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Stress and reproductive failure: past notions, present insights and future directions

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Abstract

Problem Maternal stress perception is frequently alleged as a cause of infertility, miscarriages, late pregnancy complications or impaired fetal development. The purpose of the present review is to critically assess the biological and epidemiological evidence that considers the plausibility of a stress link to human reproductive failure.

Methods All epidemiological studies published between 1980 and 2007 that tested the link between stress exposure and impaired reproductive success in humans were identified. Study outcomes were evaluated on the basis of how associations were predicted, tested and integrated with theories of etiology arising from recent scientific developments in the basic sciences. Further, published evidence arising from basic science research has been assessed in order to provide a mechanistic concept and biological evidence for the link between stress perception and reproductive success.

Results Biological evidence points to an immune–endocrine disequilibrium in response to stress and describes a hierarchy of biological mediators involved in a stress trigger to reproductive failure. Epidemiological evidence presents positive correlations between various pregnancy failure outcomes with pre-conception negative life events and elevated daily urinary cortisol. Strikingly, a relatively new conceptual approach integrating the two strands of evidence suggests the programming of stress susceptibility in mother and fetus via a so-called pregnancy stress syndrome.

Conclusions An increasing specificity of knowledge is available about the types and impact of biological and social pathways involved in maternal stress responses. The present evidence is sufficient to warrant a reconsideration of conventional views on the etiology of reproductive failure. Physicians and patients will benefit from the adaptation of this integrated evidence to daily clinical practice.

Capsule Scientific evidence in synthesis supports the plausibility of a stress trigger to human reproductive failure; higher risk may be explained by pregnancy stress syndrome.

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Introduction

Is maternal stress linked to reproductive failure? This question, existing since ancient times and across all cultures, is at the centre of an ongoing scientific debate framed by claims that reproductive losses, ranging from implantation failure to

miscarriage to stillbirth, are either purely biological or preventable, for at least the considerable proportion of pregnancy losses characterized by a normal fetal karyotype and exposure to adverse environmental and psychosocial factors. Increasingly, stress exposure has been hypothesized to lead to pregnancy failure. The purpose of this review is to synthesize and critically evaluate the biological and epidemiological evidence that considers the plausibility of a stress link to human reproductive failure, a research base that includes multi-disciplinary and multi-level contributions from molecular, clinical, community and population level research.

Biological responses to stress are known to suppress reproductive function across the human life course. For example, the frequency of intense exercise in adolescent athletes has been correlated with delayed menarche [1]; hypothalamic amenorrhea, a clinical condition without endocrine or systemic cause, is triggered by metabolic, physical or psychological stress [2]. High stress perception is a risk factor for severe premenstrual pain [3], ovarian dysfunction [4], pregnancy outcomes including preterm delivery [5, 6] and low birth weight [7], as well as postpartum depression [8–10] and early onset of perimenopause [11, 12]. Impaired reproductive outcomes may be triggered by stress-inducing events and may be more prevalent in women susceptible to a physiological stress over-response. Evolutionary theory has long been used to explain the relationship posited between human reproductive failure and stressful events [13, 14]. In addition, more recently a stress-compromised blighted fetal environment in utero has been proposed [15–17]. The impetus for a paradigmatic shift is emerging along with new notions about human physiological and reproductive limits and advancing scientific insight into the deterministic mechanisms of reproductive failure at various scales from the cell to society and the environment. New multi-disciplinary research on brain–body interactions triggered by stress in early pregnancy has shown that maternal biological responses, including localized inflammation in uterine tissue and sustained depression of progesterone production, challenge the endocrine–immune steady state during pregnancy, leading to serious consequences for the fetal environment [18–20]. Recent basic science findings and new theoretical development around a ‘pregnancy stress syndrome’ associated with over-activation of the hypothalamic–pituitary–adrenal (HPA) axis [21, 22] warrant a new look at the epidemiological evidence around the age-old question of whether or not stress can actually cause human reproductive failure.

The biological mechanisms of the stress response

Psychological stress is a prevailing facet of daily life, usually triggered by a stimulus (stressor), which induces a reaction in the brain (stress perception). Subsequently, so-called supersystems (immune, endocrine, nervous) are activated in the body (stress response) [23]. Based on a hypothesis originally postulated by Walter Cannon, the stress response may be an evolutionarily adaptive psychophysiological survival mechanism [24], which would enable the individual to mount either ‘fight or flight’ in response to an acute stressor like a predator or, if the exposure is chronic stress, to focus the available energy. But daily stressors have changed (particularly for women) and are changing, and the present nuances of stress effects do not necessarily fulfil the “all or one” ‘fight or flight’ concept. The pathophysiological changes associated with the stress response are subtly re-routed towards an altered steady state of the supersystems. These alterations may serves as either an aggravating or triggering factor in the pathogenesis of many diseases, for example inflammatory, autoimmune or allergic diseases [25–28].

Pathophysiological changes in response to stress are extremely complex and current research endeavours focus on identifying the impact and hierarchy of individual markers involved. Sufficient published evidence supports the notion that stress triggers the release of neurohormones by the hypothalamus–pituitary–adrenal (HPA) axis, and subsequently the activation of the HPA axis stimulates up-regulation of key stress hormones such as corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and glucocorticoids (GCs) [23, 29, 30]. In addition to the HPA axis, neurotrophin nerve growth factor (NGF) is now recognized as a critical arbitrator of stress responses. Published evidence specifies that circulating levels of NGF undergo considerable modification during a stress challenge [31–33] and promote ‘cross-talk’ between neuronal and immune cells, ultimately skewing the immune response towards inflammation [34].

Neurohormonal responses to stress also include an activation of the sympathetic nervous system with successive increased secretion of catecholamines, a phenomenon that has received much less attention than the stress-triggered activation of the HPA axis. It has long been known that lymphoid organs are highly innervated by noradrenergic nerve fibers [35] and proposed that immune system regulation occurs via the sympathetic nervous system and catecholamine releases at regional, local, and systemic levels [23]. For example, lymphocytes express adrenergic receptors and respond to catecholamine stimulation with the development of stress-induced lymphocytosis and distinct changes in lymphocyte trafficking, circulation, proliferation, and cytokine production [36, 37].

