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REVIEW

Understanding the pathophysiology of postpartum psychosis: Challenges and new approaches

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Abstract

Postpartum psychosis is a severe psychiatric condition which affects 1-2 of every 1000 mothers shortly after childbirth. Whilst there is convincing evidence that the condition is precipitated by a complex combination of biological and environmental factors, as yet the pathophysiological mechanisms remain extremely poorly defined. Here, I critically review approaches that have been, or are being, employed to identify and characterise such mechanisms; I also review a recent animal model approach, and describe a novel biological risk model that it suggests. Clarification of biological risk mechanisms underlying disorder risk should permit the identification of relevant predictive biomarkers which will ensure that "at risk" subjects receive prompt clinical intervention if required.

Key words: *CCN3*; Immune system; Steroid sulfatase; Nephroblastoma-overexpressed; Mouse; Animal model; Risk factor

Core tip: Postpartum psychosis is a severe psychiatric condition affecting a small proportion of women shortly after childbirth. The pathophysiological mechanisms underlying risk for the condition are extremely poorly-defined, but may include perturbed immune function, altered tryptophan metabolism and serotonergic dysfunction. Here, I critically review evidence underlying these assumptions, and discuss a novel model for postpartum psychosis risk, involving maternal deficiency for the enzyme steroid sulfatase, and overexpression of the *CCN* gene family, based upon emerging data from a recently-developed mouse animal model. Identifying

and characterising predictive biomarkers for postpartum psychosis risk will help to ensure prompt clinical intervention if required.

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INTRODUCTION

What is postpartum psychosis?

Postpartum, or puerperal, psychosis (PP) is a severe psychiatric disorder which typically manifests within days of childbirth in a small proportion of women (1-2 in every 1000 new mothers)[1,2]. The main symptoms of PP include hallucinations and delusions, cognitive disorganisation and confusion, anxiety and sleep problems[1,2]; rarely, affected mothers may attempt to injure themselves or their child, with maternal suicide and infanticide observed in some cases. Pharmacological treatments are relatively efficacious if administered promptly and in combination with psychotherapy and psychoeducation[1,2]: These include a range of typical and atypical antipsychotic drugs and mood stabilisers (given that mood fluctuations, or bipolarity, may precede and/or be exacerbated by PP); prophylactic pharmacotherapy may also be used judiciously in women at high risk of PP[1,2].

Risk and protective factors

The single largest risk factor for PP is a personal, or family, history of bipolar disorder or related psychotic disorder (seen in about 40%-50% of PP cases[1,2]). Other risk factors that have been suggested as modulators of PP risk include: Primiparity, maternal age, stress levels in the puerperium, and maternal sleep problems[1-4]; in contrast to postpartum depression, adverse early-life events do not appear to significantly enhance risk of developing PP in women with bipolar disorder[5]. The condition is associated with obstetric complications, notably pre-eclampsia[6], a potentially-damaging increase in maternal blood pressure. In common with other psychotic spectrum conditions such as schizophrenia, psychosis-related phenotypes in the perinatal period seem to be higher in immigrant populations, possibly as a function of being exposed to new infections, or to high levels of stress[7]. A recent intriguing study has tentatively suggested that women who smoke exhibit reduced risk of developing PP[8], although the questions as to whether this association is genuine, whether cigarettes somehow confer biological protection, or whether the smoking and non-smoking groups differ on some other critical demographic, biological or psychological measure unrelated to smoking remain to be directly addressed.

A biological basis to risk?

The temporal proximity of PP onset to childbirth, its high relapse rate, and its relatively stable prevalence and nature across societies and cultures, indicates that risk for the condition may be substantially influenced by biological factors[1,2]. The maternal body undergoes extreme physiological changes in the postpartum period, notably a massive drop in circulating oestrogens upon expulsion of the placenta. It has been suggested that abnormal sensitivity to this endocrinological disturbance may confer vulnerability to PP in some women[1,2], an idea supported by the fact that oestrogen supplementation may be beneficial to some patients[9,10]. The fact that PP is often responsive to antipsychotic treatment indicates that abnormal serotonergic and/or dopaminergic function may play a role in its pathogenesis; there is a well-established link between oestrogen levels and serotonergic function[11]. An increasing body of literature has implicated immune system dysfunction in psychotic disorders in general[12] and in PP specifically[13], whilst thyroid system abnormalities[14] and other autoimmune conditions[15] have been reported in some cases of PP.

Although the epidemiology, risk/protective factors, and comorbid phenotypes associated with PP have been systematically investigated and several have been consistently replicated (albeit by a small number of research groups), the molecular, cellular and neural pathophysiology of the condition is currently very poorly understood. Below, I list some contemporary approaches aimed at addressing this issue and their successes and limitations. Understanding the biological factors that confer PP risk will be important for identifying and characterising novel drug targets for more efficacious, less toxic, pharmacotherapy; however, given the reasonable efficacy of currently available medications this is perhaps not the main goal. A more pressing aim once biological risk pathways have been identified will be to describe predictive biomarkers which may be used to classify individuals at risk of the condition early in their pregnancy, and to ensure that they are closely monitored and have prompt access to appropriate clinical expertise and facilities if required.

