RATIONALE OF THE STUDY

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The trophoblast of the human placenta plays key roles in anchoring the placenta to the uterine wall, in supplying the foetus with oxygen and nutrients, and in helping to detach the placenta from the uterus during birth. An intricate balance of signals is required throughout pregnancy and, in a gestational disease, this balance may be disturbed. This disease occurs predominantly in the younger reproductive age group and has a high hospital prevalence rate in the State of Kerala accounting for 1.2% of deliveries. It is socially important in that it affects women in reproductive age and repeated pregnancies are a matter of marital disharmony. Methods to identify the vesicular moles with high risk of malignant transformation, the drug resistant forms, and the risk of recurrent moles are not yet available. Likewise, not much information is available on the molecular mechanisms, which leads to the formation of a molar placenta. The identification of molecular alterations in terms of oncogenes and growth factors could be of great value in understanding the biology of the disease and hence it would be useful in identifying high-risk tumours at an earlier stage.

Since in GTDs there is increased propensity for abnormal proliferation, survival and accumulation of the trophoblastic cells, and that EGFR expression in trophoblastic tissue plays a role in cell survival, as shown by previous studies, it logically follows that the EGFR signal transduction pathway might be a deciding factor behind the abnormal accumulation of trophoblastic cells. The alterations at molecular level in the placenta, a conversion to molar phenotype and its role in persistence of the disease has not been looked into to date.

EGFR may play a role in the pathogenesis of gestational trophoblastic diseases (Tuncer et al, 2000). EGFR expression has been associated with secretion of human chorionic gonadotropin, and following exposure to chemotherapy EGFR binding sites have been noted to be diminished in choriocarcinoma cells (Cao et al, 1994; Cao et al, 1995; Filla and Kaul, 1997; Chen et al, 1990). While EGFR has been demonstrated in placental and molar trophoblasts and choriocarcinoma cells, data concerning its intensity of expression and its clinical significance have been conflicting (Filla and Kaul, 1997; Chen et al, 1990; Muhlhauser et al, 1993; Ladines-Llave et al, 1993). It was interesting to note a discrepancy in the results observed between the immunohistochemical scores and the concentrations of the EGFR in the spontaneous regressing and persisting disease groups by a previous study from our lab (John et al, 1997). While an increasing trend of intensity of staining with aggressiveness of the disease was noted in immunohistochemical assays, the concentration of EGFR was

seen to be higher in the spontaneously regressing group. A similar decreasing trend with aggressiveness was also noticed by Ladines-Llave et al who used an antibody to the external EGF-binding domain of the EGFR in her immunohistochemical studies (1993). This type of result was observed whenever the external domain was being detected. The difference in the results probably suggests the presence of truncated EGFRs in GTD (Balaram et al, 1997). Alteration of this receptor by genetic or other mechanisms can lead to its over-expression (Liberman et al, 1985 and Kraus et al, 1989) or to deletions of specific regions which can lead to constitutive activation of the receptor, thereby bypassing the requirement of ligand binding (Kraus et al, 1989).

In particular, the literature concerning molecular changes within these GTDs is sparse. The aim of this study was to expand on these data, especially with regard to the putative role of EGFR expression, activation and gene amplification accompanied by gene mutations. The downstream signalling pathways were also looked into to assess the functional alterations of this receptor in the initiation and progression of this abnormal condition.

Cells that over express EGFR, release increased quantities of its extra-cellular domain (ECD) into the extracellular environment (Brandt-Rauf et al, 1995). Increased amounts of the extracellular domain of EGFR can be detected immunologically by ELISA (Partanen et al, 1994). Since over-expression of EGFR represents an early alteration of growth control, allowing cells to proliferate continuously and escape terminal differentiation, detection of circulating ECD could act as a potential biomarker of identification of molar placenta at an early stage. This aspect has also been looked into.

Our studies allow for novel insights into EGFR-mediated effects on cellular processes in the pathological trophoblast and may help to explain the initiating events in GTD. We present the first comprehensive study addressing on the biologic profiles of EGF receptors and their signalling targets in GTDs, and their pathologic and prognostic significance