The neuropeptide substance P (SP) is another major mediator of the systemic stress response. von Euler—a later Nobel laureate in medicine—and Gaddum first described SP more than 70 years ago [38], and recently it has been substantiated that SP can be considered a pivotal stress-

related neuropeptide, inevitably triggering distortion of the immune response towards inflammation [32, 34, 39]. Strong support for a central role of SP in the neuro-immune context is further provided by the observation in mice that a reduced response to pain or stress occurs along with a subsequent lack of inflammation when SP or its respective neurokinin (NK)-1 receptor are removed by genetic engineering [40, 41].

Over the past decade, a multifaceted concept has arisen to explain how stress impacts the immune system, challenging the paradigm (or dogma) that stress-induced immunosuppression is solely caused by the HPA axis activation [34, 42–44].

To summarize what is known currently about the human biological response to stress, the sympathetic nervous system is activated and NGF and SP are released and trigger an intense local inflammatory response, whereas a systemic inflammatory response generally may be suppressed [37, 39, 44–46]. Accordingly it may be proposed that the immune response plays a sentinel role within the complex bodily response to stress, characterized on the one hand by the bias towards pro-inflammation/Th1 in response to SP, NGF and catecholamines, and on the other by the bias towards immunosuppression/Th2 in response to glucocorticoids. Thus, the evaluation of the Th1/Th2 ratio may be a helpful tool to understand the effect of the 'stress cocktail' of neurohormones and peptides released upon stress challenge in distinct organs. The Th1/Th2 ratio may serve as a simplified indicator of the 'immune net balance' in response to a stress cocktail.

Intriguingly, the peripheral immune response may also regulate the central nervous system (CNS) [47, 48]. Immune mediators such as cytokines are important partners in this cross talk and modulate the HPA axis responses at all three levels of the hypothalamus, the pituitary gland and the adrenals [47]. During inflammation, cytokines secreted from inflamed peripheral epithelial tissue sites such as the intestinal mucosa may signal to the brain and subsequently influence behaviour and other complex body reactions, this is commonly referred to as sickness behaviour [47, 48]. Immunological events in the periphery may even affect certain brain areas to induce depression-like behaviour. For example, immune cells activated in response to infection, inflammation, trauma or stress release pro-inflammatory cytokines which signal the central nervous system and create exaggerated pain perception and/or induce physiological, behavioural, and hormonal changes. The term for such changes accompanied by the release of pro-inflammatory cytokines by glia within the brain and spinal cord is sickness response [48]. Besides psychosocial stress induced by, for example, external demands or situations, the stress system can clearly be activated by a variety of endogenous inflammatory stimuli arising from the periphery.

The biological mechanisms underlying stress-triggered reproductive failure

Pregnancy is an environment characterized by increased HPA axis function and progressively increasing levels of serum concentrations of stress hormones including cortisol and ACTH after 12 weeks gestation, reaching values seen in Cushing's syndrome [49]. Critically, the timing of stress hormone release and the location of releases in the peripheral tissues are deterministic to pregnancy maintenance and fetal development. Pregnancy is rare in well-established Cushing's syndrome due to increased circulating cortisol and adrenal androgen levels that suppress the activity of the pituitary female reproductive system [49, 50]. High circulating stress hormones can interfere with the timing of ovulation and shorten the luteal phase. Diminished progesterone availability in the luteal phase post-conception lessens the likelihood of a successful implantation; a 12-day luteal phase [51] and ≥8 mm endometrial thickness [52] have been put forward as minimums for fertility. Accordingly, the circulation of elevated levels of stress hormones during the period between pre-conception and early pregnancy may prevent implantation and early pregnancy maintenance by luteal phase defect mechanisms.

Corticotropin-releasing hormone (CRH), the principal regulator of the hypothalamic–pituitary–adrenal axis, has been identified in most female reproductive tissues including the uterus, the placenta, and the ovary [53]. CRH produced in the endometrium may participate in decidualization, implantation, and early maternal tolerance to the semi-allograft embryo possibly by killing activated T cells through the Fas–FasL interaction [54]; ovarian CRH is involved in follicular maturation, ovulation, and luteolysis; placental CRH has been proposed to directly modulate the endocrine function of placental trophoblasts, including the production of estrogen, ACTH, and prostaglandin, and is involved in the timing of parturition [55–57]. Remarkably the trajectory of CRH increase during pregnancy has been described to differ by ethnicity and also upon statistical adjusting for socio-demographic and biomedical factors. These findings may be consistent with the possibility that ethnic disparities in adverse birth outcomes may be due, in part, to differences in HPA axis and placental function [58], however it remains to be elucidated whether stress perception and stress coping, as facilitated by social networks across ethnic populations, may relate to the differential ethnicity-dependent CRH levels during pregnancy.

Besides the regulatory function of CRH during pregnancy and parturition, a wealth of data indicates that high levels of glucocorticoids wield harmful effects on the uterus and fetus, and inhibit pituitary luteinizing hormone, and ovarian estrogen, and progesterone secretion [59]. Such inhibitory effects of stress hormones on female reproduc-

tive organs are responsible for the so-called 'hypothalamic' amenorrhea of stress, and—as shown in mice—may also account for inadequate levels of progesterone during pregnancy, subsequently resulting in fetal loss [14]. The notion of stress-triggered inhibition of progesterone secretion—or a more rapid metabolism—is supported by experimental evidence from animal studies. Here, exposure to stress in the form of restraint [60] or sound [61] induces abortion in pregnant mice via a significant reduction in progesterone levels, along with a reduce expression of progesterone receptor at the feto-maternal interface [18].

Maternal immune tolerance in early pregnancy involves selective immune adaptations to prevent rejection of the semi-allogeneic trophoblast cells, which include the presence of $CD4^{+}CD25^{+}$ regulatory T cells, expression of transforming growth factor-β1 [TGF-β1]) signals as well as levels of Th2 cytokines unopposed by Th1 cytokines. A critical new role was described recently for progesterone, acting synergistically with galectin-1 as the first described member of the growing family of glycan-binding proteins, in the rescue of a failing immune adaptation in stress-challenged pregnancies in mice [62]. Adequate levels of progesterone confer properties of stress-resistance to human pregnancy, for example by exerting an anti-abortive response through binding to the progesterone-receptor, which induces the release of progesterone-induced blocking factor (PIBF) from lymphocytes. PIBF is highly pregnancy-protective by inducing Th2 biased immune activity [20, 61]. Szekeres-Bartho et al. [63] showed that abortion of mice by RU486 could be prevented by administering PIBF, suggesting that in this situation abortions are caused not by 'collapse of the decidua' but via immunomodulation. Efficacious progesterone treatment by substitution with dydrogesterone has been observed to lessen the abortigenic effects of stress exposure by decreasing the frequency of abortigenic cytokines, a pregnancy-protective effect that has been observed require CD8 T cells [18, 19, 64, 65].

