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REVIEW

Habiba et al.: Wharton's jelly depletion

Wharton's jelly insufficiency and its implications for perinatal outcomes and regenerative medicine: A review

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ABSTRACT

Wharton's jelly (WJ) is the hydrated extracellular matrix (ECM) of the umbilical cord, providing mechanical protection for the umbilical vessels and a niche for WJ-derived mesenchymal stromal cells (WJ-MSCs). This narrative review examines WJ insufficiency in relation to perinatal vascular risk and the functional quality of cells harvested for regenerative medicine. PubMed and Google Scholar were searched through October 2026 for studies of WJ structure, cord pathology, prenatal assessment, and WJ-MSC function. A lean cord, defined by a cross-sectional area below the 10th percentile for gestational age, was reported in 73.8% of fetuses with fetal growth restriction (FGR) in one cited cohort. The reported clinical spectrum includes reduced umbilical vein blood flow, thrombosis, and intrauterine fetal death (IUFD). Nine case reports and case series published between 1978 and 2021 describe structural cord abnormalities associated with WJ deficiency. Broader clinical findings are organized into a proposed five-tier severity continuum that has not been prospectively validated. WJ-MSCs from pregnancies complicated by gestational diabetes mellitus (GDM) or maternal obesity show functional alterations that are not captured by cell yield alone. Whether reduced WJ content or a lean cord independently lowers MSC potency remains untested. For preeclampsia and intrauterine infection, the proposed effects on WJ-MSC quality are inferred from adjacent evidence rather than demonstrated directly. Sonographic WJ-area assessment, Doppler monitoring, molecular biomarkers, and potency-based donor stratification are proposed research approaches. Prospective studies linking antenatal WJ measurements to perinatal outcomes and post-isolation MSC function are needed before the severity framework or proposed surveillance and cord-banking strategies can be adopted clinically.

Keywords: Fetal growth restriction, mesenchymal stromal cells, umbilical cord, perinatal, Wharton's jelly deficiency, Wharton's jelly-derived mesenchymal stromal cells.

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INTRODUCTION

Wharton's jelly (WJ) has historically been defined as a protective cushioning substance that keeps the umbilical vein and arteries from being compressed during uterine contraction, cord coiling, and fetal movement [1]. Although crucial, this mechanical function is only one aspect of WJ biology. The arteries, placental circulation, and gross cord anomalies have often received more attention in obstetrics and fetal pathology than WJ, unless it is significantly diminished or missing [2]. Although WJ is well recognized as a rich and readily accessible source of mesenchymal stromal cells (MSCs), the original tissue environment from which these cells originate is often overlooked [3]. WJ has been investigated as a postnatal therapeutic cell source and as a structural element of fetal survival, but these two roles have not been examined together.

The human umbilical cord matrix is a hydrated, viscoelastic, and physiologically active tissue made up of hyaluronan, sulfated glycosaminoglycans, proteoglycans, collagens, matricellular proteins, and local stromal cell populations [2, 4]. The cord can withstand compression and torsion due to its high hyaluronan content, which also supports hydration, swelling pressure, and viscoelasticity [5]. Proteoglycans and sulfated glycosaminoglycans aid in matrix organization, water binding, and growth factor availability regulation. Collagen, fibronectin, versican, and decorin all influence tensile strength, cell adhesion, and matrix remodeling [6]. These elements not only offer structure but also establish a signaling environment that affects the behavior of resident cells [7]. Within this matrix, WJ-derived MSCs and perivascular stromal cells take part in immunological control, tissue homeostasis, endothelial support, and paracrine signaling [8]. WJ is therefore better understood as a dynamic stromal milieu that promotes fetal vascular function throughout gestation rather than just as the material around the umbilical arteries [3, 9]. By decreasing the protective matrix around the umbilical vessels, WJ deficiency might jeopardize fetal health by increasing susceptibility of the vessels to compression, possibly leading to decreased blood flow, thrombosis, fetal growth limitation, and intrauterine fetal death (IUFD) [10]. Since WJ is a living stromal niche, its loss may compromise both the mechanical protection of the umbilical vessels and the function of resident WJ-MSCs, which normally promote immunological control,

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angiogenesis, and vascular stability, although an effect on WJ-MSC function has not been shown directly [11].

This review examines WJ as a tissue with two identities. Its extracellular matrix (ECM) and resident cell populations are a resource for regenerative medicine. The same structural properties, when compromised *in vivo*, are a cause of fetal death. MSC potency, secretory profile, and functional quality may depend on the biochemical and structural state of WJ. Functional deficits have been shown directly in WJ-MSCs from pregnancies complicated by gestational diabetes and maternal obesity, but not in cells from lean cords. The following sections examine the molecular and developmental biology of intact WJ, the clinical consequences when it is compromised, the diagnostic approaches available, and the implications for cord-banking quality control. Because several links between WJ loss, fetal outcome and MSC function have not been tested directly, this review presents them as hypotheses to guide future work rather than as established mechanisms.

LITERATURE SEARCH AND STUDY SELECTION

For this narrative review, PubMed and Google Scholar were searched without date restrictions, and all records available up to the final search in October 2026 were considered. Search terms combined WJ and umbilical cord matrix terms (e.g. “Wharton’s jelly”, “umbilical cord”, “lean umbilical cord”, “Wharton’s jelly deficiency”, “absence of Wharton’s jelly”) with terms for perinatal outcomes (e.g. “fetal growth restriction”, “cord stricture”, “cord torsion”, “intrauterine fetal death”), maternal conditions (e.g. “gestational diabetes”, “obesity”, “preeclampsia”, “chorioamnionitis”) and cell biology (e.g. “mesenchymal stromal cells”, “hyaluronan”, “potency”, “methylation”). The full search strings are provided in Appendix 1. Reference lists of retrieved articles and earlier reviews were screened by hand for further studies. Studies were selected for their relevance to the structure and biology of WJ, the clinical and pathological consequences of its loss, its prenatal assessment, and the properties of WJ-MSCs from pregnancies affected by maternal disease. Original human and experimental studies were prioritized; reviews were used for background. For the case evidence in Table 1, we included case reports and case series describing umbilical cord stricture, torsion or focal WJ absence

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with documented histopathology or fetal outcome, and excluded reports in which WJ status was not described.

WHARTON'S JELLY AS AN INTACT LIVING EXTRACELLULAR MATRIX

ECM molecular architecture

WJ is not a passive filler. It is a hydrated, structurally organized ECM with distinct signaling properties that change across gestation, respond to physiological stress, and maintain the resident stem cell population in a state of regulated quiescence. Understanding WJ at the molecular level is a prerequisite for understanding what is lost when it atrophies. The dominant macromolecule is a non-sulfated glycosaminoglycan called hyaluronan that is assembled as long, unbranched chains of repeating disaccharide units. In fetal tissues, hyaluronan molecular weight commonly exceeds one million daltons, and at this size, it produces the gel-like viscoelastic properties that give the umbilical cord its characteristic resistance to compression and torsion [5]. Hyaluronan is not inert. It transduces mechanical and inflammatory signals through two major receptors. The first is CD44, which is constitutively expressed on WJ-MSCs, and the second is RHAMM (receptor for hyaluronan-mediated motility), which is upregulated under situations of matrix stress or injury. During normal gestation, CD44 ligation by hyaluronan preserves the stem cell pool by suppressing differentiation and maintaining MSC quiescence [20]. The receptor-ligand balance changes and the cells react appropriately when the matrix is broken down, whether by hyaluronidase activity, mechanical disruption, or short-term physiological depolymerization [20]. Heparan sulfate and chondroitin sulfate sit in the pericellular space directly around WJ-MSCs and along the abluminal vessel surface. The sulfate groups on these chains carry a net negative charge, and growth factors including FGF-2, TGF-β, VEGF, and HGF bind to them through electrostatic attraction. This keeps each factor anchored near the cell surface rather than dispersed through the interstitium. The local sulfation pattern determines how tightly each factor is held and, therefore, how much of it reaches its receptor at any given moment. Reduce the GAG content, and that anchoring is lost. The factors do not disappear, but they are no longer held in the right place at the right concentration, and the cell receives a signal that no longer matches what the tissue needs

