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Pregnancy outcome and ultraviolet radiation; A systematic review

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ABSTRACT

Background: Season and vitamin D are indirect and direct correlates of ultraviolet (UV) radiation and are associated with pregnancy outcomes. Further to producing vitamin D, UV has positive effects on cardiovascular and immune health that may support a role for UV directly benefitting pregnancy.
Objectives: To investigate the effects of UV exposure on pregnancy; specifically fetal growth, preterm birth and hypertensive complications.
Methods: We conducted a systematic review of Medline, EMBASE, DoPHER, Global Health, ProQuest Public Health, AustHealth Informit, SCOPUS and Google Scholar to identify 537 citations, 8 of which are included in this review. This review was registered on PROSPERO and a. narrative synthesis is presented following PRISMA guidance.
Results: All studies were observational and assessed at high risk of bias. Higher first trimester UV was associated with and improved fetal growth and increased hypertension in pregnancy. Interpretation is limited by study design and quality. Meta-analysis was precluded by the variety of outcomes and methods.
Discussion: The low number of studies and risk of bias limit the validity of any conclusions. Environmental health methodological issues are discussed with consideration given to design and analytical improvements to further address this reproductive environmental health question.
Conclusions: The evidence for UV having benefits for pregnancy hypertension and fetal growth is limited by the methodological approaches utilized. Future epidemiological efforts should focus on improving the methods of modeling and linking widely available environmental data to reproductive health outcomes.

1. Introduction

The developmental origins of health and disease are well established, with birthweight, gestational length and geography of birth linked to general health outcomes in both childhood and later life (Barker, 1995; Barker, 2000; Godfrey and Barker, 2000). An association between preterm birth, low birth weight and season has been suggested, with immune, infectious, vitamin D and hormonal pathways implicated (Beltran et al., 2013; Chodick et al., 2009). However using meteorological season as the exposure variable in epidemiology has intrinsic limitations. Season is not just a meteorological phenomenon, but has associated with it biological, psychological and behavioral effects (Weinberg et al., 2015) affecting conception rates, pregnancy numbers and characteristics of the mothers which can confound reproductive outcomes. Analytical techniques to address this include considering a 'fetus at risk' approach and within-mother modeling which have been used to demonstrate 'seasonal' outcome differences may be attributable to confounding (Beltran, 2013; Curie, 2013; Weinberg et al., 2015).

Nevertheless, the association of pregnancy outcome with season is intriguing. Ultraviolet (UV) radiation is central to season and varies temporally and geographically (Lucas et al., 2006; Porojnicu et al., 2007). Solar UV is made up of three components determined by wavelength; UVA, UVB and UVC. The total UV spectrum encompasses wavelengths between 290 and 400 nm (nm) with UVA wavelengths between 315–400 nm and UVB between 290–315 nm. The main

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determinant of UV exposure on the ground is solar zenith angle which is determined by calendar date as well as factors such as altitude, the degree of cloud cover and proximity to the coast as well as behavioral determinants including time spent outdoors, clothing and sun cream use (Cherrie et al., 2015).

In the general health of adults, higher rates of cardiovascular disease mortality are associated with less available sunlight, winter season and increasing latitude (Brøndum-Jacobsen et al., 2013; Fares, 2013; Fleck, 1989; Wong, 2008). In pregnancy increased UV exposure is associated with reduced multiple sclerosis and schizophrenia in the adult offspring (Staples et al., 2010). Furthermore, in meta-analysis low vitamin D concentration, a surrogate marker of low sunlight exposure is associated with low birth weight [odds ratio (OR) 1.52 (CI 1.08, 2.15)], preterm birth [OR 1.58 (CI 1.08, 2.31)], pre-eclampsia [OR 2.09 (CI 1.50, 2.90)] and gestational diabetes [OR 1.38 (CI 1.12, 1.70)] (De-Regil et al., 2016; Wei et al., 2013). However, a number of vitamin D oral supplementation trials in pregnancy have been completed and the results have been mixed. The Cochrane Systematic Review includes 15 small RCTs with meta-analysis demonstrating moderate quality evidence for effects of vitamin D supplementation alone on preterm birth with RR 0.36 (95%CI 0.14, 0.93) and low birth weight (< 2500 g) with RR 0.40 (95%CI 0.24, 0.67). However, combining vitamin D with calcium appeared to increase the risk of preterm birth and the final conclusion by the author's is that more rigorous data is required before recommending routine supplementation (De-Regil et al., 2016).

