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Hair cortisol concentration (HCC) as a measure for prenatal psychological distress — A systematic review

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ABSTRACT

Prenatal environment reportedly affects the programming of developmental trajectories in offspring and the modification of risks for later morbidity. Among the increasingly studied prenatal exposures are maternal psychological distress (PD) and altered maternal hypothalamus-pituitary-adrenal (HPA) axis functioning. Both prenatal PD and maternal short-term cortisol concentrations as markers for HPA axis activity have been linked to adverse child outcomes and it has been assumed that maternal PD affects the offspring partially via altered cortisol secretion patterns. Yet, the existing literature on the interrelations between these two measures is conflicting. The assessment of cortisol levels by using hair cortisol concentration (HCC) has gained interest, as it offers a way to assess long-term cortisol levels with a single non-invasive sampling. According to our review, 6 studies assessing the associations between maternal HCC during pregnancy and various types of maternal PD have been published so far. Measures of prenatal PD range from maternal symptoms of depression or anxiety to stress related to person's life situation or pregnancy. The aim of this systematic review is to critically evaluate the potential of HCC as a biomarker for maternal PD during pregnancy. We conclude that HCC appears to be inconsistently associated with self-reported symptoms of prenatal PD, especially in the range of mild to moderate symptom levels. Self-reports on PD usually cover short time periods and they seem to depict partly different phenomena than HCC. Thus, methodological aspects are in a key role in future studies evaluating the interconnections across different types of prenatal PD and maternal HPA axis functioning. Further, studies including repetitive measurements of both HCC and PD during the prenatal period are needed, as timing of the assessments is one important source of variation among current studies. The significance of prenatal HCC in the context of offspring outcomes needs to be further investigated.

1. Introduction

Starting from the Barker hypothesis (Barker, 1986) on the developmental origins of adult disease, the importance of fetal environment for human development has been increasingly recognized (O'Donnell and Meaney, 2017). The characteristics of prenatal environment prepare the fetus for postnatal circumstances but the impact may also be maladaptive, ultimately leading to negative developmental outcomes in the offspring. One of the environmental factors gaining increasing interest is exposure to maternal prenatal psychological distress (PD), a heterogenic concept that comprises varying types of maternal distress, such as symptoms of depression or anxiety, experiences of stress related to either pregnancy itself or to everyday life situations and major life events (Dunkel Schetter, 2011; Scheinost et al., 2017). The topic is clinically very relevant as it has been estimated that the effects of prenatal PD could explain up to 17% of the variance in childhood cognitive abilities (Bergman et al., 2007) and that exposure to prenatal anxiety may double the prevalence of child psychiatric disorders (O'Donnell et al., 2014). Although PD has sometimes been associated with accelerated development of the offspring (e.g. DiPietro et al., 2006; Li et al., 2013), it has more consistently been linked to impaired neurological and psychosocial development (for a review, see van den Bergh et al., 2017; Capron et al., 2015; Grace et al., 2016; Pearson et al., 2016; Rijlaarsdam et al., 2017). Thus, prenatal PD is an important target for focused prevention and intervention programs (Glover, 2014), and identification of phenotypes with the greatest risk to affect the fetal programming is essential.

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1.1. Maternal prenatal psychological distress (PD) and cortisol concentrations

Cortisol, the hormonal end-point of the main human stress regulation system hypothalamic-pituitary-adrenal (HPA) axis, has been suggested to have a significant role in mediating the effects of maternal stress on the fetus. In general, increased maternal prenatal glucocorticoid levels as measured by maternal salivary, blood or urine cortisol concentrations have been linked with similar child developmental outcomes as prenatal PD (Braun et al., 2013; Moisiadis and Matthews, 2014; Painter et al., 2012). Elevated maternal prenatal cortisol concentrations are reportedly associated with compromised cognitive and motor development, affective problems, blunted cortisol reaction to stress, and alterations in regional brain volumes and connectivity in children (Buss et al., 2012; Davis and Sandman, 2012; Huizink et al., 2003; Kim et al., 2017; O'Connor et al., 2013). However, the data are inconsistent (Zijlmans et al., 2015), and also positive associations between maternal cortisol concentration and child cognitive performance have been reported (Davis et al., 2017).