Methodological search strategy employed in the present review

The search strategy applied in the present review included MEDLINE, EMBASE, PUBMED, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, article cross-linkage and multi-disciplinary exploration in order to identify all studies, 1980–2007, that tested the link between stress and reproductive failure in a study population of pregnant women. Thirteen articles presenting human epidemiological evidence were identified. Nine studies met the inclusion criteria, that: (1) reproductive failure outcomes were clearly defined and recorded in gestational time, (2) stress exposure(s) were clearly defined by type and period for all study participants, and (3) a specific evaluation framework was employed in order to test the association between failure outcomes and stress exposure. These nine studies form the primary evidence base; a second group is derived from epidemiological and population-based studies beyond the specific inclusion criteria, and from clinical trials results on interventions to reduce stress (psychosocial therapy, bed rest, early pregnancy counseling). The objective was to review the evidence for methodological and biological credibility (given the themes raised) to assess how well epidemiological data integrate with theories of etiology arising from recent scientific developments in the basic sciences.

Studies on stress exposure and reproductive outcomes

A direct causal link or a statistically significant association between stress exposure and human reproductive failure was found in seven of the nine studies evaluated that met inclusion criteria [15, 66–71] as well as in three of four excluded studies [72–74]. One included and one excluded study found no evidence of association [75, 76]. One included study found no overall association but significant interaction effects and a higher risk for specific subgroups [77]. All studies are displayed in Table 1.

Two IVF studies identified a relationship between higher stress and unsuccessful outcomes for IVF-assisted pregnancies and live births [73, 74]. The reproductive outcome of interest in both studies was successful embryo transfer; post-conception pregnancy failures, while integral to both study designs, were not described sufficiently to meet the inclusion criteria.

Critical assessment of the epidemiological evidence

Nine studies meeting inclusion criteria were evaluated on the basis of how well stress exposure and pregnancy failure outcomes were measured with epidemiological methods and on the basis of how well hypotheses were integrated with contemporary concepts for explaining how stress may trigger dysregulations of the in utero environment. Primary consideration was given to the plausibility of the biological mechanisms proposed in relation to current scientific knowledge. Consideration was also given to the strength of association and evidence supporting a dose–effect relationship.

Evaluation of measures of stress exposure

Research on stress exposure in pregnant women poses inherent methodological and ethical challenges, in particu-

Table 1 Epidemiological studies investigating a direct causal link between stress and human reproductive failure

Authors, year	Stress exposure	Study design and numbers at recruitment	Definition of reproductive failure outcome and number analyzed
O'Hare and Creed, 1995 [66]	Stressful life events: LEDS life event inventory/past 3 months	Retrospective case control 48 miscarried; 48 pregnant	SP=no; EP=20 weeks; 48[a]
Fenster et al., 1995 [77]	Psychologic work stress+ social support stressful life events/past 6 months; stressful job by strain+demands/control	Prospective case control 5,144 pregnancies	SP=1st trimester 6–13 weeks, mean 10th; EP=20 weeks; 499 miscarriages[c], 32 stillbirth[c], 4,613 livebirths[c]
Neugebauer et al., 1996 [67]	Stressful life events/past 4–5 months	Retrospective case control 192 miscarried	SP=last menstrual period; EP= 28 weeks gestation; 192[a]=111 losses of normal karyotype, 81 abnormal karyotype losses
Hjollund, 2000 [68]	Work stress and strain: daily diary kept	Prospective cohort 181 pregnancies 51 miscarried	SP=pregnancy identification by hCG, urine samples taken days 1–10 each menstrual cycle. Follow-up=diary for six cycles or until pregnancy diagnosis. EP=28 weeks; 19[c], 32[c]
Hamilton Boyles et al., 2000 [69]	Stressful life events: life event inventory	Retrospective nested case control 570 pregnant > 22 weeks	SP=no; EP=22 weeks; 211[b], 189[c]
Arck et al., 2001 [15]	High stress perception, cytokine profile (PSQ, SOZU; tissue biopsy)	Retrospective cross sectional 94 miscarriages	All miscarriage patients admitted to the hospital clinic; 94[b]
Sugiura-Ogasawara et al., 2002 [70]	Psychological factors and personality traits: interview, extensive screening; Symptom Checklist 90-R; NEO 5 Factor Index	Prospective cross-sectional 45 pregnancies 10 miscarriages	SP=4 weeks; EP=ND; all participants admitted at 4 weeks gestation for 1 month rest; 10[c]
Nelson et al., 2003 [75]	Psychosocial stress: perceived stress scale, prenatal social environment inventory, index of spousal abuse	Case control, mixed prospective (58%) and retrospective (40%); 228 pregnant; ≥22 weeks; 98 miscarriages	SP=no; EP=22 weeks; 42[a,b]; 56[c]
Neponmaschy et al., 2006 [71]	Stress biomarker: cortisol (daily flux, peaks from urine samples 3 times per week, medical exam 1 time per month)	Prospective, cross-sectional (22 pregnancies)	SP=pregnancy detection (3 times per week urinary hCG); EP=any pregnancy loss; 13[c]