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[21, 22]. The collagen scaffold provides tensile integrity. Collagen type I is the primary fiber-forming component, type III contributes elasticity to the interstitial space, and type VI forms the immediate pericellular network of the microenvironment in direct contact with MSC surfaces [23]. Type VI collagen is of particular interest because it interacts directly with cell adhesion receptors (integrins α1β1 and α2β1) and with versican. Disruptions in type VI collagen assembly have been associated with skeletal myopathies in which satellite cells lose the niche support they require for regeneration [24, 25]. Whether analogous niche disruption occurs in WJ when type VI networks are compromised by lean cord conditions is not yet established, but the structural parallel is instructive. Fibronectin, versican, and decorin round out the major non-collagenous components. Fibronectin mediates cell attachment through RGD (Arginyl-Glycyl-Aspartic acid)-sequence binding to integrin heterodimers and provides a scaffold for matrix assembly during early gestation [26]. Versican is a large aggregating proteoglycan that cross-links with hyaluronan to form distensible pericellular networks. Its expression is highest in fetal stages and declines postnatally [7]. Decorin, by contrast, is a small leucine-rich proteoglycan whose primary function is TGF-β sequestration. Decorin binds TGF-β with high affinity and, in doing so, attenuates its signaling which drives fibrogenic differentiation [27]. When decorin content falls, that buffering fails. TGF-β reaches the concentrations at which it activates Smad2/3, shifts MSC fate toward an α-SMA-positive phenotype, and alters the paracrine signals that the perivascular cells deliver to the vessel wall. The two consequences are not independent, an MSC that has begun differentiating toward a fibrogenic fate is no longer producing the Ang-1 and HGF output that the endothelium depends on [28].

Developmental dynamics across gestation

WJ content is not fixed. It follows a defined developmental trajectory in which both composition and biomechanical properties change in response to cord growth, vessel caliber expansion, and fetal size. Hyaluronan content peaks at mid-gestation, when the cord is most compliant and the matrix most hydrated. In the late gestation term, hyaluronidase activity increases and HA chain length decreases, producing a matrix that is comparatively firmer and less expansile. This shift contributes to the physical coiling

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of the umbilical cord. As WJ compliance decreases, the differential tension between the cord surface and the umbilical vessels, which continue elongating, produces helical torques that establish the umbilical coiling index (UCI). The UCI is defined as the number of complete helical coils per centimeter of cord length. That number reflects the compliance state of WJ at the time the coils formed, not just the geometry of the finished structure [29]. Hypocoiling is associated with reduced WJ content, and a mechanism has been proposed. Reduced hyaluronan content lowers the differential compliance between the vessels and the surrounding matrix, which in turn reduces the torque available to generate coiling [30]. Collagen remodeling follows a complementary trajectory. The early-gestation cord is dominated by type III collagen, which confers compliance but provides limited tensile strength. As gestation advances, the ratio shifts toward type I, and the total collagen density per unit area increases [6, 31]. In the near term, a stiffer collagen scaffold is appropriate, as the cord must withstand increasing mechanical loads from fetal movement and the compressive forces of labor. The problem arises when the WJ content is already reduced. Stiffening then occurs without the surrounding gel that normally absorbs external loads, and the vessels are left exposed before the collagen has finished maturing. We propose that lean cords are most vulnerable to thrombosis in the interval between peak HA loss and completed collagen reinforcement, when the matrix has lost its hydrated cushioning, but the collagen scaffold is not yet mature. This window has not been defined empirically [1]. WJ-MSC yield correlates positively with gestational age and birth weight, although maternal age was the only independent predictor in multivariate analysis [32]. Cords harvested at term from metabolically healthy mothers with normal UCI and normal WJ content yield more cells per gram of tissue than those from growth-restricted or lean-cord pregnancies [33].

The resident MSC niche

WJ contains three anatomically defined MSC subpopulations namely perivascular cells adjacent to the vessel adventitia, mid-matrix cells in the bulk stroma, and subamniotic cells near the cord surface, the last carrying higher expression of neural crest-associated transcripts [34, 35]. The perivascular subpopulation is the most functionally consequential. These cells express PDGFR-β and NG2, extend cytoplasmic processes

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into the vessel wall, and act as the cord's sole endothelial regulators throughout gestation. The umbilical vessels have neither vasa vasorum nor autonomic innervation [36]. In the perivascular zone, HA binding to CD44, together with integrin co-signaling, is proposed to keep focal adhesion kinase activity regulated and to help maintain the cells in an undifferentiated state. When HA is lost, whether through matrix atrophy or enzymatic digestion during isolation, this regulation may be disrupted and the cells may begin committing to a lineage before they ever reach the laboratory (Figure 1) [37]. Erkan et al. (2025) examined 16 cord samples and found a cell population in WJ stroma that had not been described before. These cells were CD34, PDGFR-α, and c-Kit triple-positive, carried elongated bipolar bodies with thin cytoplasmic projections (telopodes), and measured nine times longer relative to width than the MSCs beside them. The morphological and immunophenotypic profile matched telocyte-like cells documented in cardiac and placental stroma [38]. TLCs were located at intervascular stromal clefts in direct contact with MSCs, consistent with an intercellular relay role seen for telocytes in cardiac and placental stroma. Their functional significance in WJ remains to be established, but the finding revises the WJ niche from a two-component (cell plus matrix) to a three-component system [38].

Paracrine output and immune identity

Under low oxygen conditions, WJ-MSCs maintain a trophic and immunomodulatory secretome that more closely resembles the native MSC niche, rather than the largely inflammatory phenotype seen at atmospheric oxygen. While WJ-MSC-derived soluble factors and extracellular vesicles (EVs) promote endothelial migration, proliferation, tube formation, VEGF-A release, permeability modulation, and tissue healing, oxygen tension regulates important paracrine factors, including VEGF and HGF [39]. HLA-G is expressed by WJ-derived MSCs, and under conventional culture conditions, UC-derived MSCs exhibit greater HLA-G1 expression than adipose or dental pulp tissue [40]. HLA-G can engage inhibitory receptors such as ILT2 and ILT4 on immune cells, contributing to reduced NK-cell and T-cell cytotoxicity and immune tolerance. In parallel, WJ-MSCs can suppress T-cell activation and proliferation through licensed immunomodulatory pathways, including IDO-mediated tryptophan catabolism and kynurenine production,

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which can inhibit activated T cells and promote regulatory T-cell differentiation [41]. Thiruvenkataramani et al. (2025) treated alveolar epithelial A549 cells and THP-1 monocytes with small extracellular vesicles (sEVs) derived from WJ-MSCs, without direct cell contact. LPS-induced apoptosis was reduced and IL-6 and IL-8 release fell in both cell types [42]. At least part of the immunomodulatory activity therefore resides in the vesicle cargo itself rather than in the cells that produced it. We infer from this that WJ atrophy would carry a threefold cost, namely loss of paracrine factors, reduced HLA-G-mediated tolerance and depletion of the sEV pool, although no study has measured sEV yield or cargo composition in relation to WJ content [42].

FROM MATRIX LOSS TO UMBILICAL CORD DYSFUNCTION

Lean cord phenotype: Epidemiology and etiology

A lean cord is defined as an umbilical cross-sectional area below the 10th percentile for gestational age. It was found in 73.8% of fetuses with FGR, compared with 11.3% of gestational-age-matched controls ($p < 0.0001$) [43]. As uteroplacental insufficiency worsens, WJ content falls. Gestational diabetes mellitus (GDM), oligohydramnios, preeclampsia, cigarette smoking, and nutritional restriction all reduce either the rate of HA synthesis or the hydration state of the matrix. The prevalence figures for lean cord in both populations reflect this shared reduction in hyaluronan synthesis and the loss of matrix hydration that follows from it. The resulting cord is not uniformly thinner in diameter but rather reduced in WJ cross-sectional area, since the vessels retain their caliber while the surrounding matrix contracts [1]. WJ is an instructive ECM and an MSC niche. Therefore, the lean cord phenotype represents concurrent loss of both the scaffolding and the resident cellular protection (what this review terms a dual niche failure) [1].