Associations between maternal cortisol concentrations and prenatal PD are also inconsistent, partially due to the biological heterogeneity of and variety between the phenotypes of PD. Maternal symptoms of pre- and postnatal depression were correlated with maternal salivary, blood or urine cortisol concentrations in only 24 out of 47 studies assessing their associations (Seth et al., 2016). Some studies have reported increased prenatal maternal salivary cortisol concentrations in the context of pregnancy-related anxiety (Kane et al., 2014; Obel et al., 2005). Interestingly, maternal exposure to traumatic events during pregnancy has been associated with lower maternal plasma cortisol concentration (Perroud et al., 2014). However, assessing long-term cortisol levels with momentary measurements is challenging and multiple sampling is varyingly applied (Seth et al., 2016; Short et al., 2016).

One factor potentially producing variance in these findings is that maternal HPA axis functioning alters significantly during the normal course of pregnancy (see Fig. 1; Benediktsson et al., 1997; Challis et al., 2001; Petraglia et al., 1992). It is known that the physiological 2–3-fold increase in maternal cortisol levels towards the end of pregnancy (Jung et al., 2011) is essential to the maturation of several organ systems of the fetus and plays an important role in initiating parturition (Moisiadis and Matthews, 2014). Thus, the timing of assessments is of special importance during pregnancy and findings in a given trimester cannot necessarily be generalized to other trimesters (Kane et al., 2014). On the other hand, HPA axis overall reactivity is attenuated during pregnancy (de Weerth and Buitelaar, 2005; Schulte et al., 1990), further illustrating the complexity of the picture.

Importantly, maternal cortisol is not the only mechanism relating prenatal PD to offspring outcomes. The importance of placental functioning – specifically, the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in converting cortisol into inactive metabolites – is gaining support from recent evidence (Janssen et al., 2016). Other mechanisms that could mediate the fetal programming effects of PD include direct effects of placental CRH (pCRH), changes in maternal immune system functioning, gut microbiota composition, serotonin levels and epigenetic changes as well as maternal lifestyle during pregnancy (Abbott et al., 2018; Beijers et al., 2014; Elwenspoek et al., 2017; Glover, 2015; Howland et al., 2016; Karlén et al., 2015; Zijlmans et al., 2015).

1.2. Rationale of using hair cortisol concentration (HCC) as a measure of prenatal PD

During the past few years, hair cortisol concentration (HCC) has been presented as a method to assess *long*-term levels of cortisol (Stalder and Kirschbaum, 2012). Cortisol is accumulated into hair as it grows and thus, with the generally accepted average hair growth rate of one centimeter per month (Wennig, 2000), one or several segments of selected length can be analyzed for the mean levels of cortisol during the corresponding months. Instead of the more traditional short-term measurements of cortisol assessing either the reactivity or diurnal profile of cortisol by repetitive samples of saliva or blood (Adam and Kumari, 2009; Vining et al., 1983), HCC provides a possibility to measure retrospectively cumulative cortisol levels of previous months to gain a more complete picture of the mean cortisol levels during the chosen period, via a single sample (Davenport et al., 2006; Kirschbaum