FU: follow up, *RSA*: recurrent spontaneous abortion, *SP*: start point in gestational time, *EP*: end point in gestational time
[a] Number occurring prior to measurement
[b] Number occurring during measurement
[c] Number occurring after exposure measurement

lar there are unanswered questions about the critical exposure as a stress *event* versus a stressful *environment* versus stress *susceptibility* in the mother or father, and questions about the efficacy of stress measurement based on participants' self-report versus biomarkers. Self-reported stress perception is most often used as an indicator of how an individual is coping with a stressor. Sugiura-Ogasawara et al. [70] used numerous stress perception questionnaires to evaluate the risk relationship between spontaneous abortion and different qualities of psychological traits in a Japanese study population of couples attending a recurrent loss clinic, and identified depression as a determinant of subsequent miscarriage (P=0.004; P=0.036 with Bonferroni adjustment). High stress perception, as evaluated by questionnaire scores, was the primary measure used in eight of nine studies. Nepomnaschy et al. [71] however, used a

biomarker (daily cortisol fluctuations) as a surrogate for the maternal stress response to environmental challenges within a study population of young rural Mayan women in Guatemala, and observed that failed pregnancies in the study population were associated with higher than average individual cortisol readings (0.32 relative to 0.05, SD=0.11 P=0.01) and a significantly larger proportion of peak cortisol episodes (≥90th percentile) [71]. A total of three of the studies reviewed took biological samples at the time of reproductive failure to establish stress biomarkers or proxies including cortisol levels in urine [71] and blood [75], the cytokine profile of the tissue products of conception [15], and tobacco, alcohol and drug use according to urine, blood and hair analyses [75]. Nelson et al. [75] used a combination of high stress perception scores and high cortisol levels to define stress as an environmental or behavioral exposure for its study population of predominantly young, low income and African-American women and found no association with reproductive failure. This prospective study was comprehensive but by including in the risk analyses a significant proportion (40%) of study participants who were in the process of miscarrying or had already miscarried when stress exposure was evaluated the results are not persuasive inferentially (the data needed to conduct a reanalysis of the risks excluding these retrospective cases is not provided). However, the Nelson study is among five studies that measured stress exposure during the reproductive failure event in an emergency room setting [15, 66, 67, 69, 75]. This is a challenging study design because heightened stress events cannot be separated from the effect of the reproductive failure outcome temporally, also patient selection according to study criteria is more difficult in an emergency room setting; but on the positive side, timing recruitment to coincide with the reproductive failure event in a clinical setting allows for sampling of reproductive tissues needed for biological analyses. Arck et al. [15] measured maternal stress perception and the cytokine profile of a tissue sample obtained during a pregnancy loss for a Berlin study population that excluded women with a recurrent loss history. A positive correlation was observed of higher stress scores with decidua basalis mast cells, $CD8^+$ T cells and expression of TNF-α, a potent Th1 inflammatory cytokine family member; results that support current theories of etiology linking spontaneous abortion to immunological imbalances triggered by stress [15].

Three US hospital-based studies defined stress exposure in terms of self-report of previous negative life events [66, 67, 69]. Each of these retrospective studies identified at least a two-fold increase in risk for reproductive failure for those women who recalled recent pre-loss, high stress events. O'Hare and Creed [66] found 54% of women who miscarried had also experienced ≥1 stressful life event beforehand, compared with 15% of controls who had successful births (P=0.0001). Neugebauer et al. [67] and Hamilton Boyles et al. [69] tested the hypothesis that the odds of spontaneous abortion given recent negative life events would be higher in women who had losses of embryos with normal versus abnormal karyotype. Neugebauer et al. karyotyped every loss and found 70% of women with losses of normal karyotype embryos had reported one or more negative life events in the preceding 4–5 months compared with 52% of the women with chromosomally abnormal losses for an adjusted odds ratio of 2.6 (95%CI=1.3–5.2) overall. Hamilton Boyles et al. confirmed that risk for a normal chromosomal loss was higher among women who reported ≥1 recent stressful life event and added that pregnancy failure after 11 weeks was associated with more life event stress (adjusted odds ratio= 2.9, 95% confidence interval=1.4–6.2); however the use of gestational age at time of fetal loss as a marker of chromosomal status, as opposed to formal karyotyping, poses limitations on the conclusions. In terms of epidemiological credibility, Neugebauer et al. set the bar high, as one might expect from a team including Kline, Stein, Susser, and Warburton and in consideration of their landmark conclusions about increased miscarriage during the Dutch Hunger Winter and the extensive earlier work on pregnancy loss in relation to maternal exposure to the 'stresses' of smoking, drinking and under-nutrition, see for example Kline et al. on smoking [78], Kline et al. on alcohol use [79] and Stein et al. on the Dutch Hunger Winter [80]).

Measurement of reproductive failure outcomes

The frequency and timing of human reproductive failure outcomes related to stress are suspected to vary across subgroups defined by age, body-mass index and progesterone levels [81], smoking and social status [82], gravidity and parity [77], and also to vary over the course of gestational time [83]. Considering that over gestational time the incidence rate for reproductive failure is a negative exponential curve, representing as high a loss rate as 50–70% near conception and as low a loss rate as 2% by 16 weeks, the biological timing of outcome measurement is highly relevant. Stress-related failure outcomes include failed conception (IVF), implantation, placentation, spontaneous abortion due to maternal rejection of the fetal semi-allograft, and stillbirth: each of which occupies a specific period in gestational time where failure outcomes are explained by potentially distinct theories of etiology. The timing of failure outcomes relative to stress exposure was shown to be critical in five studies that assessed this link. Increased risk of spontaneous abortion was found among women reporting high physical strain during the time of

implantation for example in a prospective study by Hjollund et al. for the Danish First Pregnancy Planners series [68]. Participants kept daily diaries to record work and physical strain for a period from pre-conception through to clinical pregnancy confirmation, and hCG was analyzed from urine samples throughout the follow-up period. Hjollund et al. were able to corroborate a direct coincidence in timing between self-reported stress exposure and pregnancy failure. The Danish series also produced the finding that male psychological stress has an effect on semen quality and couple fecundability, with odds of pregnancy reduced by approximately 30% in cycles with a male stress score in the highest quartile compared with lowest-quartile stress cycles [84].

Subgroup analysis identified significant (though marginal) interaction effects between stressful work and maternal age over 32 years (P=0.04), cigarette smoking (P=0.02), and primigravidity (P=0.06) in a private insurance register study of 5,144 predominantly employed pregnant American women by Fenster et al. [77]. Odds ratios given stressful work were higher by 2.45 (95%CI=1.03–5.81) for older women, 2.96 (95%CI=1.16–7.52) for smokers, and 2.27 (95%CI=0.97–5.27) for primigravid women relative to women engaged in stressful work who were young, nonsmoking, and multigravid with <2 previous losses. Another subgroup at high risk was identified in women with low social support who also worked >40 h/week [77].

