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**Article** *in* European journal of obstetrics, gynecology, and reproductive biology · October 2009

DOI: 10.1016/j.ejogrb.2009.09.008 · Source: PubMed



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European Journal of Obstetrics & Gynecology and Reproductive Biology 147 (2009) 120–123

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Review

# Contribution of myo-inositol to reproduction

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ARTICLE INFO

*Article history:*
Received 9 April 2009
Received in revised form 11 August 2009
Accepted 11 September 2009

*Keywords:*
Inositol
Oogenesis
PCOS
Fertility

ABSTRACT

Myo-inositol is involved in several aspects of human reproduction.

Elevated concentrations of myo-inositol in human follicular fluids appear to play a positive function in follicular maturity and provide a marker of good quality oocytes.

Nevertheless its positive role in PCOS women is a consequence of a defect in the insulin signaling pathway (inositol-containing phosphoglycan mediators) that seems to be primarily implicated in the pathogenesis of insulin resistance.

This article will review the involvement of inositol in female reproduction. After describing the biologic function of inositol and its derivatives, studies are quoted in which the role of inositol in fertility, oogenesis, and polycystic ovary syndrome are examined.



**Contents**



## 1. Introduction

Since Beemster review in 2002 [1], increasing evidence supports the physiological and therapeutic role of myo-inositol in human reproduction and in particularly in oogenesis.

Myo-inositol (MYO) is one of nine stereoisometric of a C6 sugar alcohol that belongs to the vitamin B complex group [2,3].

MYO plays an important role in cell morphogenesis and cytogenesis, lipid synthesis, structure of cell membranes and cell growth [4,5].

Other studies have shown that MYO is incorporated into phosphoinositides and inositol phosphates in rabbit embryos [6] and can enhance bovine blastocyst development from in vitro culture with medium supplemented with MYO [7]. Taken together, the results from these studies support the notion that MYO serves as a precursor for the synthesis of phosphoinositides. This constitutes the phosphatidylinositol (PtdIns) signal transduction system known to be involved in the regulation of diverse cellular functions including cell proliferation [8].

Human adults consume approximately 1 g of inositol per day in different biochemical forms [9]. Free inositol is actively transported across the intestinal wall by a mechanism dependent on sodium and energy, a process that can be inhibited by glucose. Circulating free inositol is taken up by most tissues by a membrane-associated sodium-dependent inositol co-transporter [10].

Since the deciphering of the molecular details and importance of the inositol phospholipids-calcium second messenger system [11], the amount of cellular processes known to be directly or indirectly controlled by this class of lipids has tremendously expanded in recent times [12,13]. The long standing evidence indicates that this signal transduction system involves a receptor-dependent hydrolysis of phosphatidylinositol 4,5-bisphophate to

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doi:10.1016/j.ejogrb.2009.09.008

form the two second messengers, inositol 1,4,5-trisphosphate ($InsP_3$) and diacylglycerol (DAG) [8]. $InsP_3$ diffuses through the cytosol and binds to $InsP_3R$ on the surface of endoplasmic reticulum where it triggers the release of intracellular $Ca^{2+}$ whereas DAG activates protein kinase C (PKC) which alters the cell function by phosphorylating a variety of cell proteins [11,12]. These signaling pathways will operate throughout the life of a cell to regulate a variety of cellular processes including gametogenesis, fertilization, cell proliferation and development, secretion and contraction and neural activity [14–16].

### 1.1. The role of inositol in oogenesis

Increasing evidence has indicated that $InsP_3Rs$ play a primary role in generating calcium signals in mammalian oocytes [11]. Two types of receptor-operated channels, namely inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$) and ryanodine receptors ($R_yR$) are found in mammalian cells known to mediate intracellular $Ca^{2+}$ release [17–19]. Of the three isoforms of $InsP_3Rs$ that have been identified, type I $InsP_3Rs$ are the major receptors present in mouse oocytes [20]. Subsequent studies have demonstrated that similar receptors are also present in human oocytes [21]. Besides, calcium release mechanisms are shown to undergo modification during oogenesis and maximal sensitivity of calcium release is acquired during the final stages of oocyte maturation in preparation for successful activation at the time of fertilization [18,22]. This evidence points to the putative role of the inositol phospholipids-calcium second messenger system in oocyte development.

Calcium signalling in oocytes has been extensively studied in various species because of its putative role in oocyte maturation and the early stages of fertilization [23,24,18]. It had been demonstrated that fully grown mammalian GV oocytes exhibiting spontaneous intracellular calcium oscillations are associated with a higher incidence of germinal vesicle breakdown (GVBD) and supplementation of MYO can promote meiotic progression of these GV oocytes [25]. Depletion of inositol will desensitize PtdIns signaling by slowing down the re-synthesis of the PtdIns [4,5] $P_2$ precursor used to release $InsP_3$ as proposed by Berridge and Irvine [8]. This, in turn, can disrupt the dynamics of the intracellular calcium transients necessary for proper initiation of oocyte maturation. Thus supplementation of MYO can avoid inositol depletion and also enhances the intracellular inositide-calcium second messenger system involves in meiotic progression of mammalian oocytes. By the same token, we have demonstrated that follicles containing higher levels of MYO have better quality of oocytes which may be related to the intricate relationship between MYO and inositol phosphates involve in the PtdIns cycle activation for oocyte maturation. The presence of higher levels of MYO can indicate the well being of the follicle and the quality of the oocytes [26].

Indeed, a recent review has provided evidence to support the important regulatory roles of inositol phospholipids in nearly all aspects of cell physiology including cellular signal transduction, regulation of membrane traffic, nuclear events, cytoskeleton organization and transport functions of membranes [27].

