

Effects of histamine and diamine oxidase activities on pregnancy: a critical review

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BACKGROUND: Histamine has been assumed to contribute to embryo–uterine interactions due to its vasoactive, differentiation and growth-promoting properties. However, its exact functions in pregnancy are unclear. The histamine-degrading enzyme diamine oxidase (DAO) is produced in high amounts by the placenta and has been supposed to act as a metabolic barrier to prevent excessive entry of bioactive histamine from the placenta into the maternal or fetal circulation. **METHODS:** The literature available on PubMed published in English between 1910 and 2008 has been searched using the isolated and combined key words histamine, diamine oxidase, pregnancy, placenta, endometrium, miscarriage, implantation, pre-eclampsia, intrauterine growth retardation, diabetes and embryonic histamine-releasing factor (EHRF). **RESULTS:** High expression of the histamine-producing enzyme histidine decarboxylase in the placenta, histamine receptors at the feto–maternal interface and the existence of an EHRF suggest a physiological role of histamine during gestation. The balance between histamine and DAO seems to be crucial for an uncomplicated course of pregnancy. Reduced DAO activities have been found in multiple heterogeneous complications of pregnancy such as diabetes, threatened and missed abortion and trophoblastic disorders. Whether women with histamine intolerance suffer from more complicated pregnancies and higher abortion rates due to impaired DAO activities and if low DAO levels or genetic modifications in the *DAO* gene might therefore represent a prognostic factor for a higher risk of abortion, has not been investigated yet. **CONCLUSIONS:** Low activities of the histamine-degrading enzyme DAO might indicate high-risk pregnancies, although high intra- and inter-individual variations limit its value as a screening tool.

Keywords: diamine oxidase; histamine; histamine intolerance; placenta; pregnancy

Introduction

The biogenic amine histamine (2-[4-imidazolyl]ethylamine) was discovered in 1910 by Dale (Dale and Laidlaw, 1910) and acts as a key mediator of allergic and pseudoallergic reactions. Histamine has various roles in allergic and inflammatory processes and neuro-endocrinological actions in the central nervous system. In addition, a contribution to the menstrual cycle and pregnancy has been described, which is most likely based on an interplay between histamine and female steroids and its vasoactive, cell growth- and differentiation promoting properties (Pap, 2004).

Histamine exerts multiple effects via binding to its four histamine receptors

Histamine is synthesized by the pyridoxal phosphate containing L-histidine decarboxylase (HDC) from the amino acid histidine. It is produced mainly by mast cells, basophils, platelets,

histaminergic neurons and enterochromaffine cells, where it is stored intracellularly in vesicles and released upon stimulation.

Histamine exerts its effects by binding to its four receptors [histamine 1 receptor (H1R), H2R, H3R and H4R] on target cells in various tissues. It causes smooth muscle cell contraction (H1R), vasodilatation (H1R, H2R), increased vascular permeability (H1R, H2R) and mucus secretion (H1R), tachycardia, arrhythmias (H1R, H2R), alterations of blood pressure (H1R, H2R) and stimulates gastric acid secretion (H2R) as well as nociceptive nerve fibres (H1R) (Maintz and Novak, 2007).

Histamine enhances Th1-type response by triggering H1R, whereas both Th1- and Th2-type responses are negatively regulated by H2R through the activation of different biochemical intracellular signals (Jutel *et al.*, 2001). H3Rs are predominantly involved in the functions of the central nervous system as presynaptic autoreceptors influencing neuronal histamine release and thus various biological responses such as arousal, circadian

rhythm, food intake, cognitive and memory processes (Igaz and Hegyesi, 2004). The most recently described histamine receptor, H4R, contributes to chemotaxis, cytokine and chemokine production and release in various types of immune cells including mast cells, eosinophils, dendritic cells and T cells. H4R antagonists have been shown to have anti-inflammatory properties and efficacy in a number of disease models, such as those for asthma and colitis *in vivo* (Zhang *et al.*, 2006, 2007).

Extracellular histamine is catabolized by DAO, whereas intracellular histamine is metabolized by HNMT

Histamine can be metabolized by two alternative ways: oxidative deamination by DAO (former name: histaminase) or ring methylation by histamine-*N*-methyltransferase (HNMT) (Schwelberger, 2004). Whether histamine is catabolized by DAO or HNMT, is supposed to depend on the localization of histamine. The DAO protein is stored in plasma membrane-associated vesicular structures in epithelial cells of kidney and intestine and is secreted into the circulation upon stimulation (Schwelberger and Bodner, 1997; Schwelberger *et al.*, 1998).

Therefore it has been proposed that DAO might be responsible for scavenging extracellular histamine after mediator release. Conversely, HNMT, the second important enzyme inactivating histamine, is a cytosolic protein (Brown *et al.*, 1959), which can convert histamine only in the intracellular space of cells (Kufner *et al.*, 2001; Klocker *et al.*, 2005).

DAO also catabolizes other polyamines such as putrescine and spermidine. The highest expression of DAO has been observed in the intestine (Bieganski, 1983, Bieganski *et al.*, 1983; Raithel *et al.*, 1999), kidney and placenta (Schwelberger *et al.*, 1998; Klocker *et al.*, 2005).

A decreased activity of DAO has been discussed as a potential indicator of intestinal mucosa damage in inflammatory and neoplastic diseases (Schmidt *et al.*, 1990; Raithel *et al.*, 1998; Backhaus *et al.*, 2005) or after chemotherapy (Tsujikawa *et al.*, 1999).

How is histamine and its metabolism actually linked to pregnancy?

The balance between histamine and the histamine-degrading enzyme DAO seems to be crucial for an uncomplicated course of pregnancy (Brew and Sullivan, 2001). Reduced or precipitously falling DAO activities have been found in high-risk pregnancies (Fig. 1), whereas maternal plasma enzyme titres within the normal range have been mostly associated with a favourable fetal prognosis. DAO at the feto–maternal interface has therefore been supposed to act as a metabolic barrier to prevent excessive entry of bioactive histamine from the placenta into the maternal or fetal circulation.

