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Pioneering drugs for overactive bladder and detrusor overactivity: Ongoing research and future directions

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the limitations of currently licensed pharmacotherapies, such as antimuscarinics, β_3 -adrenergic agents, and botulinum neurotoxin, has been reviewed performing a systematic literature review and web search. The review covers the exploratory agents alternative to available medications for OAB and that may ultimately prove to be therapeutically useful in the future management of OAB patients based on preclinical and early clinical data. It emerges that many alternative pharmacological strategies have been discovered or are under investigation in disease-oriented studies. Several potential therapeutics are known for years but still find obstacles to pass the clinical stages of development, while other completely novel compounds, targeting new pharmacological targets, have been recently discovered and show potential to translate into clinical therapeutic agents for idiopathic and neurogenic OAB syndrome. The global scenario of investigational drugs for OAB gives promise for the development of innovative therapeutics that may ultimately prove effective as first, combined or second-line treatments within a realistic timescale of ten years.

Key words: Detrusor overactivity; Drug therapy; Lower urinary tract symptoms; Overactive bladder; Urinary incontinence

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Core tip: The forefront of global research scenario of investigational drug candidates for the management of patients with overactive bladder and detrusor overactivity was reviewed. Among a huge amount of exploratory compounds with completely new mechanisms of action, some promising pharmacological principles show potential to translate into novel therapeutics to be clinically used as first-line alternative treatments, or in combination with established drugs, or as second-line treatments in refractory patients.

Abstract

The ongoing research on pioneering drug candidates for the overactive bladder (OAB) aimed to overcome

Sacco E, Recupero S, Bientinesi R, Palermo G, D'Agostino D, Currò D, Bassi P. Pioneering drugs for overactive bladder and detrusor overactivity: Ongoing research and future directions. *World J Obstet Gynecol* 2015; 4(2): 24-39 Available from: URL: <http://www.wjgnet.com/2218-6220/full/v4/i2/24.htm> DOI: <http://dx.doi.org/10.5317/wjog.v4.i2.24>

INTRODUCTION

Overactive bladder (OAB), defined as urinary urgency with or without urgency urinary incontinence, usually associated with increased urinary frequency and nocturia^[1], is a very bothersome and debilitating chronic condition that severely affects the patient's quality of life^[2]. The socioeconomic burden is very high due to the aging population, the OAB-associated comorbidities and the increased risk of hospitalization^[3]. The pathophysiology is largely unknown, although multiple causes have been proposed, such as a primary detrusor dysfunction, observed as detrusor overactivity (DO) during urodynamic studies, an overactivity of the afferent arm of the micturition reflex, a primary dysfunction of higher central nervous system (CNS) inhibitory centers^[4]. OAB is underdiagnosed and undertreated, however, the increase in patient awareness, the rise in the geriatric population, and the availability of more pharmacological principles have triggered a significant growth in the OAB market with a estimated market size of over \$2 billion in 2012.

Pharmacological treatment has been based for years on antimuscarinic agents, but recently other two pharmacological principles have been approved for OAB by the United States Food and Drug Administration (FDA): the first β 3-adrenergic agent, mirabegron (Myrbetriq®, Astellas, approved in June 2012), and the botulinum neurotoxin (Botox®, Allergan, approved in January 2013)^[5,6]. Although many novel antimuscarinic and β 3-adrenergic agents, and alternatives to the botulinum neurotoxin are under development, the ideal medication for the cure of OAB with an optimal profile in terms of safety, tolerability and efficacy is still to be discovered. A huge amount of preclinical studies is ongoing exploring the therapeutic potential of many novel compounds some of which already advanced to the clinical phases of development, which mixed results^[7,8].

This review provides an extensive update on the exploratory drugs, alternative to available medications for OAB that may ultimately prove to be therapeutically useful in the future treatment of lower urinary tract symptoms (LUTS) and OAB.

LITERATURE RESEARCH

A systematic literature review search of peer-reviewed English-language full papers published by November 2014 has been performed. Medline databank was searched employing both "MeSH" and "free text" protocols, and using a combination of the following

search terms: "urinary bladder, overactive", "urinary incontinence, urge", "lower urinary tract symptoms" AND "drug therapy". Scopus and ISI Web of Science databanks were also searched using the same search terms. A search of articles related to each specific compound was also performed. A hand search of reference lists of retrieved articles was performed in order to identify further studies not captured by the above used terms. Clinical trials and pharmaceutical companies' websites were also searched for pipeline projects. All the investigational pharmacological principles with at least preclinical evidence of activity against OAB/DO have been discussed.

DRUGS ACTING ON INHIBITORY CENTRAL MECHANISMS

GABA_B-receptor agonist

Compounds with agonist activity on γ -aminobutyric acid (GABA) receptors in the CNS exploit the inhibitory effect of this neurotransmitter on micturition reflex^[9]. Baclofen, a GABA_B-receptors agonist, is used for the treatment of neurological spasticity, particularly in the lower limb. Baclofen is pumped directly into the subarachnoid space by means of a programmable pump *via* a catheter system. Preclinical studies showed that intrathecal baclofen was effective in attenuating oxyhemoglobin-induced DO^[10] and, in rats with spinal cord injury (SCI), produced a dose-dependent inhibition of non-voiding bladder contractions and a decrease in micturition pressure^[11]. Clinical studies based on urodynamic evaluations showed that the continuous intrathecal baclofen pump infusion is effective in the management of patients with medically-refractory neurogenic DO (NDO) and decreased bladder compliance^[12]. Although baclofen gained approval for treatment of NDO in SCI patients, the narrow therapeutic window and the tolerability profile limited its widespread clinical use. ADX71441, a novel, potent and selective agonist of GABA_B-receptor, showed efficacy in rodent models of OAB and may allow further exploitation of this central inhibitory mechanism^[13].

Anticonvulsants

The inhibition of the GABA transporters (GAT) that are thought to provide a GABA inactivation mechanism in the CNS, has been explored as a possible pharmacological principle aimed to treat DO. Tiagabine, an anticonvulsants that selectively inhibits the GABA re-uptake *via* the GABA transporter GAT1, given intravenous or intrathecal in rats, improved storage phase parameters suggesting a potential utility for OAB treatment^[14].

Gabapentin is a putative GABA analog crossing the blood-brain barrier originally developed to treat epilepsy, and currently used for neuropathic pain and other conditions. Its mechanism of action has not been fully elucidated although it appears to have inhibitory

activity on afferent C-fibers likely by binding to α -2-delta subunit of voltage-dependent calcium channel^[15]. Carbone *et al.*^[16] reported in a pilot study that gabapentin improved both symptoms and urodynamic parameters in NDO patients. Kim *et al.*^[17] reported that the drug was well tolerated and improved symptoms in 14 out of 31 antimuscarinics-refractory OAB patients. Recently, beneficial clinical effects of gabapentin as an add-on therapy have been reported also in 16 out of 30 children with antimuscarinics-refractory OAB^[18]. Phase II trials are ongoing comparing gabapentin with solifenacin in OAB patients^[19] and evaluating the efficacy and tolerability of a combination of low doses of gabapentin and oxybutynin^[20].

Pregabalin (Lyrica®, Pfizer) is an anticonvulsant drug mainly used for neuropathic pain and fibromyalgia. Like gabapentin, pregabalin binds to the α -2-delta subunit of the voltage-dependent calcium channel in the CNS, leading to decreased release of several neurotransmitters^[21]. A phase II trial is ongoing in patients with idiopathic OAB comparing pregabalin with tolterodine and their combination^[22]. Furthermore, preclinical data showed significant improvement on the urodynamic parameters of an animal model of NDO providing a rationale for future proof-of-concept clinical trial on NDO patients^[23].

Levetiracetam is an antiepileptic drug with a mechanism of action not yet clarified, although the drug binds to the synaptic vesicle glycoprotein SV2A and inhibits presynaptic calcium channels reducing neurotransmitter release and acting as a neuromodulator^[24]. Experimental findings in spinal cord transected rats have shown that levetiracetam, administered by subcutaneous osmotic minipump, improved urodynamic parameters in this animal model of NDO^[25].

GABAergic gene therapy

An alternative strategy is based on increasing GABA in the spinal cord *via* viral-mediated gene delivery. Injection in SCI rats of HSV-GAD (replication-defective herpes simplex virus vectors encoding genes of glutamic acid decarboxylase, the GABA synthesis enzyme) significantly decreased the number and amplitude of non-voiding contractions compared with controls, without blunting micturition pressure likely *via* the inhibition of the afferent limb of the micturition reflex^[26]. Thus, GAD gene therapy gives promise to become a novel therapy of urinary dysfunctions in SCI patients.

Glycinergic drugs

Glycine is a major inhibitory neurotransmitter in the spinal cord. Animal studies suggest that glycinergic neurons have an important inhibitory effect on the spinobulbospinal micturition reflexes at the level of the lumbosacral cord^[9].

The extracellular concentration of glycine at synapses is regulated by two types of glycine transporters (GlyTs):

GlyT1 and GlyT2^[27]. In rats, GlyT2 plays a major role in the clearance of extracellular glycine in the spinal cord and its inhibition leads to amelioration of cyclophosphamide-induced DO and pain behavior^[28]. As a result, activation of glycinergic inhibitory mechanisms by GlyT2 inhibitors has been suggested as a novel therapeutic strategy for OAB and bladder pain syndrome.

