Pregnancy-associated diabetes insipidus in Japan—a review based on quoting from the literatures reported during the period from 1982 to 2019

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Abstract. This Review Article overviews the literature on diabetes insipidus (DI) associated with pregnancy and labor in Japan published from 1982 to 2019. The total number of patients collected was 361, however, only one-third of these cases had detailed pathophysiologic information enabling us to identify the respective etiology and subtype. Pregnancy-associated DI can be divided into 3 etiologies, central (neurogenic) DI, nephrogenic DI, and excess vasopressinase-associated DI. Neurogenic DI has various causes: for example, DI associated with tumoral lesions in the pituitary and neighboring area, DI associated with Sheehan’s syndrome and/or pituitary apoplexy, and DI associated with lymphocytic infundibuloneurohypophysitis (LINH, stalkitis). Nephrogenic DI results from defective response of the kidney to normal levels of vasopressin. However, the most interesting causal factor of pregnancy-associated DI is excess vasopressinase, caused either by excess production of vasopressinase by the placenta or defective clearance of vasopressinase by the liver. Hepatic complications resulting in pregnancy-associated DI include acute fatty liver of pregnancy (AFLP) and HELLP syndrome (syndrome of hemolysis, elevated liver enzymes, low platelets), as well as pre-existing or co-incidental hepatic diseases. A possible role of glucose uptake in putative stress-induced DI and the importance of correct diagnosis and treatment of pregnancy-associated DI, including use of 1-deamino 8-D arginine vasopressin, are also discussed.

Key words: Diabetes insipidus, Pregnancy, Vasopressin, Vasopressinase, 1-Deamino 8-D arginine vasopressin

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Introduction

Diabetes insipidus (DI) is caused by deficient vasopressin (AVP, arginine vasopressin; also known as antidiuretic hormone, ADH) responses resulting in excessive water loss and dehydration [1, 2]. DI associated with pregnancy is a rare endocrinopathy that can be caused by exacerbation during pregnancy of pre-existing DI or by decreased release of AVP by the posterior pituitary, defective response to AVP by the kidney, or by excessive vasopressinase-mediated degradation of AVP during pregnancy in patients without pre-existing DI [3-9].

In Japan, Dr. Taya was the first presenter to report a case of DI associated with pregnancy [10]. Since this report was made as an oral presentation, detailed records are not available, but we speculate that his case was a pre-existing DI exacerbated by pregnancy. In 1984, Kaneko et al. [11] analyzed 38 pregnancies associated with DI in Japan; 23 cases developed DI during pregnancy and recovered after parturition. Four cases of DI in pregnancy did not remit after delivery and one case became worse after delivery, possibly due to perinatal or...
postpartum complications that affected the posterior pituitary. Three years later, Higuchi et al. [12] reported a case of DI triggered by pregnancy and estimated that the number of cases of DI associated with pregnancy in Japan identified to that point in time was about 60. The present paper presents a summary of DI associated with pregnancy reported in Japan from 1982 to 2019, with brief descriptions of a few outstanding cases which could help our understanding of DI that develops during pregnancy.

Summary of case reports of pregnancy-associated diabetes insipidus in Japan from 1982 to 2019

Upon reviewing the published literature and the data therein available from the Japan Medical Abstract Society (JAMAS), the Japan Endocrine Society, the Japanese Society of Internal Medicine, and the Japan Society of Obstetrics and Gynecology, we found 361 cases (including our case report). On the basis of the total number of babies born during this period, the incidence of pregnancy-associated DI in successful pregnancies was calculated as 0.81 per 100,000 successful pregnancies (361/44,342,265) [13].

In the majority of the cases reported, pregnancy-associated DI followed the expected pattern of vasopressinase-mediated DI subtypes; DI develops later in pregnancy, as the levels of vasopressinase produced by the placenta are becoming elevated, and spontaneously remits postpartum, after delivery of the placenta. Both central DI and nephrogenic DI in pregnancy are generally responsive to the AVP analogue 1-deamino 8-D arginine vasopressin (DDAVP) [14, 15]. However, except for response to DDAVP, the majority of reports did not contain information concerning the pathological conditions of the patients. About one-third of the total reports did contain information pertaining to pituitary and liver pathologies in patients that developed pregnancy-associated DI (Table 1). These cases are discussed in further detail below.

