

# Transient Improvement in Glycemic Control

## The impact of pregnancy in women with IDDM

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**OBJECTIVE** — Good glycemic control throughout pregnancy in patients with diabetes is of paramount importance but often appears to deteriorate in the postpartum period. The aim of this study was to ascertain the timing of the improvement in glycemic control associated with pregnancy in women with IDDM and to examine changes in glycemic control after delivery.

**RESEARCH DESIGN AND METHODS** — Peripartum glycemic control was assessed in a retrospective study of 30 women with IDDM whose age was  $28 \pm 6$  years (means  $\pm$  SD) and whose diabetes duration was  $14 \pm 6$  years.

**RESULTS** — Mean total HbA<sub>1c</sub> fell incrementally from a peak at 2–3 years preconception to a nadir between 24 weeks and term, only to return to preconception levels within a year after delivery. Of the 30 women, 15 (50%) attained an HbA<sub>1c</sub> in the nondiabetic range for pregnancy at some point during their pregnancy, and 7 (23%) women achieved this by 24 weeks gestation. Women with an HbA<sub>1c</sub>  $>9\%$  at booking had a significantly higher HbA<sub>1c</sub> at 0–6 and 6–12 months preconception, and throughout pregnancy their HbA<sub>1c</sub> was significantly higher. After delivery, attendance rates at routine diabetes review clinics were low, with 11% of women not attending for longer than 24 months.

**CONCLUSIONS** — Nearly all women with IDDM can achieve near normoglycemia during pregnancy, irrespective of previous glycemic control, although those with high HbA<sub>1c</sub> levels at booking are less likely to achieve this. After delivery, glycemic control deteriorates. Efforts to improve glycemic control should be intensified in the preconception period and maintained after delivery. The poor postpartum attendance at diabetes clinics requires specific action.

Poor glycemic control during pregnancy has been shown to be associated with both higher maternal and infant morbidity (1–5). Recently, the St. Vincent Declaration set a target of achieving pregnancy outcomes in women with diabetes similar to those for nondiabetic women (6). Very poor glycemic control in early pregnancy has been shown to be associated with high levels of miscarriage and congenital abnormalities (1,7,8). Although birth weight is associated with glycemic control, the absolute blood glucose levels that minimize fetal morbidity and mortality

have not been established. Maternal hypoglycemia is a serious problem especially during early pregnancy (9,10) and precludes the achievement of near normoglycemia in some women.

Combined obstetric/diabetes clinics and the introduction of preconception counseling appear to have gone partway to meeting the aims of the St. Vincent Declaration, and there is evidence that the improved glycemic control achieved during pregnancy has reduced both maternal and infant morbidity (5,11). Although improved glycemic control during pregnancy is pos-

sible to achieve, there are limited data on the specific degree of glycemic control achieved by women after pregnancy. The Diabetes Control and Complications Trial (DCCT) (12) has proved the importance of achieving good glycemic control to minimize the risk of microvascular complications and has also provided data on achievable levels of control. The improved metabolic control achieved in the DCCT was largely caused by increased commitment by patients, carers, and health professionals, a situation similar to that seen in pregnancy.

The aim of the present study was to document glycemic control before, during, and after pregnancy, using total HbA<sub>1c</sub> concentrations as an indicator of glycemia, and to identify factors that were associated with the level of control during these periods.

### RESEARCH DESIGN AND METHODS

The case records of 34 women with IDDM who delivered during the period from November 1992 to July 1994 at the Simpson's Memorial Maternity Pavilion of the Royal Infirmary of Edinburgh were reviewed. Thirty cases were included in the study; four were excluded for the following reasons: two women attended the Royal Infirmary halfway through the pregnancy because they had only recently moved to the area, insufficient data were recorded in one set of notes, and one set of case records could not be traced. Demographic details of the 30 women are given in Table 1.

All women of child-bearing age were offered preconception counseling if they attended routine diabetes review clinics (8). The rate of attendance for preconception counseling is 54% at the clinic in which the study took place. Once pregnant, women were seen every 2 weeks from the time of booking (usually 6–10 weeks) until 30 weeks gestation and then weekly until delivery. Patients were reviewed at a joint clinic by a diabetologist, an obstetrician, a midwife, a diabetes nurse specialist, and a dietitian. Between visits, patients were encouraged to adjust their insulin according to home blood glucose measurements

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**Abbreviations:** DCCT, Diabetes Control and Complications Trial.