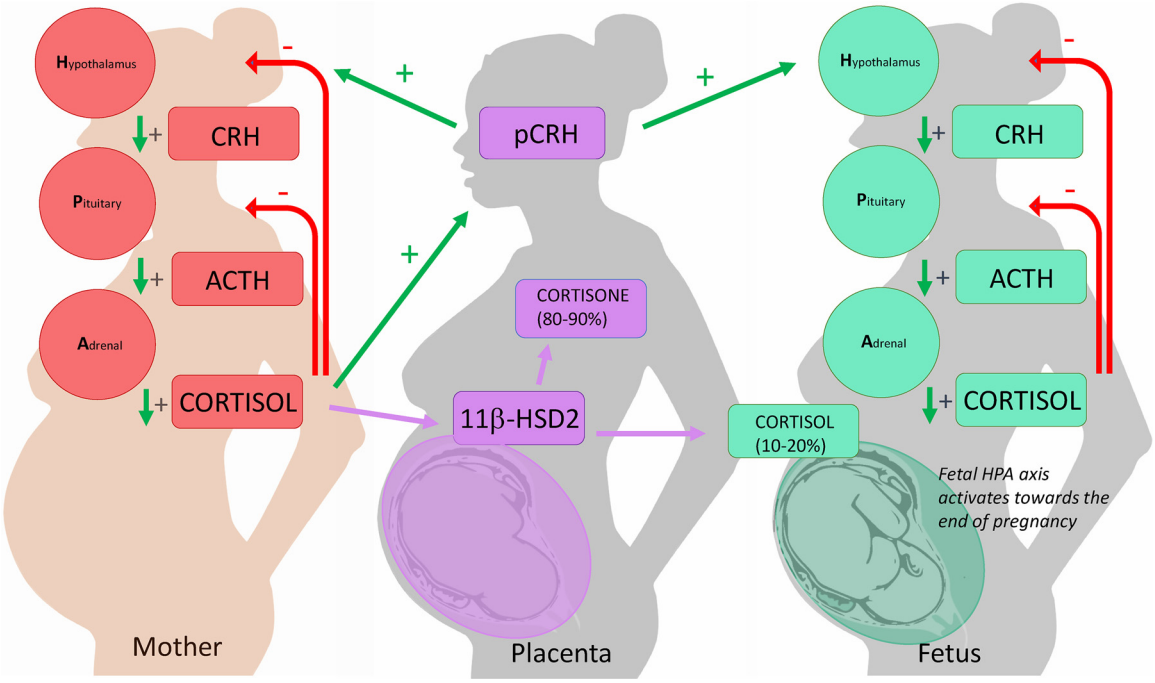

Fig. 1. Functioning of the HPA-axis during pregnancy. Maternal HPA-axis (in left) continues to funtion similarly as in non-pregnant states, but with the effects of placental pCRH (in the middle) and its positive feedback, the amounts of circulating CRH and cortisol increase. In left is pictured how the fetus is affected both by maternal pCRH (activating the fetal HPA-axis towards the end of pregnancy) and the inconverted proportion of maternal cortisol passing through the placenta.

et al., 2009; Raul et al., 2004). Although the comparison of methods depicting different aspects of the HPA axis is not straightforward, salivary cortisol and HCC do correspond when the saliva sampling protocol adequately models the long-term fluctuation of cortisol levels with a minimum of three saliva samples during consecutive days (D'Anna-Hernandez et al., 2011; Short et al., 2016).

When evaluating studies on HCC, it should be noted that there is methodological variation in the laboratory analysis protocols and analytical methods (e.g. utilization of either immunoassay or mass spectrometry techniques) leading to subsequent inter-laboratory variance in the absolute HCC concentrations (Stalder et al., 2017). In addition to the methodological factors, several characteristics of study subjects and hair samples, such as age, sex, hair washing frequency, hair treatments and oral contraceptive use have been identified as significant determinants of HCC (Stalder et al., 2017). The selected segment length is relevant as cortisol concentrations have been shown to decrease along the hair shaft (wash-out effect) up to 30–40% from a 3 centimeter segment to the next (Kirschbaum et al., 2009). The components contributing to this wash-out or degradation of cortisol include hair washing and hair treatments (Hoffman et al., 2014) as well as exposure to sunlight (Wester et al., 2016).

To date, HCC has been reported to be useful in responding to various research questions across different study populations (Chau et al., 2015; Steudte-Schmiedgen et al., 2017; Wright et al., 2015; Yamada et al., 2007). The meta-analysis by Stalder et al. (2017) covering 66 independent HCC studies concluded that HCC was elevated in subjects with ongoing exposure to a chronic stressor such as caregiving stress, unemployment or natural disaster and declined in patients with an anxiety disorder. Self-report measures of perceived stress, social support or depressive symptoms were not associated with HCC (Stalder et al., 2017).

Several studies (D'Anna-Hernandez et al., 2011; Hoffman et al., 2017; Karlén et al., 2013; Kirschbaum et al., 2009; Schreier et al., 2016; Smy et al., 2015; Wikenius et al., 2016) have assessed the change in HCC levels during pregnancy. The physiological increase in cortisol levels was evident in all these studies. This is consistent with previous data based on salivary cortisol measurements (Kirschbaum and Hellhammer, 1994), which lends support for the suitability of HCC as a measure for cortisol concentrations also during pregnancy.