CURRENT APPROACHES TO UNDERSTANDING POSTPARTUM PSYCHOSIS AND THEIR LIMITATIONS

There are a number of diverse approaches that have been employed in trying to understand the pathophysiology of PP. These investigational methods, and their relative advantages and limitations are summarised in Table 1.

Clinical biochemistry

One conceptually-simple approach to understanding the biology of PP is to compare the biochemistry of patients diagnosed with PP with that of appropriate controls

Table 1 The advantages and limitations of methods for investigating biological risk factors in individuals with postpartum psychosis

Investigational method	Advantages of method	Limitations of method
Clinical biochemistry or gene expression analyses	Direct assessment in patient or "at risk" groups Possibility of identifying peripheral biomarkers for PP risk	Difficult to access central nervous system; peripheral changes may not reflect central functional abnormalities Potential issues with obtaining consent for samples Substantial fluctuation of markers with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Neuroimaging	Direct assessment of brain structure, function or chemistry in patient or "at risk" groups	Cannot easily be performed during psychotic episodes Substantial exclusion criteria for procedure Limited resolution; cannot provide information on most neurochemical, cellular or molecular abnormalities Substantial fluctuation of measures with participant demographics, experiences and treatments Possible issues related to reverse causation, *i.e.,* are abnormalities a cause or consequence of the disorder?
Genetics	DNA can be readily obtained from patient or "at risk" groups from peripheral tissues DNA sequence is stable and unaffected by variability in patient's circumstances Possibility of identifying biomarkers that can predict risk at an early stage Few issues with reverse causation	Low power of genome-wide studies as a consequence of low prevalence of the condition; possibility of false positives and negatives
Porcine infanticide model	Some degree of face validity Direct access to brain tissue for detailed examination and DNA for genetic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Difficult and expensive to breed and maintain Not readily amenable to pharmacological studies; predictive validity unclear Difficult to systematically assess all brain regions
STS-inhibition mouse model	Some degree of face and predictive validity Direct access to brain tissue for detailed examination Relatively cheap to breed and maintain Amenable to pharmacological and genomic studies	Questionable relevance of animal behavioural phenotypes to PP symptoms Face and predictive validity require further confirmation STS deficiency unconfirmed in PP cases, hence construct validity unsubstantiated

PP: Postpartum psychosis; STS: Steroid sulfatase.

(either postpartum mothers without psychosis, or non-postpartum females). Studies to date have focussed on levels of tryptophan and its metabolites (*i.e.,* precursors of serotonin)[16], and the immune[13] and thyroid[14] systems, the latter two systems being in considerable flux during pregnancy and in the perinatal period. The main findings of these studies may be summarised, respectively, as: (1) deficient tryptophan breakdown, and lower kynurenine production, is evident in women with postpartum mood disorders; (2) abnormally low T cell numbers, and over-activation of the monocyte/macrophage arm of the immune system is evident in the postpartum period in women diagnosed with PP; and (3) patients with PP have a higher prevalence of autoimmune thyroid disease than controls.

Whilst this type of study undoubtedly provides clinically-relevant knowledge about the abnormal biology associated with PP, it is limited in several key ways. First, it is difficult to obtain biological samples from psychotic patients, particularly where these patients lack capacity to consent to experimental procedures, and where they may be socially and geographically isolated from individuals who can give consent on their behalf. Second, the biological samples that can be obtained are peripheral (typically blood or serum); accessibility to more relevant tissue from patients [brain, or even cerebro-spinal fluid (CSF)] is very limited or impossible. Whilst this may not be a major concern with regard to developing predictive peripheral biomarkers, the relationship between any peripheral tissue changes and abnormal brain function underlying behavioural phenotypes is difficult to characterise. Finally, biochemical measures can fluctuate substantially as a function of demographic variables, physiological and general health status, psychosocial factors and drug regime; hence, identifying physiological measures which definitively and reliably differentiate individuals with PP from healthy individuals, and establishing exactly how these measures correlate with phenotype, is extremely challenging. Moreover, there is the potential issue of reverse causation whereby it is difficult to establish unambiguously whether specific biochemical differences between individuals with PP and healthy controls are a cause or a consequence of the condition and its treatment.