Integration of study outcomes with current theory on etiology and pathogenesis of pregnancy failure

Three of nine studies are linked to current theories of etiology and pathogenesis; others are valuable for defining the boundaries of the relevant stress exposures. The Neugebauer et al. study hypothesized that a relationship between stress and a first trimester reproductive failure would be more frequently observed in a normal chromosomal profile. Defining the cases and controls according to the karyotypic status of fetal remains stratified the potentially preventable from inevitable pregnancy failures. It also increased the chances of identifying a stress association in the study population given the evidence regarding frequency of a normal embryonic karyotype loss increasing significantly with the number of previous losses [85–88]. Arck et al. designed a study to test, in human subjects, the psycho-immunological mechanisms found in an animal model of stress-triggered reproductive failure specifically the Th1/Th2 cytokine balance present in tissue and blood samples taken during a pregnancy failure correlated with self-reported high stress perception scores [15]. Nepomnaschy et al. used daily cortisol levels as the primary measure of stress exposure in a small and culturally-homogenous population in order to test the theory that reproductive suppression due to environmental stress is related to the human capacity for evolutionary adaptation, where increased stress susceptibility is considered an evolved human characteristic [83].

Secondary evidence

Table 2 presents a summary of results from clinical trials on interventions that may have a stress-mitigating effect on human pregnancies [89–96], including psychosocial interventions and the patient-centered clinical support known as ‘tender loving care’, bed rest, vitamin supplementation, administration of uterine relaxants drugs and dydrogesterone, a progesterone supplement. Support for mitigating the stress–failure link is apparent in findings that a significant protective effect against miscarriage outcomes is conferred to women receiving supportive but not pharmacological cares in a clinical setting, as compared to controls who did not attend an early pregnancy clinic [91], and couples who received antenatal counseling and psychological support in a clinical setting had 86% pregnancy success, compared to 33% in controls given no antenatal care [92]. Social support appears to be an important consideration. Women living alone had a much higher risk for 14–21 weeks spontaneous abortions than did married women in the Europop series with 278 cases, 4,592 controls from 7 European countries. Moreover, Ancel et al. [97] and Elsenbruch et al. [82] found that pregnant women who perceive low social support also reported increased depressive symptoms and reduced quality of life; the effects of social support on pregnancy outcomes were particularly pronounced among those who smoked during pregnancy. Results from this Berlin cohort (n=864, cases=55 spontaneous abortions) also indicate that risk for spontaneous abortion was increased in women at higher age (>33 years; OR=2.19, 95%CI=1.20–4.02, P=0.011), lower body mass (<20 kg/m^2; OR=0.429, 95%CI=0.24–0.77, P=0.0047) and lower serum progesterone levels at recruitment (<12 ng/ml; OR=0.448, 95%CI=0.25–0.79, P=0.005) [81]. Analysis to assess interaction showed that lower progesterone, a predicted outcome of a maternal biological stress response, was associated with an increased risk of spontaneous abortion in women at higher age in both very early (4–7) and later (8–12) weeks of gestation (OR=0.51, 95%CI=0.28–0.92, P=0.0257). Lower BMI also proved to be a risk factor in the very early weeks of the first trimester, irrespective of the age of the woman (OR=0.36, 95%CI=0.19–0.67, P=0.001).

Much new research explores the notion of a pregnancy stress syndrome or heightened stress susceptibility to reproductive failure and adverse pregnancy outcomes. Individual differences are explained using evolutionary models that

Table 2 Summary of findings from intervention studies relevant to stress and human reproductive failure

Study type	Outcome	Intervention overview	Authors, year
Review: psychosocial interventions in pregnancy—25 independent evaluation studies	≥1 pregnancy outcome in any infertile group	More successful interventions were group format, lasted 6–12 weeks, >6 months follow up, emphasized strong educational and skills training, medical knowledge and acquisition of stress management and coping techniques. These were significantly more effective in producing positive change across a range of outcomes than counseling interventions emphasizing emotional expression or discussion of feelings related to infertility. Overall pregnancy rates were unlikely to be affected by psychosocial interventions. Note this review excluded 'TLC'-type patient-centred care, as tested by Stray Pedersen and Stray Pedersen [92].	Boivin, 2003 [89]
Clinical guidelines and treatment evaluations: 'tender loving care' patient-centred routine clinical care	Pregnancy success after RSA	Women with unexplained recurrent first trimester miscarriage have an excellent pregnancy outcome without pharmacological intervention offered supportive care alone in a dedicated miscarriage clinic.	RCOG-UK [90]
		Supportive care in early pregnancy conferred a significant beneficial effect on the outcome of the pregnancy (79% success for women <40 years <6 misc. offered supportive care).	Clifford et al., 1997 [91]
		Couples receiving antenatal counseling and psychological support in a clinical setting had 86% pregnancy success, compared to 33% in controls given no antenatal care.	Stray Pedersen and Stray Pedersen, 1984 [92]
Cochrane review: bed rest interventions to prevent miscarriage (two studies, total 84 women)	Miscarriage	There was no statistically significant difference in the risk of miscarriage in the bed rest group versus the no bed rest group (placebo or other treatment) (relative risk (RR) 1.54, 95% confidence interval (CI) 0.92 to 2.58).	Aleman et al., 2005 [93]
Cochrane Review: Any uterine muscle relaxing drugs compared with placebo or no drugs (One trial, 170 women)	Miscarriage, stillbirth, maternal death	There was a lower risk of intrauterine death associated with the use of a beta-agonist (relative risk [RR]=0.25, 95% confidence interval [CI]=0.12 to 0.51).	Lede and Duley, 2005 [94]
Cochrane review: vitamin supplementation to prevent miscarriage (17 trials, 37,353 pregnancies)	Pregnancy failure	No difference seen between women taking any vitamins compared with no-supplementation controls for total fetal loss (relative risk [RR]=1.05 (95%CI=0.95–1.15), early or late miscarriage (RR=1.08, 95%CI=0.95–1.24) or stillbirth (RR=0.85, 95%CI=0.63–1.14) and most other primary outcomes, using fixed-effect models. However, women taking vitamin supplements may be less likely to develop pre-eclampsia and more likely to have a multiple pregnancy.	Rumbold et al., 2005 [97]
Cochrane review: aerobic exercise during pregnancy (11 trials, 472 women)	Maternal fitness and pregnancy maintenance	Regular aerobic exercise during pregnancy appears to improve physical fitness, but the evidence is insufficient to infer important risks or benefits for the mother or baby. The trials were small, not high methodologic quality.	Kramer and Macdonald, 2003 [96]