**Table 1—Demographic data for 30 IDDM women whose HbA<sub>1c</sub> levels were followed before, during, and after pregnancy**

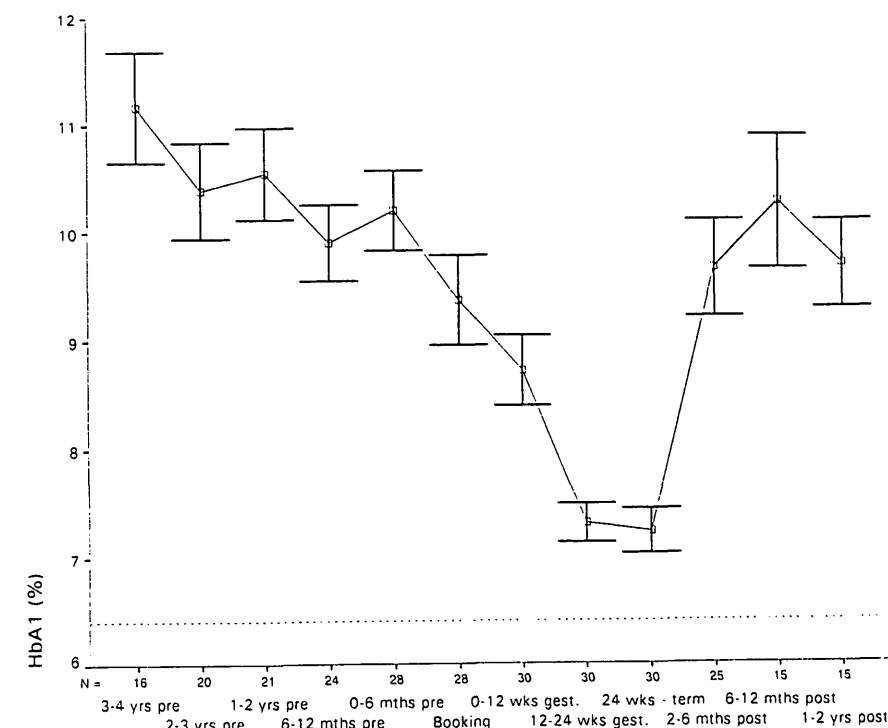
Age (years)	28 ± 5
Duration of diabetes (years)	14 ± 7
Age at diagnosis (years)	14 ± 7
Duration of follow-up postdelivery (months)	31 ± 7
Previous live births	
0	17 (57)
1	7 (23)
2	4 (14)
3	1 (3)
4	1 (3)

Data are means ± SD or n (%).

and were in regular contact with the diabetes specialist nurse. During pregnancy, all patients monitored blood glucose at least four times per day. However, none of these home blood glucose data were available because of the retrospective nature of the study.

In the prepregnancy period, HbA<sub>1c</sub> concentrations were recorded for the following time periods, where available: 3–4 years, 2–3 years, 1–2 years, 6–12 months, and 0–6 months before conception. If more than one result was available, the mean HbA<sub>1c</sub> was taken for that period. If a patient had another pregnancy during the 4 years before the index pregnancy, data were only collected for the period 6 months after the previous delivery to minimize the effect of the previous pregnancy on glycemic control. Total HbA<sub>1c</sub> was measured using high-speed liquid chromatography based on ion exchange reversed-phase partition method (Hi Auto A1c HA 8121 Biomen). Unfortunately, in the early part of the study only HbA<sub>1c</sub> was recorded, and therefore data are presented as HbA<sub>1c</sub>, not HbA<sub>1c</sub>. In Edinburgh the nondiabetic nonpregnant normal range of HbA<sub>1c</sub> is 5.2–6.8%, and the normal range for pregnancy is 4.8–6.4% (13).

