1.

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FETAL MEDICINE

Digital atlas records the ideal development of the brain during pregnancy (https://revistapesquisa.fapesp.br/atlas-digital-registra-a-evolucao-ideal-do-cerebro-na-gestacao/)

3D ultrasound scans of the brains of 899 healthy babies have made it possible to map the development of the organ from the 14th week of pregnancy

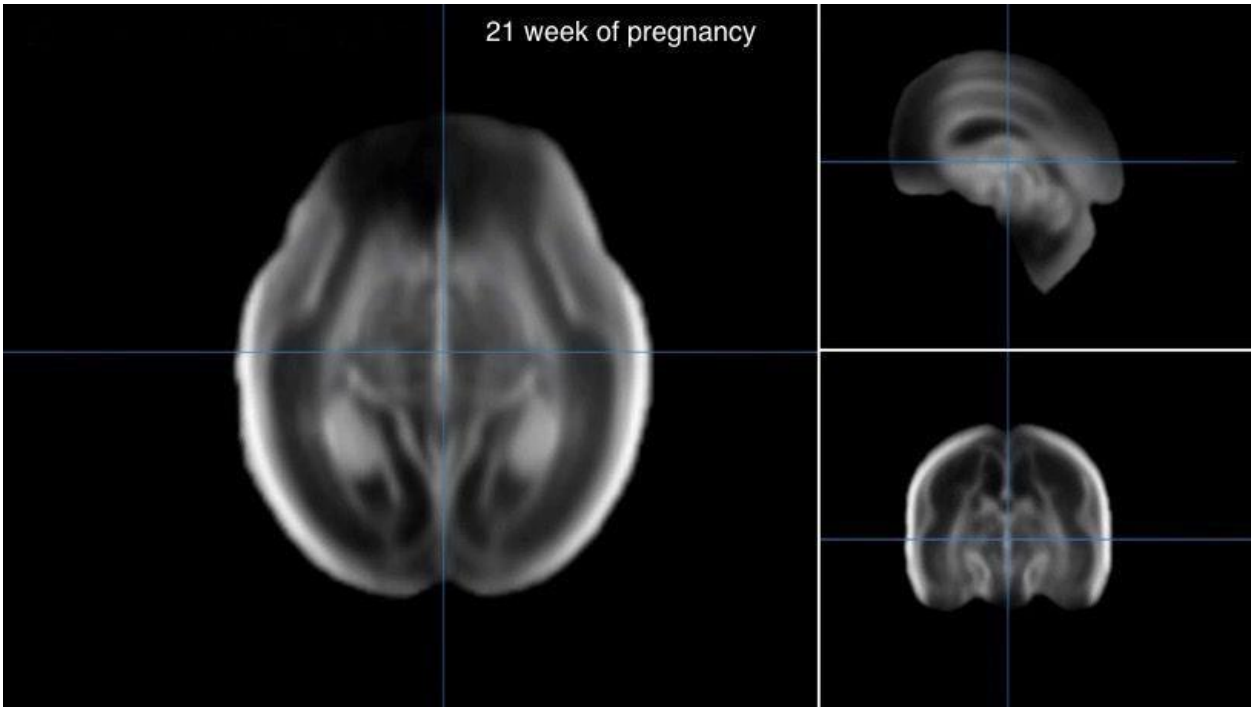

Image of the internal structures of the brain seen from above (left), from the side (right, top) and from the front (direct, bottom) at the 14th, 21st and 30th week of gestation

Brain Atlas / Intergrowth-21st / NAMBURETE, A. I. L. *et al*. **Nature**. 2023

High-resolution ultrasound images of 899 babies enabled an international group of

researchers to accurately map the development of the brain and other portions of the encephalon in healthy children in the womb. Compiled into a digital atlas available online, the results of this work are expected to serve as a reference for the expected and desirable evolution of the brain during gestation. It is also expected to help doctors identify lesions or neurological maturation issues early on, which could lead to future impairments. The study was conducted under the coordination of obstetrician José Villar and human reproduction specialist Stephen Kennedy, both from the University of Oxford in the United Kingdom, with the participation of Brazilian researchers, and was published in October in the journal *Nature*.