Brief overview of pathophysiological mechanisms of diabetes insipidus associated with pregnancy

Osmoregulation is markedly altered during normal human pregnancy. Decreased osmotic thresholds for thirst and AVP result in increased water intake and increased AVP expression and water retention [16], which among other effects results in increased blood volume and also softening of the body to allow for fetal growth. AVP is produced in the hypothalamus and is transported and released from the posterior pituitary. Central/neurogenic DI is due to impaired biosynthesis of AVP in the hypothalamus or impaired transport to and release from the posterior pituitary [1, 17, 18]; nephrogenic DI is due to lack of response of the kidney to AVP [1, 17, 18]; and vasopressinase-mediated DI is due to excess degradation of AVP by vasopressinase during pregnancy [3-7] (Fig. 1).

Presently vasopressinase is designated as Leucyl/cystinyl aminopeptidase (LNPEP) officially by Human Genome Organization Gene Nomenclature Committee. LNPEP has several nomenclatures such as oxytocinase, placental leucine aminopeptidase (P-LAP), insulin regulated aminopeptidase (IRAP), and angiotensin IV receptor (AT4) reflecting a broad range of substrates. Originally human vasopressinase had been identified and cloned as P-LAP from the placenta [19]. One year before, IRAP had been identified and cloned from rat fat tissue vp165 [20]. Subsequently it was discovered that P-

Table 1  Pregnancy-associated DI with pituitary, liver and kidney pathologies

| Pathophysiology                                                                 | Number of cases |
|---------------------------------------------------------------------------------|-----------------|
| 1. Pregnancy-associated DI due to pituitary injury:                             |                 |
|   a) Tumoral lesions of the pituitary and neighboring area                      | 19              |
|   b) Sheehan’s syndrome                                                         | 14              |
|   c) Pituitary apoplexy and bleeding                                            | 10              |
|   d) Lymphocytic hypophysitis, infundibuloneurohypophysitis and stalkitis       | 12              |
| 2. Pregnancy-associated DI due to liver pathologies:                            |                 |
|   a) Development of DI during pregnancy associated with acute fatty liver      | 15              |
|   b) Development of DI during pregnancy associated with HELLP syndrome        | 8               |
|   c) Development of DI during pregnancy associated with pre-existing liver or coincidental diseases | 27              |
| 3. Nephrogenic diabetes insipidus complicated with pregnancy                   | 12              |
| Total                                                                           | 117             |
LAP and IRAP were the homologues of the same protein. Furthermore, vasopressinase had been identified as AT4 by protein purification and sequencing of specific angiotensin IV binding site [21].

Oxytocin plays important roles in delivery, breastfeeding and maternal bonding behavior [22]. In particular, oxytocin is well known to induce strong uterine contractions. Vasopressinase is an insulin-regulated aminopeptidase expressed in syncytiotrophoblasts and increases during pregnancy as the placenta grows [16, 23, 24]. Vasopressinase degrades oxytocin as well as AVP, and the metabolic clearance rate of oxytocin increases markedly during pregnancy [25]. It has been suggested that vasopressinase may be involved in maintaining pregnancy homeostasis [26], and low levels of vasopressinase are associated with miscarriage and premature birth [27, 28]. In a normal pregnancy, increased synthesis and release of AVP is adequate to maintain functional AVP levels in the presence of the vasopressinase produced by the placenta [24]. However, in patients with pre-existing subclinical central or nephrogenic DI, the normal increase in vasopressinase that occurs during pregnancy can lower AVP levels sufficiently to exacerbate/unmask the disorder resulting in central or nephrogenic DI in pregnancy [29-32].

Patients with normal production and responses to AVP can develop DI during pregnancy if pregnancy-associated vasopressinase levels become excessive [16, 33, 34]. Patients with excess vasopressinase-associated DI can have up to 300 times higher levels of vasopressinase than normal healthy pregnant women [3, 4, 33, 35]. In these patients, degradation of AVP by vasopressinase decreases AVP to levels resulting in DI. Excess vasopressinase levels during pregnancy can be caused by excessive production of vasopressinase by the placenta [36] or by decreased degradation of vasopressinase in the liver [5, 6].