DRUGS ACTING ON MONOAMINES RECEPTORS

Inhibitors of monoamine-reuptake

Inhibitory effects on micturition are known side-effects of drugs with inhibitory action on the monoamine reuptake, including tricyclic antidepressants. Furthermore, depression is more common in patients with OAB and a shared deficiency of monoamine (serotonin and noradrenaline) behind both depression and OAB has been suggested^[29].

Imipramine, a tricyclic antidepressant, improves storage LUTS and DO at the cost of not negligible side-effects. Antidepressants selective serotonin reuptake inhibitors, such as escitalopram, are under evaluation for efficacy in OAB patients^[30].

Duloxetine, an antidepressant acting as a selective serotonin-norepinephrine reuptake inhibitor (SNRI) and approved for the treatment of stress urinary incontinence for its stimulatory activity on external urethral sphincter, demonstrated significant efficacy compared to placebo in relieving urinary symptoms in women with OAB^[31]. However, the side-effects of this compound significantly limit patient's compliance.

Based on animal experiments showing that besipirdine, a SNRI that interacts also with α 1 (agonist) and α 2 (antagonist) receptors, significantly and dose-dependently improves storage function and external urethral sphincter activity^[32], a human proof-of-concept study has been initiated by UroGene in patients with storage LUTS^[33].

Serotonin receptors agonists

Increasing evidence indicates that serotonin [5-hydroxytryptamine (5-HT)] is involved in a complex way in the control of micturition at central and peripheral sites, with both inhibitory and facilitatory effects^[34-41], although the serotonergic pathway generally enhances urine storage by facilitating the vesical sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway.

The 5-HT_{1A} receptor agonist 8-OH-DPAT has been investigated in alpha-chloralose anesthetized or conscious chronic SCI cats^[37]. This compound significantly increased the bladder volume threshold for eliciting a large amplitude micturition contraction, but only slightly reduced the amplitude of the contractions, indicating that drugs that activate 5-HT_{1A} receptors might be useful in treating NDO after SCI. 8-OH-DPAT also improved voiding efficiency and maximum intravesical pressure, and enhanced the external urethral sphincter

tonic and bursting activity in a rat model of incomplete cauda equina/conus medullaris injury^[38].

5-HT₂ and 5-HT₃ receptors mediate excitatory effects on sympathetic and somatic reflexes to increase outlet resistance, and preclinical studies have shown that 5-HT_{2C} and 5-HT₃ receptors play an inhibitory role on micturition reflex suggesting that agonists at this site may have potential as candidate drugs for OAB^[36].

Serotonin receptors antagonists

The peripheral excitatory function of serotonin is increased in disorders known to be associated with DO, such as bladder outlet obstruction (BOO) and diabetes^[39]. The facilitatory action on micturition reflex of the 5-HT_{2A} receptor has been demonstrated in rats and its overexpression observed in BOO rat bladder^[36]. Accordingly, sarpogrelate (a 5-HT_{2A} selective antagonist) counteracted in diabetic rat bladder the increased contractile response to 5-HT in a dose-dependent manner^[39]. Accordingly, Takimoto *et al.*^[40] reported a symptomatic benefit in patients with diabetes and refractory OAB treated with sarpogrelate.

5-HT₄ and 5-HT_{1A} receptors have been also involved in micturition control and their selective antagonists such as piboserod and WAY100635, respectively, potently inhibited the micturition reflex in animal models and human detrusor^[34,41]. However, disappointing results have been reported with Rec-0545, a potent and selective antagonist of the 5-HT_{1A} receptor evaluated by Recordati in a proof-of-concept trial for the treatment of OAB patients^[42]. The combination of WAY100635 with duloxetine has been evaluated in a cat model of DO with promising results^[43].

5-HT₃ receptor is another candidate target for the development of novel drugs for the OAB according to recent preclinical findings^[44]. Dynogen Pharmaceuticals, Inc. is developing a drug (DDP225) with both 5-HT₃ receptor-antagonist and noradrenaline reuptake inhibitor properties for the treatment of OAB in patients who are not incontinent^[45].

PURINERGIC RECEPTORS ANTAGONISTS

Several pharmacological approaches have been driven for a more in depth understanding of the physiology of the "mucosal bladder network" (the functional unit consisting of the urothelium, interstitial cells and afferent nerves) (Figure 1). An interesting hypothesis-driven approach for the future treatment of OAB is represented by the antagonism of purinergic receptors, namely P2X₁ and P2X₃/P2X_{2/3}^[46]. Thus, several studies suggested that the adenosine 5'-triphosphate (ATP) and purinergic ionotropic (P2X) receptors are involved in DO^[47-49]. This is not surprising taking into account that purinergic transmission has been found on both afferent and efferent signalling pathways within the lower urinary tract and appears to be abnormally enhanced

with aging^[50] and DO^[51]. In particular, P2X₃ receptors on sensory nerve terminals are involved in voiding dysfunctions of conscious chronic SCI rats, raising the possibility that P2X₃ receptor antagonists might be useful for the treatment of NDO^[46]. In human bladders with DO an increase in P2X₃ receptor expression was observed^[52].

The growing appreciation for the role of purinergic receptors in mediating nociceptive neurotransmission prompted the development of P2X receptor-selective antagonists as potential therapeutics for pain management^[53]. The novel P2X₃/P2X_{2/3} receptor antagonists possess attributes that offer the potential for optimization into candidate drug molecules not only for inflammatory and painful bladder conditions but also for OAB, in particular the recently developed RO3 compound (Roche Palo Alto) and the AF-742 (Afferent Pharmaceuticals), which is ongoing a phase II trial for bladder pain syndrome^[54]. Finally, P2X₃ antisense oligonucleotides and RNA interference-mediated treatment, that appear to be promising for neuropathic pain management, might open up new avenues for therapeutic OAB strategies^[55].

NEUROKININ RECEPTORS ANTAGONISTS

Substance P (SP) and neurokinin A (NKA) are neuropeptides with the highest affinity for NK1 and NK2 receptors, respectively. NK-receptors have been demonstrated in CNS regions involved in micturition control^[56]. Many experimental observations are available indicating that spinal and supraspinal NK1 and NK2 receptors may modulate the micturition reflex^[57-59].

Tachykinins are also released from urothelial/suburothelial capsaicin-sensitive afferents and are able to stimulate muscle tone and bladder contractions (NKA > NKB > SP), and to influence vascular tone and permeability ("neurogenic inflammation")^[60,61]. Intravenous NK1 and NK2 receptor selective antagonists reduced DO in rat with SCI^[61,62]. Perfusion of bladder with a NK1 receptor antagonist improved DO in rats with cyclophosphamide-induced cystitis^[48].

Mixed clinical results have been reported on some compound in this class. Aprepitant (Merck Sharp and Dohme Corp.) is a CNS-penetrating NK-1 antagonist used to treat chemotherapy-induced nausea. A pilot, proof-of-concept randomized controlled trial (RCT) including 125 post-menopausal women with urge or mixed (urge-predominant) incontinence reported satisfactory tolerability and efficacy of aprepitant over placebo in ameliorating OAB symptoms^[63]. Serlopitant (MK0594, Merck Sharp and Dohme Corp.) has been evaluated in a RCT and, although it significantly decreased the primary endpoint of daily micturitions, no advantages in efficacy have been found vs tolterodine^[64]. Netupitant (by Helsinn Healthcare) is another potent and selective NK1 receptor antagonist that failed to demonstrate superiority over placebo in a phase II trial^[65].