Mechanical failure cascade

The mechanical effect of WJ depletion is the loss of viscoelastic buffering surrounding the umbilical vessels, and the thin-walled vein is the most vulnerable to compression. Umbilical vein blood flow is 93.7 ± 17.8 mL/kg/min in lean cords and 126.0 ± 23.4

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mL/kg/min in cords of normal diameter [44]. Among 160 fetuses with a sonographically lean cord, those with an umbilical vein area at or below the 10th percentile had higher rates of perinatal death (6/64 versus 1/96, $p < 0.05$) and neonatal intensive care unit admission (22/64 versus 17/96, $p < 0.05$) than those with a lean cord but preserved vein area [45]. In the absence of the surrounding gel, the likely mechanism is compressive stress on the vessel wall. This repeated compression triggers the Virchow triad of stasis, endothelial damage, and local hypercoagulability, and external mechanical forces that WJ normally absorbs are transmitted directly to the vessel [1]. Umbilical artery thrombosis is the end-stage expression of this process. Tu et al. (2024) reported Doppler findings in 76 fetuses with umbilical artery thrombosis and compared them with 76 controls. Doppler abnormalities were present at diagnosis in 49 fetuses (64.5%), most commonly in the umbilical artery (46.1%) and middle cerebral artery (44.7%), and 25% showed a ductus venosus pulsatility index for veins above the 95th centile. Adverse outcomes occurred in 40.8% of cases. The stillbirth rate was 9.2% (7/76) despite monitoring, with FGR in 18.4% and Neonatal intensive care unit (NICU) admission in 13.2%. The ductus venosus pulsatility index for veins was the only independent predictor of adverse pregnancy outcomes in multivariate analysis (OR 161.92, 95% CI 12.17 to 2155.12), although the interval is extremely wide. Its predictive accuracy was moderate (AUC 0.792, 95% CI 0.668 to 0.917) [46].

Hemodynamic consequences

The mechanical failure described above produces a hemodynamic sequence. Vessel compression that restricts flow reduces umbilical vein return to the fetal heart, thereby lowering cardiac preload and, in turn, fetal cardiac output. When this hypoperfusion is sustained, the fetus enters a state of chronic undersupply that manifests clinically as growth restriction. The proteomic and structural cord changes already noted in FGR cords are the tissue correlate of this hemodynamic process [47]. The fetal circulation compensates by redistributing flow toward the brain. Stefopoulou et al. (2025) used superior vena cava and middle cerebral artery Doppler to characterize this redistribution directly in FGR and small-for-gestational-age fetuses. FGR fetuses showed significantly lower umbilicocerebral ratio and higher volume-flow-based cerebroplacental ratio than

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appropriately grown fetuses, with the magnitude of redistribution large enough to distinguish FGR from small for gestational age (SGA) on its own [48]. It is argued that cerebral redistribution is a compensatory response, not a protective one. By the time it appears on Doppler, the cord's mechanical failure has already affected fetal perfusion.

Cell-intrinsic deficiency

A decrease in WJ content is likely to reduce the number of resident MSCs, although this has not been measured directly. Salem and Leach (2024) showed that WJ-MSCs from GDM cords are functionally impaired. However, the study did not examine lean cords or measure cell numbers in relation to WJ content. Endothelial co-cultures made with WJ-MSCs from GDM cords were 11–22% more permeable to the tracer in transwell assays than co-cultures made with MSCs from normoglycemic cords. This permeability increase was linked to endoglin-mediated VEGF-A dysregulation rather than cell count [8]. This study has practical significance since it suggests that GDM and the lean cord phenotype may affect the niche in different ways. A cord may have sufficient MSC numbers but still fail at the endothelial interface, or it may have diminished WJ content with cells that maintain normal paracrine function. Structural and cellular failure do not always co-occur, and we propose that their combination may produce the worst outcomes. Outcome prediction based just on cord caliber or cell count could misclassify a subgroup of at-risk pregnancies.

Genetic and structural vessel wall co-pathology

A structural co-pathology at the vessel wall itself was documented by Yu et al. (2025), who identified elastic fiber deficiency in the umbilical vein wall coexisting with reduced WJ in a case series of neonatal deaths [49]. Elastin provides recoil capacity to the vein wall that is independent of the surrounding matrix. Its absence means the vessel cannot restore lumen diameter after compression, even when the mechanical load is removed. The authors proposed that elastin-specific staining should be added to perinatal autopsy protocols for unexplained stillbirth, because standard hematoxylin and eosin preparation does not distinguish fibrous from elastic tissue in the cord wall [1, 49]. A 50-case series of stillbirth autopsies creates the need for this kind of protocol expansion. 18% of cases

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remained unclassified by clinical criteria alone, and detailed placental and cord histopathology resolved most of those cases [50]. The dual pathology of reduced external cushioning and impaired wall recoil produces a vessel that is both more vulnerable to compression and less able to recover from it.

CLINICAL SPECTRUM: FROM STRICTURE TO IUFD

The case-report literature for cord stricture and torsion with focal WJ absence spans more than four decades and remains the primary evidence base for the structural and fatal tiers of the severity spectrum below. It is a gap that likely reflects the rarity of the presentation rather than a decline in its clinical relevance. Rare structural anomalies of this kind generate case reports sporadically, sometimes decades apart, and the absence of recent literature does not necessarily indicate the absence of recent occurrence. Table 1 lists the directly relevant case reports and case series identified, ordered from oldest to newest. The full search strings used across PubMed and Google Scholar are documented in Appendix 1. The milder presentations that may precede these outcomes are considered in the hypothesized continuum below.

Hypothesized graded severity continuum

Placental insufficiency is staged by Doppler as absent end-diastolic flow in the umbilical artery, then reversed flow, then ductus venosus A-wave abnormality [51]. Clinicians act on each transition point rather than waiting for overt fetal compromise, and this sequential framework is designed to reduce the proportion of growth-restricted pregnancies that deteriorate to crisis before delivery [51]. WJ deficiency has no such system, but the evidence already reviewed in the section above is comparable in shape; on its own, it suggests a comparable range from a subclinical structural abnormality through detectable hemodynamic compromise to fetal death. A cord that is simply thin sits at one end. A cord with active thrombosis sits further along. A cord that has already failed, ending in IUFD, sits at the far end [16, 47]. Table 2 and Figure 2 present this as a hypothesized continuum of severity, not a confirmed sequence. It has not been tested. No study has confirmed whether clinicians reviewing the same case would assign it to the same tier, and none has tracked whether tier placement predicts outcome.

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The tiers are not assumed to occur in sequence. A cord can be present at the thrombotic or fatal tier without any prior documented abnormality, particularly in pregnancies where surveillance was infrequent or absent.

Coexisting cord anomalies as a cumulative risk framework

No prevalence data exist for isolated WJ deficiency. Reduced WJ content is frequently reported alongside other cord anomalies, including hypercoiling, velamentous insertion, single umbilical artery, and true knots [56]. We propose that the association between WJ deficiency and these anomalies is synergistic rather than additive. A cord with reduced buffering capacity has a smaller mechanical and hemodynamic margin to begin with, so each additional abnormality narrows an already reduced margin. On this view, the risk contributed by a coexisting anomaly is not a fixed increment but depends on the WJ content of the cord in which it occurs. No study has tested this statistically, and the framing is conceptual rather than demonstrated [2, 10]. The most recent clear evidence of this compounding pattern is from true knot cohorts. Perinatal death had an adjusted odds ratio of 15.46 (95% CI 9.30 to 25.70) with a true knot alone. Within the true knot group, four or more nuchal loops of cord was the only independent predictor of perinatal death, although the estimate was imprecise (OR 13.40, 95% CI 1.12 to 160.34) [57]. For example, a lean cord already has less WJ and therefore less protection against compression and torsion. If the same cord also has a true knot or excessive coiling, blood flow may be affected more severely. For this reason, we suggest that a lean cord with another abnormality should be considered a higher-risk condition rather than two separate minor findings. In addition, the cord length, not the WJ content, has been identified as the most important predictor of the severity of nuchal cords. Silva et al. (2025) analyzed 466 term deliveries and did not find the presence of a nuchal cord to be an independent predictor of adverse outcome. A tight nuchal cord was associated with a 7.52-fold increased risk of an Apgar score below 7 at one minute (95% CI 1.51 to 37.31), although the confidence interval was wide and no effect was seen on the 5-minute Apgar score (p = 0.726) or on other neonatal outcomes [58]. This finding reaffirms the previous finding by Rogers et al. (2003) that cord length, rather than jelly content, is the key determinant of

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the severity of tightening, and explains why risk models targeted at WJ should not view the extent of nuchal cord tightening as a direct indicator of WJ status [59].

DIAGNOSTICS

Ultrasound phenotyping

Two-dimensional ultrasound is the most widely used diagnostic approach to WJ assessment. Cord cross-sectional area is measured in a transverse plane and compared against gestational-age nomograms [60]. WJ area is derived by subtracting the vessel areas from the total cord area, using the reference curve of Ghezzi et al. (2001) [61]. WJ area, calculated as total cord cross-sectional area minus the combined area of the two umbilical arteries and the vein, is the more specific of the two measurements, since it isolates the matrix from the vessels it surrounds [61]. Butureanu (2025) reports that the WJ area performs well as a sonographic surrogate for placental function generally [1]. UCI provides an indirect readout of WJ compliance. A UCI below the 10th percentile is a correlate frequently associated with reduced WJ. Cord cross-sectional area, WJ area, and UCI share one technical limitation. Each is taken from a single 2D plane, which underestimates total jelly volume relative to a full 3D reconstruction of the cord. Comparative validation of 3D against 2D measurement has not been performed.

