Consequences of altered prenatal environment

Discuss the evidence that an altered prenatal environment (e. g. due to maternal nutritional status, stress or exposure to chemicals) has long-term consequences for reproductive function of the offspring.

The Developmental Origins of Health and Disease (DOHaD) hypothesis focuses on the idea that non-communicable diseases, such as coronary heart disease and diabetes, have origins in foetal development. The embryo or foetus can be exposed to certain challenges during its development that permanently alter the physiological development of that organism and this can show its effects postnatally later on in life (Moore 2017). A lot of focus has been directed towards metabolic dysfunction and problems with the cardiovascular system, but more recently it has become apparent that there are also lifelong effects of the prenatal environment on reproductive function of the offspring. Aspects of the prenatal environment include maternal malnutrition, maternal stress, maternal alcohol consumption, and maternal smoking, amongst others, which can all influence the development of the foetus and its health outcomes later on in life. However, there is a lack of evidence for humans, although offspring of mothers affected by the Dutch Famine have been followed up throughout their life to see the effects of the acute maternal undernutrition (de Rooij *et al.* 2016) (Painter *et al.* 2006), therefore a lot of the experiments are performed on rodent, porcine and ovine models. While there are a number of differences between the mammalian models and humans, such as duration of gestation and sensitivity to the maternal environment, there are periods of exceptional vulnerability that are similar in both mammalian models and humans which

allow us to map the effects of an altered prenatal environment from these animals to humans (Zambrano *et al.* 2014).

The incidence of non-communicable diseases in adults significantly increases when maternal nutrition is compromised at vital periods of foetal development (Chavatte-Palmer *et al.* 2008). During the periconceptional period, it appears that the embryo has a degree of developmental plasticity and it takes advantage of this when being exposed to certain challenges in the maternal environment. This means that it changes the way it develops and adapts to the surrounding environment, which has consequences for later life. This is illustrated by the epidemiological study of female survivors of the Dutch Famine in World War II, which has shown altered reproductive function of their female offspring who were conceived during the famine. The offspring were found to have irregular menstrual cycles, increased risk of breast cancer and a younger age at which they underwent menopause (Sloboda *et al.* 2011). There was no significant change in the reproductive function in adults whose mothers were exposed to the famine during late stages of pregnancy when compared to adults who were born before the famine (Painter *et al.* 2006), which suggests that the time around conception is very sensitive to the maternal environment. The study was conducted by authors who were fortunate to be able to collect the data that they did because, for obvious ethical reasons, a study like this could not be purposefully carried out on humans. As inhumane as the famine was, it has provided us with some useful data to ascertain what is happening *in utero* when maternal nutrition is compromised.

Animal studies of maternal undernutrition have been conducted to add to the findings of the Dutch Famine epidemiology. In ewes, the female offspring had decreased rates of ovulation after experiencing prenatal undernutrition. Even earlier, it was found that the foetal ovary at day 47 already had altered concentrations of oogonia and meiotic arrest in the ovary was delayed even longer than usual on day 62 of foetal life (Sloboda *et al.* 2011). Growth restricted rats have shown staggered onset of signs of sexual maturation, for example first oestrus, mating and attainment of full fertility were separated in time rather than being simultaneous (Sloboda *et al.* 2011). Moreover, pregnant ewes on a calorie restricted diet produced offspring who grew up to have reduced ovarian and granulosa cell proliferation and increased apoptosis in their ovaries. This could be due to a change in the hypothalamic-pituitary-gonadal axis activity or hormonal environment in the ovary which is regulated by the mother's nutritional status (Sloboda *et al.* 2011).

Furthermore, maternal protein restriction in rats delays seminiferous tubule lumen formation and increases apoptosis of germ cells during the neonatal period. Histological sections of the testes of male offspring show some tubules with no lumen at all at even when they have a control diet after birth (Zambrano *et al.* 2014). Also, apoptosis in the testes of male neonates at postnatal day 14 is increased in those who have experience maternal protein restriction either during pregnancy, during lactation, or during both (Zambrano *et al.* 2014). There have been many animal studies done using various mammalian models to produce data that we can apply to humans. So far, the data has been reproducible but it is still early days in this field of

science so the longer these experiments are reproduced in different models, the better and more sure we can be when advising mothers of the risk their diet may have on the health and reproductive potential of their offspring.

Although poverty and undernutrition remain global crises, it is clear that overfeeding and the obesity epidemic in the Western World come with severe implications on health of the population and future generations. Several studies in animal models have demonstrated that maternal overnutrition can affect the fertility of the offspring later on in life. For example, in pregnant sheep that are overfed, the offspring experience intrauterine growth restriction and are born small for their gestational age, but also the females are born with ovarian retardation (Chavatte-Palmer *et al.* 2008). Additional studies have been done and have other, similar conclusions for female offspring fertility. A mouse study shows that mothers fed high fat diets during pregnancy produced female offspring with a 4-fold reduction in the number of primordial follicles in their ovaries (Cheong *et al.* 2014). This could be due to them having an early onset of puberty, similar to the female offspring of mothers who had calorie restricted diets. Similarly, the female offspring in this cohort also had fewer (1. 4-fold decrease in number) antral follicles developing into Graafian follicles in their ovaries (Cheong *et al.* 2014). However, the cohort sizes in this study were unfortunately quite small (10-15 mice per group) and it is unclear whether or not the groups were exposed to different nutritional challenges at the same time to ensure that the process was standardised. The results could be improved by repeating them with another cohort of mice and perhaps repeating the study in different species of mice to eliminate species-specific

adaptations to maternal nutrition. If the same results are able to be replicated across other mouse species, then it is more plausible that these results might also be seen in humans.