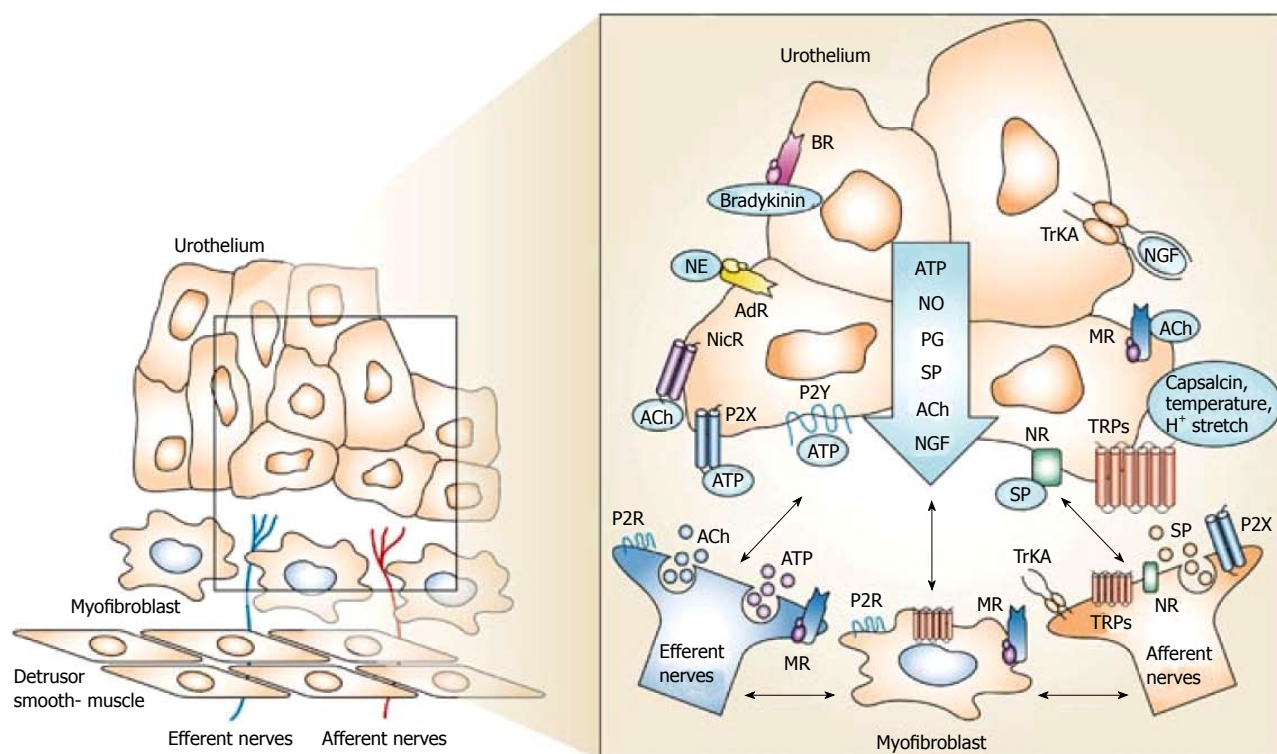


Figure 1 Hypothetical model that depicts possible interactions between bladder afferent and efferent nerves, urothelial cells, smooth muscle and myofibroblasts (interstitial cells). Stimulation of receptors and channels on urothelial cells can release mediators that target bladder nerves and other cell types; urothelial cells can also be targets for neurotransmitters released from nerves or other cell types. Urothelial cells can be activated by either autocrine (*i.e.*, autoregulation) or paracrine (release from nearby nerves or other cells) mechanisms (from Birder LA and de Groat WC^[67], with permission of Nature Publishing Group). ACh: Acetylcholine; AdR: Adrenergic receptor; BR: Bradykinin receptor; MR: Muscarinic receptor; NE: Norepinephrine; NGF: Nerve growth factor; NR: Neurokinin receptor; NicR: Nicotinic receptor; NO: Nitric oxide; P2R: Purinergic 2 receptor unidentified subtype; P2X and P2Y: Purinergic receptors; PG: Prostaglandin; SP: Substance P; Trk-A: Receptor tyrosine kinase A, high affinity receptor for nerve growth factor; TRPs: Transient receptor potential channels.

VANILLOIDS AND TRANSIENT RECEPTOR POTENTIAL VANILLOIDS-ANTAGONISTS

Several "Transient receptor potential" (TRP) neuroreceptors have been involved in nociception and mechanosensory transduction in various organ systems as well as in storage bladder function and DO, offering the possibility to target bladder dysfunctions at the level of sensory signal initiation (Figure 1)^[66].

"Transient receptor potential vanilloids 1" (TRPV1) is the principal transduction channel for nociception. TRPV1 is also found in myelinated A δ -fibres and sensory unmyelinated C-fibres located in the pelvic nerve afferents and in a sub/intraurothelial plexus; it is sensible to bladder filling, bladder contractions and noxious stimuli^[67]. TRPV1 is expressed also by the urothelial cells themselves^[67].

C-fibres are normally silent but have been found to become active and to convey signal to the spinal cord in pathological situation such as OAB, NDO and SCI, resulting in the bothersome sensation of urinary urgency^[68].

"Vanilloids" such as capsaicin are the best-known natural TRPV1 agonists and several trials showed that, given intravesically, they could cause a sustained activation of the TRPV1 receptor resulting in a desensitization of

C-fibers with beneficial effects in patients with neurogenic or idiopathic DO, but at the cost of nonnegligible side-effects^[69,70]. Resiniferatoxin is at least as effective as capsaicin, without the local side-effects although formal RCTs are needed to determine its appropriate use and dosage^[71,72].

Potent orally-available small-molecule TRPV1 antagonists are undergoing clinical trials for chronic pain, but the lack of bladder-selectivity and potential effects on thermoregulation may be serious barriers for the clinical development^[73,74]. XEN-D0501 (Provesica Ltd.) is a highly potent oral TRPV1 antagonist that was found to improve storage bladder function and reduce the intensity of capsaicin-induced bladder contractions in animal models; a phase I study reported a satisfactory tolerability and safety^[75]. XEN-D0501 is currently being assessed for efficacy in OAB in an international phase II dose-ranging trial. JTS-653 (Japan Tobacco), MCP-101 (Mt. Cook Pharma) and SAF312 (Novartis Pharmaceuticals)^[76], are other compounds in this class under investigation for the treatment of NDO.

Other TRP channels are expressed in the lower urinary tract (TRPV2, TRPV4, TRPM8, and TRPA1), and based on recent preclinical observations, TRPA1^[77,78] and TRPV4^[79-82] appear to have a critical role in bladder storage function and overactivity. Selective antagonists

for these ion channels are already available making the superfamily of TRP channels a very interesting class of potential targets for drugs aimed to treat LUTS/OAB/DO.

OPIOIDS

μ-opioid receptor-agonists

μ-opioid receptor (MOR) agonists are known for decades for their analgesic efficacy and excellent tolerability. Tramadol, an effective and safe analgesic, is a weak MOR-agonist, but its metabolites have a stronger MOR-agonist effect and also inhibit the reuptake of noradrenaline and 5-HT and elicit effects by indirectly activating serotonergic and α 2-adrenergic receptors^[83]. Promising clinical results in OAB patients were published on tramadol by Safarinejad *et al.*^[84] but the study has been retracted due to statistical errors. Singh *et al.*^[85] evaluated urodynamic effects of epidural tramadol in 15 subjects reporting that it increased bladder capacity and compliance and delayed filling sensations without affecting voiding phase, even for those with BOO.

Tramadol-like compounds with less incidence of nausea might have a treatment potential in patients with NDO and the development of novel MOR-agonists is ongoing. KN203 (KeyNeurotek Pharma) is the first compound of this class to be developed against OAB, and the results of a proof-of-concept study are expected to clarify its role in this clinical setting^[86].

δ-receptor agonists

A growing volume of information supports a role for the *δ*-receptor in the regulation of bladder activity^[87]. In contrast to *μ*-agonists, *δ*-receptor agonists present with lower toxicity and no addiction, their most crucial safety aspect being the incidence of seizure-like convulsions in rodents. MCP-202 is a compound in this class and in the development pipeline of Mt Cook Pharma for the treatment of OAB. A novel nonpeptide, orally bioavailable *δ*-receptor agonist (DPI-221) with satisfactory safety profile and high potency in extending micturition interval in mice has been recently developed^[88].

NOP RECEPTOR AGONISTS

Nociceptin or orphanin FQ (N/OFQ) is the endogenous ligand of opioid-like receptor-4 (or NOP receptor)^[89]. N/OFQ has a variety of effects both in the CNS and peripherally and there is evidence suggesting that N/OFQ inhibits the micturition reflex in rats by acting on the afferent bladder signalling and on supraspinal micturition sites^[60,90], although a peripheral excitatory effect was also detected^[90].

Lazzeri *et al.*^[91] reported that N/OFQ given intravesically was able to elicit an acute inhibitory effect on voiding reflex in 9 patients with NDO but not in 5 normal subjects. A RCT by the same authors including 14 NDO patients found that N/OFQ, but not placebo, increased significantly bladder capacity and reflex volume^[92] and

the results were replicated in a multicenter study^[93]. Further investigations are required in order to establish if available selective NOP receptor agonists may become a new pharmacological way of treatment of NDO.

CANNABINOID

The Cannabis Sativa (marijuana) plant contains a group of biologically active substances, termed cannabinoids (CBs). The endocannabinoid system comprises the cannabinoid receptors (CB₁ and CB₂), their endogenous ("endocannabinoids") and exogenous ("exocannabinoids", such as plant-derived and synthetic cannabinoids) ligands, and related enzymes for biosynthesis and degradation, such as fatty acid amide hydrolase (FAAH)^[94]. Recently, an orphan human G-protein coupled receptor, GPR55, was claimed to be a novel cannabinoid receptor^[95].

These components have been located to animal and human lower urinary tract tissues (detrusor, bladder afferent nerves, and, particularly, urothelium) and have been involved in regulation of bladder function and bladder inflammation^[94,96-100]. Intravesical, intrathecal and systemic administered CB-agonists are reported to inhibit bladder afferent signalling in animal models of bladder inflammation and improve urodynamics parameters in naive and DO animals models^[98,101-103]. Plasticity of the endocannabinoid system in the spinal cord has been reported in rats with BOO-induced DO^[104].

In patients with MS, cannabis extracts and delta-9-tetrahydrocannabinol (THC) were found to reduce OAB symptoms in open-label^[105] and randomized trials^[106], respectively. Nabiximols (Sativex, GW Pharmaceuticals), a standardised mixture of compounds (mainly THC and cannabidiol) derived from Cannabis plants, failed to achieve primary endpoint (incontinence episodes) in a RCT including MS patients with OAB, however significantly improved other OAB symptoms (*e.g.*, voids per 24 h, nocturia, and bladder symptom severity)^[107].

Neurological side-effects of CB₁-agonists, together with the unknown consequences of long-term use of such drugs, generated concern about their safety^[108]. However, the intravesical administration of CB-agonists, the possible exploitation of CB₂ (mainly peripheral) receptors and the inhibition of the FAAH by systemic, intravesical or intrathecal-administered inhibitors may be alternative approaches to target the endocannabinoid system averting CNS side-effects^[94,97,104,109,110].

ANTIANDROGENS

Gonadotropin releasing hormone receptor (GnRH-R) antagonists have been reported to have beneficial effects on LUTS in patients with benign prostatic hyperplasia (BPH)^[111], although they are considered still investigational in this setting, especially in light of the disappointing results of a phase III RCT on cetrorelix^[112].