Doppler indices

Doppler ultrasonography may add a functional layer to the assessment of a lean or hypocoiled umbilical cord. The most frequently recorded parameter is umbilical vein blood flow, calculated as the cross-sectional area of the umbilical vein multiplied by the time-averaged maximum velocity (TAMXV) [44, 62]. Di Naro et al. reported a mean flow of 93.7 ± 17.8 mL/kg/min in lean cords compared with 126.0 ± 23.4 mL/kg/min in cords of normal diameter [44]. The pulsatility index (PI) is calculated as the difference between peak systolic and end-diastolic velocity divided by the time-averaged maximum velocity of the waveform. The umbilical artery pulsatility index (UA-PI) is sometimes recorded alongside umbilical vein flow, but it should be interpreted with caution in this context, since it reflects placental vascular resistance rather than the condition of the cord and is therefore not a direct indicator of WJ deficiency. The cerebroplacental ratio (CPR),

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calculated as the middle cerebral artery pulsatility index (MCA-PI) divided by UA-PI, is likewise informative about fetal circulatory adaptation to placental or cord compromise rather than diagnostic of cord pathology. These Doppler parameters are not part of a validated surveillance protocol for WJ deficiency. As a hypothesis for future research, in pregnancies where a lean or hypocoiled cord has been identified, cord area, umbilical vein blood flow and CPR could be assessed together, with fortnightly measurement from 28 weeks. No study has validated these parameters or this interval for WJ deficiency. The interval is borrowed from growth restriction surveillance, and the scheme should be tested in prospective studies before any clinical use.

Emerging imaging modalities

Three-dimensional ultrasound, prenatal magnetic resonance imaging (MRI), and automated image analysis are active areas of fetal imaging research, but none has yet been directed specifically at WJ volume. 3D ultrasound combined with tomographic imaging has already improved detection of placental vascular anastomoses in monochorionic twins, and a deep-learning model trained on 3D ultrasound volumes has detected delayed brain maturation in early-onset FGR fetuses, the same population in which lean cord is most common [63–65]. Neither study measured WJ, but both confirm 3D acquisition and AI-based analysis are increasingly feasible in obstetric imaging to be redirected at a new structure once training data exists.

Toward a molecular biomarker framework for WJ assessment

The biochemical composition of WJ has been characterized at the tissue level in excised cord specimens, but that characterization has never been extended into a diagnostic application. Ultrasound and Doppler measure structure and flow. Neither measure directly the molecules that define whether WJ is intact or depleted. Sonographic appearance does reflect tissue water content, which depends on hyaluronan, so the relationship is indirect rather than absent. No *in vivo* test for WJ molecular status exists, and no published study has reported an attempt to develop one. Gogiel et al. (2003) were the first to characterize WJ proteoglycans directly. The study shows that 1 g of WJ contains 2.43 ± 0.63 mg of sulfated glycosaminoglycans, with chondroitin/dermatan

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sulfate as the dominant GAG chain, decorin as the most abundant proteoglycan core protein, and versican present in smaller amounts [66]. Raio et al. (2004) extended this to HA using fluorophore-assisted carbohydrate electrophoresis on WJ tissue from trisomy 21 and healthy fetuses. They demonstrated that hyaluronan amount and distribution in WJ is measurable directly from cord tissue and differs quantifiably across conditions [67]. Conrad et al. (2022) applied mass spectrometry proteomics to WJ tissue from FGR and FGR-plus-preeclampsia cords and identified 28 (FGR vs. control) and 48 (FGR-plus-preeclampsia vs. control) proteins significantly different in abundance from controls, the majority in ECM, inflammatory, and angiogenesis pathways, with WJ area itself also reduced in FGR cords [47]. Together, these three studies indicate that WJ molecular composition is measurable, differs in FGR and chromosomal abnormality states, and changes in a direction consistent with matrix breakdown.

EFFECTS OF WJ PATHOLOGY ON MSC QUALITY

The therapeutic potential of WJ-MSCs depends on what happened to the cord before harvest. Four maternal conditions (GDM, preeclampsia, obesity, and intrauterine infection) alter the WJ niche in ways that may carry into cell quality, although the strength of evidence differs considerably between them. Direct functional studies of isolated WJ-MSCs exist for GDM and maternal obesity. For preeclampsia and intrauterine infection, no such study has been published, and the two subsections on these conditions therefore present mechanistic hypotheses rather than direct evidence. This has practical implications for cord banking. Donor eligibility for cord tissue is determined by communicable disease screening and testing under 21 Code of Federal Regulations (CFR) Part 1271 [68] and product identity is established by the International Society for Cell and Gene Therapy (ISCT) minimal criteria of plastic adherence, surface marker expression and trilineage differentiation [69]. Neither addresses cell function, and a potency assay is expected at release only for advanced-phase clinical trials, where such assays remain unstandardized [70]. Functional impairment independent of yield would therefore not be detected at banking intake.

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Gestational diabetes mellitus

GDM is the best-characterized of the four conditions, with three independent lines of evidence converging on the same conclusion that intrauterine hyperglycemia imprints WJ-MSCs in ways that persist after isolation and expansion. The functional deficiency was most clearly demonstrated by Salem and Leach (2024). GDM damages WJ-MSC function through two independent routes: oxidative stress that depletes antioxidant capacity and Endoglin-mediated VEGF-A dysregulation. Under standard normoxic culture without exogenous stimulation, WJ-MSCs from GDM cords released 3.8 times more VEGF-A into the conditioned medium than cells from normoglycemic cords. Additionally, depending on the GDM treatment group, they generated HUVEC co-cultures that were 11–22% more permeable to the tracer in transwell assays and expressed greater amounts of Endoglin (CD105). Salem and Leach (2024) silenced Endoglin in WJ-MSCs from normoglycemic cords using siRNA. The silenced cells secreted more VEGF-A and failed to maintain VE-cadherin-dependent junctional integrity in co-culture, reproducing the barrier defect seen with GDM-derived cells. Because the effect was produced by manipulating Endoglin expression in cells of normoglycemic origin under identical culture conditions and seeding densities, it reflects a cell-intrinsic mechanism rather than a difference in proliferation rate or culture environment between GDM and control cells [8]. Tozour et al. (2018) identified the molecular basis for a parallel cell-intrinsic deficit. WJ-MSCs from large-for-gestational-age infants of GDM mothers showed elevated ROS levels and reduced glutathione peroxidase (GPx) activity under oxidative stress in culture, compared with cells from normoglycemic controls. GPx downregulation in self-renewing stem cells produced a susceptibility to oxidative damage that was maintained across passages, a finding that implies the GDM environment programs antioxidant capacity in the stem cell pool in a way that persists after delivery, rather than acting only as a transient exposure during gestation [71]. Amrithraj et al. (2017) extended this to metabolic function, finding that WJ-MSCs from offspring of GDM-affected pregnancies had lower mitochondrial oxygen consumption rates and that paired HUVECs from the same cords showed impaired tube formation and reduced BCL-xL expression. CD44, a surface receptor constitutively expressed on WJ-MSCs that contributes to niche maintenance and regulates endothelial

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tube formation, was under-expressed in GDM-derived HUVECs, pointing to a CD44-mediated pathway through which GDM may contribute to cardiovascular risk programming in umbilical cord-derived cells [72]. Taken together, these three studies point to the same conclusion. GDM damages WJ-MSC function through at least two independent routes, oxidative stress that depletes antioxidant capacity and Endoglin-mediated VEGF-A dysregulation. Standard yield-based quality metrics detect neither. Banking protocols that pass GDM cords on yield alone may therefore release cells that meet quantitative release criteria but show functional impairment in downstream applications (Figure 3).