Table 2 (continued)

Study type	Outcome	Intervention overview	Authors, year
Cochrane review: dydrogesterone effects on cytokine production in lymphocytes from women with recurrent miscarriage; controlled prospective maternity hospital study	Inhibition of Th1 cytokines in lymphocytes	Dydrogesterone significantly inhibited the production of the Th1 cytokines IFN-gamma (P=0.0001) and TNF-alpha (P=0.005) and induced an increase in the levels of the Th2 cytokines IL-4 (P=0.03) and IL-6 (P=0.017) resulting in a substantial shift in the ratio of Th1/Th2 cytokines. Dydrogesterone effect blocked by mifepristone a progesterone-receptor antagonist, indicating dydrogesterone acts via the progesterone receptor. Dydrogesterone induced the production of PIBF.	Raghupathy et al., 2005 [64]
Cochrane review: dydrogesterone in threatened abortion; prospective open clinical study	Pregnancy outcome after dydrogesterone treatment for vaginal bleeding ≤13 weeks	The continuing pregnancy success rate was significantly (P=0.037) higher in women treated with dydrogesterone (95.9%) compared with women who received conservative treatment (86.3%). The odds ratio of the success rate between dydrogesterone treatment and non-treatment was 3.773 (95%CI=1.009–14.108).	Omar et al., 2005 [65]

describe stress resilience and psycho-neuro-endocrine equilibria as functions that evolve via interactions between genes and environments [98]. Wadhwa has described the significant and independent role that is played by a prenatal maternal stress response within the etiology of prematurity-related adverse pregnancy outcomes as being mediated through the maternal–placental–fetal neuro-endocrine axis by placental CRH [98–100]. During primate pregnancy (but not in any non-primate species), the CRH gene and receptors are richly expressed in the placenta and expression of *hCRHmRNA* rises exponentially over the course of gestation, altering CRH placental production and releases. In vitro studies using human placental tissue cultures have suggested that the modulation of CRH output follows positive dose–response relationships with several major biological effectors of stress, including cortisol, catecholamines, interleukin-1, and hypoxia; accordingly Wadhwa suggests that placental CRH output is modulated in a positive dose response manner by maternal pituitary–adrenal hormones. Maternal psychosocial stress and level of social support have been proposed as significant influences on fetal development and infant birth outcomes and are thought to be influenced in turn by race, ethnicity and genetic predispositions [99] and also by heritability [100]. Significant ethnic disparities exist in reproductive outcomes and variable functioning of the hypothalamic–pituitary–adrenal (HPA) axis and placenta during pregnancy may be contributing factors, according to Glynn et al. who observed significant differences in the longitudinal patterns of stress hormone levels in African American, Hispanic and non-Hispanic White women at 18–20, 24–26 and 30–32 weeks gestation, with African American women exhibiting lower levels of cortisol than non-Hispanic women, higher levels of ACTH than Hispanic women, and the lowest levels of CRH both early and late in pregnancy [58]. Efforts were made to characterize endocrine, autonomic, and psychological responses to standardized psychosocial stressors at different stages of pregnancy by Nierop et al., in possibly the first study ever to purposefully apply stress to pregnant women in order to compare human with murine findings and to test the efficacy of different biomarkers, including salivary cortisol and salivary α-amylase, for measuring a maternal stress response [101]. Pregnancy in women, in contrast to pregnancy in rats, was found not to result in hypo-activation of the hypothalamic–pituitary–adrenal axis following prolonged psychosocial stress. Further, maternal recovery from stress, as indicated by the return of cortisol levels to baseline, was found to take much longer in specific gestational periods for example at the beginning of second-trimester, indicating an increased vulnerability to stress-related pregnancy complications during this time. When the biological mechanisms behind the stress-buffering effects of social support were examined the combination of oxytocin and social support was associated with the lowest cortisol concentrations in study participants in a study by Heinrichs et al. as well as increased calmness and decreased anxiety during stress [102].

Evidence also suggests that early reproductive failure in relation to environmental stressors may have a polygenetic nature [103]. No significant differences were observed for miscarriage risk in proportion to daily caffeine intake in a study population of pregnant Japanese women however, for a subgroup homozygous for *CYP1A2*1F* alleles, daily caffeine

intake of 300 mg or more was associated with significantly increased risk (OR=5.23; 95%CI=1.05–25.9) [104]. Little is known yet about how the human genotype might confer susceptibility to stress-triggered reproductive failure, but hypothesizing an increased susceptibility for risk-defined subgroups could yield important new insights. Bundled hypotheses are needed to investigate high intra-group variation in pregnancy outcome; for example, why pregnancy rates were significantly lower in an IVF treatment group of individuals exposed to vaginal and cervical Enterobacteriaceae (22.2% exposed versus 51% unexposed) and Staphylococcus species (17.6% exposed versus 44% unexposed) in relation to individuals found to have negative cultures ($P<$ 0.001) [105]. It may be relevant that high levels of chronic stress during pregnancy have been associated with bacterial vaginosis independently of the effects of other established sociodemographic and behavioral risk factors [106].