To establish the parameters of what appears to be the optimal development of the human brain in the womb, nearly 200 researchers followed the pregnancies of 899 women in eight countries—from the Americas, Europe, Asia, and Africa—between 2009 and 2016. Among these countries was Brazil. Specialists performed periodic 3D ultrasound scans of the fetuses from the 14th week of pregnancy until just before delivery, always using the same type of equipment and standardized procedures. This allowed them to reconstruct the week-by-week development of the encephalon. All the mothers were healthy and had the highest educational levels within their communities. None smoked or had illnesses that could compromise the baby's development.

The reason for selecting this group is that women with more years of education tend to take better care of their health and face fewer risks during pregnancy. Only by monitoring fetuses gestated under the best conditions is it possible to determine the supposedly ideal evolution of the brain's structures and other parts of the encephalon.

"Our atlas fills a six-week knowledge gap in understanding how the brain matures early in fetal life," said Ana Namburete, a researcher at the University of Oxford and the study’s lead author, in a press release. "We also revealed significant asymmetries in brain maturation, such as in the region associated with language development, which peaked between 20 and 26 weeks of gestation and persisted without differences between sexes," she explained.

Measuring the structures of the fetal brain is not simple. From the 14th to the 31st week of pregnancy, the period detailed in the current atlas, the total volume of the brain increases 13-fold, growing from 24 cubic millimeters (mm^3) to 318 mm^3. This phase involves intense cell proliferation, the establishment of connections between them, and the migration of cell groups to specific regions that will form control centers for different functions. "During this period, errors in neuronal proliferation can occur, potentially leading to clinical consequences," explains neuroscientist Andrea Jackowski from the Federal University of São Paulo (Unifesp), who studies brain development but did not participate in this study. "These are moments when the brain is most vulnerable to environmental influences, and any form of aggression could impact the child later on. However, this stage can also serve as a window of opportunity to intervene and solve problems," she notes.

Asymmetries

Another factor complicating measurements is that during this period, the right and left hemispheres begin to become asymmetrical, with certain regions gaining more volume on one side than the other. This means that the brain assumes the configuration it will have for life while still maturing and undergoing changes later on. "This is a crucial phase of maturation, where, following initial formation, processes of specialization and regional development of brain structures occur. It lays the foundation for newborns to be ready for their first cognitive developmental milestones," says psychiatrist Pedro Pan, also from Unifesp, who did not contribute to the *Nature* study.

Adding to these challenges, the fetus moves frequently in the womb, complicating image acquisition. In the current study, artificial intelligence enhanced the imaging process. "The authors had to use machine learning techniques, deep neural networks, and complex image processing methods to build the atlas," says statistician and neuroscientist João Ricardo Sato from the Federal University of ABC (UFABC), who reviewed the study for *Pesquisa FAPESP*.

Several groups had previously documented fetal brain development, but they captured later stages (from the 19th week of pregnancy onward) with fewer participants (12 to 197), often studied at a single center without follow-up after birth.

The *Nature* study included pregnant women from diverse ethnic backgrounds and tracked their children until the second year of life. It is part of the International Fetal and Newborn Growth Consortium for the 21st Century (Intergrowth-21st), which followed nearly 20,500 children from gestation through their early years, producing growth curves from intrauterine life to age 2 (see *Pesquisa FAPESP* No. 225).

"This is the largest study, to our knowledge, describing the normative early development of the human brain," the *Nature* authors wrote. "Our fetal brain reconstructions provide the first in vivo representation of the entire second trimester [of pregnancy]."

"The material provides a standard of normal fetal brain growth, which is important for diagnosing neurological issues during this phase of life," explains pediatrician and epidemiologist Fernando Barros from the Federal University of Pelotas (UFPel), coauthor of the *Nature* study and coordinator of Brazil's participation in Intergrowth-21st, which contributed images of 86 fetuses to the study. "The atlas could become a valuable tool for healthcare professionals, aiding clinical decision-making and prenatal care, as well as being useful for teaching," he says.

"Routine ultrasound exams typically identify problems starting at the 22nd week of pregnancy. With the development standard presented in the atlas, it may be possible to

detect abnormalities earlier," concludes fetal surgery specialist Denise Lapa from the Albert Einstein Hospital in São Paulo.