1.3. Objectives of the review

So far, studies using HCC during pregnancy have not been included in the reviews considering the mechanisms of prenatal PD or its outcomes (Seth et al., 2016; Zijlmans et al., 2015). As both these reviews conclude that the comparability and accuracy of short-term cortisol measurements are a major limitation in the studies (Seth et al., 2016; Zijlmans et al., 2015), HCC could serve as a potential means in elucidating the phenomena. Because of potential programming effects on fetal development, assessing long-term levels of maternal prenatal cortisol is of special interest.

The aim of this systematic review is to explore the existing literature on the associations between HCC and maternal prenatal PD.

2. Methods

To identify all relevant studies, we conducted a systematic search (see Fig. 2). The databases PUBMED, Ovid MEDLINE®, Embase, PsycINFO, WorldCat and WEB of SCIENCE were used for a literature search (latest update December 26, 2017). The following search terms were used: (hair cortisol OR (hair AND cortisol)) AND (pregnancy OR prenatal OR antenatal OR gestational). The inclusion criteria were 1. original human studies 2. written in English 3. assessing maternal HCC and 4. maternal PD 5. during pregnancy. As the associations between maternal prenatal HCC and PD are the main focus of the systematic review, we excluded papers that only assessed these factors as mediators for other principal outcomes as they did not include systematic reports of the associations between HCC and PD. Abstracts for presentations and case-report studies were excluded. The search originally resulted in 69 articles in PUBMED, 57 in Ovid MEDLINE®, 139 in Embase, 19 in PsycINFO, 360 in WorldCat, and 75 in WEB of Science. The papers were filtered by reading the titles, abstracts and full articles. Bibliographies of identified papers were examined to identify further eligible papers. Six papers meeting the selected inclusion and exclusion criteria were found (Braig et al., 2016; Hoffman et al., 2016; Kalra et al., 2007; Kramer et al., 2009; Scharlau et al., 2018; Wikenius et al., 2016). A total of 1226 subjects were included in the studies. The papers were then reviewed in detail and substantial data were extracted (see Table 1; table reference numbers presented here are used as references later in the text: 1. Kalra et al., 2007; 2. Kramer et al., 2009; 3. Braig et al., 2016; 4. Hoffman et al., 2016; 5. Wikenius et al., 2016; 6. Scharlau et al., 2018).

Due to substantial heterogeneity between the papers in key research questions and methods, statistical analyses of the data were not feasible and a critical review was carried out instead. For this review, data assessing the associations between HCC during pregnancy and maternal prenatal PD measures (perceived stress, symptoms of depression and anxiety, and pregnancy-related stress) were gathered from all the papers. Prenatal maternal exposure to stressful or traumatic life events could not be included as a type of PD as our search did not yield any studies assessing its effect on HCC during pregnancy.

3. Results

Here, we review the results of the identified studies. We start with an overview of study characteristics of the identified papers. Then, we present results on the associations between different types of prenatal PD and HCC.

3.1. Study characteristics

In the included studies, the types of prenatal PD comprised perceived stress (i.e. the degree to which life situations are appraised as stressful), depressive and anxiety symptoms and pregnancy-related anxiety (for specific measurements, see Table 1). Prenatal PD was measured exclusively with self-report questionnaires in all the studies. Each study utilized a different set of questionnaires to assess these varying types of PD (Table 1). As a general remark, the questionnaires on prenatal PD symptoms always covered shorter time periods than what HCC reflected. Heterogeneity of the measures hampers comparability and possibilities for drawing generalizable conclusions on specific type of prenatal PD and its relation on HCC.

The number of study subjects ranged from 25 (Table 1, ref 1.) to 768 (Table 1, ref 3.). Some of the studies measured HCC at several time points (Table 1, refs 4.; 6.) and others at one time point either during pregnancy (Table 1, ref 1.; 5.) or at postpartum (Table 1, refs 2.-3.). The length of the analyzed hair segment varied from 1 cm (Table 1, ref 1.; 5.; 6.) to 9 cm (Table 1, ref 2.), theoretically reflecting cortisol levels from one to nine months. One study also measured cortisone concentration from the hair samples and reported its associations with prenatal PD measures (Table 1, ref 6.).