Data recorded during the pregnancy included all HbA<sub>1c</sub> concentrations. HbA<sub>1c</sub> was measured every 2–4 weeks, and the mean HbA<sub>1c</sub> was calculated for 0–12 weeks' gestation, 12–24 weeks' gestation, and 24 weeks to term. The lowest HbA<sub>1c</sub> achieved and the gestational week at which this occurred were recorded. Birth weight and gestation at delivery were documented, and birth weights were adjusted (according to tables produced for nondiabetic pregnancy in the clinic in which the study took place)



**Figure 1—HbA<sub>1c</sub> measured before, during, and after pregnancy in patients with IDDM (mean ± SE). (· · ·), upper limit of the reference range for nondiabetic pregnancy.**

for gestational age, parity, and sex of the child and were expressed as z-scores.

For the postpartum period, HbA<sub>1c</sub> was recorded for the following time periods, where available: 0–6 months, 6–12 months, and 1–2 years. If the patient had a subsequent pregnancy, recording of data was discontinued 6 months before the pregnancy.

The default rate (the number of women who failed to attend clinics) in the postpartum period was recorded.

#### Statistical analysis

All data (analyzed using SPSS for Windows) are presented as means ± SD unless otherwise specified. The women were divided into groups for comparison using unpaired *t* tests: 1) those with an HbA<sub>1c</sub> >9 vs. <9% at booking and 2) those who achieved an HbA<sub>1c</sub> within the nondiabetic range for pregnancy versus those who never achieved an HbA<sub>1c</sub> in the nondiabetic range during the pregnancy. To assess the effect of demographic variables on glycemic control, unpaired *t* tests were performed between the following groups: nulliparous versus multiparous women, age of diagnosis of diabetes <15 or >15 years of age, and present age <25 or >25 years of age. A *P* value of <0.05 was considered significant.

## RESULTS

### Glycemic control

The serial measurements of mean HbA<sub>1c</sub> levels for each time period are shown in Fig. 1. The mean ± SD HbA<sub>1c</sub> 2–3 years before pregnancy was 10.5 ± 1.9% and at booking was 9.4 ± 2.2%; the mean lowest HbA<sub>1c</sub> (not shown in Fig. 1) achieved during pregnancy was 6.6 ± 0.9%. One patient (3%) had an HbA<sub>1c</sub> in the normal range for pregnancy at the time of booking. Fifteen (50%) women achieved an HbA<sub>1c</sub> within the normal range for pregnancy at some time during the pregnancy, and seven (23%) achieved an HbA<sub>1c</sub> in the normal range by 24 weeks' gestation. During the postpartum period, the glycemic control rapidly reverted to levels similar to those in the prepregnancy period (Fig. 1). One year after delivery, HbA<sub>1c</sub> levels had risen to 9.7 ± 1.6%, a level very similar to that 1 year before conception (9.9 ± 1.7%).

### Follow-up in the postpartum period and default rate

The mean ± SD duration of follow-up in the study after delivery was 32 ± 8 months. Eleven (37%) women failed to attend their first postnatal appointment (between 2 and

**Table 2—Comparison of glycemic control between women who had an HbA<sub>1c</sub> at booking >9% vs. <9%**

Period	HbA <sub>1c</sub> >9%	HbA <sub>1c</sub> <9%	P
3–4 years preconception	11.9 ± 2.2 (9)	10.4 ± 1.3 (6)	NS
2–3 years preconception	10.6 ± 1.0 (10)	10.3 ± 2.7 (9)	NS
1–2 years preconception	10.8 ± 1.6 (11)	10.3 ± 2.4 (9)	NS
6–12 months preconception	10.8 ± 1.3 (12)	8.6 ± 1.3 (11)	0.001
0–6 months preconception	11.0 ± 1.8 (14)	8.9 ± 1.6 (12)	0.006
0–12 weeks' gestation	9.8 ± 1.7 (15)	7.4 ± 1.0 (13)	<0.001
12–24 weeks' gestation	7.8 ± 1.0 (15)	6.6 ± 0.5 (13)	<0.001
24 weeks to term	7.6 ± 1.2 (15)	6.7 ± 0.8 (13)	0.01
Lowest pregnancy HbA <sub>1c</sub>	7.0 ± 1.0 (15)	6.0 ± 0.5 (13)	0.003
2–6 months postpartum	10.2 ± 2.4 (14)	8.9 ± 1.7 (11)	NS
6–12 months postpartum	11.0 ± 2.9 (6)	9.8 ± 2.0 (9)	NS
1–2 years postpartum	11.0 ± 1.4 (6)	8.7 ± 1.0 (8)	0.01

Data are means ± SD (n).