Maternal obesity

Badraiq et al. (2017) conducted the only published study directly comparing WJ-MSCs from obese (BMI ≥30) and normal-weight donors in a matched case-control design [73]. WJ-MSCs from obese donors showed slower population doubling than those from normal-weight donors, a finding that runs counter to the assumption that more maternal adipose mass would produce a richer cord matrix. Paradoxically, cells from obese donors showed stronger immunosuppressive activity in PBMC co-culture, suggesting that the pro-inflammatory intrauterine environment from maternal obesity primes WJ-MSCs toward a more activated immunosuppressive phenotype. Genome-wide DNA methylation analysis across triple-positive (CD73/CD90/CD105) cells found 67 genes with methylation differences of 0.2 or greater at CpG sites in four or more obese donors. The gene showing the most consistent change across the methylome, transcriptome and protein levels was PNPLA7, a lysophospholipase that hydrolyzes lysophosphatidylcholine and participates in glycerophospholipid turnover and lipid droplet metabolism. Its function in WJ-MSCs has not been investigated, but three consequences can be hypothesized. Altered lysophospholipid handling would change membrane phospholipid composition, which in turn influences membrane fluidity and the lipid microdomains through which receptor signaling is organized. Because extracellular vesicles bud from these same membranes, a shift in phospholipid turnover could alter vesicle biogenesis and cargo loading, and therefore the paracrine activity on which WJ-MSC therapeutic effect largely depends. Lysophosphatidylcholine is also a pro-

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inflammatory lipid mediator, so reduced clearance could contribute to the activated immunosuppressive phenotype observed in the same donors. These are inferences from lysophospholipase biology in other cell types and have not been tested in WJ-MSCs [73]. Findings published since 2017 support the oxidative component of this work while diverging on differentiation. Bellalta et al. (2026) compared WJ-MSCs from 15 normal-weight and 15 obese pregnancies and found higher total FOXO1, reduced acetyl-FOXO1 and increased cytoplasmic FOXO1 localization in obese-donor cells, consistent with reduced FOXO1-mediated repression of PPARγ and earlier adipogenic commitment. The same group had previously reported raised mitochondrial superoxide levels and altered redox pathways in these cells, and FOXO1 dynamics were modulated by H_2O_2 *in vitro*, placing oxidative stress upstream of the adipogenic shift. Independent cohorts have reported greater adipogenic potential, altered fatty acid oxidation and AMPK activity with associated DNA methylation changes, and adipocyte hypertrophy in MSCs from infants of mothers with obesity [74]. The oxidative mechanism is therefore supported by more than one group and converges with the GPx depletion described in GDM cords, which strengthens the case that maternal metabolic exposure acts on WJ-MSCs through a shared redox route. The differentiation findings remain inconsistent, since Badraiq et al. (2017) found no difference in lineage propensity whereas later studies report enhanced adipogenic commitment, and differences in donor number, passage and differentiation protocol may account for this. For banking, the relevant point is that none of these changes, oxidative, epigenetic or adipogenic, is detected by cell yield or surface phenotype.

Preeclampsia (hypothesis-based)

No published study has isolated WJ-MSCs from preeclamptic pregnancies and compared their functional properties with normotensive controls in a formal experimental design. What follows is therefore a mechanistic case for why such a comparison is warranted, not a summary of direct evidence. Three features of the preeclamptic intrauterine environment are relevant to the WJ niche. First, preeclampsia is characterized by placental oxidative stress arising from intermittent perfusion and repeated hypoxia-reoxygenation, which generates ROS in tissues downstream of the placental circulation.

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The WJ-MSC deficits already described in GDM cords, namely GPx depletion and loss of antioxidant capacity, arose through an oxidative route, so the same mechanism operating in preeclampsia would be expected to affect the resident stromal population. Second, the maternal syndrome involves an anti-angiogenic circulating profile, with excess sFlt-1 and soluble Endoglin sequestering VEGF and TGF-β. Endoglin-mediated VEGF-A dysregulation has already been shown to impair endothelial support by GDM-derived WJ-MSCs, which makes the same axis a plausible point of disruption in preeclampsia. Third, hyaluronan and versican turnover in the WJ is sensitive to inflammatory and oxidative signaling, so a sustained systemic insult would be expected to act on the matrix and on the cells it maintains at the same time. Each of these expectations is inferred from other conditions and has not been tested in preeclamptic cords. Gauthier-Fisher et al. (2019) reviewed pericytes in the umbilical cord and noted that obstetric complications, including GDM and preeclampsia may alter WJ-MSC yield, properties and potency, citing the mechanistic plausibility of oxidative stress and hypoxia-reoxygenation injury in the cord [75]. This is a narrative observation rather than experimental evidence. The Conrad et al. (2022) proteomics study is sometimes taken as partial support, but it cannot serve that purpose. The preeclampsia arm of that study consisted of cords from pregnancies with both FGR and preeclampsia, and the same study showed that FGR alone reduces WJ area and alters the WJ proteome. Every change observed in the combined group is therefore equally consistent with an FGR effect, and the design provides no isolable evidence of a preeclampsia-specific contribution [47]. A study isolating WJ-MSCs from preeclamptic pregnancies without concomitant FGR and measuring clonogenic frequency, ROS levels, antioxidant enzyme activity and Endoglin expression against normotensive controls would resolve this directly, and the absence of such a study leaves preeclampsia the largest untested maternal exposure in this review.

Intrauterine infection and chorioamnionitis (hypothesis-based)

This subsection sets out a hypothesis rather than a body of direct evidence. No published study has isolated WJ-MSCs from cords with clinically confirmed chorioamnionitis and measured their HLA class II status, so the argument below is assembled from adjacent findings and each inferential step is identified. The cord stroma does respond to

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intrauterine inflammation. Topping et al. (2013) found IL-33-positive macrophages in the umbilical cord in acute but not chronic chorioamnionitis, and showed that IL-1β treatment of WJ myofibroblasts in culture induced IL-33 expression and altered ST2 receptor expression in HUVECs, indicating that the WJ cellular compartment responds to intrauterine inflammation through an IL-1 and IL-33 pathway [76]. Two limits apply when this finding is carried toward WJ-MSCs. The cells examined in culture were myofibroblasts rather than isolated MSCs, and the stimulation was applied *in vitro* rather than arising from infection *in vivo*. A second inference concerns the immunological consequence. IFN-γ stimulation upregulates HLA-DR on adult-source MSCs *in vitro*, and sustained IFN-γ or IL-1β exposure in the cord stroma during chorioamnionitis could plausibly produce the same effect. This extrapolation crosses from adult to fetal-derived cells, which differ in baseline HLA expression and immunomodulatory phenotype, and it assumes that activation acquired *in utero* persists through isolation and expansion. Neither assumption has been tested. The mechanism is therefore biologically plausible but unverified at every link. Cords from confirmed chorioamnionitis cases, isolated under standard conditions and assessed for HLA class II expression and immunomodulatory function, would establish whether the pathway operates as proposed.

EPIGENETIC SIGNATURES OF WJ-MSCs

WJ-MSCs produce more colony-forming unit fibroblast centers and express higher levels of Oct4A, Nanog, and Rex1 at 5% than at 21% O_2. Upregulated HIF-1α and HIF-2α at 5% O_2 have been observed [77]. WJ-MSCs maintained at 5% O_2, the physiological level in cord stroma, also resisted the spontaneous neural lineage drift that develops progressively when the same cells are cultured at 21% O_2. Drela et al. (2014) showed that trichostatin A, a histone deacetylase inhibitor, blocked both HIF expression and the stemness-maintaining effect of low oxygen, indicating that histone deacetylation is required for the pathway linking oxygen concentration and MSC phenotype [77]. Transferring WJ-MSCs from 5% to 21% O_2 during isolation therefore not only changes the culture environment but also removes a chromatin-level maintenance signal that was active in the native niche. The WJ-MSC methylome at baseline is hypomethylated at loci that are not hypomethylated in other cell types. Govarthanan et al. (2020) applied a