Treatment with subcutaneous degarelix (Ferring), a long-acting GnRH-R antagonist, improved experimental

DO in rats and also promoted more efficient bladder emptying; isolated detrusor from degarelix-treated rats responded with larger carbachol-contractions than controls^[113]. Another compound in this class, ganirelix, given systemically counteracted experimental DO in rats^[114]. Interestingly, intravesical ganirelix and degarelix improved urodynamic parameters in rats^[113,114]. Based on these results and since the GnRH-R is expressed in the rat bladder^[113], a local intravesical administration of this class of drugs may be considered.

PHOSPHODIESTERASE INHIBITORS

Phosphodiesterases (PDE) are enzymes that degrading cyclic nucleotides (cAMP and cGMP), can counteract the detrusor relaxation^[115]. Among eleven PDE isoforms so far identified, PDE1-5 are described in the bladder and preclinical studies showed that PDE inhibitors (PDE-Is) are able to reverse the cholinergic-induced contraction of human detrusor and to enhance cAMP/cGMP-mediated detrusor relaxation^[116]. Selective inhibitors of the different PDE types have been showed to can counteract DO^[117].

Although a pilot study suggested a possible role for vinpocetine, a PDE1-inhibitor, in the treatment of refractory OAB^[118], in a multicentre, placebo-controlled RCT in patients with DO, vinpocetine showed a statistically significant superiority over placebo for only one parameter^[115].

Rolipram, a PDE4-I, has been showed to inhibit phasic myogenic contractile activity of human detrusor^[119]. Other PDE4-I have been showed to reduced DO in rats with BOO, without affecting the voiding phase, suggesting that PDE4-Is might represent an alternative strategy for the treatment of the OAB^[120,121].

A PDE9-I (ASP4901) is also under evaluation in a phase II trial by Astellas Pharma enrolling male patients with BPH^[122].

Sildenafil, a PDE5-I, reversed the tonic cholinergic-induced contraction of human detrusor smooth muscle and produced relaxation *via* activation of cGMP- and cAMP-dependent pathways, K⁺ channels and the hydrogen sulfide [H(2)S] signaling pathway^[123,124]. A series of RCTs provided substantive evidence of the efficacy and tolerability of PDE5-Is (sildenafil, tadalafil, vardenafil, and United Kingdom-369003) for the treatment of LUTS in male patients with or without erectile dysfunction, confirmed by meta-analyses^[125,126]. Tadalafil received the FDA approval in October 2011 for the treatment of males with LUTS secondary to BPH or concurrent LUTS and ED.

PDE-Is require further evaluations in order to better define their mechanism and site of action in lower urinary tract, their role and optimal dosage in different group of patients and in women, long-term safety and efficacy and cost-effectiveness.

NITRIC OXIDE-DONOR DRUGS

Nitric oxide (NO) is a potent biological messenger that

promotes detrusor relaxation, likely *via* the elevation of intracellular cGMP.

HCT-1026 (nitroflurbiprofen, by NicOx SA) is a NO-releasing derivative of the nonsteroidal anti-inflammatory drugs (NSAID) flurbiprofen^[127]. Nitroflurbiprofen combines the anti-inflammatory activity of flurbiprofen with the smooth muscle relaxant activity of the NO moiety and promising preclinical (internal report of NicOx SA) and phase II clinical efficacy results have been announced in the treatment of NDO patients and women with OAB, providing a rationale for phase III trials^[128,129].

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Several lines of evidence suggest an important role of prostaglandins (PGs) in the modulation of the bladder function^[130]. PGF2 α , PGE1, and PGE2 slowly contract isolated animal and human detrusor and a role of PGs in the maintenance of detrusor tone and in the modulation of efferent and afferent neurotransmission has been suggested^[131]. Release of PGE₂, which acts *via* mainly EP receptors, is elevated in DO due to SCI^[132] or to BOO^[133,134]. The intravesical instillation of PGE₂ also induces DO, urgency and decreases bladder capacity in humans^[135].

PGs are locally synthesized in human bladder by constitutive (COX-1) and inducible (COX-2) cyclooxygenase^[130]. Several factors including stretch, nerve stimulation, injury, exposure to ATP and other inflammatory mediators may induce the synthesis of PGs^[131].

COX-inhibitors such as NSAID were found to be able to increase bladder capacity and prolong micturition interval without affecting voiding phase in rats, and favorable clinical effects have been reported in OAB patients treated with aspirin, indometacin, flurbiprofen, ketoprofen and loxoprofen^[136,137]. Other preclinical findings have also indicated COX-2-selective inhibitors as potential drugs aimed to treat OAB, also by intravesical instillation^[138,139]. It seems that NSAIDs might open a novel treatment opportunity for OAB although clinical evidence of efficacy of COX-inhibitors in OAB patients remains scarce and side-effects are important issues with these drugs^[140].

PROSTAGLANDIN RECEPTOR ANTAGONISTS

The use of selective antagonists of PG receptor subtypes has been explored as a possible way to treat OAB. EP₁ and EP₂ PGs receptors have been demonstrated in the mucosal bladder network where they may trigger DO by eliciting bladder afferent activity during inflammation (possibly through TRPV1) and likely through the activation of interstitial cells^[141,133]. There are data showing that EP₃ receptors also participate in PGE₂-induced DO^[142].

Encouraging observations reported with novel EP₁

antagonist compound (e.g., ONO-8539) in animal models^[134] prompted their evaluation in a clinical proof-of-concept trial with disappointing results^[143], thus reducing the likelihood of an oncoming introduction of EP₁ receptor antagonists in the clinical management of OAB.

DRUGS ACTING ON RHO-KINASE PATHWAY

Rho-kinase inhibitors

The Ras homologue family member A (RhoA) is a guanosine triphosphate hydrolase (GTPase) that, together with one of its downstream effectors, the type I and type II Rho-kinase (ROCK), have been shown to play an important role in calcium-independent pathway of smooth muscle contraction (the so-called "calcium-sensitization") both in animal and human bladder^[144-147]. The upregulation of RhoA pathway has been implicated in cystopathy associated to diabetes, BOO and DO^[148].

Nonclinical *in vitro* studies showed that Y-27632 and HA-1077 (fasudil), ROCK1 and ROCK 2 inhibitors, respectively, significantly blocked carbachol-induced contractions and caused concentration-dependent relaxation of human detrusor strips^[146]. It has been showed in pig urinary bladder tissues that this effect involved both urothelium-dependent and independent pathways^[149].

Inhibition of Rho-kinase activity with Y-27632 produced a significant suppression of DO in spontaneously hypertensive rats (SHR) that also showed significantly higher RhoA protein expression in bladder tissues^[150]. Treatment with oral fasudil partly but significantly ameliorated the development of DO in a rat model of BOO^[151].

ROCK inhibitors may be a new pharmacological approach to treat OAB/DO if novel bladder-selective ROCK-inhibitors will be discovered in order to overcome the hypotensive side-effects of nonselective compounds.

Vitamin D3 receptor agonists

Vitamin D3 receptor (VDR) is expressed in prostate and bladder tissues and BKL-628 (elocalcitol, BioXell), an agonist of vitamin D3-receptors, entered the pipeline for the therapy of BPH^[152,153]. Elocalcitol is able to counteract the RhoA/ROCK pathway in the prostate and in both rat bladder strips and human bladder cells^[154]. Elocalcitol appears to modulate bladder contractility by decreasing calcium sensitization and increasing L-type-mediated calcium entry^[154,155]. The oral treatment with elocalcitol suppressed DO in two animal models of OAB and exerted strong suppressive effect on urinary bladder sensory signaling during filling in mice^[156]. Encouraging results of a proof-of-concept clinical study prompted a phase IIb RCT including 308 OAB women^[157]. The primary endpoint was not met but a favourable efficacy/tolerability profile and the statistically significant

improvement of relevant secondary endpoints in the elocalcitol group vs placebo make this compound worthy of future reappraisal.

NERVE GROWTH FACTOR BLOCKADE

It has been suggested that selective inhibitors of nerve growth factor (NGF) may be a new way to treat OAB^[158]. Several findings corroborate this hypothesis: urinary NGF levels decreased after successful treatment of OAB with antimuscarinics or BoNT^[159,160]; NGF overexpression in the bladder and bladder afferent pathways has been reported to be involved in the emergence of hyperexcitability in bladder C-fiber sensory pathways^[161]; the intrathecal administration of NGF antibodies decreased NGF levels in bladder afferent pathways and normalized bladder/urethral function in SCI rats^[162].

There is nonclinical evidence that the local instillation of antisense oligonucleotides against the NGF, suppresses DO and the expression of NGF and chemokines^[163]. In particular, the intravesical liposome-delivered antisense NGF-suppressing therapy could be an attractive approach for OAB, avoiding the toxicity of systemic nonspecific blockade^[163].

DRUGS ACTING ON ION CHANNELS

Potassium channels openers

Potassium channel opening drugs (KCOs) cause hyperpolarization and reduction in intracellular calcium concentration, promoting detrusor relaxation^[164,165]. Furthermore, these agents may inhibit overactive bladder afferent pathways or influence the release of various urothelial mediators^[166].

