VERMONT REGENERATIVE MEDICINE
JONATHAN E. FENTON, D.O., F.A.A.P.M.&R.

Board Certified in:
Physical Medicine and Rehabilitation
Neuromusculoskeletal Medicine
Orthopaedic Medicine
Musculoskeletal Ultrasound

Practice limited to:
Osteopathic Physical Medicine
Image Guided Injections
Interventional Regenerative Orthopedic Medicine

February 28, 2020

Vermont Senate Committee on Health and Welfare

Dear Committee Members,

I'm writing for 2 purposes. One to present evidence for why using bone marrow concentrate (BMC) in orthopedic applications (as done at UVM in orthopedic surgery) as a source of multiple types of stem cells meets criteria for acceptable clinic practice, and then second to inform you of the fraudulent "stem cell" clinics and their practices, such as the one presently operating in Williston, VT.

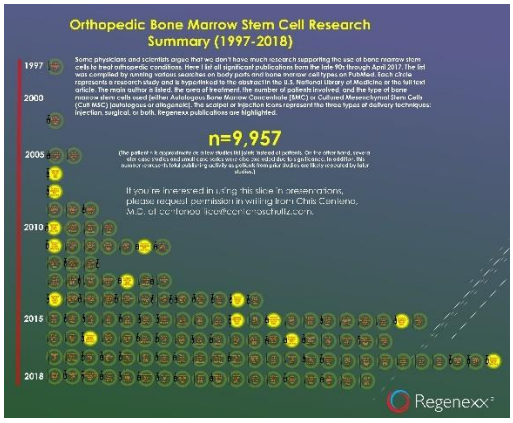
These clinics claim to inject stem cells but use placental and cord products that are devoid of viable cells, as per independent laboratory testing and published peer reviewed literature (1-3), and that put patients at significant risks. The FDA has well defined rules regarding these products (see links at the very bottom of this letter). I have included 2 other documents in the file that better delineate the problems associated with use and marketing of birth tissue products as stem cells.

BMC Use in Orthopedics

The committee may not be familiar with the use of bone marrow concentrate (BMC) in orthopedics. First, BMC is created from a bone marrow aspirate, which involves use of a trocar to aspirate the liquid portion of the bone marrow, usually from the back of the pelvis (9). To create a BMC, commercially available and FDA cleared centrifuges extract a fraction from the bone marrow called the "buffy coat" which is rich in many cells including hematopoietic and mesenchymal stem cells, other nucleated cells, and growth factors (10).

The first instances of BMC use to promote orthopedic tissue repair appears in the literature in the 1990s (11-13). By the early 2000s, Hernigou had published the 10-year results of hip osteonecrosis patients treated with BMC showing the avoidance of Total Hip Replacement in 94% of patients (14). BMC has been used extensively to promote surgical fusions in both non-union and in spinal surgery to enhance intervertebral fusion (5, 18).

To speed up the literature review, below (and as a separate pdf document) is a review of BMC use for orthopedic applications that is up to date as of last year. Each of these circles represents a study link and the icons/symbols are explained in the document. Click on the image below to be taken to a PDF document with active links:



Hence, as you can see from the document, the data supporting BMC use in orthopedics is mature and evolving. Claims of "no proof" by local and national academic physicians are therefore unfounded.

This literature compares favorably to orthopedic surgery where only 20% of procedures are supported by at least one high-level randomized controlled trial (15). Here is a quote from that editorial (written by an orthopedic surgeon): *"The evidence base for orthopedics (surgery) compares unfavorably with other fields of medicine. Only 20% of procedures are estimated to be supported by at least one low-risk-of-bias randomized controlled trial showing that surgery is superior to a non-operative alternative."*

FDA uses the term "human cells, tissues or tissue-based products" (or "HCT/P") when describing human cells or tissues that are "intended for implantation, transplantation, infusion or transfer into a human recipient." FDA's regulation of HCT/Ps involves a tiered risk structure and a several part test. The "tiered, risk-based approach" to the regulation of HCT/Ps was first announced by FDA in 1997 and was finalized in regulations found at 21 C.F.R. Part 1271 in 2005. 21 C.F.R. § 1271.10 includes an important test through which all HCT/Ps must be vetted in order to determine whether any specific HCT/P will be subject to FDA's Investigational New Drug (IND) and Biologics License Application (BLA) requirements, or merely the Part 1271 regulations themselves.