Neuroimaging

The biochemical studies above are limited by their ability to directly assay brain function. The development of elegant neuroimaging techniques, including functional magnetic resonance imaging (fMRI) and Diffusion Tensor Imaging over the past couple of decades, has opened up the possibility of identifying neural substrates associated

with PP vulnerability. Neuroimaging studies in this area are scarce, presumably due to issues with participant recruitment and testing. To date, no brain circuitry has consistently be shown to develop or function abnormally in cases of PP. A recent case-control study has suggested that individuals developing PP have a reduced anterior cingulate cortex (ACC) volume[17]. As the ACC plays an important role in cognitive and emotional processing, including in impulse control, decision-making and cognitive organisation, it represents an interesting neural candidate for further study. Rare cases with PP who have been imaged have reported altered ventricular morphology[18], abnormal orbitofrontal cortex reactivity[19] and structural abnormalities of the corpus callosum[20].

Imaging studies, like biochemical studies, are limited in several ways. First, for practical reasons, it is not possible to examine brain function during psychotic episodes, and this has to be assessed in "recovered", or "at risk" participants - hence, the relevance of findings from, *e.g.,* fMRI studies to psychotic experiences is questionable. Moreover, imaging measures, particularly "snapshot" studies, may be confounded by a patient's demography, life history and comorbid diagnoses, and current and previous medication regimes. Finally, whilst neuroimaging can identify brain regions and circuits that may be of potential interest, and sophisticated techniques like magnetic resonance spectroscopy might identify reasonably highly spatially-resolved changes in limited brain neurochemistry, such approaches cannot identify most changes in neurochemistry, nor altered cellular or molecular function.

Genetics

Psychiatric genomics has recently come of age, with genetic risk variants associated with psychosis risk now being reliably identified *via* genome screens in patients with psychotic and mood disorders such as schizophrenia and bipolar disorder[21]. Genetic studies offer two key advantages over the above approaches: First, genomic material (DNA) can be reliably obtained from accessible tissues (typically saliva or blood), and DNA sequence is essentially conserved between these peripheral tissues and the brain. Second, genetic sequence is stable throughout life, and unlike biochemical or brain function measures, is not affected by environmental, psychosocial or pharmacological influences.

The robust identification of common risk variants that increase risk of complex psychiatric disorders by a small amount, or of rare variants that confer greater risk, necessitates the use of large sample sizes (conceivably up to 100000 cases to detect a high proportion of risk variants). For relatively common psychiatric disorders such as schizophrenia and bipolar disorder obtaining this number of cases is feasible through collaborative enterprises such as the Psychiatric Genomics Consortium[22]. For rare disorders such as PP it is unlikely that such large numbers of participants can be recruited, even with extensive inter-institutional working. Based upon our existing knowledge, it seems likely that, in common with related mood and psychotic disorders, genetic risk for PP will be complex and polygenic; hence, genomic analyses in PP, even with several thousand cases, will be limited by relatively low power.

Genetic studies that have been performed in PP to date have employed small sample sizes (< 1000 cases), and hence their conclusions should be regarded with caution: Low power implies a high rate of both false positive and false negative findings. A seminal genetic (linkage) study in bipolar affective postpartum psychosis suggested evidence for significant and suggestive risk loci at 16p13 and 8q24 respectively[23]; the regions implicated contained multiple genes, many of which could theoretically have mediated PP risk. Efforts are currently underway to undertake a sufficiently-powered genome-wide association study (GWAS) in bipolar affective postpartum psychosis, but as yet these have not yielded significant findings. Candidate gene-led studies in PP have focussed upon serotonergic system genes given the therapeutic efficacy of antipsychotics; one study provided suggestive evidence for association within the serotonin transporter and serotonin 2A receptor genes[24]. However, candidate gene association studies, which focus upon genes of likely biological relevance to a condition, often have low replication rates and are inevitably biased by our very limited current knowledge base[25]. Other candidate gene association studies in PP have examined a number of genes important in serotonergic and oestrogenic signalling, and the immune response, but, as yet, these have yielded mixed findings with little consistent evidence for robust risk variants[1]. Genomic techniques such as exome, or even whole-genome, sequencing are feasible in the relatively small number of PP samples available, but here again, low power will make drawing any conclusions about the pathogenicity of any potentially-causal genetic variants difficult.

Besides looking at the DNA sequence *per se*, insights into PP pathogenesis may be obtained by comparing the epigenome or gene expression profiles in individuals with PP and controls. One such study focussed upon microRNAs known to regulate the immune response and demonstrated altered expression of miR-146a and miR-212 in patients with PP relative to healthy controls[26]. However, whether these changes were a cause or consequence of the disorder (and associated medications) is unclear. Moreover, like with candidate gene association studies, expression studies focussing on just a handful of pre-selected genes provide limited information on the specificity of the changes or on general risk pathways; for example, it could feasibly be the case that the expression of a large proportion of microRNAs is perturbed in PP.