Many types of potassium channels have been demonstrated in the detrusor smooth muscle^[167]: (1) big, intermediate and small calcium-activated channels (BK or maxi-K, IK and SK, respectively); (2) voltage-dependent (K_v) channels; (3) inward-rectifying ATP-dependent channels (K_{ATP}, also known as K_{ir}6 channels, a subtype of the K_{ir} channels family); and (4) two-pore-domain (K_{2P}) channels (also known as "leak potassium channels").

BK channels (also called Maxi-K or slo1) have been extensively studied in animal and human detrusor smooth muscle and are arguably the most important physiologically relevant potassium channels regulating detrusor muscle cells action potential, resting membrane potential, and contractility^[168-170]. Convincing data suggest that BK channels are also involved in mediating the relaxing effects of β₃-ARs stimulation^[171]. An important role of BK channels has been also advocated in etiopathogenesis of DO based on experimental *in vitro* observations in animal and human bladder tissues^[170-173].

The role of K_v channels in normal and pathological detrusor activity remains controversial and largely unexplored^[174]. A reduction in potassium currents through K_v channels has been involved in the hyperexcitability of the afferent neurons^[175,176]. The structural diversity

and the variety of the K_v channels may allow for the identification of bladder-specific channels paving the way for the development of bladder-selective agent and genetic therapies for OAB^[167,177].

Promising preclinical data from both *in vitro* and *in vivo* studies have been published supporting the possibility to restore normal detrusor function with openers of BK channel^[168,178] and A-type K_v channel^[179,180]. Although their role is still debated, interesting preclinical observations are also available on openers of K_{ATP} channel^[181-184], SK channel^[185,186], combined SK/IK channel^[187] and putative TREK-1 K_{2P} channel^[188].

Unfortunately, clinical trials with some of these drugs (e.g., ELB245 and ZD0947) were disappointing because of failure to demonstrate superiority vs placebo for the treatment of OAB^[189], or because of side-effects leading to early termination^[190]. Nevertheless, there is an ongoing effort to develop new classes of more potent and selective KCOs that may lead to the development of bladder-selective agent in the future.

Sodium channels blockers

Tetrodotoxin-resistant sodium channels (Nav1.8 subtype) are expressed in primary afferent capsaicin-responsive neurons innervating the bladder and their blockade by antisense oligodeoxy-nucleotide reduced the frequent voiding evoked by acetic acid-induced irritation of the bladder^[191]. Ralfinamide (NW-1029) is a sodium channel blocker that suppresses tetrodotoxin-resistant sodium currents in C-type dorsal root ganglia neurons^[192]. *Via* selective inhibition of capsaicin-responsive nociceptive neurons expressing tetrodotoxin-resistant sodium channels, ralfinamide is thought to elicit anti-nociceptive effects in animal models of inflammatory and neuropathic pain, as well as beneficial effects in DO^[193].

Mechanosensitive ion channels, such as degenerin family/epithelial, amiloride-sensitive, sodium channel (ENaC) and TRP channel superfamily, have been recently demonstrated to play key roles in the mechanosensory signalling of the urinary bladder^[194]. Acid-sensing (voltage-insensitive) cation channels (ASIC) are a subgroup of neuronal ENaC channels highly expressed also in the urothelium and suburothelial nerve plexus^[195]. An increase in intrabladder pressure or upregulation of these channels may trigger afferent signalling during bladder filling^[196]. ASIC channels seem involved in nociception in various pathological conditions including human bladder inflammation^[197,198]. Consequently, ENaC/ASIC ion channels may become novel targets for the pharmacological treatment of inflammatory and overactive bladder conditions^[194].

CONCLUSION

The complex neurophysiological control of the micturition reflex at both central and peripheral level, and the emerging recognition of the role of the different cell types involved in bladder physiopathology, prompted the

development of many lines of research mostly aimed to the discovery of new pharmacological principles using receptor ligands as starting point. However, it appears that very few candidate agents, discovered starting from ligands-like compounds have passed the proof-of-concept stage in patient-oriented studies.

The pharmacological manipulation of central micturition circuitry is supported by the growing evidence on the central origin of OAB, although side-effects limit the use of currently available neuropharmacological agents and clinical results with selective antiserotonergic are disappointing. It emerges a growing appreciation at preclinical level for the role of purinergic receptors as new targets for the treatment of OAB. Although the first clinical data are disappointing, NK-1 antagonists have attracted the interest of several companies and proof-of-concept studies are ongoing evaluating other compounds in this pharmacological class. Proof-of-concepts data are awaited also on novel opioids receptors agonists. Based on the recent evidence on the key role of the mucosal bladder network in the regulation of bladder function, many novel pharmacological principles targeting urothelium and afferent nerve fibers are under development. Although unsatisfactory clinical results have been reported with compounds based on this strategy (PG receptor antagonists, KCOs, elocalcitol), many other investigational agents show promise such as TRPV1-antagonists, modulators of endocannabinoid system, COX-2 inhibitors, ENaC/ASIC ion channels modulators. Intravesical strategies using N/OFQ, GnRH-R antagonist and liposome-delivered targeting NGF also deserve future investigations. Another strategy that seems encouraging is based on the modulation of second messengers by using PDE and ROCK inhibitors, and NO-donor drugs. Although the exciting expectations rose from gene therapy still need to be realized, the advances in this field are promising also in the clinical setting of OAB.

It is likely that the future will provides the clinicians with a variety of drugs, with distinctive mechanism of actions, to be used in combination or sequentially, and in groups of patients with different clinical phenotypes.

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Effect of the maternal-fetal interface immunoregulation on the occurrence of intrahepatic cholestasis of pregnancy

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of pregnancy (ICP). However, the precise etiology and mechanism of immune imbalance in the occurrence of ICP is still unknown. In order to clarify the potential immunologic mechanisms of ICP, this review summarizes the recent studies of the decidual immunology micro-environment and the potential immunologic mechanisms related to the development of ICP.

Key words: Intrahepatic cholestasis of pregnancy; Decidual lymphocytes; Trophoblast; Human lymphocyte antigen-G

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Core tip: In this paper, we reviewed the recent publications regarding the role of immunological interactions at the maternal-fetal interface on the occurrence of intrahepatic cholestasis. The literature shows that the decidual immunological microenvironment may relate to the development of intrahepatic cholestasis of pregnancy. Any approach that modulates immune tolerance at the maternal-fetal interface toward the natural state could provide insight in the treatment of intrahepatic cholestasis of pregnancy.

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Abstract

Maternal immune tolerance of the fetus is indispensable for a healthy pregnancy. Currently, the study of the immune microenvironment of the maternal-fetal interface has been a heated topic in reproductive immunology research. More and more studies show that the immune imbalance in the maternal-fetal interface plays a very important role in the incidence of intrahepatic cholestasis

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a metabolic disease occurring in the second and third trimester. Experiments show that bile acids have

cytotoxic effects, leading to apoptosis and necrosis *in vivo*. Exposure to high blood bile acids in pregnancy can cause damage to the fetal heart, liver, lungs and other organs^[1]. In addition, bile acids can increase the expression of oxytocin receptors in the uterine muscle fibers increasing sensitivity to oxytocin^[2]. These factors can lead to vasospasm and hypoxia at the surface of the placenta and increased vascular permeability^[3]. Thus ICP is an important risk factor for perinatal morbidity and mortality^[4]. The etiology and pathogenesis of ICP is not clear. It may be related to the mutation of genes such as *MDR3*, *BSEP*, *ATP8B1*^[5-7], imbalance of estrogen and progesterone^[8], or thyroid hormones^[9]. These changes may cause metabolism disorders. When this happens in the liver, the Na⁺-K⁺-ATP activity and the biliary bile salt transportation function may decrease, inducing intrahepatic cholestasis. Over the past decade, the relationship of placental immunological changes has been found to be increasingly related to the development of ICP^[10]. The embryo, as an alloantigen with paternal ingredients, is essentially an allogeneic allograft to the uterus. The maternal immune system identifies the fetus as an allograft, gradually establishing a balance of tolerance between the maternal and fetal components of the pregnancy.

Once this balance is disrupted, the maternal-fetal interface's unique dynamics in the local immune microenvironment cannot be maintained, resulting in direct placental trophoblast and decidual cell damage, while a number of inflammatory cytokines are released into the peripheral blood, resulting in changes of the immune microenvironment in liver tissue, inducing cholestasis.

Maternal-fetal immune regulation is a core issue of reproductive immunology. How the maternal-fetal immune interaction influences ICP has plagued scientists. Maternal-fetal interface immune regulation during pregnancy in ICP has been a hot research topic in recent years. A systemic review on the correlation between the etiology and pathology of the maternal fetal interface immunity will help to clarify the immunological mechanisms of ICP and promote and improve the diagnosis, treatment, and understanding of ICP.

RESEARCH ADVANCES ON IMMUNE TOLERANCE BETWEEN THE MATERNAL-FETAL INTERFACE

The maternal-fetal interface is a direct maternal and fetal tissue contact surface, which consists of a large number of immune cells, decidual cells and fetal trophoblast cells. Nevertheless, the number of immune cells, surface antigens, and the effect on receptors in the maternal-fetal interface are very different compared to other organs. Such immune conditions in the maternal-fetal interface protect the placenta as an immune privileged organ. This kind of immune tolerance occurs

in the interaction between decidual cells and trophoblast cells.