The vast variation in the ranges of HCC in the reviewed studies is noteworthy as the mean HCC values (when converted into pg/mg) varied from less than 10 pg/mg (Table 1, refs 3., 4., 6.) to 190 pg/mg (Table 1, ref 2.). Due to the lack of standardization in the HCC analysis protocol, several methodological differences were identified: e.g variation in sample weight from 5 to 50 mg per segment, washing protocol (not washed − washed from one to three times), and extraction of cortisol from whole, cut or pulverized hair. In four of the 6 selected studies, the HCC analysis was conducted using immunoassay techniques (Table 1, refs 1.; 2.; 4.; 5.) and in two, using mass spectrometry analysis (Table 1, refs 3.; 6.). Detailed discussion of the influence of

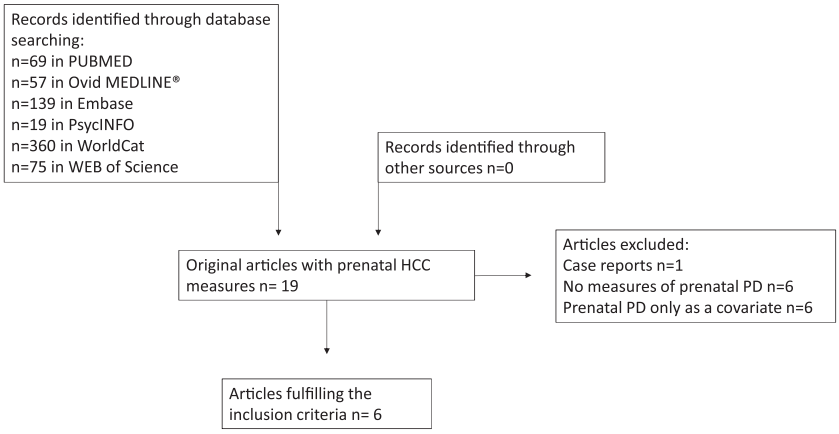

Fig. 2. Systematic search for identification of studies for inclusion.

these technical aspects of the method is outside the scope of this review.

In all but two studies (Table 1, refs 1.; 2.), the statistical analyses were conducted using logarithm-converted values to obtain normal distributions. The descriptive statistics (means/medians, standard deviations and/or ranges) of HCCs are presented in Table 1 for the studies providing the information; some papers only presented logarithm-converted values. Statistical approaches of the original papers included analyses of correlation coefficients, analyses of variance/covariance, linear and logistic regression models and mediation analyses.

3.2. Associations between maternal prenatal HCC and PD

Five studies included in this review assessed the associations between HCC and perceived stress related to mother's life situation (Table 1, refs 1.-4.; 6.). Two of them (Table 1, refs 1.; 4.) reported a positive association, while no association was found in three (Table 1, refs 2.; 3.; 6.). Anxiety symptoms were assessed in two of the studies (Table 1, refs 3.; 4.) and depressive symptoms in five (Table 1, refs 2.-6.). One of these five studies (Table 1, ref 4.) found a positive association between HCC and both depressive and anxiety symptoms while others reported no associations. Two studies assessed pregnancy-related anxiety (Table 1, refs 2.; 3.) finding no associations with HCC.

Most of the papers investigating the relationship between prenatal HCC and some type of prenatal PD (Table 1, refs 2.-4.; 6.) evaluated multiple types of stress simultaneously with respective self-report questionnaires. The studies either found no associations between any type of prenatal PD and HCC (Table 1, refs 2.; 3.; 6.) or found HCC to be associated with all the selected measures of PD (Table 1, ref 4.). This implies that characteristics of the study population and study design might partly explain whether associations between HCC and PD were observed at all.

There are notable converging factors between the studies with and without correlations between HCC and reported prenatal PD symptoms, one of the most substantial being the timing of the measurements. Two studies (Table 1, refs 2.; 3.) collected the hair samples and self-reports of PD after delivery at postpartum thus reflecting the cortisol and PD levels during the last trimester. Neither one of these studies found any associations between maternal PD symptoms and HCC. Instead, two of the four studies (Table 1, refs 1.; 4.-6.) assessing both PD and HCC in mid-pregnancy (Table 1) found positive correlations between them. All the studies included subjects from the general population with overall low levels of PD. Moreover, many of the studies (Table 1, ref 3.; 4.; 6.) were biased towards higher socioeconomic status and in these populations no associations between HCC and prenatal PD symptoms were noted. In contrast, a study performed in a population of large ethnic and educational variance, yielded significant associations between PD (including perceived stress, depressive and anxiety symptoms) and HCC (Table 1, ref 4.). In general, studies reporting a positive association between prenatal PD and HCC appeared to have a larger variance in PD symptom severity than those reporting no associations, even though the variances of different self-report measures cannot be compared in a straightforward manner.