Some oestrogenic compounds have been observed to have effects on ovary development in later life of neonatal rodents that were exposed to the compounds prenatally. Two examples are activin and oestrogen derivatives (Woodruff and Walker 2008). Female rats exposed prenatally to oestradiol benzoate had delayed follicle and interstitial development by day 14 of age. By day 21, many of the larger follicles in the ovary were delayed in development at the preantral and small antral follicular stage. This suggests that oestrogens inhibit follicular development (Ikeda *et al.* 2001). As the rats mature, the inhibited development could delay the onset of sexual maturity in the females and puberty wouldn’t occur until later.

It is known that steroidogenic factor 1 (SF1-) controls development of the ovary (Hanley *et al.* 2000), so expression levels of genes that SF-1 regulates were studied in ovaries treated with oestradiol benzoate (Ikeda *et al.* 2001). It was found that ovarian tissue treated with oestradiol benzoate had downregulated SF-1 as well as genes including StAR and P450 $_{SCC}$, which have their expression controlled under SF-1 activity. This downregulation was present from postnatal day 6-21 and was relative to control ovary. Other genes were found to not change with oestradiol benzoate treatment and some had increased expression after treatment. This results indicate that oestrogen derivatives can influence different genes related to SF-1 to be upregulated or downregulated during development of the ovary (Ikeda *et al.* 2001).

Maternal stress during pregnancy is another important factor affecting development and function of the offspring's reproductive system. Corticosteroids are an important class of steroid hormone involved in the stress response and over exposure to these hormones can elicit changes in the developing reproductive system of the foetus. Administration of dexamethasone during pregnancy in rats is associated with various outcomes, such as delayed onset of puberty in both offspring sexes, less follicles in the ovaries of female pups, and lower blood testosterone levels in male pups (Zambrano *et al.* 2014). Other corticosteroids, such as betamethasone, have shown impaired sperm quality and fertility in male pups (Zambrano *et al.* 2014). These findings indicate that maternal stress should be kept to a minimum during pregnancy in order to maximise the reproductive potential of her offspring. Although a certain degree of maternal stress is to be expected during pregnancy, chronic exposure to certain stress hormones can be detrimental to the developing foetus. Having said this, it is unclear what concentrations of these corticosteroids were administered to the pregnant rats, therefore it is difficult to determine what levels of these in the mother could cause developmental restrictions in the foetus. These results arguably are difficult to translate into humans when thinking about impact of human maternal stress on our offspring. Furthermore, human stress is difficult to control, unlike diet or smoking, so it is unfair to attribute blame to the mother for the relative fertility of her offspring when she perhaps cannot control the changes in her uterine environment if she's become stressed during pregnancy.

Evidence in the literature supporting this hypothesis is vast and thus not all evidence has been covered. Even though the evidence provided is mostly from animal models, the results can be translated to humans as well, since there are similarities in physiology and metabolism across all mammalian species. The animal models do have their limitations, such as being more or less sensitive to certain stimuli than humans and having different behavioural adaptations, but they also come baring less ethical issues with their exposure to laboratory experiments. That being said, it should also be considered that these animal models have been exposed to extremes of malnutrition and specific nutrient deficiencies, so when interpreting the results to advise pregnant women they should be presented to show that a balance of nutrition is fundamental to maintain a healthy pregnancy and ultimately healthy offspring with normal reproductive function.

References

CHAVATTE-PALMER, P. *et al.* , 2008. Nutrition maternelle : incidence sur la fertilité de la descendance et importance de la période périconceptionelle pour le long terme. *Gynécologie Obstétrique & Fertilité* , 36(9), 920-929

CHEONG, Y. *et al.* , 2014. Diet-induced maternal obesity alters ovarian morphology and gene expression in the adult mouse offspring. *Fertility and Sterility* , 102(3), 899-907

HANLEY, N. A. *et al.* , 2000. Steroidogenic factor 1 (SF-1) is essential for ovarian development and function. *Molecular and Cellular Endocrinology* , 163(1-2), 27-32

IKEDA, Y. *et al.* , 2001. Neonatal estrogen exposure inhibits steroidogenesis in the developing rat ovary. *Developmental Dynamics* , 221(4), 443-453

MOORE, S. E., 2017. Early-Life Nutritional Programming of Health and Disease in The Gambia. *Annals of Nutrition & Metabolism*

PAINTER, R. C. *et al.* , 2006. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *The American Journal of Clinical Nutrition* , 84(2), 322-327

DE ROOIJ, S. R. *et al.* , 2016. Prenatal Undernutrition and Autonomic Function in Adulthood. *Psychosomatic Medicine* , 78(9), 991-997

SLOBODA, D. M., M. HICKEY and R. HART, 2011. Reproduction in females: the role of the early life environment. *Human Reproduction Update* , 17(2), 210-227

WOODRUFF, T. K. and C. L. WALKER, 2008. Fetal and Early Postnatal Environmental Exposures and Reproductive Health Effects in the Female. *Fertility and sterility* , 89(2 Suppl), e47-e51

ZAMBRANO, E. *et al.* , 2014. Fetal programming of sexual development and reproductive function. *Molecular and Cellular Endocrinology* , 382(1), 538-549