In general, the immune tolerance embodied in the maternal-fetal interface consists of cellular and humoral immune tolerance. Maternal decidual immune cells include NK cells and T lymphocytes. Studies demonstrate that more than 80% of the maternal-fetal interface lymphocytes are NK cells and the decidual NK cells are mainly CD⁵⁶⁺, which secrete cytokines and growth factors to induce local immunosuppression and help embryo development^[11]. It is reported that the type of T lymphocytes in pregnancy also shows a decreased CD⁴⁺/CD⁸⁺ ratio, as well as a helper T cell (Th)1-Th2 shift phenomenon^[12]. Th1 secrete interleukin (IL)-2, IL-12, interferon (IFN)- γ and tumor necrosis factor (TNF)- β/α mediated cytotoxic response; Th2 secrete IL-4, IL-5, IL-6 and IL-10, inducing a humoral immune response, and stimulation of B lymphocytes produces antibodies^[13]. Studies have shown a shift in the balance of cytokine profiles away from Th1 type reaction to Th2 type reaction in ICP. It disrupts the immune tolerance balance between mother and fetus^[10,14]. Th3 secrete transforming growth factor β 1 (TGF- β 1) which has a strong immunosuppressive effect on cytotoxic T cells, natural killer cells, T cells and natural killer T cells^[15]. It is well established that the fetal trophoblast does not express classical human lymphocyte antigen (HLA)-A and HLA-B which can be identified by maternal decidual T lymphocytes, but has a high expression of non-classical HLA-G and HLA-E, and HLA-I like proteins^[16,17]. Thus, damage to the fetus from NK cells and T lymphocytes of the mother is prevented.

Kovats *et al.*^[18] found that maternal expression of leukemia inhibitory factor (LIF) begins early in pregnancy. LIF can selectively induce HLA-G expression in the maternal-fetal interface on the outer membrane of the chorionic trophoblast cells^[18]. CD8⁺ and CD4⁺ T cells interact with HLA-G in trophoblast cells to activate the Fas/FasL signaling pathway, inducing CD8⁺ T cell apoptosis, and inhibiting the proliferation of CD4⁺ T-positive cells. This may be the reason why T cells in the decidua are far less numerous than in the outer periphery circulation^[19]. Bainbridge proved that the leading strand of HLA-G can strongly induce the expression of HLA-E in the outer chorionic trophoblasts^[20]. And the decidual NK cells expression of CD94/NKG2A receptors is 5 fold that of the periphery circulation^[21]. Carretero found that the CD94/NKG2A receptor and HLA-E binding by SHP-1 molecules recruits the intracellular delivery of immune inhibitory signals. At the same time, it is found that the HLA-G is the ligand for the expression of the KIR 2DL4 and ILT2 receptors in NK cells in the decidual membrane. Their interaction could inhibit the activity of NK cells^[19]. Thus, trophoblast cells are immune to injury by the expression of non-MHC-I receptors to inhibit antigens from NK cells. In addition, HLA-G and HLA-E could inhibit the killing effect of macrophages and T cells on the decidual membrane^[22].

Humoral immune tolerance at the maternal fetal interface is effected through blocking antibody (BA) IgG and its subclasses. BA are produced idiotypically of anti-anti-HLA antibodies which are reactive with the fetal half of the self HLA antigens^[23]. It can bind the epitope surface antigen of the trophoblast to avoid the maternal killer T cell recognition, allowing the fetus to escape the maternal immune response^[24]. Studies show that the HLA-G antigen can stimulate maternal BA production. Furthermore, placental BA concentration is 3 fold that of the maternal symmetric antibody concentration. Th2 factor IL-6 can regulate the production of blocking antibodies through glycosylation^[25].

IMMUNE TOLERANCE DISORDER AND THE PATHOGENESIS OF ICP

In recent years, the study of immune pathogenesis in ICP has become a popular research area. More and more research shows that the dynamic imbalance of the maternal fetal interface is closely related to immune tolerance in ICP^[26]. Patients with ICP usually demonstrate changes in humoral and cellular immune tolerance associated with antigens, receptors and cytokines, and these changes are not only reflected in the maternal fetal interface but also in maternal peripheral blood.

Studies have shown that the level of IgG in the serum of pregnant women with ICP is significantly decreased, but IgM, IgA and C3, C4 show no significant changes. This suggests that decreased IgG blocking antibody leads to a weakened immune protection effect and failure of maternal fetal immune tolerance.

Cellular immune microenvironment changes in ICP

Studies have shown that TNF- α concentration is higher in peripheral blood of women with ICP than in pregnant women without ICP. It is also confirmed that a decreased TGF- β 1 in ICP placental tissue can promote secretion of TNF α and IL-1. The expression of TNF- α and IL-1 are increased in placental tissue in patients with ICP, which promote the secretion of TGF-1^[27]. Recent studies have found that TNF- α increase significantly in serum of ICP patients. The increase of TNF- α is positively related to the severity of ICP, which demonstrates that TNF- α may be involved in the occurrence of ICP^[28]. Prior to these findings, it was found that an increasing IFN- γ expression in placental tissue from ICP patients as well as TNF- α was related to the occurrence of ICP^[29,30]. Increases of IFN- γ and IL-4 may play an important role in the pathogenesis of ICP^[31]. These results suggest that ICP generally shows an increased Th1 type cytokine phenomenon, leading to a increase of the Th1-Th2 ratio demonstrating pathological changes of cell immune imbalance^[32].

Immune cellular surface antigen changes in ICP

Changes of Th2-Th1 cells in the maternal fetal interface are likely to represent the cellular immune reaction

activity of the maternal-fetal interface. The changes of the cellular immune surface antigen of the maternal fetal interface in ICP have received much research attention. A decrease in CD8⁺ cells and an increase in CD4⁺ cells in ICP patients lead to an increase of CD4/CD8 ratio. Meanwhile, it is also found that NK cells decrease significantly^[14,33]. In recent studies, it is found that leukocyte CD3 antigen, CD4/CD8 ratio, and Th1 were all elevated in the ICP group compared to the control group, while CD8 and Th2 were lower in the ICP group than in the control group. Women with ICP have abnormal expression of T cells and helper T cells in peripheral blood^[26,34].

The results from these studies demonstrate that the surface antigen on Th2 cells and NK cells have enhanced cellular immune function, and promote the Th1/Th2 type cytokine balance *via* Th1. The lack of such balance may be a cause of the liver cell damage noted to be present in ICP.

Trophoblast cell surface antigen and decidual cell receptor changes in ICP

Immune tolerance in pregnancy begins as immune recognition of decidual cells and trophoblast cells. High expression of specific inhibitory ligands on trophoblast cells and specific inhibitory receptors of NK cells in decidua are important factors of immune tolerance. Changes in the expression of trophoblast cell surface antigens and decidual cell receptors inevitably lead to immune dysfunction, which may cause ICP. Peng *et al*^[21] found that decreased expression of HLA-G and HLA-E protein in trophoblast cells are related to ICP. It may be one of the important mechanisms involved in pregnancy immune tolerance imbalance disorders^[21]. Dexamethasone increases expression of HLA-G and HLA-E, which may be the critical pharmacological mechanism in the treatment of ICP. Other studies found increased Th1 and decreased HLA-2G in placental tissues from ICP patients, which demonstrate that changes of surface antigens on trophoblast cells may be another cause of ICP^[29]. In a different study, downward expression of VEGF receptors was found in syncytiotrophoblast, cytotrophoblast, placental vascular endothelial cells and villi in ICP placentas but it is not clear which is the cause and which is the effect^[35].

IMMUNE ETIOLOGY STUDIES ON ICP

Genetic factors influence immune balance of ICP

Genetic factors in the pathogenesis of ICP have been studied for several decades. Many studies have shown that ICP may be the result of multiple factors including a well recognized genetic predispositions^[36-39]. That some liver cell secretory transport genes act as genetic factors in the pathogenesis of ICP has been confirmed, but the relationship between immunologically related genes and ICP is not clear. Some scholars believe that the HLA- II antigen promotes the production of blocking antibody. The compatibility is high when the mother and fetus have similar HLA- II antigen expression. The

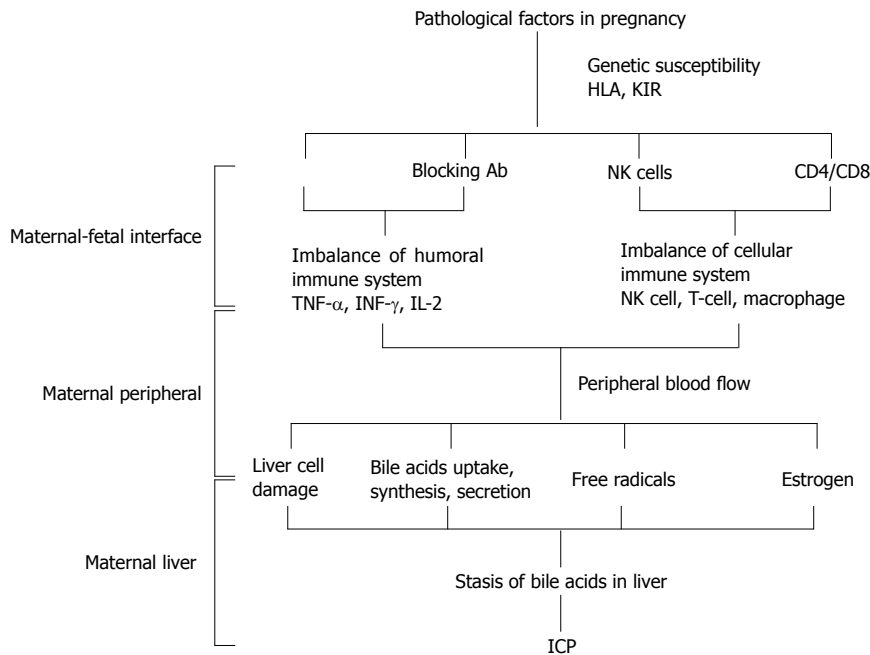


Figure 1 Pathogenesis of intrahepatic cholestasis of pregnancy caused by immune intolerance. ICP: Intrahepatic cholestasis of pregnancy; KIR: Killer cell immunoglobulin-like receptor; IFN: Interferon; IL: Interleukin; TNF: Tumor necrosis factor; HLA: Human lymphocyte antigen.