3 months after delivery), but data were eventually obtained for 26 (87%) women for the period 0–6 months after delivery and for 15 (50%) women for the period up to 1 year after delivery. Five women (17%) embarked on another pregnancy during the postpartum period of study and were excluded from the analysis. In addition, one woman left the area, and one woman died. Of those patients who were theoretically available to attend follow-up clinics (n = 23), 17% (n = 4) did not attend the clinic during the 1st year following delivery, and 13% (n = 3) had not attended at all during the follow-up period for >25 months (range 25–46).

**Insulin regimens**

Nineteen percent of the studied women used a basal bolus insulin regimen (three injections of soluble insulin before meals and one injection of isophane at bedtime), 11% split their evening injection and used three injections per day, and 70% were on conventional twice-daily soluble and isophane insulin regimens. HbA<sub>1c</sub> did not differ between insulin regimens.

**Associations of level of glycemic control**

When the women were divided into two groups according to whether the HbA<sub>1c</sub> at booking was <9 or >9%, significant differences in glycemic control were observed for the periods 0–6 months and 6–12 months preconception, but not for the period before this (Table 2). (Only 28 women were included in this analysis as booking HbA<sub>1c</sub> concentrations were not available for two women.) Comparison of women who achieved an HbA<sub>1c</sub> in the nondiabetic range

during pregnancy with those who did not achieve an HbA<sub>1c</sub> in the nondiabetic range, demonstrated a significantly lower HbA<sub>1c</sub> at booking but not at any other time before this (Table 3). The week of the lowest HbA<sub>1c</sub> did not differ between the groups.

Women with one or more previous live births (n = 13) achieved poorer glycemic control from 24 weeks gestation to term (HbA<sub>1c</sub> 7.7 ± 1.2 vs. 6.9 ± 0.9%, P = 0.05), and the lowest HbA<sub>1c</sub> achieved was also significantly higher (HbA<sub>1c</sub> 7.0 ± 1.0 vs. 6.3 ± 0.7%, P = 0.05).

Attained age had no association with the degree of glycemic control achieved during the pregnancy, whereas an age at diagnosis of diabetes of <15 years was associated with a slightly lower HbA<sub>1c</sub> during the pregnancy (P = 0.05, HbA<sub>1c</sub> 6.3 ± 0.7 vs. 7.0 ± 1.1%), a lower HbA<sub>1c</sub> during the 6–12

months postdelivery (P = 0.003, HbA<sub>1c</sub> 9.3 ± 1.7 vs. 12.8 ± 2.8%) and over 12 months postdelivery (P = 0.03, HbA<sub>1c</sub> 9.1 ± 1.4 vs. 11.1 ± 2.5%). Duration of diabetes had no effect on the degree of glycemic control achieved during the pregnancy.

The mean birth weight was 3,592 ± 480 g with a median gestational age of 37 weeks, and all pregnancies resulted in live births. There was one twin pregnancy, and birth weight data were not included for this pregnancy. Data were not available for two other pregnancies. Only one infant (4%) weighed >4,500 g, and seven infants (26%) weighed >4,000 g, four of whom were ≤37 weeks' gestation. Of babies born, 56% were within 2 standard deviations of their expected birth weight (median 1.68, range 0.1–5.1).

**CONCLUSIONS** — In the present study of 30 women with IDDM, glycemic control as assessed by HbA<sub>1c</sub> improved considerably during pregnancy but, after delivery, rapidly reverted to levels observed in the prepregnancy period. The degree of glycemic control achieved at booking appeared to be associated with glycemic control 0–12 months preconception, but not with any other period. During this period, some women were contemplating pregnancy and therefore improving control. In addition, those who achieved an HbA<sub>1c</sub> in the nondiabetic range during pregnancy had significantly lower HbA<sub>1c</sub> levels at booking, and this difference persisted throughout the pregnancy. This suggests that any patient should be capable of achieving improved glycemic control during pregnancy, and those who have achieved good control (i.e.,

**Table 3—Comparison of glycemic control between women who achieved a nadir HbA<sub>1c</sub> in the nondiabetic range (6.4%) versus those who did not at some point during the pregnancy**