Liver diseases, including hepatitis (viral hepatitis, drug-induced hepatitis, and hepatitis of unknown etiology), acute fatty liver of pregnancy (AFLP), and HELLP syndrome (syndrome of hemolysis, elevated liver enzymes, low platelets), affect approximately 3% of pregnancies [37, 38]. Hepatic dysfunction can result in significant impairment of vasopressinase degradation [6,
Pregnancy-associated DI due to pituitary injury

We found 55 cases of pregnancy-associated DI that were caused by damage to the pituitary (Table 1). Nineteen cases were caused by damage to the pituitary and its stalk by cysts and tumors (Table 1). These cases included patients with invasion into the pituitary or oppression of the pituitary by prolactinomas (8 cases), pinealomas, non-functional pituitary adenomas, and other brain tumors and one patient with von Hippel-Lindau disease [51]. A well-known cause of another type of DI associated with pregnancy is Sheehan’s syndrome, which occurs as a result of pituitary necrosis due to postpartum hemorrhage, with DI developing within a few days after delivery [29, 50]. We found 14 cases of patients with Sheehan’s syndrome DI (Table 1). Patients with pituitary apoplexy and bleeding (10 cases), as well as twelve cases of lymphocytic hypophysitis and stalkitis were also collected (Table 1).

As noted above, DI associated with Sheehan’s syndrome occurs as a result of pituitary necrosis due to postpartum hemorrhage, and develops within a few days after delivery [29, 50]. However, an abstract entitled “Late onset postpartum diabetes insipidus: a case report” [52] appeared recently describing a case in which postpartum DI associated with Sheehan’s syndrome developed 6 months postpartum. The authors of the abstract note that it is not clear whether this case was simply coincidental or was triggered in the postpartum period by an unknown mechanism.

It is known that there are many cases having lymphocytic inflammatory lesions not only in the anterior pituitary (lymphocytic adenohypophysitis) but also in the posterior pituitary and pituitary stalk (lymphocytic infundibuloneurohypophysitis, stalkitis) [53, 54]. As in the general population, lymphocytic hypophysitis is the most common subtype of hypophysitis associated with pregnancy and parturition [55, 56]. Pregnancy/parturition-associated granulomatous hypophysitis has also been reported [57, 58]. Although the authors could find no reports of IgG4-related hypophysitis associated with pregnancy or the postpartum period in the literature, we noted 8 patients with pregnancy-associated hypophysitis and DI. Clinical features of these cases of pregnancy-associated DI related to lymphocytic hypophysitis are shown in Table 2 [59-66]. Among them, 4 cases developed lymphocytic hypophysitis in the postpartum period. Differing subtypes of lymphocytic hypophysitis is suggested by the fact that some cases of lymphocytic hypophysitis remit spontaneously while others lead to permanent hypopituitarism [53, 67]. Notably, lymphocytic hypophysitis is known to sometimes recur on pregnancy after a latent period as long as 5 years [63].

Conflicting results and poor specificity impaired the clinical usefulness of using anti-pituitary antibodies to diagnose hypophysitis. In 2015 Iwama et al. [68] identified rabphilin-3A as potentially useful marker of lymphocytic infundibuloneurohypophysitis and in 2017 Sakurai et al. [69] used antibodies against rabphilin-3A to diagnose central DI due to lymphocytic infundibuloneurohypophysitis that developed in the third trimester of a patient. However, the usefulness of rabphilin-3A antibodies for diagnosis of lymphocytic infundibuloneurohypophysitis remains to be confirmed. Currently, the most accepted diagnosis for hypophysitis and neighboring inflammatory lesions that can oppress the pituitary is careful reading of MRI images for homogenous swelling.
of these areas, including the pituitary stalk, compression of the floor of the sella turcica, and suprasellar extension of adenoma-like images [55]. Biopsy of the pituitary gland is the most reliable method for diagnosing the lymphocytic lesions, however, this method is invasive and is only undertaken in select cases in which diagnosis is uncertain and the results of the biopsy are likely to change the course of management of the disorder [55].

**DI due to liver pathology associated with pregnancy**

It is important to diagnose liver disease during pregnancy as early as possible and determine a relevant therapeutic course. Liver diseases in pregnancy are divided into 2 groups according to the recent article by Ma et al. [37]: (1) liver diseases specific to pregnancy and (2) liver diseases that are preexisting or coincident with pregnancy but not specific to pregnancy.