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customized 180K human DNA methylation microarray to untreated WJ-MSCs and found that cardiac-specific gene promoters were hypomethylated without any pharmacological intervention. The methylation profile at these loci in untreated cells more closely resembled that of human cardiac tissue, although no other MSC source was profiled alongside, so it remains unknown whether this pattern is specific to WJ-MSCs. The result positions WJ-MSCs as cells that retain epigenetic permissiveness for cardiac lineage differentiation, rather than cells that must be chemically unlocked before differentiation becomes possible [78]. The matrix itself protects the cells it contains from senescence [79]. Hao et al. (2013) cultured MSCs on WJ extract-coated plates through late passages and measured β-galactosidase activity, telomere length, p53 expression, p16INK4a/pRb expression, and ROS levels at each point. Telomere length was better conserved, and all remaining four senescence indicators namely β-galactosidase activity, p53 expression, p16INK4a/pRb expression and ROS levels, were reduced in WJ extract-cultured cells compared to standard-culture controls [79]. Differentiation capacity, which often decreases with passaging, was retained through late-phase culture at 50 population doublings. Coating with the WJ extract, which contains ECM components and cytokines, was associated with reduced p53 and p16INK4a/pRb expression, although the constituents responsible were not identified. The mechanism linking matrix contact to chromatin-level senescence suppression was not fully elucidated, but the effect was reproducible across passages. This provides strong evidence that the WJ matrix is an epigenetically active niche rather than a passive collagen gel. GDM alters the methylome at a particular locus that may be explained mechanistically. Wu et al. (2023) assessed the methylation of the PGC-1α promoter in WJ-MSCs from both normoglycemic and diabetic pregnancies. Cells from diabetic donors showed higher methylation of the PGC-1α promoter, with correspondingly decreased PGC-1α expression. These cells also had reduced mitochondrial DNA content and reduced myogenic differentiation potential. After cells were subjected to myogenic differentiation protocols, AMPK activation by metformin or AICAR (Acadesine) reduced methylation, and restored PGC-1α expression, and the demethylated state remained stable through one cell-fate transition [80]. This leads to two conclusions for the current review. In addition to the GPx depletion reported by Tozour et al. (2018) and the Endoglin-VEGF-A dysregulation reported by Salem and

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Leach (2024), a third unique GDM-induced mechanism in WJ-MSCs is PGC-1α hypermethylation. Metformin reverses this mark, and it is one of the two pharmacological arms in the Salem and Leach GDM cohort. It is therefore possible, although untested, that its epigenetic effect on WJ-MSC mitochondrial programming contributes to the different permeability profiles seen between diet-controlled and metformin-treated GDM cords in that study [8, 71]. These four studies describe three epigenetic mechanisms by which WJ-MSC identity is maintained in the native niche, together with three corresponding routes by which it is lost when that niche is disrupted. These are chromatin remodeling when oxygen levels rise during isolation, removal of matrix signals when cells leave WJ contact, and locus-specific methylation when the intrauterine environment undergoes metabolic insults. Banking and isolation protocols that do not account for these chromatin-level effects are operating below the resolution at which WJ-MSC quality may ultimately need to be assessed.

THE LEAN CORD AS A DEPLETED THERAPEUTIC SOURCE

Cord banking programs select donor cords on the basis of communicable disease testing and the viable cell count obtained at the time of collection. WJ content at the time of collection is not taken into consideration by either criterion, and this gap directly affects production quality. Direct evidence linking WJ content to MSC yield is limited, but several indirect findings suggest that WJ content and MSC yield may be proportional and that lean cord donors may contribute fewer cells per cord to a banking inventory. Whether these cells are also functionally impaired has not been tested. If both were confirmed, a lean cord donor would affect a banking inventory in two ways, by contributing fewer cells and by contributing cells that are more likely to be functionally compromised. Compared with the single-donor case described above, the pooled inventory problem is harder to detect and potentially broader in effect. Mebarki et al. (2025) showed that pooling WJ-MSCs from three donors in a 1:1:1 ratio reduced inter-donor immunomodulatory variability and improved batch consistency compared with single-donor products [81]. That finding provides preliminary evidence favoring pooling as a manufacturing strategy. However, the effectiveness of pooling depends on functional equivalence among constituent donors. A pooled batch that contains one lean cord donor

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and two normal donors may not compensate for the deficiency of the lean cord donor. It would dilute the batch's overall potency in ways that are unlikely to be picked up by traditional post-pooling quality control, which examines phenotypic and general viability. The ISCT minimal criteria define MSC identity by plastic adherence, surface marker expression, and trilineage differentiation, and none of these measures function [69]. Potency assays are expected for release in advanced-phase trials, but they are not standardized and are mostly designed around immunomodulatory activity [70]. A donor-derived deficit in endothelial support or antioxidant capacity could therefore pass both identity testing and an immunomodulatory potency assay. This situation has not been directly evaluated in any published study. The conclusion is based on two independently established facts of unequal strength. First, pooling is being explored as a way to reduce inter-donor variability in WJ-MSC products, although current evidence comes mainly from a single proof-of-concept study [81]. Second, lean cords may yield fewer MSCs, which is supported by indirect evidence, whereas their lower potency has not been shown directly and is inferred from functional deficits reported in cells from GDM and obese-donor pregnancies [71]. The combination results in a quality-control gap that has not been addressed as a combined issue by either the pooling literature or the lean cord literature. The practical question this raises for banking is whether WJ area or cord cross-sectional area should be recorded at donation and used as a donor stratification variable, the way birth weight or placental weight is recorded in obstetric databases. Currently, it is not. Butureanu (2025) reports that WJ area shows promise as a surrogate for placental function and can be measured sonographically before delivery [1]. If that measurement were incorporated into prenatal screening for cord banking candidates, lean cord donors could be identified before donation. This matters because a pooled batch can meet standard release criteria for viability and surface phenotype while showing reduced functional potency, such as weaker immunosuppressive or angiogenic activity. No published study has yet traced reduced potency of this kind to lean cord donors. The link therefore remains hypothetical, and antenatal screening would allow it to be tested prospectively instead of being investigated only after a batch had shown poor potency. This is a suggested workflow modification rather than a proven methodology, and before

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it can be adopted into practice guidelines, prospective research connecting antenatal WJ area to post-isolation cell yield and potency is needed.

DISCUSSION

The evidence reviewed here points to one process with two sets of consequences. When WJ content falls, the umbilical vessels lose their viscoelastic protection, and we propose that the resident MSC pool is reduced at the same time, a combined loss we have termed dual niche failure. For the fetus, we propose that this loss can be placed along a hypothesized severity continuum from a lean cord with FGR through Doppler-detectable redistribution and thrombosis to structural occlusion and IUFD [46–48]. For cell therapy, the direct evidence comes from maternal conditions rather than from cord thinning itself. WJ-MSCs from GDM and obese-donor pregnancies carry oxidative, mitochondrial, endothelial-support and epigenetic deficits [8, 71–73, 80], and reduced WJ area and altered ECM and angiogenic protein profiles have been reported in cords from pregnancies with both preeclampsia and FGR, although these changes cannot be separated from the effect of FGR [47]. These deficits persist after isolation and are not detected by yield or surface phenotype. No study has yet measured MSC potency in relation to WJ area or lean cord status, so the link between matrix loss and cell quality is an inference from these maternal-condition studies. In pooled manufacturing, which assumes that donors are functionally equivalent [81], a single lean or metabolically exposed donor may lower batch potency without failing any release test. The fetal and therapeutic problems may therefore share a cause, arise before delivery, and go unmeasured, because neither WJ area nor MSC function is routinely recorded. Earlier reviews have treated these consequences separately. Butureanu (2025) linked WJ pathophysiology to fetal and neonatal outcomes without considering the cells derived from it [1], and reviews of WJ-MSCs as a therapeutic product have generally treated the donor cord as a uniform starting material [11]. Gauthier-Fisher et al. (2019) noted that obstetric complications may alter WJ-MSC potency but did not connect this to cord vascular pathology or banking practice [75], and case-based reviews of WJ absence have described its fatal presentation in isolation [10]. To our knowledge, this review differs from these and from recent appraisals of WJ-derived biologics [6]. It links WJ

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insufficiency, perinatal vascular risk and MSC donor quality in a single framework. This contribution is conceptual rather than empirical, and the severity continuum and banking quality-control gap are proposals built from published studies that require direct testing.

Future work should begin with a prospective cohort combining antenatal WJ area measurement with standardized MSC isolation and potency testing at delivery. Such a cohort would define the WJ area at which MSC function becomes inadequate, test the population-based 10th percentile threshold, validate the severity tiers, and, with paired maternal serum and amniotic fluid, test HA fragments and versican DPEAAE neoepitopes as prenatal biomarkers. For manufacturing, condition-specific potency screens, epigenome-wide profiling across serial passages, and comparison of batches pooled from donors above and below a WJ area threshold would show whether donor WJ status needs to be controlled. Validation of 3D against 2D sonographic WJ measurement and elastin staining of the cord in unexplained stillbirth would improve detection at both ends of the continuum [49].

