Journal of Developmental Origins of Health and Disease (2015), **6**(5), 407–414.
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doi:10.1017/S2040174415001099
Themed Issue: David Barker commemorative meeting, September 2014; the future of the science he inspired

ORIGINAL ARTICLE

Applying developmental programming to clinical obstetrics: my ward round

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The theory of developmental programming is supported by accumulating evidence, both observational and experimental. The direct application of the principles of developmental programming by clinicians to benefit pregnant women remains an area of limited attention. Examining a selection of inpatients at an obstetric referral center, I searched for situations in which clinical decision making could be driven by the principles of developmental programming. I also looked for situations in which the clinical research agenda could be dictated by these concepts. In the decision to undertake preventive measures to avoid preeclampsia, the offspring's perspective may support more liberal application of calcium and aspirin. Consideration of the long-term health perspective of the offspring could drive choices in the management of obesity and diabetes in pregnancy. The administration of corticosteroids in women delivering by elective cesarean at term may have modest short-term benefits, but additional trials are necessary to investigate long-term offspring health. The offspring of women suffering hyperemesis gravidarum may benefit from nutritional therapy. The long-term health of the offspring could affect couples' choice for IVF or expectant management. Applying the principles of developmental programming to the management of pregnant women could drive clinical decision making and is driving the clinical research agenda. Increasingly, developmental programming concepts are becoming an integral part of clinical practice, as well as determining the choice of outcomes in trials in obstetrics and fertility medicine. The presented cases underscore the need for more research to guide clinical practice.

Received 12 January 2015; Revised 16 March 2015; Accepted 5 April 2015; First published online 13 May 2015

Key words: human, pregnancy, offspring

Background

When first published, David Barker's hypothesis that conditions during early development could hold consequences for long-term health was widely critiqued. Over past decades, epidemiological and experimental studies have established a broad evidence base for the hypothesis of developmental programming.[1,2] More recently, the United Nations,[3] UNICEF[4] and the 1000-Day Initiative[5] have recognized the importance of the environment during early development for long-term health and the need to incorporate this awareness in the shaping of public health policy. Yet the implementation of the principles of developmental programming in clinical obstetrics and fertility medicine is less evident. Increasingly, the long-term effects of interventions in pregnancy are being considered in clinical trials.[6,7] Integrating the emerging science of the developmental origins of adult health presents a paradigm shift in clinical decision making in current obstetric practice.

I hypothesized that there are clinical situations in which the principles of developmental programming could be applied to decision making, and the clinical research agenda could usefully reflect the concepts of developmental programming.

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Methods

During my ward round, which included a selection of inpatients at an obstetric tertiary referral center in the Netherlands, I searched for situations in which clinical decision making could be driven by the principles of developmental programming. I tried to identify situations in which the clinical research agenda could be served by refocusing around these principles.

Room 1: preeclampsia

Patient A was a 28-year-old primigravida with a gestational age of 31 + 1/7 weeks. She had been admitted to the tertiary referral center 4 days earlier with a diagnosis of severe early onset preeclampsia. The fetus was growth restricted (fetal weight estimated by ultrasound 1235 g), but had normal umbilical artery Doppler flow profiles and a normal cardiotocogram (CTG). Mrs A was being managed with multiple antihypertensive drugs and magnesium sulfate to reduce the risk of eclampsia. Corticosteroids had been administered on admission to increase neonatal lung maturity in the likely event of iatrogenic premature delivery. Due to further clinical deterioration, I was now discussing a cesarean section with her. She and her partner wanted to know what risks the baby would face in the short and long term. Her partner had grown up with an older sibling who had survived prematurity with cerebral palsy, and was particularly concerned about long-term health.

https://doi.org/10.1017/S2040174415001099 Published online by Cambridge University Press

After covering the short- and long-term risks of prematurity, we briefly discussed long-term outcomes after preeclampsia. Follow-up studies of children of preeclamptic mothers have consistently shown increased blood pressure,[8–10] from as early as the 1st week of life.[11] In the first study to report on mortality among the offspring of women that had severe preeclampsia, Kajantie *et al.*[12] found a 2.2-fold increase in stroke mortality in comparison with the offspring of pregnancies that had not been complicated by hypertensive disease of pregnancy. In the same birth cohort, hypertensive disease in pregnancy was associated with hypertension, depression, cognitive deficit and cognitive decline in the offspring at age 60–70 years.[13–15] Because women who had preeclampsia, especially in the case of early onset preeclampsia, have an increased risk of hypertension, cardiovascular disease[16] and cognitive impairment and white matter changes themselves in later life,[17] it is challenging to separate possible programming effects from underlying genetic susceptibility. The only study of its kind compared pulmonary hypertension and endothelial dysfunction in a small number of children exposed to maternal preeclampsia with their non-exposed sibling. This study suggested that it was in fact *in utero* exposure, and not genetic susceptibility that underlay the vascular effects in the offspring of mothers with preeclampsia.[10]

