BetterObs Matters

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- BetterObs Matters is a monthly newsletter for those with a particular interest in Obstetrics
- It is based on the published literature from the world's journals in the preceding month
- All the articles summarised are hyperlinked to the full publication. To access the original, press and hold the **Ctrl** key of your keyboard while simultaneously clicking on the underlined author's name with your mouse.

How does the mother's mood affect the fetus?

Numerous studies have shown that maternal emotions can affect fetal growth and the future behaviour of her offspring. These observations have lacked scientific explanations as to how this occurs, possibly through "stress hormones" but the molecular pathways have not been precisely defined before. It now seems that this epigenetic influence is mediated by DNA methylation in the fetus and placenta.

DNA methylation is the process whereby methyl groups are added to DNA. These methyl additions do not change the base-sequence of the DNA strand itself, which remains true to its structure. However, certain methylations can cause changes to the function of the reproductive process and thus influence the cellular mitotic division.

This is the mechanism by which depression or stress in the mother during pregnancy can influence the infant's overall programming *in utero*. The result can be the impairment of growth somatically during gestation and the possible development of mental health disorders in children. These can be measured in fetal brain growth and childhood cognitive/behavioural function. The work underpinning this concept has demonstrated specific positions in the feto-placental genome that respond to maternal stress (Tesfaaye et al *Epigenomics* 2021 doi 10.2217/epi-2021-0192). The researchers followed 300 women and were able to define 16 epigenetic changes that were linked to depression and 2 to stress which they measured at 6 different times during each woman's pregnancy. Cryptically, they add that some of the changes "were located close to genes which are known to have important roles in brain development and occurrence of psychiatric disorders."

Editor's comments: Although derived through complex genetic research, this gives a logical explanation to a concept which is centuries old – namely that maternal mood and pregnancy outcomes are inextricably linked. It may explain why in times of hardship it is not only nutrition that is affected but the mental development of the fetus. Let us give thought to those pregnant women in the conflict situation in Ukraine as this summary is being written and read.

How does the mother's SES affect the fetus?

Does maternal socio-economic status (SES) affect the fetus; and if so, how? It is known that the parents' SES is linked to adverse obstetric outcomes such as growth restriction, low birth weight and preterm delivery, but it is not clear quite how SES causes these growth and maturational effects.

One explanation is genetic, in that the fetus conceived in a low SES situation and nurtured intra-uterinely with the same factors operating, will have a more rapid cellular mitosis than a comparable

fetus in a higher SES situation. It is possible to gauge the rapidity of cellular reproduction by studying a cell's genetic structure, specifically measuring its telomere lengths.

Telomere length

A telomere is the portion at the end of a gene. It has been likened to a shoelace aglet (the plastic tip which stops it fraying). The telomere becomes shorter by a very small amount each time a cell's DNA replicates itself. It can thus be used as a "biological clock", not to work out the cell's chronological age, but to estimate how many divisions it has left before the telomere length is reduced to zero and can no longer perform its protective function. The cell then undergoes senescence, which is deterioration, followed by apoptosis (programmed cell death).

If this reasoning is correct, then higher SES will be related to longer telomere lengths, as measured in cord blood, compared with infants from parents of lower SES. These were the findings in a study of more than 1 000 infants where shorter telomere length was incrementally associated with lower parental SES, especially in boys (Martens et al *JAMA Netw Open* 2020;3:e204057). The researchers postulate these early socially induced disadvantages may be the mechanisms whereby intergenerational effects are mediated.

However, it is not established whether telomere length is a biomarker or a biological mechanism for stress-related signals, nor is it clear if these early indicators can be overcome by interventions (Notterman et al *JAMA Netw Open* 2020;3:e204352).

What is now clear is that short telomere length in mature adults is associated with increased overall mortality rates and with some specific life-shortening disorders. The UK Biobank project has data derived from half a million citizens from whom they can correlate genetic findings with morbidity and mortality rates (Schneider et al *JAMA Int Med* 2022;182:291-300). It was found that short telomere length identified more than 200 disorders associated with ill-health, so its veracity as a "Geroscience-Guided Biomarker" is indisputable, and that now demands interpretation (Bauer et al *JAMA Int Med* 2022;182:300-2).

Editorial comment – The science is fascinating, but its clinical usefulness should be circumspect. It is unknown whether interventions can slow telomere shortening or not, although certain indulgences are associated with accelerated shortening, such as smoking and alcohol consumption.

Paying for telomere length measuring out of curiosity is not recommended by experts, as it is a blunt predictor of health or longevity. Interestingly, most people, if asked if they want to know their "death date" – and assuming it were possible to predict it – said they would decline to ask for it.