In this review, we provide an overview of histamine and its metabolism during uncomplicated and pathological pregnancies and discuss the question whether reduced maternal plasma DAO activities serve as a reliable marker for pregnancy disorders.

Materials and Methods

The literature available on PubMed published in English between 1910 and 2008 has been searched using the isolated and combined key words histamine, diamine oxidase, pregnancy, placenta, endometrium, miscarriage, implantation, pre-eclampsia, intrauterine

growth retardation, diabetes and EHRF. A total of 16 observational and various experimental studies and reviews concerning histamine and histamine metabolism, especially during pregnancy have been evaluated following the MOOSE guidelines for systematic reviews of observational studies. The current data regarding this topic using standardized assays for measurement of DAO activity is limited. In an effort to include all available studies investigating DAO activity during gestation, also heterogeneous studies have been included.

Results

Histamine in pregnancy

Maternal blood histamine levels are comparable to non-pregnant values in the first trimester and decrease during the second and third trimester of normal pregnancies

Maternal total blood histamine (TBH) levels are highest during the first trimester (mean ca 60 ng/ml) (Dubois *et al.*, 1977) and do not differ significantly from normal non-pregnancy values (range TBH 50–60 ng/ml (Haimart *et al.*, 1985), plasma histamine levels 0.3–0.7 ng/ml (Lorenz *et al.*, 1972; Kimura *et al.*, 1999; Brew and Sullivan, 2006). TBH levels decrease during the second (week 13–24: 9–48 ng/ml; Dubois *et al.*, 1977; Clemenson and Cafaro, 1981) and third trimester (week 25–40: 30–54.7 ng/ml; Kapeller-Adler, 1949; Gunther and Glick, 1967; Achari *et al.*, 1971; Dubois *et al.*, 1977; Sharma *et al.*, 1984) of normal pregnancy showing a nadir in the second trimester (Brew and Sullivan, 2006). Study results on puerperal blood histamine are contradictory and limited (Brew and Sullivan, 2006), varying between a rapid decrease (Brew and Sullivan, 2006) and increase (Sharma, 1982) of maternal TBH after delivery (Brew and Sullivan, 2006).

The human endometrium and myometrium features high amounts of mast cells which are thought to be the main source of uterine histamine (Massey *et al.*, 1991; Pap, 2004). Functional mast cells have also been demonstrated in the placenta itself (Purcell and Hanahoe, 1991). However, also decidual cells have been shown to release histamine upon stimulation of the IgE receptor *in vitro* (Schrey *et al.*, 1995).

High expression of the histamine-producing enzyme HDC in the placenta, histamine receptors at the feto–maternal interface and the existence of an EHRF suggest a physiological role of histamine during gestation

Histamine has been supposed to contribute to embryo–uterine interactions during implantation. In the placenta, the expression of the histamine-producing enzyme HDC is about 1000 times higher than in other organs (Pap, 2004). This might be explained by the finding that HDC gene transcription is regulated by progesterone (Paria *et al.*, 1998) which increases during pregnancy. Moreover, HDC transcription correlates with endometrial differentiation for blastocyst implantation (Paria *et al.*, 1998). Inhibition of HDC has been shown to induce delayed implantation in the rabbit (Dey, 1981). Murine preimplantation blastocysts have been found to express H2R (Zhao *et al.*, 2000). Conversely, histamine seems to promote cytotrophoblast invasiveness specifically through activation of H1R in humans (Liu *et al.*, 2004). In humans, H1Rs are expressed in syncytiotrophoblasts of placental villi, which play important roles in the exchange of substances

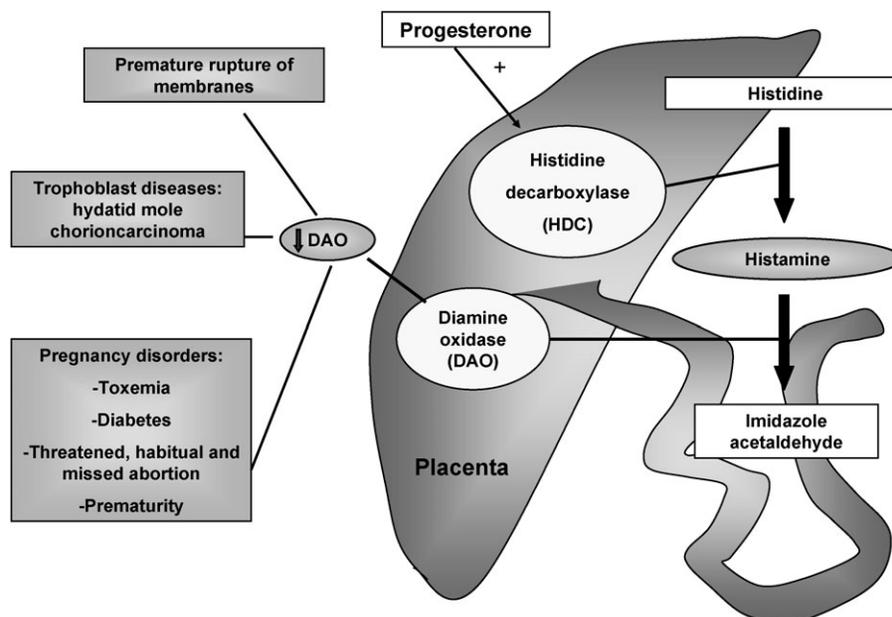


Figure 1: High amounts of both the histamine synthesizing enzyme histidine decarboxylase (HDC) and the histamine-degrading enzyme diamine oxidase (DAO) are produced by the placenta.