Prevention of hypertensive disease of pregnancy is a clinical challenge. Calcium supplementation has been shown to reduce hypertensive disorders of pregnancy.[18,19] In support of the notion that maternal preeclampsia prevention could lead to decreased risk of hypertension in the offspring, follow-up studies of calcium have demonstrated that blood pressure is indeed lower among the offspring of calcium-treated mothers.[20] One limitation of the evidence in favor of calcium supplementation in preeclampsia prevention is that the effects are primarily measurable in women with low calcium intake.[19] Although generally low calcium intake is uncommon in pregnant women in western countries, there may be cultural minorities with low dairy consumption who would benefit from calcium supplementation.

Preeclampsia prevention through low dose aspirin administration enjoys a broad evidence base, and has been shown to decrease preeclampsia in women at high risk,[21] particularly when administered before gestational age 16 weeks.[21–24] Among women treated with aspirin, intrauterine growth restriction and adverse perinatal outcome are less common.[22,24] Aspirin is recommended by various international guidelines, although the range of patients deemed eligible for aspirin varies from country to country. The Netherlands guidelines reserve aspirin treatment for women with a history of early onset preeclampsia or anti-phospholipid syndrome only, whereas the RCOG[25] and Canadian[26] guidelines recommend aspirin for preeclampsia prevention more broadly. Ongoing studies are investigating the role of aspirin in women identified as high risk in early pregnancy, including uterine artery Doppler and first trimester biomarkers.[15] To date, limited follow-up studies of the offspring's health have been carried out,[27–29] and offspring's blood pressure and other markers of cardiovascular disease have not been assessed in existing studies. Clinicians need to be able to inform patients of the possible long-term benefits of aspirin for their offspring. Future trials need to information ascertain its effectiveness for the long term. This information could guide clinicians to employ aspirin, even in the absence of short-term maternal benefits.

In conclusion, due to their presumed effects in improving placental function, strategies to prevent preeclampsia could benefit the offspring's future cardiovascular health, warranting their broader clinical implementation. However, more studies are necessary before implementing this notion in clinical practice. Mrs A expressed her hope that she would have access to information on the long-term effects of aspirin before planning her next pregnancy.

Room 2: obesity

Patient B was a 32-year-old primigravida with a preconception body mass index (BMI) of 41 kg/m^2. Mrs B had been about to deliver at a gestational age of 41 0/7 after she had gone into spontaneous labor the preceding night. Mrs B's pregnancy had been achieved after the second intracytoplasmic sperm injection (ICSI) stimulation cycle. ICSI had been indicated due to male infertility. Oral glucose tolerance testing in pregnancy had been unremarkable, both at 16 and at 24 weeks. Fetal ultrasound growth scans had been technically challenging due to obesity but had indicated fetal growth within the normal range. Her gestational weight gain had not been recorded in her hospital notes.

I was called to her room urgently after the midwife diagnosed shoulder dystocia. The baby was eventually delivered with the help of rotation maneuvers 3 min after the fetal head had been born. The Apgar scores were 3 after 1 min and 6 after 5 min; cord blood gas found no evidence of perinatal asphyxia (pH_a 7.18, pH_v 7.23). The macrosomic baby girl weighed 4350 g (p 97.7). There was no evidence of clavicular bone fracture or brachial plexus damage.

Afterwards, Mrs B and I discussed the events. Mrs B asked what had led to the shoulder dystocia, and what it might mean for the baby's health in future. She was also concerned about the baby's large size, and wondered if the baby was going to be at risk of obesity later in life. After having gone over the important role of her own obesity in the baby's macrosomia and the shoulder dystocia, we came to talk about the long-term effects of maternal obesity in pregnancy.