The porcine infanticide model of PP

A further approach towards understanding the biological basis of PP risk is through the use of animal models. Animal models permit a degree of experimental control that cannot be achieved in clinical, or other human,

studies and allow procedures that would be ethically prohibited in humans to be conducted; however, there is some resistance to the use of animals, and particularly non-primate species, for modelling complex psychiatric phenotypes characterised by deficits in "uniquely-human" aspects of behaviour and cognition. The first published animal model for PP is the infanticidal sow pig, which exhibits several epidemiological, behavioural and endocrinological traits associated with the condition[27]. An early quantitative trait locus (QTL) study in this model identified four possible genomic loci of interest on chromosomes 2, 10 and X, corresponding to human chromosomal loci 5q14.3-15, 1q32, Xpter-Xp2.1, and Xq2.4-Xqter respectively[27]; an independent linkage study confirmed an association between X-linked loci and maternal aggression, and suggested regions of interest on chromosomes 2, 6, 14 and 15[28]. Examination of hypothalamic gene expression in the maternal infanticide model identified multiple genes, the expression of which was altered in pigs showing aberrant behaviour; several of these mapped to the previously-implicated QTL regions [of particular note were the *HTR2C* (serotonin receptor 2C), *DRD2* (dopamine receptor 2) and *PRL* (prolactin) genes, the first two encoding antipsychotic drug targets[29]]. A genome-wide association study in this model indicated candidate regions on porcine chromosomes 3, 4 and 15, syntenic with human chromosomal regions implicated in bipolar disorder and postpartum psychosis (including 16p13)[30], whilst a candidate gene association study suggested preliminary evidence for association with oestrogen receptor (*ESR1*), excitatory amino acid transporter 2 (*EAAT2*) and dopamine receptor 1 (*DRD1*) genes, but not *HTR2C*[31].

The fact that the pig model described above shows some superficial phenotypic similarities to patients with PP ("face validity"), and that it indicates genomic regions, and specific gene candidates, of possible functional relevance, suggests that it may represent a reasonable model for PP. However, it should be acknowledged that the model is compromised in a number of ways which may limit its utility. First, there is a relatively poor correlation between the clinical and animal behavioural profiles, in that the vast majority of women with PP are not aggressive, and even those who are aggressive will not attempt infanticide. Second, this large animal model is difficult and expensive to breed, maintain, and analyse experimentally. Of particular note, it is difficult to test whether the infanticide phenotype is sensitive to antipsychotic administration - hence it is difficult to determine the extent to which this phenotype is analogous to PP, and to assess whether or not the model has any degree of predictive validity. Another main issue is that, because the brain of the pig is relatively large, it is difficult to investigate all regions where abnormal activity may be observed; whilst previous work has understandably focused on the hypothalamus given its known role in maternal behaviour, there is, as yet, little convincing evidence for impaired hypothalamic function in PP cases.

PATHWAYS TO PROGRESS

Despite decades spent studying the illness, and the availability of cutting-edge experimental techniques and research hardware, we are still far from understanding the biological and psychological risk factors underpinning PP and hence how to identify women at greatest risk for the condition. Below, I briefly outline what I believe is required in order to make progress in this area over the next decade.

Perhaps the main factor hindering progress in PP research is sample size. It is now well recognised in psychiatry that groups from around the world must collaborate in order to generate an adequately-powered, consistently and deeply-phenotyped cohort of patients (and their affected and non-affected relatives) in which genetic, biochemical and neuroimaging analyses can be undertaken; such a large sample will permit factors such as drug treatment, demography and symptomatology to be covaried for, and hence for robust genotype-biology-phenotype correlations to be ascertained. There are ongoing collaborative efforts in the field of PP research involving centres of excellence across Europe and the United States, and these should soon begin to bear fruit. One research area that has been relatively neglected to date is deciphering the fundamental psychological processes that distinguish mothers who develop PP from: (1) those who have bipolar disorder and do not develop the condition; or (2) from healthy mothers. Specifying how "at risk" women differ from "protected" women on measures of behaviour and cognition, may feasibly permit the development of a simple screening test to be applied prior to childbirth, and may provide clues as to underlying neurobiology.

Even with larger numbers of cases available for genome-wide genetic analyses, there is a strong possibility that only a handful of polymorphisms or mutations associated with PP risk will be identified, and that many will not reach genome-wide levels of significance after the requisite stringent multiple testing corrections. Hence, there may still be a role for sensible candidate gene association studies comparing variant frequency in cases and controls, where higher levels of alpha (as a consequence of reduced multiple testing) are more likely to give rise to statistically significant findings. However, as discussed above, traditional candidate gene studies based upon theoretical causal or therapeutic mechanisms have frequently been shown to be irreproducible, or to give rise to findings of a much smaller magnitude than initially suspected[25,32]. Moreover, genome-wide association studies have repeatedly demonstrated that genetic variants robustly associated with disorder risk are often poorly-annotated and have unknown effects on biology, and hence would not have been prioritised in candidate-led approaches[32]. Bearing in mind these caveats, proposals for candidate *PP* genes should be supported by multiple converging lines of evidence, and should ideally exhibit both positional and functional relevance. In the following section, I describe a candidate gene backed by

such evidence.