The pregnancy stress syndrome model

A pregnancy stress syndrome concept is needed to explain and predict interaction effects. Pregnancy stress has already been deemed to pair with under-nutrition in a risk combination thought to be detrimental to pregnancy maintenance and fetal development. A feedback loop is suspected whereby maternal adversity inhibits optimal fetal growth via over-secretion of adrenal glucocorticoids; and alterations of maternal physiology and behaviour are then mediated by environmental adversity that programs HPA activity in the offspring [107]. Maternal stress *and* under-nutrition cause changes in maternal glucocorticoid secretions that trigger fetal adaptations including developmental changes in blood pressure control, metabolic homeostasis, and long-term tissue-specific adaptations within a range of organs, including adipose tissue and the kidney [107]. Intriguingly, the effects of under-nutrition and stress on embryonic development are not the same. A research review found that the relevant evidence suggests that the maternal physiological response to stress depends on the stage of gestation at which the mother's nutrient intake was too little or, in animals, was manipulated [108]. Periconceptional under-nutrition is proposed to be antagonistic to development of the fetal HPA axis and to the timing of parturition [109]. A review of 36 animal studies investigated if maternal stress might enhance the effects of prenatal chemical exposure and found that an interactive teratogenic response may occur depending on stressor severity and the timing of chemical exposure relative to maternal stress [110]. Given the above, an integrated multi-disciplinary conceptual framework is needed in order to situate known variables, risk relationships and suspected interaction effects within a basic hierarchical model of the mind/body interactions believed to be responsible for a maternal stress trigger to human reproductive failure.

This review's evaluation of the secondary evidence also raises questions about how stress susceptibility is measured in pregnant women generally and also in infertile subgroups. Fertility distress, a constant emotional stressor that is often perceived as a rare state of mind affecting only 3–5% of couples with infertility problems, may be widespread at the population-level. A survey of fertility distress among 580 Mid-Western American women aged 25–50 found that 61% had experienced a fertility problem and 28% of the total sample had been unable to conceive for a period of at least 1 year, and these fertility barriers had long-term psychosocial consequences. The highest level of distress measured in this study was experienced by women who self-identified as "infertile" [111]. A similar survey of couples attending a fertility clinic found 41% of women had depression and 87% had anxiety [112] and a review suggests that pregnant women who have experienced miscarriage previously may experience even higher rates of stress disorder symptoms [113]. In a population-level study of the impacts of large-scale social and economic upheavals in China 1955–1987 on miscarriage and stillbirth prevalence, an overall pattern of two peaks corresponding with the Cultural Revolution and Great Leap Forward were identified by Cai and Feng [114]. Data from the 1988 Chinese National Survey of Fertility and Contraception, a register of over 1.5 million pregnancies with retrospective interview data showed dramatic increases in involuntary fetal loss at the height of the Cultural Revolution in 1967 and the famine of the Great Leap Forward in 1955. The 1967 peak was concentrated in urban subpopulations of highly educated women with high social status whereas the 1955 peak was concentrated among the rural poor. Fertility dropped below the replacement rate in Shanghai and total fertility level for the Chinese urban population dropped by 25% temporarily during the Cultural Revolution.

Methodological issues

Time and stress measurement issues are unresolved. Most reproductive failures occur very early on and as this is also likely so for stress-triggered losses, every effort should be made to recruit earlier in gestational time and to clearly declare the start point of enrolment. Less than half of the studies reviewed declared a start point in gestational time for the reproductive outcome of interest, namely three of five prospective studies [15, 68, 70] and one retrospective study of four [67]. Risk estimates are not readily comparable across studies with unspecified or widely varying failure time parameters, for example comparing very early (4–8 weeks) with later (10+ weeks) gestation is not feasible

because the etiological profile of the loss changes over time with uterine and fetal development.

The best way to measure stress exposure remains an open question because stress responses are polyspecific and inherently complex. Many regions of the body and the brain are involved in mounting a stress response with simultaneous activations and suppressions; for example, thymus-mediated adaptive immunity is suppressed while innate immune functions are dramatically amplified; cytokines stimulate CRH to boost the innate immune response and also vasopressin (VP) for healing and recovery of immunocompetence [115]. Within the brain, the amygdala mounts a fear response during an acute stress event, but it is the hippocampus that is called upon to communicate stress perception. Mujica-Parodi et al. tested the ability of skydivers to articulate their stress perception after a jump [116]. While their bodies were experiencing severe stress shock at a cellular level, as detected by functional MRI, the skydivers expressed elation. They were incapable of communicating their physiological stress response in ways that may be analogous to human stress perception at the time of reproductive failure. Use of stress biomarkers like daily cortisol fluctuations, as in Neponmaschy et al. [83], shows good potential but cortisol levels are not perfectly reliable because of variations in circadian rhythms and with age [117] and also by gender [118]. Different levels of cortisol are associated with stress in early and late pregnancy, providing further indication that the maternal stress response and its impacts are dependent on pregnancy stage [119]. More work is needed to establish the best parameters of use for cortisol as a stress biomarker, and cortisol measurements are recommended for future studies. The definitive critical measurement remains perplexing: is it actual stress or perception of stress, and will either necessarily be accompanied by a biomarker presence of stress?

A synthesis of the results

The current body of epidemiological evidence supports an independent association between self-reported (perceived) stress and pregnancy loss at an evidence level of II-3. Nine studies (no trials) have tested the association directly in humans. The overall weight of evidence supports the plausibility of a stress trigger to human reproductive failure. However, study results expressed as statistical associations are not comparable due to a lack of congruence in study designs, population sizes, characteristics and strategies for defining stress exposures and reproductive failures in gestational time. Results from intervention trials (Table 2) on various preventive treatments (pharmaceuticals, bed rest, counseling) offer an informative look at the evidence base for treatments that may modify the effects of stress exposure.

Toward an integrated theory for pregnancy stress syndrome

"Stress and anxiety predict assisted reproductive outcome. Stress and anxiety predict pregnancy loss. Stress and anxiety predict postpartum depression." With these provocative statements George Chrousos recently introduced a theoretical model for a 'stress syndrome' with direct and immediate deleterious effects for critical reproductive tissues in pregnancy. Stress is suspected of contributing to reproductive failure in critical windows of gestational time [120] via anovulation, implantation failure, and dysregulation of placentation. This theory is substantiated by results from three prospective studies showing an association between self-reported stress and failed implantation [68], placentation [71] or both [70].