Persistently low or falling DAO plasma curves have been shown in pregnancy disorders, trophoblast diseases and premature rupture of membranes. Therefore DAO has been suggested to serve as a screening tool for complicated pregnancies.

between maternal and fetal blood and in the secretion of many hormones [e.g. human chorionic gonadotropin (HCG), estrogen etc.] (Matsuyama *et al.*, 2004). H1R (Fukui *et al.*, 1994), and H2R are expressed in both decidual and placental components (human amnion, chorion, decidua, villous cytotrophoblast and stromal cells) of the fetomaternal interface (Fukui *et al.*, 1994; Brew and Sullivan, 2001), suggesting a role of histamine at the fetomaternal interface after implantation (Brew and Sullivan, 2001; Pap, 2004).

Histamine has been shown to modulate vascular resistance during gestation in human (Maguire *et al.*, 1985) and animal models (Berhe *et al.*, 1988). Via H1R, histamine has been shown to mediate vasoconstriction in the fetal circulation of the guinea pig placenta (Berhe *et al.*, 1988), guinea pig umbilical arteries (Nair and Dyer, 1974) and of human umbilical arteries and veins (Altura *et al.*, 1972). Conversely, histamine has been observed to cause a dose-dependent dilatation of the fetal circulation via H2Rs in the dually perfused human placental cotyledon under low PO₂ conditions, when tone is already elevated with angiotensin II (Maguire *et al.*, 1985). This effect might be beneficial in hypoxia. Histamine has also been shown to increase permeability of guinea pig placentas to macromolecules (Berhe *et al.*, 1988).

Implantation of the placenta depends on the complex process of trophoblast differentiation which goes along with the expression of various adhesion molecules (Szewczyk *et al.*, 2006). The invasive trophoblast becomes $\alpha 6\text{-}\beta 4$ integrin negative and $\alpha 5\text{-}\beta 1$, $\alpha 1\text{-}\beta 1$ and $\alpha v\text{-}\beta 3$ integrin positive (Aplin, 1993). *In vitro*, stimulation with histamine has been shown to enhance the physiological $\alpha v\text{-}\beta 3$ integrin expression (Szewczyk *et al.*, 2008).

The embryo is thought to contribute to the release of histamine in mast and endometrial cells by an EHRF (Pap, 2004; Cocchiara *et al.*, 1987a; 1987b; 1988). Pre-embryos growing *in vitro* produce an EHRF from the 2-cell to the 8-cell stage in humans (Cocchiara

et al., 1987a, b, 1988) and from the 2-cell to the blastocyst in rats (Cocchiara *et al.*, 1992, 1996) which has been shown to release histamine in human basophils and rat uterine mast cells (Cocchiara *et al.*, 1992). Whereas administration of anti-histamines (Hoos and Hoffman, 1983) and indomethacin (Saksena *et al.*, 1976; Hoos and Hoffman, 1983) have been shown to inhibit implantation in rabbits (Hoos and Hoffman, 1983) and mice (Saksena *et al.*, 1976), this effect could be partially compensated in mice by an injection of histamine and reversed completely by administration of histamine and prostaglandin (PGF₂ α) (Saksena *et al.*, 1976). However, mice do not feature the human hemochorial placentation. Therefore transfers from the murine to the human model have to be regarded critically.

Anyhow, in view of all these findings, histamine has been implicated as a paracrine signal during endometrial decidualization and embryo implantation (Noskova *et al.*, 2006).

Histamine functions as a paracrine oxytocic directly on gestational myometrium and indirectly by an increased production of the uterotonic PGF₂ α

Histamine has been shown to stimulate arachidonate release and PGF₂ α production in human decidual cells *in vitro* (Schrey *et al.*, 1995). An increased PG production by the uterine decidua is thought to play a key role in the initiation and maintenance of normal labour (Casey and MacDonald, 1988; Schrey *et al.*, 1995). PGs have also been implicated as mediators of preterm labour associated with intrauterine infection (Lopez *et al.*, 1989; Schrey *et al.*, 1995). Elevated histamine plasma levels have been shown in women during preterm compared with term labour (Caldwell *et al.*, 1988). Hence, histamine might stimulate both preterm and term labour in an indirect and direct way. Histamine may function directly as a paracrine oxytocic due to its potent positive ionotropic action on gestational myometrium (Cruz *et al.*, 1989; Schrey *et al.*, 1995). Moreover, PGF₂ α and histamine

are able to potentiate each others contractile effects (Rudolph *et al.*, 1992).

Excessive histamine levels had fatal effects on pregnancy in animal models

Elevated histamine concentrations in pregnancy due to histamine injection (Dale and Laidlaw, 1910; Woods *et al.*, 1976) or DAO inhibition with aminoguanidine (Roberts, 1954; Nava and Fraile, 1988) had fatal effects in various animal models (Brew and Sullivan, 2006). Histamine injection resulted in uterine contraction and spontaneous abortion in cats (Dale and Laidlaw, 1910), fetal ductus arteriosus constriction in lambs (Woods *et al.*, 1976), whereas inhibition of DAO led to liver, lung and head haematomas in fetuses from treated rats (Nava and Fraile, 1988), abnormal fetal cranial skeletal ossification (Nava and Fraile, 1988) and spontaneous abortion (Roberts, 1954) in pregnant rats. These observations stress the impact of a sufficient histamine degradation during pregnancy.

DAO is synthesized by decidual and trophoblast cells, leading to high DAO levels during pregnancy

It has long been observed that maternal plasma DAO activity levels rise (Ahlmark, 1944) exponentially during the first 20 weeks of gestation to levels which are about 1000 times higher than before pregnancy (Southren *et al.*, 1966b; Carrington *et al.*, 1972), leading to a decline of circulating maternal histamine levels (Dubois *et al.*, 1977; Brew and Sullivan, 2001; Brew *et al.*, 2007).