Limitations

The review has limitations. It is a narrative review based on PubMed and Google Scholar searches, formal quality appraisal or risk-of-bias assessment, and studies indexed only in other databases may have been missed. The structural and fatal tiers of the continuum rest on nine case reports and case series from 1978 to 2021. Because fatal and unusual cases are more likely to be published, the continuum may overstate how often structural WJ loss ends in IUFD. Several conclusions depend on single studies, including those on maternal obesity [73], chorioamnionitis [76] and elastin co-pathology [49]. No study has examined the function of WJ-MSCs from preeclampsia without concomitant FGR or from confirmed chorioamnionitis, so the mechanisms proposed for these two conditions remain hypotheses [47, 75]. Most functional data come from cells expanded at atmospheric oxygen, which itself alters WJ-MSC phenotype [77], and no study has linked donor WJ area to MSC potency or to recipient outcomes. The pooled-batch argument combines two separate findings and has not been tested directly. Some findings allow other interpretations. A lean cord may cause fetal compromise, result from it, or both. Because WJ contracts as uteroplacental insufficiency worsens, the thin cord in FGR may

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partly mark placental disease rather than act as an independent mechanical threat, and current cohorts cannot separate the two [47]. Structural and cellular failure also do not always coincide. Cords of normal caliber may yield MSCs with impaired endothelial support [8], so dual niche failure describes the most harmful combined phenotype rather than an obligatory coupling. The direction of some effects is uncertain. Obese-donor WJ-MSCs proliferated more slowly but were more immunosuppressive [73], which may suit some indications, and metformin reverses PGC-1α hypermethylation in GDM-derived cells [80], so treated and untreated maternal conditions may not be equivalent donor categories. Finally, cord length rather than WJ content governs nuchal cord tightening [58], which limits how far WJ deficiency explains cord accidents in general.

CONCLUSION

WJ integrity is central to the mechanical protection of the umbilical vasculature during gestation and may also influence the functional quality of the MSCs later harvested from the cord for therapy. The literature has examined these two outcomes separately, and to our knowledge this is the first review to treat fetal vascular insufficiency and therapeutic source depletion as consequences of the same matrix failure. We offer three original contributions. The first is a dual-niche-failure model, in which loss of WJ content is proposed to compromise vascular cushioning and the resident stromal niche at the same time. The second is a hypothesized severity continuum which proposes that progressive matrix loss may lead to outcomes ranging from silent FGR through Doppler-detectable hemodynamic impairment to cord thrombosis and IUFD. This is a hypothesis-generating model that requires prospective validation before any clinical use. The third is the identification of a quality-control gap in cord banking, since current release criteria do not detect the functional deficits already shown in MSCs from GDM and obese-donor pregnancies, and may also miss deficits in MSCs from lean cords if these are confirmed. We propose measuring WJ integrity in obstetric surveillance, cord-banking intake, and perinatal autopsy instead of treating it as background anatomy. The monitoring and cord-banking strategies suggested here are proposals that require prospective validation before any clinical use.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Case reports and case series describing WJ deficiency and associated cord abnormalities

Reference	Sample size	Findings
Virgilio and Spangler, 1978 [12]	1	Localized WJ absence identified as the cause of cord constriction and subsequent torsion; outcome was stillbirth
Robertson et al., 1981 [13]	2	WJ deficiency noted at the constriction site in one case; both pregnancies ended in fetal demise following midtrimester amniocentesis
Chen et al., 1993 [14]	1 twin pregnancy	Focal WJ deficiency at the fetal end of the cord implicated in torsion causing one twin's death; the surviving co-twin lived a further 39 days without complications
Hallak et al., 1994 [15]	3	Cord stricture; all three pregnancies ended in second-trimester IUFD
Sun et al., 1995 [16]	25 reviewed + 8 new	WJ absence, vessel stenosis, and intravascular thrombosis at the narrow cord segment identified as the major pathological features; fetal death occurred shortly after reduced fetal movement in the great majority of cases
Bakotic et al., 2000 [17]	3 pregnancies, same mother	WJ fibrosis and deficiency at the torsion site in each pregnancy; all three ended in intrauterine fetal demise, suggesting a possible familial predisposition
Peres, 2012 [18]	1	Umbilical cord split at 13 weeks' gestation, proposed as the extreme end of the longitudinal WJ deficiency spectrum; fetal death was attributed primarily to a coexisting congenital heart defect rather than to the cord finding itself

Rippinger et al., 2016 [19]	1	Presented at 29+4 weeks with vaginal bleeding and cervical incompetence, followed by premature rupture of membranes and acute placental insufficiency requiring emergency cesarean section at 31+2 weeks; a lean (thin) cord was the only notable intraoperative finding after other causes were excluded
Botezatu et al., 2021 [10]	1	Absence of WJ over approximately 1 cm of the umbilical vessels at the abdominal cord insertion; a persistently abnormal CTG at 39 weeks led to cesarean section of a healthy 3,500 g newborn, and the exposed vessels required surgical ligation after delivery

"25 reviewed + 8 new" indicates previously published cases reviewed together with newly reported cases in the same article. Gestational ages are expressed as weeks + days where applicable. **Abbreviations:** CTG, cardiotocography; IUFD, intrauterine fetal death; WJ, Wharton's jelly.

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Table 2. Hypothesized severity continuum from subclinical WJ deficiency to fatal cord pathology

Severity tier	Clinical phenotype	Supporting evidence
Subclinical	Lean cord alone; FGR (birth weight <10th percentile); normal CTG; no acute event	Cord cross-sectional area and WJ area reduced in FGR cords versus controls, with concurrent ECM proteomic changes [47]
Functional	Variable decelerations; non-reactive NST; abnormal umbilical vein Doppler	Hemodynamic redistribution measurable on SVC and MCA Doppler in FGR fetuses before overt decompensation [48]
Thrombotic	UV/UA thrombosis; emergency delivery required; fetal distress	76-fetus UAT series: Doppler abnormalities in 64.5%, DV-PIV the strongest independent predictor (OR 161.9), 9.2% stillbirth despite surveillance [46]
Structural	Cord stricture with focal WJ absence; torsion; mechanical occlusion	Nine case reports and case series spanning 1978–2021 (see case evidence Table 1), including Sun et al.'s 1995 synthesis of 33 cases; the gap after 2016 reflects how rarely this presentation occurs, not a decline in clinical relevance
Fatal	IUFD; cord pathology as a contributing or sole cause	Cord-related stillbirth was the only category to show a statistically significant rising trend across 20 years of regional surveillance, even as FGR-, abruption-, and asphyxia-related stillbirth all declined

The proposed severity tiers are descriptive and hypothesis-generating; they have not been validated for interobserver agreement, clinical staging, or outcome prediction. **Abbreviations:** CTG, cardiotocography; DV-PIV, ductus venosus pulsatility index for veins; ECM, extracellular matrix; FGR, fetal growth restriction; IUFD, intrauterine fetal death; MCA, middle cerebral artery; NST, nonstress test; OR, odds ratio; SVC, superior vena cava; UA, umbilical artery; UAT, umbilical artery thrombosis; UV, umbilical vein; WJ, Wharton's jelly.