Obesity prevalence is rapidly increasing around the world,[30] with maternal obesity rates keeping pace with the global rise. In the Netherlands, maternal overweight and obesity have increased from 30% in 1981 to 42% in 2004 and from 6 to 12%, respectively.[31] In the United Kingdom (16%)[32] and United States (>30%),[30] rates of maternal obesity are estimated to be higher still. Among children born to mothers with preconception obesity, the risk of obesity in later life is increased.[33] A recent study by Reynolds *et al.* demonstrated, that offspring of obese mothers were more likely to have

https://doi.org/10.1017/S2040174415001099 Published online by Cambridge University Press

cardiovascular disease (HR 1.29) or to die a premature death (HR 1.35) compared with offspring of mothers with a normal weight in pregnancy. The findings remained significant after multivariable correction, suggesting that it is maternal obesity during pregnancy that underlies these effects, and not postnatal and socioeconomic factors.[34] Animal evidence also suggests that maternal obesity has independent programming effect on offspring's long-term health. In a range of cross-fostering animal models, maternal obesity has been shown to increase the offspring's intake and appetite regulation, adiposity, induce features of non-alcoholic fatty liver disease,[35] and decrease insulin sensitivity.[36,37] Mechanistic studies have suggested impaired leptin signaling and altered neuronal development underlie these associations.

Several dietary and exercise interventions trials aimed at improving pregnancy outcomes have been carried out, systematically reviewed by Thangaratinam *et al.*[38] In 44 studies among 7278 women, the authors found a pooled effect of dietary or exercise interventions of 1.43 kg lower weight gain in pregnancy, in the absence of any effects on birth weight or the incidence of macrosomia. There was low-quality evidence in favor of a reduction of preeclampsia and shoulder dystocia. Not included in the systematic review, one large recent randomized controlled trial (RCT)[39] employed a comprehensive lifestyle intervention among 2212 women with overweight or obesity (BMI $\geqslant 25$ kg/m^2), and found no difference in the primary outcome measure fetal macrosomia, or any of the prespecified maternal outcomes. Taken together, this evidence could be interpreted as a disappointingly low return on the large investment made by pregnant women and their health care providers involved in lifestyle intervention programmes. However, at present we are uninformed about the long possible long-term effects of lifestyle interventions in pregnancy. The studies of men and women conceived during the Dutch Famine have made clear that long-term health can be profoundly affected by maternal nutrition *in utero*, even in the absence of effects on size at birth.[40] Partial reversal of the offspring phenotype induced by maternal obesity could make a contribution to breaking the cycle of transgenerational transmission of obesity. Taken into consideration, follow-up studies of the RCTs of lifestyle interventions in pregnancy could thus provide solid evidence for implementation of such strategies, even in the absence of sizeable short-term benefits. On reflection, Mrs B said she was planning on making every effort possible to lose weight before her next pregnancy.

In conclusion, given their small effects on maternal and short-term neonatal outcomes, the utility of lifestyle interventions in obese pregnant women should be judged by long-term outcomes among their offspring. At present, however, there are insufficient data on offspring outcomes to clearly guide practice.

Room 3: gestational diabetes

Patient C was a 33 year old woman from China in her second ongoing pregnancy, with a history of macrosomia and a cesarean section due to failure to progress. In the current pregnancy, gestational diabetes had been diagnosed by oral glucose tolerance testing in week 28 of pregnancy. Mrs C had a normal BMI: 23 kg/m^2. Mrs C had only migrated to the Netherlands 6 months previously, and had limited command of the Dutch or English language. There had been several miscommunications, which had led to infrequent monitoring and suboptimal control of her blood glucose. Despite the fact that ultrasound measurements of fetal growth were consistent with recurrent macrosomia, insulin therapy had not been initiated, again due to problems in communication. She had been booked for an elective cesarean section at 39 4/7 weeks, and was delivered of a macrosomic daughter of 4800 g. Neonatal blood sugar values were unremarkable.