Group (1) in our case collection is the group of 15 patients with pregnancy-associated DI due to hepatic dysfunction caused by AFLP [70]. AFLP was described in 1940 as a specific clinical entity unique to pregnancy [71]. AFLP is a life-threatening complication of pregnancy with high maternal and fetal mortality. Symptoms include general malaise, fatigue, hypoglycemia, hypertension, nausea and/or vomiting, abdominal pain, jaundice, and skin pruritus [72, 73]. However, AFLP can be difficult to distinguish from HELLP syndrome [74]. The Swansea criteria [75] have a high negative predictive value for hepatic microvesicular steatosis, thus eliminating the need for liver biopsy in management of the disease [74, 76]. It is recommended that patients with AFLP have their pregnancies terminated upon diagnosis of the disease, either by Caesarean section or by forced labor [39, 74-76].

In our case collection (2), the onset-age of pregnancy-associated DI due to hepatic dysfunction caused by HELLP syndrome ranged from 26 to 39 years. The onset of initial symptoms ranged from the 32nd to 37th week.

| Case No | Age (year-old) | Initial symptoms | Onset of DI | Clinical and laboratory data | Image diagnosis | Therapy and effects | Ref. |
|---------|----------------|------------------|------------|-----------------------------|----------------|----------------------|------|
| 1.      | 28 y           | polydipsia, polyuria | 36th week  | elevated liver enzymes thrombocytopenia | MRI            | C-section improved     | [59] |
| 2.      | 32 y           | thirst, polyuria   | 32nd week  | elevated liver enzymes prolonged prothrombin time  elevated serum Na⁺ | MRI            | oxytocin-induced delivery DDA VP improved | [60] |
| 3.      | 23 y           | malaise, thirst, polyuria | 35th week  | elevated liver enzymes high bilirubin prolonged prothrombin time | MRI            | transvaginal delivery DDA VP improved | [61] |
| 4.      | 37 y           | fatigue, bitemporal anopia | 24th week  | low plasma cortisol low plasma thyroxine complication of IgA nephritis | MRI            | C-section transsphenoidal surgery hormone replacement DDAVP | [62] |
| 5.      | 34 y           | headache, poor appetite | 4 month postpartum | recurried infilabulo-hypophysitis abducens paralysis | MRI            | transvaginal delivery steroid with DDAVP | [63] |
| 6.      | 34 y           | thirst, polyuria, visual disturbance | 42nd week  | MRI | C-section due to placenta abortion steroid with DDAVP improved | [64] |
| 7.      | 32 y           | headache, fatigue | 32nd week  | visual field defect biopsy revealed lymphocytic hypophysitis | CT                  | transvaginal delivery DDAVP with T4 | [65] |
| 8.      | 42 y           | poor lactation, malaise, polydipsia, polyuria | after C-section in 34th week | hypothyroidism | MRI                  | C-section for hypertension under DDAVP and cortisol | [66] |

**Table 2** DI during or after pregnancy complicated with lymphocytic hypophysitis and infundibuloneurohypophysitis

- week, gestational week; C-section, Caesarean section; DDAVP, 1-deamino 8-D arginine vasopressin

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of pregnancy. Minimal platelet count was \(1.5 \times 10^4\). A slight difference in the initial symptoms of the patients with HELLP syndrome from those with AFLP was a complaint of abdominal pain: epigastralgia. All cases underwent Caesarean sections, stillbirth was observed in two cases (Cases 1 and 5). It is noteworthy that the pathological factor of Case 3 was pituitary apoplexy. Another notable case was reported by Yamanaka et al. in 2002 [77]: a patient with twin pregnancies and suffering from HELLP syndrome developed DI during the postpartum period. The patient responded to administration of DDAVP. The authors hypothesize that the DI was due to somewhat increased vasopressinase production by the placenta due to the twin pregnancies coupled with decreased vasopressinase degradation by the liver due to hepatic dysfunction caused by HELLP syndrome [77].

Twenty-seven cases were also collected of pregnancy-associated DI due to preexisting liver diseases or liver diseases coincident with pregnancy but not specific to pregnancy (Table 1).