In conclusion, the results of the reviewed studies were rather inconsistent, which is in keeping with recent reviews on short-term measurements of cortisol during pregnancy and studies on HCC and stress in non-pregnant populations (Herane et al., 2015; Seth et al., 2016; Stalder et al., 2017; Zijlmans et al., 2015). In the studies reviewed here, self-reported symptoms of perceived stress related to person's life situation (Table 1, refs 1.-4.; 6.), symptoms of depression (Table 1, refs 2.-6.) or anxiety (Table 1, refs 3.; 4.) were correlated with maternal HCC in less than half of the reviewed studies. Pregnancy-related anxiety was not correlated with HCC in either of the two studies assessing their associations (Table 1, refs 2.; 3.). Studies using postnatal assessments did not detect any significant associations between HCC and maternal prenatal symptoms of PD. The variance in symptom severity and the prevalence of individuals reporting high levels of prenatal PD were typically low in the studies reporting no associations between PD and HCC. Finally, none of the studies included data on psychiatric diagnoses or major life events, such as natural disasters.

4. Discussion

Our aim was to systematically review studies that investigated the associations between maternal prenatal self-reported symptoms of different types of prenatal PD and HCC across pregnancy. To sum up, the existing data imply that in a population with low levels of self-reported prenatal PD, the associations with HCC are rather weak or can be seen only or most clearly in mid-pregnancy. However, this association might be strengthened when studying populations with a greater variance in PD and higher frequency of elevated levels of PD. The observed associations between anxiety symptoms and HCC during pregnancy need further research before making any definitive conclusions, as the number of studies is still very low. However, the lack of consistent correlations between HCC and self-reported experience of prenatal PD can be explained by several methodological and patophysiological factors.

In fact, assuming a biomarker to consistently correlate with a variety of self-report questionnaire scores is not necessarily well-grounded. Self-reports assessing even a single type of stress most likely comprise a more or less heterogeneous group of behavioral phenotypes with diverse biological pathways. Only some of these phenotypes are likely to be related to altered maternal cortisol concentrations with the potential to affect fetal HPA axis programming. Subjective assessments of psychosocial stress can, nevertheless, be significant predictors of

Table 1
Overview of papers assessing the association between maternal prenatal psychosocial distress and HCC.