The day after the cesarean, Mrs C and I talked about the effect gestational diabetes had on her own increased risk of developing type 2 diabetes, and the effects it may have had on her daughter's growth *in utero* and future health. In an effort to make her more aware of the necessity of better glucose control in the event for a future pregnancy, I described the continuous association between maternal glucose and adverse perinatal outcome, including macrosomia and neonatal hypoglycemia, described in the HAPO study.[41] Maternal hyperglycemia leads to fetal hyperinsulinemia by inducing fetal pancreatic β-cell islet hyperplasia and hyperactivity, as well as causing disruption of the fetal adipoinsular axis. This can cause neonatal hypoglycemia, and may predispose to insulin resistance in later life. In their study among Pima Indians, Franks *et al.*[42] showed that the offspring of mothers with gestational diabetes demonstrated a linear increase in their own risk of diabetes in later life with the degree of maternal hyperglycemia in pregnancy. In type 1 diabetic women, poor glucose control during pregnancy as evident from macrosomia was associated with increased offspring adiposity at age 6–8 years.[43] Because the pregnant women in the study by Rijpert *et al.* had a mean BMI within the normal range, in contrast to the higher mean BMI of women with gestational diabetes, the findings indicate that programming effects of offspring obesity through maternal hyperglycemia operate independently from those operating through maternal obesity.[44]

Since the publication of the ACHOIS study[45] and the trial by Landon *et al.*,[46] screening, monitoring and treatment of gestational diabetes are justified by their established effect in reducing maternal and perinatal morbidity. Further studies are planned, applying lower glucose thresholds for the diagnosis of gestational diabetes.[47] Lower cut-off values for diagnosing gestational diabetes will lead to an increase in numbers of women diagnosed, with increasing screening and treatment costs, whereas the benefits in terms of perinatal morbidity of expansion of diagnosis criteria are expected to diminish. Follow-up of offspring in the ACHOIS study demonstrated that, in comparison with routine care, treatment of gestational diabetes led to normalization of cord blood glucose, leptin and adiponectin.[48] At present, long-term follow-up beyond the neonatal period of children from the trials investigating the

https://doi.org/10.1017/S2040174415001099 Published online by Cambridge University Press

utility of treatment strategies for gestational diabetes are lacking. In the face of the global increase in type 2 diabetes, such follow-up studies could estimate the effect of such interventions during pregnancy on the health of future generations.

In conclusion, screening, monitoring and treating gestational diabetes may hold benefits for offspring obesity and glucose tolerance, and could therefore be another incentive for investment in screening and treatment programmes. Future follow-up studies of the offspring of women in trials of interventions in gestational diabetes could supply such data, which are at present lacking.

Room 4: corticosteroids at term

Patient D was a 32-year-old G1P0. She was 37 1/7 weeks pregnant with spontaneously conceived dichorionic twins, of which the first was presenting in breech. Until 2 days previously, the pregnancy had been uncomplicated. She had been scheduled to deliver at 39 weeks by cesarean section because of the breech presentation. However, she had been admitted to hospital the previous day after having been diagnosed with mild term preeclampsia based on multiple blood pressure measurements in the range of 130–140/95–100 mmHg, without any complaints, and with a normal fetal CTG. Her blood pressure had remained well controlled without antihypertensive medication. The 24 h urine collection showed 430 mg of proteinuria. Her preeclampsia had made her eligible for delivery before the initially planned date.

On Mrs D's request, we went over the additional risks an earlier delivery may hold for her twins; based on the available data in singletons, such risks include an increase in respiratory morbidity (wet lung and infant respiratory distress syndrome) of 8.2% compared with 3.4% for delivery at 39 weeks and increased risk of admission to the neonatal intensive care ward of 12.8 *v.* 5.9%.[49] We also discussed the options for reducing this admittedly small risk. The RCOG guideline recommends women delivering by cesarean section before they reach 39 0/7 weeks gestation should be offered a course of corticosteroids to decrease the risk of neonatal respiratory morbidity.[50] This recommendation is based on a single randomized open label trial,[51,52] which found that a 2-day course of betamethasone decreased neonatal admission rates for respiratory reasons with an RR of 0.15; 95% CI 0.03 to 0.64. The trial, which included almost 1000 women, was unable to find any statistically significant differences in other clinical outcomes. Importantly, the trial did not include twin pregnancies.

Animal studies have provided a firm basis for understanding the programming effects of antenatal corticosteroids. In a range of animal species, maternal treatment with corticosteroids during pregnancy was associated with impaired fetal growth,[53] poor glucose tolerance,[54] increased adiposity,[55] decreased kidney function[56,57] and alterations in the hypothalamic–pituitary–adrenal axis in the adult offspring.[58] Animal studies employing multiple doses of glucocorticoids have shown significant effects on brain development, including delayed myelination, accelerated degeneration and decreased brain growth, as reviewed by Aghajafari *et al.*[59] Fewer studies are available in human populations, the outcomes on long-term health are, however, generally not alarming after a single course of corticosteroids in premature labor.[60] The benefits of corticosteroids in terms of survival after premature delivery outweigh any subtle long-term outcomes. However, for term delivery, the short-term benefits of corticosteroids do not involve survival, or avoiding severe disability. Long-term effects, as predicted by animal studies, may therefore have a substantial effect on clinical decision making.