Scientific article

NAMBURETE, A. I. L. *et al*. Normative spatiotemporal fetal brain maturation with satisfactory development at 2 years. **Nature**. 25 out. 2023.

2.

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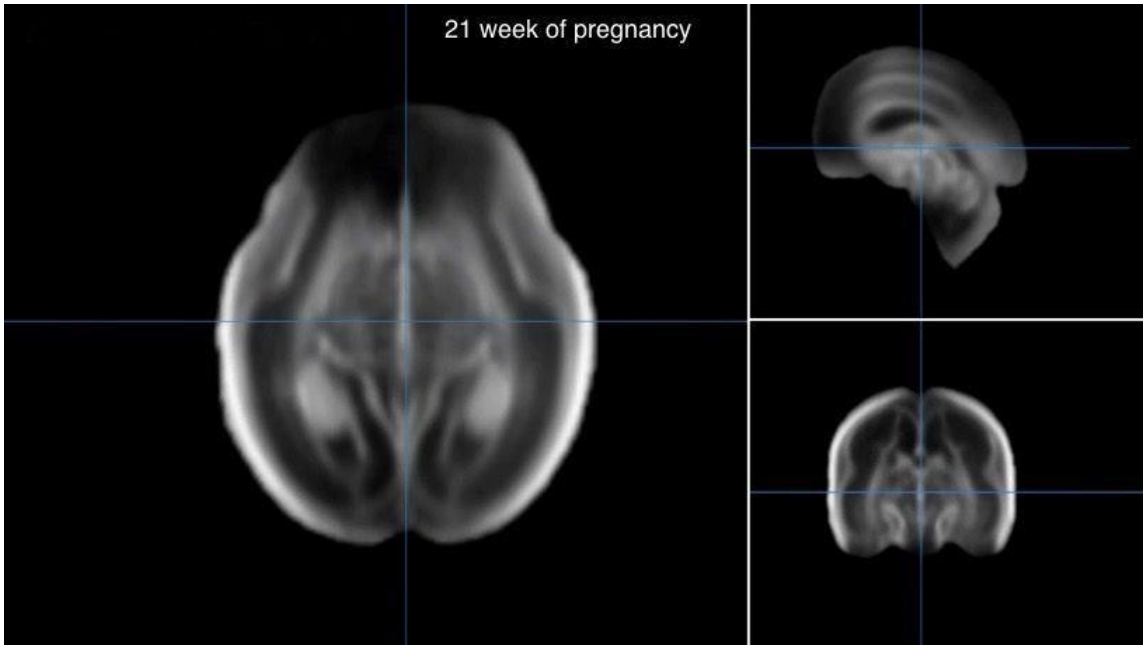
Digital atlas records the ideal development of the brain during pregnancy (https://revistapesquisa.fapesp.br/atlas-digital-registra-a-evolucao-ideal-dbhdhdhdj do-cerebro-na-gestacao/)

3D ultrasound scans of the brains of 899 healthy babies have made it possible to map the development of the organ from the 14th week of pregnancy



High-resolution ultrasound images of 899 babies enabled an international group of researchers to accurately map the development of the brain and other portions of the encephalon in healthy children in the womb. Compiled into a digital atlas available online, the results of this work are expected to serve as a reference for the expected and desirable evolution of the brain during gestation. It is also expected to help doctors identify lesions or neurological maturation issues early on, which could lead to future impairments. The study was conducted under the coordination of obstetrician José Villar and human reproduction specialist Stephen Kennedy, both from the University of Oxford in the United Kingdom, with the participation of Brazilian researchers, and was published in October in the journal *Nature*.

To establish the parameters of what appears to be the optimal development of the human brain in the womb, nearly 200 researchers followed the pregnancies of 899 women in eight countries—from the Americas, Europe, Asia, and Africa—between 2009 and 2016. Among these countries was Brazil. Specialists performed periodic 3D ultrasound scans of the fetuses from the 14th week of pregnancy until just before delivery, always using the same type of equipment and standardized procedures. This allowed them to reconstruct the week-by-

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The reason for selecting this group is that women with more years of education tend to take better care of their health and face fewer risks during pregnancy. Only by monitoring fetuses gestated under the best conditions is it possible to determine the supposedly ideal evolution of the brain's structures and other parts of the encephalon.