### 1.2. The role of inositol in polycystic ovary syndrome

Some actions of insulin may involve low-molecular weight inositolphosphoglycan (IPG) mediators (also known as putative insulin mediators or second messengers) [28–30].

Further supportive evidence of the association between insulin sensitivity and D-Chiro-Inositol-IPG release can be gathered from clinical trials comparing oral DCI or MYO supplementation (which can be converted to DCI intracellularly) vs placebo in women with PCOS.

DCI administration led to a reduction in serum testosterone levels and an improvement in ovulation and metabolic parameters such as blood pressure and triglycerides in women with PCOS [31]. These findings have since been supported independently by Gerli et al. [32] who conducted a randomized, double-blind, placebo-controlled trial of 283 women with PCOS. Frequency of ovulation was increased by almost 2-fold in women who received DCI; and serum HDL cholesterol increased, effects consistent with improved insulin sensitivity. Similar findings were found after oral administration of MYO, a precursor of DCI in vivo [33] and [34]. Although the above data suggest that decreased DCI concentrations, and/or bioactive DCI-IPG release, may contribute to insulin resistance, the association between an increase in DCI-IPG release and improvement in insulin sensitivity has not been directly assessed.

Those hypothesis had been demonstrated in a study in which myo-inositol administration improved reproductive axis functioning in PCOS patients reducing the hyperinsulinemic state that affects LH secretion [35].

In this study all out of 20 overweight PCOS patients, after 12 weeks of MYO administration, presented plasma LH, PRL, T, insulin levels and LH/FSH reduced. Nevertheless insulin sensitivity, expressed as glucose-to-insulin ratio and HOMA index resulted significantly improved. Furthermore menstrual cyclicity was restored in all amenorrhoic and oligomenorrhoic subjects.

In fact both American and Greek women affected by polycystic ovary syndrome present an increased urinary clearance of inositols that reduce tissue availability of DCI and decrease the release of DCI-IPG mediator, which could contribute to insulin resistance and compensatory hyperinsulinemia [36,37].

In patients with PCOS, undergoing standard protocol of ovulation induction for intracytoplasmic sperm injection, the treatment with myo-inositol and folic acid, but not folic acid alone, reduces germinal vesicles and degenerated oocytes at ovum pick-up without compromising total number of retrieved oocytes. This approach, reducing oestradiol levels at hGC administration, could be adopted to decrease the risk of hyperstimulation in such patients.

Taking into account dermatological disorders as an additional end-point of treatment in PCOS women, MYO was tested to evaluate the effects on the lipid pattern and insulin sensitivity of hirsute women [39].

Its administration to 46 hirsute women significantly reduced hirsutism and hyperandrogenism and ameliorated the abnormal metabolic profile of those patients. Total androgens, FSH and LH concentrations decreased while oestradiol concentrations increased. Insulin resistance, analysed by homeostasis model assessment, was reduced significantly after therapy.

## 2. Discussion

MYO may represent one of the maturational factors in follicular fluid responsible for the in vitro growth of human oocytes. Perhaps, the content of MYO in follicular fluids may represent a more appropriate physiological indicator than follicular volume for monitoring the status of the developing follicles. Follicles containing good quality oocytes have higher concentrations of MYO in follicular fluids, probably due to the intricate relationship between MYO and inositol phosphates in the PtdIns cycle activation for oocyte maturation.

Regarding embryo development the animal models shows some contradictory results. For example while different glucose

concentration can inhibit embryo development in bovine, on the contrary short-term treatment of in vitro produced bovine preimplantation embryos with Insulin-like growth factor (IGF-I) can block induction of apoptosis caused by heat shock through signaling events requiring phosphatidylinositol 3-kinase (PI3K) [40].

In cryopreserved mouse oocytes, maturation, and fertilization, are positively related to the structure and function of the endoplasmic reticulum. These oocytes had the capacity to release Ca(2+) following injection of inositol 1,4,5-trisphosphate, demonstrating that Ca(2+) release mechanisms developed during meiotic maturation [41].

In human this data are not yet well established, and research in first stage embryo development and early pregnancy is still ongoing.

Recently MYO role powerfully emerged in the pathogenesis of polycystic ovary syndrome and in particularly linked with insulin resistance.

Whilst a significant progress has recently been made in the diagnosis for PCOS [42], the optimal infertility treatment for PCOS women remains to be determined [43,44].

In infertile patients with PCOS who present to reproductive endocrinologists desire pregnancy immediately, and for them time is of the essence, a rapidly acting induction agent such as clomiphene would be most appropriate [42].

On the contrary, young patients with PCOS whose timeline for achieving pregnancy differs from "immediately", often present with concerns unrelated to immediate fertility and might seek to postpone pregnancy; these women may be quite accepting of a pregnancy when it comes. Such women with longer timelines for achieving pregnancy constitute at least one "well-defined subset" for whom MYO, with its gradual onset of action minus the potential risk of multiparity, may be the drug of choice to re-establish ovulatory menses and fertility.

Moreover MYO may ameliorate the availability of DCI in these patients and acts as an ovarian insulin-sensitizing agent whereby a significant reduction in estradiol levels was detected in PCOS women undergoing ovarian stimulation compared to the controls [38]. The serum oestradiol level at hCG injection in MYO treated PCOS patients is well below the recommended normative threshold level of E2 (2500 pg/mL) suggested by Practice Committee of the ASRM [45].

In conclusion long-term co-treatment with MYO for patients with PCOS undergoing ICSI cycles does not improve the response to stimulation but significantly ameliorate oocytes quality and reduces the risk of OHSS.

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