### Case report

A 34-year-old patient was referred to the Department of Internal Medicine, KKR Maizuru Hospital, from the Department of Obstetrics and Gynecology (KKR Maizuru Hospital) because of marked polydipsia and pedal edema during her third trimester of pregnancy. Previously, she had an abortion at the 9th week of her first pregnancy. At that time, she had marked polydipsia and polyuria, as much as 10 liters a day. However, no abnormalities were noted during her annual health check-ups. One week after admission, the chief obstetrician decided to perform a Caesarean section, because of delayed labor. No serious complications occurred during the operation and a healthy male baby was delivered. Next morning, according to the opinion of the chief of the Internal Medicine, therapy using a nasal spray of DDA VP was begun, based on the data shown in Table 3. After delivery polydipsia and polyuria continued, suggesting that the patient’s pregnancy-associated DI was due to exacerbation of pre-existing central DI. Therefore, therapy with the DDAVP nasal spray was continued until DDAVP oral tablets became available. To investigate the possibility of hereditary neurogenic diabetes insipidus, mutational analysis was performed, however, no mutations in the patient’s AVP gene were found. Based on the absence of a high intensity signal in the posterior pituitary lobe on T1-weighted images, she was diagnosed to have central diabetes insipidus. The results of routine laboratory examinations, performed every 3 weeks after the operation, were within normal limits: serum electrolytes were low but near the normal limit, hepatic and renal function were normal. Also body weight remained constant at 63–64 kg under a nasal spray of DDAVP. Therefore, the patient was discharged 4 weeks after admission.

### Nephrogenic diabetes insipidus in pregnancy

Nephrogenic diabetes insipidus (NDI) is classified into either acquired or hereditary. Acquired NDI can occur secondarily to various renal diseases such as polycystic kidney disease, amyloidosis or sarcoidosis, and prolonged hypokalemia or hypercalcemia. Also those who prescribe or take medicine should be mindful that some medications such as lithium for emotional diseases, some antibiotics, and angiotensin II receptor antagonist can induce NDI.

Hereditary NDI is due to genetic defects causing malfunction of the kidney vasopressin receptors (AVPR2, X-linked, commonest) or mutations affecting the aquaporin-2 gene (AQP2, usually autosomal recessive).

Currently, options for the therapy of NDI are limited to the use of thiazide, NSAID (Non-Steroidal Anti-Inflammatory Drug), and potassium-sparing diuretics (Amiloride) [78].

Transient renal resistance to vasopressin during pregnancy is rare but well recognized. Pregnancy is a stress condition that unmask insufficient abilities to secret and respond to vasopressin. Consequently, subclinical forms

### Table 3  Arginine-vasopressin test

| Time   | Urine volume (mL) | Serum Na (mEq/L) | Osmolality (mOsm/kg) |
|--------|-------------------|------------------|----------------------|
| 8 am   | 2,000             | 153.7            | 68                   |
| 10:30 am | 70                | 152.1            | 382                  |
| 11 am  | 170               |                  | 403                  |
| 11:30 am |                  |                  |                      |
| 12:30 am |                  |                  |                      |

Drinking water was prohibited from 8:00 am, and 5 units of water-soluble vasopressin (pitressin®) were injected at 10:30 am.
of NDI are exacerbated by increased vasopressinase activity and decreased reactivity to vasopressin during pregnancy [29, 79]. Since 1984, 12 cases of pregnancy-related NDI have been confirmed in Japan. Although not always clear, the causes or related abnormalities in each case include hypokalemia (4 cases) [31, 80-82], renal tubular injury (1 case) [80], drug (lithium, 1 case [83]; gentamicin, 1 case [15]), acute hepatic failure (1 case) [84], trisomy X (47, XXX) (1 case) [85], and NDI family history (2 cases) [29, 86].

The cause of hypokalemia is not always clear, but in one case, it was caused by refeeding syndrome following hyperemesis gravidarum [82]. A combination of hypokalemia and renal tubular injury was confirmed in one case [80]. In a patient with acute hepatic failure, the cause of NDI was unclear [84]. Three cases show recurrence of transient NDI during pregnancy [14, 29]. Another patient experienced both neurogenic and nephrogenic DI during pregnancy. The cause of NDI was unknown in this patient, but the coexistence of both neurogenic and nephrogenic DI suggested the possibility of a cystic lesion in the posterior pituitary [87]. A family history of NDI suggests mutations in either the AVPR2 or AQP2 genes. The clinical phenotype can be mild depending on the mutation [88, 89]. In the case of an AVPR2 mutation associated with the X chromosome, skewed X chromosome inactivation can make the clinical phenotype mild [90]. No genetic search has been performed, but patients with trisomy X or a family history are expected to have abnormalities similar to those described here.