"Our atlas fills a six-week knowledge gap in understanding how the brain matures early in fetal life," said Ana Namburete, a researcher at the University of Oxford and the study's lead author, in a press release. "We also revealed significant asymmetries in brain maturation, such as in the region associated with language development, which peaked between 20 and 26 weeks of gestation and persisted without differences between sexes," she explained.

Measuring the structures of the fetal brain is not simple. From the 14th to the 31st week of pregnancy, the period detailed in the current atlas, the total volume of the brain increases 13-fold, growing from 24 cubic millimeters (mm^3) to 318 mm^3. This phase involves intense cell proliferation, the establishment of connections between them, and the migration of cell groups to specific regions that will form control centers for different functions. "During this period, errors in neuronal proliferation can occur, potentially leading to clinical consequences," explains neuroscientist Andrea Jackowski from the Federal University of São Paulo (Unifesp), who studies brain development but did not participate in this study. "These are moments when the brain is most vulnerable to environmental influences, and any form of aggression could impact the child later on. However, this stage can also serve as a window of opportunity to intervene and solve problems," she notes.

Asymmetries

Another factor complicating measurements is that during this period, the right and left hemispheres begin to become asymmetrical, with certain regions gaining more volume on one side than the other. This means that the brain assumes the configuration it will have for life while still maturing and undergoing changes later on. "This is a crucial phase of maturation, where, following initial formation, processes of specialization and regional development of brain structures occur. It lays the foundation for newborns to be ready for their first cognitive developmental milestones," says psychiatrist Pedro Pan, also from Unifesp, who did not contribute to the *Nature* study.

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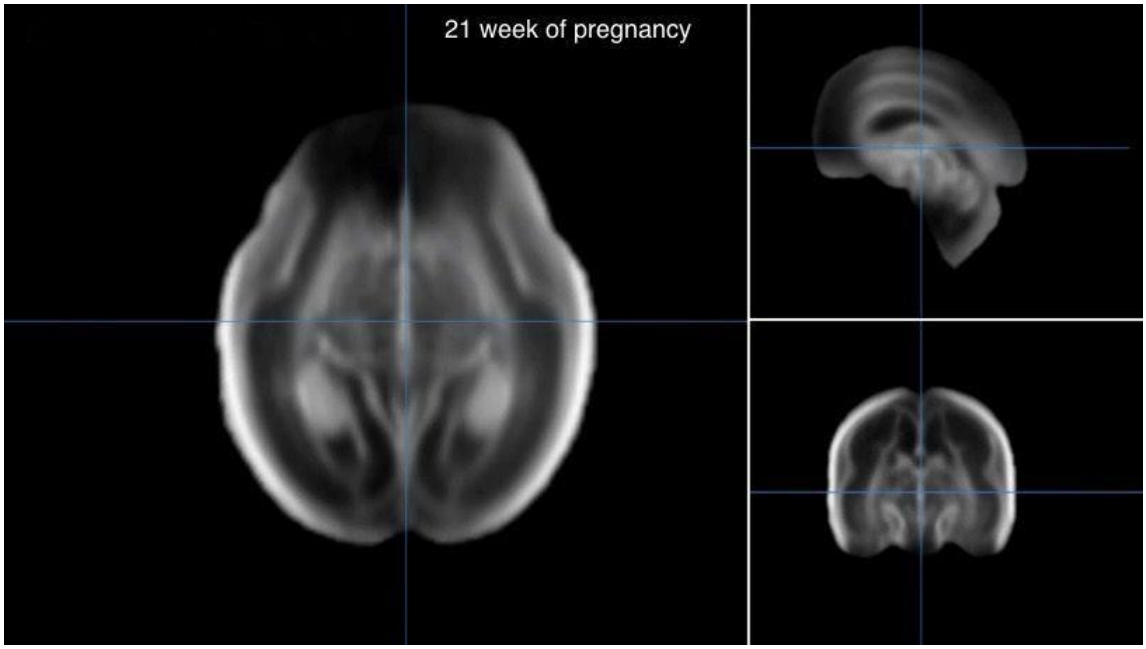
3D ultrasound scans of the brains of 899 healthy babies have made it possible to map the development of the organ from the 14th week of pregnancy