DAO has been identified as the main enzyme for histamine catabolism at the feto–maternal interface (Kapeller-Adler, 1944; Lindberg *et al.*, 1963; Brew and Sullivan, 2001). DAO is located predominately in the cytosol (Weisburger *et al.*, 1978) and intercellular space (Lin *et al.*, 1978) of decidual cells (Swanberg, 1950a, b; Southren *et al.*, 1965; Gunther and Glick, 1967; Bell, 1986) and has been regarded for a long time as an exclusively maternal but not fetal product in this tissue (Weisburger *et al.*, 1978). Negative immunofluorescent staining of DAO has been reported for syncytio- and cytotrophoblast of the chorionic villi (Lin *et al.*, 1978). However, the expression of mRNA for DAO has also been shown in the villous trophoblast besides decidual cells (Brew and Sullivan, 2001). During pregnancy, maximal DAO activity has been found in the retroplacental decidua (Weingold and Southren, 1968), followed by fetal membranes, placental cross sections, amniotic fluid, maternal plasma, cord and fetal plasma (Weingold and Southren, 1968). The amniotic fluid has been reported to possess approximately a 2- to 3-fold enzyme activity over an equivalent amount of maternal plasma (Weingold and Southren, 1968). Fetal plasma DAO levels have been found to be ~50-fold lower than maternal plasma DAO levels at parturition following uncomplicated pregnancies (Southren *et al.*, 1964). Decidual DAO activity increased from 6 to 17 weeks of pregnancy (Holinka and Gurpide, 1984). The course of maternal DAO plasma activities has been studied during normal (Table I) and pathological pregnancies with various demographic and medical complications (Table II) (Bradshaw and Jessop, 1955; Southren *et al.*, 1964, 1966a, b; 1968; Resnik and Levine, 1969; Southren and Weingold, 1970; Torok *et al.*, 1970; Carrington *et al.*, 1972;

Beaven *et al.*, 1975; Jones and Kelly 1976; Dubois *et al.*, 1977; Legge and Duff, 1981; Gahl *et al.*, 1982a, b).

A sharp increase of DAO levels during the first trimester (Southren *et al.*, 1964; Dubois *et al.*, 1977) with a following plateau phase during the second and third trimester has been described in normal pregnancies (Southren *et al.*, 1964; Dubois *et al.*, 1977). In conception cycles, plasma DAO activity has been shown to increase between 9 to 28 days following ovulation and to rise exponentially with a doubling time of 4–5 days during the first 10 weeks of pregnancy (Beaven *et al.*, 1975). In humans, implantation is thought to occur on Day 7 to 8 post-ovulation (Beaven *et al.*, 1975). The initiation of the rise has been reported to depend on non-pregnant DAO levels. An earlier rise (beginning 8–19 days following ovulation) has been described in patients with lower non-pregnant DAO levels compared with patients with higher non-pregnant values (Beaven *et al.*, 1975). DAO peak activities seem to be reached between 12 (Southren *et al.*, 1964) and 24 weeks (Dubois *et al.*, 1977) of gestation. Beyond the 20th week, DAO levels of ≥ 500 U/ml have been regarded as normal (Southren and Weingold, 1970; Carrington *et al.*, 1972) (Fig. 2). After delivery, maternal enzyme titres decline to normal non-pregnancy levels in ~10–15 days (Southren *et al.*, 1964) with a half-life of DAO of ~24 h (Carrington *et al.*, 1972).

The various different studies conducted on histamine metabolism during pregnancy show the same tendency, but values are only roughly comparable, as different techniques have been used to determine DAO activity (Okuyama and Kobayashi, 1961; Tufvesson and Tryding, 1969). Clearly defined, homogenous study populations are rare and various study designs with diverse (normal and multiple heterogeneous pathological pregnancies) at different ages of gestation complicate comparability.

In general, it has been proposed that the high decidual DAO activity acts as a counter-regulation to elevated histamine concentrations in pregnancy (Kahlson, 1962; Southren *et al.*, 1965) due to the high placental HDC activity and the EHRF. This is assumed to be an adaptive response designed to protect both the pregnant woman and the fetus against the exposure of excessive amounts of histamine (Carrington *et al.*, 1972).

Histamine intolerance

Histamine intolerance (HIT) results from a disequilibrium of accumulated histamine and the capacity for histamine degradation. Ingestion of histamine-rich food (Sattler *et al.*, 1988), alcohol (Wantke *et al.*, 1994, 1996; Zimatkin and Anichtchik, 1999) or drugs (Sattler *et al.*, 1987; Sattler and Lorenz, 1990; Wantke *et al.*, 2001; Jarisch R *et al.*, 2004) releasing histamine or blocking DAO may provoke diarrhoea, headache, in particular premenstrual headache (Jarisch and Wantke, 1996), congestion of the nose, asthmatoïd wheezing (Sattler *et al.*, 1988; Wantke *et al.*, 1996; Wohrl *et al.*, 2004), hypotension, arrhythmia, urticaria (Schmidt *et al.*, 1990; Pollock *et al.*, 1991), pruritus, flushing, dysmenorrhoea and others in these patients (Maintz and Novak, 2007). Symptoms can be reduced by a histamine-free diet or be eliminated by antihistamines, mast cell stabilizers or substitution of DAO.

Approximately 1% of the population suffer from HIT. Most of them are middle-aged females (Missbichler, 2004). Due to the multifaceted symptoms, the existence of HIT is frequently

Table I. Plasma DAO activity in normal pregnancies.

