

June 1, 2016

Howard Bauchner, MD  
Editor in Chief  
JAMA and The JAMA Network

Dear Dr. Bauchner:

Pursuant to your request, this letter provides specific references for the nine clinical literature quotes at the outset of my article “Fetal Pain Facts and Falsehoods.”

Note that the textbooks and journals I cited use different chronological methods of reckoning pregnancies: fertilization or last menstrual period (LMP). The reckoning method in my article is from “fertilization,” which typically occurs two weeks after the LMP.<sup>1 2</sup> For the purposes of accuracy and cautiousness, I used the latest plausible timeframes for these developmental milestones and preceded each reference with the phrase “By ... weeks.” In other words, some of these milestones may actually occur before the timeframes I specified.

**1) By 7 weeks, pain “sensory receptors appear in the perioral [mouth] area.”**

Anand K, Hickey P. Pain and Its Effects in the Human Neonate and Fetus. *New England Journal of Medicine*. 1987;317(21):1321-1329. doi:10.1056/nejm198711193172105.

Page 1322: “Cutaneous sensory receptors appear in the perioral area of the human fetus in the 7th week of gestation; they spread to the rest of the face, the palms of the hands and the soles of the feet by the 11th week, to the trunk and proximal parts of the arms and legs by the 15th week, and to all cutaneous and mucous surfaces by the 20th week.”

Reckoning: LMP

**2) By 10 weeks, “All components of the brain and spinal cord are formed, and nerves link the stem of the brain and the spinal cord to all tissues and organs of the body.”**

Dulbecco R. *Encyclopedia Of Human Biology*. San Diego: Academic Press; 1997. Volume 3. Allan, F. Fetus.

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<sup>1</sup> Moore K, Persaud T. *Before We Are Born: Essentials of Embryology and Birth Defects*. Philadelphia: Saunders; 1998. Page 109: "The expected date of delivery (EDD) of a fetus is 266 days, or 38 weeks, after fertilization; that is, 280 days, or 40 weeks, after LNMP (Table 7-1)."

<sup>2</sup> England M. *Color Atlas Of Life Before Birth*. Chicago: Year Book Medical Publishers; 1983. Page 12: “Most clinicians do not know the fertilization date; the only date available to them is the first day of the last menstrual period. They use this date to define a menstrual age stretching from time 0, which is usually 14 days before fertilization....”

Page 955: “10 weeks ... All components of the brain and spinal cord are formed, and nerves link the stem of the brain and the spinal cord to all tissues and organs of the body.”

Reckoning: uncertain

**3) By 12 weeks, “Electrical activity of the nervous system is discernible” and “attempts to suckle” are observed “in utero and in aborted fetuses.**

Dulbecco R. *Encyclopedia Of Human Biology*. San Diego: Academic Press; 1997. Volume 3. Allan, F. Fetus.

Page 962:

Initial nervous activity begins in the third fetal month ... Reflexes that develop during the third month involve the mouth and head (e.g., sucking, swallowing, gagging, and moving the mouth, and therefore, the head toward a perioral stimulus). Electrical activity of the nervous system is discernible at the same time, but periods of electrical silence can occur up to midterm. ... Attempts to suckle have been seen in utero and in aborted fetuses of 3 months.

Reckoning: uncertain

**4) By 14 weeks, “limb movements ... become coordinated.”**

Moore K, Persaud T. *Before We Are Born: Essentials of Embryology and Birth Defects*. Philadelphia: Saunders; 1998.

Page 106: “Limb movements, which occur at the end of the embryonic period (8 weeks), become coordinated by the 14th week, but are too slight to be felt by the mother.”

Reckoning: fertilization

**5) By 14 weeks, preborn humans exhibit conscious “motor planning” and “social behavior.”**

Castiello U, Becchio C, Zoia S et al. Wired to Be Social: The Ontogeny of Human Interaction. *PLoS ONE*. 2010;5(10):e13199. doi:10.1371/journal.pone.0013199.

Page 9:

Twin pregnancies constitute an experiment of nature which offers the unique opportunity to explore social behaviour before birth. By investigating kinematic profiles of movements in five pairs of twin foetuses, we demonstrated that, by the 14th week of gestation, twin foetuses not only display movements directed towards the uterine wall and self-directed movements, but also movements specifically aimed at the co-twin. ...

Analysis of the kinematic profiles for the different categories of movements corroborates our main hypothesis that these early contacts do not occur accidentally, but reflect motor planning.

Page 10: “These findings force us to predate the emergence of social behaviour: when the context enables it, as in the case of twin foetuses, other-directed actions are not only possible but predominant over self-directed actions.”

Reckoning: uncertain

**6) By 14 to 22 weeks, “a physiological fetal reaction to painful stimuli” occurs.**

Van de Velde MDe Buck F. Fetal and Maternal Analgesia/Anesthesia for Fetal Procedures. *Fetal Diagn Ther.* 2012;31(4):201-209. doi:10.1159/000338146.

Page 206: “Whether a fetus is capable of experiencing pain as a conscious and emotional feeling remains unclear and is subject to great debate [67], but we cannot deny that the fetal nervous system mounts protective responses to tissue injury. A physiological fetal reaction to painful stimuli occurs from between 16 and 24 weeks’ gestation on.”

Reckoning: LMP

**7) By 18 weeks, pain sensory receptors spread to “all cutaneous [skin] and mucous surfaces,” and the cerebral cortex (the portion of the brain responsible for higher functions like reasoning and language) has the same number of nerve cells as a full-grown adult.**

Anand K, Hickey P. Pain and Its Effects in the Human Neonate and Fetus. *New England Journal of Medicine.* 1987;317(21):1321-1329. doi:10.1056/nejm198711193172105.

Page 1322: “Cutaneous sensory receptors appear in the perioral area of the human fetus in the 7th week of gestation; they spread to the rest of the face, the palms of the hands and the soles of the feet by the 11th week, to the trunk and proximal parts of the arms and legs by the 15th week, and to all cutaneous and mucous surfaces by the 20th week.”

Page 1322: “Development of the fetal neocortex begins at 8 weeks of gestation, and by 20 weeks each cortex has a full complement of  $10^9$  neurons.”

Reckoning: LMP

**8) By 18 to 20 weeks, the human fetus “elaborates pituitary-adrenal, sympatho-adrenal, and circulatory stress responses to physical insults.”**

Fisk N, Gitau R, Teixeira J, Giannakouloupoulos X, Cameron A, Glover V. Effect of Direct Fetal Opioid Analgesia on Fetal Hormonal and Hemodynamic Stress Response to Intrauterine Needling. *Anesthesiology.* 2001;95(4):828-835. doi:10.1097/00000542-200110000-00008.

Page 828: “Our group has shown that the human fetus from 18-20 weeks elaborates pituitary-adrenal, sympatho-adrenal, and circulatory stress responses to physical insults.”

Reckoning: LMP

**9) By 20 weeks, the fetus “now sleeps and wakes and hears sounds.”**

*American Medical Association Complete Medical Encyclopedia.* New York: Random House Reference; 2003.

Page 558: “At 20 weeks, the fetus is 10 inches long and about 11 ounces. The limbs have lengthened, and teeth and hair are beginning to form. The fetus now sleeps and wakes and hears sounds.”

Reckoning: uncertain

Sincerely,

A handwritten signature in cursive script that reads "James D. Agresti".

James D. Agresti  
President  
Just Facts