higher the compatibility of the maternal fetal HLA- II antigen, the less the immune response. The strength of the maternal immune system response to paternal antigens of the fetus correlates to the susceptibility of the onset of ICP^[40]. Nowak pointed out that women with activation of killer cell immunoglobulin-like receptor (KIR) gene and the KIR inhibitory receptor gene ratio between 0.33-0.83 were prone to have spontaneous abortion while women with a ratio between 0.86-1.25 tend to have a NK cell protective effect, suggesting that the KIR genotypes most likely associate with pathologic pregnancies, such as spontaneous abortion^[30,41]. Guimond found that women with missing T cells may have a normal pregnancy but those missing NK cells exhibit pathological changes of pregnancy. He believes these results demonstrate that NK cell immune activity not only has potential immune protective effects, but also is the main cellular immune recognition mediated by the maternal fetal interface^[31,42]. These prompted explanation of immune genetic factors in the pathogenesis of ICP, including the ligand NK cell surface antigen, receptor, and their interaction in trophoblast cells. Unfortunately the genetic mechanism for the pathogenesis of ICP in immune gene is still not clear.

Pathogenesis factors disrupt immune tolerance during pregnancy

Without a doubt, research results have clarified our understanding of the changes in immune cell activation and other immune factors in ICP. But factors disrupting the balance of immune tolerance in the maternal fetal interface is not clear. The study of immune tolerance disorders has received little attention. Excluding genetic susceptibility factors, it is not difficult to understand why

some factors which cause strong immune responses likely to be associated with ICP. In addition, maternal factors such as nerve - endocrine interactions also affect the decidual immune microenvironment. Social and psychological stress may cause an increase of proinflammatory cytokines. Stress during pregnancy causes changes of IL-6 and IL-10 levels^[43,44]. Even though IL-6 and IL-10 level are associated with ICP^[45], further studies are necessary to clarify whether prenatal stress may be part of the pathogenesis of ICP.

TO INVESTIGATE THE IMMUNE IMBALANCE AS A MECHANISM OF ICP

Is immune dysfunction the cause of ICP or the result? If the immune imbalance is the result of ICP, then what is the pathogenesis? Previous studies of immunologic changes in ICP seem unable to determine immune dysfunction and ICP causality. It is difficult to carry out research on the causality of ICP because changes in immune regulation cannot be monitored before the onset of the maternal-fetal interface to clarify the immune changes with the onset of ICP. However, we still have some evidence to support that immune regulation disorders can cause the occurrence of ICP. Peng found that dexamethasone can treat ICP and up-regulate HLA-G and HLA-E, which suggests that the expression of surface antigen on trophoblast in ICP can be effectively influenced. This supports the notion that immune imbalance is more likely the initiating factor of ICP^[46].

In addition, the up-regulation of Th1 type cytokines such as IL-2, IL-12, IFN- γ , and TNF- α/β and their

release into the maternal circulation can generate liver injury and induce ICP. Interaction of TNF- α and IL-2 can promote NK cell change into cytotoxic LAK cells, resulting in damage to liver cells. TNF can also activate neutrophils, promote their aggregation in the liver and prompt degranulation, releasing proteases and oxygen free radicals, causing liver cell damage^[27,47]. In addition, TNF- α can promote the uptake, synthesis, and secretion of bile acids in liver cells resulting in cholestasis^[45,48]. Furthermore, TNF- α increases the synthesis and secretion of placental estrogen, which is associated with ICP^[49].

In conclusion, immune pathogenesis leading to ICP might including the following: In the genetically susceptible population, pathogenic factors promote changes in gene expression of trophoblast leukocyte antigen and receptors on decidual NK cells, which lead to an unbalance of blocking antibody and cytokine pathways. Then the cellular immune system activates and secretes Th1 cytokines into the maternal circulation causing damage to the liver cells, resulting in ICP (Figure 1).

Thus, these pathological changes contribute to an increased fetal morbidity due to maternal changes, mediated (at least in part) by disruption of the maternal-fetal immune balance. Because of the etiological factor and the pathogenesis of ICP, there is currently no effective clinical standard to prevent and cure ICP. Any approach that modulates the immune tolerance of the maternal-fetal interface toward the natural state could provide insight in the understanding of ICP, which could lead to a targeted treatment.

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Mental health of perinatal women

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Abstract

Pregnancy and childbirth are major stressors for some women. They can be followed by deterioration in mental health status and cause mental illnesses during perinatal period. Undetected and untreated perinatal mental illnesses can have negative unexpected impacts on parenting skills of the women and children's development. Mentally ill mothers may not effectively attend their children's needs in a timely manner and may experience an unfavourable mother-child attachment affecting the child's language, social, emotional and cognitive development. The rate of pregnancy and postnatal health complications and interventions is

higher among mentally ill women with some certain risk factors. The mentally ill mothers along with their partners need comprehensive support and counselling to be able to care for their infants and establish strong parent-child bond and attachment. Mental health campaigns across the world have endeavoured to increase the knowledge and awareness of the public towards perinatal mental health illnesses. To this aim, a routine screening is recommended in order to identify the women who are at risk of mood or anxiety disorder during perinatal period. The development of knowledge on perinatal mental illnesses among public and the health professionals has resulted in timely recognition and treatment of perinatal mental illnesses. Although great volumes of research show high prevalence of perinatal mental illnesses and their impacts on parenting confidence and competence as well as child's developmental process, there is still lack of research on various aspects of perinatal mental illnesses. To enable early prevention, diagnosis and intervention, it is crucial to identify families who are at an increased risk of perinatal mental illnesses and provide support and intervention to minimise the adverse outcomes. The children's needs may not be met by providing treatment to parental mental illnesses alone. It is also important to understand the impact of specific parenting behaviours on child outcomes which is modified by the quality of parenting.

Key words: Perinatal mental illness; Depression; Anxiety; Pregnancy; Childbirth

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Core tip: Pregnancy and childbirth are major stressors for some women. Undetected and untreated perinatal mental illnesses can have negative unexpected impacts on parenting skills of the women and children's development. Mentally ill mothers may experience an unfavourable mother-child attachment. Perinatal mental illness affects the child's language, social, emotional and cognitive development.

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INTRODUCTION

Pregnancy and childbirth are expected to be blessing times in women's life, when physiological and psychological changes prepare the women for motherhood tasks. Pregnancy and childbirth are, however, perceived as major stressors for some women as they struggle with self-depreciation and undermining of self-esteem followed by feeling incapable of caring for the newborn. These negative feelings are followed by deterioration in mental health status and can cause mental illnesses during perinatal period^[1].

Perinatal mental illnesses are described as "psychiatric disorders that are prevalent during pregnancy and as long as 1 year after delivery"^[2]. Various types of perinatal mental illnesses have been reported in the literature including postpartum blues, perinatal depression, postpartum anxiety disorders and postpartum psychosis (bipolar disorders)^[2].

Perinatal mental illness has been identified as one of the most important issues in women's health. Perinatal mental illnesses negatively affect women's interpersonal relationship and quality of life and have direct and indirect negative impacts on short-term and long-term physical and mental health of their children. The greater concern is for those women who abstain to disclose their mental health problems due to fears of stigma, losing parental rights and being judged as incompetent and unqualified parents. Some women also discontinue their psychiatric medications during pregnancy and lactation due to concerns regarding the baby's well-being^[3], which can result in an increased risk of suicidal thoughts or attempts at self harm^[4-6].

PREVALENCE AND RISK FACTORS OF PERINATAL MENTAL ILLNESSES

A review of the literature shows that although any woman can experience perinatal mental illness, this problem is not randomly distributed among the population of perinatal women. A combination of biological, socio-environmental and psychological factors can affect mental health of women across their life span and predict their mental illnesses^[7] (Table 1). A previous history of mental health problem, such as depression or anxiety, has been reported to be a strong predictor of perinatal mental illnesses. Half the women with prenatal depression will continue to feel depressed throughout pregnancy and during postnatal period. Major depressive disorder and bipolar episodes may also occur before pregnancy and relapse

during pregnancy and after childbirth^[1]. Nevertheless, somatic complaints and sleep difficulties may be attributed to the changes happening during pregnancy and postnatal, obscuring the diagnosis of the mental illnesses and leaving the women with no appropriate treatment^[8].

According to the report by the World Health Organisation, the mean prevalence of non-psychotic common mental disorders in low- and lower-middle-income countries was 15.6% during antenatal period and 19.8% postnatal. Factors such as a higher education, a permanent job, the ethnic majority and having a supportive intimate partner were shown to be protective against mental health problems^[9].

Research has shown that women who carry the following risk factors are more likely to develop mental illnesses during pregnancy and after childbirth: socioeconomic disadvantage, a history of trauma, sexual abuse, unplanned pregnancy, high risk pregnancy, young age, being unmarried, lack of support from the intimate partner, intimate partner violence, inter-personal issues with in-laws, insufficient emotional and practical support, giving birth to a female baby, low level of education, cigarette smoking, career insecurity and ethnic minority^[2,9-11].