A case of putative stress-induced DI associated with pregnancy

There is a report of a case of DI in pregnancy that was believed to have been triggered by The 2016 Kumamoto Earthquake. The authors [45] suggest that the earthquake triggered stress-mediated release of oxytocin in this patient, resulting in premature uterine contractions. The placenta might have responded to an upregulation of oxytocin by increasing synthesis of vasopressinase, thereby causing DI. In addition to the marked increase in vasopressinase in the placenta of the patient, Kondo et al. also found increased production of glucose transporter 4 (GLUT4) in the placenta, co-localization of GLUT4 with vasopressinase, and increased placenta weight [45]. They hypothesized that increased GLUT4 increased glucose uptake by the placenta, resulting in growth of the placenta, and that the relatively large placenta produced an increased amount of vasopressinase [45]. This is a fascinating case report and hypothesis, however, further investigation is indispensable.

Vasopressinase and Insulin

Vasopressin is also known as insulin regulated amino-peptidase (IRAP). The activity of IRAP promotes vesicles’ translocation to cell surface in response to insulin. Accordingly it is assumed that vasopressinase would improve insulin sensitivity. In accord with this premise, vasopressinase deficient mice showed diminished basal and insulin-stimulated glucose uptake in muscle and adipocytes [91].

Under basal conditions, IRAP localizes to the intracellular membrane compartments, and in response to insulin IRAP redistributes to the cell surface [92]. In type 2 diabetes, insulin production is inadequate and the response to insulin is also lower than normal, resulting in increased urine volume in response to increased blood sugar levels. However, decreased insulin responses also decrease the amount of vasopressinase translocated to the cell surface, and subsequently, the degradation rate of vasopressin would also be decreased. Thus, theoretically, increased vasopressin acts to depress the increased urine volume in type 2 diabetes patients.

Concluding remarks regarding our review of pregnancy-associated DI in Japan

Pregnancy-associated DI can be divided into 2 subtypes: one being vasopressinase-dependent and the other vasopressinase-independent. Vasopressinase is produced during pregnancy by the placenta, and its activity increases as the placenta grows during pregnancy and becomes undetectable at about 4–6 weeks postpartum [23]. Consequently, vasopressinase degradation of vasopressin and vasopressinase-mediated DI follow this pattern. Vasopressinase-independent DI occurs as a result of damage to the pituitary caused by perinatal and postpartum complications. Our collection of cases mostly followed the pattern expected of vasopressinase-mediated DI during pregnancy, with only about 15% (55/361) of the cases of pregnancy-associated DI resulting from pituitary damage. However, the overall incidence of pregnancy-associated DI cases we collected (approximately one in 100,000 successful pregnancies) is lower than expected (approximately 2 to 4 cases per 100,000 pregnancies). It is likely that this discrepancy resulted from under-assessment of pregnancy-associated DI. One factor that would have an effect on this underassessment is the fact that mild cases are likely to be underestimated as thirst and polyuria are normal symptoms of pregnancy [1, 5, 6, 9, 35], and this under-diagnosis is not necessarily similar in different regions. Another factor is that we collected cases from abstracts and partial reports available from JAMAS, the Japan Endocrine Society, the
Japanese Society of Internal Medicine, and the Japan Society of Obstetrics and Gynecology, and many of the abstracts and reports were too simplified, omitting essential data, particularly in the case reports presented at local meetings, to allow a confident diagnosis of pregnancy-associated DI. Consequently, many abstracts and reports were confined to the topics of the pathophysiological entities of pregnancy-associated DI, i.e., DI associated with lymphocytic hypophysitis, infundibuloneurohypophysitis (stalkitis), AFLP, and HELLP syndrome. Overall, our results are consistent with those from other regions.

Pregnancy-associated DI caused by excessive vasopressinase activity can be effectively treated with DDAVP. However, in our collection of cases, 3 stillborn births were documented, two stillborn births were from a mother suffering from AFLP and one stillborn birth was from a mother suffering from HELLP syndrome. These cases highlight the need to diagnose and treat liver dysfunction that occurs during pregnancy. In addition, work needs to continue to identify auto-antibodies that can help to diagnose cases of auto-immune hypophysitis.

Correct diagnosis and treatment, and prevention of pregnancy-associated DI are important in order to maintain healthy conditions during pregnancy and labor, for normal development of fetus, for ensuring healthy babies, and for contributing to earlier diagnosis and treatment of DI inherited by the next generation.

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Disclosure

None of the authors has any potential conflicts of interest associated with this study.

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