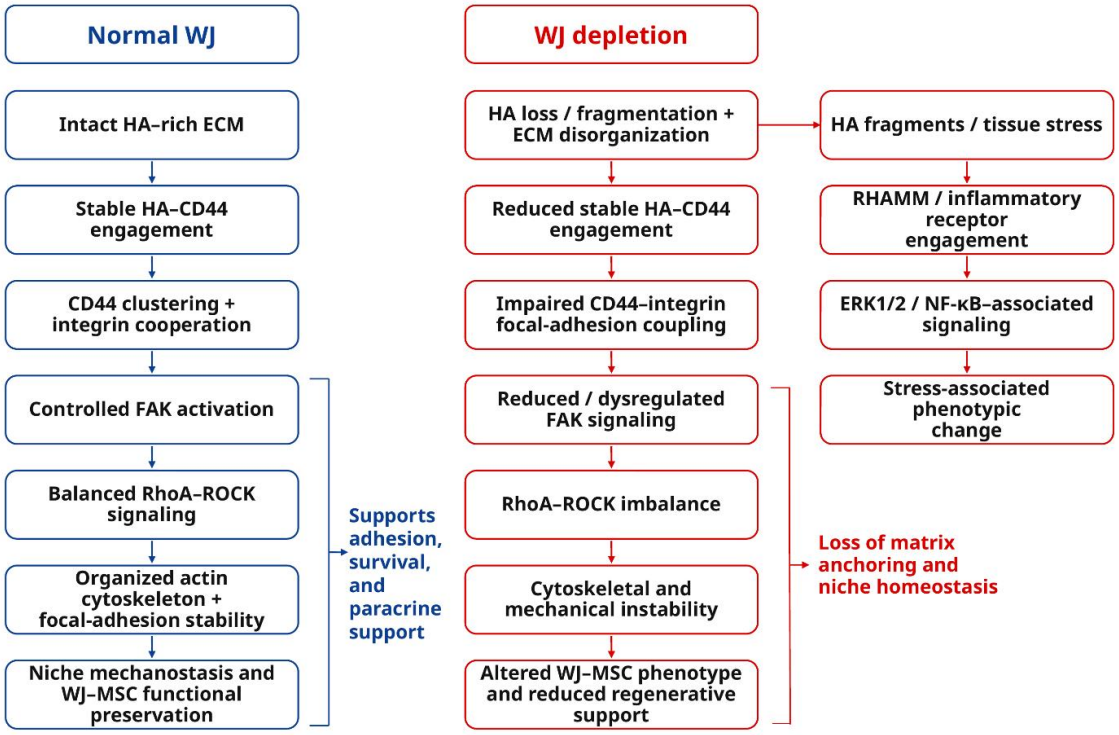

Figure 1. Proposed signaling model in normal and depleted Wharton's jelly. This conceptual model illustrates proposed signaling pathways rather than an anatomical cord cross-section. In normal WJ, stable HA–CD44 engagement and integrin cooperation are proposed to regulate FAK activation, support balanced RhoA–ROCK signaling, and preserve cytoskeletal stability and WJ-MSC function. With WJ depletion, reduced HA–CD44 engagement is proposed to disrupt focal-adhesion coupling and FAK–RhoA–ROCK signaling. HA fragments and tissue stress may also engage RHAMM and inflammatory receptors, with ERK1/2- and NF-κB-associated signaling and phenotypic changes. These pathways have not been fully characterized in WJ-MSCs. **Abbreviations:** ECM, extracellular matrix; ERK1/2, extracellular signal-regulated kinases 1 and 2; FAK, focal adhesion kinase; HA, hyaluronan; NF-κB, nuclear factor κB; RHAMM, receptor for hyaluronan-mediated motility; RhoA, Ras homolog family member A; ROCK, Rho-associated coiled-coil-containing protein kinase; WJ, Wharton's jelly; WJ-MSCs, Wharton's jelly-derived mesenchymal stromal cells.

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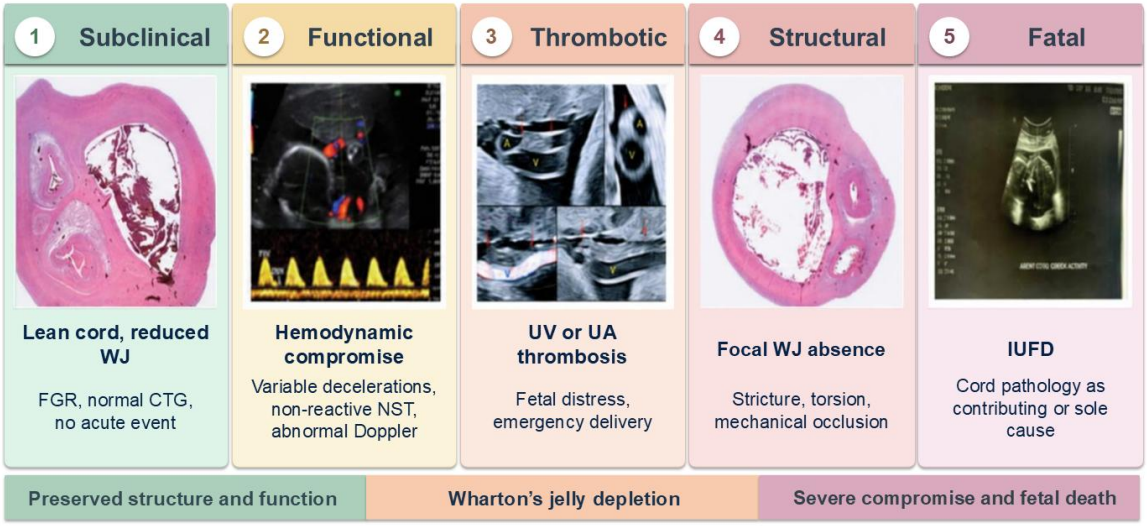

Figure 2. Hypothesized five-tier severity continuum of Wharton's jelly insufficiency. The proposed tiers comprise subclinical matrix reduction (Tier 1), hemodynamic compromise (Tier 2), umbilical vessel thrombosis (Tier 3), focal WJ absence with structural cord abnormalities (Tier 4), and intrauterine fetal death (Tier 5). The framework is descriptive and has not been validated. The tiers do not represent an established sequential progression and require prospective validation. Images are adapted from Damasceno and de Lima [52] (Tiers 1 and 4), Barbieri et al. [53] (Tier 2), Santana et al. [54] (Tier 3), and Al-Obaidi et al. [55] (Tier 5). **Abbreviations:** CTG, cardiotocography; FGR, fetal growth restriction; IUFD, intrauterine fetal death; NST, non-stress test; UA, umbilical artery; UV, umbilical vein; WJ, Wharton's jelly.

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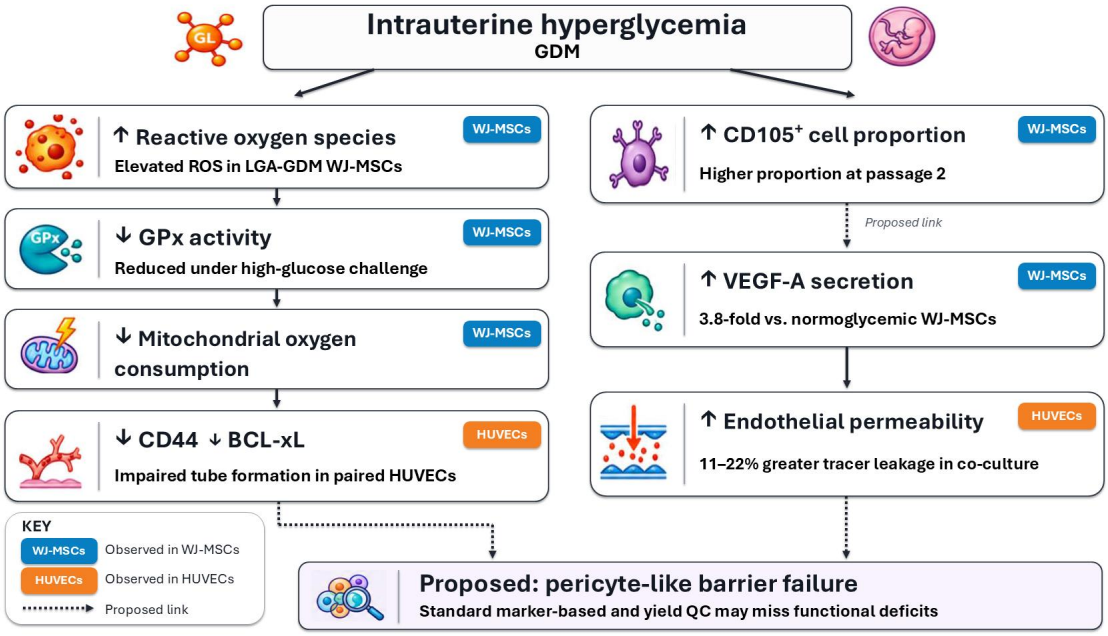

Figure 3. Proposed pathways by which gestational diabetes mellitus may impair WJ-MSC function. In the oxidative pathway, elevated ROS, reduced GPx activity, and lower mitochondrial oxygen consumption were observed in WJ-MSCs, whereas reduced CD44 and BCL-xL expression and impaired tube formation were observed in paired HUVECs from the same cords. In the endoglin pathway, higher CD105 expression and 3.8-fold greater VEGF-A secretion were observed in WJ-MSCs, and an 11–22% increase in permeability was measured in HUVEC monolayers co-cultured with them. Blue and orange labels identify observations in WJ-MSCs and HUVECs, respectively. The dashed arrow denotes a proposed link. The endoglin–VEGF-A link is supported only by endoglin knockdown in WJ-MSCs from normoglycemic cords; convergence on pericyte-like barrier failure remains a proposed interpretation. **Abbreviations:** GDM, gestational diabetes mellitus; GPx, glutathione peroxidase; HUVECs, human umbilical vein endothelial cells; LGA, large for gestational age; QC, quality control; ROS, reactive oxygen species; VEGF-A, vascular endothelial growth factor A; WJ-MSCs, Wharton's jelly-derived mesenchymal stromal cells.

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