Some mothers may experience 'wrong time, wrong place' stress during influential windows of fetal development. Others may have a higher-than-average sensitivity to environmental stress or lower resilience for coping with psychosocial stress. Just as not every child born to a woman who ingested thalidomide in pregnancy suffered from identical birth defects, not every woman exposed to stress should be expected to abort according to a fixed pattern. Different tools are needed to identify and explore risks that have been shown to have adverse effects on pregnancy outcomes. The results of this review indicate that future studies would benefit by measuring negative life events along several dimensions. For future prospective studies we recommend more exploration of the use of biomarkers to measure stress exposure, specifically cortisol in addition to perceived stress assessments. Low progesterone and low body-mass index appear to be reasonable proxies for stress susceptibility and risk factors that may yield important benefits in new studies. For studies on miscarriage, the two strongest predictors during pregnancy, aside from pre-existing co-morbidities, are age and number of previous losses [121] and need be measured and controlled and adjusted for in future research. We recommend further exploration to identify questionnaires that can successfully measure the qualities of self-perceived stress most likely to be associated with increased risk of reproductive failure. On the basis of the evidence to date, depression should be included in future study designs as potential risk factor and social support as a well-evidenced stress-buffering mechanism. Attention should also be paid to the roles of time, place and heredity as mediators of pregnancy stress susceptibility and resilience. Researchers must be explicit about temporal relationships assumed to exist between the particular stress exposures and pregnancy failure outcomes being studied. Ethnicity and cultural character are also important considerations and possible effect modifiers of the stress–pregnancy failure relationship. Lower average

cortisol levels found in African American women in one study [58] might reflect not only heredity influences but also cultural aspects of stress perception. For example, Black Caribbean women living in the UK were significantly less likely to report above-average depression scores in pregnancy than were White British women, despite their relative social disadvantage, in a 2005 study by Edge and Rogers [122]. This is thought to be a culturally appropriate way of normalizing distress, rejecting psychological labels of disempowerment, and reinforcing resilience and coping strategies. Finally we recommend that researchers interested in the concept of a pregnancy stress syndrome seek to contribute further to its theoretical development.

Evolutionary theory has long been drawn upon to describe an axiomatic relationship between reproductive fitness, vulnerability and environmental stressors where stress is proposed as a mechanism used by would-be parents to assess their environment for reproductive threat. So-called reproductive deficits are proposed to be adaptive and evolutionarily important strategies for surviving life-saving emergencies by shifting energy away from reproduction. Animal studies provide abundant supporting evidence, recently anti-predator behaviour in elk was associated with reproductive deficits, expressed by reduced fecal progesterone levels, and linked by extension to demographic deficits. The authors, Creel et al. argued that reproductive losses to stress are the cost of inducible defenses [123]. Certainly female mammals experience a very high and often unappreciated rate of reproductive failure [124], and subgroups defined by high-risk traits experience higher-than-average rates of loss. Jane Goodall observed that female baboons of high rank and advanced age had the most miscarriages (P=0.0129 for miscarriage with social rank; P=0.0008 for miscarriage with advancing age) in a Gombe, Tanzania population [125]. Thus complex social relationships might also be critical with regard to pregnancy failure patterns in human beings. Past notions of evolutionary fitness seem to offer insufficient explanation for today's complicated global trends. Fertility is declining and is already below the replacement rate in many industrialized countries including Germany, Finland and Japan. More couples are well-off or working and choosing to delay child-bearing until the upper limits of female reproductive potential (mid-thirties) and beyond, simultaneously there is tremendous new demand globally for assisted reproduction services.

Recent research suggests a coherent new explanation of the impact of stress on reproduction. Pregnancy stress syndrome and the possibility of stress susceptibility from womb to adulthood have been associated with reproductive dysregulation via immune priming and over-activation of the hypothalamo–pituitary–adrenal (HPA) axis. Maternal stress is increasingly recognized as a determinant of in utero fetal programming of disease in ways that serve to weaken, not strengthen, future generations [126]. The Barker hypothesis posits that environmental effects mediate maternal–fetal interactions during pregnancy in ways that can determine birth outcomes that predict health over the lifespan. New questions about the impact of maternal stress on fetal development are being cast back to early gestation and to the peri-conceptual period, when the incidence of human reproductive failure is highest.

Conclusion

Reproductive failure in humans is not often a single entity event but the result of complex interdependencies of demographic, anamnestic, physiological and psychological risk factors. Evidence considering the plausibility of an independent association between stress and pregnancy failure was evaluated critically, synthesized and found to support this interdependence. The biological evidence points to disequilibria among immune–endocrine interactions in response to stress. The epidemiological evidence provides complementary findings of positive correlations between various pregnancy failure outcomes with pre-conception negative life events and daily urinary cortisol. Recent evidence describes a hierarchy of biological mediators involved in a stress trigger to reproductive failure and a relatively new conceptual approach describes the programming of stress susceptibility in mother and fetus via a pregnancy stress syndrome. The synthesis of evidence demonstrates that a greater specificity of knowledge is available about the types and qualities of mechanisms involved in maternal stress responses. Human physiology, as a product of evolution, is designed to negotiate stressful events and environments; however, science is only beginning to explore the boundaries of physiological and reproductive limits primarily set by evolution for earlier stress contexts. Today's stressors may trigger old responses leading to harmful rather than helpful bodily reactions, and it may be that early human pregnancy failures are not perfectly inevitable but environmentally dependent in some cases. New interdisciplinary research explores this ancient topic beyond its vague past notions of sink or swim reproductive fitness. The pregnancy stress syndrome model postulates that within the multiple pathways wherein the neurological, endocrine and immunological mechanisms interact to support pregnancy maintenance, that there may be several common pathways wherein, in response to maternal stress perception, the interactions may become dysregulated, threaten maintenance, and trigger pregnancy failure. A completely congruent conceptual model awaits. The present evidence is sufficient to warrant a reconsideration of conventional views on the etiology of reproductive failure. Physicians and patients will benefit from the adaptation of this integrated evidence to daily clinical practice.

Box 1

Stress and human reproductive failure: recommendations for future research

Prospective study design with multiple evaluation time points during pregnancy and a large number of patients (500 or more)
Development of measurable indices for pregnancy stress syndrome
Psychometric tools
Biological markers such as neurohormones (urinary cortisol, CRH), neuropeptides (substance P), sex/pregnancy-related hormones (progesterone, estradiol, βHCG)
Environmental risk assessment (noise, chemical exposure)
Indicators of increased susceptibility or resilience to a stress risk to pregnancy failure via hereditary, cultural/ethnic and gender factors
Genetic profile
Cultural/ethnic context of the study population
Consideration of risk subgroups combining variables suspected to confer high risk, for example
High stress perception with low social support, age over 30 years, low BMI, low progesterone and smoking

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