There is also clearly a need for more experimentally-tractable animal and cellular models, in which molecular, cellular and circuit mechanisms that may influence PP risk can be characterised. In terms of animal models, ideally these should be available to be tested in large, well-defined batches, be neurobiologically-amenable, and exhibit some degree of face, construct and predictive validity (the latter in contrast to the porcine infanticide model). In terms of cellular models, the advent of induced pluripotent stem cell technology technology now means that "pathological" samples such as brain cell cultures can ultimately be generated from patient fibroblast, or other peripheral, cells[33]. Any data generated from *in vitro* studies in which derived-brain cells are examined in isolation, should be extrapolated cautiously given that PP risk, in common with the risk of related psychiatric conditions such as schizophrenia and depression, is likely to be modulated by complex ongoing interactions between a multitude of intra-brain and extra-brain (*e.g.,* hormonal, placental or immune system) factors[34].

A NEW CANDIDATE GENE

I have previously proposed, based upon numerous lines of clinical and basic scientific evidence, that maternal deficiency for the enzyme steroid sulfatase, encoded by the X-linked *STS* gene, may represent one candidate risk mechanism for PP[35]. The STS enzyme cleaves sulfate groups from a variety of steroid hormones, notably dehydroepiandrosterone sulfate (DHEAS), thus allowing them to be used as precursors for a variety of androgens and oestrogens; hence it is a key modulator of the steroid hormone axis. There are a number of criteria that candidate genes and pathways for PP may be expected to meet based upon our existing knowledge; the *STS* gene and the processes which it modulates meet many of these.

One might expect the candidate system to be in flux in the postpartum period, and to influence immune function at this time; in mice, and perhaps also in man, brain levels of STS are elevated specifically shortly after giving birth[36]. In healthy women, reduced levels of serum DHEA in the postpartum period are associated with activation of the immune system[37]; conceivably, in STS-deficient women, abnormally low levels of postpartum DHEA (as a consequence of impaired DHEAS desulfation) may result in hyperactivation of the immune system.

The steroid hormone axis has repeatedly been implicated in the pathogenesis of PP given the sudden drop in circulating oestrogen levels in the mother following birth, and the suspected protective effects of oestrogens against psychosis[38]; indeed, early candidate gene association studies focussed upon those regions of the genome thought to be regulated by oestrogens[39]. STS is a key player within this axis. STS is highly expressed in key reproductive tissues (testis, mammary gland, placenta, uterus, brain[40]) and hence its dysfunction may, a priori, be expected to impact upon normal reproductive physiology. Recently, placental mis-expression of the *STS* gene has been implicated in pre-eclampsia risk[41]. It is plausible that in STS-deficient mothers, where baseline oestrogen levels may already be low[42], expulsion of the oestrogenic placenta precipitates psychosis vulnerability. There is also some evidence that women who are carriers for *STS* mutations, and who are STS-deficient, are at increased risk of psychological abnormalities (unpublished results) and of delayed, or prolonged labour, and related obstetric complications[43]; such complications, and the accompanying psychological stress, may be one precipitant of postpartum psychiatric distress, although a specific link to PP remains unconfirmed[1,44].

In the developing and adult brain, *STS* is expressed in regions implicated in postpartum psychosis. Specifically, it is highly expressed in the thalamus (involved in the integration and usage of sensory information) and throughout the cortex (including the cingulate cortex)[45,46]; it is also highly expressed in the hypothalamus, and outside the brain in the thyroid gland[45,46]. Hence, its absence may feasibly give rise to abnormal hypothalamic-pituitary-adrenal or hypothalamic-pituitary-thyroid function, consistent with notions of an abnormal stress response, or thyroid pathology, in cases of PP.

Parallel clinical and animal model studies have demonstrated that STS deficiency (or genetic variation within *STS*) gives rise to behavioural phenotypes of relevance to PP including psychosis, cognitive disorganisation, anxiety, depression and, rarely, aggression (unpublished results and ref.[46-49]). Moreover, there is a positive correlation between serum levels of DHEAS and psychoticism (anxiety, paranoia, psychosis) in healthy women and women exhibiting postpartum psychiatric distress[50,51]. Data from genetic and pharmacological rodent models suggest that deficiency for STS may impact upon neurochemistry of relevance to psychosis vulnerability including altered levels of hippocampal serotonin (and Htr2c receptors) and acetylcholine[52,53].

Finally, *STS* was explicitly suggested as a candidate gene underlying significant X-linked QTLs in the porcine maternal infanticide model of PP[27].

INSIGHTS FROM A NEW MOUSE MODEL

The only existing animal model for PP, the porcine maternal infanticide model, is sub-optimal. We have recently attempted to develop a more experimentally-tractable mouse model for the condition, based upon the idea that maternal steroid sulfatase deficiency is a putative risk factor[54].