Other biologically plausible pathways exist that support the potential for an association between UV and pregnancy outcomes that is independent of the vitamin D pathway. For example, clinical research has shown that sunlight, specifically UVA, has a direct effect on vascular health by reducing blood pressure through the release of nitric oxide stores from the skin (Liu et al., 2014). A 20 min UVA exposure in healthy adults reduced mean arterial pressure by 3.50 mmHg (SD 0.73 mmHg, p0.0004) and diastolic blood pressure by 4.90 mmHg (SD 0.70 mmHg, $p < 0.05$) (Liu et al., 2014). Animal models also demonstrate beneficial effects of UVA on the immune and metabolic systems; mice fed a high fat diet gained 40% less weight when exposed to UV ($p < 0.05$) and had less metabolic derangement with lower fasting glucose, insulin and less glucose intolerance (Geldenhuys et al., 2014; Hart PH 2011) and Hart and Finlay-Jones (2011) summarizes the complex interactions between the innate and adaptive immune system and UV (Hart PH 2011). These systems are integral to pregnancy and moderation of these could underlie an association between UV and pregnancy outcome.

We hypothesize that UV radiation could influence maternal and perinatal outcomes. The aim of this study was to systematically review the literature on the relationship between UV radiation and singleton pregnancy outcomes, including birthweight, gestational length, preterm birth and hypertensive complications. A secondary aim was to review methods used to measure, quantify, estimate and apply available environmental data quantifying UV radiation at the Earth's surface and health outcomes specific to pregnancy. Understanding the environmental factors associated with pregnancy outcomes has implications for obstetric, environmental and public health research as well as improving clinical outcomes.

2. Methods

The review protocol was developed with peer review and registered on the Prospero Database of Systematic Reviews on 12 June 2015. It can be accessed at http://www.crd.york.ac.uk/PROSPERO/index.asp and the unique digital object identifier (DOI) 10.15124/CRD42015020367. Two authors Lauren Megaw (LM) and Tom Clemens (TC) undertook the review, with a third author Sarah Stock (SS) available to resolve conflict.

2.1. Eligibility criteria

We included studies that examined a relationship between pregnancy outcome and UV radiation exposure. Singleton pregnancies, with a gestation longer than 20 weeks were considered. The primary outcomes of interest were birth weight, gestational length perinatal mortality and hypertensive disorders of pregnancy including pregnancy induced hypertension(PIH), pre-eclampsia and eclampsia.

A measure of exposure to UV radiation had to be reported. These included direct measures of solar radiation or insolation, or an indirect measure such as sunshine or sunlight hours. We included prospective and retrospective studies and the search was conducted in August 2015 and repeated in March 2016 and included studies since 1946. English language studies only were included in this review as translational services were not available and 1 study was excluded on these grounds. Environmental factors such as food availability, infectious diseases and physical work requirements vary with season; these can confound studies focusing on pregnancy outcomes. To reduce this risk, only studies based in high-income countries, where the seasonal variation in these factors is less, were considered in this review.

2.2. Information sources

We searched MEDLINE (1946–2015), EMBASE (1980–2015 week 40), Database of promoting health effectiveness reviews (DoPHER 2006 – 2015), Global Health (1973 – 2015), ProQuest Public Health (1938–2015), AustHealth Informit (1985–2015), Google Scholar, Google and SCOPUS (1960–2015). We also hand searched citation lists of relevant articles. The majority of the search was performed in August 2015 and the last database was searched on 6th October 2015.

2.3. Search

A systematic search was developed with librarian support and search terms included pregnancy, ultraviolet radiation, sunlight, sunshine, insolation, solar, clear skies, pregnancy outcome, perinatal mortality, stillbirth, preterm birth, prematurity, low birth weight, small for gestational age, hypertension, pre-eclampsia, eclampsia, gestational hypertension. Full search strategy for Medline included in Appendix A.

2.4. Study selection

Title and abstracts were screened for duplication and language eligibility by LM and TC. Correspondence, editorials and those that did not include a reference to pregnancy and any environmental factor were excluded. Full text review was performed on the remaining studies by LM and TC independently to assess against eligibility criteria with discussion to resolve any discrepancies.

2.5. Data collection

A data collection form was developed and used by both authors for data extraction from the studies. This was based on previously published data extraction methods by the Agency for Healthcare and Research Quality (AHRQ) (Seida and DD Hartling, 2013). It was agreed upon by the second author and used by both authors for data extraction. Investigator data was sought from one study.

2.6. Data items

The data items extracted from the paper include title, author, journal of publication, year of publication, location and timing of study, type of study, exposure variable, method of measurement, outcome reported and method of measurement, population characteristics, inclusion and exclusion criteria, statistical method, confounders and adjustment and main results. Separate data extraction was done for each outcome.