Period	HbA <sub>1c</sub> >6.4%	HbA <sub>1c</sub> <6.4%	P
3–4 years preconception	10.8 ± 1.4 (8)	11.5 ± 2.6 (8)	NS
2–3 years preconception	10.1 ± 1.2 (9)	10.6 ± 2.4 (11)	NS
1–2 years preconception	10.1 ± 1.0 (10)	10.9 ± 2.5 (11)	NS
6–12 months preconception	10.3 ± 1.5 (11)	9.4 ± 1.8 (13)	NS
0–6 months preconception	10.7 ± 1.7 (16)	9.4 ± 2.0 (12)	NS
Booking	10.3 ± 2.2 (15)	8.2 ± 1.7 (13)	0.01
0–12 weeks' gestation	9.5 ± 1.7 (17)	7.7 ± 1.4 (13)	0.004
12–24 weeks' gestation	7.8 ± 0.9 (17)	6.6 ± 0.7 (13)	0.001
24 weeks to term	7.9 ± 0.9 (17)	6.3 ± 0.6 (13)	<0.001
2–6 months postpartum	10.6 ± 2.5 (13)	8.6 ± 1.2 (12)	NS
6–12 months postpartum	11.1 ± 3.2 (5)	9.8 ± 1.8 (10)	NS
1–2 years postpartum	9.9 ± 0.9 (7)	9.4 ± 2.0 (8)	NS

Data are means ± SD (n).

HbA<sub>1c</sub> <9%) by the time of booking go on to maintain better control throughout the pregnancy and achieve a lower nadir of HbA<sub>1c</sub>. However, those with the lowest HbA<sub>1c</sub> during pregnancy were not necessarily those who had better control in the years before pregnancy. This emphasizes the importance of optimizing control preconceptionally because this will influence the overall control during the pregnancy and the nadir HbA<sub>1c</sub> achieved.

Women who had previous pregnancies had poorer glycemic control, particularly during the latter part of pregnancy. This suggests that mothers with young children may find it more difficult to maintain good glycemic control, possibly because of their existing family commitments. It is also possible that because of the increased risk of hypoglycemia associated with strict glycemic control, they may choose to allow blood glucose levels to be a little higher. An alternative explanation is that women who had experienced a previous successful pregnancy may have been reassured and become overconfident, resulting in a degree of complacency in their self-management. However if this were the whole explanation, it would be expected that glycemic control would be universally higher throughout the pregnancy, and not just during the last trimester.

In the present study, total HbA<sub>1c</sub> was used as the measure of overall glycemic control, although in clinical practice, home blood glucose monitoring was used to monitor glycemic control. Unfortunately, because of the retrospective nature of the study, none of the blood glucose data was available for analysis. Most of the improvement in glycemic control during pregnancy is caused by improved diet, more frequent blood glucose monitoring, and alterations in insulin doses. The improvement was mostly achieved on conventional twice-daily insulin regimens. In nondiabetic women, HbA<sub>1c</sub> falls slightly during pregnancy, possibly resulting from a combination of a lower fasting glucose concentration during pregnancy and changes in red cell age (13,14); however these factors account for a small change of ~0.5% in the HbA<sub>1c</sub>. There is a lag between the improvement in blood glucose and a decrease in total HbA<sub>1c</sub> (15). Thus, lower concentrations of blood glucose in weeks 12–14 will be reflected by a lower total HbA<sub>1c</sub> in weeks 24 to term. Figure 1 clearly demonstrates that the nadir for the HbA<sub>1c</sub> is reached by 24 weeks, suggesting that during the period 16–24 weeks

glycemic control is at its lowest level. However the fall from 6 months preconception to 12 weeks' gestation, and thence to 24 weeks, suggests that glycemic control is continuing to improve during the early weeks of pregnancy. Ideally, the nadir in HbA<sub>1c</sub> should be achieved either at or before the booking visit, or the decrease in HbA<sub>1c</sub> between the booking visit and 24 weeks' gestation should be small. However, in the present study the nadir of HbA<sub>1c</sub> occurred at a similar time in those women who had better control at booking compared with those who had poorer control. The time of the nadir in the HbA<sub>1c</sub> is not earlier in those with better control in the preconception period, further emphasizing the importance of planning pregnancies. If preconception counseling can optimize preconceptional glycemic control (8,16) this will facilitate lower HbA<sub>1c</sub> levels during the pregnancy.