<i>n</i>	DAO range	Unit	Week of gestation	Complications	Fetal outcome	References
70	0.1–0.9	nm/ml/min	4–40	no	n.s.	Dubois <i>et al.</i> (1977)
83	0.5–4.9	μg/h	14–40	no	n.s.	Bradshaw and Jessop (1955) ^a
110	5–500	mμM/ml	8–40	no	Term infants	Resnik and Levine (1969)
15	1–460	U/ml	4–40	no	n.s.	Southren <i>et al.</i> (1964)
6	120–2300		8–40	no	n.s.	Southren <i>et al.</i> (1966a)
34	0–2200		8–40	no	Full-term	Southren <i>et al.</i> (1966b)
89	12–1940		8–40	no	n.s.	Jones and Kelly (1976)
66	7–1800		0–39	no	n.s.	Carrington <i>et al.</i> (1972)
66	0.9–2.5	10 ⁻³ DAO (U/ml) ^a	8	n.s.	Live births	Gahl <i>et al.</i> (1982a, b) ^a
261	2.8–7.6		12			
261 ^b	0–29		8–34	no	8 twins, 11 infants with minor defects	

Values were mostly read from figures and might therefore deviate from the measured values which were often not exactly given in the manuscripts. ^aSerum DAO activity is measured whereas the other studies use plasma DAO activity; ^bnumber of subjects varies between *n* = 20 and *n* = 261 at different gestational age periods. *n*, number of patients; n.s., not specified.

underestimated or its symptoms misinterpreted. Whether women with HIT suffer from more complicated pregnancies and higher abortion rates due to impaired DAO activities and if low DAO levels might therefore represent a prognostic factor for a higher risk of abortion, has not been investigated yet.

DAO measurement avails diagnosis of PROM

Due to the presence of DAO in amniotic fluid, but absence in vaginal secretions, measurement of DAO in vaginal secretions has been suggested as a method for the diagnosis of premature rupture of membranes (PROM) (Gahl *et al.*, 1982a, b). In patients with suspected PROM, a higher sensitivity (90.9%) and specificity (100%) has been observed for the measurement of DAO activity compared with vaginal fluid pH (Amnicator) (81.81; 83.33%) (Gaucherand *et al.*, 1995; De Meeus *et al.*, 1997). However, currently, the detection of insulin-like growth factor binding protein-1 in cervicovaginal secretions is regarded as the most accurate diagnostic test and predictor of latency in patients with suspected PROM (Erdemoglu and Mungan, 2004).

Low DAO activities as a screening tool for trophoblast diseases

In patients with trophoblast diseases mimicking pregnancy such as hydatid mole (Torok *et al.*, 1970) and choriocarcinoma (Southren *et al.*, 1964; Weingold and Southren, 1968; Torok *et al.*, 1970; Beaven *et al.*, 1975), low DAO activities have been observed despite high titres of HCG (Weingold and Southren, 1968). In molar pregnancies, DAO values have been shown to be comparable to normal pregnancies during the first trimester, but fall after the 15th week of gestation (Weingold and Southren, 1968). In contrast, no DAO activity has been found in patients with choriocarcinoma associated with molar pregnancy and most of the patients with choriocarcinoma of other than molar origin (Torok *et al.*, 1970). Similar to the absence of estriol in these neoplasias, it has been concluded that the presence of the fetus seems to be necessary to induce DAO production (Weingold and Southren, 1968). Therefore the measurement of DAO has been proposed as a differential test between normal pregnancy and trophoblastic diseases (Southren *et al.*, 1964).

Are high maternal histamine levels or reduced plasma DAO activities a reliable marker for pregnancy disorders?

Elevated maternal histamine levels in pre-eclampsia, hyperemesis gravidarum, spontaneous and threatened abortion, but a decreased placental number of mast cells and histamine concentration in intrauterine growth retardation

Pregnancies lacking an increase of DAO activity (Dubois *et al.*, 1977) lead to elevated plasma and urine histamine concentrations (Beaven *et al.*, 1975). These pregnancies are at increased risk for pre-eclampsia, hyperemesis gravidarum, spontaneous and threatened abortion (Kapeller-Adler, 1941a; Ahlmark, 1944; Beaven *et al.*, 1975; Dubois *et al.*, 1977; Clemetson and Cafaro, 1981; Brew and Sullivan, 2006).

In pre-eclampsia, mean TBH levels seem to increase with the severity of the disease (Kapeller-Adler, 1941b; Achari *et al.*, 1971; Sharma *et al.*, 1984) with TBH levels at gestational weeks 28–40 ranging between 63 and 87 ng/ml (Achari *et al.*, 1971; Sharma *et al.*, 1984) compared with 49–55 ng/ml (Sharma *et al.*, 1984) for the same gestational age in normal pregnancies (Brew and Sullivan, 2006). An increased number of mast cells (Szukiewicz *et al.*, 1999a) and elevated histamine concentrations in pre-eclamptic compared with normal placentae have been shown in most (Kapeller-Adler, 1952; Southren *et al.*, 1966b; Szukiewicz *et al.*, 1999a; Szewczyk *et al.*, 2005), but not all (Brew *et al.*, 2007) studies. Plasma levels of the histamine precursor histidine are similar in both normal and pre-eclamptic pregnancies (Page *et al.*, 1955; Glew *et al.*, 2004; Brew and Sullivan, 2006). Conversely, production of histamine by HDC is higher in pre-eclamptic placentae than in control tissues (Brew *et al.*, 2007). A direct relationship between maternal TBH levels and maternal hypertension has been observed (Achari *et al.*, 1971), which were inversely correlated with serum DAO levels (Achari *et al.*, 1971; Brew and Sullivan, 2006). Therefore, higher maternal TBH levels in pre-eclamptic women might derive both from an increased placental HDC activity and from an impaired DAO activity in these patients (Brew *et al.*, 2007).

Moreover, trophoblast cells in pre-eclampsia show an altered response to histamine (Szewczyk *et al.*, 2008). An impaired trophoblast invasion mirrored by a decreased expression of the adhesion molecule αv-β3 integrin is thought to be a major

Table II. Plasma DAO activity in complicated pregnancies.

