This study characterised a novel gene, previously identified as uniquely regulated at implantation in mouse uterus. We cloned its full mRNA sequence encoding a serine protease possessing an IGF-binding domain and named it pregnancy-related serine protease (PRSP). PRSP is structurally similar to mammalian HtrA1 (56% amino acid similarity); thus it represents an additional member of the mammalian HtrA protein family. Northern analysis revealed that the uterine expression of PRSP mRNA was low before pregnancy, but it was increased at implantation and dramatically up-regulated post-implantation. Both in situ hybridisation and immunohistochemistry localised PRSP expression at a low level in the epithelium and stroma during very early pregnancy, but at a high level in the decidual cells on day 8.5, primarily at the mesometrial pole where the placenta was forming. By day 10.5, a high level of PRSP was localized in the decidual compartment of the newly formed placenta. We also cloned an alternatively spliced PRSP mRNA that is expressed at a very low level in the mouse uterus. We determined the genomic structure of PRSP and revealed how the two mRNA variants are produced through alternative splicing. Based on its protein domain structure and unique expression during pregnancy, we propose that PRSP plays an important role in the formation/function of the placenta during pregnancy.