AUTHOR	STUDY POPULATION	HAIR SAMPLE CHARACTERISTICS	ANALYSIS	PD MEASUREMENT	CORRELATION BETWEEN PD AND HCC	HCC MEAN & RANGE	MAIN FINDINGS
		1. weight (mg) 2. segment lenght (cm) 3. sample taken 4. N of segments /sample				mean +-SD and range (pg/mg) for the proximal segments	
Kalra et al. (2007)	25 pregnant women	1. at least 10 mg 2. 1–1,5 cm 3. < beginning of second trimester 4. 1	ELISA	PSS	+	mean 48.21 +-17.39 range 23.20 - 84.82	HCC correlated with PSS (Rs = 0.47, P < 0.05)
Kramer et al. (2009)	Total 5337 mothers, HCC n = 117	1. n/a 2. 9 cm 3. postpartum 4. 1	n/a (ELISA used in the article cited regarding methodology)	PSS, CES-D and pregnancy-related anxiety questionnaire by Dunkel-Schetter	-/+ for each	mean preterm 171.7 +-76.4 and term 190.6 +- 99.0 range n/a	No correlations between HCC and any of the acute/chronic stress measures.
Braig et al. (2016)	768 mothers (total 970)	1. 7,5 mg 2. 3 cm 3. postpartum 4. 1	HPLC/MS	PRAQ-R, SSCS-TICS, HADS-D, HADS-A	-/+ for each	mean 9.4 range 0.3 - 80.3 (+ N = 23 excluded ouliers)	HCC not correlated with self-reported chronic stress, anxiety, or depressive symptomatology correlation coefficients varying from r = 0.00 (PRAQ-R) to r = −0.07 (HADS-D). Investigation of sub-populations did not reveal substantial differences of HCC across highly and low stressed women.
Hoffman et al. (2016)	90 pregnant women	1. 5–20 mg 2. 3 cm 3. 16, 28 and 40 gwks 4. 1	ELISA	PSS, CES-D, STAI-S	+ for each	mean (converted to natural numbers, reported in LN) term 6.0–11.0 ± 2.0 and preterm 10.0–14.9 ± 1.5–2.0 range n/a	HCC at 26gwk correlated with gwk 16 PSS (r = 0.28, P = 0.007) and earlier gestational age at birth (HCC term vs preterm 2.0 +-0.7 and 2.7 +-0.4 LN pg/mg, respectively, p < 0.001). Statistically significant correlations between the HCC of 16, 28 and 40 gwks and STAI-S and CES-D. In mediation analyses, HCC more strongly associated with gestational age at birth than psychological measures.
Wikenius et al. (2016)	181 pregnant women	1. 5–13 mg 2. 1 cm 3. mean gwk 24.8, SD = 3.9, range 17–32gwks 4. 1	RIA	EPDS	-/+	mean 60.1 +- 26.3 range 25.9–280.6	HCC and EPDS not correlated (non-significant Pearson correlation of 0.096). HCC and gestational age at sample taking showed a Pearson correlation of 0.168 with a *p*-value of 0.024
Scharlau et al. (2018)	45 pregnant women	1. 4.9–47.1 mg 2. 1 cm 3. gwks 25 and 37 4. 1	LC–MS[3]	PHQ	-/+	median 3.7 (2nd trimester) and 3.8 (3rd trimester) range 0.4–36.4	HCC not associated with any of the PHQ subscales (depression, somatization, stress symptoms) at either of the time points.

Notes of abbreviation: HCC = hair cortisol concentration; gwk = gestational week; PSS = Perceived Stress Scale; CES-D = Center for Epidemiological Studies − Depression scale; PRAQ-R = Pregnancy-Related Anxiety Questionnaire, Revised; SSCS-TICS = Trier Inventory for Chronic Stress; HADS-D and HADS-A = Hospital Anxiety and Depression Scale (depression and anxiety subscales); LSC-R = Life Stressor Checklist, Revised; PCL-C = PTSD CheckList, Civilian version STAI-S = Spielberger State-Trait Anxiety Inventory (state subscale); EPDS = Edinburgh Postnatal Depression Scale; PHQ = Patient Health Questionnaire

different biological outcomes and may correlate well with biological measures (Kane et al., 2014; Monk et al., 2016).

The rationale for developing a biomarker for prenatal PD is to be able to differentiate between physiologically distinct conditions with different potentials to affect fetal programming rather than to aim at finding consistent correlations between reported prenatal PD and HCC. Momentary or short-term states of stress might not significantly affect either the long-term biological measures or the offspring risks related to prenatal PD, but identifying situations with different risk profiles would enable further understanding of the mechanisms linking prenatal PD to adverse offspring outcomes. As HCC enables retrospective assessment of cortisol levels, it is methodologically attainable to design studies assessing the effects of major external stressors, such as natural disasters, on prenatal cortisol levels at different trimesters, for instance.

The vast methodological variation in the sampling and analysis protocols of HCC (e.g. hair sample weight and segment length, sample preparation, and the use of either immunoassay or mass spectrometry techniques) calls for standardization of the procedure. The aspects of sample processing and analyses were often incompletely described. The significant discrepancies in the time periods the questionnaires and HCC cover, varying from one week to months, respectively, are one evident reason for the lack of associations. In addition, all the statistical tests included in the analyses of the identified papers assessed linear correlations between the variables. In a study by Wells et al. (2014) in a non-pregnant population, the correlation between perceived stress and HCC was reported to follow an inverse U curve suggesting that the results can be diluted when assessing only linear relationships. Use of more advanced statistical approaches, which would enable characterization of similarly reacting groups or trajectories of HCC over time, could increase our understanding of the complex associations between HCC and psychological phenotypes.