<i>n</i>	Range of plasma DAO activity	Unit	Gestational week	Complications of pregnancy	Fetal outcome	References
25	40–1300	U/ml	0–37	19 normal, 6 anovulatory with HCG	24 term, 1 abortion	Beaven <i>et al.</i> (1975)
9	10–2400		4–42	Age <15 years (<i>n</i> = 9), toxemia (<i>n</i> = 2)	1 late abortion, 1 premature	Southren and Weingold (1970)
23	75–1300		10–40	Age 15–19 Toxaemia (<i>n</i> = 13), poor obstetric history (<i>n</i> = 5), diabetes (<i>n</i> = 4), antepartum bleeding (<i>n</i> = 3), anaemia (<i>n</i> = 2), pyelonephritis (<i>n</i> = 6), Obesity or anorexia (<i>n</i> = 21)	1 abortion, 3 stillbirths, 9 premature infants, 1 congenital anomaly	
79	0–2100		6–42	Age 15–19, uncomplicated		
23	400–1400		14–41	Patients age ≥40 years Toxaemia (<i>n</i> = 7), excessive weight gain (<i>n</i> = 5), anaemia (<i>n</i> = 2), poor obstetric history (<i>n</i> = 1)	1 abortion, 3 premature, 1 anomaly, 1 neonatal death	
44	200–1050	U/ml	12–42	Underweight ≤99 pounds (<i>n</i> = 44), poor obstetric history (<i>n</i> = 5), toxemia (<i>n</i> = 6), excessive weight gain (<i>n</i> = 3), anaemia (<i>n</i> = 3)	1 abortion, 1 ectopic pregnancy, 1 congenital anomaly, 3 neonatal deaths, 9 premature births	
30	350–1650		11–40	Obesity (≥200 pounds) (<i>n</i> = 30); Toxaemia (<i>n</i> = 18), excessive weight gain (<i>n</i> = 10), diabetes (<i>n</i> = 7), poor obstetric history (<i>n</i> = 3), anaemia (<i>n</i> = 1)	3 premature, 2 neonatal deaths, 1 abortion, 4 weight ≥10 pounds	
208	10–2200		8–42	Normal and complicated pregnancies 17% toxemia, 6.2% diabetes	25 premature, 9 perinatal death	
6	50–3174		10–32	Threatened abortion	n.s., pregnancies continued >20 week	Southren <i>et al.</i> (1966a, b)
3	10–400		8–20	Threatened abortion, treatment with progestational agents	Unsuccessful termination of pregnancy	
3	25–120		8–24	Missed abortion	Abortion >16 week	
5	10–800		8–40	History of habitual abortion	Live infants	
4	100–1950		12–34	Incompetent os syndrome	4 premature, 1 neonatal death	
3	100–900	U/ml	16–36	Incompetent os syndrome	Live, term	
5	80–1700		12–36	Poor obstetrical history ^a	Premature, 1 antepartum death, 1 neonatal death	
5	0–1800		8–38	Poor obstetrical history	term	
68	20–2085		10–40	Diabetes mellitus	4 stillbirths	Southren <i>et al.</i> (1968)
44	0–0.5	10 ⁻³	8	n.s.	Early deaths <21st week	Gahl <i>et al.</i> (1982a, b) ^b
29	0.5–2.9	DAO (U/ml) ^a	12	n.s.	Late deaths >21st week	
29	0.8–4.8		12	n.s.	47.83% (<i>n</i> = 11) continued pregnancies, 52.17% (<i>n</i> = 12) aborted	Legge and Duff (1981)
23	'normal'	IU/l	>8	Antepartum bleeding at ≤20 weeks of gestation	19.35% (<i>n</i> = 6) pregnancies continued, 80.65% (<i>n</i> = 25) aborted	
31	'below normal'				3 aborted	
4	Normal (>8)		≤8		4 aborted, 4 pregnancies continued	
8	Low (≤8)				n.s.	Torok <i>et al.</i> (1970) ^b
120	10–510	nM/0.6 ml	8–40	no	Term infants	Resnik and Levine (1969)
110	5–500	mμM/ml	8–40	No	Premature, >2500 g	
6	60–300		12–34	No	Term infants	
25	20–450		18–40	'high-risk' i.e. toxemia, diabetes, anaemia, erythroblastosis, dysmaturity		
5	0–225		24–39	'high-risk': toxemic, anaemic, alcoholic	premature	

Values were mostly read from figures and might therefore slightly deviate from the measured values which were often not given numerically in the manuscripts. ^aPoor obstetrical history was defined by the authors as a history of recurrent abortions, premature deliveries and stillbirths mixed with infrequent successful pregnancies (Southren *et al.*, 1966a, b); ^bserum DAO activity is measured whereas the other studies use plasma DAO activity. *n*, number of patients; n.s., not specified.

reason for the pathogenesis of pre-eclampsia (Szewczyk *et al.*, 2008). *In vitro*, stimulation with histamine has been shown to enhance the physiological $\alpha v\text{-}\beta 3$ integrin expression in

trophoblast cell cultures derived from normal placentae via HIR (Szewczyk *et al.*, 2006), but not from pre-eclamptic placentae (Szewczyk *et al.*, 2008).

Furthermore, placental extracts from women with pre-eclampsia have been observed to exacerbate histamine-induced vasoconstriction in porcine carotid artery compared with extracts from normotensive women (Thomson *et al.*, 2000).

The resemblance of some symptoms of pre-eclampsia such as hypertension, proteinuria, oedema, nausea and headaches to those of hyperhistaminemia might insinuate a causation by high levels of histamine, probably due to its vasomodulating capacities (Brew *et al.*, 2007).

Increased blood, plasma and urine histamine levels and a reduced DAO activity have also been shown in hyperemesis gravidarum (Kapeller-Adler, 1944; Uuspaa and Jarvinen, 1955; Brew and Sullivan, 2006).