Interestingly, the authors of the only trial to investigate corticosteroids in term cesarean section, did report on the long-term follow-up of children in the trial.[61] Although there were no differences in a range of neurodevelopmental tests, at age 7 children whose mothers had been randomly assigned to receive corticosteroids were twice as likely to be in the bottom quartile of their class, as rated by their teachers.

Hearing the possible long-term effects, and modest benefits of corticosteroids at term, Mrs D opted out of a course of corticosteroids. Here, long-term effects of the various therapeutic options drove clinical decision making. In conclusion, taking long-term effects of corticosteroid administration at term into consideration could alter clinical practice. At present, insufficient evidence on the offspring's long-term health is available to implement in clinical guidelines. Such data should be collected in future clinical trials of corticosteroid administration.

Emergency department: hyperemesis gravidarum (HG)

Before continuing my rounds, I was called down to the emergency department to see Mrs E, a 28-year-old G2P1, with a history of HG in her previous pregnancy, now presenting with severe nausea, vomiting and weight loss at a gestational age of 10 1/7 weeks. Mrs E, despite having received outpatient management of her symptoms with anti-emetics and intravenous rehydration, had continued to lose weight and said that she had been unable to eat more than a couple of small mouthfuls a day for weeks. Her pre-pregnancy weight had been 76 kg, her weight on presentation was 68 kg. Physical and laboratory examination revealed dehydration, ketonuria and mild hypokalemia in the absence of any signs of gastrointestinal obstruction or infection. Mrs E was offered admission for intravenous rehydration, electrolyte correction and anti-emetics. She expressed concern that her continuing weight loss could harm the fetus.

Nausea and vomiting in pregnancy (NVP) is common: up to 80% of women report some degree of symptoms. HG is defined as severe nausea and vomiting in the first half of pregnancy, in any combination with poor intake, significant weight loss, electrolyte disturbance or dehydration. HG is much less common than NVP: only 0.3–2% of pregnant women are affected.[62] The pathophysiology of HG is poorly understood.[63] Despite its relatively low incidence, HG remains the most common reason for hospital admission in the first half of pregnancy.[64,65] There are no treatments available with proven effect.[66]

https://doi.org/10.1017/S2040174415001099 Published online by Cambridge University Press

HG may be associated with poor pregnancy outcome, including increased perinatal mortality, small for gestational age and preterm birth.[67] There are indications that women with HG that have concurrent low weight gain,[68] weight loss in early pregnancy[69] or persistent symptoms in the second trimester[70] are at particular risk of poor pregnancy outcome. There are very few studies investigating the possible longer term outcomes for the offspring of hyperemetic mothers.[67] The few studies that looked at HG offspring beyond birth, suggested increased adiposity, blood pressure[69] and insulin resistance[71] compared with controls. Despite the fact that poor maternal nutritional intake is an established risk factor for poor outcomes both in the short as in the long term, interventions aimed at restoring nutritional intake in HG patients have to date not been properly explored.

I discussed the lack of evidence for the treatment options for HG with Mrs E, and our lack of knowledge concerning the long-term outcomes for her offspring. Mrs E was offered participation in an RCT to investigate the short- and long-term effects of tube feeding in HG.

In conclusion, the outcomes of the offspring of women with HG, particularly those with marked weight loss, are of concern to scientists and patients alike. In deciding on HG management, such concerns could direct the choice of treatment towards more nutrition-centered options, although at present there is insufficient evidence to inform clinical guidelines of the possible long-term benefits of nutritional therapy for the offspring of women with HG.

Room 5: assisted reproduction

Patient F was a 31-year-old G2P2. Mrs F had just been delivered by emergency cesarean section at a gestational age of 29 + 5/7 weeks after the CTG had shown signs of fetal distress. Her daughter, now in neonatal intensive care, was severely growth restricted, weighing 885 g. Mrs F had been admitted to hospital a week earlier at a gestational age of 28 + 3/7 weeks for intensive fetal monitoring, after the fetal growth ultrasound indicated severe growth restriction with abnormal uteroplacental blood flow and absent end diastolic flow in the umbilical artery. She had also been diagnosed with preeclampsia, which had been controlled without medication. Corticosteroids had been administered on admission, to improve neonatal lung maturity in the event of an iatrogenic preterm delivery.

