigenetic event early on in embryogenesis. This restricted number of aberrantly methylated cells distribute among the total number of embryos in a multiple pregnancy, so that the additive clinical score is consistent for each pregnancy, leaving the individual score of the twin to vary relative to the score of the proband (Figure 1). This concept of "diffused" or "shared" mosaicism is further corroborated by our analysis showing that the relative risk of the monochorionic twin being phenotypically affected is dependent on the clinical score of the proband. This suggests that if a monochorionic proband presents with a high clinical score (i.e., >8) they have the bulk of affected cells, with an unequal distribution of cells, and the proband's twin is more likely to be phenotypically unaffected.

As a result of our findings, we suggest a specific algorithm to evaluate and manage multiple gestation patients for BWS (Figure 4). In dizygotic dichorionic gestations, the patient presenting to medical attention should be clinically and molecularly evaluated and no

evaluation is indicated for their twin. In monozygotic gestations (monochorionic or dichorionic), the patient presenting to medical attention should be clinically and molecularly evaluated. Their twin should be evaluated with a preliminary abdominal ultrasound to evaluate for organomegaly and clinical examination by a geneticist. Twins with a BWS clinical diagnosis based on a clinical score ≥4 (excluding all shared placental features) and who display one or more cardinal features, warrant BWS tumor screening with alpha fetoprotein (AFP) and abdominal ultrasounds. This is our conservative but recommended approach at this time (Figure 4), taking into consideration the general approach in the United States for tumor screening in BWS patients (Kalish et al., 2017). Since no evidence supports or clearly refutes the need for tumor surveillance in twins with clinical scores <4 or twins with clinical scores ≥4 owing solely to suggestive features, a discussion between the family and physician should occur in these instances.

5 | CONCLUSION

We have attempted to categorize and manage phenotypically discordant BWS multiple pregnancies, taking into consideration the timing of twinning and its relationship to the higher prevalence of monozygotic twins observed among BWS patients. As a result, we propose molecularly testing the proband and clinically evaluating the twin. Future studies including analysis of multiple tissue types and specific quantification of methylation in this population of multiple gestations, along with long-term follow-up data on tumor formation in these children, will allow for the continued update of these recommendations.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose. Author JLC was a one-time consultant for Sobi, Inc.

ORCID

Jennifer L. Cohen https://orcid.org/0000-0002-0385-1025
Jennifer M. Kalish https://orcid.org/0000-0003-1500-9713

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