Conversely, a decreased number of mast cells and histamine concentration has been observed in placentae of intrauterine growth retarded pregnancies compared with placentae obtained from gestationally matched preterm controls (Szukiewicz *et al.*, 1999b). Ischaemia due to placental insufficiency has been regarded as a main pathological factor associated with intrauterine

growth retardation (Szukiewicz *et al.*, 1999b). It has been speculated that the decreased number of mast cells in intrauterine growth retarded pregnancies might lead to an impaired adaptive response to hypoxia due to a deficiency of angiogenic factors derived from mast cells (Szukiewicz *et al.*, 1999b).

Precipitously falling or persistently low maternal plasma DAO activities in heterogenous pregnancy complications such as toxæmia, diabetes, threatened, habitual and missed abortions

Plasma DAO has been proposed to be of value as an indicator of fetoplacental integrity (Southren *et al.*, 1966b; Weingold and Southren, 1968; Southren and Weingold, 1970). As a consequence, precipitously falling DAO curves have been regarded indicative for fetal distress or intrauterine death (Southren and Weingold, 1970).

Serial plasma enzyme titres within the normal range have been shown to indicate maintenance of pregnancy into the third trimester in the majority of the patients (Southren *et al.*, 1966b). Persistently low or falling DAO plasma curves have been shown in various pregnancies complications such as toxæmia, diabetes, anaemia, threatened and missed abortion (Fig. 3) compared with normal pregnancies (Southren *et al.*, 1966b; Weingold and Southren, 1968; Legge and Duff, 1981), especially during the last trimester (Southren *et al.*, 1966b; Southren and Weingold, 1970; Legge and Duff, 1981).

In patients with threatened (Legge and Duff, 1981) or missed abortion (Weingold and Southren, 1968), DAO levels within the normal range were associated with continuing pregnancies, whereas levels below the normal range were associated with subsequent abortion (Legge and Duff, 1981). A single period of antepartum bleeding accompanied by a rapid linear rise of plasma DAO titres in the first 20 weeks of gestation has been associated with a favourable prognosis (Southren *et al.*, 1966b; Weingold and Southren, 1968). Conversely, cases of recurrent bleeding have been associated with a falling or flat plasma DAO curve and a poor prognosis (Southren *et al.*, 1966b; Weingold and Southren, 1968). There is only very limited data available on the DAO activity in patients with habitual (≥ 3 consecutive) abortions. One study

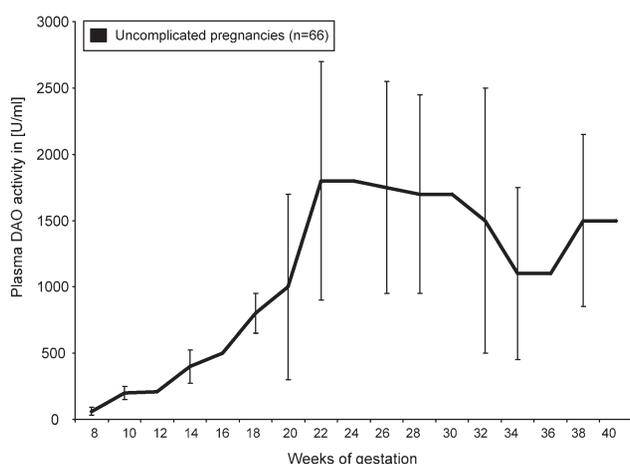


Figure 2: Plasma DAO activities of 66 women with uncomplicated pregnancies. Means and standard deviations are given. Data are taken and figure is adapted from (Carrington *et al.*, 1972).

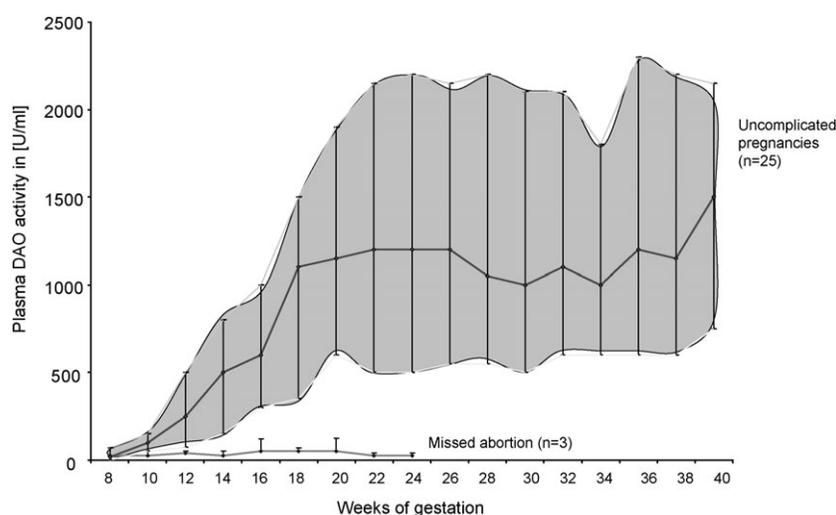


Figure 3: Range of Plasma DAO activities during gestation. Normal DAO ranges (black lines, grey field) ($n = 34$) and DAO ranges of women with missed abortions (grey lines) as an example for high-risk pregnancies are given. Data are taken, and the figure is adapted from (Southren *et al.*, 1966b).

showed 5 patients with a history of habitual abortion who featured increasing DAO levels, although slowly rising and at the lower level of normal, which were associated with live infants in spite of their history (Southren *et al.*, 1966b; Weingold and Southren, 1968).

Older mothers (age ≥ 40 years) have been shown to feature a higher percentage of abnormal DAO values than young (≤ 19 years) mothers (Southren and Weingold, 1970). Conversely, no significant differences have been observed between obese patients without other major health problems and normal weight patients whereas in maternal underweight (< 99 pounds), a high incidence of prematurity was found in association with a low maternal plasma DAO curve (Southren and Weingold, 1970).