In the context discussed here (physician use of bone marrow concentrate in offices or operating rooms), these regulations create a binary regulatory pathway where one category is regulated only by the Part 1271 regulations themselves or exempt form FDA regulation, while the other is regulated as a drug requiring the full gamut of FDA's drug approval process. Autologous HCT/Ps that are "more than minimally manipulated" are deemed by FDA to present more risk and cannot be used in the United States without FDA's permission in the form of an approved IND or BLA. Alternatively, autologous HCT/Ps that are "minimally manipulated" may either be regulated as a tissue product, subject to FDA's registration, listing, and Part 1271 requirements, or as surgical procedures, which would fall into FDA's "same surgical procedure" exemption found at 21 CFR 1271.15 and regulated primarily at the state medical board level. Finally, bone marrow is exempt from regulation as an HCT/P if it is minimally manipulated and used for a homologous purpose; 21 CFR 1271.3(d)(4).

Given the minimal processing involved in the creation of bone marrow concentrate, it fits squarely under FDA's minimal manipulation definition. Indeed, using a parallel example involving a blood product, FDA wrote in its guidance that when a "manufacturer performs cell selection…to obtain a higher concentration of hematopoietic stem/progenitor cells for transplantation…[t]he HCT/P would generally be considered minimally manipulated because the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristics…"*Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use*, Food and Drug Administration, December 2017, at p.14.

The FDA has 510K cleared multiple devices that create bone marrow concentrate (6-8). Hence, the agency's actions of approving devices that can concentrate bone marrow aspirate to create bone marrow concentrate is not consistent with a prohibition on BMC. In addition, given that no FDA regulation exists governing physician use of bone marrow concentrate, physicians cannot "escape" a regulation when there is none.

The literature supporting BMC orthopedic use is "good enough" for multiple university physicians at institutions such as Harvard, Stanford, Mayo Clinic, Emory, University of Michigan, University of Pittsburgh, Cornell, UVM, and others to begin adding this to their practices. Please see the Delphi panel results which will be discussed below.

Two large-scale clinical safety trials using BMC have been published representing 2,372 and 1,873 patients followed for up to 9 and 21 years respectively. The first paper shows no significant adverse events in the BMC injected patients that would not normally be expected with patients undergoing other injections and the second shows no evidence of tumor formation or neoplasm.

What Should be Done?

First and foremost, clinics must comply with basic FDA and FTC rules to not falsely advertise amniotic and cord products as having stem cells. In a similar vein no clinic should promise or falsely advertise results that are not supported by any evidence, such as claims they can restore cartilage thickness in joints, heal spinal cord injuries, treat neurodegenerative diseases, or treat advanced lung diseases.

In fairly recent meetings with the FDA the 3 professional organizations I'm involved with have agreed to only train physicians (MD & DO) in regenerative interventional orthopedics / pain management who are board-eligible / board-certified in one of the following: Interventional Pain Management; Physical Medicine & Rehabilitation; Interventional Radiology; Orthopedic Surgery; Primary Care Sports Medicine.

A recent Delphi panel on the use of bone marrow concentrate was conducted with 27 physicians with either an academic appointment, publications in the field, or who held leadership influence roles in physician professional organizations (19). Physicians who have academic appointments at multiple universities participated. The panel recommended that providers who utilize BMC (bone marrow concentrate) for orthopedic use should:

- Use a treatment registry
- Provide patients with candidacy grades (i.e. Good, Fair, Poor, not a candidate))
- Use expanded informed consent
- Publish their results
- Restrict advertising to claims that can be backed up scientifically
- Use an Institutional Review Board if they use BMC for an orthopedic condition where limited evidence exists
- Only use mid-levels (P.A.'s, N.P.'s, N.D.'s) who are directly supervised
- Use imaging guidance to place cells

In conclusions, as you can see, the discussion around stem cell clinics that are fleecing consumers should exclude the use of BMC for orthopedic indications. The committee could use and/or consider the adoption of some or all of the recommendations of the Delphi panel.
The legislation that is pending in Florida to regulate these clinics may prove an excellent template for Vermont.

Thank you for your attention to this matter.

Sincerely,

Jonathan E. Fenton, DO, FAAPM&R

References:

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(7) https://www.arthrex.com/orthobiologics/arthrex-angel-system-for-bone-marrow-concentrate
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LINKS: FDA & FTC

FDA warning from Dec, 2019 regarding Umbilical cord and exosome products
https://www.fda.gov/safety/medical-product-safety-information/public-safety-alert-due-marketing-unapproved-stem-cell-and-exosome-products

FDA warning from Sept, 2019 https://www.fda.gov/news-events/press-announcements/fda-sends-warning-company-selling-unapproved-umbilical-cord-blood-and-umbilical-cord-products-may

https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies

https://www.fda.gov/news-events/press-announcements/fda-puts-company-notice-marketing-unapproved-stem-cell-products-treating-serious-conditions

https://www.washingtonpost.com/national/health-science/fda-sends-letters-to-20-companies-in-attempt-to-rein-in-stem-cell-industry/2019/04/03/7e01556e-564e-11e9-8ef3-fbd41a2ce4d5_story.html

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