Half of the women in the present study achieved normal HbA<sub>1c</sub> values, although in the majority this was not until the second half of the pregnancy. The mean nadir HbA<sub>1c</sub> achieved was 2.5 SD away from our nondiabetic pregnancy mean. In the DCCT, women who became pregnant achieved a mean HbA<sub>1c</sub> during pregnancy of 3 SD from the reference population (12,17). In the present study, all women achieved significant improvements in glycemic control during pregnancy. This is probably caused by a combination of the desire to deliver a healthy baby combined with the increased professional interest in the women and regular feedback from clinic visits. In addition, the benefits of maintaining good control during pregnancy are readily seen within 9 months compared with the long-term benefits of good control in the avoidance of microvascular disease, which will not be realized by the patient for many decades.

There are many reasons why women do not achieve near-normal glycemic control during pregnancy. The most important limiting factor is the increased risk of hypoglycemia associated with improved glycemic control (12). For many women, the increased requirement for monitoring and the risk of hypoglycemia may not be compatible with their lifestyle, particularly if they are working or looking after small children at home. Unfortunately, because of the retrospective nature of the present study, it was not possible to estimate the incidence of hypoglycemia. A study from Germany (10) examined the incidence of severe hypoglycemia in pregnant women with IDDM. For most women, the blood glucose control

achieved was very good, but at an increased risk of severe hypoglycemia. Although there were no adverse fetal outcomes, the possible risks of exposing women to hypoglycemia sufficient to cause impairment of consciousness must be considered carefully and for many women will not be acceptable. In another study by Hepburn et al. (9), a higher incidence of hypoglycemia was documented during the 1st trimester, and this appeared to be related to an alteration of the symptom profile manifest as a diminution in the intensity of autonomic symptoms. These changes in awareness of hypoglycemia may be related to the improvement in glycemic control or may be related to the pregnancy per se. However, in women who may already have impaired awareness of hypoglycemia, it may provide another reason why the target of near normoglycemia may not be desirable.

One of the most important findings of this study is that after delivery, glycemic control quickly returned to prepregnancy levels. These levels are suboptimal, especially in light of the DCCT results (12). Although women with particularly tight glycemic control and those with a history of recurrent hypoglycemia are encouraged to relax their glycemic control slightly, the observed deterioration in glycemic control was dramatic. The reasons for this are likely to be related to the decrease in intensive education and assessment provided by health professionals and reduced motivation combined with the added burden to the patient of looking after a young baby and not being able to devote as much time to themselves. The fear of hypoglycemia while looking after a small baby may further reduce the incentive to maintain good control.

A disturbing finding in the present study was the high default rate for clinic appointments in the postdelivery period, despite attempts made by the diabetes specialist nurse to reinitiate contact. It is unlikely that women defaulted for geographic reasons, since most were attending this clinic because it was the nearest hospital clinic. There was no difference in attendance between those who had more than one child to care for and those with only one child. It is possible that the mothers perceived that their control had deteriorated and wished to avoid being confronted with this fact at the clinic. This high default rate, resulting in missing data for the postpartum period, means it is not possible to identify any meaningful associations between the glycemic control in the postpartum period

and control at other time points. For the period of 32 months, which was the mean duration of the postpartum follow-up, it is estimated that each woman should have been seen five times. However the mean number of appointments that women attended over this period was 2.3, i.e., they were seen less than once per year. However, although it is likely that many of these women may wish to conceive again, the present study did not demonstrate that those who defaulted were those who had poorer control at booking. Making clinics more user-friendly to mothers with small children, or even considering home visits, may help improve postnatal glycemic control.

The importance of good glycemic control at conception and during the first few weeks of pregnancy in preventing fetal malformation is well documented (1,2,5,11, 18). This study suggests that almost any patient with IDDM is able to improve glycemic control during pregnancy, irrespective of a history of poor previous glycemic control. However, despite intensive input from health care professionals, HbA<sub>1c</sub> does not reach a nadir until the second half of pregnancy. This emphasizes the importance of preconception counseling. The potential for a marked deterioration in glycemic control after delivery should be anticipated early, and education of women and targeting of care should be planned to try and maintain the improved glycemic control achieved during pregnancy.

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