High resolution ultrasound images from 899 babys enabled a internacional group of researcher to map accurate the development of the brain and others portion of encephalons in healthy childrens on womb. Compiled in a digital atlas online, the result of this work are expect to serve like a reference to what would be the expected and desirable evolution of brain during gestation. Also are expect it help doctors to identify lesion or problems of neurological maturation earlier, which could cause future impairments. The study was made under coordination of obstetrician José Villar and human reproduction specialist Stephen Kennedy, both from Oxford University in United Kingdom, with participation of Brazilians researchers, and published in October at Nature journal.

To get the parameters of what seems like the best development of the human brain inside womb, almost 200 researcher follow the pregnancies of 899 womans in eight countries — from Americas, Europe, Asia and Africa — between 2009 and 2016. Brazil was one of this countries. Specialist done periodically 3D ultrasounds on fetus from 14th week of pregnancy till almost birth, always used same kind of equipment and standardized procedures. This

allow they to rebuild the development of encephalons week by week. All the

mothers was healthy and had the bigger educational levels of theirs community. Nobody smoke or had disease which could damage the development of babys.

The reason of chose this group is because womans with more education care better for their own health and have less risk of problems during pregnancy. Only monitoring fetus gestated in the bests conditions is possible to know what is ideal evolution for the structures of brain and others parts of encephalons.

"Our atlas fill a gap of six weeks knowledge in understand how brain mature in begin of fetal life," says Ana Namburete, researcher in Oxford University and first author of study, in press release. "We also reveal importants asymmetry in maturation of brain, like in region of language development, what reach peak between 20 and 26 week of gestation and stay without differences for genders," she explain.

Measure the structures of fetal brain isn't easy. Between 14th and 31th week of gestation, the time detailed in atlas, total volume of encephalons grow 13 times, from 24 cubic millimeter (mm^3) for 318 mm^3. In this phase, have intense proliferation of cells, connection between them and migration of cells groups to specific places that make nucleus of control for different functions. "In this time could happen errors of neuronal proliferation which can bring clinical consequences," explain neuroscientist Andrea Jackowski from São Paulo Federal University (Unifesp), who study brain development but don't participated of this study. "This moments is when brain is more vulnerable for environmental influence, and any aggression can have repercussions in child later. But this stage also is opportunity window for intervene and fix problems," she explain.

Asymmetries

Another factor make measurement hard is that in this time, the right and left hemispheres start to get asymmetrical, with some region get more volume in one side than in another. This mean the brain take the configuration it going have for life, even it still immature and go through changes later. "This is fundamental stage of maturation, when after first formation happens specialization and regional developments of brain structures. This make the base so babys when born are ready for first cognitive development acts," says psychiatrist Pedro Pan, also from Unifesp, who no contribute for the Nature study.

The fetus also move a lot in the womb, make hard to get the images. In the actual study, artificial intelligence help improve the imaging. "Authors need use machine learn techniques, deep neural networks, and complex methods for image processing for make the atlas," says statistician and neuroscientist João

Ricardo Sato from ABC Federal University (UFABC), who review the study for *Pesquisa FAPESP*.

Many groups had already document the fetal brain development, but most was later time (after 19 week pregnancy) and with few participants (12 till 197), usually in only one center and no follow-up after baby born.

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"This are the bigger study, to our know, what describe the normal early development of human brain," the authors from Nature wrote. "Our reconstruction of fetal brain is first in vivo representation of all second trimester [pregnancy]."

"The material give standard of normal growth of brain for fetus, which is important for diagnose problems neurological in this time of life," say pediatrician and epidemiologist Fernando Barros from Federal University of Pelotas (UFPel), coauthor of Nature study and coordinator of Brazilian participation in Intergrowth-21st, which give images of 86 fetus for study. "The atlas can become very valuable tool for health professionals, help make clinical decisions and prenatal care, and good for teach," he said.

"Normally ultrasound exams identify problems starting on 22 week pregnancy. With the standard development in atlas, maybe is possible detect abnormalities more early," finish fetal surgeon specialist Denise Lapa from Albert Einstein Hospital in São Paulo.