Mrs F's obstetric history was unremarkable, with a term vaginal delivery of a 3575 g boy, now 19 months old. Both pregnancies had been conceived by ICSI for unexplained infertility. The first (uncomplicated) pregnancy had been of a cryopreserved embryo, her second pregnancy had been a fresh embryo transfer. Mrs F asked if the complications in the current pregnancy could be explained by the fact that she had undergone ICSI, and whether the fact that the two ICSI procedures had differed could underlie the profoundly different outcome. Also, she wanted to know what the impact would be on the future health of her children.

Since the birth of the first test-tube baby Louise Brown in 1978, assisted reproductive technology (ART) has increasingly been used to treat millions of subfertile couples worldwide. This procedure presents the early embryo with a radically different environment from *in vivo*. After its introduction and rapid dissemination, many alterations have been made to ART protocols aimed at maximizing pregnancy rates per treatment cycle. We have seen the introduction of ovarian hyperstimulation, the switch from urinary to recombinant FSH, various methods of oocyte fertilization, the use of numerous embryo culture media, the extension of the duration of embryo culture and the freezing of gametes and embryos.[72]

In retrospect, it is surprising that all these methods were simply introduced into clinical care without preclinical safety studies. This was the result of both the strong desire of patients to have children and the willingness and sudden ability of clinicians to help these patients, in the absence of a generally accepted framework for evaluation of new techniques. Some of these adaptations, in spite of achieving higher pregnancy rates, have since been shown to have adverse effects. For example, in many countries the policy of transferring two or more embryos has now been restricted[73] because of unacceptably high multiple pregnancy rates,[74] with accompanying high perinatal morbidity and mortality. However, singletons conceived by ART have also been demonstrated to have increased rates of prematurity, low birth weight and perinatal mortality.[75] Recently, two commonly used culture media were observed to be associated with a 200 g difference in birth weight – a similar difference to that seen among women that smoke throughout pregnancy compared with non-smoking women.[76]

Numerous studies in animal model systems have shown that ART can have important and lasting consequences on health in later life. Animals conceived through ART display hypertension,[77] altered endocrine function and increased postnatal growth compared with those conceived *in vivo*.[78–80] In light of these findings, it is disconcerting that very few studies have been performed on human ART offspring.[81] Studies of children born after ART broadly confirm the animal model evidence: ART conceived children have a slightly higher rate of congenital abnormalities,[82] higher blood pressure,[83,84] endothelial dysfunction,[85] increased intima media thickness,[86] increased adiposity[87] and alterations in endocrine function.[88,89]

At present, it is largely unclear which aspects of the ART treatment, or underlying subfertility, are causally involved in the alterations in offspring outcomes. Moreover, increasingly, the effectiveness of ART in comparison with expectant management for some indications, including unexplained infertility, is being called into question.[90]

In conclusion, ICSI may have contributed to poor perinatal outcome in Mrs F's pregnancy. Mrs F, after having gone over the above, expressed her disappointment about the fact that she had not been made aware of these aspects of ART. Clinicians have an obligation to inform couples considering ART of the possible long-term consequences of the procedure, and an obligation to minimize iatrogenic harm to the health of future

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generations of ART children. Further investigation into the health of individuals conceived by ART is on the clinical research agenda.

Conclusion

I found that, in a broad range of patients in a tertiary referral obstetrics ward, the principles of developmental programming can affect patients' preference, and clinical decision making, and should inform the future research agenda. I demonstrated that patients who are being offered steroids in cesarean section at term opt out of treatment if long-term outcomes are included in counseling. Also, I found that couples being offered assisted reproductive techniques may prefer long-term offspring outcomes to be included in counseling, and may be willing to let their decision for treatment depend on such outcomes. Women with HG can be distressed by possible effects of their inability to eat on their developing fetus, making them willing to participate in nutrition-based intervention studies. In clinical research, the outcomes of children born in obstetric intervention trials in general, and in trials among women with preeclampsia, obesity and gestational obesity in particular, could determine the clinical utility of these interventions. At present, however, there is insufficient knowledge to guide clinical practice.

In conclusion, David Barker walks with me every day during my ward round, and has almost ubiquitous effects on my clinical management of patients.

Acknowledgments

The patient histories in this review have been modified to protect patients' privacy.

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