Briefly, we showed that pharmacological inhibition of the steroid sulfatase enzyme in new mouse mothers resulted in behavioural, endocrinological and genetic phenotypes partially mirroring those seen in PP ("face validity"). Whilst STS inhibition did not affect gross health, maternal behaviours or activity, it did have subtle effects on

exploration of the elevated plus maze (increased rearing and reduced latency to enter the exposed open arms) and the startle response (reduced with enzyme inhibition); a reduced startle response is a feature of patients with bipolar disorder[55]. These observations support the notion of STS as a modulator of postpartum maternal behaviour. STS inhibition did not seem to influence levels of the main stress hormone corticosterone in mice, consistent with data indicating that women with PP show normal cortisol levels[56].

Previous work had suggested that a small genomic region on mouse chromosome 15 harboured a QTL influencing rearing and open arm latency measures in the elevated plus maze[57]; excitingly, this region of chromosome 15 was syntenic with human chromosome 8q24, a region implicated in PP pathogenesis by linkage[23]. Expression screening of the small number of genes within the mouse chromosome 15 interval revealed just one, *Nov*/*Ccn3*, whose expression was significantly altered (upregulated) in STS-inhibited brain; the expression of two other genes from the Ccn family (*Ctgf/Ccn2* and *Wisp1/Ccn4*), as well as genes whose products may be co-regulated with *Nov/CCN3* (*Arhgdig*, *Adcy8* and *Ccl2*) was also increased in STS-inhibited brain tissue[54].

An advantage of the mouse model is that it is possible to test whether putative PP-relevant behavioural and molecular features are sensitive to antipsychotic administration, *i.e.,* to test whether it has potential predictive validity. We showed that administration of clinically-relevant doses of the atypical antipsychotic ziprasidone reverses the deficient startle response, and tempers the over-expression of *Nov/Ccn3* in the STS-inhibited mouse, indicating that these facets of the model may be relevant to psychotic pathophysiology[54].

Although the STS-inhibited mouse shows some degree of promise as a model for PP, its face validity needs to be defined more thoroughly. For example, does it show the abnormalities in the tryptophan-kynurenine pathways and immune system that have been reported in PP cases? One limitation of the current pharmacological model is that steroid sulfatase is solely inhibited in the postpartum period - if STS deficiency is truly a risk factor for PP, it would likely be genetic in origin, and operate throughout life (including pregnancy and the postpartum period). Hence, it would be useful to examine the behaviour and physiology of new mouse mothers that lack one (or both) functional *STS* alleles, and hence have reduced constitutive STS expression; such knockout mice have historically proved difficult to generate due to the complex genomic architecture around the *STS* locus, but this difficulty may potentially be overcome with new genetic engineering technologies such as CRISPR.

A NEW PATHWAY TO PATHOLOGY AND TREATMENT?

The new mouse model described above indicates, on the basis of analyses agnostic to gene function, that dysregulation of the *CCN* gene family arising downstream of dysfunction of the STS axis may be implicated in PP risk. Is this a reasonable concept? If so, can this evaluation suggest molecular, cellular and neural pathways that could be perturbed in PP and that could feasibly be targeted *via* re-purposing of existing drugs, or through developing new drugs?

The *CCN* gene family encodes a number of secreted extracellular matrix-associated proteins that are highly-expressed in the brain[58]; impaired function of the extracellular matrix, and the subsequent abnormal cell-cell interactions, have recently received attention as a possible pathophysiological mechanism in a number of mood disorders[59]. This gene family is also known to be important in female reproductive function[60], exhibits dynamic brain expression throughout pregnancy and the puerperium[61], and modulates Notch and Wnt signalling pathways[57] that are disrupted in bipolar disorder[62] and cases of postpartum psychiatric disturbance[63]. Interestingly, the expression of CCN family members may also be altered by the administration of substances that induce psychosis-like states[64,65], by social stress[66] and by small molecules including cytokines and serotonin[67] suggesting these members as possible mediators of analogues of psychosis.

CCN3 is of particular interest as a candidate modulator of PP risk given the location of the associated gene directly under the 8q24 linkage peak. There is also emerging evidence from a study in human female (cervical cancer) cells that STS and DHEA can directly influence the expression of the integrin β1 molecule[68], a known interactor with CCN3 in the brain and a putative mediator of CCN3-induced effects on cytokine secretion[69].