Although a falling or persistently low activity of plasma DAO in early pregnancy has been associated with significant fetal wastage (Southren *et al.*, 1966b, 1968; Weingold and Southren, 1968; Beaven *et al.*, 1975; Gahl *et al.*, 1982a, b), some of these pregnancies have been shown to continue, some to successful term deliveries (Southren *et al.*, 1966b). The different studies show comparable data in term of the course of DAO activity during normal pregnancies, but not all studies could confirm precipitously falling or persistently low DAO activities in high-risk pregnancies (Resnik and Levine, 1969; Carrington *et al.*, 1972). Unfortunately, screening for chromosomal aberrations as a frequent reason for miscarriage is not indicated in the studies. The relative risk for fetal demise associated with a low DAO activity has been shown to increase from 3.7 at 8 weeks of gestation to 16.6 at 12 weeks of gestation (Gahl *et al.*, 1982a, b). A reduction of placental growth caused by the death of the fetus with subsequently low DAO production has been discussed as a reason for the decrease of DAO activity (Gahl *et al.*, 1982a, b). However, study results are discussed controversially regarding this parameter (Southren *et al.*, 1966b; Southren and Weingold, 1970). Anyhow, the contractile effect of high amounts of insufficiently degraded histamine on the uterine musculature might contribute to a higher rate of abortion in patients with a low DAO activity.

Histamine competes with the other DAO substrates spermidine and putrescine for the enzyme (Holinka and Gurspide, 1984). However, the decreased DAO activity in complicated pregnancies seems to affect only the degradation of histamine and not of other polyamines (Kapeller-Adler, 1944; Kapeller-Adler, 1965a, b; Brew and Sullivan, 2001), as no significant differences have been found for the concentration of other polyamines of normal term placenta compared with placenta from growth retarded and pre-eclamptic pregnancies (Kumazawa *et al.*, 1991; Sooranna and Das, 1995; Brew and Sullivan, 2001). DAO activities have therefore been suggested to act as an indicator of the fetal environment (Lin *et al.*, 1978) and serial measurements have been proposed for the early detection of 'high-risk' pregnancies and trophoblast diseases (Southren *et al.*, 1966b; Weingold, 1968; Weingold and Southren, 1968; Beaven *et al.*, 1975; Lin *et al.*, 1978). Due to low DAO activities in early pregnancy and the presence of DAO in the plasma of non-pregnant women, measurement of DAO as a prognostic marker has been recommended to be of value only from the 8th week of gestation (Legge and Duff, 1981).

Discussion

High expression of the histamine-producing enzyme HDC in the placenta, histamine receptors at the fetomaternal interface and

the existence of an EHRF indicate a physiological role of histamine during implantation. Later in pregnancy, histamine functions as a paracrine oxytocic directly on gestational myometrium giving rise to contraction and indirectly by an increased production of the uterotonic PGF 2α by the decidua. It might therefore contribute to both term and preterm labour.

Without the protective action of an increased DAO activity, an excess of histamine exerts pathological effects on the course of pregnancy. The presence of the HRs at the fetomaternal interface also support the view that prolonged exposure of fetomaternal interface tissues to high levels of histamine might have fundamental roles in the pathogenesis of pre-eclampsia (Szewczyk *et al.*, 2005), spontaneous abortion and other pregnancy related diseases in which high levels of histamine have been demonstrated (Southren *et al.*, 1966b; Beaven *et al.*, 1975; Dubois *et al.*, 1977; Brew and Sullivan, 2001). However, the techniques used for determination of histamine levels in the older studies are considered inaccurate by modern standards (Brew and Sullivan, 2006). Moreover, the instability, and wide inter- and intraindividual variations of histamine (Brew and Sullivan, 2006) complicate reliable comparisons of values between normal and complicated pregnancies.

DAO at the fetomaternal interface is supposed to serve as a metabolic barrier to prevent excessive entry of bioactive histamine into the maternal or fetal circulation as well as to impede prolonged exposure of decidual cells (Brew and Sullivan, 2001). Persistently low or falling DAO plasma curves have been shown in various pregnancies complications such as toxemia, diabetes, anaemia, threatened and missed abortion compared with normal pregnancies (Southren *et al.*, 1966b; Weingold and Southren, 1968; Legge and Duff, 1981), especially during the last trimester (Southren *et al.*, 1966b; Southren and Weingold, 1970; Legge and Duff, 1981). Fetal organic and skeletal abnormalities (Nava and Fraile, 1988) as far as spontaneous abortion (Roberts, 1954) after DAO inhibition with aminoguanidine observed in pregnant rats (Nava and Fraile, 1988) stress the impact of a sufficient histamine degradation during pregnancy.

However, high intra- and interindividual variations have been found in both normal and pathological pregnancies which query the identification of reliable deviations from normal pregnancy levels (Southren *et al.*, 1964; Resnik and Levine, 1969). Moreover, data of homogeneous study collectives and standardized serial measurements of DAO are limited and show intraindividual variations during pregnancy which did not necessarily have prognostic significance (Southren *et al.*, 1966a; Resnik and Levine, 1969; Southren and Weingold, 1970). Together with the high financial costs of the DAO assay these might be the reasons why the measurement of DAO activity has not become accepted in daily clinical practice yet. More studies with standardized assay procedures and large well-defined and homogeneous study collectives are needed to allow a final statement regarding the prognostic value of DAO activities for the course of pregnancies. Anyhow, especially in conjunction with other tests, detection of an increased relative risk of fetal death with the help of DAO measurement might prompt certain obstetrical precautions late in pregnancy (Gahl *et al.*, 1982a, b).

Whether patients with complicated pregnancies mirrored by low DAO values also suffer from HIT-like symptoms during this period or before pregnancy and whether they feature abnormal low DAO activities already in the non-pregnant-status, which

might serve as diagnostic tool to identify women at risk for pregnancies complicated by insufficient histamine degradation, has not been investigated yet. Moreover, a substitution of DAO might present a therapeutical option for patients with high-risk pregnancy or women with yet-to-be identified genetically predetermined defects in DAO activity in the future.

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