The reports from the Beyondblue postnatal depression screening program show that 5%-10% of Australian women experienced symptoms of depression after childbirth^[12]. A population-based survey by Eastwood *et al*^[13] demonstrated that the prevalence of postnatal depression after 2 wk postpartum was 6.2%. It was also reported that the risk of postnatal depression was significantly associated with maternal country of birth, financial difficulties, unplanned pregnancy, not breastfeeding and poor maternal health.

The study by Melville *et al*^[14] in the United States showed that the prevalence of antenatal depressive disorders was 9.9% and panic disorder was 3.2%. In addition, 2.6% of the participants reported current suicidal thoughts. The odds of probable antepartum major depressive disorder increased in the women who reported psychosocial stress, domestic violence, chronic medical conditions and Asian and African-American ethnic group.

PERINATAL MENTAL ILLNESS AND CHILD'S WELL-BEING

Women with mental illnesses are less likely to care for themselves during pregnancy and after childbirth. Research has shown that maternal anxiety during pregnancy is associated with higher level of cortisol in the fetus which continues to be higher than normal levels throughout the child's life span and may be a marker for the children's anxiety, mood and behavioural disorders. The risk is even higher in women who continue to suffer mental illness from pregnancy to postnatal period^[15].

Table 1 Risk factors of perinatal mental illnesses

Socioeconomic disadvantage	High risk pregnancy
Young age	Giving birth to a female baby
Maternal country of birth	Being unmarried
Ethnic minority	Lack of support from the intimate partner
Low level of education	Intimate partner violence
Financial difficulties	Inter-personal issues with in-laws
Career insecurity	Insufficient emotional and practical support
Cigarette smoking	Not breastfeeding
History of trauma	Previous history of mental health problem
Sexual abuse	
Unplanned pregnancy	

The association between antenatal depression and fetal and neonatal outcomes have been investigated in two meta-analyses^[16,17]. Reports of the studies indicate a significant association between antenatal depression and an increased risk of premature delivery (less than 37 wk of gestation) and infant's low birth weight (especially when mother lives in a low-income country). It was, also, suggested that the level of risk depends on the severity of the symptoms of depression.

The rate of pregnancy and postnatal health complications and interventions is higher among women with perinatal mental illness and their infants require higher rate of intensive care^[18,19]. It has been shown that children of these mothers are at higher risk of child neglect, maltreatment, attachment difficulties, delayed growth and motor development, emotional problems and a range of negative cognitive outcomes in early childhood. Nutritional neglect, severe starving and malnutrition are also other enormous problems in these children most of whom are females and below five years of age^[20-22]. In addition these children are at heightened risk of clinical depression in late adolescence while suffering the consequences of stress associated with caring for their mentally ill parent/s. These issues have resulted in increased concerns regarding the child's wellbeing in the family and have brought a great numbers of families into the attention of child protection agencies^[23-26].

PREVENTION AND DIAGNOSIS

Early detection of any mental health problems can help prevent future serious psychological disorders. Not only women with symptoms of depression need assessment and evaluation of psychological problems, but also all well women need to be screened as part of their perinatal health check. The American College of Obstetricians and Gynecologists (ACOG) states that "screening for depression has the potential to benefit a woman and her family and should be strongly considered. Women with a positive assessment require follow-up evaluation and treatment if indicated"^[27].

Child and Family Health nurses, general practitioners

and obstetricians, as the primary care providers, are the first and most often point of contact for perinatal women. This provides them with a great opportunity to effectively detect perinatal psychological problems and identify those who need care and support. There are, however, some barriers to timely screening and identification of the perinatal mental illnesses by the obstetricians. Research has shown that some obstetricians feel unconfident in their own level of knowledge and believe that they have had inadequate training to provide mental health support and assistance. Time constraint during each visit has also been reported as another barrier to effective screening^[28].

Pediatricians can also play a significant role in screening for postnatal depression. They can provide support to the mothers and facilitate their access to appropriate professional resources. This can in turn help optimise the healthy development of the children followed by the healthy functioning of the entire family. Similar to other screening initiatives, there are barriers to implementation of this practice such as lack of time, inadequate training, lack of sufficient mental health referral resources and reimbursement insecurity^[29,30].

Research by Kim *et al*^[31] reported barriers to mental health diagnosis and treatment at four levels as follows: Patient level (including lack of time, using other support and spontaneous improvement of symptoms); Provider level (including provider unavailability and unresponsive provider); Patient-provider interaction level (including poor match to need, poor patient-provider fit and use of phone tag); System level (including cost-insurance mismatch, geographic mismatch and inconvenient location).

TREATMENT

The mentally ill mothers need comprehensive support and counselling to be able to care for their infants and establish strong mother-child bond and attachment^[32,33]. Not only mothers but also fathers need psychological interventions during perinatal period as they may be well affected by the changes during pregnancy and after childbirth and are prone to mental illnesses. Even when the fathers become involved in the assessment and treatment, the majority of the therapeutic options focus on the treatment of maternal or paternal mental illnesses in isolation. Since the wellbeing of both parents is important in achieving normal development of the child, there is a need for inclusive perinatal mental health care. The wellbeing of both parents should be taken into account simultaneously and the fathers need to be routinely involved in the mental health assessment and care plan, which in turn improves the health outcomes for the whole family^[34,35].

MENTAL HEALTH INITIATIVES

Mental health campaigns across the world have

endeavoured to increase the knowledge and awareness of the public towards perinatal mental health illnesses. The development of knowledge on perinatal mental illnesses among public and the health professionals has resulted in timely recognition and treatment of perinatal mental illnesses. During the perinatal period, GPs and Child and Family Health nurses are key primary care providers engaged with women. They can identify women at risk, offer them an effective pathway and help alleviate postnatal mental health problems for the majority of women^[36,37].

Research on mental health problems in the United States and other countries have demonstrated that despite high prevalence rates of mental illnesses in these countries, many people do not seek professional advice and support or delay seeking help for as long as they can. For instance, the World Health Initiative by the World Health Organization^[38] investigated data from 28 countries and showed that both in developed and developing countries only a small proportion of the population received treatment for their mental illnesses such as mood or anxiety disorders. It was also shown that the median delays to receive treatment for severe psychotic disorders was a few months, for mood disorders ranged from one to 14 years and for anxiety disorders ranged from three to 30 years.

In a telephone survey, Highet *et al*^[39] recruited 1201 adults from each State and Territory of Australia in 2009. Results of the study demonstrated that 43.6% of the participants believed that postnatal depression was the most common health problem for women after childbirth. Furthermore, 94% of the participants believed that postnatal depression needs timely and specialised treatment. About two-third of the participants perceived postnatal depression as a biological rather than psychosocial aetiology. It was also revealed that more than 80% of the adult Australians believed that there should be a routine assessment for depression in all new mothers. Nevertheless, 55% of them viewed antenatal depression as a "normal" condition.

Results of a more recent survey in 2012 demonstrated remarkable improvements in mental health literacy in the Australian population over 16 years including improved recognition of depression, better perception about the usefulness of health professionals (General Practitioners, psychiatrists, psychologists and mental health nurses) and increase in beliefs about the helpfulness of antidepressants and antipsychotics^[40].

Failure to receive treatment or delay in seeking support and advice can have serious consequences. Therefore, early detection and prevention of mental illnesses is crucial and can be achieved by establishing a routine screening during perinatal period. It has been recommended that a comprehensive primary health care assessment as well as an enquiry of a history of anxiety, depression or other mental health problems are conducted at the following times: (1) Antenatally: At the first appointment with the clinician

for antenatal care before 20 wk of pregnancy; (2) Postnatally: At the first postnatal home visit by the clinician; (3) Six to eight week postnatal check: Performed by the child and family health service; and (4) A further assessment at 6-8 mo postpartum. It is also recommended that the Edinburgh Postnatal Depression Scale should be administered at each visit during antenatal and postnatal period^[41].

CONCLUSION AND DIRECTION FOR FUTURE RESEARCH

Undetected and untreated perinatal mental illnesses can have many negative unexpected impacts on parenting skills of women and children's development. Mentally ill mothers may not effectively attend their children's needs in a timely manner and may experience an unfavourable mother-child attachment affecting the child's language, social, emotional and cognitive development. It is crucial to identify families who are at an increased risk of perinatal mental illnesses in order to enable early prevention, diagnosis and intervention and prevent the serious adverse outcomes. The children's needs may not, however, be met by providing treatment to parental mental illnesses alone. It is important to understand the impact of specific parenting behaviours on child outcomes which is modified by the quality of parenting^[42].

Although great volumes of research show high prevalence of perinatal mental illnesses and their impacts on parenting confidence and competence as well as child's developmental process, there is still lack of research on various aspects of perinatal mental illnesses. There is a need for further research to investigate parenting education interventions for parents with perinatal mental disorders. No clinical trial has investigated the effect of psychological interventions and counselling on parenting skills or child's outcomes to find out whether children benefit from the interventions. Future longitudinal, population-based studies may unearth how environmental factors, such as education and social support, moderate the influence of perinatal mental illnesses on the child outcomes, which may help to find preventive approaches. In addition, the focus of most interventional trials has been on postnatal mental illness, but not the delivery of the intervention prophylactically before or during pregnancy and its long-term impacts on the mental health of the whole family^[2]. It is hoped that future studies and their findings will assist families affected by these problems.

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