The CCN3 protein exhibits a variety of additional features that strengthen its candidacy. First, it regulates intracellular calcium signalling[70] a process that goes awry in both bipolar disorder[71] and PP[72]. Second, it is highly expressed in the brain's cortex and limbic system[58], and its expression is dampened by circulating oestrogens[73]. It is apparently a regulator of axonal outgrowth of callosal projection neurons[74], a finding of interest in light of possible corpus callosum abnormalities in cases of PP[20]. The fact that CCN3 modulates placental angiogenesis[60], that the associated gene is located 70kb from a GWAS hit for hypertension[75] and that it, and its family members, are regulated by thyroid hormone derivatives in the cortex of the brain[76], is consistent with the epidemiological studies showing overlap between PP, pre-eclampsia and thyroid abnormalities. Given the preliminary findings regarding a potential attenuation effect of smoking on PP risk, it is interesting to note that the *CCN3* gene lies close to a single nucleotide polymorphism nominally associated with smoking cessation[77], and that in female mouse tissues *Ccn3* expression is reduced upon exposure to cigarette smoke[78]. The protein DDR1 is a putative receptor mediating CCN3 signalling[79]; there is some evidence suggesting association of genetic variants within DDR1 with psychotic illness[80,81].

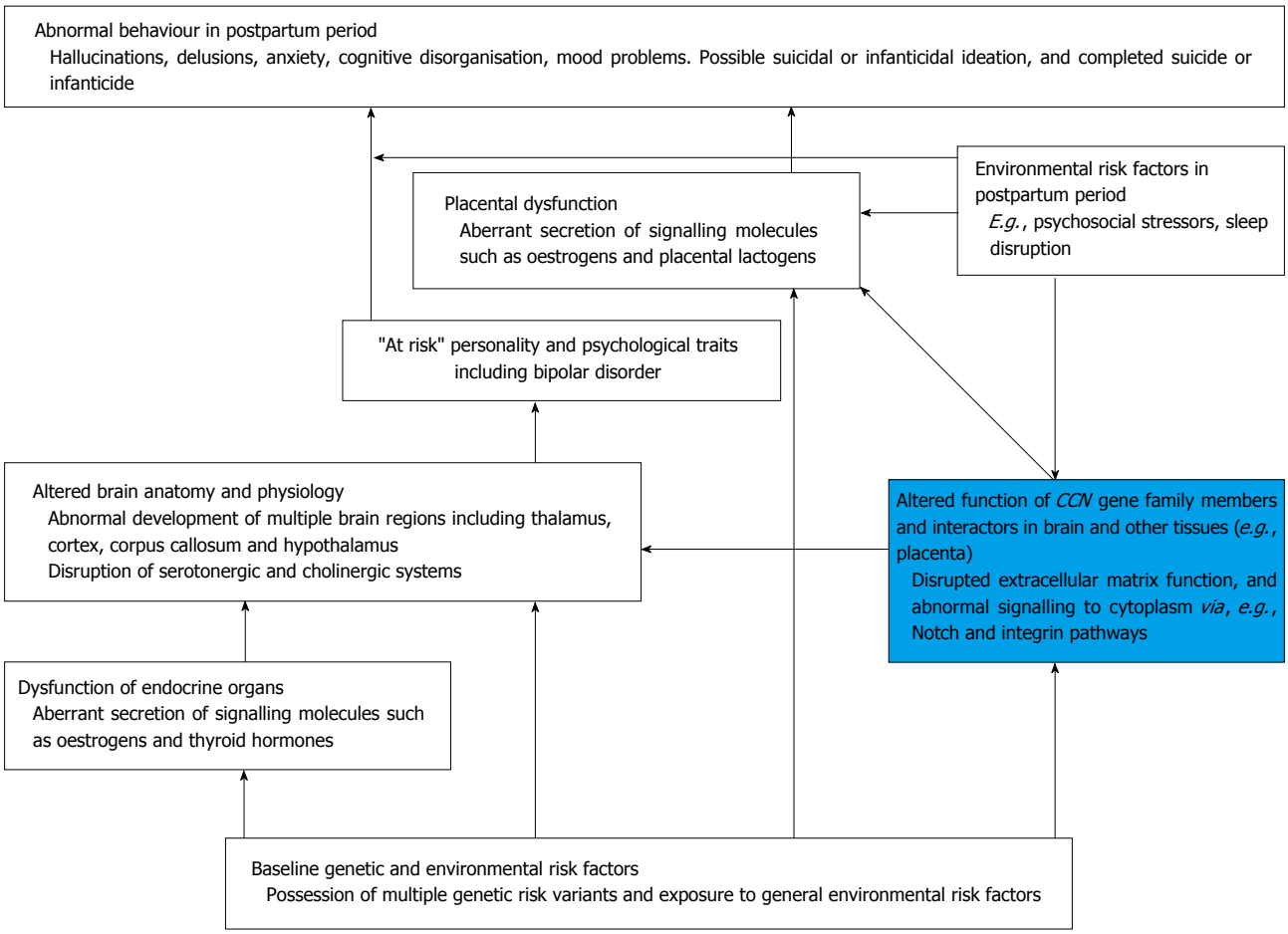

Figure 1 A revised model for postpartum psychosis risk. We suggest that multiple genetic risk variants (potentially influencing STS and CCN family member function), in combination with environmental risk factors, adversely affect the function of multiple endocrine organs (notably placenta and thyroid gland) and increase expression of CCN family members in brain and placenta, to elicit functional changes in brain architecture and neurochemistry which predispose to postpartum psychosis risk. This risk may be further exacerbated by acute environmental risk factors acting within the postpartum such as psychosocial stressors (plausibly also acting *via* CCN-mediated pathways). Putative and well-characterised protective factors such as smoking and antipsychotic administration respectively could potentially exert their effects *via* normalisation of CCN family member function.