Importantly, it is not clear how much the HPA axis reactivity in response to stressors changes throughout pregnancy or whether there is variation in reactivity for different types of stress at different trimesters (Van den Bergh et al., 2005). It is plausible that some of the subtle changes in cortisol concentrations attributable to mild psychological stress could be overpowered by the normal physiological elevation in cortisol levels and the hyporeactivity of the HPA axis during pregnancy (de Weerth and Buitelaar, 2005). Based on the studies reviewed here, associations between prenatal PD and HCC were evident mainly during the second trimester. For instance, the absence of associations between HCC and pregnancy-related anxiety could result from the fact that only postnatal measurements were used. Prior studies have found pregnancy-related anxiety to be associated with salivary cortisol concentrations when assessed in mid- to late pregnancy (Kane et al., 2014). More studies assessing the trajectories of both maternal PD and HCC throughout pregnancy are needed. In addition, we lack sufficient knowledge on how individual differences and pregnancy-related physiological changes in hair growth contribute to the reliability of the method.

To gain a more complete picture of the phenomena, we need to include measurements of other biological factors, such as 11β-HSD2 and pCRH. It is also necessary to consider the role of factors programming the HPA axis function already prior to pregnancy. In addition, cortisol may not be the only useful marker to be measured from hair, as hair cortisone concentration has been reported to associate with maternal PD even when HCC did not (Table 1, ref 6.) and hair dehydroepiandosterone concentration might be altered related to maternal childhood maltreatment (Schury et al., 2017).

From the fetal viewpoint, it may be that the programming factors of maternal lifetime HPA axis functioning play an important role alongside prenatal factors. For instance, maternal exposure to adverse life events in her own childhood can cause repeated “hits” to the stress regulation system and thus, program her HPA axis towards aberrant reactivity, which is then reflected in HCC during pregnancy (Carpenter et al., 2011; McEwen, 2017; O’Donnell and Meaney, 2017; Schalinski et al., 2015; Steudte-Schmiedgen et al., 2016). In line with this, some (Schreier et al., 2015, 2016) but not all studies (Schury et al., 2017) report that maternal life-time adverse events associate with prenatal HCC. The burden from previous adversity may also affect the sensitivity to acute stress, which can further convolute the phenomena (Daskalakis et al., 2013). In addition, we should be aware that also hyporeactivity of HPA axis should be included as a focus of the studies in the field, as blunted cortisol reactivity has been linked with suboptimal functioning of the brain’s fronto-limbic system (Carroll et al., 2017) and with negative somatic health outcomes (Phillips et al., 2013).

Finally, future studies with transgenerational prospective approach are needed to assess the potential of HCC to function as a predictor of different traits in child development. There are some studies suggesting that higher maternal prenatal HCC could be a stronger predictor for lower gestational age at birth than self-reported prenatal PD (Table 1, ref 6.; Braig et al., 2015). In addition, maternal prenatal HCC has been linked with child HCC at 1 and 3 years (Karlén et al., 2013). In fact, it could be hypothesized that HCC could accurately identify physiological stress responses related to the offspring’s outcome risks even though it would not necessarily be related to all self-reported prenatal PD conditions.

5. Conclusions

As the number of studies of meeting the criteria of this review was low, it is difficult to draw definite conclusions on the role of HCC as a measure for PD based on these data alone. The incongruity of the existing results is likely related to both the complexity of the prenatal PD phenomenon itself and the variation in the study protocols and methods in the current database. In fact, considering all the aspects on which HCC differs from the self-reported questionnaires assessing prenatal PD, the lack of consistent associations is not surprising. Attempts to standardize HCC analysis methods are important to enhance its reliability. While the self-reports of mild, momentary PD do not seem to be consistently associated with HCC, more research is needed to assess whether HCC is associated with long-term alterations in cortisol levels (e.g. life-time programming of the maternal HPA axis) or more severe levels of PD symptoms. HCC could still be an important marker for evaluating the developmental risk of the fetus, but to gain more insight on this aspect, prospective and transgenerational studies are needed.

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Conflicts of interest

The authors declare no conflicts of interest.

Authors’ contributions

The design of the review was conceived by PM, LK, AJR, NMS and HK. PM conducted the identification of the papers for the review and prepared the draft and was responsible for writing and revising the manuscript. LK, AJR, NMS, SK, BC and HK contributed in the interpretation of the papers and advised on the manuscript. All authors contributed to writing and critical revisions and approved the final version of the manuscript.

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