What is possible is to count your moles (pigmented naevi). It has been demonstrated that a high naevus count correlates with long telomere length which, in turn, is related to longevity. If you have more than 100 naevi, you will probably outlive someone with less than 25, by six years (Bataille et al Cancer Epid Bio Prev 2007;16:1499-502). So, count your blessings.

Natural selection and epigenetic influences

These explanations of how maternal mental health and social circumstances affect her fetus highlight the differences between natural selection and epigenetic influences.

The survival of the fittest paradigm relies on random genetic "mis-replications" for the progeny to be better equipped to survive and reproduce. These chance occurrences produce an improved version

of the species which has superior health and function, so the fitter specimen dominates and goes on to enrich the strain, possibly replacing the "previous model". It is a change in the cell's DNA and will be faithfully reproduced until another chance event occurs. This evolutionary process is extremely slow, but accounts for the earth's diversity of species in all forms of life.

Changes that can occur in response to the environment can obviously be more agile and act by affecting the gene's expression – not its DNA sequence. Thus, methylation can result from nutrition, hormones, temperature, radiation, infections, medications, as well as factors impinging on the uterine environment. The range of influences is wide; from obstetric disorders to climate change.

These epigenetic effects dictate changes in the fetus, which can result in long-term outcomes (for example: adult cardiovascular pathology) or short-term adaptations (growth restriction) and are passed on to the offspring as intergenerational inheritances. The uterus is not an insensitive incubator, but a responsive organ reflecting a much wider environment.

We have moved from David Barker's fetal origins of disease to an epigeneticlly explicable field that explores the developmental origins of health and disorders.

The interplay of the maternal-fetal interface with the wider context of the human condition is elegantly discussed in Sarah Richardson's book "*The Maternal Imprint: The Contested Science of Maternal-Fetal Effects"* The University of Chicago Press.

References

Richardson S The Maternal Imprint
Lyerly *Lancet* 2022 doi 10.1016/S0140-6736(22)00117-9

Cannabis use in pregnancy

There is concern that cannabis may turn out to be as detrimental to the fetus (and its subsequent development) as alcohol and cigarettes.

Research into its short-term teratogenic and long-term behavioural effects is relatively new, but what is being published is not reassuring. Risks associated with cannabis use in pregnancy are:

- THC is slowly metabolised, being detectable in adults for 30 days
- cannabinoid receptors are present in the fetal brain from 13 weeks gestation
- cannabis is perceived to be relatively harmless for the management of minor disorders of pregnancy such as nausea, constipation, and anxiety
- more than one third of pre-pregnancy users continue with its use through pregnancy
- cannabis use is associated with the following adverse neonatal outcomes: preterm delivery, birth weight less than 2 500g, small for gestational age (SGA or growth restriction), low Apgar scores, and decreased head circumferences (Marchand et al *JAMA Netw Open* 2022;5:e2145653).

These data have been collected against a background of cannabis potency that "has tripled in recent decades"; many policy makers are hesitant to allow unconsented toxicology testing, so self-reporting with probably under-reporting is likely; many women using one substance are known to be polysubstance users of alcohol and tobacco, as well as cannabis (Lupattelli et al *JAMA Netw Open* 2022;5:e221964) and where cannabis used disorders are diagnosed in pregnancy, there is often

evidence of concomitant psychiatric and medical conditions, to which attention should be given (Meinhofer et al *JAMA Psychiatry* 2022;79:50-58).

Editorial comment: The use of cannabis carries significant health and social risks, and it is my view that all products containing it should have quantities displayed as well as health warnings – especially pertaining to pregnancy.

*There is rightly much talked about mental health in the media, which I applaud and support, but should we as obstetricians not be calling for primary prevention? Children from a single or polysubstance gestational environment are at risk of behavioural difficulties, for example Attention-Deficit/Hyperactivity Disorder (ADHD) which is now reported as affecting more than 10% of monitored cohorts (*Garrison-Desany et al *JAMA Netw Open* 2022;5:e221957).

People diagnosed with ADHD and Autism Spectrum Disorders carry a higher mortality risk than other adults, enhancing the case for prevention at every level (Catala-Lopez et al *JAMA Ped* 2022 doi 10.1001/jamapediatrics.2021.6401).

Pregnant women should not use cannabis and we should insist on its regulation to protect the next generation (Skelton et al *JAMA Netw Open* 2022;5:e2145666).

BetterObs Matters **is produced by Athol Kent**
atholkent@mweb.co.za