Finally, converging evidence from a genetic mouse model is consistent with the notion that *Ccn3* over-expression is associated with abnormal maternal behaviour. Specifically, wildtype mouse mothers carrying pups with genetic modifications which affect placental (spongiotrophoblast) function exhibit abnormal maternal and anxiety-related behaviours in the postpartum period and significantly increased hippocampal *Nov/Ccn3* gene expression[54,82]; this finding is intriguing as it suggests the possibility that the secretion (or lack thereof) of one or more circulating factors from the placenta can indirectly affect brain expression of *Nov/Ccn3*, and subsequently maternal behaviour. The spongiotrophoblast is involved in the synthesis and secretion of multiple compounds which have been shown to influence maternal behaviour in rodent models and which may plausibly mediate this effect (*e.g.,* placental lactogens and pregnancy-specific glycoproteins[83]). Interestingly, in humans, placental lactogen is secreted by the syncytiotrophoblast of the placenta[84], a site of high STS expression[85].

An integrated model showing how PP risk may conceivably be influenced by STS deficiency, placental dysfunction, and disruption to CCN family members based upon current knowledge is presented in Figure 1. This model may be updated and refined as new data emerge from avenues including larger genomic screens, hypothesis-free gene expression screens in model systems, and physiological measurements in patients with PP. The model makes several readily-testable clinical predictions for PP cases relative to control subjects: (1) there will be an excess of genetic variants that reduce STS function and enhance CCN3 expression; (2) there will be an increased DHEAS:DHEA tissue ratio; and (3) there will be elevated levels of CCN3 in accessible fluids including serum, cerebrospinal fluid and urine[86]. In parallel to these clinical studies, we could potentially demonstrate whether or not CCN3 contributes significantly to abnormal maternal behavioural phenotypes in mice by administering an STS inhibitor to wildtype mice and readily-available *Ccn3* knockout mice[87], with the prediction being that wildtype mice would exhibit behavioural abnormalities whereas knockout mice would not.

Should CCN family member over-expression be confirmed as a PP risk factor by future clinical and basic

studies, it may be amenable to pharmacological amelioration by, amongst other approaches, antibody-targeting or knockdown strategies[88]; such interventions may have therapeutic benefits and offer an alternative to more conventional mood stabiliser and antipsychotic approaches.

CONCLUSION

Numerous features of postpartum psychosis (notably its low prevalence, its high degree of heterogeneity, its relative unpredictability and a lack of relevant animal and cellular models) make understanding its pathophysiology difficult. Whilst research to date has provided tantalising hints at pathways and systems that may be perturbed in the condition, the questions as to whether or not they are truly pathogenic remains to be addressed. Undoubtedly, there are many more risk pathways to be discovered.

To make meaningful progress in understanding the molecular, cellular, neural and psychological mechanisms underlying PP risk it will be necessary to adopt a converging experimental approach comprising large-scale genetic (association, copy number variations and sequencing), gene expression and genetic neuroimaging studies, clinical studies correlating behavioural phenotypes with physiological markers of immune, neurochemical and neuroendocrine dysfunction, and animal (pig and mouse) and cellular (*e.g.,* induced pluripotent stem cells) model studies, bearing in mind the many caveats raised above. Importantly, hypothesis-free approaches such as the genomic and animal/cellular model approaches may identify non-obvious risk pathways which can then be followed up in more focussed clinical analyses. The prioritisation of candidate pathways may be informed by work examining the physiology of related conditions and behaviours including bipolar disorder, other postpartum mood disorders, pre-eclampsia and smoking.

A main goal in PP research is to identify biomarkers within easily accessible tissues that can be sampled before, or during, pregnancy (*e.g.,* blood, saliva) that can accurately predict risk, a substantial challenge for such a rare condition; early identification of "at risk" individuals should facilitate rapid access to appropriate facilities and medical care (including close monitoring, administration of psychological or pharmacological treatments, and counselling). The experimental analyses proposed above are likely to result in the identification and characterisation of such biomarkers.

A recent study has shown that the expression of *Nov*/*Ccn3* in rat tissues is sensitive to the administration of the mood-stabilising drug lithium which has clinical efficacy in some cases of PP[89].

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